Tetrahedron. Vol. 27, pp. 5631 to 5639. Pergamon Press 1971. Printed in Great Britain

FURANO- AND PYRANO-IDOLINES—MODEL COMPOUNDS FOR INDOLE ALKALOID STUDIES

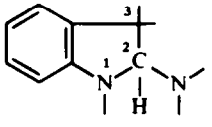
A. Z. BRITTEN†
The Department of Pharmacy, University of Aston in Birmingham

W. G. BARDSLEY and C. M. HILL
The Department of Physiology, University of Manchester

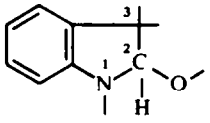
(*Received in the UK* 10 *June* 1971; *Accepted for publication* 22 *June* 1971)

Abstract—The tautomeric PhNCN and PhNCO systems, as present in indole alkaloids are briefly compared. Nine potentially tautomeric PhNCO containing compounds have been synthesised and their tautomerism studied. Some criteria for the position of equilibrium of the tautomeric species have been established. The reactivity of the compounds to reduction and alkylation has been explored.

THE PhNCN and the PhNCO systems as shown in the part structures I and II respectively. are well established features of a number of indole alkaloids.



I

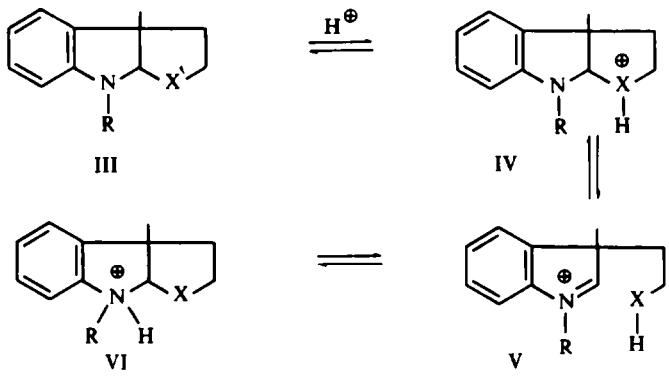


II

The PhNCN linkage is found in the ring systems of the physostigmine alkaloids such as. esermethole and deoxynoreseroline[1,2] and in other alkaloids such as chimonanthine. calycanthine.[3] corymine[4] and echitinolide.[5]Likewise the PhNCO linkage is present in alkaloids such as quinamine,[6] echitamine base,[7] pseudo-akummigine.[8] picraline.[9] villalstonine.[10] and aspidodasycarpine.[11]

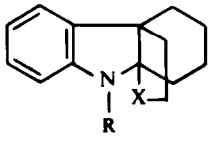
A characteristic feature of these two linkages is their UV absorption behaviour in neutral and acid solutions. Both systems show a modified indoline absorption spectrum in neutral solutions which in dilute acid solutions undergoes a hypsochromic shift and in strong acid solutions changes to a 3H-indolium cation absorption. These spectral changes result from the production of cationic species IV and V respectively from the protonation of III.

The hypsochromic shift of 8–10 nm observed for the PhNCN system in dilute acid solutions is attributed[5] to the partial inhibition of delocalisation of the lone pair of electrons on $N_{(a)}$ over the aromatic nucleus due to the proximity of the positive charge on $N_{(b)}$ ($X{=}{-}N_b{=}$). The PhNCO system shows a similar hypsochromic shift of 2–3 nm in dilute acid solutions but only in those compounds which possess a further $N_{(b)}$ atom as well as the PhNCO linkage.[12] Both systems in concentrated acid solution tend to produce the 3H-indolium cationic species V by. in general. reversible ring opening,[1,8,9,12] These changes have been observed for the two systems when present

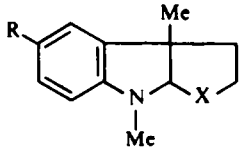


Scheme I (X=—O– or –N= and R=H or Me)

in indole alkaloids and have served as a diagnostic test for their presence. Although the above behaviour is in general a criterion of the presence of these systems. it is not strictly applicable to all PhNCN and PhNCO containing compounds. For example the PhNCN group in the alkaloid calycanthine does not appear to form the expected 3H-indolium cation in concentrated acid solution.[7] Similarly folicanthine and chimonanthine. both with PhNCN linkages. show only the hypsochromic shift in both dilute and concentrated acid solutions and decompose rapidly in the latter.[1] A further example of 'abnormal' behaviour of the PhCNC system is found in the compounds VII **a** and VII **b**. These compounds in dilute acid show no hypsochromic shift but go over to the ring open form V giving a 3H-indolium cation absorption.[13]



