Configurational and Conformational Isomerism in 2-γ-Picolinylidene-indolin-3(2*H*)-one Derivatives

By **K. N. Kilminster** and **M. Sainsbury,*** School of Chemistry and Chemical Engineering, Bath University, Claverton Down, Bath, Somerset

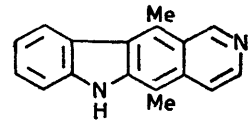
The reaction between indolin-3-one and 4-acetylpyridines gives rise to configurational and rotational isomers. Potential-energy barriers to rotation are calculated and the n.m.r. spectra of a number of derivatives are interpreted.

In the course of studies towards the synthesis of the alkaloid ellipticine (1),[1] 1-acetylindol-3-yl acetate was treated with the 4-acetylpyridine (2; R = OMe). Two products, green needles (m.p. 180—181°) and orange rods (m.p. 181—182°), were formed and separated by hand. Both products have the same electronic spectrum and mass spectrometry indicates them to be isomers of the molecular formula, $C_{18}H_{18}N_2O_2$. The orange substance is allocated structure (3; R = OMe), while the green isomer is represented as (4; R = OMe).

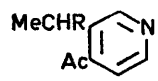
These assignments may be made with confidence, since in the former compound the methyl group joined to the double bond lies in the deshielding zone of the carbonyl function, and in the n.m.r. spectrum ($CDCl_3$) of the orange product the signal due to the olefinic methyl group is observed at lower chemical shift (δ 2·6 p.p.m.) than that of the corresponding resonance in the spectrum of the green material (δ 2·2 p.p.m.).

Figure 1A illustrates the n.m.r. spectrum of the green isomer (4; R = OMe) recorded at 36° and Figure 1B shows the high field portion of the spectrum of this compound measured at 87°. These results are rationalized as follows. Since the pyridine nucleus of the molecule (4; R = OMe) bears an asymmetric substituent,

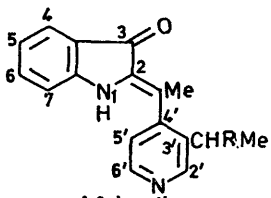
[1] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.



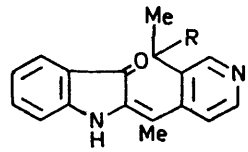
(1)



(2)



(3)



(4)

it is clear that restricted rotation about the single bond between the pyridyl group and the enone system allows diastereoisomerism at the lower temperature. As the temperature is increased this second chiral feature is gradually eliminated, until the observed spectrum becomes that of the racemate.

A similar phenomenon is observed in the case of the orange material (3; R = OMe) and, from the results of variable temperature experiments, it is possible to calculate the potential-energy barriers to rotation in both samples from the Arrhenius equation $k = k_0\exp(-E_a/RT)$, where the constants E_a (potential-energy barrier) and k_0 (frequency factor) can be deduced from the temperature-dependence of the n.m.r. spectra using the Gutowsky–Holm expression.[2] Thus for the (*Z*)-isomer (3; R = OMe) $E_a = 75{\cdot}4$ kJ mol^{-1} and for the (*E*)-isomer (4; R = OMe) $E_a = 77{\cdot}5$ kJ mol^{-1}.

In the reaction between 1-acetylindol-3-yl acetate and 4-acetyl-3-ethylpyridine (2; R = H), only one isomer (3; R = H) was isolated. Diastereoisomerism is not possible in this product and the interpretation of the observed n.m.r. spectrum is straightforward, in particular the olefinic methyl resonance appears as a 3-proton singlet (δ 2·56 p.p.m.).

