Synthesis of Heterocycles from Anthranilic acid and its Derivatives

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Abstract

Anthranilic acid (2-aminobenzoic acid, Aa) is the biochemical precursor to the amino acid tryptophan, as well as a catabolic product of tryptophan in animals. It is also integrated into many alkaloids isolated from plants. Aa is produced industrially for production of dyestuffs and pharmaceuticals. The dissertation gives a historical background and a short review on the reactivity of Aa. The synthesis of several types of nitrogen heterocycles from Aa is discussed.

Treatment of anthranilonitrile (2-aminobenzonitrile, a derivative of Aa) with organomagnesium compounds gave deprotonation and addition to the nitrile triple bond to form amine-imine complexed dianions. Capture of these intermediate with acyl halides normally gave aromatic quinazolines, a type of heterocyclic compounds that is considered to be highly interesting as scaffolds for development of new drugs. When the acyl halide was a tertiary 2-haloacyl halide, the reaction instead gave 1,4-benzodiazepine-3-ones via rearrangement. These compounds are isomeric to the common benzodiazepine drugs (such as diazepam, Valium®) which are 1,4-benzodiazepine-2-ones. Capture of the dianions with aldehydes or ketones, led to 1,2-dihydroquinazolines. Unsubstituted imine anions could be formed by treatment of anthranilonitrile with diisobutylaluminium hydride. Also in this case capture with aldehydes gave 1,2-dihydroquinazolines.

Several different dicarboxylic acid derivatives of Aa were treated with dehydrating reagents, and the resulting products were more or less complex 1,3-benzoxazinones, one of which required X-ray crystallography confirm its structure.

During the work on preparation of N-substituted derivatives of Aa, necessary for synthesis of 1,4-benzodiazepine-3,5-diones, it was noted that many of the obtained products were in fact not N-substituted, but O-substituted. This challenged the established notion that Aa reacts nucleophilically at the N-terminal under most conditions. Several grave errors in the recent literature were revealed.

In 1976 researchers from the group that originally developed the common benzodiazepine drugs published a retraction of a claim of synthesis of a benzodiazepine by Gärtner in 1904. They found that the method actually gave a 6-membered ring system, not a 7-membered 1,4-benzodiazepine-3,5-dione as originally claimed. Because the 1,4-benzodiazepine skeleton is highly interesting as a scaffold for development of new drugs, a few publications on synthesis of this target has appeared. However, repetition of several of the described syntheses failed to yield the poorly described products. Studies on how to ring close N-carbamoyl derivatives of Aa were undertaken. It became clear that *Umpolung* of the substrates by N-derivatisation was a necessary prerequisite for ring closure. The introduction of the N-nitroso group was developed to this end, leading to N1-nitroso substituted 1,4-benzodiazepine-3,5-diones. The nitroso group could be removed after ring closure. Heating of one of these compounds induced a ring contraction rearrangement. A proposed mechanism involves elimination of HNO (nitrosyl) and proton mediated loss of CO.

Keywords: Anthranilic acid, synthesis, heterocycles, benzodiazepines, HNO (nitrosyl)

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W. SHAKESPEARE.

Synthesis of heterocycles from anthranilic acid and its derivatives

Contents

A note on numbering of compound structures:
Only compounds which are discussed in the context of the current work are numbered. Compound numbers appear in **bold**, or ***bold italic*** for compounds not described in the printed papers. The preparation of the latter compounds can be found in the appendix.

List of papers

The dissertation is based on the following papers:

I "Ring forming reactions of imines of 2-aminobenzaldehyde and related compounds"
Per Wiklund, Jan Bergman
Org. Biomol. Chem., **2003**, 1, 367–372

II "Products from dehydration of dicarboxylic acids derived from anthranilic acid"
Per Wiklund, Ivan Romero, Jan Bergman
Org. Biomol. Chem., **2003**, 1, 3396–3403

III "Alkylation and acylation of basic salts of anthranilic acid"
Per Wiklund, Jan Bergman
Tetrahedron Lett., **2004**, 45, 969-972

IV "Synthesis of 1,4-benzodiazepine-3,5-diones"
Per Wiklund, Mark Rogers-Evans, Jan Bergman
Manuscript

List of abbreviations

Ac	acetyl
atm	atmosphere
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DIBAL-H	diisobutylaluminium hydride
DIMBOA	2,4-dihydroxy-7-methoxy-(2*H*)-1,4-benzoxazine-3(4*H*)-one
DMSO	dimethylsulfoxide
ESI	electron spray ionisation
Et	ethyl
GABA	*gamma*-aminobutyric acid
*i*Pr	*iso*-propyl
LAH	lithium aluminium hydride
M	molar concentration
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mp	melting point
MS	mass spectroscopy
NAD	nicotinamide dinucleotide
NMDA	*N*-methyl-D-aspartate
NMR	nuclear magnetic resonance
Ph	phenyl
rt	room temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

Introduction

This is a book about *anthranilic acid*.

Well, it is not just about *anthranilic acid*, but also about its derivatives, its reactivity and chemical behaviour, but most especially the book is about my efforts to use *anthranilic acid* as a starting material for synthesis of heterocyclic compounds. It has been the basic ingredient in my making of organic molecules which do not only contain carbon and hydrogen (as organic molecules do), but also an elemental dash of nitrogen and oxygen. I am not the first to use anthranilic acid in such a fashion, far from it. Nature was first, then came Man.
Anthranilic acid flows in your veins as a by-product of your very life. It appears imbedded in alkaloids, the nitrogen heterocycles produced by plants. Transformed it colours the robes royally red and gives the bombastic blue of indigo.
A man took indigo apart and found *anthranilic acid* to be the blueprint. Mankind used *anthranilic acid* in her discovery of chemistry, and made drugs from it, drugs that ease the pain or cause agony to the soul on abuse. The quintessential quest continues.

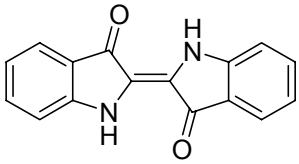
For better or for worse, this book is about *anthranilic acid*.

There are more things in heaven and earth, Horatio,
Than are dreamt of in your philosophy.

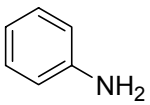
William Shakespeare
Hamlet prince of Denmark
Act I, Scene V

1. Anthranilic acid

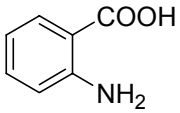
Discovery and historical perspective



indigo



aniline



anthranilic acid

Discovery in chemistry in the 19th century was fundamentally connected to dyes. The history of anthranilic acid starts when Carl Julius Fritzsche (1808-1871) experimented in his laboratory in St. Petersburg with degradation of the ancient dye indigo in the late 1830s.[1] The chemical structure of indigo was not known at the time, but it was of interest to the flourishing textile industry which together with the steel industry spearheaded the industrial revolution. In a paper published in 1840 Fritzsche identified a compound with basic properties as one of the degradation products from treatment of indigo with alkali.[2] He named it "Anilin" after a Spanish word for indigo, *añil*. The compound had actually been isolated in much the same way already in 1826, but then named "Krystallin".[1] Fritzsche also isolated an acid from the alkaline degradation, one which he could not determine the composition of. The acid, which he called "Chrysanilsäure", could be further degraded with mineral acids to yield yet another compound with acidic properties, and he could accurately determine its composition. He named the compound "Anthranilsäure", from Greek *anthrax* meaning coal, and *añil* for indigo. It decomposed to aniline and carbon dioxide on heating above the melting point, but Fritzsche had no means to determine its actual structure. Freiherr Justus von Liebig (1818-1873)[i], one of the most influential chemists of the time, took notice of Fritzsche's work and also repeated and confirmed the results.[3]

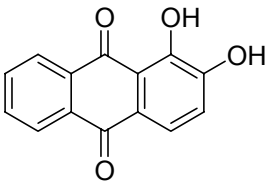
One of Liebig's students was August Wilhelm von Hoffman (1818-1892) who spread Liebig's method of teaching chemistry by laboratory exercise to other parts of Europe. Hoffman moved from Liebig's laboratory in Giessen in Germany to become director of the Royal College of Chemistry[ii] in London in 1845.[4] He created a school that was to train many of the distinguished chemists in the era to come. The development of the science of chemistry boomed in the wake of the soda industry and the identification of many simple organic compounds from coal tar (which was an abundant by-product from the production of lighting gas) by Hofmann and his co-workers and students. Among the students was William Henry Perkin (1838-1907)[iii] who made a failed attempt to synthesise the alkaloid quinine at home during a break from the chemistry course in 1856. Perkin was left with a dark tarry "mud", a sad scenario which all chemists even today have to confront once in a while. Perkin happened

[i] Liebig founded the journal *Annalen der Pharmacie und Chemie* in 1832, which was published monthly until 1998 under the name *Justus Liebigs Annalen der Chemie*. Among other things Liebig was the first to suggest usage of chemical fertilisers.

[ii] Hoffman stayed there until 1864 when he returned to Germany. The Royal College of Chemistry was incorporated into The Royal School of Mines in 1853.

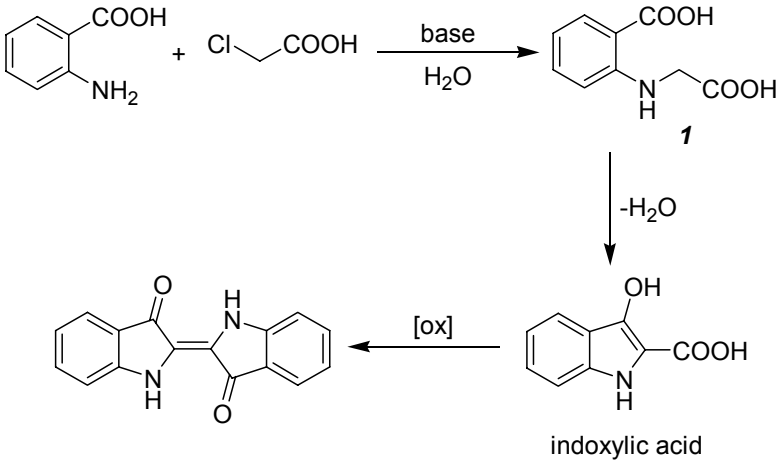
[iii] He was knighted in 1906 at the 50th anniversary of his discovery of Mauve. His son was W.H. Perkin Jnr.

to notice that a cloth he had used to clean up the mess with was heavily stained. He quickly set up an ambitious plan to use this material as a synthetic dyestuff that was to be called "Mauve".[5] Although silk dresses coloured with this dyestuff were popular for a short time, business soon plummeted when it became clear that the dye was not colour-fast enough over time. Even though it was not a big commercial success, Mauve was the first fully synthetic dyestuff to be marketed and also the first of the so called aniline dyes.



alizarin

Perkin was later involved in the much more commercially successful introduction of synthetic alizarin.[6] This dye had traditionally been extracted from the common madder, *Rubia tinctorum* (Swedish: krapprot). Graebe and Liebermann, co-workers of Johann Friedrich Wilhelm Adolf von Baeyer (1835-1917), reduced alizarin with zinc and obtained anthracene.[7] This inspired Perkin, as well as Heinrich Caro of BASF in Germany, to develop commercial syntheses of alizarin by oxidation of anthracene in 1869.[5] Baeyer later worked on the chemistry of indigo, leading first to a synthesis from isatin.[8] He could then deduce the structure of indigo (and indoxylic acid)[9] and device a synthesis[i] from 2-nitrobenzaldehyde.[10] The two latter publications appeared on consecutive pages in *Berichte der Deutschen Chemischen Gesellschaft* in 1882. Baeyer was awarded the Nobel Prize for Chemistry in 1905 for this work.

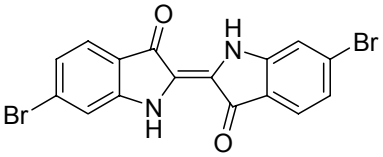


indoxylic acid

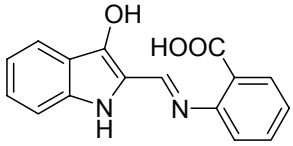
A commercial synthesis of indigo from anthranilic acid was developed by Carl Heumann who published it in 1880.[11] This procedure, variants of which are still widely used today, involves ring closure of *N*-carboxymethylanthranilic acid (***1***) by dehydration to form indoxylic acid

[i] This reaction is commonly known in English as "*the Baeyer-Drewson indigo synthesis*". However, the second author of the paper was one Viggo Drewsen, most likely of Danish origin.

