342. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part VII.*[1] *The Nature of the Keto-base* $C_8H_{13}NO$ *from Dioscorine, and an Attempt at its Synthesis.*

By I. G. Morris and A. R. Pinder.

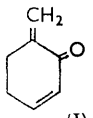
The $C_8H_{13}NO$ keto-base obtained as a degradation product of dioscorine is shown to be 2-methyl-5-oxoisoquinuclidine (VI), and dioscorine must consequently be re-formulated as (XXII).

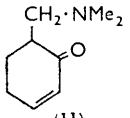
In a recent paper [2] we showed unequivocally that the ketonic base $C_8H_{13}NO$ obtained by degradation of the alkaloid dioscorine [3] was not tropan-2-one, and that the corresponding deoxo-base, $C_8H_{15}N$, was not tropane.

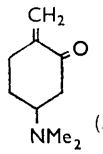
An interesting observation concerning the base $C_8H_{13}NO$ is the sensitivity of its methiodide to very mild basic conditions, the salt undergoing smooth Hofmann degradation in the presence of sodium hydrogen carbonate at room temperature.[4] We have confirmed this and have investigated the reaction closely. Two products have been isolated, a base $C_9H_{15}NO$ and a neutral compound C_7H_8O. The methiodide of the former yields the latter on similar mild basic treatment.

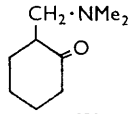
The neutral product is an unstable, ketonic liquid, with a sharp odour. Its ultraviolet absorption shows a maximum at 243 mμ (ε 11,500 in methanol), a value roughly intermediate between those expected for a conjugated enone and a conjugated dienone. In the infrared region, its carbon tetrachloride solution shows bands at 1675 (αβ-unsaturated ketone), 1620 (conjugated C=C), and 942 cm.$^{-1}$ (conjugated C=CH_2).[5] The relative intensities of the first two bands ($\varepsilon_{CO}/\varepsilon_{C=C}$ ~1·3) indicate that the αβ-unsaturated ketone system is *cisoid* in configuration,[6] suggesting that a carbonyl-conjugated C=CH_2 is present. Considered in conjunction with the ultraviolet absorption data, these observations are in harmony with the presence of a cross-conjugated dienone system, with the anomalous ultraviolet absorption frequently encountered with such groupings.

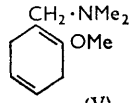
The neutral product polymerised to a resinous material on storage or in contact with acid. When shaken in ethanol solution in hydrogen with palladised charcoal, which had been shaken previously in hydrogen, it was isomerised smoothly to *o*-cresol, with virtually no uptake of hydrogen. We therefore formulate this degradation product as 6-methylenecyclohex-2-enone (I).


(I)


(II)


(III)


(IV)


(V)

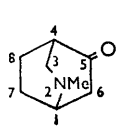
The Hofmann base $C_9H_{15}NO$ must accordingly be formulated either as 6-dimethylaminomethylcyclohex-2-enone (II) or as 6-methylene-3-dimethylaminocyclohexanone (III). Ultraviolet-absorption studies ($\lambda_{max.}$ 227 mμ, ε 12,240 in MeOH) supported the presence of an αβ-unsaturated ketone system. In the infrared region the product (in CCl_4) showed bands at 1678 (αβ-unsaturated ketone), 1620 (conjugated C=C), and 712 cm.$^{-1}$ (*cis*-CH=CH); there was only very feeble absorption in the 942 cm.$^{-1}$ region [contrast (I)], which suggests that the product is mainly of structure (II), with perhaps a trace of (III).

[1] Part VI, Davies, Jones, and Pinder, *J.*, 1960, 3504. For a preliminary report see Davies, Morris, and Pinder, *Chem. and Ind.*, 1961, 1410.
[2] Davies, Morris, and Pinder, *Tetrahedron*, 1962, **18**, 405.
[3] Jones and Pinder, *J.*, 1959, 615.
[4] Büchi, Ayer, and White, XVIth Internat. Congr., Pure Appl. Chem., Paris, July 1957.
[5] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, Chapters 3 and 9.
[6] Erskine and Waight, *J.*, 1960, 3425.

