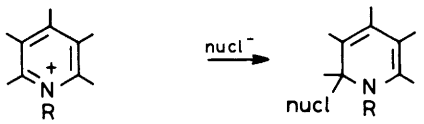
Cyclising Nucleophilic Addition to Azinium Systems. Part 1. Reaction of 3-Indol-2-ylpyridine, 3-Indol-2-ylquinoline, 4-Indol-2-ylisoquinoline and Pyrido[3,4-*a*]carbazoles with Acetic Anhydride

M. Mehdi Baradarani, Lesley Dalton, Frank Heatley, Demetrios Cohylakis, and John A. Joule*
Chemistry Department, Manchester University, Manchester M13 9PL

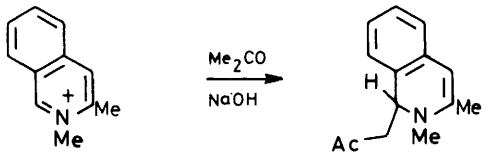
Two pyrido[3,4-*a*]carbazoles were shown to react smoothly with acetic anhydride to give 1-acetyl-1,12a-dihydro[1,6]naphthyridino[4,6-*am*]carbazol-11(12*H*)-ones. 3-Indol-2-ylquinoline and 3-indol-2-ylpyridine reacted in an analogous fashion though with further complications in the latter case. 4-Indol-2-ylisoquinoline gave *E*-2-acetyl-1-(1-acetylindol-2-ylmethylene)-2,3-dihydro-3-(2-oxopropyl)-1*H*-isoindole, the structure of which was determined by a detailed study of its ^{1}H n.m.r. spectrum with decoupling, n.O.e. and relaxation time measurements.

The chemistry[1] of *N*-alkyl, *N*-aryl, and *N*-acylpyridinium salts (**1**) abounds in examples of intermolecular addition of nucleophiles—hydride, carbon-centred and hetero-atom-centred—usually at the pyridine α-position, though attack can occur at the γ-position especially with pyridinium salts carrying electron withdrawing substituents at the β-position. The fate of such non-aromatic adducts (**2**) depends on the added nucleophile, the nitrogen substituent, and on subsequent treatment; it includes oxidative re-aromatisation of the adduct, and hetero-ring opening. The dihydropyridine adducts are more stable when R in (**2**) is an acyl group.

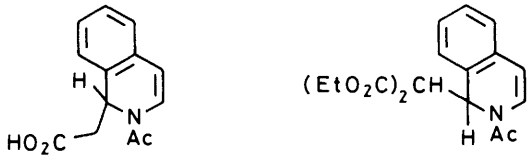


(**1**) (**2**)

R = Alkyl, Aryl or Acyl

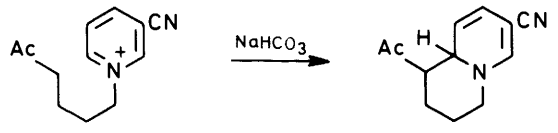


(**3**) (**4**)

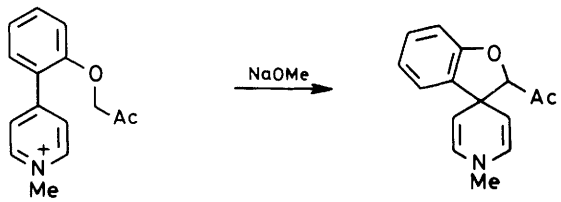


(**5**) (**6**)

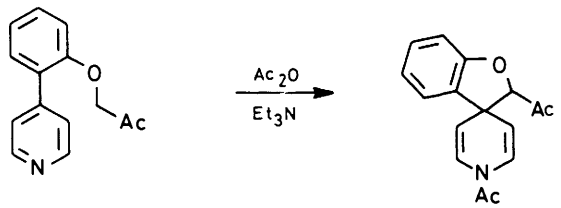
Amongst examples of carbon-centred intermolecular nucleophilic addition and of particular relevance to what follows are those in which enolates add to the isoquinolinium system of the quaternary alkaloid berberine,[2] or in a simpler, analogous case, to 3-methylisoquinolinium methiodide [(**3**) ⟶ (**4**)].[3] Isoquinoline itself reacted with acetic anhydride to give (**5**)[4] and with acetic anhydride in the presence of active methylene compounds to produce[4b] substances such as (**6**) for which an intermediate *N*-acetylisoquinolinium salt was suggested.



(**7**) (**8**)



(**9**) (**10**)



(**11**) (**12**)

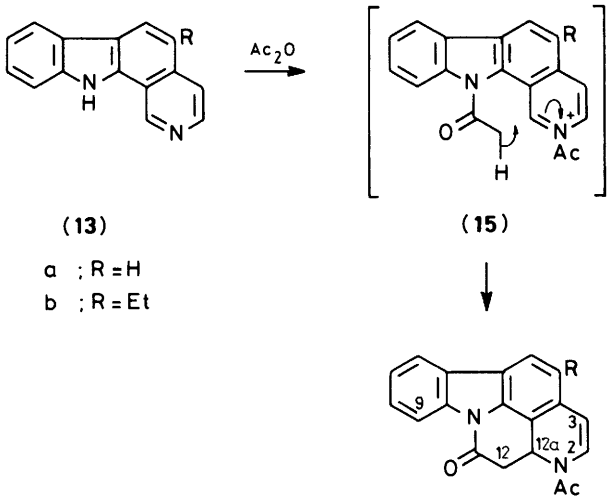
During the last few years there have been a small number of reports[5–14] of *intramolecular* carbon-centred nucleophilic additions to pyridinium systems, in which an additional carbon–carbon bond and an additional ring have been generated. One may cite as examples the conversion[6] of (**7**) into (**8**) with aqueous bicarbonate, and of (**9**) into (**10**)[10] with sodium methoxide. The conversion of (**11**) into (**12**)[10] must be presumed to involve the *N*-acetylpyridinium salt.

