Unexpected Formation of a 10*H*-Pyrido[2,3-*h*]pyrazolo[3,4-*b*]quinoline Derivative, A New Ring System

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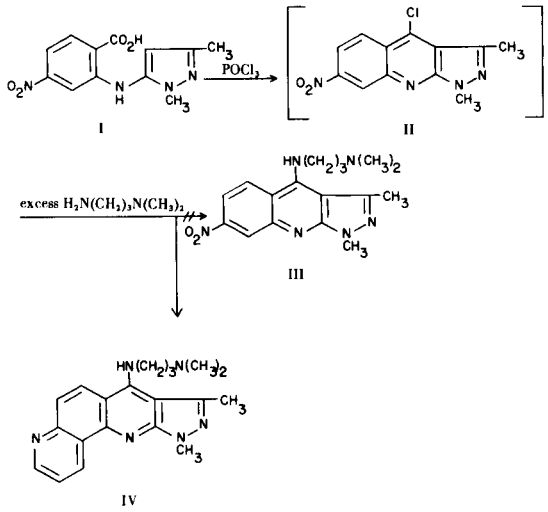
Treatment of *N*-(1,3-dimethylpyrazol-5-yl)-4-anthranilic acid with phosphorus oxychloride gave an intermediate which was condensed with 3-dimethylaminopropylamine to yield 10,8-dimethyl-7-(3-dimethylaminopropylamino)-10*H*-pyrido[2,3-*h*]pyrazolo[3,4-*b*]quinoline (IV). The structure of IV, which represents a previously undescribed ring system, was confirmed by an independent synthesis.

In a study designed to investigate effects of structural changes on biological activity in a series of pyrazolo[3,4-*b*]quinolines, an attempt was made to convert *N*-(1,3-dimethylpyrazol-5-yl)-4-nitroanthranilic acid (I) via the sequence depicted in Scheme 1 to the 7-nitropyrazolo[3,4-*b*]quinoline derivative III. Experimental conditions employed where those which had previously given high yields of a number of variously substituted 1,3-dimethyl-4-(3-dimethylaminopropylamino)-1*H*-pyrazolo[3,4-*b*]quinolines (1). The reaction product in this instance, however, contained none of the expected 7-nitro derivative III. The crude reaction product showed only one major component (IV) dectectable by vpc or tlc analysis. (None of the minor components present corresponded in retention time to an authentic sample of III subsequently prepared as described in reference 1). The pure product isolated from the reaction mixture showed no infrared absorption for a nitro group; nmr proton absorbances were seen for the dimethylpyrazole ring, the side chain diamine, and five aromatic protons. On the basis of a detailed analysis of the splitting pattern of the aromatic protons (*cf.* Experimental), structure IV was proposed for the product. Elemental and mass spectral analyses provided additional support for structure IV. The 10*H*-pyrido[2,3-*h*]pyrazolo[3,4-*b*]quinoline ring system of IV has not been previously described.

Confirmation of the proposed structure IV was provided by the independent synthesis depicted in Scheme 2. The sodium salts of 5-aminoquinoline and 5-chloro-1,3-dimethylpyrazole-4-carboxylic acid (2) were condensed in hexamethylphosphoric triamide to yield the acid V. The acid V then was elaborated in good yield to a product identical with that obtained from Scheme I.

Scheme 1



We suggest that formation of IV occurred from II via a Skraup type mechanism. It seems likely that the nitro intermediate II and 3-dimethylaminoproyplamine undergo redox reactions under the experimental conditions to form intermediates analogous to those present in a Skraup quinoline synthesis (3). A redox mechanism has been postulated to account for the observation that 6-nitrocoumarin can replace 6-aminocoumarin as a substrate in a Skraup synthesis (4).

EXPERIMENTAL (5)

1,3-Dimethyl-5-(quinol-5-yl)aminopyrazole-4-carboxylic Acid (V).

A mixture under nitrogen of 5-aminoquinoline (4.50 g., 0.031 mole) and sodium hydride (0.031 mole) in hexamethylphosphoric

triamide (40 ml.) was stirred at 42° for 2.5 hours. Similarly, 5-chloro-1,3-dimethylpyrazole-4-carboxylic acid (2) (5.45 g., 0.031 mole) and sodium hydride (0.031 mole) were stirred in hexamethylphosphoric triamide (40 ml.) at 20° for 2 hours. The two salt solutions were mixed and stirred at 122° for 16 hours under nitrogen.

