A Novel Dehydrogenation Occurring During the Synthesis of the New Heterocyclic System 1*H*-Pyrazolo[3,4-*b*][2,7]naphthyridin-8-one

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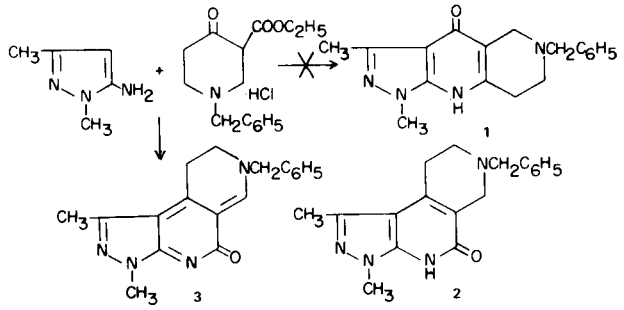
1,3-Disubstituted-5-aminopyrazoles and *N*-alkyl-3-carbethoxy-4-piperidones condense in refluxing acetic acid to give 1,3,6-trisubstituted 4,5-dihydro-1*H*-pyrazolo[3,4-*b*][2,7]naphthyridin-8(6*H*)ones (a new heterocyclic system) with loss of one molecule of hydrogen.

We have discovered that an interesting dehydrogentation occurs in the synthesis of the new heterocyclic system - pyrazolonaphthyridine.

In order to synthesize amino substituted pyrazolopyridines, we condensed 1,3-dimethyl-5-aminopyrazole with 1-benzyl-3-carbethoxy-4-piperidone hydrochloride in boiling acetic acid expecting either **1** or **2**.

Scheme I



Examination of the ir and nmr spectra showed that neither **1** nor **2** could be the structure of the product. No NH or OH peaks were present. Nmr showed CH_2CH_2, but only one CH_2N. An unexpected olefinic proton appeared at δ = 8.70 ppm. In addition, the mass spectrum showed the empirical formula to be $C_{18}H_{18}N_4O$. All this evidence showed that a loss of 2*H* occurred from the expected product.

This could either support structure **3** or a linear isomer (related to **1**). There are conflicting reports in the literature on whether 5-aminopyrazoles condense with β-keto esters to give pyrazolopyridines which are lactams or ketones. Tabak (1) reports that 5-amino-3-methyl-1-phenylpyrazole condenses with ethyl acetoacetate in refluxing acetic acid to give a pyrazolopyridine with a lactam structure (related to **2** and **3**). Dorn and Zubek (2) report that 5-amino-1-methylpyrazole and ethyl acetoacetate condense in refluxing acetic acid to give a pyrazolopyridine with a keto structure (related to **1**). However, in the accompanying paper, Swett and Ratajczyk (3) show that Dorn and Zubek are incorrect and that their compound also has the lactam structure.

C-13 nmr spectroscopy strongly favors structure **3**. The carbonyl carbon is expected to have the largest chemical shift (from TMS). The largest chemical shift of our compound is 164.5 ppm in either deuteriochloroform or DMSO. This compares favorably with 4-methyl-2-quinolone (δ = 162.3 DMSO) but not 2-methyl-4-quinolone (δ = 177.9 DMSO).

On the basis of the above work, we assign structure **3** to our compound. The possible intermediate **4** could air oxidize to **3** because a decrease in energy owing to increased π conjugation would occur.

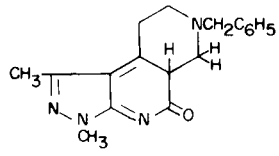


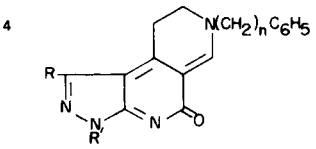
Table I shows the various analogs of **3** prepared at our laboratories. Several of these compounds showed anti-inflammatory activity. As a side note, we have shown that phenyl substituted 5-aminopyrazoles can be smoothly hydrogenated to cyclohexyl pyrazoles with no reduction of the pyrazole ring. Aminopyrazoles with a cyclohexyl group in the 3 position (3-cyclohexyl-1-methyl-5-aminopyrazole) fail to condense with our keto ester.