Discussion

We report here further examples of intramolecular carbon-centred nucleophilic addition to *N*-acetylpyridinium systems. Thus the pyridocarbazoles (**13a**)[16] and (**13b**)[17] on refluxing with acetic anhydride afforded products in which the elements of diketene had been added, *i.e.* in which it seemed that two

positions had been substituted with acetyl groups. Structures (**14a**) and (**14b**) were assigned by the absence of an n.m.r. signal for *N*-hydrogen, the presence of low-field aromatic signals at δ 8.47 and 8.40 respectively (9-H), the presence of only one acetyl methyl singlet (δ 2.37 and 2.30 respectively) and ABX systems for the protons at C-12/C-12a. For example (**14a**) showed double doublets for 12-H_2 centred at δ 4.46 and 3.04. The signal for the proton at C-12a lay over that for the C-3 enamide proton at δ 5.80, the other enamide (2-H) resonated as a doublet at δ 6.72.

We envisage the formation of (**14a** and **b**) as proceeding *via* a species such as (**15**) in which the extra ring is formed by intramolecular addition of the enolised indole *N*-acetyl group to the pyridinium α-position.



(**13**)

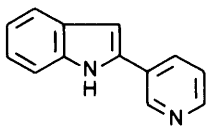
a ; R = H

b ; R = Et

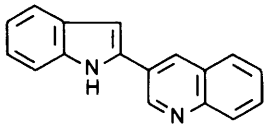
(**15**)

(**14**)

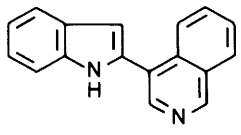
It seemed that comparable cyclisations might be possible with analogues of (**13**), such as indoles (**16**),[18] (**17**), and (**18**). 3-Acetylquinoline[19] phenylhydrazone underwent the Fischer reaction with hot polyphosphoric acid to give indole (**17**). Similarly the phenylhydrazone of 4-acetylisoquinoline[20] prepared by reaction of 4-lithioisoquinoline[21] with acetaldehyde followed by oxidation with manganese dioxide, was transformed into indole (**18**) using the same acid.



(**16**)



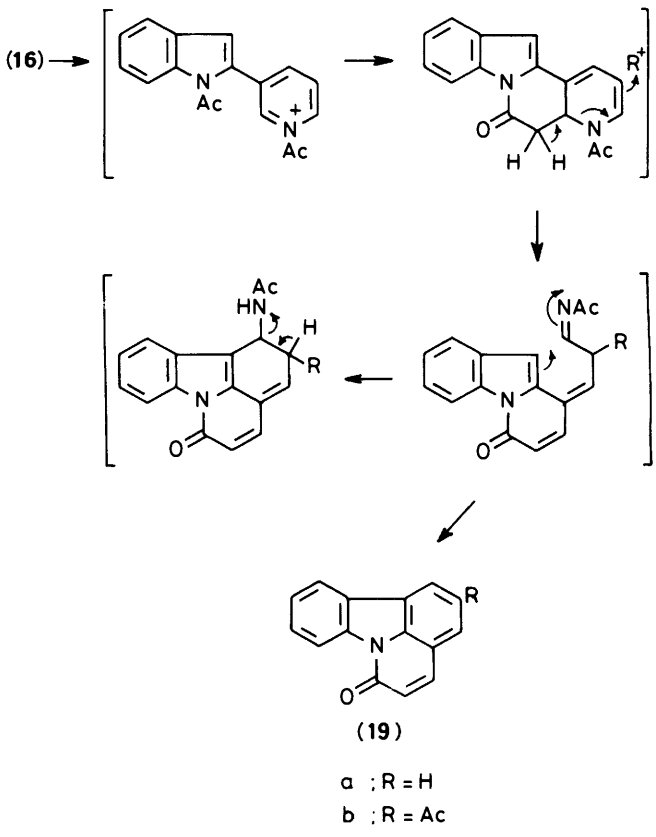
(**17**)



(**18**)

The three analogues (**16**), (**17**), and (**18**) differ from (**13a** and **b**) in having a free indole-β-position. In order to encourage the desired indole *N*-acetylation rather than indole-β-acetylation, each was treated with hot acetic anhydride, as for (**13**), but in the presence of anhydrous sodium acetate.[22]

After 20 h in hot acetic anhydride-sodium acetate, the simplest analogue (**16**) had been converted into a mixture of products from which two major components could be isolated pure by chromatography. The least abundant of these proved to be the known pyridocarbazole (**19a**) whose spectral and physical data were in accord with those published.[23] The major product (13%) was simply the acetyl derivative (**19b**) of this carbazole. A sequence which explains the formation of these products is presented in Scheme 1.



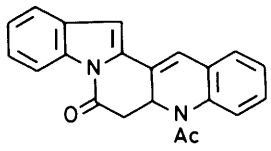
(**19**)

a ; R = H

b ; R = Ac

Scheme 1.

