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Synthesis of Isomeric 3-Aminopyridopyrimidin-4(3*H*)ones*

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It could be established that the reaction between hydrazine and enamines, formed from ethyl 2(or 3)-aminopyridine-3(or 2)carboxylates and diethyl ethoxymethylenemalonate or ethyl ethoxymethylenecyanoacetate, afforded 3-aminopyrido(2,3-*d*)pyrimidin-4(3*H*)one or 3-aminopyrido(3,2-*d*)pyrimidin-4(3*H*)one, respectively. Similarly, these aminopyridinecarboxylates condense with *N*,*N*-dimethylformamide dimethylacetal and react further with hydrazine to give the same bicyclic compounds.

It has been proposed that 1,3,4-benzotriazepines are formed in the reaction between 2-aminobenzophenones and diethyl ethoxymethylenemalonate and subsequent treatment of the intermediate enamine with hydrazine.[1] We would like to present evidence that related reactions which we have investigated in the pyridine field led only to pyridopyrimidones.

Esters of 2-aminopyridine-3-carboxylic or 3-aminopyridine-2-carboxylic acids when condensed with diethyl ethoxymethylenemalonate or ethyl ethoxymethylenecyanoacetate afforded the corresponding condensation products (V, R_1 = COOEt or CN). In view of the possibility that the enamines formed in the reaction with the last mentioned reagent may exist as *cis* or *trans* isomers (I or II) or as a mixture of both, we have examined the product which was obtained from the reaction between 3-amino-2-carbethoxypyridine and ethyl ethoxymethylenecyanoacetate. From NMR spectroscopic assignements it could be established that the relative amounts of the *cis*-enamine (I) and *trans*-enamine (II) were present in a ratio of about 3 : 2. As anticipated, the signal for the olefinic proton of the *trans*-enamine is at lower field than that of the *cis*-enamine.

These enamines, when treated in cold with excess of hydrazine hydrate formed readily 3-aminopyrido(2,3-*d*)pyrimidin-4(3*H*)one (III, R = NH_2) or 3-aminopyrido(3,2-*d*)pyrimidin-4(3*H*)one (IV, R = NH_2). The formation of these bycyclic compounds can be envisaged as to result by addition of hydrazine to the exocyclic double bond followed by elimination of the diethyl malonate or ethyl cyanoacetate part and cyclization. This is consistent with the observation that substituted methylenemalonates add hydrazines[2] or form hydrazones,[2,3] the diethyl malonate moiety being in this case the leaving group.

Further support for intermediates of the type VI is given in the reaction between aminopyridinecarboxylates and *N*,*N*-dimethylformamide dimethylacetal, a well documented reaction also for some aminoheterocyclic compounds.[4]

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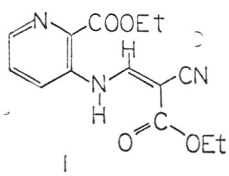
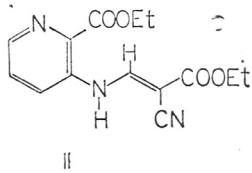
* Part XCII in the Series Heterocycles.



I



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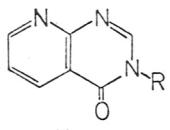
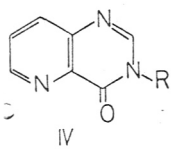


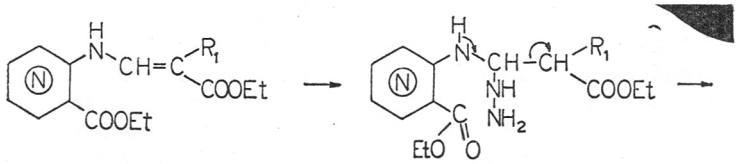
III



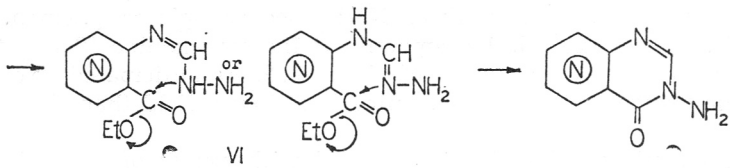
IV

Here, the intermediate *N,N*-dimethylaminomethylene derivative could be isolated and characterized and is readily converted with hydrazine into the corresponding bicyclic 3-amino compound (III or IV).