In addition, the ratio $\varepsilon_{CO}/\varepsilon_{C=C}$ was high (*ca.* 4), indicating that the enone system is *transoid*, as in (II).[6]

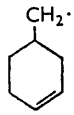
Hydrogenation of the Hofmann base afforded a saturated keto-base $C_9H_{17}NO$, which, on the basis of the above argument, should be 2-dimethylaminomethylcyclohexanone (IV). The reduction product did not absorb intensely in the ultraviolet region; in the infrared it had $\nu_{max.}$ 1718 cm.$^{-1}$ (in CCl_4) (saturated >C=O). Both bases were optically unstable.

6-Dimethylaminomethylcyclohex-2-enone (II), which has been prepared from cyclohex-2-enone by a Mannich reaction,[7] was synthesised by a straightforward route from salicylaldehyde. The penultimate step was the Birch reduction of 2-methoxy-*NN*-dimethylbenzylamine to the dihydro-derivative (V), which on acid hydrolysis afforded the racemic ketone (II). An infrared comparison between the synthetic and the " natural " keto-bases (in solution) established that they were identical. 2-Dimethylaminomethylcyclohexanone (IV) was synthesised by reduction of the synthetic cyclohexenone (II), and by a Mannich reaction between cyclohexanone, dimethylamine, and formaldehyde.[8-10] Infrared comparisons of the two synthetic products (in solution) with each other and with the reduced Hofmann base, $C_9H_{17}NO$, showed identity.

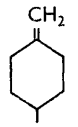


(VI)

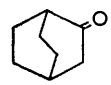
(VII; R = CH_2Ph)



(VIII)



(IX)



(X)

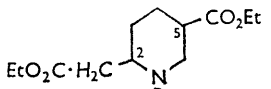
We consequently formulate the base $C_8H_{13}NO$ as 2-methyl-5-oxoisoquinuclidine (VI). The fact that its Hofmann degradation product has structure (II) rather than (III) is in harmony with Werner and Ricca's observation that 2-benzylisoquinuclidine (VII) yields the base (VIII) on Hofmannn degradation, to the exclusion of the alternative possibility (IX); the formation of an endocyclic rather than exocyclic double bond is preferred.[11] We account for the abnormally high infrared carbonyl frequency (1741 cm.$^{-1}$) of the base (VI), first, in terms of the strain in the bicyclic isoquinuclidine system. Bicyclo[2,2,2]-octan-2-one (X), which we synthesised from homoterephthalic acid,[12] shows ν(C=O) at 1733 cm.$^{-1}$ (in CCl_4), compared with cyclohexanone at 1715 cm.$^{-1}$, and abnormally high carbonyl stretching values are frequently found with bridged ketones.[13] Secondly, the strongly basic nitrogen atom in the same ring as the carbonyl group also raises the frequency.[3,14] The very ready Hofmann degradation of the keto-base (VI) may be explained partly by strain and partly by the activating influence of the carbonyl group on the hydrogen atoms at position 6, β to the nitrogen atom; the latter explanation also accounts for the similar ease of Hofmann degradation of the keto-base (II).

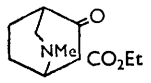
Reduction of the keto-base $C_8H_{13}NO$ yields an oxygen-free base $C_8H_{15}N$, formerly erroneously identified [1] as tropane. On the basis of the above argument, this base would be formulated as 2-methylisoquinuclidine (XI). This compound was synthesised from *p*-aminobenzoic acid by successive hydrogenation, lactamisation,[11,15] reduction with lithium aluminium hydride, and methylation. The penultimate step required prolonged treatment with the hydride in boiling tetrahydrofuran; it has been reported [11] that

