

Studies in the formation of heterocyclic rings containing nitrogen:
Part XXIII. Condensation of *o*-aminobenzamide with aldehydes
and Schiff bases

P. HANUMANTHU, S. K. V. SESHAVATHARAM, C. V. RATNAM AND
N. V. SUBBA RAO*

Department of Chemistry, Osmania University, Hyderabad 500007

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ABSTRACT

N-Arylidene orthanilamides undergo isomeric cyclisation in acetic acid to the corresponding 2-aryl-1,2,3,4-tetrahydro-4-oxoquinazolines. The u.v. and n.m.r. spectra of some of the arylidene derivatives and their isomeric tetrahydroquinazolines have been studied. Condensation of *o*-aminobenzamide either with aromatic aldehydes in nitrobenzene or Schiff bases in acetic acid has yielded 2-aryl-4 (3H)-quinazolinones.

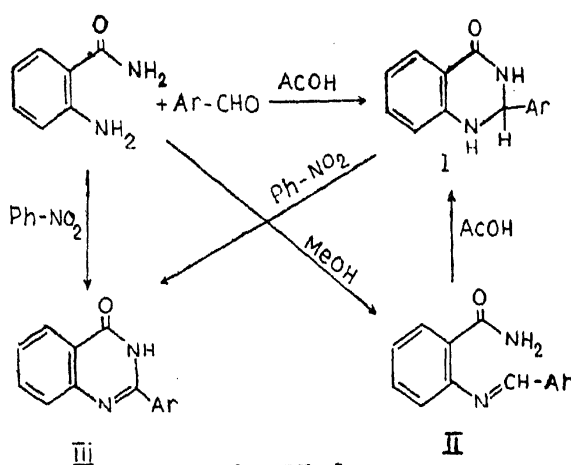
I. INTRODUCTION

A STUDY of the 'ring-chain' tautomerism of 2-aryl-1,2,3,4-tetrahydro-4-oxoquinazoline (I) and N-arylideneorthanilamides (II) and the dehydrogenative cyclisation of either of these to obtain 2-aryl-4 (3 H) quinazolinones (III) are presented in this publication. From the survey of the literature¹⁻⁷ it has been concluded that 1:1 reaction of *o*-aminobenzamide and aromatic aldehydes in acetic acid and in methanol, at room temperature, constitute the optimum conditions for obtaining I and II respectively. Following these conditions, seven pairs of compounds have now been prepared (table I). It has also been observed that N-arylidene orthanilamides (II) readily undergo smooth conversion to 1,2,3,4-tetrahydro-4-oxoquinazolines (I) when left in acetic acid (Chart I).

* Deceased.

Table 1. Formation of I (and II) from *o*-aminobenzamide and aldehydes in acetic acid and methanol respectively.

| Sl. No. | Ar-CHO employed Ar = | m.p. of N-arylidene orthanilamides (°C) | m.p. of 1,2,3,4-tetra- hydro-4-oxoquinazolines (I) (°C) |
|---------|--------------------------|---|---|
| 1. | Phenyl | 217 | 288 (228) ⁶ |
| 2. | <i>p</i> -methylphenyl | 220-2 | 218 (230) ⁶ |
| 3. | <i>p</i> -methoxyphenyl | 160 (158) ⁶ | 189-90 (195) ⁶ |
| 4. | <i>p</i> -chlorophenyl | 160 (159-61) ⁷ | 203 (201-3) ⁷ |
| 5. | <i>m</i> -nitrophenyl | 188-9 (199) ⁶ | 200 |
| 6. | <i>p</i> -nitrophenyl | 184 (191) ⁶ | 205 |
| 7. | 3,4-methylenedioxyphenyl | 117-9 | 201 (202) ⁶ |



RING-CHAIN TAUTOMERISM OF (I) AND (II)

While N-arylideneorthanilamides (II) and 2-aryl-1,2,3,4-tetrahydro-4-oxoquinazolines (I) appear to be 'chain-ring' tautomers, interconvertible through the normal 1, 3-proton shift, their independent existence at room temperature necessitates the use of the term 'isomers' for denoting them. Treatment with acidic reagents and basic reagents facilitates the conversion of the former to the latter. In addition, action of heat facilitates this change as observed by earlier workers and also noticed in the melting point determination of the arylidene compounds (II). Thus, the Schiff base obtained from *o*-aminobenzamide and piperonal was found to resolidify after melting initially at the given temperature (117-19°) and melting again around the temperature (187°) corresponding to the melting point of the cyclic product