Another approach to the formation of the bicyclic system represents the reaction between 2-aminonicotinic acid hydrazide and diethoxymethyl acetate. The formed 3-ethoxymethyleneamino compound (III, R = —N=CHOEt) is converted into the 3-amino compound (III, R = NH_2) upon hydrolysis. The spectral evidence which is in accord with the above structure as a 6/6 and not as a 6/7 bicycle is supported also by chemical evidence. Both 3-amino deri-



V

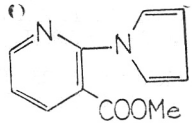


VI

vatives (III, IV, R = NH_2) when treated under mild reaction conditions with amyl nitrite in the presence of glacial acetic acid are transformed into their desamino derivatives (III, IV, R = H) which were found identical with authentic specimens[5,6]. Although the 3-amino group of related 3-aminoquinazolines behaves normally in chemical reactions as anticipated for an amino group, 3-aminopyrido(2,3-*d*)pyrimidin-4(3*H*)one did not condense with benzaldehyde, but a monoacetyl derivative could be prepared.

Furthermore, it is noteworthy that under normal conditions 2-amino-3--carbethoxypyridine-*N*-oxide did not form the corresponding enamine with diethyl ethoxymethylenemalonate. However, the amino group of methyl 2-

-aminopyridine-3-carboxylate reacted with *cis,trans*-2,5-diethoxytetrahydrofuran to give the corresponding pyrrolopyridine (VII). In an attempt to convert



VII

this compound into a tricyclic system with polyphosphoric acid the pyrrole ring was eliminated and methyl 2-aminopyridine-3-carboxylate was isolated and identified.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are corrected. NMR spectra were recorded on a JEOL JNM-C-60HL spectrometer (TMS as internal standard) and mass spectra were obtained on a CEC 21-110C instrument.

Diethyl [3-carbomethoxy-N(2-pyridinyl)]aminomethylenemalonate

Methyl 2-aminopyridine-3-carboxylate (4.56 g.), and diethyl ethoxymethylenemalonate (6.5 g.) were heated at about 160° and heating was discontinued in order to moderate the exothermic reaction. Thereafter heating was continued and the mixture was heated at about 180° for 10 min. Upon cooling the oily mass crystallized after standing on ice. Crystallization from aqueous ethanol afforded the pure compound (2.86 g.) with m. p. 79—80°.

Anal. $C_{15}H_{18}N_2O_6$ (322.31) calc'd.: C 55.89; H 5.63; N 8.69%
found: C 55.58; H 5.44; N 8.87%

The following compounds were prepared in a similar manner:

Ethyl [3-carbomethoxy-N(2-pyridinyl]aminomethylenecyanoacetate

M. p. 136—137° (from ethanol). IR spectrum: (KBr) 2217 (CN), 1715 and 1695 cm^{-1} (COOMe and COOEt). Mass spectrum: $M^+ = 275$.

Anal. $C_{13}H_{13}N_3O_4$ (275.26) calc'd.: C 56.72; H 4.76; N 15.27%
found: C 56.65; H 4.70; N 15.49%

Diethyl [3-carbamoyl-N(2-pyridinyl)]aminomethylenemalonate

M. p. 199—201° (from ethanol). IR spectrum (KBr): 3367 and 3279 (NH, NH_2) and 1887 cm^{-1} (COOEt). Mass spectrum: $M^+ = 307$.

Anal. $C_{14}H_{17}N_3O_5$ (307.30) calc'd.: C 54.72; H 5.58; N 13.68%
found: C 54.91; H 5.42; N 13.92%

Ethyl [2-carbethoxy-N(3-pyridinyl)]aminomethylenecyanoacetate

M. p. 188—189° (from ethanol). IR spectrum (KBr): 2217 (CN) and 1692 cm^{-1} (COOEt). NMR spectrum: DMSO-d_6 at 80°: $\tau = 1.85$ (dd, H_4), 2.46 (dd, H_5), 1.58 (dd, H_6), 5.75 (q, 2-COOC**H**$_2$CH$_3$), 8.70 (t, 2-COOCH$_2$C**H**$_3$), 5.60 (q, = C(CN)COOC**H**$_2$CH$_3$), 8.61 (t, = C(CN)COOCH$_2$C**H**$_3$), 1.70 (s, —NH—C**H** =, *cis*), 1.50 (s, —NH—C**H** =, *trans*); $J_{4,5} = 8.5$, $J_{5,6} = 4.2$, $J_{4,6} = 1.5$, $J_{CH_2CH_3} = 7.5$ Hz.

