About the Structure of Two Isomeric Pyrazoloquinolines

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Several structures are possible for the pyrazoloquinolines, formed in the Skraup synthesis from 5- or 6-aminoindazole. By nmr spectroscopic examination in the presence of shift reagents it was possible to assign the correct structures for both products, *i.e.*, the angular 1*H*-pyrazolo-[3,4-*f*]quinoline (**4**) and 3*H*-pyrazolo[4,3-*f*]quinoline (**2**).

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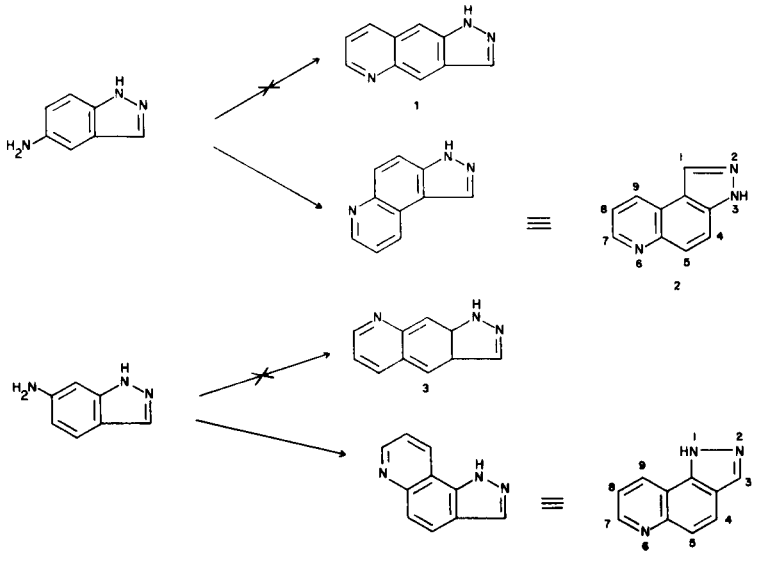
As a continuation of our work on indazoles (1,2) and heterocycles derived thereof, we like to report on the synthesis and structural assignment of two isomeric pyrazoloquinolines (pyridoindazoles).

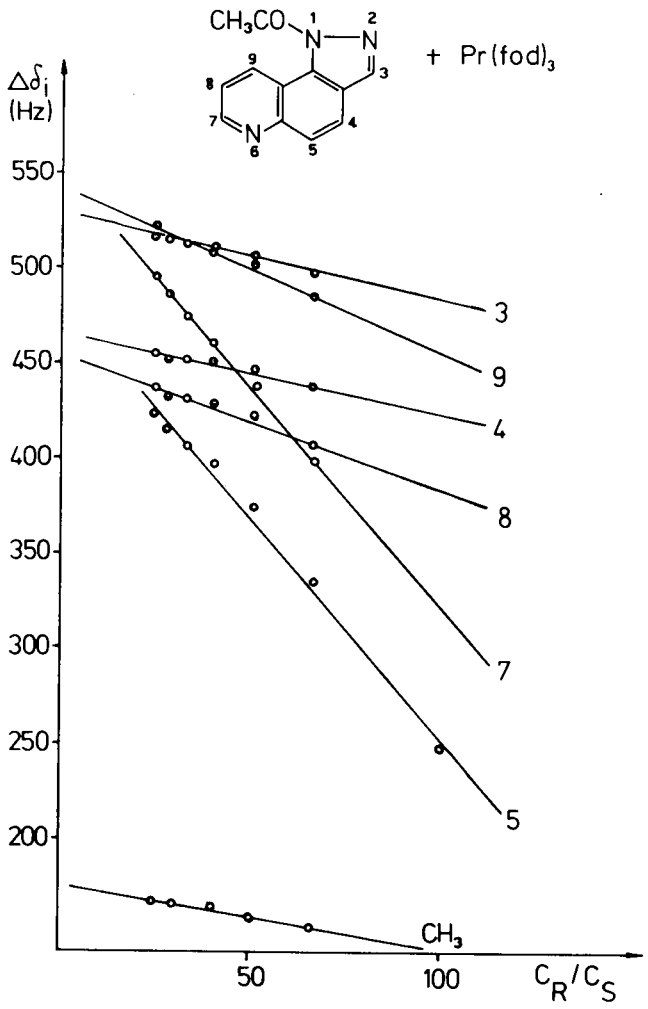
5- And 6-aminoindazole, when submitted to the Skraup synthesis, afforded in each case only one product. For these two products four structures are theoretically possible, the linear (**1** or **3**) or the angular ones (**2** or **4**). It has been reported (3) that 6-aminoindazole undergoes the Skraup synthesis and to the product the structure of 1*H*-pyrazolo[3,4-*f*]quinoline (**4**) has been assigned without structural proof. In a similar manner, it has been postulated that the formation of a fused pyridine ring, starting from 5-amino-2-methylbenzothiazole (4) or 5-aminobenzo-1,2,3-thiadiazole (5), takes place in such a manner to give only the angular heterocycles. The isomeric ring system (**2**), as a dihydro derivative, has also been synthesized, yet another synthetic approach has been used (6,7).