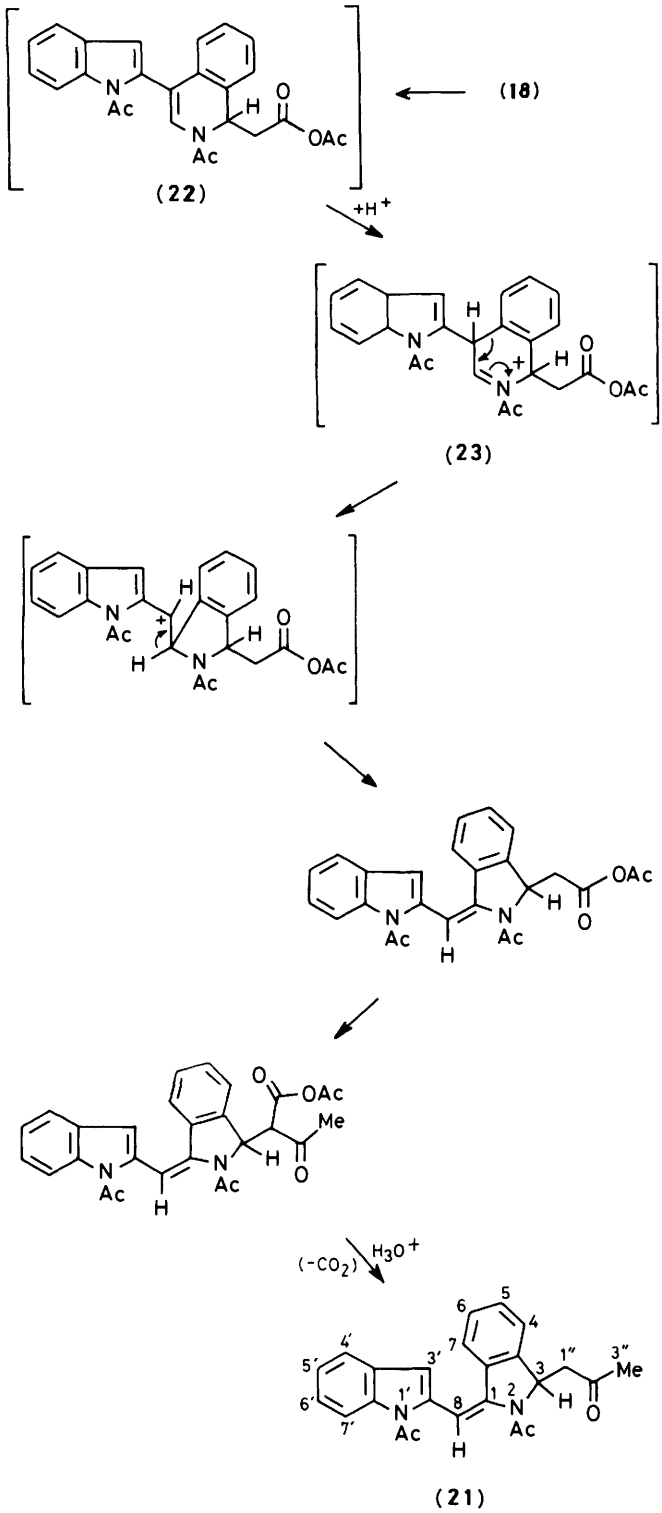
The quinoline analogue (**17**) reacted more cleanly with hot acetic anhydride–sodium acetate, to give one major product (25%) accompanied by traces of others. The structure was demonstrated to be the expected product (**20**) by its elemental analysis, which again corresponded to the addition of the elements of diketene, the absence of *N*-hydrogen, presence of an indole β-proton singlet (overlying that for the quinoline 4-H), only one acetyl methyl, and an ABX system with H_X at δ 5.87, and the A and B protons between δ 2.72 and 3.43.



(**20**)

In turning to the last analogue (**18**) examined in this context, we were aware both that the analogous cyclising nucleophilic addition would have to be at a less favoured isoquinoline 3-position and also that in any product cyclised in the fashion described above and therefore near planar there would be

steric interference between the indole β-proton and the isoquinoline 5-proton. It was accordingly not surprising that acetic anhydride–sodium acetate treatment of (**18**) led to a quite different and, as far as we are aware, novel reaction involving the isoquinoline nucleus.



Scheme 2.

The crystalline product (17%) had a molecular formula of $C_{24}H_{22}N_2O_3$ demonstrating the net addition of $C_7H_{10}O_3$, apparently corresponding to the substitution of three acetyl groups and the addition of methane! The i.r. spectrum of the product showed strong absorption in the carbonyl region at 1 675, 1 705, and 1 720 cm^{-1}, suggesting the presence of amide, indole *N*-acyl and ketone carbonyl groups. Important mass spectroscopic fragmentation corresponded to loss of 57 ($M^+ - C_3H_5O$) and 99 (base peak) ($M^+ - C_5H_7O_2$), and to *m/z* 243, 244, and 245 [244 is the molecular weight of starting indole (**18**)]; these ions suggested the ready loss of a CH_3COCH_2 moiety then successive losses of this unit together with one and two ketene units respectively.

Preliminary examination of the major peaks in the ^1H n.m.r. spectrum revealed the absence of an NH group and the presence of three Me singlets at δ 2.08, 2.41, and 2.56. A CH_2CH fragment with non-equivalent CH_2 protons was present, together with two 1H singlets in the olefinic region. There were eight aromatic protons, four doublets and four triplets arising from two *ortho*-disubstituted benzene rings. Particularly interesting was the observation of several minor peaks which were reproducible in position and intensity even after repeated purification to a chromatographically pure state.

Consideration of these results and possible reaction pathways led to the formulation of several working hypotheses for the structure. A detailed study described below using variable-temperature, spin-decoupling and measurement of spin-lattice relaxation times (T_1) and nuclear Overhauser enhancements (n.O.e.) resulted in the selection of (**21**).