Anal. $C_{14}H_{15}N_3O_4$ (289.28) calc'd.: C 58.12; H 5.23; N 14.53%
found: C 58.39; H 5.23; N 14.78%

3-Aminopyrido(2,3-d)pyrimidin-4(3H)one (III, R = NH_2)

A. — A solution of diethyl [3-carbomethoxy-*N*-(2-pyridinyl)]aminomethylenemalonate (1.61 g.) in ethanol (30 ml.) was treated with hydrazine hydrate (1.5 ml. of 100%) and the mixture was left at room temperature overnight. The separated cry-

stals were collected (1.37 g.) and crystallized from water. M. p. 249—250°. IR spectrum (KBr): 1689 (CO) and 3311 cm^{-1} (NH_2). Mass spectrum: $M^+ = 162$. NMR spectrum: in DMSO-d_6 at 112°: $\tau = 1.56$ (s, H_2), 1.55 (dd, H_5), 2.53 (dd, H_6), 1.10 (dd, H_7), 5.1 (broad, NH_2); $J_{5,6} = 8.0$, $J_{6,7} = 5.9$; $J_{5,7} = 1.5$ Hz. In TFAA at 25°: $\tau = 1.02$ (s, H_2), 0.55 (dd, H_5), 1.87 (dd, H_6), 0.84 (dd, H_7); $J_{5,6} = 8.0$; $J_{6,7} = 5.9$, $J_{5,7} = 1.5$ Hz.

Anal. $C_7H_6N_4O$ (162.15) calc'd.: C 51.85; H 3.73; N 34.56%
found: C 52.22; H 3.82; N 34.74%

B. — A mixture of ethyl 2-aminopyridine-3-carboxylate (1.16 g.) and *N,N*-dimethylformamide dimethylacetal (3.0 ml.) was heated under reflux for 2 hrs. and evaporated *in vacuo*. A small amount of the residual oil was for analysis distilled at 120—130°/0.1 mm (*Anal.* $C_{11}H_{15}N_3O_2$ (221.25) calc'd.: C 59.71; H 6.83; N 18.99%. Found: C 59.52; H 6.70; N 19.48%). The residual crude *N,N*-dimethylaminomethylene derivative was dissolved in some ethanol and treated with excess of 100% hydrazine hydrate. The product had after purification m. p. 249—250° and had identical IR spectrum with the product obtained as described under *A* and mixed m. p. was without depression.

*3-Acetylaminopyrido(2,3-*d*)pyrimidin-4(3*H*)one* (III, R = CH_3CONH)

The above amino compound (0.162 g.), acetic anhydride (1.0 ml.) and pyridine (1.5 ml.) were heated under reflux for 15 min. The cooled solution was diluted with water (5.0 ml.), extracted with chloroform and after evaporation of the solvent the residual oil crystallized after several days. Upon crystallization from triethyl orthoformate the pure compound had m. p. 225—227°. NMR spectrum (in DMSO-d_6 at 21°): $\tau = 1.64$ (s, H_2), 1.55 (dd, H_5), 2.53 (dd, H_6), 1.10 (dd, H_7), 7.90 (s, $COCH_3$), — 1,1 (broad, NH); $J_{5,6} = 7.6$, $J_{6,7} = 4.5$, $J_{5,7} = 2.0$ Hz.

Anal. $C_9H_8N_4O_2$ (204.19) calc'd.: C 52.94; H 3.95; N 27.44%
found: C 52.90; H 4.17; N 27.29%

*3-Ethoxymethyleneaminopyrido(2,3-*d*)pyrimidin-4-(3*H*)one* (III, R = EtOCH=N-)

