Linearly Fused Isoquinolines. Part II (1). The Synthesis of the *s*-Triazolo[4,3-*b*]isoquinoline System

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3-Hydrazinoisoquinoline (**2**) was synthesized *via* its *N*-oxide derivative by removal of the *N*-oxide function with titanium trichloride. Acylation of the hydrazino compound (**2**) led to suitable starting materials (**4** and **6**) for cyclization to the novel, linearly fused ring system: triazolo[4,3-*b*]isoquinoline, which was more stable in the form of its perchlorate salt. The structure of the first representatives of the new ring system was proved by ir, nmr and ms spectroscopy.

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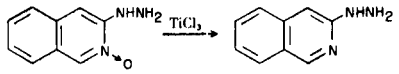
The availability of 3-hydrazinoisoquinoline 2-oxide (**2**) (**1**) prompted us to make efforts for preparing the deoxy compound: 3-hydrazinoisoquinoline (**2**) which seemed to be a convenient starting material for the synthesis of further fused isoquinoline systems. It is noteworthy that due to the extra stability of the halogen atom in the third position of the isoquinoline ring towards nucleophilic attack (3), 3-chloroisoquinoline could not be converted into the corresponding hydrazino compound directly with hydrazine hydrate even under forced conditions.

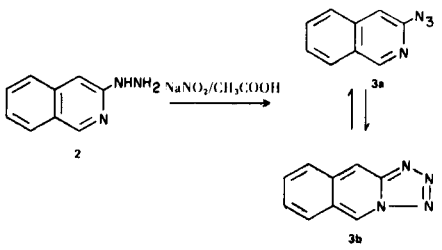
3-Hydrazinoisoquinoline 2-oxide (**1**), however, could be selectively reduced to 3-hydrazinoisoquinoline (**2**); titanium trichloride (4) proved to be a useful reagent for removing the *N*-oxide function with retention of the hydrazino group.

Chart 1



3-Hydrazinoisoquinoline (**2**) obtained in crystalline form is relatively unstable in air, it forms a much more stable dihydrobromide salt, and gives a crystalline hydrazone with benzaldehyde. Its reaction with sodium nitrate in acetic acid led with excellent yield to 3-azidoisoquinoline (**3a**) ⇌ tetrazolo[1,5-*b*]isoquinoline (**3b**) equilibrium described recently (2).

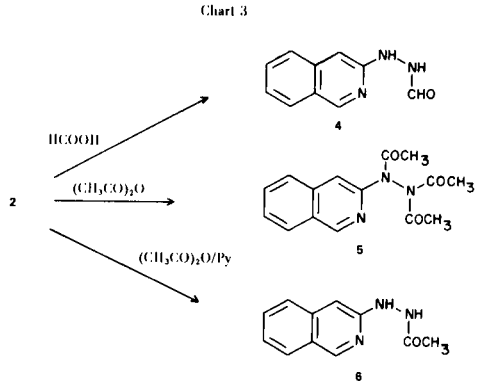
Chart 2



Our attempts to convert 3-hydrazinoisoquinoline (**2**) to an *s*-triazoloisoquinoline under the various conditions described in the literature (5,6) were, however, unsuccessful. Thus, 3-hydrazinoisoquinoline (**2**), on boiling in formic acid, gave only a formylhydrazino compound (**4**) and no cyclization occurred even after a long period of reflux.

While the reaction of the isomeric 1-hydrazinoisoquinoline with boiling acetic anhydride, described by Reimlinger, *et al.*, (7) afforded 3-methyl-*s*-triazolo[3,4-*a*]isoquinoline in high yield, the 3-hydrazino isomer (**2**) in our hands

Chart 3



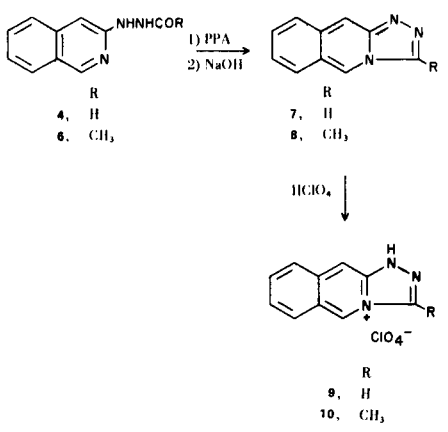
resulted, interestingly, in a triacetyl derivative without any cyclization.

