

Potential Ambifunctionality of 2-Azidopyrido[1,2-*a*]pyrimidin-4-one

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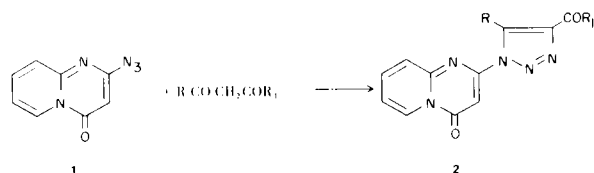
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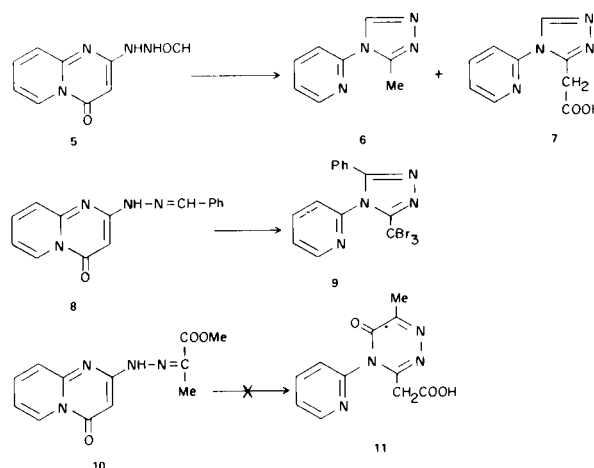
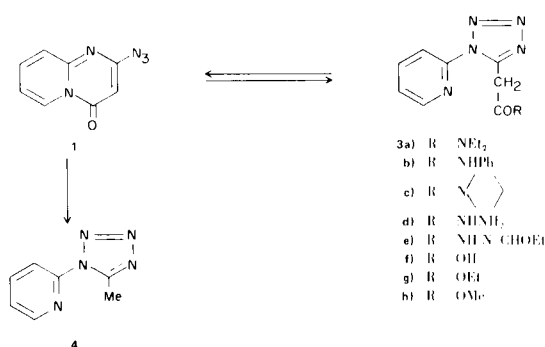
2-Azidopyrido[1,2-*a*]pyrimidin-4-one can exist only in the azido form and undergoes cycloaddition reaction with 1,3-dicarbonyl compounds to form 1,2,3-triazole derivatives. Under the influence of bases or hydrochloric acid the carbonyl group is attacked with subsequent opening of the pyrimidine ring. This causes an immediate cyclization of the azide group to give a tetrazolo derivative. In a similar way a triazole ring can be formed from the appropriate hydrazino derivatives of pyrido[1,2-*a*]pyrimidin-4-one.

Heterocyclic azides having the azido group attached to the cyclic carbon atom adjacent to an annular nitrogen atom are generally in the tetrazolo form (1). On the contrary, the tetrazolo form can be destabilized to such an extent that compounds exist exclusively in the azido form. This is the case of azido-1,3,5-triazines, (2-5).

However, there are some heterocyclic azides where the tetrazolo form on structural grounds cannot be generated. A representative of this type of compounds is 2-azidopyrido[1,2-*a*]pyrimidin-4-one (1). As a part of our investigation on related systems it seemed worthwhile to investigate this compound for its reactivity.



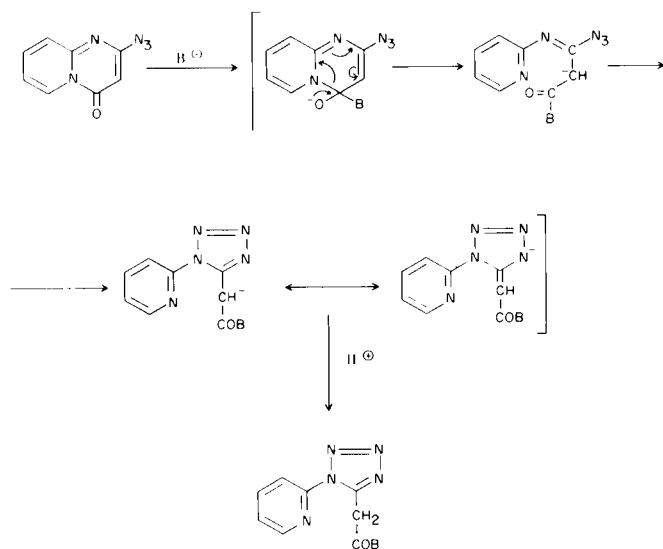
The azide (1) reacted with 1,3-dicarbonyl compounds to form 1,2,3-triazoline derivatives (2) in a similar manner as described recently (6). The structural assignment follows from the decomposition of these triazoles into 2-diazo-1,3-dicarbonyl compounds, as described previously