(originally by heating in NaOH/KOH). Air-oxidation of the indoxylic acid affords indigo.[i] The production of synthetic indigo, which quickly wiped out the agricultutal industry based on cultivation of plants for indigo production, had a profound effect on politics and culture in Europe, Asia and Africa.[13] About 20 000 tons of indigo is currently produced *per annum* worldwide. The classic *blue jeans* gets its colour from indigo.[14]



6,6'-dibromoindigo



chrysanilic acid

There is another dye called Tyrian purple which was produced in the ancient cultures around the eastern mediteranian. It was prepared by treatment of extracts from a molusc, *Murex brandaris*, or related species.[15] The red dye was associated with kingship and robes of Roman emperors were commonly dyed with it.[16] In 1909 Paul Friedländer (-1923)[17], a former pupil of Baeyer, could show that the main component of Tyrian purple is 6,6'-dibromoindigo.[18] A year later he also showed the identity of Fritzsche´s chrysanilic acid (Chrysanilsäure) to be the imine of indoxylic aldehyde with anthranilic acid. Although the structure was correct, it has later been shown that the keto-enamine tautomer is more stable.[19]

[i] There are many variants of the dehydration in the literature. The most common reagent is Ac_2O/NaOAc. Whereas the oxidation/dimerisation of indoxylic acid to indigo has been studied extensively,[12] no mechanistic study of the initial ring closure has been published.

Properties of anthranilic acid

Anthranilic acid (2-aminobenzoic acid) is a white to pale yellow solid compound with a sweetish taste. The melting point is 144-146 ºC, and it can be crystallised from hot water. Solutions in alcohols or ether exhibit an amethyst-like fluorescence.[20]

Like other amino acids anthranilic acid is amphoteric. Due to the donating effect of the amino group anthranilic acid is a weaker acid than benzoic acid (pK_a 4.20). Anthranilic acid also contains both a hydrogen bonding acceptor and a donator, and they are conjugated. It is therefore not surprising to find that the acid strength varies substantially in different media.

pK_a	**medium**
6.53[21]	50 % dioxane in H_2O
6.51[22]	84.2 % wt. MeOH in H_2O
5.40[23]	EtOH/H_2O
5.00[24]	H_2O
4.95[25]	H_2O
3.71[24]	pyridine

pK_a of anthranilic acid

pK_a	**Medium**
2.15[26]	H_2O
2.11[27]	H_2O
2.36[26]	Nitromethane
1.57[22]	84.2 % wt. MeOH in H_2O

pK_a of protonated anthranilic acid

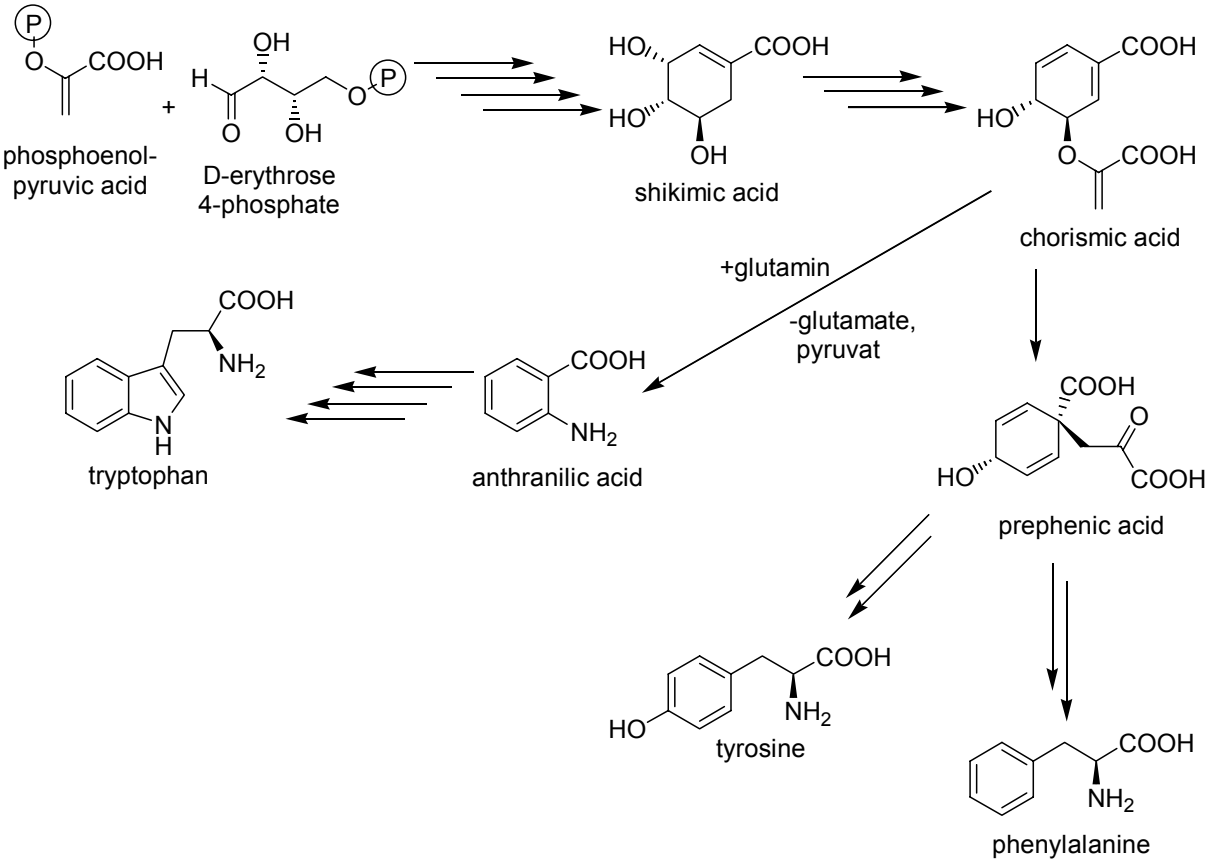
From the tables above it is clear that the acid strength increases with the polarity of medium. An explanation for this observational fact is that in more polar environments the acidic proton is less bound in intra- or intermolecular hydrogen bonds.
As a base anthranilic acid is much weaker than aniline (pK_a 4.61) because of the pronounced electron withdrawing effect of the carboxy function.

Anthranilic acid can form coordination complexes with many metals. The structure of complexes with gallium and aluminium,[28] lithium, sodium and potassium,[29] magnesium[30], thalium,[31]rubidium and cesium,[32] have all been determined by X-ray crystallography. The stability of chelates with copper and cadmium have also been investigated.[21]

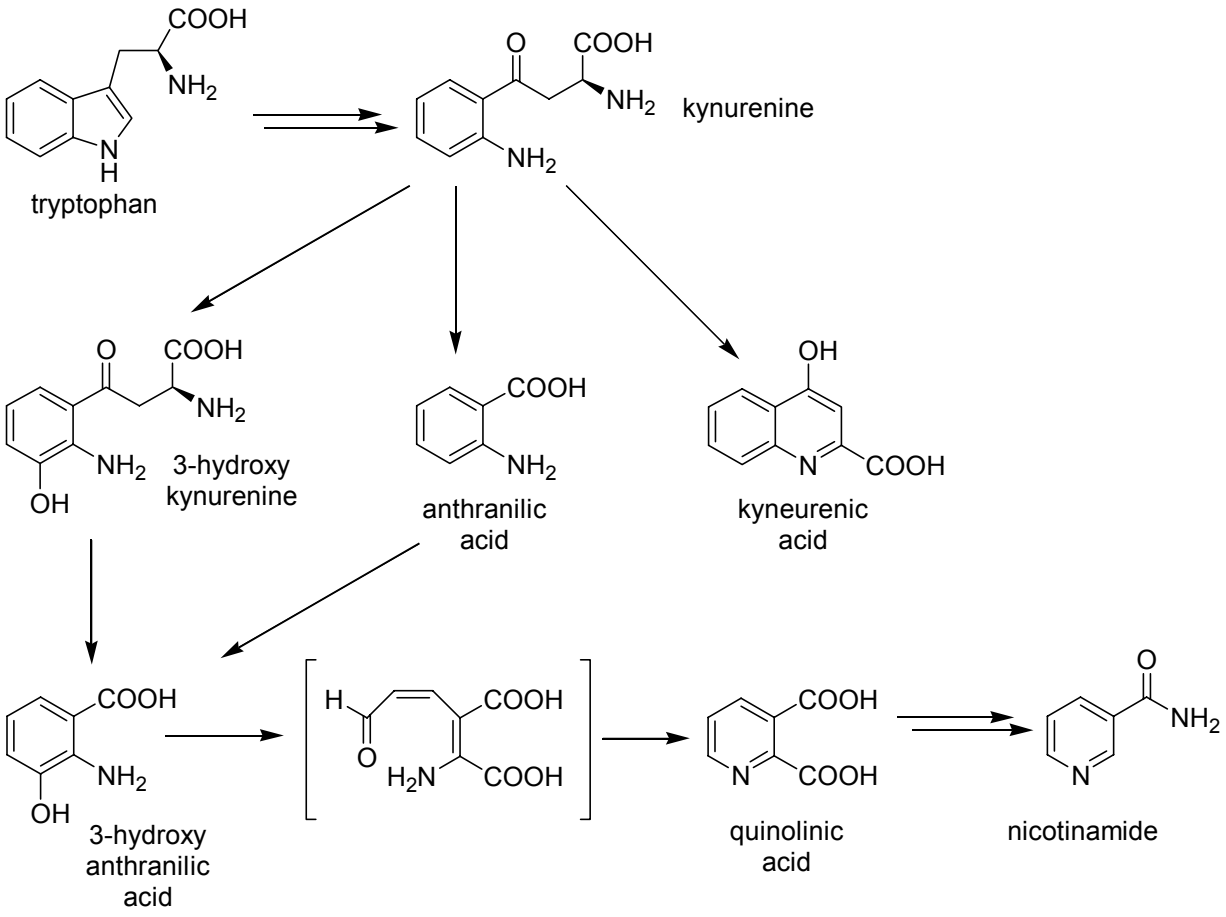
The biochemistry of anthranilic acid

Biochemical pathways

Anthranilic acid plays a part both in the anabolism and catabolism of the amino acid tryptophan. These biochemical pathways also involve anabolism of phenylalanine and tyrosine, as well as synthesis of quinolinic acid, a precursor to the important energy carrying molecule NAD.



Anthranilic acid is produced in bacteria and plants through a series of enzymatic reactions from phosphoenolpuruvic acid and erythrose-4-phosphate.[33] In shikimic acid the 6-membered ring has formed and it is further transformed into chorismic acid which the common precursor of tyrosine, phenylalanine and tryptophan.[34] Glutamate donates its amino group to chorismic acid and pyruvate is cleaved off to form anthranilic acid. The latter reaction step is catalysed by the enzyme *anthranilate synthase*. Tryptophan is formed through a series of enzymatic reactions from anthranilic acid.

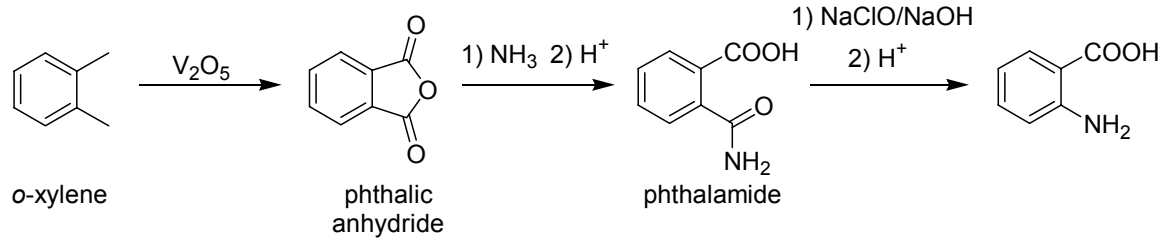


In the catabolism of tryptophan in animals the intermediate kynurenine, which is a ring opened oxidised form of tryptophan, is further transformed into several important biologically active molecules.[35]Hydroxylation of kynurenine, followed by cleavage of alanine, leads to 3-hydroxyanthranilic acid. Direct cleavage of alanine (catalysed by *kynureninase*) leads to anthranilic acid. Side chain deamination, followed by ring closure, leads to kynurenic acid. In this pathway anthranilic acid can also be oxidised (hydroxylated) to form 3-hydroxyanthranilic acid,[36]which is the precursor to quinolinic acid via enzymatic opening of the aromatic ring (catalysed by *3-hydroxyanthranilic acid oxidase*)[35], followed by a non-enzymatic ring closure. Quinolinic acid can interact with a subgroup of NMDA-receptors and is neurotoxic at high concentrations.[37] It is also the precursor to nicotinamide (and NAD).