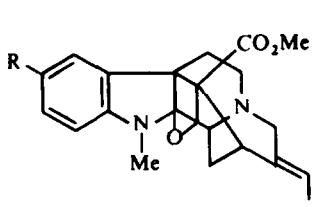
VII **a**. R=H. X=NH
b. R=H. X=NMe.
XIII **a**. R=H. X=O
b. R=Me. X=O



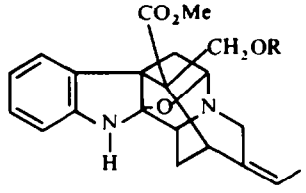
VIII x=NR. NH
XII **a**. R=OCONHMe. X=O
b. R=OEt. X=O

It is clear that the lack of a hypsochromic shift of 8–10 nm of a suspected PhNCN compound in dilute acid or the non-formation of the 3H-indolium cation in concentrated acid solution should be interpreted with caution as indeed should the interpretation of the position of equilibrium of species III. IV and V be treated. The behaviour of the PhNCN linkage as present in several compounds with structure VIII has been examined carefully by Jackson and Smith and found to behave 'normally' in producing species IV and V. successively. with decreasing pH of solution.[1] The properties of the PhNCO system. on the other hand. have in the main been recorded for it as present in several indole alkaloids. For example the linkage is found in pseudo-aknammigine IX**a**.[8] O-methylakuammine IX**b**,[14] picraline X**a**.[9] deacetylpicraline X**b**.[9] aspidodasycarpine XI.[11] and physovenine XII**a**.[15] Further to the above

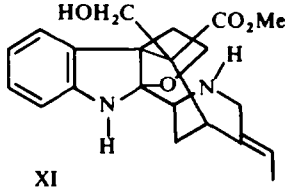
alkaloids only three synthetic PhCNO containing indolines XIIb[16] XIIIa and XIIIb[17] have been examined for their absorption spectra properties.



IX a. R=H
b. R=OMe

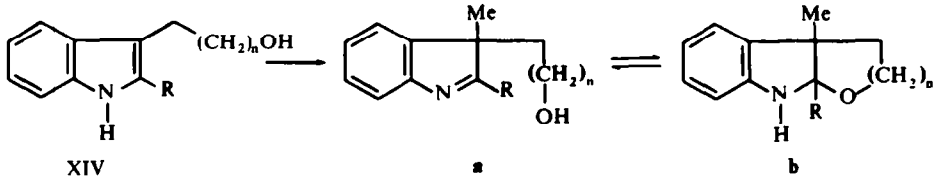


X a. R=Ac
b. R=H



XI

Compounds represented by structures IX[12] and X[18] have a modified indoline absorption in neutral solution which shows a hypsochromic shift of 2–3 nm in dilute acid and changes, reversibly, to a 3H-indolium cation absorption in concentrated acid. The latter absorption maximum appears at or above 310 nm which is at a significantly longer wavelength than usually observed for the 3H-indolium cation at 275–290 nm. Esermethole VIII (R=Me. R^1=OMe) in the PhNCN series is also reported to produce a 3H-indolium cation absorbing at 331 nm.[1] In contrast to IX and X, aspidodasycarpine XI is found to have an indoline type absorption in neutral solution which in concentrated acid gives a benzenoid absorption and not the expected 3H-indolium cation absorption. Compounds XIIa, XIIb and XIIIb are reported to have an indoline type absorption in neutral EtOH and likewise XIIIa in hexane solution. When XIIIa is placed in neutral alcohol and XIIa and XIIb in 1·5 N ethanolic HCl respectively, it is reported that the absorption of XIIIa is characteristic of a mixture of indoline and indolenine and that of XIIa and XIIb characteristic of a mixture of indoline and 3H-indolium cation chromophores. The absorptions of structures IX, X, XII and XIII are readily accounted for in terms of the species III, IV and V. The absorption of aspidodasycarpine in concentrated acid however requires the production of species VI, to account for the benzenoid type absorption of the anilinium cation produced by the protonation of $N_{(a)}$. There is no instance of this type of behaviour recorded for any PhNCN containing compounds.