(6). In all cases one type of addition product was isolated, except for the reaction with benzoylacetone. Here, both isomers 2 (R = Me, R₁ = Ph or R = Ph, R₁ = Me) were formed in a ratio of about 1:2 as determined from nmr examination. The signal for the benzoyl group appeared as multiplet at $\tau = 2.65$ whereas the signal for the 5-phenyl group of the isomeric triazolo compound appeared as a broad singlet at $\tau = 3.65$.

In the presence of bases a new kind of transformation could be observed. When heated with amines, the azide (1) reacted by ring opening of the pyrimidine part of the bicycle and simultaneous cyclization of the azido group to give the tetrazolo ring (3a, b, c). Piperidine reacted smoothly, whereas reaction with aniline proceeded slower and with diethylamine heating under reflux for 5 days was required. The reaction can be envisaged as to proceed by an attack of the base on the carbonyl group. Subsequent ring opening of the six-membered ring and simultaneous cyclization of the azido group generated the tetrazolo ring (Scheme 1).

Scheme 1



In a similar manner the reaction with hydrazine took place to give the corresponding tetrazoleacetic acid hydrazide (**3d**). This, when transformed with triethyl orthoformate into the corresponding ethoxymethylene derivative (**3e**) and after treatment with polyphosphoric acid underwent cyclization to afford the starting azido compound (**1**). This indicates the reversibility of the isomerization and upon the formation of the fused pyrimidine ring the tetrazole ring is simultaneously forced to assume the azido form. Instead of the ethoxymethylene compound, the hydrazide (**3d**) could be converted straightforward into the azide (**1**) after treatment with diethoxymethyl acetate.

On the other hand, treatment of 2-azidopyrido[1,2-*a*]pyrimidin-4-one (**1**) with ethanolic hydrochloric acid afforded a mixture of the tetrazoleacetic acid (**3f**) and its ethyl ester (**3g**) indicating again that the above described process of ring opening and cyclization took place. However, prolonged heating of the azide with hydrochloric acid afforded exclusively the methyltetrazole (**4**), formed from the corresponding acid (**3f**) by decarboxylation. It is well known that tetrazoleacetic acids are readily decarboxylated at moderate temperature (7).

It could be further demonstrated that the formation of a triazole ring which involves the participation of the pyrimidine ring nitrogen at position 1 can also force ring opening of the pyrimidine part of the bicycle. In this manner, 2-formylhydrazinopyrido[1,2-*a*]pyrimidin-4-one (**5**), after treatment with polyphosphoric acid afforded the corresponding methyltriazole (**6**) and triazoleacetic acid (**7**) in the ratio of about 1:2. The methyl compound (**6**) is formed in the same manner as mentioned above for the corresponding tetrazole, *i.e.* by decarboxylation.

Moreover, an attempt to use the previously described technique of cyclization by bromination of a hydrazone (**8**) was successful in the case of **8**. However, in addition to the ring opening of the bicycle and cyclization of the triazole ring, the product was decarboxylated to give the corresponding methyltriazole and this was finally brominated to give the tribromomethyl compound (**9**). Finally, it should be mentioned that an attempt to form a 1,2,4-triazine ring (**11**) from **10** has been so far unsuccessful.

EXPERIMENTAL

All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer (TMS as internal standard) and mass spectra were taken on a Hitachi Perkin-Elmer RMU-61 instrument using direct sample insertion into the ion source.

2-Azidopyrido[1,2-*a*]pyrimidin-4-one (**1**).

2-Hydrazinopyrido[1,2-*a*]pyrimidin-4-one (**9**) (1.76 g.) was mixed with 10 ml. water and the solution treated with hydrochloric acid (5 ml. of 1:1). The solution was cooled to 0-5° and an aqueous solution of sodium nitrite (0.7 g. in 5 ml. water) was added dropwise under stirring. The separated product was filtered off, washed with iced water and air dried.

Yield almost quantitative. The product was pure enough for further experiments, but it can be crystallized from aqueous ethanol, m.p. 160-163°.

Anal. Calcd. for C₈H₅N₅O: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.58; H, 2.91; N, 37.60.