The reaction solution was concentrated to about 50 ml. at 0.1 mm, and then was diluted to about 500 ml. with water. The mixture was extracted several times with chloroform, and then was cooled, treated with aqueous 1*N* hydrochloric acid (31.2 ml.), and stored at 0° for 64 hours. Filtration yielded V (0.51 g., 6%), m.p. 179-182° dec. An aliquot was recrystallized from 1-propanol to yield an analytical sample, m.p. 188.5-189.5° dec.; nmr (TFA): δ 2.83 (s, 3, C-CH_3), 3.57 (s, 3, N-CH_3), 7.82 (m, 1, H_6, $J_{6,7}$ = 6 Hz, $J_{6,8}$ = 2 Hz), 8.1-8.5 (m, 3, H_3, H_7, H_8), 9.12 (s, 1, NH), 9.26 (m, 1, H_2, $J_{2,3}$ = 5 Hz, $J_{2,4}$ = 1 Hz), 9.62 (m, 1, H_4, $J_{4,3}$ = 8 Hz); mass spect (70 eV) m/e 282(M^+).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.84. Found: C, 63.86; H, 5.07; N, 19.81.

10,8-Dimethyl-7-(3-dimethylaminopropylamino)-10*H*-pyrido-[2,3-*h*]pyrazolo[3,4-*b*]quinoline (IV).

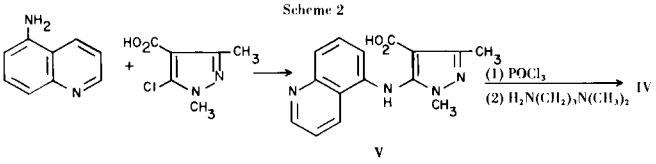
A. Scheme 1.

A mixture of *N*-(1,3-dimethylpyrazol-5-yl)-4-nitroanthranilic acid (1) (15.00 g., 0.054 mole) and phosphorus oxychloride (150 ml.) was heated at reflux for 2 hours. Excess phosphorus oxychloride was evaporated (5 mm) and the residue was treated cautiously while cooling with 3-dimethylaminopropylamine (150 ml.). The mixture was stirred uneventfully at 25° for about 10 minutes. Heating then was initiated, and after a few minutes, an exothermic reaction occurred. When this had subsided, the mixture was heated at 130° for 16 hours. The cooled reaction mixture was concentrated at 5 mm to a syrup which was dissolved in chloroform, and the resulatnt solution washed in succession with aqueous 5% sodium carbonate solution, water and saturated brine solution. Drying (sodium sulfate) and evaporation left an oil (26 g.). Chromatography on alumina (elution with 98:2 dichloromethane:ethanol) yielded 5.30 g. (28%) of IV; recrystallization (nitromethane) gave material of constant m.p. 137-138.5°; nmr (deuteriochloroform): δ 1.94 (m, 2, $CH_2CH_2CH_2$), 2.39 (s, 6, $N(CH_3)_2$), 2.65 (t, 2, $CH_2N(CH_3)_2$), 2.81 (s, 3, C-CH_3), 3.90 (m, 2, $HNCH_2$), 4.17 (s, 3, pyrazole NCH_3), 7.5 (broad, 1, NH; exchangeable), 7.56 (m, 1, H_2, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 4.5 Hz), 7.69 (d, 1, H_5, $J_{5,6}$ = 10 Hz), 8.11 (d, 1, H_6), 8.98 (m, 1, H_3, $J_{1,3}$ = 1.5 Hz), 9.60 (m, 1, H_1); mass spect (70 eV) m/e 348 (M^+).

Anal. Calcd. for $C_{20}H_{24}N_6$: C, 68.94; H, 6.94; N, 24.12. Found: C, 68.36; H, 7.19; N, 24.25.

B Scheme 2.

Scheme 2



V

A mixture of the acid V (400 mg., 1.41 mmoles) and phosphorus oxychloride (15 ml.) was heated at reflux for 2.3 hours. The mixture was concentrated at 5 mm to a semi-solid which was cooled and treated with 3-dimethylaminopropylamine (20 ml.). The resultant mixture was heated at 115° for 16 hours, and then was worked up as described above. Chromatography on alumina (elution with 98:2 diethyl ether:ethanol) yielded IV (0.36 g., 73%). Two recrystallizations (nitromethane) gave material of constant m.p. 138-140°; identical (ir, nmr, mixture m.p., mixture vpc analysis) with IV prepared as described above.

REFERENCES AND NOTES

(1) R. R. Crenshaw, G. M. Luke and P. Siminoff, *J. Med. Chem.*, in press.

(2) D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **36**, 2542 (1971).

(3) *Cf.* R. H. F. Manske and M. Kulka, *Organic Reactions*, **7**, 59 (1953).

(4) B. B. Dey and M. N. Goswami, *J. Chem. Soc.*, **115**, 531 (1919).

(5) Melting points are capillary and are uncorrected. Nmr spectral data were obtained using a Varian HA-100 spectrometer. In refering to nmr data for aromatic protons, H_n represents the hydrogen attached to carbon number *n* in the parent molecule. Mass spectral data were obtained on a LKB 9000 mass spectrometer.