(I, Ar = 3, 4-methylenedioxyphenyl). Solvents like DMSO, do not appear to facilitate this conversion. The reverse change of (I) to (II) could not be effected in DMSO or pyridine medium. Very poor solubility of these compounds (I) in most organic solvents came in the way of our studies in this regard. With a view to obtain better insight into their structure, the u.v. and n.m.r. spectra of some of the products have been studied.

U.V. SPECTRA OF (I) AND (II)

The u.v. spectra of I (Ar = phenyl), along with *o*-aminobenzamide and benzamide as reference, have been recorded in methanol. The enhanced u.v. absorption at longer wave length by *o*-aminobenzamide [$\lambda_{\text{max}}^{\text{MeOH}}$ (log ϵ)] [223 nm (4.09), 246 (3.85), 325 (3.66). Giuseppe⁸ *et al* reported 208 (4.36), 247 (3.94), 325 (3.56) for this compound] compared to benzamide [226 (3.96)] may be chiefly attributed to the electron releasing effect of the aromatic primary amino group. I (Ar = phenyl) essentially contains the same chromophoric system present in *o*-aminobenzamide along with an isolated phenyl. However, due to more effective planarity consequent of cyclisation, there is a further bathochromic shift in the u.v. spectrum of the former [226 (4.5), 344 (3.57)].

While II (Ar = phenyl) has apparently a more conjugated chromophoric system than I, both the absorption maxima are in fact at slightly lower wavelength [225 (4.28), 263 (4.14)] compared to I (Ar = phenyl) and the simple Schiff base, benzylideneaniline [231 (3.88), 276 (4.02)]. This hypsochromic shift may be explained on the basis of two factors. Firstly, an accurately constructed F.M. model of II (trans-benzylideneorthanilamide, more stable of the two geometric isomers and also the one best suited for heterocyclisation is considered for this purpose) revealed that considerable

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steric hindrance forces the —C—NH₂ and —N=CH—Ph moieties somewhat out of plane with phenylene ring system. Secondly, the effect of amide nitrogen also leads to the hypsochromic shift.

The u.v. spectra of II and I (Ar = *p*-methoxyphenyl) also showed two bands [227 (4.25), 320 (4.25) and 227 (4.56), 342 (3.40) respectively] as expected with a bathochromic shift compared to II and I (Ar = phenyl). The absorptions of II and I (Ar = *p*-nitrophenyl) [221 (4.3), 260 (4.16), 286 (4.22) and 224 (4.46), 264 (4.19), 340 (3.63)] are in agreement with those reported in literature.⁸

N.M.R. SPECTRA OF (I) AND (II)

The compound obtained from the condensation with benzaldehyde in alcohol medium showed signals at δ 6.67 to 8.16 (complex multiplet

11 H, aromatic protons and two deuterium exchangeable protons of $\text{—}\overset{\text{O}}{\parallel}\text{C—NH}_2$) and at δ 8.35 (s, 1H). The signal at δ 8.35 is assignable to azomethine proton (—CH=N—), thus supporting the given N-benzylideneorthanilamide structure (II, Ar = phenyl). The n.m.r. spectrum of its isomeric product obtained from acetic acid medium revealed signals

at δ 5.83 (1 H, m, $\text{—N—}\overset{\text{O}}{\parallel}\text{C—N—}$) and at δ 6.5–7.83 (complex multiplet, 10 H, aromatic protons along with one deuterium exchangeable —NH—)

and a distorted doublet at δ 8.33 (1H, $\text{—}\overset{\text{O}}{\parallel}\text{C—NH—}\overset{\text{O}}{\parallel}\text{C—}$ deuterium exchangeable). These data are in agreement with structure I (Ar = phenyl). The n.m.r. spectra of the other pairs of products are found to conform to the same pattern. Again, due to poor solubility of these compounds in a variety of solvents, the spectra could be recorded only in DMSO.