Also the rather general method with triethyl orthoformate did not lead to formation of triazole compound; only tarry material could be obtained.

Successful synthesis of the desired new ring system (**7**) could be carried out from the monoacylhydrazino compounds (**4** and **6**) by cyclization with polyphosphoric acid (PPA).

After extraction of the neutralized reaction mixture of 3-formylhydrazinoisoquinoline (**4**) and PPA with di-

Chart 4



chloromethane, a crystalline product was obtained which slowly decomposed either on storage or by treatment with any common organic solvent. Compound **7** obtained by this way, can be, however, stabilized by conversion into its perchlorate salt (**9**) which can also be obtained directly from the cyclization reaction mixture with perchloric acid.

The evidence of the cyclization was supported by ms, nmr, ir and uv spectroscopy. In the mass spectrum of the neutral product (**7**), the most intense peak corresponds to the molecular ion calculated for the proposed structure. In the nmr spectrum of **9** three singlets (those of H_3, H_5 and H_{10}) are characteristic for the structure of product. The ir spectrum shows disappearance of the C=O band at 1680 cm^{-1} in agreement with cyclization.

Similarly to compound **4**, 3-acetylhydrazinoisoquinoline (**6**) afforded the corresponding 3-methyl-*s*-triazolo[4,3-*b*]isoquinoline (**8**) and its perchlorate salt (**10**), respectively. Comparison of the nmr spectrum of **10** with that of **9** gives further evidence for the structure of the products.

The observed feature of the free base product gives a possible explanation for the unexpected difficulties of the ring closure reaction. The uncharged *s*-triazolo[4,3-*b*]-isoquinoline (**7**) seems to be relatively unstable because of its "quinoide" structure. The electronic structure of the protonated form (**9**), however, partly resembles isoquinoline itself ("benzenoid structure") which might explain its relative stability and ease of formation compared with the uncharged system.

EXPERIMENTAL

Infrared spectra were recorded on a Unicam Sp 200 instrument. Nmr spectra were obtained with a Varian XL-100 spectrometer. Melting points were determined on a Büchi apparatus and are uncorrected.

3-Hydrazinoisoquinoline 2-Oxide (**1**).

This compound was prepared from 3-chloroisoquinoline 2-oxide according to the method in reference (2). 3-Chloroisoquinoline described by Robinson and Robinson (8) was prepared by an improved method.

3-Chloroisoquinoline 2-Oxide.

m-Clorobenzoic acid of 85% purity (20.0 g., 10.0 cmoles) was added to a solution of 3-chloroisoquinoline (10.0 g., 6.1 cmoles) in benzene (100 ml.). The mixture was stirred at room temperature for 6 hours and allowed to stand for 48 hours. Sodium carbonate solution was then added to the mixture, the organic layer was separated, and the water phase was extracted with methylene chloride. The combined fractions were then extracted with sodium carbonate solution, dried and evaporated. The residue was recrystallized from ethyl acetate to yield 7.5 g. (63%) of 3-chloroisoquinoline 2-oxide. This compound was identified by m.p., tlc and ir spectroscopy with the product obtained by the method described in the literature (8).

3-Hydrazinoisoquinoline (2).