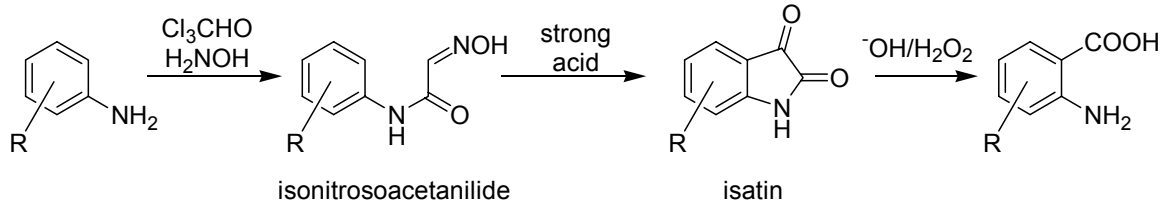
Other occurrence in nature

As a consequence of the occurrence of anthranilic acid in the major biochemical pathways of bacteria, plants and animals, anthranilic acid is also the starting material for several other types of compounds in nature. Among these are alkaloids[38] (*vide infra*), plant signalling compounds like DIMBOA[39] and indole-3-acetic acid.[34, 40] Ethyl and methyl anthranilate are important odorants in wine, such as in *Pinot noir* from Burgundy.[41] The level of methyl anthranilate in grapes generally increases on ripening.[42] A type of beetle, the *black chafer*, use anthranilic acid as a pheromone.[43] N-acylated derivatives of anthranilic acid has been found in oats.[44]

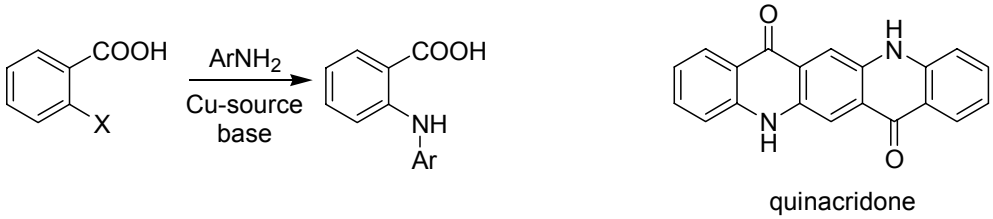
Synthesis of anthranilic acids



The industrial synthesis of anthranilic acid is based on oxidation of *o*-xylene giving phthalic anhydride. The anhydride is opened by ammonia to form phthalamide, which is then treated with sodium hypochlorite under basic conditions to induce a *Hofmann rearrangement*.[45-47] Sodium hypobromite has also been used.[48] Phthalimide reacts the same way as phthalamide.



Ring substituted anthranilic acids are available through oxidation of the corresponding isatins with alkaline hydrogenperoxide. The procedure has been performed on alkyl, halo, alkoxy, trifluromethyl, nitro and also on N-substituted isatins.[49] *Baeyer-Villiger oxidation* of isatins (with *e.g*. *m*-CPBA or H_2O_2 in AcOH) gives the corresponding isatoic anhydride.[49, 50] Isatins are available through the *Sandmeyer isatin synthesis* by treatment of an aniline with chloral hydrate and hydroxylamine. The use of the procedure as been reviewed.[49, 51]



N-aryl anthranilic acids are available through the Ullman-Goldberg reaction. The original reaction involved coupling of anthranilic acid with bromobenzene catalysed by copper at high temperatures to give *N*-phenylanthranilic acid.[52] The publication by Irma Goldberg appeared directly followed by a publication of Fritz Ullmann (1875-1939)[53] and Maag on the synthesis of quinacridone (widely used as colour fast dye in many modern demanding applications)[54, 55] by the same method from anthranilic acid and *p*-phenylene diamine.[56] The following year Ullmann and co-workers published the details of a copper catalysed coupling of aniline and 2-chlorobenzoic acid.[57] Later developments of the reaction utilize 2-halobenzoic acids and anilines, or other amino aryls, together with a base and a source of copper. The reaction can be promoted by sonication,[58] and in this case even be performed with great success in water.[59] Recent development of the reaction for a broader range of substrates has seen the use of copper complexes.[60] Similar reaction conditions can also be used in high yielding

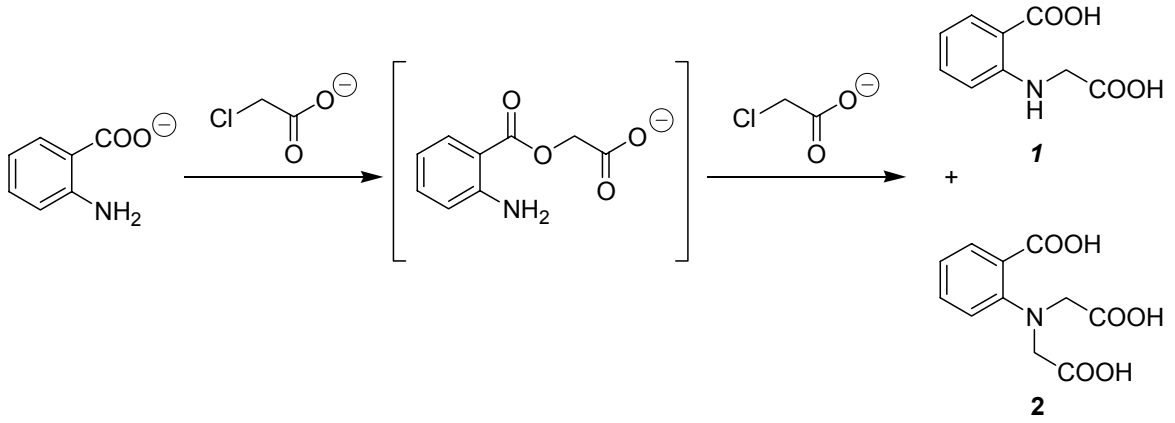
N-arylations of amides.[61] There is also a broad, but somewhat dated, review on copper assisted nucleophilc substitution of aryl halogen.[62]

Anthranilic acid, and several of its derivatives, can also be formed in disproportionation reactions of 2-nitrotoluene.[63]

Reactivity of anthranilic acid

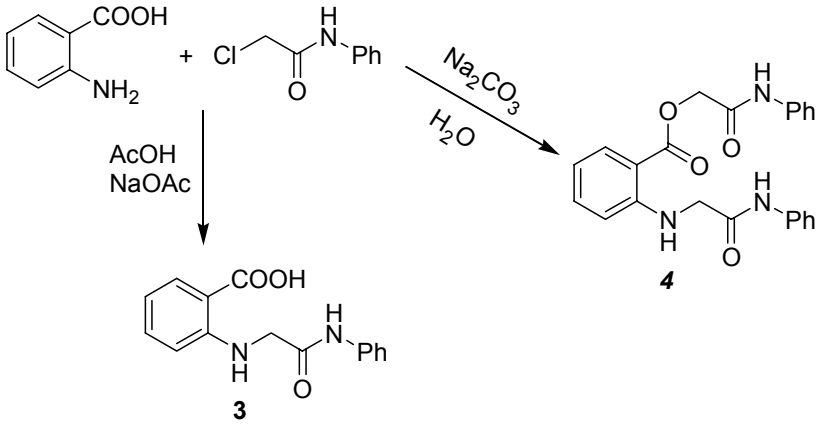
Acylation/alkylation

Anthranilic acid contains two nucleophilic centers, the amino group and the carboxy group. Under neutral conditions the nucleophilic properties of the amino group dominate, especially in reactions with acylating agents when the great stability of the product amide contributes to the outcome. In reactions with acyl halides anthranilic acid itself can function as a hydrogen halide scavenger, *i.e.* only half of the amount of starting material can form product whereas the other half is trapped as hydrohalide salt. Since the carboxy group is many orders of magnitude more acidic than the aniline-like amino group, addition of base inevitably gives the carboxylate. The results in **paper III** show that in this case electrophiles are attacked by the carboxylate and not by the amino group, as many chemists seem to assume. This misconception stems from two facts; Several simple N-alkylated derivatives of anthranilic acid have historically been prepared in basic aqueous solution (see **paper III**, and an early treatment of N-alkylation by Houben[64]). Secondly, most textbooks in organic chemistry make no mention of alkylation of carboxylates, a procedure that is in fact used industrially to prepare esters. The hypothesis in **paper III** is that in non-aqueous systems esters are exclusively formed in reactions with alkylating agents under basic conditions (if there is not more than one equivalent of the alkylating agent present), but that reactions in water often lead to N-alkylation. The latter can be explained if the formed esters are N-alkylated and then hydrolysed under the basic conditions.



An example of this is the synthesis of *N*-carboxymethylanthranilic acid (***1***)[i], a starting material for synthesis of indigo (*vide supra*) and also used as a starting material in **papers II**, **III** and **IV**. There are many methods in the literature to prepare ***1***, most of which utilize reaction of anthranilic acid and chloroacetic acid in aqueous sodium carbonate solution. This is also how Heumann first prepared this diacid,[11]and it is also basically the method in a 1901 patent of BASF.[65] The reaction inevitably also gives the N-disubstituted compound **2**, which can be subjected to oxidative conditions for dealkylation to ***1***.[66] For the present projects ***1*** has been prepared in a sodium hydroxide solution. This procedure has the definite advantage that there is no foaming on dissolution of the anthranilic acid. Anthranilic acid was dissolved in water with one equivalent NaOH and then allowed to react with 1.7 equivalents of sodium chloroacetate at reflux temperature. This gave a 75 % yield of ***1*** (and about 5 % of **2**). After the reaction the mother liquor was slightly acidic (pH≈5). Addition of more sodium chloroacetate increased the yield of **2** on the expense of ***1***. Addition of more NaOH gave very insoluble salts of ***1*** and **2**. These results support the hypothesis above, and it could be proved if lactic acid, cleaved off from the intermediate ester, could be detected in high concentration in the reaction mixture.

[i] Often called phenylglycine *o*-carbonic acid (or carboxylic acid) in older literature.

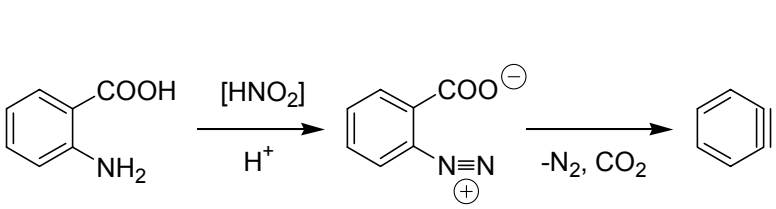


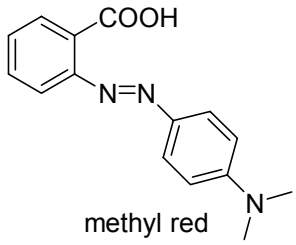
Another example of this phenomenon was obeserved in attempted synthesis of the N-carbamoyl deriviative **3**, which was later to be used as a starting material for synthesis of a 1,4-benzodiazepine-3,5-dione (**paper IV**). Heating of anthranilic acid with chloroacetanilide in Na_2CO_3-solution gave the O,N-dialkylated derivative ***4***. Prolonged heating of the two reactants in acetic acid with sodium acetate as HCl-scavanger, did in fact give a moderate yield of **3**.

Halogenation

Treatment of anthranilic acid with sulfuryl chloride (SO_2Cl_2) in ether has been reported to give an easily separable mixture of 5-chloroanthranilic acid and 3,5-dichloroanthranilic acid.[67, 68] Treatment of anthranilic acid with bromine in acetic acid gives 5-bromination in high yield.[69, 70]

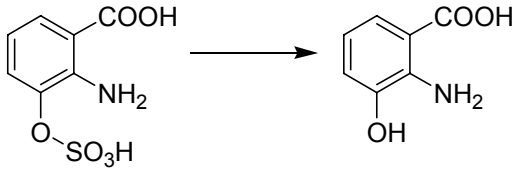
Diazotisation

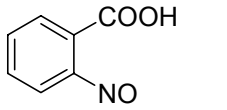




Like other anilines anthranilic acid can be diazotised, but in non-aqueous media the diazonium salt has the possibility to have an intramolecular counter-ion, thus forming a zwitterionic inner salt.[71] This benzenediazonium carboxylate, prepared in EtOH with isoamyl nitrite, can be isolated and is completely stable below -70 ºC.[72] On heating to 40-60 ºC the salt is fragmented to nitrogen gas, carbon dioxide and benzyne and can thus be utilized as a source of this highly reactive compound. There is a review published on the use of arynes in synthesis covering the years 1990-2002 with references also to preceding reviews.[73]
Under more normal diazotisation conditions, *i.e.* $NaNO_2$ in cold aqueous HCl, the zwitterionic species does not seem to form. Heating of such a reaction mixture gives salicylic acid,[72] *i.e.* water simply adds to the diazonium salt with the release of nitrogen gas. With the addition of suitable nucleophiles, 2-substituted benzoic acids can be prepared from diazotised anthranilic acids. This procedure has been used to prepare 2-chloro-,[74] 2-fluoro-,[75] 2-bromo-[76] and 2-iodobenzoic acid,[77] as well as the very useful 2-azidobenzoic acid.[78]
Addition of an aniline or a phenol gives diazo-coupling. An example of this is the preparation of the diazo dye methyl red from diazotised anthranilic acid and *N*,*N*-dimetylaniline.