The hydrazide of 2-aminopyridine-3-carboxylic acid[7] (0.87 g. with m. p. 190—191°; lit.[7] gives m. p. 176°) was treated with diethoxymethyl acetate (5.1 g.) and the resulting solution was heated under reflux for 15 min. The separated product was filtered, washed with triethyl orthoformate and recrystallized from the same solvent (yield 1.05 g.). M. p. 142—143°. IR spectrum (in KBr): 1681 cm^{-1} (CO). Mass spectrum: $M^+ = 218$. NMR spectrum (in DMSO-d_6): $\tau = 1.58$ (s, H_2), 1.58 (dd, H_5), 2.53 (dd, H_6), 1.13 (dd, H_7), 1.48 (s, =C**H**OEt), 5.66 (q, —OC**H**$_2$CH$_3$), 8.62 (t, OCH$_2$C**H**$_3$); $J_{5,6} = 7.8$; $J_{6,7} = 4.8$, $J_{5,7} = 2.1$, $J_{CH_2CH_3} = 6.8$ Hz.

Anal. $C_{10}H_{10}N_4O_2$ (218.21) calc'd.: C 55.04; H 4.62; N 25.68%
found: C 54.77; H 4.39; N 26.02%

The same product was obtained when employing triethyl orthoformate in this reaction.

If the product was heated in the presence of glacial acetic acid for 2 hrs., the solution evaporated to dryness *in vacuo* and some ammonia was added, upon standing some crystals separated. They were identified as 3-aminopyrido(2,3-*d*)pirimidin-4(3*H*)one.

*Pyrido(2,3-*d*)pyrimidin-4(3*H*)one* (III, R = H)

Compound III (R = NH_2) (0.162 g.) was dissolved in glacial acetic acid (10 ml.) and the solution was treated with amyl nitrite (0.2 ml.). After standing at room temp. for 15 min. the solution was evaporated *in vacuo* to dryness and the residue was crystallized from water. M. p. 262—263° and mixed m. p. with an authentic specimen was undepressed (lit.[5] gives m. p. 258°). NMR spectrum (in DMSO-d_6 at 112°): $\tau =$ = 1.92 (s, H_2), 1.66 (dd, H_5), 2.65 (dd, H_6) 1.26 (dd, H_7), — 0.5 (broad, NH); $J_{5,6} = 7.6$, $J_{6,7} = 4.5$, $J_{5,7} = 2.0$ Hz.

Anal. $C_7H_5N_3O$ (147.13) calc'd.: C 57.14; H 3.43; N 28.56%
found: C 56.99; H 3.54; N 28.48%

*3-Aminopyrido(3,2-*d*)pyrimidin-4(3*H*)one* (IV, R = NH_2)

A. — Ethyl 3-aminopyridine-2-carboxylate (0.83 g.) and diethyl ethoxymethylenemalonate (1.08 g.) were heated to 170—180° until the exothermic reaction started. Temperature raised to 200—210° and this temperature was held for 5 min. Upon cooling the residual oil did not crystallize and it was dissolved in absolute ethanol (10 ml.) and hydrazine hydrate (1.5 ml. of 100%) was added. The separated crystals were crystallized from ethanol, m. p. 285—287°. NMR spectrum (in DMSO-d_6 at 80°): $\tau = 1.73$ (s, H_2), 1.82 (dd, H_6), 2.35 (dd, H_7), 2.04 (dd, H_8); $J_{6,7} = 4.0$, $J_{7,8} = 7.8$, $J_{6,8} = 1.5$ Hz.

Anal. $C_7H_6N_4O$ (162.15) calc'd.: C 51.85; H 3.73; N 34.56%
found: C 52.23; H 3.43; N 34.49%

B. — Ethyl 3-aminopyridine-2-carboxylate (1.16 g.) and *N,N*-dimethylformamide dimethylacetal (3.0 ml.) were heated under reflux for 2 hrs. The mixture was evaporated *in vacuo* and the residual oil, consisting of the crude dimethylaminomethylene derivative, was treated with excess of 100% hydrazine hydrate. Tre formed product, m. p. 285—288°, was found to be identical in all respects with the compound prepared as described under *A.*

*Pyrido(3,2-*d*)pyrimidin-4(3*H*)one* (IV, R = H)

The above 3-amino compound (0.324 g.) was dissolved in hot glacial acetic acid (15 ml.), the solution was cooled and amyl nitrite (0.3 ml.) was added. After standing at room temp. for 1 hr. the separated product was collected and had m. p. about 350°. It was found to be identical in all respects with an authentic specimen[6]. NMR spectrum (in DMSO-d_6 at 120°): $\tau = 2.08$ (s, H_2), 1.30 (dd, H_6), 2.40 (dd, H_7), 2.11 (dd, H_8), cca 2.7 (broad, NH); $J_{6,7} = 4.5$, $J_{7,8} = 7.6$, $J_{6,8} = 1.5$ Hz.