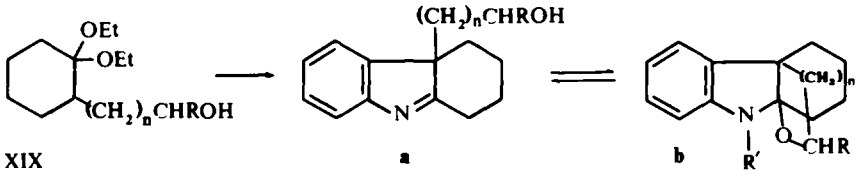


XIV a b

XV R=H. n=1
XVI R=CH_3. n=1

XVII R=H. n=2
XVIII R=CH_3. n=2

In an attempt to rationalise some of the varied behaviour observed in the cited compounds it was decided to synthesise a number of PhNCN containing model compounds. The compounds XV–XVIII were obtained by the reaction of MeI on the Grignard reagents of the indolinols XIV, following the method of Nakazaki.[19] Only product XVIII shows OH and C=N absorption when examined in a non-solvated state and so it exists most probably as an equilibrium mixture of tautomeric forms (**a**) and (**b**). Compounds XV–XVII on the other hand exist entirely in the ring closed tautomer (**b**). The products XX–XIV were all prepared by Fischer indolisation of the diethyl ketals of the hydroxycyclohexanones. XIX. (or the free ketones) by reaction with phenyl- and $N_{(a)}$-methylphenylhydrazine in glacial AcOH.