Oxidation





2-nitrosobenzoic acid

3-hydroxyanthranilic acid, an important biochemical intermediate (*vide supra*) is readily available by oxidation of anthranilic acid with sodium or potassium persulfate, giving the sulfuric ester of the product which can subsequently be hydrolysed to the free hydroxy acid.[79]

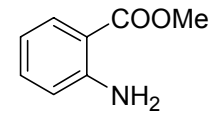
There are many examples of N-oxidation of anthranilic acids to the corresponding 2-nitrobenzoic acids. For practical purposes this transformation is of little value since nitro compounds are generally easily accessible through nitration.
Recently a very efficient oxidation, using superoxide radicals generated from hydrogen peroxide on a solid titanium catalyst,[80] has been applied to the oxidation of anthranilic acid to give 2-nitrobenzoic acid in quantitative yield.
More synthetically interesting amino oxidations to 2-nitrosobenzoic acid have also been described, using peroxyacetic acid[81] or peroxymonosulfuric acid (Caro's acid).[82]
2-nitrosobenzoic acid can also be prepared by oxidation of *N*-hydroxyanthranilic acid,[83] which in turn can be obtained by oxidation of anthranilic acid with sodium perborate.[84]

Reduction

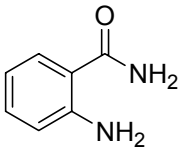
Anthranilic acid has been reduced to 2-aminophenylmethanol using sodium amalgam,[85] LAH[86] or very efficiently at rt using samarium salts.[87-89] For reductions of esters of anthranilic acids to the corresponding alcohols, $NaBH_4$[90] or $NaBH_4/ZnCl_2$[91] has been used successfully.

Birch reduction of anthranilic acid derivatives has also been undertaken.[92]

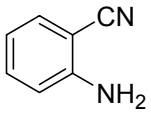
Derivatives of anthranilic acid



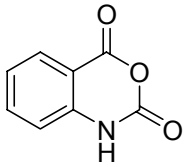
methyl anthranilate



anthranilamide



anthranilonitrile



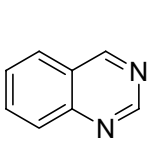
isatoic anhydride

The ester methyl anthranilate is an important ingredient in perfumes and is also used as a flavour additive in soft drinks. It can be prepared by *Fischer esterification* with methanol, or from isatoic anhydride and methanol. The annual production is estimated to be over 1000 tons.[93] The primary amide of anthranilic acid, anthranilamide, is commercially available and has been used as a starting material in numerous synthetic procedures to pharmaceuticals and natural products. The corresponding nitrile, anthranilonitrile (2-aminobenzonitrile), can be prepared industrially from 2-nitrotoluene by a gas phase reaction with ammonia catalysed by silica.[63]

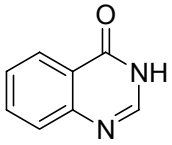
Isatoic anhydride (2*H*-3,1-benzoxazine-2,4(1*H*)-dione) is the condensation product from anthranilic acid and phosgene. It is a very versatile starting material for various syntheses where derivatives of anthranilic acid are needed. The synthetic use of isatoic anhydride has been reviewed several times.[94-96]

2. Quinazolines

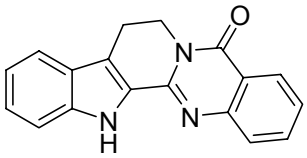
Introduction



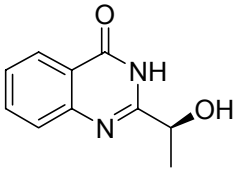
quinazoline



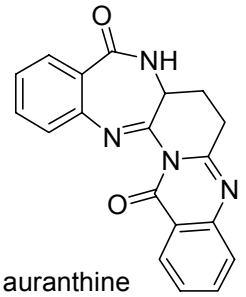
4-(3*H*)-quinazolinone



rutaecarpine



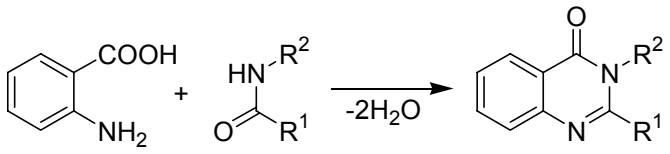
chrysogine



auranthine

The quinazoline skeleton appears in many alkaloids, most commonly in the form of 4-(3*H*)-quinazolinone moieties.[97] A few of these alkaloids have been the object of synthetic work by Bergman and co-workers, among them rutaecarpine.[98, 99] This is one of several quinazolinocarboline alkaloids isolated from various plants of the *Rutacea* family (to which e.g. *citrus* belongs). Chrysogine (isolated from molds),[100, 101] and a derivative of auranthine (a benzodiazepine alkaloid, *vide infra*)[102-104] have also been synthesised by members of the group.

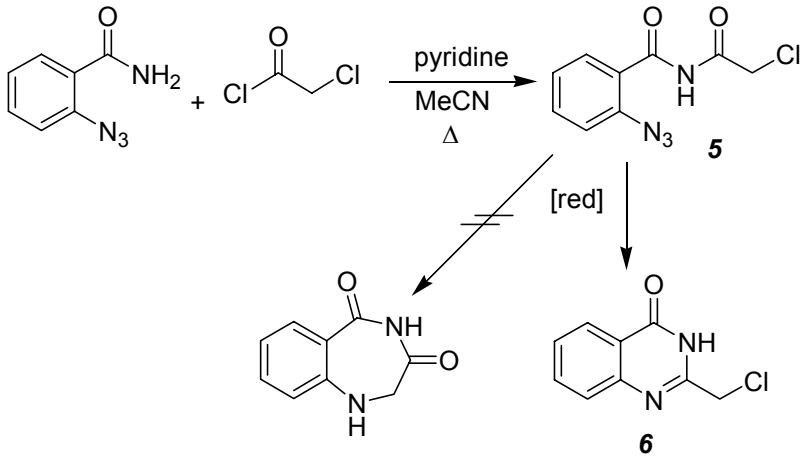
The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities as shown in a recent exhaustive review on the chemistry of 2-heteroaryl and heteroalkyl-4(3*H*)-quinazolinones.[105] Like the benzodiazepines the quinazolines are considered to be a "privileged structure" for drug development (*vide infra*).[106] Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects, useful to inhibit tumour growth.[107] This has recently inspired the development of new ring synthesis methods.[108, 109] The general synthetic chemistry of quinazolines has also recently been reviewed.[110]



The Niementowski quinazolinone synthesis

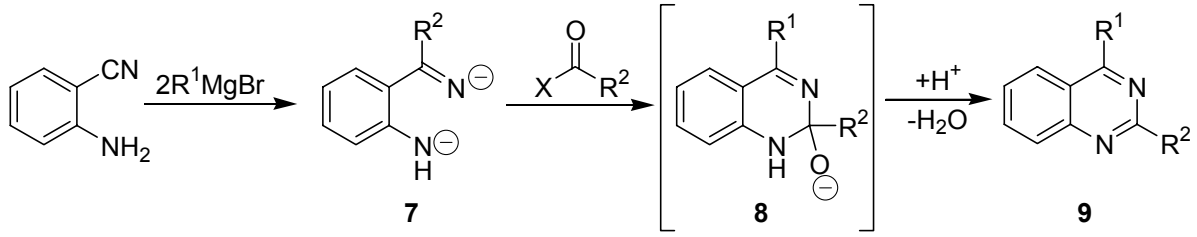
4-(3*H*)-Quinazolinones are the formal condensation products of anthranilic acid and amides, and they can also be prepared in this fashion through the *Niementowski quinazolinone synthesis*, named after its discoverer Stefan Niementowski (1866-1925).[111] The original work was published in 1895,[112] and the utility of the reaction has been reviewed.[113] The reaction has been modified to use anthranilic acid esters and isatoic anhydride,[114] as well as anthranilamides, as starting materials. The reaction continues to be used in modern development of synthetic procedures.[115, 116]

Synthesis of a 4-quinazolinone



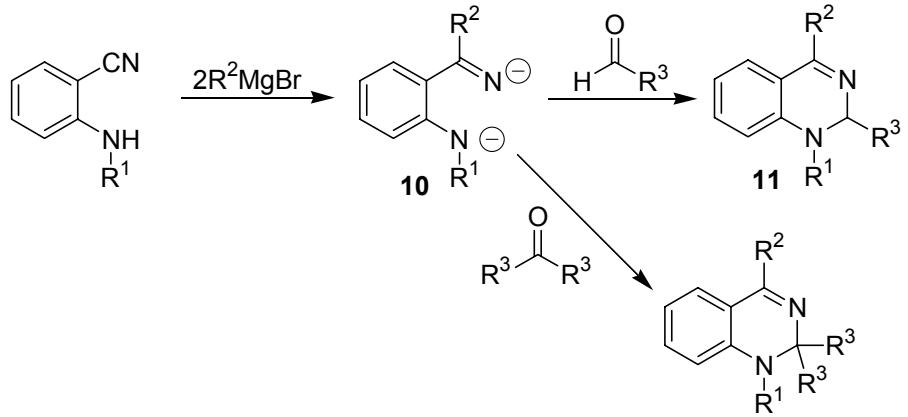
In an early effort to prepare benzodiazepinediones, the imide ***5*** was prepared from 2-azidobenzamide. This compound rapidly decomposed on storing, and reduction of the azido group did furnish neither the seven-membered ring, nor the non-ring closed amine, but instead the amine was condensed with the keto function of the original amide to form the quinazoline ***6***. This happened regardless of the nature of the reducing agent (NaSH or PPh_3). This constitutes a new variant of the *Niementowski synthesis*.

Synthesis of 2,4-disubstituted quinazolines

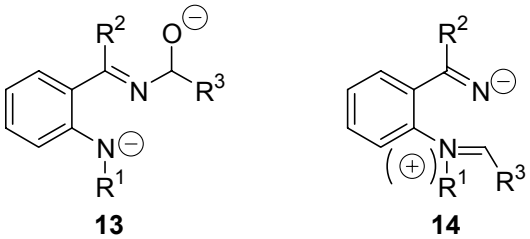


When anthranilonitrile was treated with two equivalents of aromatic or aliphatic Grignard reagents, and the intermediate amine-imine dianion **7** was trapped with acyl halides, 2,4-disubstituted quinazolines **9** resulted (**paper I**) after aqueous, slightly acidic, work up. Mechanistically this was explained by protonation of the intermediate **8** followed by elimination of water. Whether it is the imine or the amine nitrogen atom of **7** that reacts first with the acyl halide is of no preparative consequence as both routes will lead to **8**.

Synthesis of 1,2-dihydroquinazolines

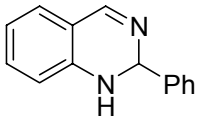


When anthranilonitrile, or alkylated anthranilonitriles, were treated with Grignard reagents and the intermediate **10** was trapped with aldehydes or ketones, 1,2-dihydroquinazolines **11** or **12** resulted (**paper I**). Note that this procedure gives product both when R^1=H and when R^1=alkyl.



In this case it does matter whether the imine or amine nitrogen atom of the intermediate dianion reacts first. An intermediate of the type **13** where the imine has reacted cannot lead to product. Therefore the imine/iminium ion/zwitterion **14** must be the true intermediate.

Addition of Grignard reagents to anthranilonitrile, followed by capture of the dianion with electrophiles, is a procedure that affords quinazolines in one pot from simple starting materials. The oxidation state of the electrophile is reflected in the product, *i.e.* derivatives of carboxylic acids give aromatic quinazolines, while aldehydes and ketones give 1,2-dihydroquinazolines. An alternative to this method is to use 2-aminobenzoketones that are condensed with ammonia to afford the protonated form of the intermediate dianion. An interesting example of this that has appeared in the literature involves condensation with hydroxyglycine to give 1,2-dihydroquinazoline-2-carboxylic acids.[117]



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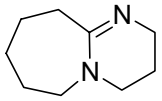
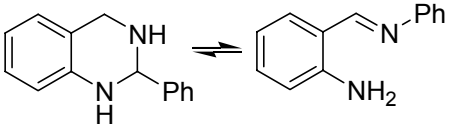


DBU



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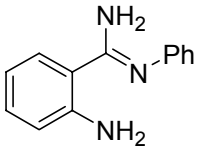
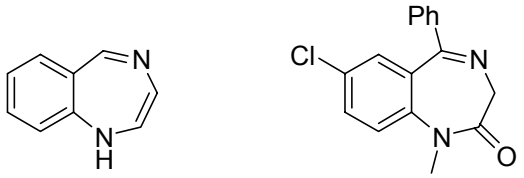


17

Anthranilonitrile could also be treated with two equivalents of DIBAL-H, to create a non-substituted amine-imine dianion . The dianion could be captured with benzaldehyde to form the 1,2-dihydroquinazoline **15**, which could be extracted from the reaction mixture by aqueous acid (**paper I**). The ease of protonation and the stability of the cation came as a surprise. The structure can be compared to the strong base DBU (pK_a 24.3)[118] which also contains conjugated amine and imine moieties (in this case in the form of an amidine). The reduced form of **15**, *i.e.* **16** (and similar compounds), shows ring-chain tautomerism.[119] The tautomerism of the amidine **17** has also been studied.[120] Further investigation of the properties **15** and similar molecules could therefore be of interest.