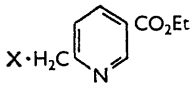
[7] Jacquier, Mousseron, and Boyer, *Bull. Soc. chim. France*, 1956, 1653.
[8] Dimroth, Resin, and Zetsch, *Ber.*, 1940, **73**, 1399.
[9] Mannich and Braun, *Ber.*, 1920, **53**, 1874.
[10] McElvain and Clampitt, *J. Amer. Chem. Soc.*, 1959, **81**, 5590.
[11] Werner and Ricca, *J. Amer. Chem. Soc.*, 1958, **80**, 2733.
[12] Komppa, *Ber.*, 1935, **68**, 1267.
[13] See Allen, Davis, Stewart, and VanAllan, *J. Org. Chem.*, 1955, **20**, 306; Alder, Schäfer, Esser, Krieger, and Reubke, *Annalen*, 1955, **593**, 23.
[14] Eglinton and Pinder, unpublished observations.
[15] Houben and Pfau, *Ber.*, 1916, **49**, 2294; Greenstein and Wyman, *J. Amer. Chem. Soc.*, 1938, **60**, 2341; Ferber and Brückner, *Ber.*, 1943, **76**, 1019.

milder conditions are not effective. An infrared comparison between the final product and the base $C_8H_{15}N$ showed that they were identical. The picrate of this base, m. p. 283—284° (decomp.), was undepressed in m. p. on admixture with authentic tropane


(XI)

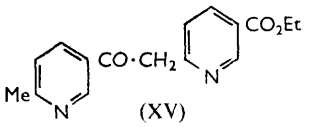

(XII)

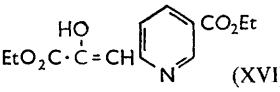

(XIII)

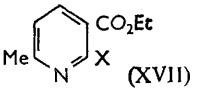

(XIV)

picrate, m. p. 284—285° (decomp.), but the infrared spectra of the two free bases were different in the " fingerprint " region.

In an attempt to synthesise 2-methyl-5-oxoisoquinuclidine (VI), an intermediate objective was the piperidine diester (XII; R = Me), which, it was hoped, would undergo a Dieckmann cyclisation to the β-keto-ester (XIII). Thence, hydrolysis and decarboxylation would afford compound (VI). A conveniently accessible starting-point was ethyl 6-methylnicotinate (XIV; X = H), the methyl group of which proved, as expected, to be rather more reactive than that of 2-picoline. Attempts to hydroxycarbonylate this group through the lithio-derivative (XIV; X = Li) were unsuccessful, whilst an effort to condense the ester with diethyl carbonate under the usual basic conditions led, not to the desired diester (XIV; X = CO_2Et), but to the self-condensation product (XV). Also the lithio-derivative failed to react with ethyl chloroformate. The lithio-derivative was a bright yellow powder, which appeared to be a true salt rather than a typical lithium alkyl, possibly owing to the relatively high acidity of the hydrogen atoms of the methyl group. On the other hand, the ester condensed with ethyl oxalate to give the pyruvate ester (XIV; X = $CO{\cdot}CO_2Et$), but this resisted attempts to decarbonylate it to the acetate (XIV; X = CO_2Et), possibly because it exists in the free state largely as the enolic form (XVI).


(XV)

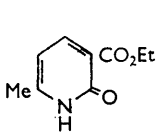

(XVI)


(XVII)

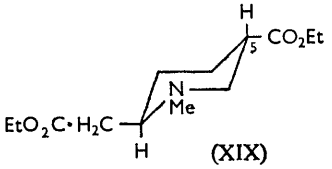
Conversion of a substituted pyridine into its *N*-oxide is known to enhance the reactivity of both nucleus and side-chain.[16] The ester (XIV; X = H) yielded an *N*-oxide, reaction of which with phosphorus pentachloride[17] yielded the nuclear-chlorinated ester (XVII; X = Cl),[18] rather than the desired chloromethylpyridine (XIV; X = Cl). The product was identified by its chemical properties and by comparison with the desired product (XIV; X = Cl), eventually obtained as described below. Reaction of the *N*-oxide with acetic anhydride[19] yielded as main product the acetoxymethylpyridine (XIV; X = OAc), mild hydrolysis of which furnished the corresponding alcohol (XIV; X = OH), together with a small yield of the hydroxypyridine (XVII; X = OH). The latter, easily separated because of its sparing solubility, arose by hydrolysis of the 2-acetoxypyridine (XVII; X = OAc), formed as minor product in the acetylation of the amine oxide. The same hydroxypyridine was obtained by mild hydrolysis of the chloropyridine (XVII; X = Cl); in the solid state it contained, on infrared evidence, none of the α-pyridone tautomer (XVIII). Treatment of the alcohol (XIV; X = OH) with phosphorus pentachloride gave the corresponding chloride (XIV; X = Cl), different from the chloropyridine (XVII;