N.m.r. Experimental

^1H Spin-lattice relaxation times (T_1) and nuclear Overhauser enhancements (n.O.e.) were measured using a Varian Associates XL-300 spectrometer operating at 300 MHz. A solution of 5.0 mg cm^{-3} in $CDCl_3$ was used, degassed and sealed *in vacuo*. T_1 Values were measured using the (π-τ-π/2) inversion recovery technique. Steady-state n.O.e. measurements were obtained using gated decoupling with the decoupler on during the relaxation period (30 s), but off during the acquisition. The reference spectrum (no n.O.e.) was obtained with the decoupler set off-resonance in a vacant region at *ca.* δ 4.5. To minimise drifts in homogeneity and spectrometer gain, the decoupler frequency was cycled in blocks of 4 transients to a total of 64 acquisitions per irradiation frequency. The n.O.e.'s were obtained by Fourier Transformation of the difference between the F.I.D. with the decoupler on resonance and the reference F.I.D.

Results

The chemical shift assignments for (**21**) resulting from the following arguments are given in the Table, together with the T_1 values. It is noteworthy that the T_1 values cover a wide range from 0.6—4 s, indicating that relaxation is dominated by intramolecular interactions. The T_1 and n.O.e. values are therefore structurally significant.

As mentioned above, the 300 MHz ^1H n.m.r. spectrum at 20 °C consisted of a set of well-resolved major peaks and a number of associated minor peaks. Of the major peaks, the aromatic proton doublets at δ 8.21 and 6.79 and the methyl singlet at δ 2.56 showed considerable broadening compared with other peaks of the same class. Also, on performing n.O.e. measurements, saturation transfer between major and minor peaks was observed. Each minor peak could be paired with a major peak such that saturation of either member produced a large saturation (40—70%) of the other. This behaviour is indicative of exchange processes, the existence of which was confirmed by variable-temperature experiments. In fact two processes occur, since on cooling to 1 °C the broad peaks mentioned above broaden further, while on warming to 40 °C,

Table. Chemical shifts and T_1 values for (**27**): 5.0 mg cm^{-3} in $CDCl_3$ at 21 °C and 300 MHz. The absence of entries for the minor form indicates that no splitting of these peaks was detected.

	Major form		Minor form	
Proton	δ	T_1/s[a]	δ	T_1/s[a]
2-COMe	2.27	1.29	2.41	1.32
3	6.24	1.60	5.65	*b*
4	7.32	2.3		
5	7.22	2.0		
6	7.15	1.84		
7	6.79	2.93		
8	6.91	2.16	7.45	*b*
1′-COMe	2.56	1.28		
3′	6.70	3.99	6.75	*b*
4′	7.59	2.91		
5′	7.32	2.3		
6′	7.39	2.17		
7′	8.21	2.22		
2″	2.99	0.61	3.27	*b*
	2.72	0.70	2.89	*b*
3″	2.19	1.99	2.08	1.95

[a] Uncertainty *ca.* 5%. [b] Not measured.

those broad peaks sharpen while the minor peaks and their associated major peaks broaden. The relative abundance of the major and minor peaks is 4:1 at 20 °C. Such effects occurring at room temperature can be explained by two acetylamino fragments exchanging between their two possible planar conformations by rotation about the N–COMe bond. One process lies in the slow exchange region and the other lies in the intermediate region at ambient temperature.

From the method of preparation, the presence of an *N*-acetylated indole unit was extremely probable. Saturation of the broadened methyl at δ 2.56 produced an 18% enhancement of the broadened aromatic signal at δ 8.21, suggesting the assignment of those peaks to 1′-$COCH_3$ and 7′-H respectively. Because of the large n.O.e., the favoured conformation of this acetyl group must place the methyl group adjacent to 7′-H. With this identification of 7′-H, the assignments of 4′-H, 5′-H, and 6′-H followed from spin-decoupling.

Saturation of 4′-H produced a 13% enhancement of the singlet at δ 6.70, thus allowing the identification of 3′-H. These chemical shift assignments were supported by comparison with the model compound *N*-acetylindole, which moreover showed identical exchange broadening of the methyl and adjacent aromatic proton signals. The T_1 data are also fully consistent with this structure. For the present purposes, assuming only intramolecular interactions, T_1 for proton i is given sufficiently accurately by equation (1),[24] where μ_0 is the magnetic

$$T_{1i}^{-1} = \frac{3}{2}\left(\frac{\mu_0}{4\pi}\right)^2 \gamma_H^4 \hbar^2 \Sigma \tau_{cij} r_{ij}^{-6} \qquad (1)$$

permeability of free space, γ_H is the ^1H magnetogyric ratio, r_{ij} is the internuclear distance between protons i and j, and τ_{cij} is the correlation time for the i-j interaction. Assuming that relaxation of 5′-H and 6′-H arises solely from their *ortho* neighbours at 248 pm, we obtain a value for τ_c for molecular tumbling of 62 ps. From Dreiding molecular models, the 3′—4′ distance is 290 pm, which, with the 4′—5′ interaction, predicts a value of 3.2 s for T_1 of 4′-H, in good agreement with the experimental value of 2.9 s. The T_1 of 7′-H is practically identical to those of 5′-H and 6′-H indicating that the relaxation of 7′-H from interaction with 1′-COMe is essentially the same magnitude (4.4 s) as the 7′—6′ interaction. The 1′-COMe relaxation from 7′-H will be 3 × 4.4 = 13.2 s because of the difference in numbers of interactions. However the 1′-COMe is relaxed predominantly by the intra-methyl interactions, whose effective correlation time is determined by that for methyl internal rotation (τ_i) as well as that for molecular tumbling (τ_c). Because of the very low barrier to rotation of an acetyl methyl (< 5 kJ mol^{-1}),[25] we have $\tau_i \ll \tau_c$ and the effective correlation time for intra-methyl interactions[26] is $\tau_c/4$. Using an intra-methyl proton separation of 178 pm, and including the 7′-H contribution, gives an expected T_1 of 1.17 s for 1′-COMe, which compares well with the experimental value of 1.28 s. Of the signals in the indole fragment, only 3′-H showed isomeric peaks due to the slow exchange process.