4 (3 H)-QUINAZOLINONES

Various oxidising agents like potassium permanganate,^{6,7} *p*-benzoquinone⁹ and potassium ferricyanide³ have been made use of for the conversion of 1,2,3,4-tetrahydro-4-oxoquinazolines (I) to the corresponding dihydro derivatives. But the direct synthesis of 4 (3 H)-quinazolinones (II) from *o*-aminobenzamide and aldehyde under dehydrogenative conditions has not been studied so far.

The utility of nitrobenzene, a well-known dehydrogenative agent, and of simple Schiff base—proved to serve¹⁰ as both aldehyde source and hydrogen acceptor—, in the preparation of III has now been studied.

(a) CONDENSATION OF *o*-AMINOBENZAMIDE WITH ALDEHYDES IN NITROBENZENE

The condensation of *o*-aminobenzamide and benzaldehyde in refluxing nitrobenzene resulted in 2-phenyl-4 (3H)-quinazolinone (III, Ar = phenyl) in good yield. Six other aldehydes have been employed in this reaction

and in every case the corresponding quinazolinone (III) has been obtained (table 2, chart I). *p*-Chlorobenzylidene orthanilamide (II, Ar = *p*-chlorophenyl) and 2-*p*-chlorophenyl-1,2,3,4-tetrahydro-4-oxoquinazoline (I, Ar = *p*-chlorophenyl) were independently refluxed in nitrobenzene and the product obtained from each of these two experiments was found to be the same 2-*p*-chlorophenyl-4-(3H)-quinazolinone (III, Ar = *p*-chlorophenyl), obtained by the direct condensation.

(b) REACTION OF *o*-AMINOBENZAMIDE WITH SCHIFF BASES IN ACETIC ACID

The reaction of *o*-aminobenzamide with two moles of benzylidene-aniline in acetic acid gave 2-phenyl-4-(3H)-quinazolinone and benzylaniline (IV, Ar = phenyl) in very good yield. Thus it is clear that benzylidene-aniline is serving both as an aldehyde source and as a hydrogen acceptor.

Table 2. Formation of III from *o*-aminobenzamide and aldehydes in nitrobenzene and of III and IV from *o*-aminobenzamide and Schiff bases

| Sl. No. | Ar-CHO or Ar-CH=N-Ph employed Ar= | m.p. of 2-aryl-4(3H)-quinazolinone (III) (°C) | m.p. of ArCH ₂ -N-Ph (IV) (°C) |
|---------|-----------------------------------|---|---|
| 1. | Phenyl | 238 (238) ⁶ | 211* (214-16) ¹¹ |
| 2. | <i>p</i> -methylphenyl | 239-40 (241) ⁶ | 182* (187-9) ¹¹ |
| 3. | <i>p</i> -methoxyphenyl | 245-6 (247) ⁶ | 47 (46.5-5.47) ¹² |
| 4. | <i>p</i> -chlorophenyl | 300-1 (303-6) ⁷ | 197* (210-11) ¹¹ |
| 5. | <i>m</i> -nitrophenyl | 352 (354) ⁶ | 86 (84-5) ¹² |
| 6. | <i>p</i> -nitrophenyl | 360 (365) ⁶ | .. |
| 7. | 3,4-methylenedioxyphenyl | 277 (279) ⁶ | .. |

* Hydrochloride of the base.

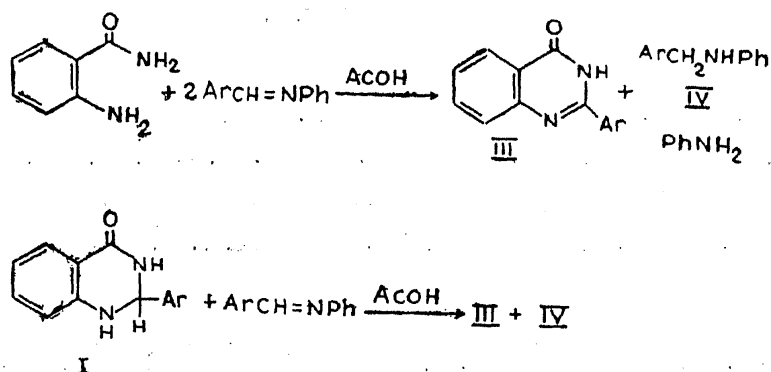


CHART - II

This reaction has been conducted with five other Schiff bases and in all the cases the corresponding reduced product (IV) of the Schiff bases (except with *p*-nitrobenzylideneaniline) and 2-aryl-4 (3H)-quinazolinones (III) were obtained in 80–90% yield (chart II, table 2). Simple Schiff bases can therefore be effectively made use of in the synthesis of (III) from *o*-aminobenzamide.