For the preparation of the tricyclic systems the Skraup synthesis, either the general method in the presence of nitrobenzene, or the modified method with sulfomix (8,9), have been attempted. The results were not satisfactory and an adaptation of the method with the use of arsenic acid (3) has been found to give the best results. The starting 5-aminoindazole was best prepared by hydrogenation of the corresponding 5-nitro compound in the presence of Raney nickel. The preparation of 5-aminoindazole was reported earlier in the literature, but the yields were poor when applying chemical reduction (3, 10) or, in addition, chlorination takes place if stannous chloride is used as reducing agent (3).

The so obtained 1*H*-pyrazolo[3,4-*f*]quinoline (**4**) and 3*H*-pyrazolo[4,3-*f*]quinoline (**2**) were acetylated in order to examine the acetyl derivatives by nmr in the presence of shift reagents. Acetylation of compound (**4**) with acetic anhydride in the presence of pyridine afforded the antic-

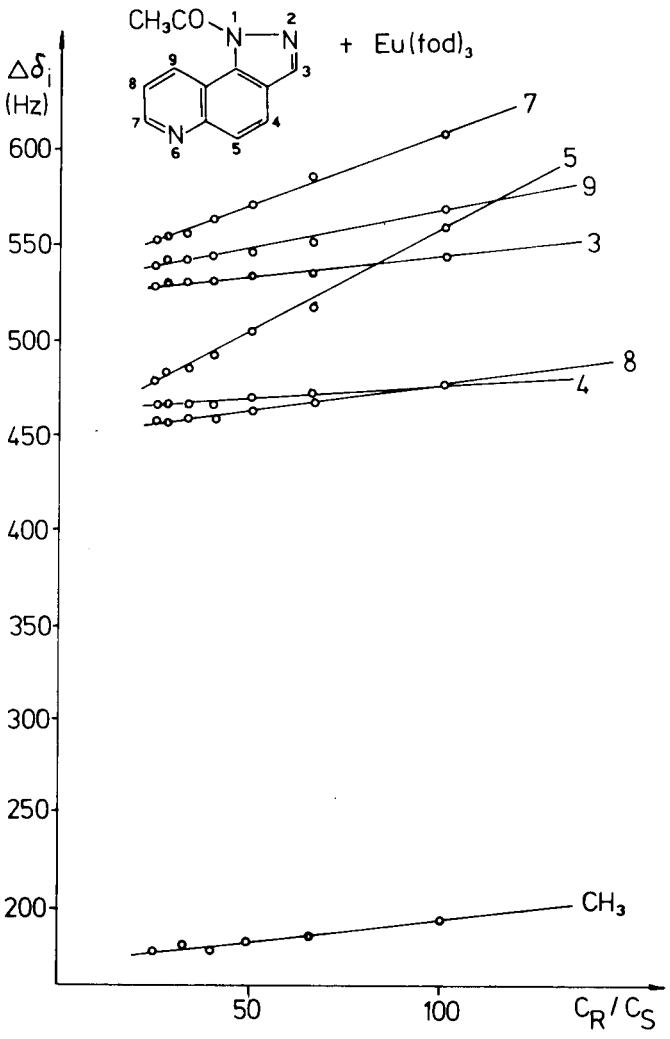


ipated 1-acetyl derivative. However, similar experiments with the isomeric tricycle (**2**) afforded a mixture of the 2-acetyl and 3-acetyl derivatives in the ratio of about 2:1, as established by nmr examination. The 2-acetyl derivative is soluble in chloroform and was thus separated from the other isomer. The structure of the acetyl



derivatives are substantiated by the following observations. Acetylation of compound **4** at N_1 is evidenced by an upfield shift for H_9 for about 0.5 ppm as compared to the parent compound. The structure for the 2-acetyl derivative of compound **2** follows from the observation that the signal for H_1 is shifted downfield for about 0.4 ppm, whereas the chemical shift for H_4 remains unchanged. In the case of the 3-acetyl derivative of **2** the signal for H_1 is shifted for about 0.1 ppm, but that for H_4 is shifted for 0.8 ppm downfield.