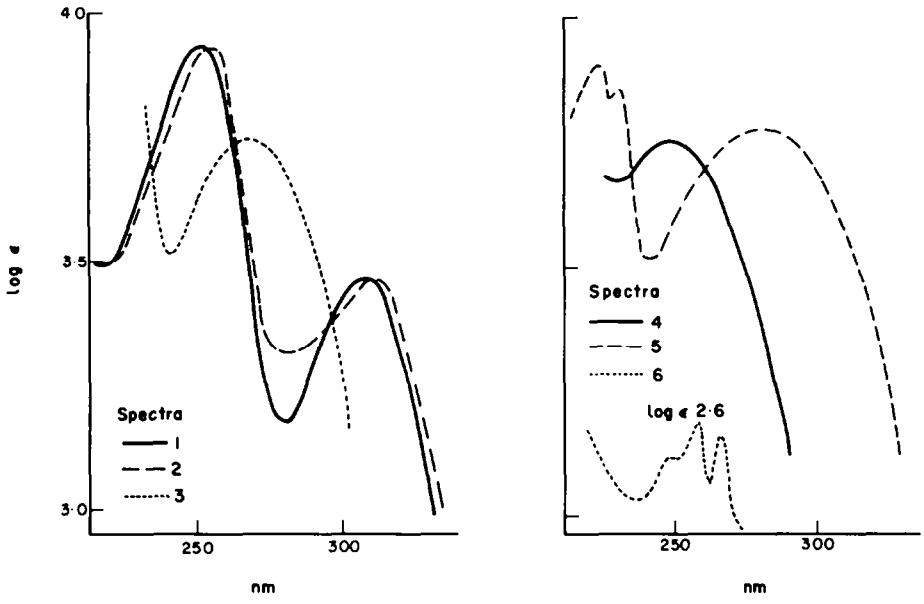


XIX a b

XX R=R¹=H. n=1
XXI R=H. R¹=Me. n=1
XXII R=R¹=H. n=2

XXIII R=H. R¹=Me. n=2
XXIV R=Me. R¹=H. n=1

All five compounds show no OH or C=N absorptions when examined in the non-solvated state and so exist as the ring closed tautomers (**b**). The UV spectra of XV–XVIII and XX–XIV in hexane solution are typical of indolines (spectrum 1) with the exception of XVIII which shows an indoline absorption but with increased absorbance at the position of minimum absorptivity (spectrum 2). This is in agreement with the presence of some of the ring open indolenine form (**a**) for XVIII existing in equilibrium with the ring closed tautomer (**b**) which is the preferred form for the other eight PhNCO compounds in hexane solution. When the absorption spectra are determined in MeOH it is found that XV. XVII. XXI. XXIII and XXIV show indoline absorption supporting the presence of the ring closed tautomer (**b**). On the other hand XVI and XX show an absorption consistent with the predominance of the indoline form (**b**) but with some of the ring open indolenine tautomer (**a**) being present. Compound XVIII however shows absorption (spectrum 3) typical of an indolenine in MeOH and so indicates the preferred form to be the ring open one (**a**). The absorption of XXII in MeOH is shown in spectrum 4 and suggests a preponderance of the indolenine form(**a**). In methanolic HCl (0·1 N) all but XV and XVII have an absorption (spectrum 5) characteristic of the 3H-indolium cation. Therefore, with the exception of XV and XVII, all model PhNCO compounds so far prepared undergo reversible ring opening in dilute acid solution to produce the cationic species V(X=O). Compounds XV and XVII in dilute acid solution give an absorption (spectrum 6) which is characteristic of the anilinium cation $PhNH_3^+$. The formation of such a species from XV and XVII can only arise from the protonation of $N_{(a)}$ without ring opening to produce the cationic species VI (R=H, X=O). The latter cation then produces the observed absorption. In concentrated acid XVII has the 3H-indolium absorption showing ring opening, but XV though showing some 3H-indolium absorption, must be, from the low intensity of this absorption (Table I), largely present



in the ring closed $N_{(a)}$ protonated form VI (R=H, X=O) even in concentrated acid solution. The resistance of XV to ring opening parallels the behaviour of aspidodasycarpine (XI).[11] Lack of thermodynamic data for the relative stabilities of the ring closed-ring opened tautomers discussed above does not allow for a full rationalisation of the tautomerism of the known PhNCO compounds. However it is possible to account for some of the observed behaviour of these compounds from a consideration of the steric and electronic effects present in these structures which would be expected to determine the position of the equilibrium between the ring open and ring closed forms. For example, the marked ease of ring opening of XVI as compared with XV may be attributed to the introduction of the Me group at C_2 of XV to give XVI. The presence of this group introduces steric crowding into the ring closed form (**b**) of XVI and also reduces the electrophilic nature of the —N=C in the ring open form (**a**) of XVI. Both these effects would be expected to facilitate ring opening to produce the tautomer (**a**) in XVI as compared with XV. Similar effects would be expected to apply to the pair XVII and XVIII, favouring ring opening in the latter. Likewise the compounds in the series XX–XIV would be expected to ring open readily by these considerations and indeed the absorption spectra of all the above compounds are in agreement with this. Thus XXII opens more readily than XX which parallels the behaviour of XVIII and XVI respectively, showing that in both instances the presence of the O atom in a six membered ring favours ring opening as compared with the same system in which the O atom is part of a five membered ring. The N-alkylated PhNCO system would be expected to favour the ring closed form (**a**) due to the increased electrophilic nature of the —RN=C bond as compared with the unalkylated —N=C bond. This is found to be the case in the pairs of compounds XX with XXI and XXII

with XXIII where the N-methylated products are ring closed in MeOH while the non-methylated ones ring open.

The data obtained for the PhNCO systems studied so far is presented in Table 1.

TABLE 1. ABSORPTION OBSERVED (λ MAX. N.M., LOG ε) IN THE FOLLOWING SOLVENTS

	n-Hexane	MeOH	O·1NHCl/MeOH	conc.HCl.
XV	245.3·9;300.3·4 Indoline	243.3·9;296.3·5 Indoline	261.2·6 Benzenoid	245.3·3;285.3·0 Benzenoid and 3H-indolium
XVI	248.3·9;295.3·4 Indoline	244.3·8;293.3·4 Indoline and indolenine	230.4·0;277.3·8 3H-indolium	244.4·0;285.3·9 3H-indolium
XVII	245.3·9;295.3·5 Indoline	241.3·88;291.3·4 Indoline	261.2·5 Benzenoid	235.3·6;285.3·5 3H-indolium and benzenoid
XVIII	241.3·9;288.3·5 Indoline and Indolenine	256.3·8 Indolenine	233.3·9;281.3·8 3H-indolium	240.3·9;285.3·8 3H-indolium
XX	240.3·9;295.3·4 Indoline	241.3·85;285.3·25 Indoline and Indolenine	230.3·9;275.3·8 3H-indolium	240.3·9;285.3·8 3H-indolium
XXI	252.3·9;302.3·3 Indoline	247.4·1;296.3·4 Indoline	230.3·9;275.3·8 3H-indolium	235.3·9;285.3·8 3H-indolium
XXII	240.3·8;290.3·5 Indoline	250.307 Indolenine	276.3·80 3H-indolium	240.3·8;280.3·8 3H-indolium
XXIII	255.4·0;300.3·6 Indoline	244.4·0.292.3·4 Indoline	230.3·9;275.3·8 3H-indolium	235/3·9;280.3·8 3H-indolium
XXIV	240.3·9;295.3·5 Indoline	245.3·8;292.3·3 Indoline	230.3·8;268.3·7 3H-Indolium	234.3·9;275.3·8 3H-indolium