The structure of the remainder of the molecule was assembled from five main arguments:

i The two remaining methyl groups both showed peaks due to the slow process and both have chemical shifts characteristic of acetyl groups. However they differed considerably in T_1, that at lower field had a value of 1.3 s, and the other a value of 2 s. As outlined above, the former is the value expected for a methyl group attached to the molecular framework and rotating rapidly about its C_3 axis. A higher value than this can occur only if one or more additional fast rotational processes intervene between the framework and the methyl group. Furthermore, the slower relaxing methyl showed no measurable n.O.e. to any other proton, indicating a remote situation possibly at the end of a flexible side-chain. The quicker relaxing methyl was therefore assigned to the COMe group at N-2, and the slower relaxing methyl to a much less hindered acetyl group at C-1″.

ii The remaining non-aromatic protons comprised a 1 H singlet (8-H) and a $CHCH_2$ multiplet system with non-equivalent CH_2 protons (3-H and 1″-H). All protons showed isomerism due to the slow exchange process, and the CH signals were strongly deshielded (δ 7.45 and 6.91 for 8-H, 6.24 and 5.65 for 3-H). At 1 °C, saturation of the major 2-COMe peak produced a 22% enhancement of the major 8-H peak only, whereas saturation of the minor 2-COMe peak produced primarily a 12% enhancement of the minor 3-H peak. Furthermore, the minor 8-H peak (δ 7.45) is downfield of the major (δ 6.91) whereas the minor 3-H multiplet (δ 5.65) was upfield of the major (δ 6.24). These data are consistent with the reasonably symmetrical location of 8-H and 3-H in the plane of the NCOMe moiety, but on opposite sides of the N–C bond. In the major form, the acetyl Me is located in the vicinity of 8-H.

iii Saturation of the major 8-H peak produced an enhancement of the major 3′-H peak of at least 10%, placing these protons in close proximity (a lower limit is given because the peaks close together and the RF field saturating one peak partially saturated the other.) From the calculations above, the T_1 contribution from the 3′—4′ interaction is estimated at 8.5 s. Since 3′-H showed an n.O.e. to 4′-H and to 8-H it can be assumed that 3′-H is relaxed principally by these two interactions. Hence using the experimental T_1 for 3′-H of 3.99 s, a value of 7.5 s was obtained for the interaction between 3′-H and 8-H, which gave an approximate average separation of 270 pm.

iv In the $CHCH_2$ fragment, the two vicinal coupling constants were both 7 Hz in the major form, but were 5 and 8.5 Hz in the minor form; the smaller coupling was attributed to the more shielded CH_2 proton. Thus the structure must show a capacity to change the conformational averaging of the $CHCH_2$ fragment on exchanging the 2-COMe group. Given the well-attested validity of the Karplus equation (2)[27] relating vicinal

$$^3J(\varphi) = 7 - \cos\varphi + 5\cos 2\varphi \qquad (2)$$

^1H–^1H coupling constants to dihedral angle φ, the equal coupling constants of 7 Hz in the major form were incompatible with any single conformation. Thus conformational freedom of the $CHCH_2$ bond was indicated.

The CH_2 T_1 values also indicated internal motion of this unit. For a single geminal interaction at 178 pm, the relaxation time predicted for the molecular correlation time above was 0.60 s. Experimentally, one of the CH_2 protons had a relaxation time of 0.70 s. Since the experimental value included a contribution from other protons, principally the adjacent CH, the effective correlation time of the geminal CH_2 must be less than that for molecular tumbling, implying internal motions. The placing, in (**21**) of the CH_2 group in a side chain near the 2-COMe group is consistent with these observations.

v Saturation of the major 3-H peak produced a 9% enhancement of a non-indole aromatic doublet at δ 7.32, thus placing this CH adjacent to an aromatic ring. This allowed the assignment of that aromatic doublet to 4-H and hence by spin-decoupling the assignments of the remaining aromatic protons.

π-Electron resonance favours a planar skeleton, but this is prevented by conflict between 7-H and either 3′-H or 1′-COMe. Elaborating point *iii*, 3′-H and 8-H are 270 pm apart when the indole and olefinic fragments are inclined to about 45°, with 8-H and 3′-C synclinal. This conformation places 7-H above the indole five-membered ring and in the vicinity of the indole COMe, thus rationalising both its anomalous high-field shift (δ 6.79) and its broadening by the indole COMe exchange.

The structure (**21**) demands that a rearrangement take place during its formation from (**18**) (Scheme 2). The simplest means for achieving the required structural change seems to be the 1,2-migration of the benzene ring in an intermediate, (**23**). The sequence would start with a process like that documented[4] for isoquinoline itself [(**5**) ⟶ (**6**)]; protonation of (**22**) would initiate the rearrangement. The Scheme suggests the introduction of the third acetate moiety in a Claisen fashion at a later stage, though clearly this could take place earlier. Finally, hydrolysis and decarboxylation during work up would complete a sequence which we feel adequately rationalises this novel transformation.