3. Benzodiazepines

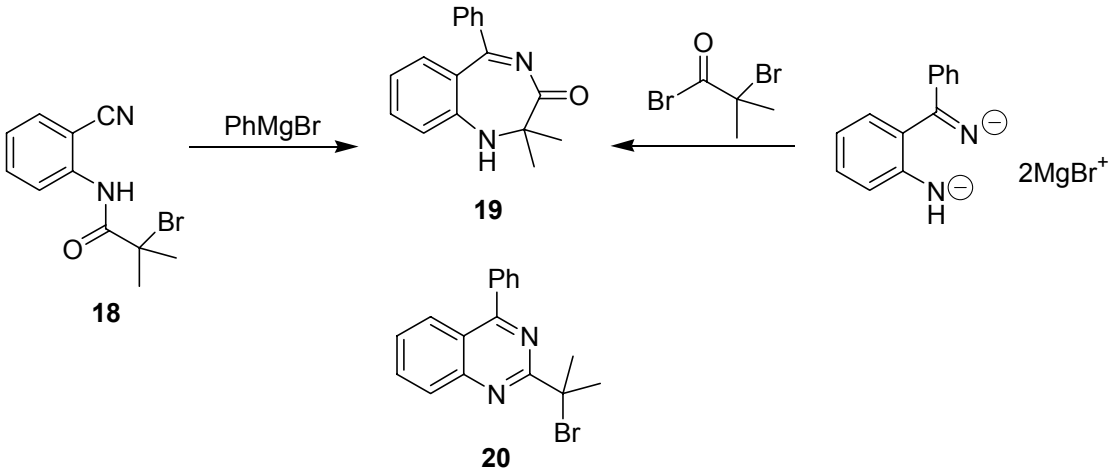
Introduction



(1*H*)-1,4-benzodiazepine diazepam

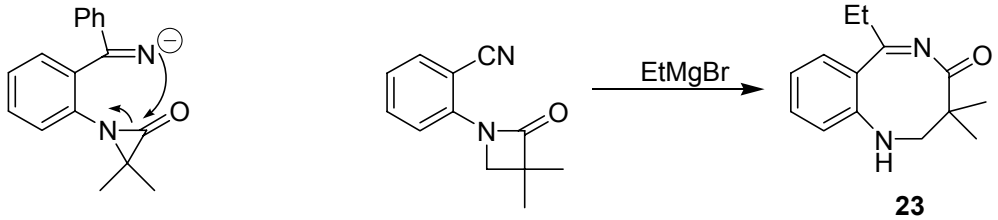
Benzodiazepines have been shown to be a very good scaffold for medicinal chemistry. In addition to the well known anxiolytic and sedative (1*H*)-1,4-benzodiazepine-2-ones (such as diazepam), other 1,4- and 1,5-benzodiazepines show many and diverse pharmacological activeties. Like the quinazolines the benzodiazepine skeleton is known in medicinal chemistry as a "privileged structure",[106] *i.e.* at type of structure that is likely to bind to many types of targets. A reason for this is that the seven-membered ring, with the two nitrogen atoms, mimics turns of endogenous peptides. Benzodiazepines have very recently been synthesised and utilized as both ß-turn[121] and γ-turn peptidomimetics.[122] For a long time after the discovery of the effects of the 1,4-benzodiazepine-2-ones, there was a search for endogenous ligands to the "benzodiazepine-receptor sub site" of the $GABA_A$-receptor. Although there are a few scattered reports on isolation of this type of benzodiazepines from natural sources,[123, 124] it is nowadays accepted that the endogenous ligands are peptides such as ODN (Octadecaneuropeptide)[125] and DBI (Diazepam Binding Inhibitor)[126]. Better understanding of the peptide interactions of the GABA-receptor subtypes has led to recent improved design on benzodiazepine ligands.[127]
There are also a number of alkaloids that contain 1,4-benzodiazepinone moieties.[128] Auranthine (*vide supra*) and several of the circumdatines has been the object of synthetic work within the group.[129, 130]

Synthesis of 1,4-benzodiazepine-3-ones



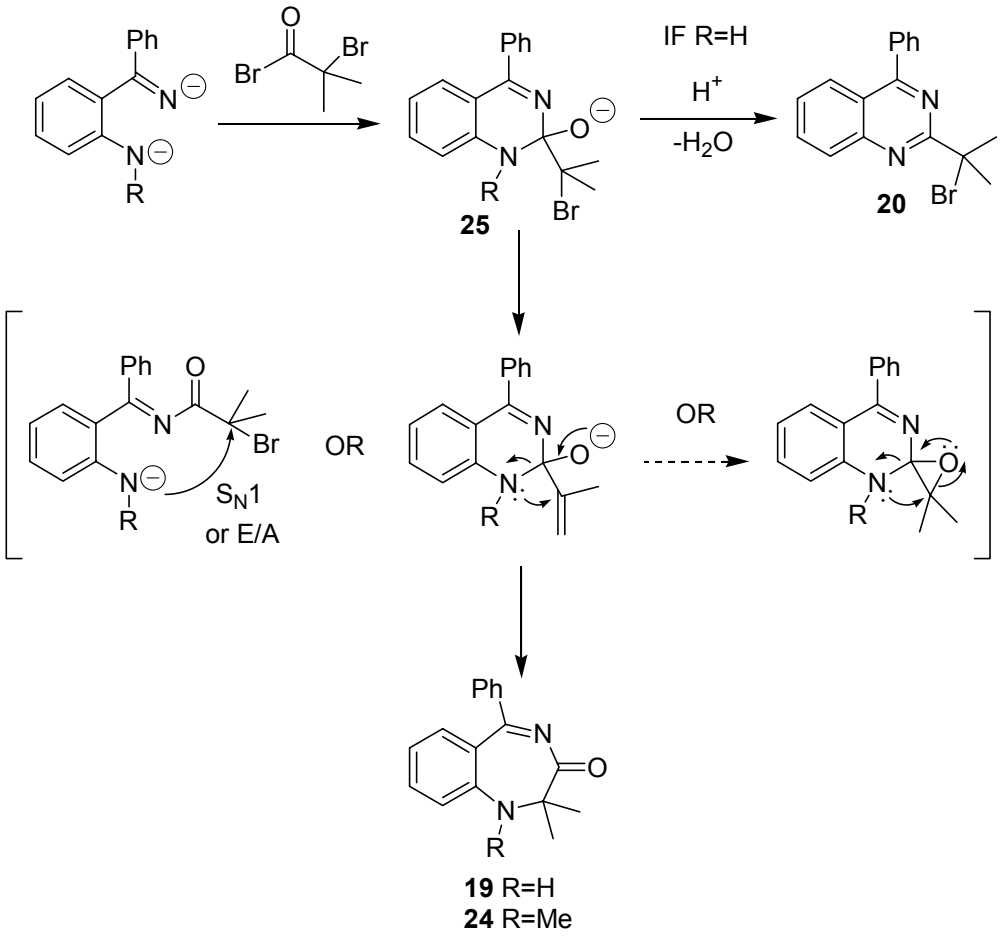
18 **19** **20**

It has been shown that treatment of the amide **18** with PhMgBr yields the benzodiazepinone **19**.[131] Compound **19** also formed when anthranilonitrile was treated with two equivalents of PhMgBr (comp. quinazolines above), and the resulting dianion was captured with 2-bromoisobutyryl bromide. The quinazoline **20** is a by-product in both cases. A sufficient, but not necessary, explanation for the formation of the 7-membered ring is that the reactions have a common intermediate. There were speculations of a mechanism involving intramolecular ring opening of the common intermediate α-lactam **21**.[132]



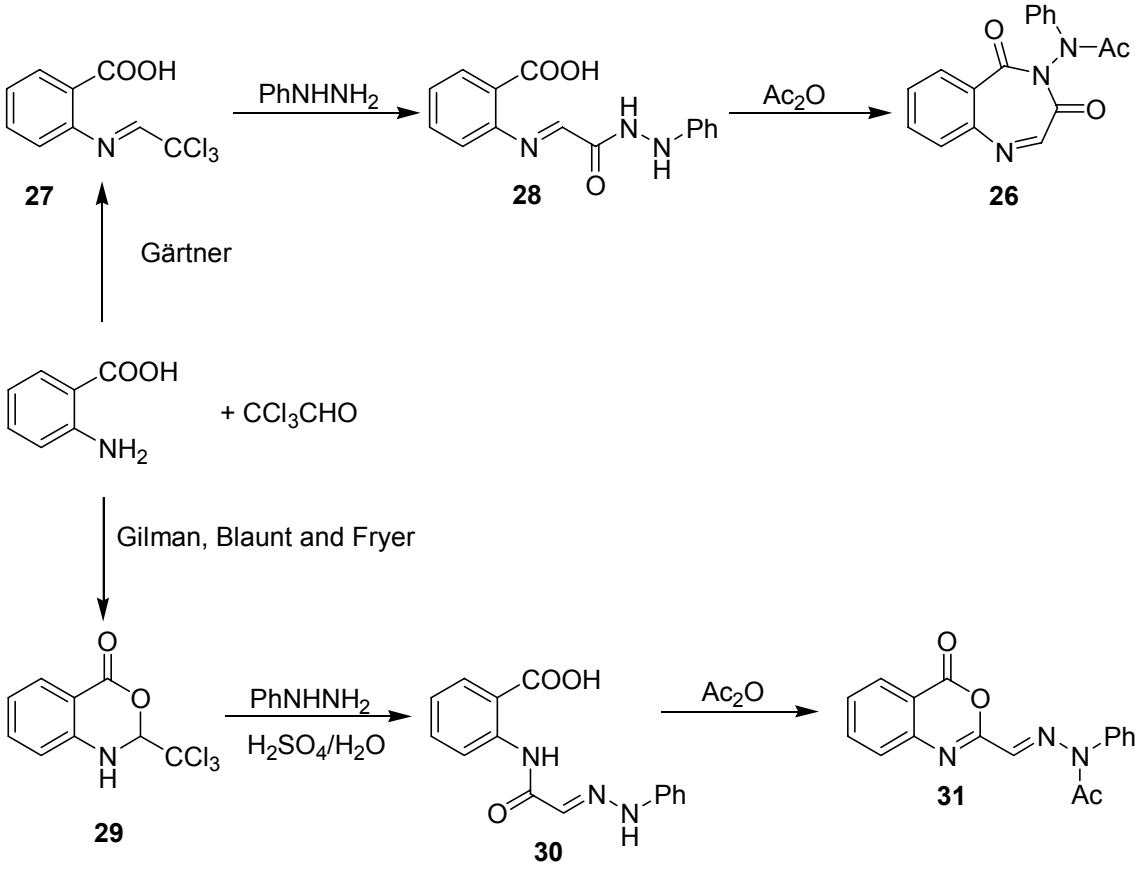
21 **22** **23**

α-Lactams are highly strained, and therefore of high energy. The formation of the product would be driven by the release of this ring strain energy. The proposed mechanism appeared to be supported by the fact that the ß-lactam **22** did indeed give ring opening (ring expansion) to the 8-membered compound **23** on treatment with EtMgBr.[133] The 8-membered structure was proven by X-ray crystallography.[134] A very similar type of ring expansion has very recently been published by Buchwald *et al*.[135]

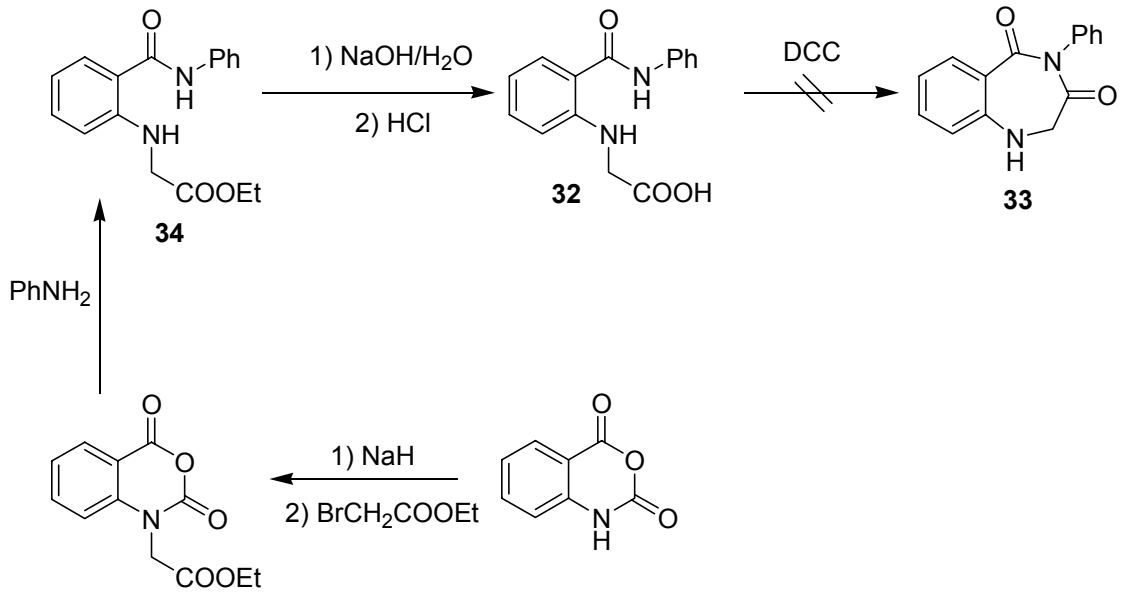


However, the results presented in **paper I** do not give support to the α-lactam mechanism. The reason is that also *N*-methyl anthranilonitrile gave a rearranged 7-membered product (**24**). A mechanism involving a 6-membered intermediate **25** was proposed. This is the same type of intermediate that can lead to quinazolines (above), and it therefore also explains the by-product quinazoline **20**. The formation of the products **19** and **24** requires apparent substitution on a quaternary carbon (regardless of the model of the intermediate). This could happen through ionisation (S_N1) or through elimination of HBr followed by 1,2-addition. Formation and rearrangement of an oxirane is also a possibility. Non-quatenary α-haloacyl halides (*e.g.* chloroacetyl chloride) gave only quinazoline products in moderate yields. Preformed anthranilonitrile amides of these reagents have been shown to give very different products, namely 4-amino-2-quinolinones, when treated with Grignard reagents[136] This may explain the moderate yields of quinazolines obtained from addition of non-quatenary α-haloacyl halides to the dianions.