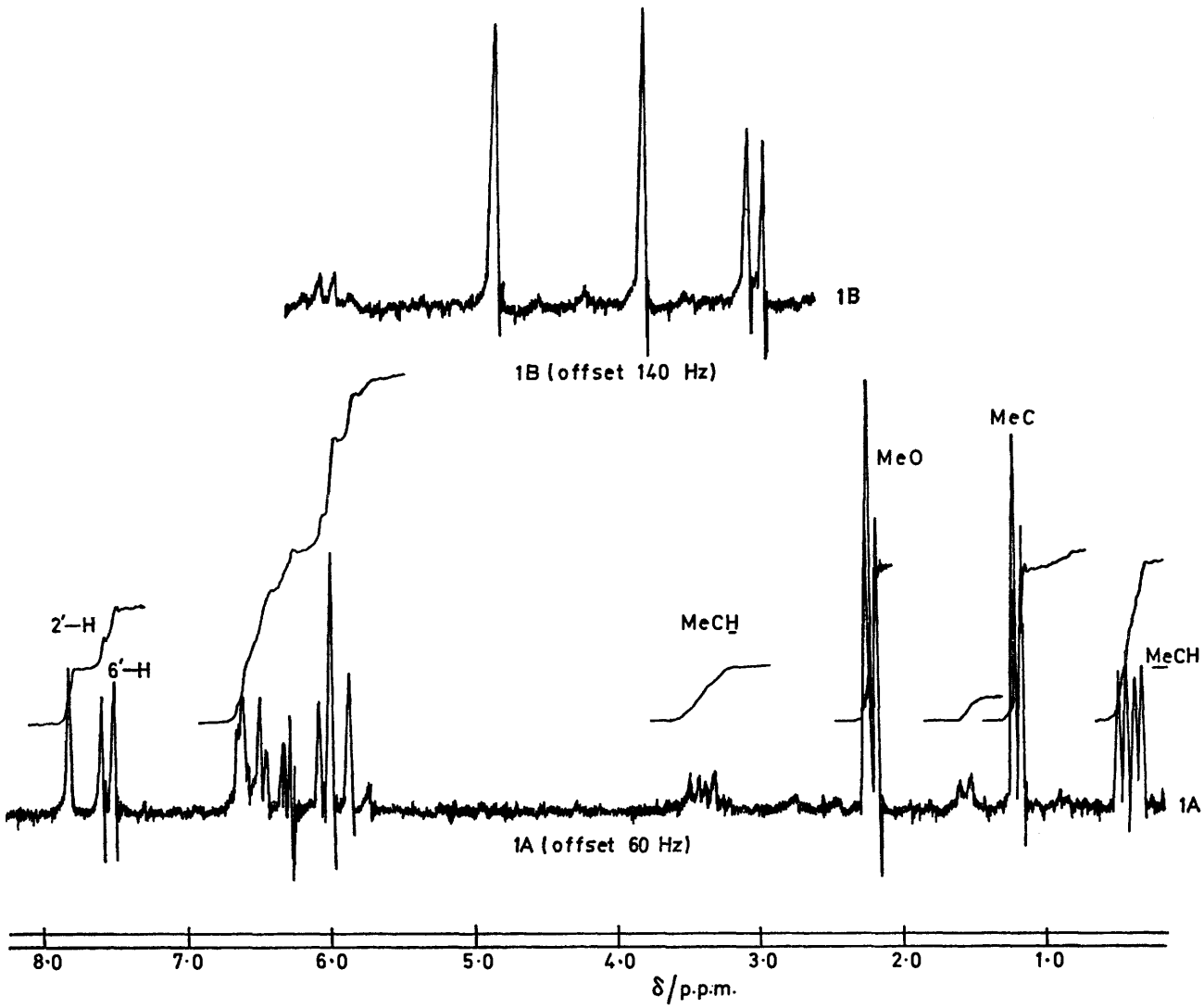


FIGURE 1

[2] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

When either isomer (3; R = OMe) or (4; R = OMe) is reduced with sodium borohydride in aqueous ethanol, the indole (5; R = OMe) is obtained. The n.m.r. spectrum of this substance shows that it is an equimolar mixture of two diastereomorphs, but this time the spectrum is unchanged by an increase * in temperature (see Figure 2).