From these results it is possible to summarize that in general:

(a) the ring closed tautomeric form is favoured by
  (i) lack of alkylation at C_2 of the indoline ring.
  (ii) presence of N-alkylation
  (iii) the presence of the O atom at the end of an Et chain as compared with a propyl chain bonded to C_3 of the indoline ring
(b) in n-hexane the compounds invariably exist in the ring closed form
(c) in alcoholic solution there is a tendency to ring open and this is almost always the case in dilute acid solution
(d) concentrated acid solution leads to full ring opening.

It is noteworthy that not any of the nine model PhNCO compounds showed an absorption maximum above 290 mm for the 3H-indolium cation produced in concentrated acid. This is in contrast to the absorption observed for the 3H-indolium cation produced from a number of indole alkaloid PhNCO systems which absorb at or above 310 mm.

The chemical reactivity of the PhNCO system during reduction and alkylation was also examined. All the compounds prepared were readily reduced by Zn/HCl and by lithium aluminium hydride (LAH) to the corresponding indolines. The reduction products were identified qualitatively by their UV absorptions in neutral and

acidic solution and were further differentiated from the starting materials by TLC. The reductions in acid solution take place most probably *via* the ring open tautomers but with LAH direct hydride ion attack on the ring closed form appears to be possible. This is borne out by the reduction of XXI which. owing to the presence of N—Me group is unable to form an anion with LAH which may form from the non N-alkylated compounds and lead to ring opening followed by reductive hydride ion attack at C_2. The reduction of the PhNCO system by LAH is not paralleled by the PhNCN system which is reduced only under acid conditions.[1] This difference in reactivity may be due to the lower nucleophilic character of the O atom in the PhNCO compounds as compared with the $N_{(b)}$ atom in the PhNCN compounds.

None of the PhNCO compounds were found to react with MeI in ethereal solution to produce either N or O alkylated products. Unchanged starting materials were recovered in all cases.

EXPERIMENTAL

All reagents and solvents used were laboratory grade unless otherwise stated. The m.ps were determined on a Kofler hot stage and are uncorrected. UV spectra were recorded on a Unicam SP500 instrument and IR spectra on a Unicam SP200 and Perkin–Elmer 337 instruments. NMR spectra were obtained on a Varian A60 in $CDCl_3$ with TMS as internal standard.

3-*Methyl*-3-(2-*hydroxyethyl*)-*indolenine*-XV. MeMgI (from 1·7 g of Mg) in ether (15 ml) was treated. by dropwise addition. with tryptophol (4·14 g. obtained by LAH reduction of indol-3-yl acetic acid) in ether (100 mL) The mixture was refluxed for 1 hr. and for a further 3 hr. accompanied by the dropwise addition of MeI. Solvent and excess MeI were removed under reduced pressure and the residue redissolved in ether and decomposed by dropwise addition of dilute AcOH. The basic material was taken up in 3N HCl and liberated by K_2CO_3. The oily product after extraction into ether was distilled (b.p. 95°/0·1 mm) and crystallized from toluene/petroleum ether at below 0° (2·1 g) m.p. 38°–39° (lit.[20] 42–43°). (Found: C. 75·3; H. 7·7; $C_{11}H_{13}NO$ requires: 1. 75·4; H. 7·48%). (film) 3300 (NH str.). 1610 (Indoline).

2.3-*Dimethyl*-3-(2-*hydroxyethyl*)-*indolenine*-XVI. Treatment of 2-methyl-3-(2-hydroxyethyl)-indole (14·0g. obtained by LAH reduction of ethyl 2-methylindol-3-yl acetate) with MeMgI and working up as for XV gave an oil (11·85 g) b.p. 117°/1 mm. which solidified and crystallized from petroleum ether to give a colourless solid m.p. 46–49° (lit.[19] 51·5–52·5°) IR absorption (film) 3300 (NH str.) 1610 (Indoline).