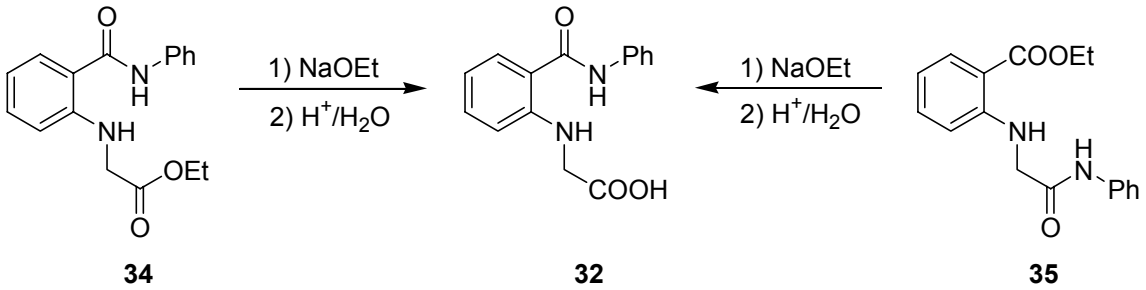
Synthesis and reactions of 1,4-benzodiazepine-3,5-diones



In 1976 three researchers from the group that originally developed the common benzodiazepine drugs (such as diazepam, Valium®) published a retraction of a claim of synthesis of the benzodiazepine **26** by Gärtner in 1904.[137] According to Gärtner treatment of anthranilic acid with chloral gave the imine **27**, which could in trun be reacted with phenylhydrazine to form compound **28**.[138] Ring closure and acetylation was reported to be the result of heating in acetic anhydride. In the retraction Gilman, Blaunt and Fryer showed this reasoning to be flawed on two crucial points; Anthranilic acid forms imines with aldehydes, but the imine double bond is immediately subject to an intramolecular attack from the carboxylic oxygen atom to form the more stable 1,2-dihydroquinazoline-4-one (in this case **29**). Secondly, the product from reaction with phenylhydrazine, under the rather odd conditions, has the inverted orientation of the amide- and imine functions, *i.e.* compound **30**. The final product, after heating in acetic anhydride, was shown to be the benzoxazine **31** by X-ray crystallography.

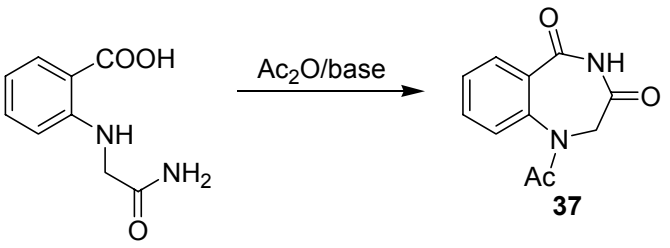


All acclaimed and published syntheses of 1*H*-1,4-benzodiazepine-3,5(2*H*, 4*H*)-diones are based on ring closure of *N*-carboxymethylanthranilamides (or esters thereof), *e.g.* **32** which was allegedly ring closed to **33** by Stavropoulos and Theodoropoulos.[139] They prepared **32** from 2-nitrobenzoic acid in a lengthy and cumbersome procedure. Compound **32** prepared more expediently from isatoic anhydride (as shown above) could not be ring closed by DCC. The reaction afforded two inseparable very insoluble products, and NMR did not show well defined peaks. Therefore the products were deemed to be polymers. Stavropoulos and Theodoropoulos curiously used sephadex column chromatography (elution with *i*PrOH) to separate their two products. No percentage or weight yield of **33** was specified and only elemental analysis and poorly resolved ^{1}H-NMR data of the product were given. It therefore seems likely that Stavropoulos and Theodoropoulos also isolated polymeric material.

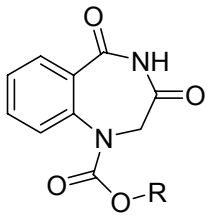


An attempt to ring close the ester-amide **34** with base resulted in isolation of the acid **32**, in itself perhaps not remarkable as the reaction was quenched with acid (aqueous citric acid and ice).[i] However, base treatment of the ester-amide **35**, with the reversed placement of the functional groups, also resulted in isolation of the acid **32**. A likely explanation for this observation is that the cyclised compound **33** was indeed formed, but that it was hydrolysed on quenching.

[i] Cold aqueous citric acid should not normally hydrolyse esters. The product **32** crystallises almost immediately on quenching.

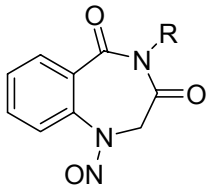


36 **37**

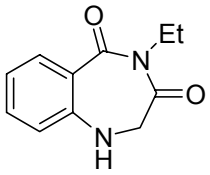


38a R=Et
b R=Me
c R=Bn

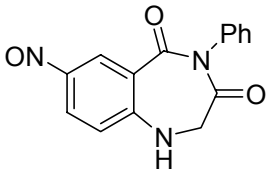
The first successful preparation of a 1*H*-1,4-benzodiazepine-3,5(2*H*, 4*H*)-dione was achieved by treatment of *N*-carbamoylmethylanthranilic acid **36** with acetic anhydride and Hünig's base in refluxing THF (**paper IV**). The procedure afforded the N1-acetylated compound **37** in a modest yield. Despite numerous attempts to improve the yield by varying the solvent, the acetylating agent and the base, no better set of conditions was found. However, it was now clear that it was possible to form the ring through a mixed anhydride approach on amino-acylated substrates. The compounds **38a-c** could be prepared in varying yields from **36** by treatment with chloroformates and base (Et_3N). Unfortunately treatment with di-*tert*-butyl dicarbonate (Boc_2O) did not yield any products which could be characterised.



39a R=Et
b R=Ph

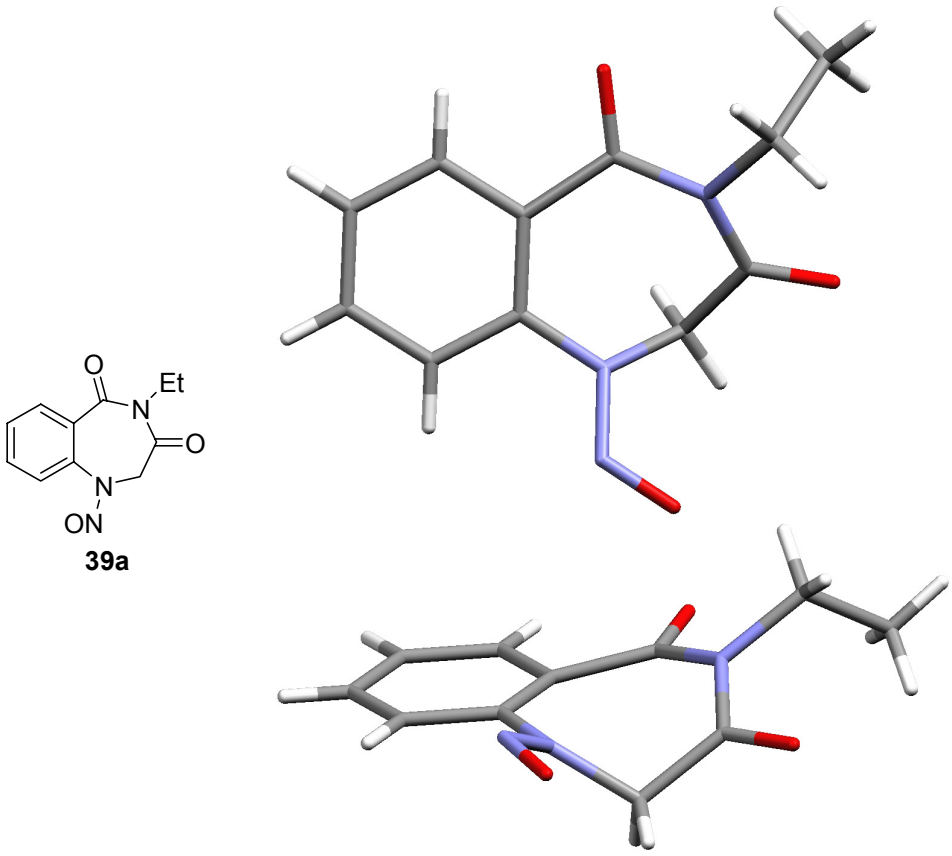


40



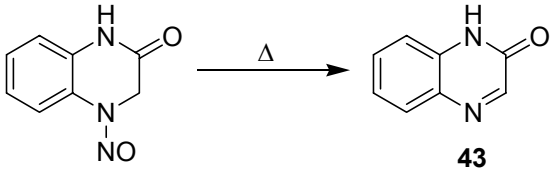
41

The realisation that electron withdrawing substituents on the amine of the starting material enabled ring closure, led to the idea to use N-nitrosated substrates. The compounds **39a** and **39b** could thus be prepared.

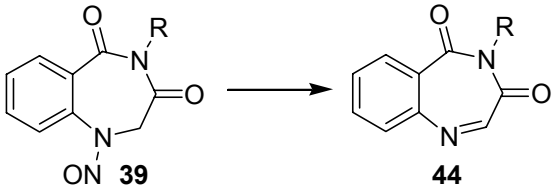


39a

The structure of **39a** was confirmed by X-ray crystallography. Under moderately acidic conditions (TFA) **39a** could be denitrosated to compound **40**. This compound has recently been described in the literature,[140] but the physical characteristics given do not match the current data. Harsher conditions (HBr/AcOH) applied to **39b** gave *Fischer-Hepp rearrangement* to the C-nitroso compound **41**. Studies on the mechanism of this rearrangement have been published.[141]



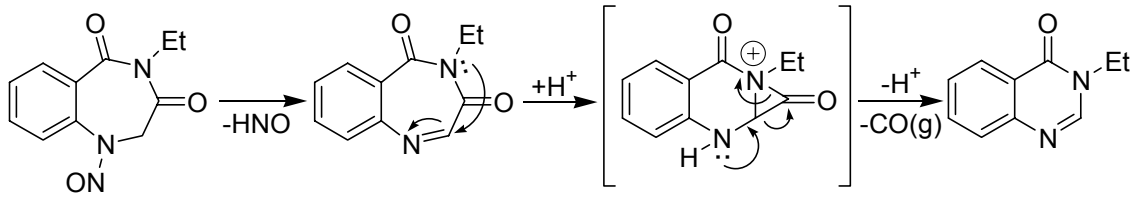
42 **43**



39 **44**

There was yet another motivation for choosing the N-nitroso approach in this project. In 1926 William Henry Perkin Jnr, professor of organic chemistry at Oxford University, reported that recrystallisation of the nitrosamine **42** needed to be performed quickly.[142] A prolonged heating gave "hydroxyquinoxaline", *i.e.* 1*H*-quinoxalin-2-one (**43**), which was known at the time. When this happended "nitrous fumes" were given off. This unwanted transformation was reported to occur on heating **42** in alcohols, benzene, and with particular ease in acetic acid. Melting of **42** also gave **43**. For the present project this behaviour was seen as a

possibility to transform the compounds **39** into the unknown parent compounds **44**. It should be pointed out that no one appears to have used this transformation in synthesis and nothing is known about the mechanism.