[16] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[17] Cf. Matsumura, *J. Chem. Soc. Japan*, 1953, **74**, 363.
[18] Cf. Bobranski, Kochanska, and Kowalewska, *Ber.*, 1938, **71**, 2385; Taylor and Crovetti, *J. Org. Chem.*, 1954, **19**, 1633.
[19] Cf. Boekelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286; Bullitt and Maynard, *ibid.*, p. 1370; Boekelheide and Lehn, *J. Org. Chem.*, 1961, **26**, 428.

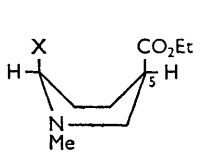
X = Cl). Nucleophilic displacement with sodium cyanide, under strictly defined conditions, then yielded the corresponding nitrile (XIV; X = CN),[20] which on ethanolysis



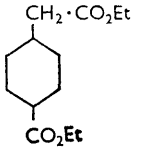
(XVIII)



(XIX)

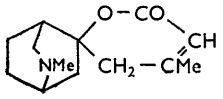


(XX; X = $CH_2 \cdot CO_2Et$)

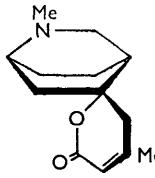


(XXI)

gave the diester (XIV; X = CO_2Et). Catalytic hydrogenation of the latter afforded the piperidine diester (XII; R = H) as a mixture of *cis*- and *trans*-forms, the latter presumably predominating, for conformational reasons. Methylation then gave the tertiary base (XII; R = Me), also as a mixture of geometrical isomers.



(XXII)



(XXIII)

Attempts to effect the Dieckmann cyclisation, in a variety of conditions, of the diester (XII; R = Me) to the β-keto-ester (XIII) have so far proved unfruitful, possibly because the isoquinuclidine ring system is slightly strained. The diester is presumably mainly the *trans*-diequatorial compound (XIX), with the reacting groups unfavourably oriented for bridging cyclisation. However, it is conceivable that under the vigorous, strongly basic conditions the 5-ethoxycarbonyl group would be inverted and become axial, and when this 5-epimer is converted into the boat form (XX), a requirement for cyclisation, the groups are seen to be favourably placed for bridge formation. It is significant, perhaps, that we had earlier failed to cyclise the carbocyclic analogue (XXI), though the corresponding diacid can be cyclised thermally.[12] Attempts to effect thermal cyclisation of the diacid corresponding to (XII; R = Me) were attended by serious decomposition involving the *N*-methyl group.

Dioscorine must now be re-formulated as (XXII), and, more exactly, on the basis of hydrogen-bonding studies on deoxydihydrodioscorinol,[21] as (XXIII).

Experimental

Hofmann Degradation of the Keto-base $C_8H_{13}NO$.—The keto-base was obtained by degradation of dioscorine as described earlier.[3,12] The methiodide, after one crystallisation from aqueous ethanol, had m. p. 295° (decomp.),[3] but crystallisation was expensive owing to the ready decomposition of the salt. A solution of the crude methiodide (1·55 g.) in water (25 c.c.) was saturated with sodium hydrogen carbonate and kept at room temperature for 24 hr. The solution was saturated with potassium carbonate at 0° and subjected to continuous ether-extraction for 24 hr. The extract was shaken with N-hydrochloric acid (3 × 20 c.c.), and the combined acid layers were basified with an excess of aqueous potassium carbonate at 0° and extracted continuously with ether for 24 hr. Evaporation of the dried (K_2CO_3) extract through a column yielded 6-*dimethylaminomethylcyclohex*-2-*enone* (II), b. p. 98—99°/9·5 mm. (0·5 g.) (Found: C, 71·1; H, 9·6; N, 9·0. $C_9H_{15}NO$ requires C, 70·6; H, 9·8; N, 9·15%), $\lambda_{max.}$ 226 mμ (ε 12,240 in MeOH), $\nu_{max.}$ (in CCl_4) 1678 (C=O), 1620 (conj. C=C), and 712 (*cis*-CH=CH) $cm.^{-1}$, $[\alpha]_D^{22}$ −1·4° (*c* 1·45 in EtOH). The *picrate*, obtained from a freshly prepared sample of the keto-base, separated from methanol in yellow elongated prisms, m. p. 142° (Found: C, 47·2; H, 4·7; N, 14·8. $C_{15}H_{18}N_4O_8$ requires C, 47·1; H, 4·7; N, 14·7%). The *methiodide* crystallised, with considerable loss owing to decomposition, from ethanol in irregular prisms, m. p. 133·5°