Experimental

1-*Acetyl*-1,12a-*dihydro*[1,6]*naphthyridino*[4,6-aml]*carbazol*-11(12H)-*one* (**14a**).—The pyrido carbazole (**13a**)[16] (400 mg) was heated in acetic anhydride (120 ml) at reflux for 5 h. The cooled solution was poured into aqueous hydrochloric acid (6M, 100 ml) and the product extracted with ethyl acetate. Evaporation of the dried extract gave a yellow solid which was recrystallised from ethyl acetate to give the *enamide* (**14a**) (310 mg), m.p. 168—171 °C, $\lambda_{max.}$(EtOH) 242, 378, 344, 358sh, 390, and 411 nm (log ε 4.40, 4.06, 3.9, 4.12, 4.06, 3.39, and 3.28); $\nu_{max.}$($CHCl_3$) 1 710s, 1 680s, and 1 630s cm^{-1}; δ($CDCl_3$) 8.47 (1 H, dd, *J* 7.5, 2.5 Hz, 9-H), 7.95 (1 H, dd, *J* 7.5, 2.5 Hz, 6-H), 7.77 (1 H, d, *J* 9 Hz, 5-H), 7.20—7.61 (2 H, m, ArH), 7.05 (1 H, d, *J* 9 Hz, 4-H), 6.72 (1 H, d, *J* 8 Hz, 2-H), 5.63—5.95 (2 H, m, 12a-H and 3-H), 4.46 (1 H, dd, *J* 5, 16 Hz, 12-H_a), 3.04 (1 H, dd, *J* 12, 16 Hz, 12-H_b), and 2.37 (3 H, s, MeCO); *m/z* 302 (M^+, 64%), 260 (39), 259 (71), and 218 (100) (Found: *M*, 302.1061; *m/z* 259.0873, 218.0843. $C_{19}H_{14}N_2O_2$ requires *M*, 302.1055. $C_{17}H_{11}N_2O$ requires 259.0871. $C_{15}H_{10}N_2$ requires 218.0844).

1-*Acetyl*-4-*ethyl*-1,12a-*dihydro*[1,6]*naphthyridino*[4,6-aml]-*carbazol*-11(12H)-*one* (**14b**).—The enamide (**14b**) was prepared exactly as described for (**14a**) above: from (**13b**)[17] (200 mg) *enamide* (**14b**) (160 mg) was obtained, m.p. 190—193 °C (from ethyl acetate), $\lambda_{max.}$(EtOH) 230, 248, 333sh, 347, 365sh, 391, and 410 nm (log ε 4.22, 4.15, 3.78, 3.92, 3.70, 3.30, and 3.11); $\nu_{max.}$($CHCl_3$) 1 710s, 1 670s, and 1 625s cm^{-1}; δ($CDCl_3$) 8.40 (1 H, d, *J* 8 Hz, 9-H), 7.85 (1 H, d, *J* 8 Hz, ArH), 7.50 (1 H, s, 5-H), 7.20—7.40 (2 H, m, ArH), 6.72 (1 H, d, *J* 8 Hz, 2-H), 5.78 (1 H, d, *J* 8 Hz, 3-H), 5.60 (1 H, dd, *J* 5, 14 Hz, 12a-H), 4.36 (1 H, dd, *J* 5, 16 Hz, 12-H_a), 2.60—3.00 (3 H, m, 12-H_b, MeCH_2), 2.28 (3 H, s, MeCO), and 1.26 (3 H, t, *J* 7 Hz, *Me*CH_2); *m/z* 330 (M^+, 100%), 288 (47), 287 (95), 246 (86), and 231 (52) (Found: M^+, 330.1368. $C_{21}H_{18}N_2O_2$ requires *M*, 330.1373).

3-*Acetylquinoline Phenylhydrazone*.—3-Acetylquinoline (602 mg) was treated with phenylhydrazine (390 mg) in refluxing toluene (50 ml) under a Dean-Stark water separator for 36 h. The solvent was evaporated and the residue washed with hot hexane then recrystallised from diethyl ether to give the title *phenylhydrazone* (382 mg), m.p. 195—197 °C (Found: C, 77.9; H, 5.5; N, 16.2. $C_{17}H_{15}N_3$ requires C, 78.2; H, 5.7; N, 16.1%).

3-*Indol*-2-*ylquinoline* (**17**).—A mixture of 3-acetylquinoline phenylhydrazone (300 mg) and polyphosphoric acid was heated at 95 °C for 1.5 h and then at 140 °C for 0.25 h. The mixture was poured into water, made basic with potassium carbonate and then extracted with ethyl acetate to give material which was recrystallised from ethyl acetate to give the *indole* (**17**) (231 mg), m.p. 238—240 °C, $\lambda_{max.}$(EtOH) 248, 293, 329, and 364 nm (log ε 4.26, 4.13, 4.22, and 4.05); $\nu_{max.}$ 3 460m cm^{-1}; δ[$^2H_6$]-DMSO) 11.78 (1 H, br s, NH), 9.43 (1 H, d, *J* 2 Hz, quinoline-α-H), 8.70 (1 H, d, *J* 2 Hz, quinoline-γ-H), 7.37—8.10 (6 H, m, ArH), 6.90—7.30 (3 H, m, ArH) (Found: M^+, 244.0998. $C_{17}H_{12}N_2$ requires *M*, 244.1000).