Anal. $C_7H_5N_3O$ (147.13) calc'd.: C 57.14; H 3.43; N 28.56%
found: C 56.82; H 3.32; N 28.32%

*2-Amino-3-carbethoxypyridine-*N*-oxide*

A solution of 2-amino-3-carbethoxypyridine (5.0 g.) in glacial acetic acid (60 ml.) was treated with hydrogen peroxide (15 g. of 72%) and left aside at room temp. for 60 hrs. Thereafter some water was added, the solution was evaporated *in vacuo* to dryness and the residual oil crystallized after standing. Upon crystallization from acetonitrile the product (2.87 g.) had m. p. 139—141°. Mass spectrum: $M^+ = 182$.

Anal. $C_8H_{10}N_2O_3$ (182.18) calc'd.: C 52.74; H 5.53; N 15.38%
found: C 52.52; H 5.62; N 14.98%

*3-Carbomethoxy-2-(*N*-pyrrolo)pyridine* (VII)

A solution of methyl 2-aminopyridine-3-carboxylate (0.15 g.) in glacial acetic acid (2.0 ml.) was treated with *cis, trans*-2,5-diethoxytetrahydrofuran (0.16 g.) and the mixture was heated under reflux for 30 min. The solution was evaporated *in vacuo* and the residual dark oil was distilled at 90—100°/3 mm (yield 80 mg.). Mass spectrum: $M^+ = 202$. NMR ($CDCl_3$): $\tau = 2.02$ (dd, H_4), 2.95 (dd, H_5), 1.53 (dd, H_6), 6.21 (s, $COOCH_3$), 3.00 (m, $H_{2'5'}$), 3.75 (m, $H_{3'4'}$); $J_{4,5} = 7.5$, $J_{5,6} = 4.6$, $J_{4,6} = 1.7$ Hz.

Anal. $C_{11}H_{10}N_2O_2$ (202.21) calc'd.: C 65.33; H 4.98; N 13.86%
found: C 65.04; H 5.16; N 14.08%

A mixture of VII (0.125 g.) and polyphosphoric acid (2 g. of acid with 80% P_2O_5) was left to stand at room temp. for 24 hrs. It was poured on crushed ice and neutralized with sodium bicarbonate. Extraction with chloroform afforded a dark oil which was sublimed at 100°/0.1 mm. The process was repeated and the product with m. p. 85° was identified as methyl 2-aminopyridine-3-carboxylate (mass spectrum: $M^+ = 152$).

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REFERENCES

1. C. Podesva, G. Kohan, and K. Vagi, *Canad. J. Chem.* **47** (1969) 489.
2. I. Goldstein, *Ber. dtsch. chem. Ges.* **28** (1895) 1450.
3. W. Wislicenus, *Ann.* **279** (1894) 23.
4. H. Bredereck, F. Effenberger, and A. Hofmann, *Chem. Ber.* **97** (1964) 61.
5. R. K. Robins, and G. H. Hitchings, *J. Am. Chem. Soc.* **77** (1955) 2256.
6. C. C. Price, and D. Y. Curtin, *J. Am. Chem. Soc.* **68** (1946) 914.
7. V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.* (1956) 1045.

IZVLEČEK

Sinteze izomernih 3-aminopiridopirimidin-4(3*H*)onov

B. Stanovnik in M. Tišler

Ugotovili smo, da vodi reakcija med hidrazinom in enamini, ki nastanejo pri reakciji med etilnim estrom 2(ali 3)-aminopiridin-3-(ali 2)karboksilne kisline in dietilnim estrom etoksimetilenmalonove kisline ali etilnim estrom etoksimetilencianocetne kisline, do 3-aminopirido(2,3-*d*)pirimidin-4(3*H*)ona oziroma do 3-aminopirido(3,2-*d*)pirimidin-4(3*H*)ona. Na podoben način se omenjeni estri aminopiridinkarboksilnih kislin kondenzirajo z *N*,*N*-dimetilformamid dimetilacetalom in nadaljnja reakcija s hidrazinom vodi do istih bicikličnih spojin.

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