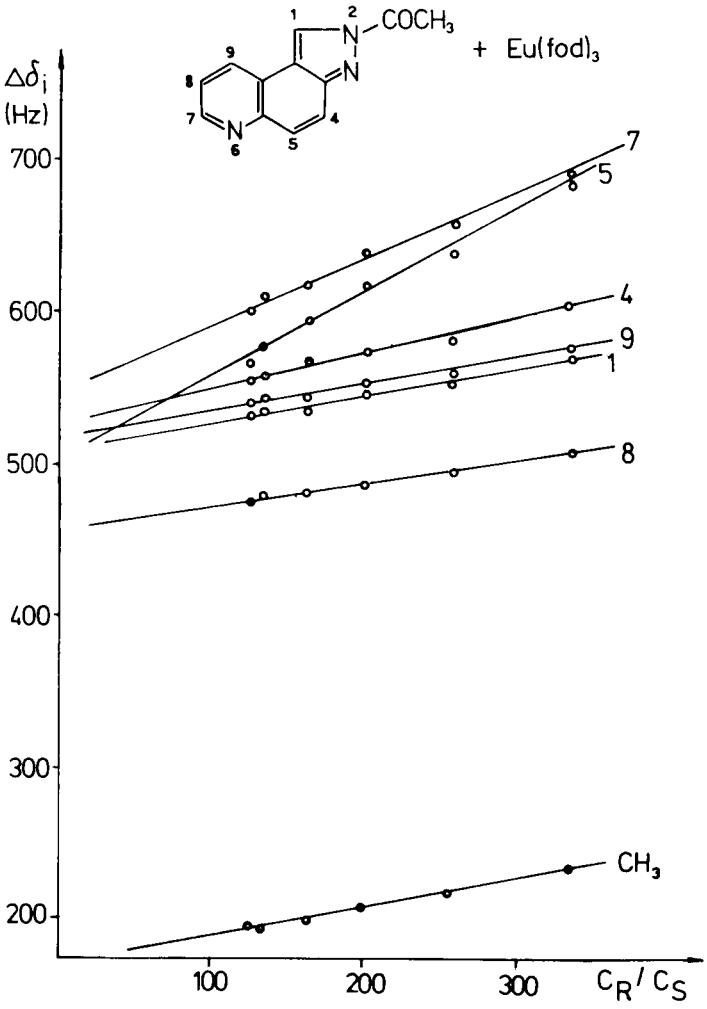
Since the introduction of nmr shift reagents many structural problems have been satisfactorily solved (11). Attempts to analyze the nmr spectra of both isomeric pyrazoloquinolines were severely hampered by the ex-



corresponding acetyl derivatives. The nmr spectra of these compounds were recorded after successive addition of small portions of the examined compounds to the solutions of lantanide salt, $Eu(fod)_3$ (12) or $Pr(fod)_3$ (13). The dependence of induced chemical shifts ($\Delta\delta_i$) on changes in concentration of the investigated compound (C_S) and lantanide shift reagent (C_R) are given in Fig. 1, 2 and 3. The addition caused increased chemical shift separation so that each proton could be analyzed in detail.

2-Acetylpyrazolo[4,3-*f*]quinoline is complexed with the lantanide shift reagent at the pyridine ring nitrogen at position 6 since the biggest difference in chemical shift is observed for protons at positions 5 and 7. In a similar manner, 1-acetylpyrazolo[3,4-*f*]quinoline is complexed with the pyridine nitrogen at position 6. Here again, the greatest change in chemical shifts was observed for protons at positions 5 and 7.

The most significant result of the nmr analysis is



system the signals for H_4 and H_5, which appeared in the normal nmr spectrum either as a broadened singlet or a straightforward assignment was not possible, become separated in the presence of shift reagents in two well defined doublets. The observed coupling constant, $J_{4,5}$ = 9.0-9.2 Hz is characteristic for two ortho protons and this eliminates the alternative linear structures (**1** and **3**) for both heterocycles. Thus, the correct structure for 1*H*-pyrazolo[3,4-*f*]quinoline (**4**) and 3*H*-pyrazolo[4,3-*f*]-quinoline (**2**) is the angular one.

EXPERIMENTAL (14)

5-Aminoindazole.

A mixture of 5-nitroindazole (3.0 g.), palladized carbon (0.3 g. of 10%) and ethanol (250 ml.) was hydrogenated at 40 psi for 3 hours. Upon filtration, the filtrate was evaporated to dryness and the product was crystallized from water, m.p. 179-180° (yield 2.5 g.) (lit. (3) gives m.p. 181°).

3*H*-Pyrazolo[4,3-*f*]quinoline (**2**).