A solution of titanium trichloride in hydrochloric acid (13.0 ml., 12.6 mmoles) was added with stirring to an aqueous suspension (5 ml.) of 3-hydrazinoisoquinoline 2-oxide (**1**) (1.0 g., 5.7 mmoles) in 5 minutes at 15-20°. After stirring for an additional 15 minutes, the turbid starting mixture turned to a deep yellow clear solution which was neutralized with an excess of sodium hydroxide solution. Extraction with methylene chloride and evaporation of the organic solvent gave 0.8 g. of solid which was recrystallized from carbon tetrachloride, yield, 0.65 g. (72%), m.p. 94-96°. The pale yellow crystals were found to decompose rapidly, in some days, on exposure to air. It is suggested that the product be stored under vacuum in a refrigerator or in the form of the dihydrobromide salt (see below); ms: m/e (relative intensity) = 159 (M^+, 100), 142 (33), 129 (35), 115 (28); ir (potassium bromide): ν max = 3400-3000, 1620 cm^{-1}; uv (ethanol): λ max = 209 (23,600), 236 (32,000), 286 (8,100), 291 (8,300), 366 (1,960); ^1H nmr (DMSO-d_6): 8.8 (s, 1H, H_1), 7.6-7.1 (m, 4H, H_{5-8}), 6.9 ppm (s, 1H, H_4).

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.69; N, 26.39. Found: C, 67.53; H, 5.86; N, 26.23.

3-Hydrazinoisoquinoline Dihydrobromide.

This compound was prepared in a mixture of glacial acetic acid and hydrogen bromide by trituration with diethyl ether, m.p. 208°, stable, yellow crystals.

Anal. Calcd. for $C_9H_{11}Br_2N_3$: C, 33.67; H, 3.45; Br, 13.08. Found: C, 34.00; H, 3.60; Br, 13.03.

Benzaldehyde 3-Isoquinolylhydrazone.

This compound separated from the combined solutions of the components, forming yellow needles, m.p. 270-271°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.70; H, 5.29; N, 16.99. Found: C, 77.52; H, 5.59; N, 16.82.

Tetrazolo[1,5-*b*]isoquinoline (**3b**).

A solution of 3-hydrazinoisoquinoline (**2**) (0.30 g., 1.9 mmoles) in acetic acid (4 ml.) and water (1 ml.) was treated with a solution of sodium nitrite (0.15 g., 2.2 mmoles) in water (2 ml.) at 0-5°. In 15 minutes, 10 ml. of water was added and the resulting precipitate was filtered. Recrystallization from aqueous methanol gave 0.22 g. (70%) of tetrazolo[1,5-*b*]isoquinoline (**3b**), m.p. 122°. The product was fully identical with that obtained by a method described elsewhere (2).

3-Formylhydrazinoisoquinoline (**4**).

A solution of 3-hydrazinoisoquinoline (**2**) (1.0 g., 6.3 mmoles) in 100% formic acid (10 ml.) was refluxed for 1 hour. After evaporation of the excess of formic acid *in vacuo*, the residue was treated with water to give 0.9 g. (76%) of crude product. After recrystallization from ethyl alcohol, white needles were obtained, m.p. 196-197°. After prolonged reflux for 5 hours the same product can be isolated; ir (potassium bromide): ν max 3150 (NH), 3000, 2900 (CH), 1680 (C=O), 1620, 1590 cm^{-1} (C=C, C=N); nmr (DMSO-d_6): 8.95 (s, 1H, H_1), 8.25 (s, 1H, H_{formyl}), 7.9-7.2 (m, 4H, H_{5-8}), 6.85 ppm (s, 1H, H_4).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.25; H, 4.84; N, 22.45. Found: C, 64.39; H, 4.89; N, 22.14.

3-Acetylhydrazinoisoquinoline (**6**).