4-(1-*Hydroxyethyl*)*isoquinoline*.—To a solution of n-butyllithium (1.65M; 3 ml) in dry tetrahydrofuran and dry diethyl ether (1:1, 25 ml) under nitrogen was added, at −70 °C in portions with stirring, 4-bromoisoquinoline[20] (0.5 g) in solution in dry tetrahydrofuran (3 ml). The mixture was stirred at −70 °C for a further 30 min and then a solution of acetaldehyde (1.1 g) in dry tetrahydrofuran (4 ml) was added in one portion. The mixture was stirred for 15 min and then cold ethanol (10 ml) was added, followed by saturated aqueous ammonium chloride (20 ml). The mixture was warmed to room temperature, separated and the aqueous phase extracted with diethyl ether. These extracts were combined with the organic phase, dried, and evaporated under reduced pressure to give a brown gum which was purified by chromatography over silica, when ethyl acetate eluted the alcohol as a white crystalline solid (0.29 g), m.p. 113—115 °C (lit.,[21] 115—116 °C).

4-*Acetylisoquinoline*.—A solution of 4-(1-hydroxyethyl)-isoquinoline (0.3 g) in dry chloroform (200 ml) was stirred at room temperature with manganese dioxide (1 g) for 48 h. The mixture was filtered through Celite and evaporated under reduced pressure to leave the ketone as a white crystalline solid (0.24 g), m.p. 69—71 °C (lit.,[20] 70—71 °C).

4-*Indol*-2-*ylisoquinoline* (**18**).—4-Acetylisoquinoline phenylhydrazone[20] (19 mg) in polyphosphoric acid (2 ml) was heated at 180 °C for 5 min. The resultant brown solution was poured into water, basified with solid potassium carbonate and then extracted into ethyl acetate. The extract was dried and evaporated under reduced pressure to give the *indole* (**18**) as a brown crystalline solid (16.5 mg), m.p. 233—235 °C (from ethanol), $\lambda_{max.}$(EtOH) 265sh, 272, 335sh, and 345 nm (log ε 4.17, 4.18, 4.18, and 4.19); $\nu_{max.}$(Nujol) 3 160w cm^{-1}; δ($CDCl_3$) 10.75 (1 H, br s, NH), 9.23 (1 H, s, isoquinoline-α-H), 8.75 (1 H, s, isoquinoline-α-H), 8.42 (1 H, d, *J* 8 Hz, ArH), 8.08 (1 H, d, *J* 6 Hz, ArH), 7.68—7.82 (3 H, m, ArH), 7.53 (1 H, d, *J* 8 Hz, ArH), 7.10—7.28 (2 H, m, ArH), and 6.83 (1 H, s, indole-β-H); *m/z* 244 (M^+, 100%) (Found: C, 83.7; H, 4.9; N, 11.1. $C_{17}H_{12}N_2$ requires C, 83.6; H, 4.9; N, 11.5%).

Pyrido[3,2,1-jk]*carbazol*-6-*one* (**19a**) *and* 2-*Acetyl*-6H-*pyrido*-[3,2,1-jk]*carbazol*-6-*one* (**19b**).—The indole (**16**) (260 mg) was

heated at reflux in acetic anhydride (20 ml) with anhydrous sodium acetate (600 mg) for 20 h. The resulting dark red solution was cooled, acidified with 6M-hydrochloric acid and extracted with ethyl acetate. The dried extract was evaporated and the residue triturated with diethyl ether to yield a gum (148 mg) which was then purified by chromatography over silica. Elution with toluene–ethyl acetate (9:1) gave firstly carbazole (**19a**) (4 mg), m.p. 130—134 °C (lit.,[22] 135—136 °C) and then the *ketone* (**19b**) (44 mg), m.p. 192—194 °C, $\lambda_{max.}$(EtOH) 223, 251, 261sh, 270sh, 324, and 380 nm (log ε 4.02, 3.88, 3.80, 3.70, 3.63, and 3.57); $\nu_{max.}$($CHCl_3$) 1 670s and 1 660s cm^{-1}; δ($CDCl_3$) 8.83 (1 H, d, *J* 8 Hz, 5-H), 8.75 (1 H, s, 3-H), 8.27 (1 H, d, *J* 7 Hz, 11-H), 8.14 (1 H, d, *J* 8 Hz, 4-H), 7.89 (1 H, d, *J* 7 Hz, 8-H), 7.54—7.72 (3 H, m, ArH), 2.90 (3 H, s, Me); *m/z* 261 (M^+, 46%), 246 (100), and 190 (29) (Found: M^+, 261.1056; *m/z* 246.0556, 190.0654. $C_{17}H_{11}NO_2$ requires *M*, 261.0790. $C_{16}H_8NO_2$ requires 246.0555. $C_{14}H_8N$ requires 190.0657).