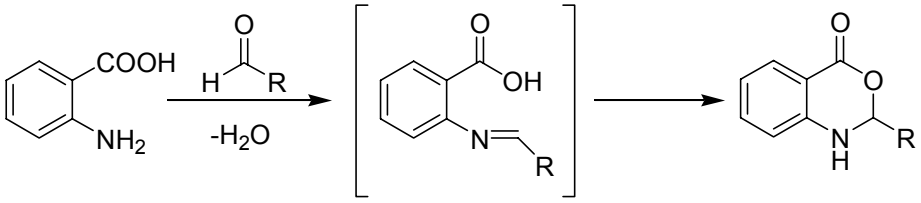


39a **44a** **45**

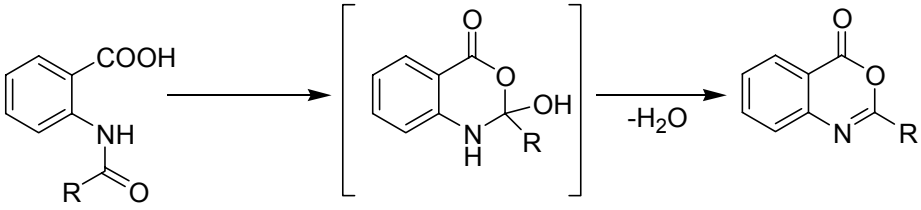
Heating of **39a** in acetic acid did not give **44a**, but rather the known quinazolinone **45** in 63 % yield. A proposed mechanism for this novel ring contraction rearrangement involves elimination of nitrosyl (HNO), followed by a proton mediated loss of CO. Nitrosyl is a known,[143] but little studied, molecule. Recent research has implicated nitrosyl as a mediator of biological effects, similar to those of NO. There are very few HNO-donors known, the most common of them is Angeli´s salt ($Na_2N_2O_3$), and a theoretical study of the reactivity of this salt has just been published.[144]

4. Benzoxazine-4-ones

Introduction



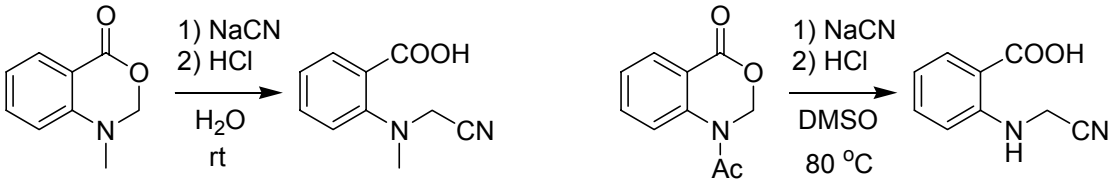
When anthranilic acid is condensed with an aldehyde, a 1,2-dihydro-(4*H*)-3,1-benzoxazine-4-one is formed through intramolecular nucleophilic attack and a proton shift. The end-product is much more stable than the intermediate imine and it cannot normally be isolated. The reactivity of these systems is surprisingly unexplored.



Even though the parent compounds, (4*H*)-3,1-benzoxazine-4-ones, could in principle also be formed by intramolecular nucleophilic attack in N-acylated anthranilic acids, it is not normally thought of as a viable process because of the low electrophilicity of the amide. Instead the reaction is induced by formation of a mixed anhydride of the starting material, commonly by heating in acetic anhydride. The amide, in its iminol form, functions as the nucleophiles. The intermediate aminol, which cannot normally be isolated, eliminates water to form the product. The chemistry of these compounds, sometimes called “acylanthranils”, has been reviewed (covering the period 1965-1998).[145]

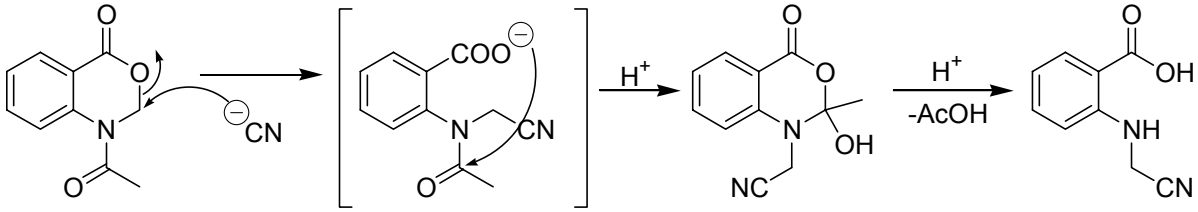
In both these types of condensations the oxidation state of the reagent (the aldehyde or the acylating agent) is reflected in the product. The situation is therefore parallel to the formation of quinazolines (*vide supra*) from aldehydes/ketones and acyl halides respectively.

Synthesis and reactivity of 1,2-dihydro-(4H)-3,1-benzoxazinones



46 **48** **47** **49**

It was found that treatment of N-substituted anthranilic acids with paraformaldehyde in refluxing acetic acid is a good method to prepare N-substituted 1,2-dihydro-3,1-benzoxazine-4-ones. Thus the compounds **46** (previously known)[146], and **47** (novel, **paper III**) could be prepared. It is known that compounds of this type can be ring opened by cyanide ion,[147, 148] and the resulting *N*-cyanomethylanthranilic acids are potential starting materials for both 2-cyanoindoxyls[149] and 1,4-benzodiazepine-3,5-diones. Compound **46** gave the anticipated *N*-cyanomethyl-*N*-methylanthranilic acid (***48***), a novel compound, when treated with cyanide. However, reaction of **47** required prolonged heating in DMSO (the starting material hydrolysed in water) to give product (**paper III**). The product was not the anticipated N-acyl compound, but in fact simply *N*-cyanomethylanthranilic acid (**49**). Although it is possible that the product was deacetylated by hydrolysis during the work up, another possibility presents itself.

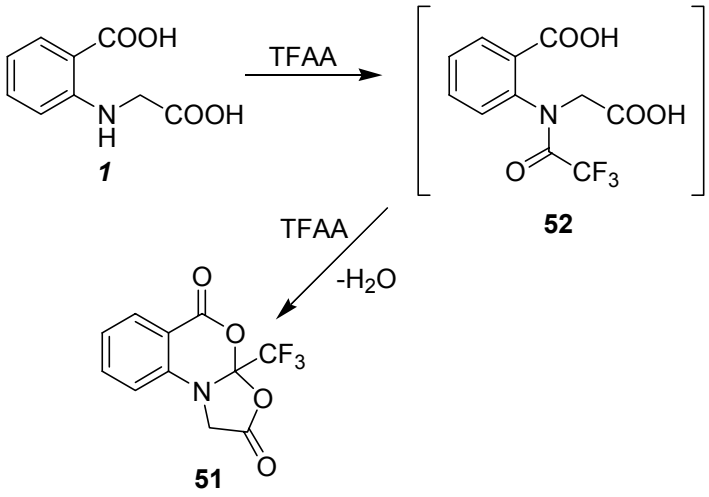


50 **49**

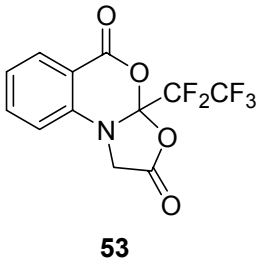
If it is assumed that the cyanide opens the starting material, then the product of the initial reaction could cyclise again by attack on the acetyl group. A cyclic aminol (**50**), similar to the intermediates in 1,3-benzoxazin-4-one synthesis (*vide supra*), would result. Were it not for the fact that the aminol would be fully N-substituted, it could eliminate water. Not until excess acid is added, such as in the work up, could acetic acid be eliminated to give the observed product (**49**).

In this mechanistic speculation it was stated that because of a fully substituted intermediate aminol, the reaction stops at that stage until the conditions are changed. What happens in a situation where the amino side chain can actually participate in a condensation?

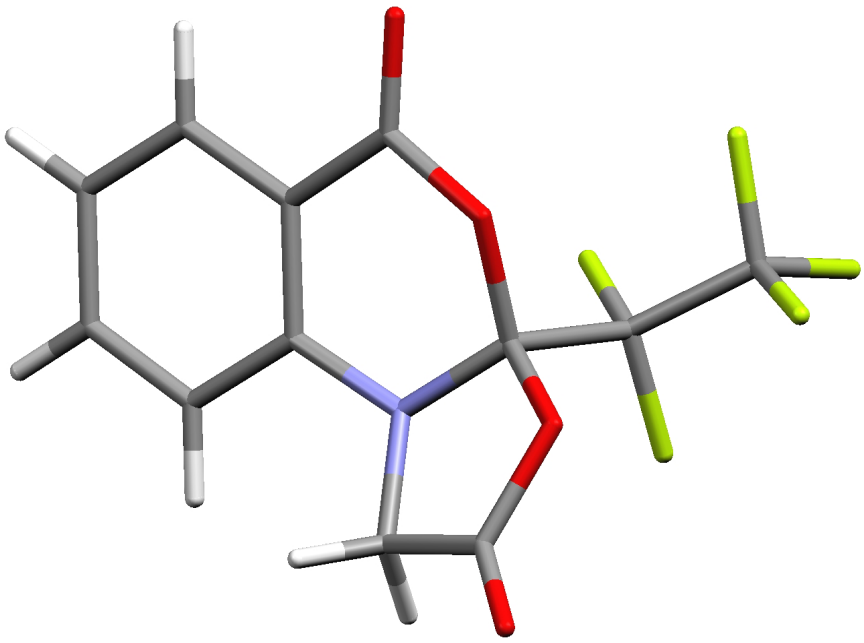
Synthesis of (4H)-3,1-benzoxazinones from dicarboxylic acid derivatives of anthranilic acid



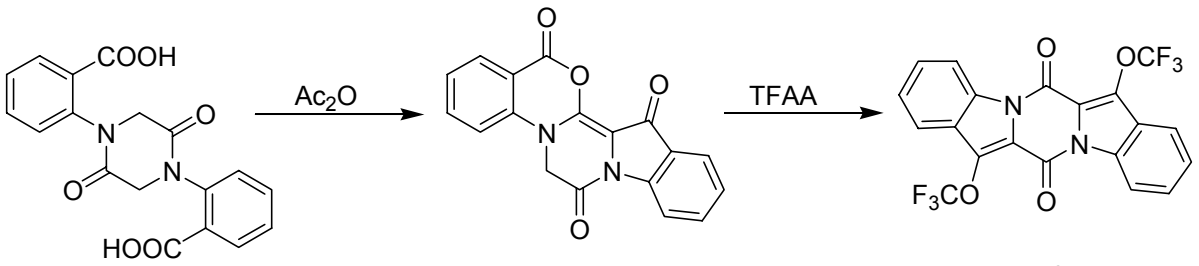
Treatment of *N*-carboxymethyl anthranilic acid (***1***) with TFAA afforded the double condensation product **51** *via* the N-trifluoroacetylated intermediate **52** (**paper II**). The amino side chain carboxy function had thus participated in the reaction and provided a possibility for elimination of water. **52** could not be isolated from the reaction mixture, but **51** could be hydrolysed to **52** and ring closed again under same conditions.



53



Treatment of ***1*** with pentafluoropropionic anhydride gave compound **53**, the structure of which could be solved by X-ray crystallography.

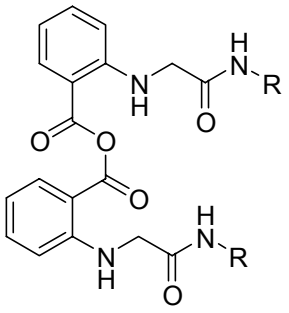


54 **55** **56**

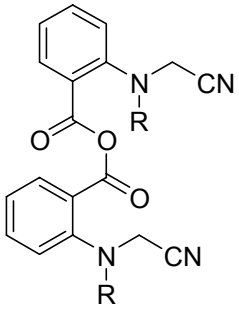
The anthranilic acid dimer **54** when treated with acetic anhydride gave compound **55**. In this case the intermediate cannot eliminate anything except by involvement of the other part of the dimer. **55** could be rearranged into the symmetric diketopiperazine indole dimer **56** by treatment with TFAA. For a full discussion on the mechanisms of these two transfrormations, see **paper II**.

5. Anhydrides of anthranilic acid

During the course of the work on synthesis of benzodiazepines and benzoxazinones (*vide supra*), not only were mixed anhydrides with anthranilic acid utilized, but it was also discovered that dimeric anhydrides of substituted anthranilic acid are easily formed. No record of these astonishingly stable anhydrides has been found in the literature.