4-Carboethoxy-5-carboethoxymethyl-1-(pyrido[1,2-*a*]pyrimidin-4'-onyl-2')-1,2,3-triazole (**2**, R = CH₂COOEt, R₁ = OEt).

2-Azidopyrido[1,2-*a*]pyrimidin-4-one (**1**) (187 mg.), ethanol (3 ml.), diethyl acetonedicarboxylate (202 mg.) and triethylamine (0.5 ml.) were heated under reflux for 24 hours. The product was crystallized from ethanol, m.p. 134-136° (yield 174 mg., 47%); nmr (DMSO-*d*₆): τ = 3.17 (s, H₃'), 1.0 (m, H₆'), 2.50 (m, H₇'₈'), 1.90 (m, H₉'), 5.65 (q, 4-COOCH₂CH₃), 8.63 (t, 4-COOCH₂CH₃), 5.42 (s, 5-CH₂COOEt), 5.93 (q, 5-CH₂COOCH₂CH₃), 8.90 (t, 5-CH₂COOCH₂CH₃), J_{E1} = 6.8.

Anal. Calcd. for C₁₇H₁₇N₅O₅: C, 54.98; H, 4.61; N, 18.86. Found: C, 55.43; H, 4.77; N, 19.06.

4-Acetyl-5-methyl-1-(pyrido[1,2-*a*]pyrimidin-4'-onyl-2')-1,2,3-triazole (**2**, R = R₁ = Me).

Compound **2** was prepared in a similar way from acetylacetone (1 hour reflux) in 85% yield, m.p. 193-195° (from ethanol); nmr (DMSO-*d*₆): τ = 3.28 (s, H₃'), 1.0 (m, H₆'), 2.45 (m, H₇'₈'), 1.96 (m, H₉'), 7.16 (s, 4-COCH₃), 7.40 (s, 5-Me).

Anal. Calcd. for C₁₃H₁₁N₅O₂: C, 57.98; H, 4.12; N, 26.01. Found: C, 57.88; H, 4.44; N, 26.21.

4-Carboethoxy-5-methyl-1-(pyrido[1,2-*a*]pyrimidin-4'-onyl-2')-1,2,3-triazole (**2**, R = Me, R₁ = OEt).

It was prepared as the above compound in 78% yield, m.p. 188-190° (from ethanol), from ethyl acetoacetate.

Anal. Calcd. for C₁₄H₁₃N₅O₃: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.28; H, 4.55; N, 23.56.

4-Carboethoxy-5-phenyl-1-(pyrido[1,2-*a*]pyrimidin-4'-onyl-2')-1,2,3-triazole (**2**, R = Ph, R₁ = OEt).

This compound was prepared similarly from ethyl benzoylacetate in 57% yield, m.p. 175-177° (from ethanol); nmr (DMSO- d_6): τ 3.42 (s, H_{3'}), 1.02 (m, H_{6'}), 2.60 (m, H_{7'}, 8'), 1.95 (m, H_{9'}), 2.60 (broad s, 5-Ph), 5.75 (q, 4-COOCCH₂CH₃), 8.85 (t, 4-COOCCH₂CH₃), $J_{E1} = 6.8$.

Anal. Calcd. for C₁₉H₁₅N₅O₃: C, 63.14; H, 4.18; N, 19.38. Found: C, 62.81; H, 4.24; N, 19.77.

4-Benzoyl-5-methyl-(**2**, R = Me, R₁ = Ph) and 4-Acetyl-5-phenyl-1-(pyrido[1,2-*a*]pyrimidin-4'-onyl-2')-1,2,3-triazole (**2**, R = Ph, R₁ = Me).

A mixture of 2-azidopyrido[1,2-*a*]pyrimidin-4-one (**1**) (187 mg.), benzoylacetone (162 mg.), ethanol (3 ml.) and triethylamine (0.5 ml.) was heated under reflux for 1 hour. The product was crystallized from ethanol and had m.p. 182-186°. On the basis of nmr spectrum examination the product consisted as a mixture of compounds **2** (R = Me, R₁ = Ph) and **2** (R = Ph, R₁ = Me) in a ratio of 1:2, yield 186 mg. (56%); nmr: compound **2** (R = Me, R₁ = Ph) (DMSO- d_6): τ = 3.50 (s, H_{3'}), 1.0 (m, H_{6'}), 2.45 (m, H_{7'}, 8'), 1.90 (m, H_{9'}), 2.65 (m, 4-COPh), 7.42 (s, 5-Me). Compound **2** (R = Ph, R₁ = Me) (DMSO- d_6): τ = 3.2 (s, H_{3'}), 1.0 (m, H_{6'}), 2.45 (m, H_{7'}, 8'), 1.90 (m, H_{9'}), 7.15 (s, 4-COMe), 3.65 (broad s, 5-Ph).