3-*Methyl*-3-(3-*hydroxypropyl*)-*indolenine*-XVII. Treatment of 3-(3-hydroxypropyl)-indole (1·0 g. obtained by LAH reduction of indol-3-yl propionic acid) with MeMgI and working up as for XV gave a basic product (560 mg).. crystals from petroleum ether m.p. 138°. (Found: C. 75·8; H. 7·65; $C_{12}H_{15}NO$ requires C. 76·15; H. 7·99%). I.R. ($CHCl_3$) 3400 cm^{-1} (NH str.) 1610 (Indoline) NMR singlet 5·25 τ (N—CH—O).

2.3-*Dimethyl*-3-(3-*hydroxypropyl*)*indolenine*-XVIII. (a) 2-*methylindol*-3-*ylpropionic acid*. 2-Methylindole (1·0 g), acrylic acid (0·6 g) in AcOH (2·0 ml) and Ac_2O (1·0 ml) were heated at 110° for 3 hr in an evacuated sealed tube. The product was partitioned between ether/water and the acid extracted into $NaHCO_3$ aq. which gave the required material (1·16 g) m.p. 135–137° from water (lit.[21] 138°).

(b) 2-*Methyl*-3-(3-*hydroxypropyl*)*indole*. The above acid (2·4 g) in THF (50 ml) was added to LAH (2·0 g) in THF (100 ml) and the mixture refluxed for 2 hr. The neutral product (2·2 g) was an oil b.p. 148–152°/0·01 mm. (Found: C, 76·0: H, 7·95: $C_{12}H_{15}NO$ requires: C. 76·15: H, 7·99%).

(c) XVIII—treatment of the indole from (b) (1·5 g) with MeMgI and working up as for XV gave an oil (1·63 g) b.p. 140–144/0·01 mm. (Found: C. 77·45; H. 8·9; $C_{13}H_{17}NO$ requires C. 76·81; H. 8·43%). Picrate m.p. 130–133° (ex. EtOH). (Found C. 53·30; H. 4·65; $C_{19}H_{20}N_3O_8$ requires C. 62·78; H. 4·66%).

11-(2-*hydroxyethyl*)-1.2.3.4-*tetrahydrocarbazolenine*-XX. The ethylene ketal. XIX. of 2-(2-hydroxyethyl)-cyclohexanone[22] (0·31 g) and phenyl hydrazone (0·20 g) in glacial HOAc (5 ml.) were refluxed for 3 hr. The resultant solution was taken to dryness under reduced pressure and taken up in 2 NHCl. After ether washing the acid solution was made alkaline with 2N NaOH and ether extracted to give a yellow oil (200 mg.) The oil showed the UV absorption of an indolenine at 250 mm in MeOH and at 230 and 275 mm in dil. HCl. and the IR indicated the presence of a mixture with absorptions at 3300 (NH/OH). 1730 (C=O).

1610 (C=N), 1230 cm^{-1} (C—O acetate). This product was taken up in MeOH (5 ml) and 4N NaOH was added (2 ml) and left at room temperature for 24 hr. The crystalline material deposited was ether extracted and crystallized from n-hexane to give a colourless solid m.p. 81–83° (lit.[17] 79–81°). IR (Nujol) 3300 (NH indoline) 1610 m^{-1} (indoline). Picrate m.p. 154–157°. (Found: C. 53·89; H. 4·53; $C_{20}H_{20}N_4O_8$ requires C. 54·0; H. 4·50%).

9-*Methyl*-11-(2-*hydroxyethyl*)-1.2.3.4-*tetrahydrocarbazolenine*-XXI. The ethylene ketal[22]XIX (n=1. R=H) 2·6 g) and asy-N-methylphenylhydrazine (1·9 g) were refluxed in glacial AcOH (35 ml.) for 3 hr. The mixture was worked up as for XX to yield an oily basic material (2·24 g) which was treated with NaOH/MeOH. The resultant non-crystalline product was chromatographed on neutral alumina. Elution with benzene/ether /1 :1. v/v) gave a colourless oil (200 mg) which crystallized slowly on standing. Recrystallization from hexane gave a colourless solid m.p. 56–58° (lit./[7] 58–60°). IR (Nujol) 1968 (indoline) 1020 cm^{-1} (C—O) Picrate m.p. 165–7° (Found: C. 55·82; H. 5·12; $1_{21}H_{22}N_4O_8$ requires C. 56·25; H. 4·91%).