The reaction of I (Ar = phenyl) with one mole of benzylideneaniline in acetic acid at room temperature also gave III and IV (Ar = phenyl). The reaction has been repeated with all other derivatives of (I), and in every case the corresponding IV (except in the case of *p*-nitrobenzylideneaniline) and III have been found to be formed in good yield (chart II, table 2). Obviously, the added Schiff base is functioning only as a hydrogen acceptor in these reactions.

Analyses of the unknown compounds obtained from these reactions were carried out and they contained the right amounts of nitrogen.

The u.v. spectra were recorded on Beckmann DB spectrophotometer and n.m.r. spectra on Varian A-60D instrument using DMSO signal as internal standard.

2. EXPERIMENTAL

I. Condensation of *o*-aminobenzamide with aldehydes in nitrobenzene.

2-ARYL-4 (3H)-QUINAZOLINONES (III): GENERAL PROCEDURE

A mixture of *o*-aminobenzamide (0.005 mole) and aldehyde (0.005 mole) was refluxed in nitrobenzene (25 ml.) for one hour and steam distilled. The non-volatile residue on purification and recrystallisation gave 2-aryl-4 (3H)-quinazolinone (table 2).

II. Condensation of *o*-aminobenzamide with Schiff bases in acetic acid.

2-ARYL-4 (3H)-QUINAZOLINONES (III): GENERAL PROCEDURE

o-Aminobenzamide (0.0025 mole) and Schiff base (0.005 mole) were dissolved in the minimum quantity of acetic acid and the mixture left aside for 24 hours. The pure crystalline 2-aryl-4-(3H)-quinazolinone that separated out from acetic acid medium was filtered and washed with methanol (table 2).

The acetic acid filtrate in each case on dilution with water gave additional amounts of 2-aryl-4 (3H)-quinazolinone. The aqueous acetic acid

filtrate on neutralization with ammonia gave the corresponding secondary amine (except in the case of *p*-nitrobenzylideneaniline).

In the same way, 2-aryl-1,2,3,4-tetrahydro-4-oxoquinazoline (0.005 mole) and the Schiff base (0.005 mole) after 24 hours in acetic acid gave 2-aryl-4(3H)-quinazolinone (III) and the secondary amine (IV).

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REFERENCES

1. Hirwe, N. W. and Kulkarni, P. Y., *Proc. Indian Acad. Sci.* **13A** 49 (1941).
2. Song, J. and Cohen, E., U.S. 3,092,631 (1963), *Chem. Abstr.* **59** 12821 (1963).
3. Somasekharam, S., Dighe, V. S. and Mukherjee, S. L., *Curr. Sci.* **33** 645 (1964).
4. Yale, H. L., U.S. 3,455,920 (1969), *Chem. Abstr.* **71** 61419 (1969).
5. Yale, H. L., U.S. 3,463,778 (1969), *Chem. Abstr.* **72** 66969 (1970).
6. Smith, T. A. K., and Stephen, H., *Tetrahedron* **1** 38 (1957).
7. Russo, F. and Ghelardone, M., *Ann. Chim.* **56** 839 (1966); *Chem. Abstr.* **66** 18696 (1967).
8. Giuseppe, B. and Sianesi, E., *Chem. Ber.* **102** (11) 3735-8 (1969); *Chem. Abstr.* **74** 21066 (1970).
9. Alaineo, R., Ger. Offen., 2,103,286 (1970); *Chem. Abstr.* **75** 98586 (1971).
10. Sarojini, A. K., Sriramulu, N. and Ratram, C. V., *Curr. Sci.* **41** 776 (1972).
11. Roe, A. and Montgomery, J. A., *J. Am. Chem. Soc.* **75** 911 (1953).
12. Billman, J. H. and Diesing, A. C., *J. Org. Chem.* **22** 1068 (1957).