Anal. Calcd. for C₁₈H₁₃N₅O₂: C, 65.25; H, 3.96; N, 21.14. Found: C, 65.30; H, 4.24; N, 21.40.

1-(Pyridyl-2')-5-tetrazoleacetic Acid *N,N*-diethylamide (**3a**).

A mixture of compound **1** (0.5 g.) and diethylamine (100 ml.) was heated under reflux for 5 days. The solvent was evaporated to dryness, ethanol (15 ml.) was added and the residue was filtered off (80 mg., m.p. 232-233°, from aqueous ethanol, $M^+ = 213$). The filtrate was evaporated to dryness, chloroform (3 ml.) and some charcoal was added. After standing for 30 minutes the solution was filtered into *n*-hexane (15 ml.). The separated product (0.32 g., 46% yield) was for analysis crystallized from chloroform and *n*-hexane, m.p. 88-90°. Mass spectrum: $M^+ = 260$; nmr (deuteriochloroform): $\tau = 1.63$ (m, H₆), 1.93 (m, H_{3,4}), 2.75 (m, H₅), 5.50 (s, CH₂CO), 6.55 and 6.68 (q, CH₂CH₃), 8.63 and 9.00 (t, CH₂CH₃), $J_{E1} = 7.0$ Hz.

Anal. Calcd. for C₁₂H₁₆N₆O: C, 55.37; H, 6.20; N, 32.99. Found: C, 54.98; H, 6.35; N, 32.60.

In a similar manner were prepared:

1-(Pyridyl-2')-5-tetrazoleacetic Acid *N*-phenylamide (**3b**).

Compound **3b** was obtained from aniline in 75% yield (reaction time 1 hour), m.p. 188-189° (from ethanol); mass spectrum: $M^+ = 280$; nmr (DMSO- d_6): $\tau = 1.55$ (m, H₆), 2.0 (m, H_{3,4}), 5.50 (s, CH₂), 2.40-3.10 (m, Ph and H₅).

Anal. Calcd. for C₁₄H₁₂N₆O: C, 59.99; H, 4.32; N, 29.99. Found: C, 60.03; H, 4.68; N, 30.05.

1-(Pyridyl-2')-5-*N,N*-pentamethyleneacetamidotetrazole (**3c**).

Compound **3c** was obtained from piperidine in 34% yield (reaction time 10 minutes), m.p. 78° (from chloroform and *n*-hexane). Mass spectrum: $M^+ = 272$; nmr (deuteriochloroform): $\tau = 1.55$ (m, H₆), 2.65 (m, H₅), 2.0 (m, H_{3,4}), 5.45 (s, CH₂), 6.50 and 8.34 (m, piperidino group).

Anal. Calcd. for C₁₃H₁₆N₆O: C, 57.34; H, 5.92; N, 30.86. Found: C, 57.17; H, 6.00; N, 31.20.

1-(Pyridyl-2')tetrazoleacetic Acid Hydrazide (**3d**).

A mixture of the azide **1** (0.4 g.), hydrazine hydrate (0.5 ml. of 98%) and ethanol (3 ml.) was heated under reflux for 20

minutes. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol (yield 0.2 g., 43%), m.p. 194°; mass spectrum: $M^+ - N_2 = 191$; nmr (DMSO- d_6): τ 1.25 (m, H₆), 1.8 (m, H_{3,4}), 2.25 (m, H₅), 5.65 (s, CH₂), 0.50 (broad, NHNH₂).

Anal. Calcd. for C₈H₉N₇O: C, 43.84; H, 4.14; N, 44.72. Found: C, 44.05; H, 4.27; N, 44.74.

The above hydrazide, when heated with triethyl orthoformate under reflux for 2 hours was transformed in 85% yield into the corresponding ethoxymethylene derivative (**3e**), m.p. 185° (from methanol); mass spectrum: $M^+ = 275$; nmr (DMSO- d_6): τ 2.0 (m, H_{3,4'}), 2.50 (m, H_{5'}), 1.50 (m, H_{6'}), 6.65 (s, CH₂CO), 2.05 (s, N=CH), 6.0 (q, OCH₂CH₃), 8.72 (t, OCH₂CH₃), $J_{E1} = 7.5$ Hz.