11-(3-*hydroxypropyl*)-1.2.3.4-*tetrahydrocarbazolenine*-XXII. (a) *Diethyl ketal of* 2-(3-*hydroxypropyl*)-*cyclohexanone* XIX (n=2. R=H). Ethyl 3-(2-2oxocyclohexyl)-propionate[23] (33·4 g) was refluxed with $HC(OEt)_3$ (35 ml) in absolute EtOH (100 ml) in the presence of NH_4Cl (1·0 g) for 12 hr. Excess solvent was removed and the product distilled under reduced pressure to give a colourless oil (30·0 g) b.p. 135°/9 mm., the ketal of the named ester. (Found: C. 66·5; H. 9·83; $C_{15}H_{28}O_4$ requires C. 66·1; H. 10·2%) IR (film) 1737 (C=O ester). 1180. 1160. 1120. 1095. 1060 980 (C—O of ester and ketal).

The ketal ester (9·8 g) in boiling abs. EtOH (50 ml) was treated in portions with Na (10·0 g) and EtOH (50 ml) over 2 hr. After removing excess solvent the product was distilled to give a colourless oil (6·1 g) b.p. 118/0·4 mm., n_{19} 1·4715. (Found: C, 67·70; H, 11·40; $C_{13}H_{26}O_3$ requires C, 67·80; H, 11·30%). IR 3400 (OH). 1160. 110. 1097. 1078. 1058. 980 (C—O ketal and pri-alcohol).

(b) The above diethyl ketal. XIX (n=2· R=H) (3·05 g) and $PhNHNH_2$ (2·14 g were refluxed in glac. AcOH (20 ml) for 2½ hr. Work up as for XX, gave a brown oil (3·1 g) which crystallized from ether to give a pale yellow crystalline solid m.p. 124–125°. (Found: C. 78·61; H. 8·3; $C_{15}H_{19}NO$ (XXII) requires C. 78·50; H. 8·29%). IR (Nujol). 3330 (NH indoline).

9-*Methyl*-11-(3-*hydroxypropyl*)-1.2.3.4-*tetrahydrocarbazolenine*-XXIII. A solution of the diethyl ketal XIX (n=Z. R=H) (3·96 g). as N-methylphenylhydrazine (2·11 g) in glac. AcOH (25 ml) were refluxed for 45 min. The mixture was worked up as for XX, to yield a brown basic oil (3·0 g) which could not be induced to crystallize. Chromatography on neutral alumina gave a colourless oil (0·71 g) eluted with C_6H_6/5% MeOH (v/v). The oil crystallized on standing to give a solid. recrystallized from MeOH, m.p. 87–89°. (Found: C. 79·00; H. 8·65; $C_{16}H_{21}NO$ (XXIII) requires C. 79·00; H. 9·18%). IR (Nujol) 3250 (NH indoline) 1600 (indoline).

2-(2-*hydroxypropyl*)-1.2.3.4-*tetrahydrocarbazolenine*-XXIV. A solution of 2-(2-hydroxypropyl)-cyclohexanone[24] (3·0 g) and $PhNHNH_2$ (2·4 g) in glac. AcOH (25 ml) were refluxed for 2 hr. Work up as for XX gave a basic brown solid (2·1 g) which on crystallization from n-hexane gave a colourless product m.p. 84–86°. (Found: C. 78·35; H. 8·00; $C_{15}H_{19}NO$ (XXIV) requires 1. 78·50; H. 8·29%). IR (Nujol) 3270 (NH indoline) 1600 cm^{-1} (indoline).

Reduction of the N—CO *compounds* XV–XVIII *and* XX–XIV. (a) *Reduction by* Zn(HCl. The reduction was carried on all nine compounds by the simultaneous addition of 50% HCl (5 ml) and excess Zn dust (3·0 g) to a solution of the compound (50 mg) in 25% HCl (5 ml) at 100°. The reduction was carried out until a sample of the mixture showed the absence of 3H-indolium ion absorption and possessed only a protonated aniline absorption in its UV spectrum. The reaction was stopped (2–3 hr) and after making alkaline with solid NaOH. was ether extracted. The UV absorption of the product was recorded and its R_f value compared with that of starting material. In all nine cases the UV spectra of the products were typically indoline in neutral MeOH. changing to the anilinium cation absorption on addition of acid. The R_f values of all products were found to be lower than for the starting material when developed with $CHCl_3$/MeOH (98·2. v/v)

All nine compounds were readily reduced by Zn/HCl.