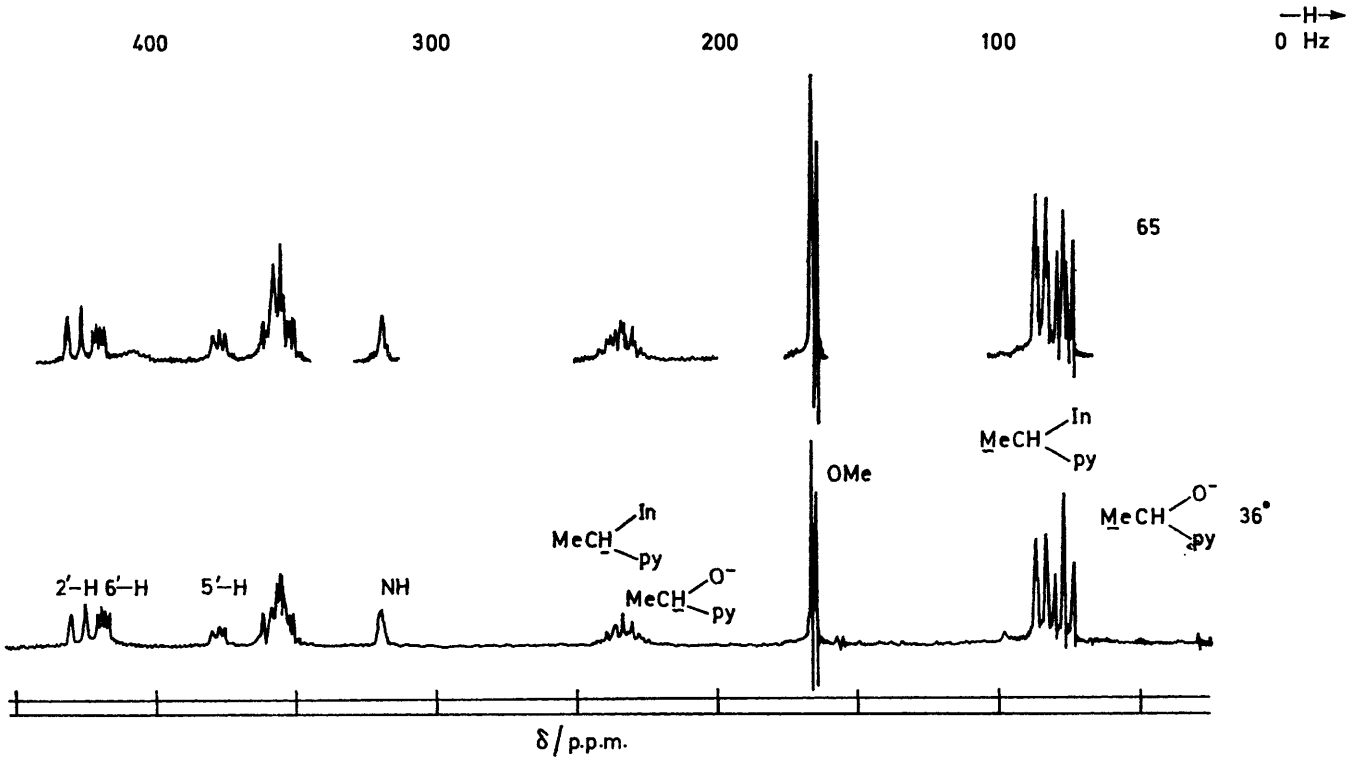
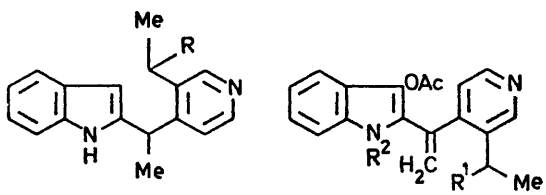


FIGURE 2

Since the proposed structure (5; R = OMe) for this indole contains two asymmetric carbon atoms the reason for the diastereoisomerism is obvious and, in



(5) (6)

confirmation, it is significant that the n.m.r. spectrum of the indole (5; R = H) gives no evidence of isomers being present.