57a R=H
b R=Me
c R=Bn



58a R=H
b R=Me

Attempted cyclisation of **36** to an unsubstituted 1,4-benzodiazepine-3,5(2*H*,4*H*)-dione resulted in the isolation of the anhydride **57a** (**paper IV**). The identity of the product was not clear until mass spectrometric data had been considered. Especially the very low solubility and the resistance to hydrolysis were puzzling. Similarly, the anhydrides ***57b,c***, **58a** (**paper III**) and ***58b*** were obtained after treatment of the corresponding acid with base and an activating agent. It is interesting to note that these anhydrides were formed from their constituent acids (not previously known, see Appendix) under virtually the same conditions that led to cyclisation for N-nitrosated derivatives (**paper IV**). Apparently carboxylate ions of N-alkylated anthranilic acids are so nucleophilic that they rapidly attack already activated species, thus giving rise to the dimeric anhydrides. In contrast, ring closure to 1,4-benzodiazepine-3,5-diones require the activated acid to be very electrophilic to be able to react with the weakly nuclephilic amide. N-nitroso derivatives of anthranilic acid fulfil these criteria.

Appendix: Experiments

***N*-Carboxymethylanthranilic acid (*1*)**
Anthranilic acid (34.3 g, 0.25 mol) was dissolved in water (300 mL) with NaOH (10.0 g, 0.25 mol). KI (2.1 g, 12 mmol) was added, followed by sodium chloroacetate (50.0 g, 0.43 mol). The mixture was heated at reflux for 4 h. On cooling, ***1*** precipitated and could be filtered off to yield 36.8 g (75 %). After several days **2** (about 5 %) could be filtered off from the original filtrate.

2-(Phenylcarbamoylmethyl-amino)-benzoic acid phenylcarbamoylmethyl ester (4)
Anthranilic acid and an excess of chloroacetanilide were heated in sat. Na_2CO_3 for 15 h. On cooling the solid product formed and it could be filtered off (65 % yield); mp 224 ºC; IR ν_{max}/cm^{-1}: 3340, 3268, 1673, 1599, 1553, 1497; ^{1}H-NMR (DMSO-d_6): 4.09 (2H, d, *J* 5.1 Hz), 4.90 (2H, s), 6.64-6.71 (2H, m), 7.03-7.10 (2H, m), 7.28-7.35 (4H, m), 7.46 (1H, m), 7.60-7.62 (5H, m), 7.97 (1H, dd, *J* 1.3, 8.1 Hz), 8.12 (1H, t, *J* 5.1), 10.18 (1H, s), 10.23 (1H, s); ^{13}C-NMR (DMSO-d_6): 46.2 (CH_2), 62.7 (CH_2), 109.3 (C), 111.7 (CH), 114.9 (CH), 119.15 (CH), 119.26 (CH), 123.36 (CH), 123.47 (CH), 128.78 (CH), 128.80 (CH), 131.5 (CH), 135.2 (CH), 138.5 (C), 138.8 (C), 150.1 (C), 165.6 (C), 167.0 (C), 167.7 (C); MS (ESI) *m/z* : 404 $[M+H]^+$.

2-Azido-*N*-(2-chloro-acetyl)-benzamide (*5*)
2-Azidobenzamide (3.24 g, 20.0 mmol) and pyridine (1.64 mL, 20 mmol) was suspended in MeCN (50 mL). Chloroacetyl chloride (2.0 mL) was added and the mixture heated to reflux temperature for 24 h. The mixture was poured on crushed ice. The solid which formed was filtered off and allowed to dry. The material was boiled in toluene and solid by-products were removed by filtration. The concentrated solution was cooled to -15 ºC over night upon which the crystalline dark product could be filtered off (3.17 g, 66%); mp 128 ºC; ^{1}H-NMR (DMSO-d_6): 4.69 (2H, s), 7.22-7.34 (2H, m), 7.63 (1H, m), 8.16 (1H, dd, *J* 1.3, 7.9 Hz), 10.41 (1H, br s); ^{13}C-NMR (DMSO-d_6): 45.7, 118.9, 122.6, 125.7, 133.3, 134.8, 138.1, 163.2, 168.15.

2-Chloromethyl-3*H*-quinazoline-4-one (*6*)
Compound ***5*** (0.48 g, 2.0 mmol) in dioxane (10 mL) was stirred with Ph_3P (0.53 g, 2.0 mmol) and pyridine (0.20 mL, 2.5 mmol) for 4 h. Water (20 mL) was added and the product could be filtered off (0.30 g, 77 %); mp 265 ºC (lit. [150] 249-253).

2-(Cyanomethyl-methyl-amino)-benzoic acid (*48*)
Compound ***59*** (1.12 g, 6.9 mmol) was stirred in water (10 mL) and acetone (1.5 mL) with NaCN (0.40g, 8.2 mmol) for 1 h. The acetone was evaporated in vacuo and the solution was acidified with concd HCl (1.5 mL). On addition of crushed ice the product preciptitated and could be filtered off to yield a white powder (1.11 g, 85 %) ; mp 89 ºC; IR ν_{max}/cm^{-1}: 2973, 2350 (w), 1699 (br), 1598, 1520 (br); ^{1}H-NMR (DMSO-d_6): 2.84 (3H, s), 4.28 (2H, s), 7.18 (1H, m), 7.31 (1H, d, *J* 8.3 Hz), 7.55 (1H, m), 7.75 (1H, dd, *J* 1.5, 7.9 Hz), 13.35 (1H, br s); ^{13}C-NMR (DMSO-d_6): 41.1 (CH_3), 44.8 (CH_2), 116.5 (C), 120.6 (CH), 123.5 (CH), 125.4 (C), 130.9 (CH), 132.5 (CH), 149.0 (C), 168.0 (C).

2-(Methylcarbamoylmethyl-amino)-benzoic acid anhydride (*57b*)
Compound ***60*** (1.04 g, 5.00 mmol) was heated to reflux temperature in THF (30 mL) with Et_3N (0.69 mL, 5.0 mmol) and trichloroacetyl chloride (0.50 mL, 4.4 mmol) for 1h. The reaction mixture was poured into cold water. The product could be filtered off to yield a yellow powder (0.66 g, 66%); mp 178 ºC; IR ν_{max}/cm^{-1}:3380, 3308, 1719, 1662, 1575, 1520; ^{1}H-NMR (DMSO-d_6): 2.64 (6H, d, *J* 4.5 Hz), 3.90 (4H, d, *J* 4.9 Hz), 6.63-6.72 (4H, m), 7.52 (2H, m), 7.88 (2H, d, *J* 7.0 Hz), 8.05 (2H, d, *J* 4.5 Hz), 8.10 (2H, t, *J* 4.9 Hz); ^{13}C-NMR (DMSO-d_6): 25.6, 45.5, 108.1, 112.1, 115.3, 132.1, 136.7, 151.2, 164.2, 168.9. MS (ESI) *m/z* : 399 $[M+H]^+$, 397 $[M-H]^-$.

2-(Benzylcarbamoylmethyl-amino)-benzoic acid anhydride (*57c*)
Compound ***61*** (0.85 g, 3.0 mmol) was heated to reflux temperature in THF (15 mL) with 2,6-lutidine (0.70 mL, 6.0 mmol) and Boc_2O (1.40 g, 6.4 mmol) for 2h. The reaction mixture was poured into cold water. The product could be filtered off to yield a yellow powder (0.33 g, 40 %); mp 152 ºC; IR ν_{max}/cm^{-1}: 3380, 3257, 2923, 1727, 1667, 1649, 1521; ^{1}H-NMR (DMSO-d_6): 4.00 (4H, d, *J* 5.3 Hz), 4.33 (4H, d, *J* 6.0 Hz), 6.65-6.75 (4H, m), 7.20-7.40 (10H, m), 7.53 (2H, t, *J* 7.5 Hz), 7.88 (2H, dd, *J* 1.1, 8.3), 8.12 (2H, t, *J* 5.3 Hz), 8.63 (2H, t, *J* 6.0 Hz); ^{13}C-NMR (DMSO-d_6): 42.1, 45.6, 108.1, 112.2, 115.3, 126.8, 127.2, 128.2, 132.1, 136.6, 139.2, 151.2, 164.2, 168.6.

2-(Cyanomethyl-methyl-amino)-benzoic acid anhydride (*58b*)
Compound ***48*** (0.95 g, 5.00 mmol) and Et_3N (1.73 mL, 12.5 mmol) were heated at reflux temperature in dioxane (20 mL) for 10 min. Ethyl chloroformate (0.48 mL, 5.00 mmol) was added and the reflux continued for 2 h. After cooling to rt, 10% citric acid (50 mL) was added and the mixture was extracted with EtOAc. The extracts were washed with sat. NaHCO3, water and brine, before it was dried over Na_2SO_4 and evaporated *in vacuo*. This gave a semi-solid material (0.48 g, 53 %); IR ν_{max}/cm^{-1}: 3106, 1769, 1715, 1598; ^{1}H-NMR (DMSO-d_6): 2.87 (6H, s), 4.31 (4H, s), 7.22 (2H, t, *J* 7.5 Hz), 7.33 (2H, d, *J* 8.2 Hz), 7.68 (2H, t, *J* 8.2 Hz), 8.00 (2H, d, *J* 7.5 Hz) ; ^{13}C-NMR (DMSO-d_6): 41.1, 44.7, 116.5, 120.4, 120.6, 122.9, 132.8, 134.9, 151.1, 161.9.

1,2-Dihydro-*N*-methylbenzoxazine-4-one (59)
N-methylanthranilic acid (7.55 g, 50.0 mmol) and paraformaldehyde (2.0 g) were heated at reflux temperature in AcOH (15 mL) for 30 min. The solvent was evaporated in vacuo and the residual dark oil purified by silica column flash chromatography 30-95 % Et_2O in hexane. This yielded a yellow oil (6.19 g, 76 %), (lit.[146] mp 48 ºC from EtOH); ^{1}H-NMR (DMSO-d_6): 3.03 (3H, s), 5.06 (2H, s), 6.83 (1H, d, *J* 8.3), 6.97 (1H, m), 7.50 (1H, m), 7.98 (1H, dd, *J* 1.5, 7.9 Hz); ^{13}C-NMR (DMSO-d_6):36.0 (CH_3), 81.6 (CH_2), 114.0 (CH), 114.4 (C), 120.5 (CH), 131.3 (CH), 135.5 (CH), 150.1 (C), 163.9 (C).

2-(Methylcarbamoylmethyl-amino)-benzoic acid (*60*)
2-[(2-Ethoxy-2-oxoethyl)amino]-benzoic acid (1.96 g, 8.78 mmol) was heated to reflux temperature in 40 % (aq) $MeNH_2$ for 12 h. Acidification yielded the solid product (1.56 g, 85 %)**;** mp 214 ºC; IR ν_{max}/cm^{-1}: 3383, 3340, 1670, 1644, 1578; ^{1}H-NMR (DMSO-d_6): 2.61 (3H, d, *J* 4.5 Hz), 3.80 (2H, s), 6.50 (1H, d, *J* 8.4 Hz), 6.59 (1H, t, *J* 7.2), 7.36 (1H, m), 7.80 (1H, dd, *J* 1.5, 7.9 Hz), 8.15 (1H, br s), 12.62 (1H, br s); ^{13}C-NMR (DMSO-d_6): 25.5, 45.8, 110.7, 111.3, 114.7, 131.6, 134.4, 150.2, 169.5, 169.6; MS (ESI) *m/z* : 207 $[M-H]^-$.

2-(Benzylcarbamoylmethyl-amino)-benzoic acid (*61*)
2-[(2-Ethoxy-2-oxoethyl)amino]-benzoic acid (1.11 g, 5.00 mmol) and benzylamine (0.80 mL, 7.4 mmol) was heated to reflux temperature in xylene (20 mL) under N_2-atm for 90 min. After cooling to rt water (20 mL) and EtOAc (40 mL) was added. After thorough mixing the aqueous layer was discarded and the organic layer was extracted with 1 M NaOH (2 x 20 mL). Acidification followed by filtration gave the product as a light yellow powder (1.05 g, 74 %); mp 218 ºC;); ^{1}H-NMR (DMSO-d_6): 3.91 (2H, s), 4.29 (2H, d, *J* 5.7 Hz);6.53-6.63 (2H, m), 7.05-7.39 (7H, m), 7.81 (1H, dd, *J* 1.5, 7.9 Hz), 8.21 (1H, br s), 8.59 (1H, t, *J* 5.7), 12.63 (1H, br s); ^{13}C-NMR (DMSO-d_6): 42.1, 45.9, 110.8, 111.4, 114.7, 126.8, 127.2, 128.2, 131.7, 134.4, 139.4, 150.2, 169.2, 169.6.

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Now my charms are all o'erthrown,
And what strength I have's mine own,
Which is most faint. Now 'tis true
I must be here confined by you,
Or sent to Naples. Let me not,
Since I have my duke got
And pardoned the deceiver, dwell
In this bare island by your spell;
But release me from my bands
With the help of your good hands.
Gentle breath of yours my sails,
Must fill, or else my project fails,
Which was to please. Now I want
Spirits to enforce, art to enchant;
And my ending is despair
Unless I be relieved by prayer,
Which pierces so that it assaults
Mercy itself and frees all faults.
As you from crimes would pardoned be,
Let your indulgence set me free.

The Tempest by William Shakespeare
epilogue spoken by Prospero

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