(b) *Reduction by* LAH. The compound (XV-XVIII and XX-XIV) 0·1 g) in ether (5·0 ml) was added dropwise to a slurry of LAH (0·1 g) in ether (20 ml). The mixture after standing at room temperature for 8–10 hr was refluxed (1–8 hr). Excess LAH add reduction intermediates were decomposed with aqueous NaOH (1%. w/v) and the products extracted into ether. The ether. after drying. was evaporated to yield an oil (0·087 g) examined by UV spectroscopy and TLC as under Zn/HCl reduction. Of the nine compounds all but XVI and XXIII were completely reduced to the corresponding indolines. Compounds XVI and XXIII appeared to produce an insoluble complex in the early stage of the reduction and were found to be unreduced

after 8 hr. TLC and UV absorption spectrum showed the presence of starting material only, which was further confirmed by IR.

Alkylation with MeI. The title compounds were reacted with MeI under three conditions: (a) The MeI was added in ether to an ethereal solution of the compound over one hr at room temperature. (b) An ethereal solution of the compound and MeI were boiled under reflux for 3 hr. (c) An ethereal solution of the compound and MeI were kept in the dark in a stoppered flask for six days.

In each case the ethereal solution after drying was evaporated under reduced pressure and the residue examined by IR and TLC All nine compounds were found to be recovered unchanged from these attempted methylations.

Acknowledgment—The authors (A.Z.B.) and (W G.B. with G.M.H.) wish to express their thanks for facilities at the Lanchester Polytechnic, Coventry, and Salford University, respectively, where much of the work was carried out.

REFERENCES

[1] A. H. Jackson and A. E. Smith. *J. Chem. Soc.* 5510 (1964)
[2] B. Robinson. M.Sc. Thesis. Manchester (1958)
[3] H. F. Hodson and G. F. Smith. *J. Chem. Soc.* 1877 (1957)
[4] A. K. Kiang and G. F. Smith. *Proc. Chem. Soc.* 298 (1962)
[5] A. J. Birch. H. F. Hodson and G. F. Smith. *Proc. Chem. Soc.* 224 (1959)
[6] B. Witkop. *J. Am. Chem. Soc.* **72**. 2311 (1950)
[7] A. J. Birch. H. F. Hodson. B. Moore. and G. F. Smith. *Proc. Chem. Soc.* 62 (1961)
[8] J. Levy. J. Le Men and M. M. Janot. *Bull. Soc. Chim.* 1659 (1961)
[9] A. Z. Britten and G. F. Smith. *J. Chem. Soc.* 3850 (1963).
[10] C. E. Nordman and S. K. Kumara. *J. Am. Chem. Soc.* **87**. 2059 (1965)
[11] J. A. Joule. M. Ohashi. B. Gilbert and C. Djerassi. *Tetrahedron* **21**. 1717 (1965)
[12] J. A. Joule. Ph.D. Thesis. Manchester (1961)
[13] H. Fritz and O. Fischer. *Tetrahedron* **20**. 1737 (1964)
[14] J. A. Joule and G. F. Smith. *J. Chem. Soc.* 312 (1962)
[15] B. Robinson. *Ibid.* 1503 (1964)
[16] R. B. Longmore and B. Robinson. *Chem. and Ind.* 1638 (1966)
[17] H. Fritz and O. Fischer. *Tetrahedron* **20**. 2047 (1964)
[18] A. Z. Britten. Ph.D. Thesis. Manchester (1963)
[19] M. Nakazaki. *Bull. Soc. Jap.* **32**. 588 (1959)
[20] T. Hoshino and K. Shimodaira. *Annalen* **520**. 19 (1935)
[21] J. Harley-Mason. *J. Chem. Soc.* 2433 (1952)
[22] A. Segre. R. Veterbo and G. Parisi. *J. Am. Chem. Soc.* **79**. 3503 (1957)
[23] G. Stork et al.. *Ibid.* **85**. 207 (1963)
[24] A. Z. Britten. W. S. Owen and C. W. Went. *Tetrahedron* **25**. 3517 (1969)