When either indolinone (3; R = OMe) or (4; R = OMe) is treated with acetic anhydride and triethylamine the rigid enone system is destroyed and a single product, the racemic *O*-acetate (6; R^1 = OMe, R^2 = H), is formed. The *NO*-diacetate (6; R^1 = OMe, R^2 = Ac) may also be isolated from these reactions and it is interesting that the signals due to the exocyclic methylene protons in the n.m.r. spectrum of this molecule appear as doublets at δ 5·66 and 5·75 p.p.m. (*J* 1·2 Hz), whereas the acetoxy methyl resonance is a singlet δ 2·27 p.p.m. [Corresponding signals in spectrum of the indole (6; R^1 = H, R^2 = Ac) are as follows: exocyclic methylene protons δ 5·70 and 5·76 (both d, *J* 1·1 Hz), acetoxymethyl 2·24 p.p.m.]. In the n.m.r. spectrum of the *O*-acetate (6; R^1 = OMe, R^2 = H) the exocyclic methylene protons resonate as singlets at δ 5·32 and 5·84 p.p.m., whereas the acetoxymethyl protons give rise to a singlet at δ 1·96 p.p.m. [In the n.m.r. spectrum of the indole (6; R^1 = R^2 = H), in dimethyl sulphoxide, the olefinic protons give rise to two singlets δ 5·26 and 6·0 p.p.m.; the hydrogen atoms of the acetoxy-group appear as a 3-proton singlet δ 1·6 p.p.m.]. The above spectra are not altered by change in recording temperature. It is probable that the deshielding influence of the carbonyl group of the *N*-acyl function is responsible for the chemical shift to lower field of one of the olefinic signals in going from the *O*- to the *NO*-diacetyl compounds, but the origin of the change in the line position of the acetoxy-signals is less easily quantified.

EXPERIMENTAL

N.m.r. spectra were recorded for $CDCl_3$ solutions unless stated otherwise. I.r. spectra were measured as Nujol mulls and u.v. data refer to solutions in 95% ethanol.

* Due to instrumental problems it was not possible to carry out variable temperature experiments below 10°.

N.m.r. Spectrum of 2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]-*ethylidene*}*indolin*-3-*one* (3; R = OMe) *at* 36°.—The spectrum showed signals at δ 8·68 (1H, s, 2′-H), 8·3 (1H, d, *J* 5 Hz, 6′-H), 7·75 (1H, bs, NH), 7·8—6·7 (5H, m, 5′-, 4-, 5-, 6-, and 7-H_5), *ca.* 4·4 (1H, 2 × interleaving q, C*H*Me), 3·30 and 3·24 (3H, 2 × s, OMe), 2·62 and 2·60 (3H, 2 × s, CMe), and 1·47 and 1·43 p.p.m. (3H, 2 × d, *J* 6 Hz). When the temperature is raised to 56° the appearance of the spectrum remains the same except the signals due to the MeO and CMe groups become singlets at δ 3·28 and 2·58 p.p.m., respectively, while the C*H*Me resonance becomes a quartet centred at δ 4·45 p.p.m. and the methyl reasonance a doublet at δ 1·44 p.p.m.

2-[1-(3-*Ethyl*-4-*pyridyl*)*vinyl*]*indol*-3-*yl Acetate* (6; R^1 = R^2 = H) *and* 1-*Acetyl*-2-[1-(3-*ethyl*-4-*pyridyl*)*vinyl*]*indol*-3-*yl Acetate* (6; R^1 = H, R^2 = Ac).—The indolin-3-one (3; R = H) (2·0 g) was heated under reflux with acetic anhydride (40 ml) and triethylamine (10 ml) for 1 h, during which time the colour of the solution changed from deep orange to pale yellow. Evaporation left a yellow gum, which when triturated with ether afforded needles of the *acetate* (6; R^1 = R^2 = H) (1·1 g, 48%), m.p. 194—195° (from benzene), M^+, 306 and 235 (*P*), $\nu_{max.}$ 1710 (OAc), 1620 (C=CH_2), 1210 (C–O), and 3100 cm^{-1} (NH), $\lambda_{max.}$ (ε) 235 (15,350), 306 (14,400), and 308 (1375) nm, δ(Me_2SO) 10·5 (1H, bs, NH), 8·52 (1H, s, 2′-H), 8·45 (1H, d, 5 Hz, 6′-H), 7·16 (1H, d, *J* 5 Hz, 5′-H), 7·4—7·0 (4H, m, 4-, 5-, 6-, and 7-H_4), 5·84 and 5·32 (2 × 1H, s, C:CH_2), 2·5 (2H, q, *J* 7·3 Hz, CH_2Me), 1·66 (3H, s, OAc), and 1·16 p.p.m. (3H, t, *J* 7·3 Hz, CH_2*Me*) (Found: C, 74·5; H, 6·0; N, 9·0. $C_{19}H_{18}N_2O_2$ requires C, 74·5; H, 5·9; N, 9·1%).