To a solution of 3-hydrazinoisoquinoline (**2**) (1.3 g., 8.1 mmoles) in absolute pyridine (8 ml.), acetic anhydride (1 ml., 1.08 g., 10.6 mmoles) was added. On standing at room temperature for 2 hours, the solvent was removed *in vacuo* and the residue was triturated with water. After filtration, 1.3 g. (79%) of crude product was obtained. Recrystallization from ethanol afforded colourless crystals, m.p. 170-172°; nmr (DMSO-d_6): 8.9 (s, 1H, H_1), 7.9-7.2 (m, 4H, H_{5-8}), 6.8 (s, 1H, H_4), 2.0 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51; N, 20.9. Found: C, 65.59; H, 5.84; N, 21.2.

3-*N*,*N*,*N*-Triacetylhydrazinoisoquinoline (**5**).

A mixture of 3-hydrazinoisoquinoline (**2**) (0.5 g., 3.1 mmoles) and acetic anhydride (5 ml.) was heated under reflux for 5 hours. The reaction mixture was separated, the residue taken up in benzene. Slowly, a crystalline material deposited to give 0.35 g. (39%) of product which, after recrystallization from methanol, melted at 115°; ir (potassium bromide): ν max 3000, 2900 (CH), 1730, 1720, 1690 (C=O), 1630, 1590 (C=C, C=N); nmr (DMSO-d_6): 9.1 (s, 1H, H_1), 8.1-7.6 (m, 5H, H_{4-8}), 2.5 (s, 6H, two CH_3), 2.3 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.29; N, 14.73. Found: C, 63.30; H, 5.42; N, 14.56.

s-Triazolo[4,3-*b*]isoquinoline (**7**) and its Perchlorate Salt (**9**).

A mixture of 3-formylhydrazinoisoquinoline (**4**) (0.7 g., 3.7 mmoles) and polyphosphoric acid (7.0 g.) was stirred at 130-135° for 2 hours. The resulting yellow transparent mixture was cooled and mixed with water. Crushed ice was added to the solution and, after careful neutralization with sodium hydroxide, the mixture was rapidly extracted with dichloromethane. Evaporation of the solvent resulted in a pale yellow solid which seemed rather unstable on further handling. Careful recrystallization from dry benzene and petroleum ether afforded pale yellow needles, m.p. 227-228°.

Anal. Calcd. for $C_{10}H_7N_3$: N, 24.83. Found: N, 24.42. Mol. wt. (mass spectrum): Calcd.: 169. Found: 169.

The reaction mixture obtained as described above was treated with water and 70% perchloric acid (0.5 ml.) was added. A crystalline product was separated which, after recrystallization from ethanol, weighted 0.6 g. (56%) m.p. 202-204°. The same compound can be obtained by treating the crude product (**7**) with perchloric acid; nmr (DMSO-d_6): 9.2 (s, 1H, H_5), 8.95 (s, 1H, H_3), 8.15 (s, 1H, H_{10}), 7.8-7.3 ppm (m, 4H, H_{6-9}); ir (potassium bromide): 3000-2500 (=N^+H-), 1640, 1610 (C=C, C=N), 1130-1070 cm^{-1} (ClO_4-).

Anal. Calcd. for $C_{10}H_8ClN_3O_4$: C, 44.54; H, 2.99; N, 15.58. Found: C, 44.89; H, 3.16; N, 15.66.

3-Methyl-*s*-triazolo[4,3-*b*]isoquinoline (**8**) and its Perchlorate Salt (**10**).

Compound **8** was prepared from 150 mg. (**6**) (0.75 mmoles) and 2.0 ml. of polyphosphoric acid by the method described for compound **7**, yield; 110 mg. (52%), m.p. 200°; nmr (DMSO-d_6): 8.8 (s, 1H, H_5), 8.1 (s, 1H, H_{10}), 7.7-7.2 ppm (m, 4H, H_{6-9}).

The perchlorate salt **10** prepared from the reaction mixture with perchloric acid melted at 264-265°.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_4$: C, 46.57; H, 3.55; N, 14.76. Found: C, 46.56; H, 3.65; N, 14.48.

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