5-*Acetyl*-5a,6-*dihydroindolo*[2,1-f]*benzo*[b][1,6]-*naphthyridin*-7(6H)-*one* (**20**).—The indolylquinoline (**17**) (130 mg) was heated in acetic anhydride (17 ml) at reflux with anhydrous sodium acetate (300 mg) for 20 h. The resulting red solution was cooled, acidified with 5M-hydrochloric acid and then extracted with ethyl acetate. The dried extract yielded a brown gum which was purified by chromatography over silica, eluting with toluene–ethyl acetate (8:1) and finally recrystallisation from ethyl acetate gave the enamide (**20**) (34 mg) as yellow crystals, m.p. 231—233 °C, $\lambda_{max.}$(EtOH) 249, 278, and 350 nm (log ε 4.31, 3.99, and 4.13); $\nu_{max.}$($CHCl_3$) 1 710s, and 1 670s cm^{-1}; δ($CDCl_3$) 8.55 (1 H, d, *J* 8 Hz, 9-H), 7.03—7.85 (7 H, m, ArH), 6.81 (2 H, s, 14-H and 13-H), 5.87 (1 H, dd, *J* 5 and 3 Hz, 5a-H), 2.92—3.43 (2 H, m, 6-H_2), and 2.37 (3 H, s, Me); *m/z* 328 (M^+, 43%), 286 (45), 285 (100), and 244 (56) (Found: M^+, 328.1208; *m/z* 286.1103; 244.1003; C, 76.5; H, 5.0; N, 8.2. $C_{21}H_{16}N_2O_2$ requires M^+, 328.1212. $C_{19}H_{14}N_2O$ requires 286.1106. $C_{17}H_{12}N_2$ requires 244.1000; C, 76.8; H, 4.9; N, 8.5%).

E-2-*Acetyl*-1-(1-*acetylindol*-2-*ylmethylene*)-2,3-*dihydro*-3-(2-*oxopropyl*)-1H-*isoindole* (**21**).—The indole (**18**) (100 mg) was heated at reflux in acetic anhydride (17 ml) with anhydrous sodium acetate (300 mg) for 48 h. The resulting dark red solution was cooled, acidified with 6M-hydrochloric acid and extracted with ethyl acetate, dried and evaporated under reduced pressure to give a red gum, which was purified by chromatography over silica when ethyl acetate eluted (**21**) (19 mg) as a pale brown crystalline solid, m.p. 195—205 °C (from EtOH); $\lambda_{max.}$(EtOH) 235sh, 285sh, and 300 nm (log ε 3.83, 3.61, and 3.62); $\nu_{max.}$(Nujol) 1 720m, 1 705s, and 1 680s cm^{-1}; for a full discussion of the n.m.r. data see text; *m/z* 386 (M^+, 16%), 343 (4), 329 (43), 287 (100), and 243 (51) (Found: C, 74.3; H, 5.6; N, 7.2. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%).

References

1 'Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Vol. 14, part II, 1963 and Supplement, 1974.
2 E. Schmidt and R. Gaze, *Arch. Pharm.*, 1980, **228**, 607.
3 T.-K. Chen and C. K. Bradsher, *Tetrahedron*, 1973, **29**, 2951.
4 (*a*) H. Yamanaka, T. Shiraishi, T. Sakamoto, and H. Matsuda, *Chem. and Pharm. Bull.*, 1981, **29**, 1049; (*b*) T. Shiraishi, T. Sakamoto, and H. Yamanaka, *Heterocycles*, 1977, **6**, 1716.
5 L. Birkhofer and C. Kaiser, *Chem. Ber.*, 1957, **29**, 2933; J. Everse, C. E. Zoll, L. Kahn, and N. O. Kaplan, *Bioorg. Chem.*, 1971, **1**, 207.
6 R. M. Wilson and F. Di Ninno, *Tetrahedron Lett.*, 1970, 289.
7 F. Di Ninno, W. L. Heckle, D. K. Rehse, and R. M. Wilson, *Tetrahedron Lett.*, 1972, 2639; R. M. Wilson, R. A. Farr, and D. J. Burlett, *J. Org. Chem.*, 1981, **46**, 3293.
8 E. Wenkert, Ching-Jer Cheng, H. P. S. Chawla, D. W. Cochran, E. W. Hageman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, 1976, **98**, 3645.
9 J. Curtze, R. Dach, K. H. Duchardt, and F. Kröhnke, *Chem. Ber.*, 1979, **112**, 2197.
10 D. D. Weller and G. R. Luellen, *Tetrahedron Lett.*, 1981, 4381; D. D. Weller, G. R. Luellen, and D. L. Weller, *J. Org. Chem.*, 1983, **48**, 3061.
11 M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Tetrahedron*, 1983, **39**, 3673.
12 G. Fraenkel and J. W. Cooper, *J. Am. Chem. Soc.*, 1971, **93**, 7228.
13 S. Goldmann, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 779.
14 D. D. Weller and D. W. Ford, *Tetrahedron Lett.*, 1984, **25**, 2105.
15 R. B. Majumdar and A. R. Martin, *Tetrahedron Lett.*, 1982, **23**, 1455.
16 R. H. F. Manske and M. Kulka, *Can. J. Research*, 1949, **27**, 163.
17 D. Cohylakis, G. J. Hignett, K. V. Lichman, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1518.
18 J. W. Huffman, *J. Org. Chem.*, 1962, **27**, 503.
19 G. Koller, *Monatsh.*, 1929, **52**, 59.
20 J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, 1945, **67**, 1268.
21 E. Glyde and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1783.
22 J. E. Saxton, *J. Chem. Soc.*, 1952, 3592.
23 V. Prelog, S. Szpilfogel, and J. Battegay, *Helv. Chim. Acta*, 1947, **30**, 366.
24 L D. Hall, *Chem. Soc. Rev.*, 1975, **4**, 400—401.
25 D. G. Lister, J. N. Macdonald, and N. L. Owen, 'Internal Rotation and Inversion,' Academic Press, London, 1978, p. 131.
26 D. E. Woessner, B. S. Snowden, and G. H. Meyer, *J. Chem. Phys.*, 1969, **50**, 719.
27 R. K. Harris, 'Nuclear Magnetic Resonance Spectroscopy,' Pitman, London, 1983, p. 220.

Received 9th November 1984; *Paper* 4/1908