Evaporation of the ethereal mother liquor from which the acetate (6; R^1 = R^2 = H) was obtained gave a yellow gum, this was extracted successively with hot light petroleum (b.p. 60—80°) (total 50 ml) and the extracts were treated with charcoal and evaporated to yield the *acetyl-acetate* (6; R^1 = H, R^2 = Ac), rosettes (800 mg, 31%), m.p. 102—103°, M^+, 348 and 235 (*P*), $\nu_{max.}$ 1715 (OAc), 1745 (NAc), and 1620 cm^{-1} (C:CH_2), $\lambda_{max.}$ (ε) 234·5sh (13,750), 280 (10,325), and 303 (7600) nm, δ 8·5 (1H, s, 2′-H), 8·34 (1H, d, *J* 5 Hz, 6′-H), 7·0 (1H, d, *J* 5 Hz, 5′-H), 8·2 (1H, m, 7-H), 7·6—7·2 (3H, m, 4-, 5-, and 6-H_3), 5·76 and 5·70 (2 × 1H, d, *J* 1·2 Hz, C:CH_2) 2·27 (2H, q, 7 Hz, CH_2Me), 2·52 (3H, s, NAc), 2·24 (3H, s, OAc), and 1·2 p.p.m. (3H, t, *J* 7 Hz, CH_2*Me*) (Found: C, 72·3; H, 5·7; N, 8·0. $C_{21}H_{20}N_2O_3$ requires C, 72·4; H, 5·8; N, 8·0%).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*vinyl*}*indol*-3-*yl Acetate* (6; R^1 = OMe, R^2 = H) *and* 1-*Acetyl*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*vinyl*}*indol*-3-*yl Acetate* (6; R^1 = OMe, R^2 = Ac).—These acetates were obtained from either indolinone (3; R = OMe) or (4; R = OMe) as described in the previous experiment. The *acetate* (6; R^1 = OMe, R^2 = H), pale yellow needles, had m.p. 173° [from light petroleum (b.p. 80—100°)], M^+, 336 and 262 (*P*), $\nu_{max.}$ 1710 (OAc), 1620 (C:CH_2), 1205 (C–O), and 3140 cm^{-1} (NH), $\lambda_{max.}$ (ε) 232 (14,000) and 310 (13,700) nm, δ 8·78 (1H, s, 2′-H), 8·68 (1H, bs, NH), 8·5 (1H, d, *J* 5 Hz, 6′-H), 7·16 (1H, d, *J* 5 Hz, 5′-H), 7·4—7·0 (4H, m, 4-, 5-, 6-, and 7-H_4), 5·84 and 5·32 (2 × 1H, s, C:CH_2), 4·48 (1H, q, *J* 6 Hz, C*H*Me), 3·14 (3H, s, OMe), 1·96 (3H, s, OAc), and 1·36 p.p.m. (3H, d, *J* 6 Hz, CH*Me*) (Found: C, 71·4; H, 6·0; N, 8·2. $C_{20}H_{20}N_2O_3$ requires C, 71·4; H, 6·0; N, 8·3%). The *acetyl-acetate* (6; R^1 = OMe, R^2 = Ac), cubes, had m.p. 126° [from light petroleum (b.p. 40—60°)], (30 mg, 23%), M^+, 378 and 262 (*P*), $\nu_{max.}$ 1710 (OAc), 1765 (NAc), and 1620 cm^{-1} (C:CH_2), $\lambda_{max.}$ (ε) 235sh (14,300), 279 (10,900), and 302sh (7400) nm, δ 8·78 (1H, s, 2′-H), 8·44 (1H, d, *J* 5 Hz, 6′-H), 7·06 (1H, d, *J* 5 Hz, 5′-H), 7·9 (1H, m, 7-H), 7·6—7·2 (3H, m, 4-, 5-, and 6-H_3), 5·75 and 5·66 (2 × 1H, d, *J* 1·2 Hz, C:CH_2), 5·54 (1H, q, *J* 6 Hz, C*H*Me), 3·15 (3H, s, OMe), 2·49 (3H, s, NAc), 2·27 (3H, s, OAc), and 1·36 p.p.m. (3H, d, *J* 6 Hz, CH*Me*) (Found: C, 69·7; H, 5·9; N, 7·35. $C_{22}H_{22}N_2O_4$ requires C, 69·85; H, 5·85; N, 7·4%).

We thank the Cancer Research Campaign and the S.R.C. for support.

[2/1077 *Received*, 12*th May*, 1972]