A mixture of 5-aminoindazole (4.0 g.), concentrated sulfuric acid (4.75 ml.), glycerol (9.4 g.) and arsenic trioxide (4.35 g.) was heated at 136-140° for 7 hours. The cold reaction mixture was treated with water (300 ml.), filtered, concentrated ammonia was added until alkaline reaction and the mixture was left to stand for 12 hours. The product was filtered off, dried and sublimed at 200-210°/0.1 mm. Upon crystallization from ethanol the pure compound had m.p. 196-198° (yield 1.1 g.); mass spectrum: M^+ 169; nmr (DMSO-d_6): τ = 1.20 (s, H_1), 2.05 (deg. dd, H_4, H_5), 0.96 (dd, H_7, partial overlap with H_9), 2.34 (dd, H_8), 1.08 (dd, H_9, partial overlap with H_7), $J_{7,8}$ = 4.0, $J_{8,9}$ = 8.2, $J_{7,9}$ = 1.8 Hz.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.69; H, 4.43; N, 24.44.

The compound (0.48 g.) when dissolved in pyridine (6 ml.) and treated with acetic anhydride (0.4 g.) at room temperature for 24 hours, was transformed into a mixture of 3-acetyl and 2-acetyl derivatives in a ratio of about 1:2 as determined by nmr analysis; nmr spectrum of the 3-acetyl derivative (DMSO-d_6): τ = 1.05 (s, H_1, partial overlap with H_9), 1.25 (d, H_4), 1.80 (d, H5),).84 (dd, H_7), 2.14 (dd, H_8), 1.02 (dd, H_9, partial overlap with H_1), 7.17 (s, CH_3), $J_{4,5}$ = 9.2, $J_{7,8}$ = 4.0, $J_{8,9}$ = 8.2, $J_{7,9}$ = 1.8 Hz. The 2-acetyl derivative had m.p. 145° (from ethanol); mass spectrum: M^+ 211; nmr (deuteriochloroform): τ = 0.84 (s, H_1), 2.16 (deg. dd, H_4, H_5), 1.12 (dd, H_7), 2.52 (dd, H_8), 1.45 (dd, H_9), 7.13 (s, CH_3), $J_{7,8}$ = 4.0, $J_{8,9}$ = 8.2, $J_{7,9}$ = 1.8, $J_{4,5}$ = 9.2 Hz (determined after addition of shift reagent).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.06; H, 4.57; N, 19.99.

1*H*-Pyrazolo[3,4-*f*]quinoline (**4**).

The compound was prepared in the same manner as described above for the isomeric tricycle (**2**). The crude product was sublimed at 210-222°/0.1 mm. and then crystallized from ethanol, m.p. 233-235° (lit. (3) gives m.p. 278°) (yield 0.7 g.); mass spectrum: M^+ 169; nmr (DMSO-d_6): τ = 1.62 (s, H_3), 2.36 (d, H_4), 1.95 (d, H_5), 1.0 (dd, H_7, partial overlap with H_9), 2.30 (dd, H_8), 1.06 (dd, H_9, partial overlap with H_7), $J_{4,5}$ = 9.0, $J_{7,8}$ = 4.0, $J_{8,9}$ = 8.2, $J_{7,9}$ = 1.8 Hz.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.01; H, 4.55; N, 24.94.

The compound was transformed into the 1-acetyl derivative in a similar manner as described above for the isomeric system, m.p. 184-187° (from ethanol); mass spectrum: M^+ 211; nmr (deuteriochloroform): τ = 1.50 (s, H_3), 1.90 (d, H_4), 1.27 (d, H_5), 1.02 (dd, H_7), 2.51 (dd, H_8), 1.50 (dd, H_9), 7.20 (s, CH_3), $J_{4,5}$ = 9.2, $J_{7,8}$ = 4.0, $J_{8,9}$ = 8.2, $J_{7,9}$ = 1.8 Hz.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.20; H, 4.40; N, 20.09.

Nmr Measurements.

A solution of 1 g. of $Eu(fod)_3$ (12) or $Pr(fod)_3$ (13) in 10 ml. of deuteriochloroform was prepared. In a nmr tube 0.2 ml. of the shift reagent was placed and 0.2 ml. of the investigated compound. The nmr spectrum was recorded, 0.1 ml. of the solution of the investigated compound was added and the spectrum recorded again. This procedure was repeated 6 times. The investigated compounds were used in the following quantities (dissolved in 1 ml. of deuteriochloroform): 2-acetylpyrazolo-[4,3-*f*]quinoline (42.188 mg. for experiments with $Eu(fod)_3$); 1-acetylpyrazolo[3,4-*f*]quinoline: 42.190 mg. for $Eu(fod)_3$ and

42.244 mg. for $Pr(fod)_3$ measurements. The dependence of chemical shifts of the investigated compounds are presented in Figures 1, 2 and 3.

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(11) R. E. Sievers, "Nuclear Magnetic Resonance Shift Reagents", Academic Press, 1973.

(12) $Eu(fod)_3$ = tris europium (III) chelate of the anion of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione.

(13) $Pr(fod)_3$ = tris praseodymium (III) chelate of the anion of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione.

(14) All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L instrument.