EXPERIMENTAL

All melting points were taken on a Thomas Hoover apparatus and are uncorrected. The ir spectra were recorded on a Perkin

TABLE I

4,5-Dihydro-1*H*-pyrazolo[3,4-*b*][2,7]naphthyridin-8(6H)ones



R	R′	n	M.p.	Formula	Cryst. Solvent	% Yield	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	1	139-141	$C_{18}H_{18}N_4O$	Chloroform-ether	30	70.50	5.92	18.21	70.36	5.74	18.12
CH_3	C_6H_5	1	146-148	$C_{23}H_{20}N_4O$	Ethanol	36	74.98	5.47	15.21	75.22	5.59	15.46
H	CH_3	1	148-150	$C_{17}H_{16}N_4O$	Chloroform-ether	40	69.84	5.52	19.17	70.02	5.34	19.18
H	C_6H_5	1	134-136	$C_{22}H_{18}N_4O$	Ethanol-ether	26	74.55	5.12	15.81	74.49	5.04	15.63
H	C_6H_{11}	1	144-146	$C_{22}H_{24}N_4O$	Ethanol-ether	27	73.55	6.71	15.55	73.30	6.74	15.75
CH_3	C_6H_{11}	1	167-169	$C_{23}H_{26}N_4O$	Ethanol	43	73.77	7.00	14.96	73.53	7.21	15.14
CH_3	CH_3	2	112-114	$C_{19}H_{20}N_4O$	Chloroform-ether	30	71.22	6.29	17.49	71.28	6.30	17.56
CH_3	$CH_2CH_2CH(CH_3)_2$	1	105-109	$C_{22}H_{26}N_4O$	Ether	25	72.90	7.23	15.46	73.01	7.19	15.40

Elmer 521 spectrophotometer, H-nmr on a Varian T-60 in deuterochloroform, mass spectrum on an AEI-MS902, and C-13 nmr spectra were recorded on a Bruker HFX-10-90MHz spectrometer with a Fabritek 1070/PDP-8 Fourier transform accessory. All new compounds had nmr and ir spectra consistent with their structures.

The preparation of the following 5-aminopyrazoles is described in the literature: 1,3-dimethyl (4), 1-methyl (5), 3-methyl-1-phenyl (4), and 1-isopentyl-3-methyl (6). 5-Amino-1-phenylpyrazole as well as the keto esters were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.

5-Amino-1-cyclohexylpyrazole.

5-Amino-1-phenylpyrazole (5.30 g.) in 200 ml. of ethanol was hydrogenated at 43 psi at 60° with 2.0 g. 5% rhodium-alumina. When uptake of hydrogen was complete, the catalyst was removed, and the solution distilled to give 4.10 g. product, b.p. 128-129/0.4 mm, m.p. 75-78°.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.40; H, 9.15; N, 25.43. Found: C, 65.64; H, 8.91; N, 25.30.

5-Amino-1-cyclohexyl-3-methylpyrazole.

5-Amino-3-methyl-1-phenylpyrazole (5.20 g.) was treated as above. The product was crystallized from hexane and ehtanol to give 4.29 g. product, m.p. 119-122°.

Anal. Calcd. for $C_{10}H_{17}N_3$: C, 67.00; H, 9.56; N, 23.44. Found: C, 67.20; H, 9.30; N, 23.47.

6-Benzyl-1,3-dimethyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*][2,7]-naphthyridin-8(6*H*)one.

5-Amino-1,3-dimethylpyrazole (11. g., 0.10 mole), 1-benzyl-3-carbethoxy-4-piperidone hydrochloride (29.7 g., 0.10 mole) and 60 ml. acetic acid were refluxed 2 hours, then 10 ml. solvent was distilled at atmospheric pressure, and the remainder refluxed overnight. The solvent was stripped in vacuum and the residue partitioned between sodium carbonate solution and chloroform. The chloroform layer was filtered from a small amount insoluble matter, concentrated and crystallization was initiated by adding ether, giving 9.30 g. product, (30% yield) m.p. 139-141°; ir spectrum showed no NH, and C=O at 1630 cm^{-1}; nmr (δ ppm): 2.53 (C-CH_3), 3.00-3.80 (CH_2CH_2), 4.01 (N-CH_3), 4.83 ($C_6H_5CH_2$), 7.25 (C_6H_5), 8.70 (=CH-N); Mass spectrum: m.w. 306.146, calcd. 306.147.

All other compounds of Table I were synthesized in a manner similar to the above.

Acknowledgments.

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