Anal. Calcd. for C₁₁H₁₃N₇O₂: N, 35.62. Found: N, 35.93.

2-Azidopyrido[1,2-*a*]pyrimidin-4-one (**1**).

A.

The ethoxymethylene compound (**3e**) (0.6 g.) was mixed with polyphosphoric acid (30 g.) and the stirred mixture was heated at 70-80° for 5 hours. Upon cooling the reaction mixture was neutralized with sodium bicarbonate and extracted with chloroform. From the extracts the crude product was obtained and purified by tlc (silica, 0.5 mm, chloroform and methanol, 9:1). The product with $R_f = 0.86$ was eluted with methanol and it was identified as 2-azidopyrido[1,2-*a*]pyrimidin-4-one (**1**) (25 mg., 6.1%) when compared with an authentic specimen.

B.

A mixture of the hydrazide (**3d**) (0.4 g.) and diethoxymethyl acetate (1 ml.) was heated under reflux for 35 minutes. Upon evaporation to dryness the residue was treated with methanol (6 ml.) and after some time a product separated from the stirred solution (71 mg. of the ethoxymethylene derivative **3e**, $M^+ = 275$). The filtrate was submitted to tlc (silica, 0.25 mm, chloroform and methanol, 50:1) and the compound with $R_f = 0.85$ was eluted (17 mg.) and identified as the azide (**1**), identical with the compound obtained as described under A.

Transformation of 2-Azidopyrido[1,2-*a*]pyrimidin-4-one (**1**) in the Presence of Hydrochloric Acid.

A.

A mixture of compound **1** (2.25 g.), ethanol (36 ml.) and concentrated hydrochloric acid (18 ml.) was heated under reflux for 1.5 hours. The reaction mixture was evaporated to dryness. A nmr examination showed that the product was a mixture of 1-(pyridyl-2')-5-carboxymethyltetrazole (**3f**); nmr (deuteriochloroform): $\tau = 1.50$ (m, H₆), 2.0 (m, H_{3,4}), 2.60 (m, H₅), 5.47 (s, CH₂), -0.40 (broad, OH) and 1-(pyridyl-2')-5-carbomethoxymethyltetrazole (**3g**); nmr (deuteriochloroform): τ 1.50 (m, H₆), 2.60 (m, H₅), 2.0 (m, H_{3,4}), 5.50 (s, CH₂COOEt), 5.95 (q, CH₂CH₃), 8.88 (t, CH₂CH₃), $J_{E1} = 7$ Hz). The product was treated with a mixture of chloroform and methanol (30 ml. of 1:1) and after standing at room temperature for 5 days the solvent was evaporated and the product purified by tlc (DC-Fertigplatten alumina T, 1.5 mm, chloroform for development and elution). The product with $R_f = 0.78$ (0.78 g.) was then purified by tlc (six times on silica, 0.5 mm, chloroform for development and elution). The compound with $R_f = 0.36$ (95 mg., 4%) was crystallized from chloroform and *n*-hexane, m.p. 82°. The compound was identified as 1-(pyridyl-2')-5-carbomethoxymethyltetrazole (**3h**). The compound with $R_f = 0.55$ (135 mg.) was crystallized from chloroform (1.5 ml.) and *n*-hexane (3 ml.). It was identified as the starting azido compound (**1**) (20 mg.) and in the filtrate 1-(pyridyl-2')-5-carbomethoxymethyltetrazole (**3g**) was identified.

The following data for compound **3h** were recorded; mass spectrum: M^+ = 219; nmr (deuteriochloroform): τ 1.50 (m, H₆), 2.55 (m, H₅), 2.0 (m, H_{3,4}), 5.50 (s, CH₂), 6.45 (s, CH₃).

Anal. Calcd. for C₉H₉N₅O₂: C, 49.31; H, 4.14; N, 31.95. Found: C, 49.55; H, 4.30; N, 32.05.

B.

Compound **1** (0.5 g.), ethanol (35 ml.) and concentrated hydrochloric acid (2.7 ml.) were heated under reflux for 30 hours. The reaction mixture was evaporated to dryness and sublimed at 130-140°/2-3 mm. The sublimate was dissolved in chloroform, charcoaled and filtered. The filtrate was evaporated to dryness and *n*-hexane was added. The insoluble part was crystallized from chloroform and *n*-hexane and dried *in vacuo* at 45-50° for 30 minutes. The compound was identified as 1-(pyridyl-2')-5-methyltetrazole (**4**), m.p. 72° (yield 0.23 g.); mass spectrum: M^+ = 161; nmr (deuteriochloroform): τ 1.45 (m, H₆), 2.55 (m, H₅), 2.0 (m, H_{3,4}), 7.05 (s, CH₃).

Anal. Calcd. for C₇H₇N₅: C, 52.16; H, 4.38; N, 43.46. Found: C, 52.26; H, 4.58; N, 43.38.

2-Formylhydrazinopyrido[1,2-*a*]pyrimidin-4-one (**5**).

A mixture of 2-hydrazinopyrido[1,2-*a*]pyrimidin-4-one (0.4 g.) and formic acid (5 ml. of 20%) was heated under reflux for 20 minutes. Upon cooling the product which separated was filtered off and crystallized from 20% formic acid (yield 78%), m.p. 246-247°; mass spectrum: M^+ = 204; nmr (DMSO-*d*₆): τ = 4.67 (s, H₃), 1.34 (m, H₆), 2.25 (m, H₉), 2.83 (m, H_{7,8}), 2.0 (s, CHO), 0.5 (broad, NHNH).

Anal. Calcd. for C₉H₈N₄O₂: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.17; H, 4.08; N, 27.36.

Cyclization of 2-Formylhydrazinopyrido[1,2-*a*]pyrimidin-4-one.

The above compound **5** (1.9 g.) was thoroughly mixed with polyphosphoric acid (27 g.) and the mixture was heated at 70-80° for 4 hours. The cooled reaction mixture was treated with water, neutralized with sodium bicarbonate and extracted with chloroform. Upon evaporation of the solvent the product (0.18 g.) (on the basis of the nmr spectrum the product is a mixture of compounds **6** and **7** in a ratio of 1:2) was purified by tlc (DC-Fetig-platten alumina Type E, 0.25 mm, chloroform and methanol, 50:1). The compound with R_f = 0.55 was eluted with methanol, the solution evaporated to dryness and the residue (40 mg.) dissolved in chloroform, charcoaled and filtered. The solvent was evaporated and pure compound **6**, m.p. 94°, was obtained; mass spectrum: M^+ = 160; nmr (deuteriochloroform): τ 2.75 (m,

H_{3',5'}), 2.25 (m, H_{4'}), 1.60 (m, H_{6'}), 1.62 (s, H₃), 7.42 (s, CH₃).

Anal. Calcd. for C₈H₈N₄: C, 59.98; H, 5.03; N, 34.99. Found: C, 59.88; H, 5.12; N, 35.10.

Nmr spectrum of compound **7** (DMSO-*d*₆): τ 2.50 (m, H_{3',5'}), 2.0 (m, H_{4'}), 1.50 (m, H_{6'}), 0.90 (s, H₃), 6.50 (s, 5-CH₂), 5.8 (broad s, OH).

1-(Pyridyl-2')-5-pyrenyl-3-tribromomethyl-1,2,4-triazole (**9**).

2-Hydrazinopyrido[1,2-*a*]pyrimidin-4-one was transformed with benzaldehyde in the hydrazone (**8**) in the usual manner: m.p. 275° (from ethanol and *N,N*-dimethylformamide, 2:1); mass spectrum: M^+ = 264; nmr (DMSO-*d*₆): τ = 4.04 (s, H₃), 1.30 (m, H₆), 2.2-3.2 (m, H_{7,8,9} and Ph), 1.96 (s, CH=N), 7.05 (broad, NH).

To a suspension of the above hydrazone (**8**) (0.66 g.) in acetic acid (10 ml.), sodium acetate (1.5 g.) was added and a 5% solution of bromine in acetic acid was added dropwise. There was no reaction at room temperature and the mixture was heated gradually to 60° when the consumption of bromine could be followed. Simultaneous decarboxylation took place and bromine was added in slight excess. After standing for 10 minutes at 60° the reaction mixture was cooled and poured into ice (30 g.). The product was filtered, suspended in methanol (5 ml.), filtered and crystallized from ethanol, m.p. 203°; mass spectrum: M^+ = 470; nmr (DMSO-*d*₆): τ 1.20 (m, H₆), 1.9 (m, M_{3,4}), 2.25 (m, H₅), 2.57 (s, Ph).

Anal. Calcd. for C₁₄H₉Br₃N₄: C, 35.55; H, 1.92; N, 11.85. Found: C, 35.84; H, 2.33; N, 11.96.

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