[20] Cf. Itai and Ogura, *J. Pharm. Soc. Japan*, 1955, **75**, 296; Hurst and Wibberley, *J.*, 1962, 119.
[21] Pinder, *Tetrahedron*, 1957, **1**, 301.

(Found: C, 40·7; H, 6·2. $C_{10}H_{18}INO$ requires C, 40·7; H, 6·1%), $\lambda_{max.}$ 222 mμ (ε 14,000 in MeOH).

The neutral ether layer from the original extraction was washed with sodium hydrogen carbonate and water, dried, and concentrated through a fractionating column, leaving *6-methylenecyclohex-2-enone* (I), b. p. 80°/20 mm. (60 mg.) (Found: C, 77·5; H, 7·4. C_7H_8O requires C, 77·8; H, 7·4%), $\lambda_{max.}$ 243 mμ (ε 11,500 in MeOH), $\nu_{max.}$ (in CCl_4) 1675 (C=O), 1620 (conj. C=C), and 942 cm.$^{-1}$ (conj. C=CH_2). The product was a liquid, with a sharp odour, which polymerised to a rubbery material on storage or in contact with concentrated acids. When the ketone (50 mg.) in ethanol (10 c.c.) was shaken in hydrogen with 10% palladised charcoal, which had previously been shaken for 30 min. in hydrogen at room temperature and pressure, it was smoothly converted, with virtually no uptake of hydrogen, into *o*-cresol, identified by comparing its infrared absorption curve with that of an authentic specimen, and by its 3,5-dinitrobenzoate, elongated prisms [from 1 : 2 benzene–light petroleum (b. p. 80—100°)], m. p. and mixed m. p. 136·5° (Found: C, 56·0; H, 3·6; N, 9·2. Calc. for $C_{14}H_{10}N_2O_6$: C, 55·6; H, 3·3; N, 9·3%).

Hofmann Degradation of the Keto-base $C_9H_{15}NO$.—The methiodide of this base (once crystallised, see above) (0·77 g.), sodium hydrogen carbonate (2·0 g.), and water (20 c.c.) were mixed and kept at room temperature overnight. The odour of trimethylamine soon became apparent. The solution was rendered just acid with N-hydrochloric acid and extracted continuously with ether for 12 hr. Evaporation of the dried extract through a column and distillation of the residue yielded 6-methylenecyclohex-2-enone, b. p. 75°/16 mm. (0·22 g.), identical (infrared comparison) with the product described above. The residual aqueous solution was made strongly basic with solid potassium hydroxide and warmed gently, the vapours evolved being absorbed in a little methanol. The methanolic solution was mixed with methanolic picric acid, and the crystalline picrate collected. It separated from ethanol in yellow, elongated prisms, m. p. 216—217°, alone or mixed with trimethylamine picrate, m. p. 217°.

Hydrogenation of the Keto-base $C_9H_{15}NO$.—The base (0·22 g.) in N-hydrochloric acid (40 c.c.) was shaken in hydrogen with 5% palladised charcoal (uptake 1 mol.). The solution was filtered, basified with potassium carbonate solution, and extracted continuously with ether for 12 hr. The dried extract on evaporation yielded 2-dimethylaminomethylcyclohexanone (IV), b. p. 93—94°/8 mm. (0·20 g.) [Found: C, 69·6; H, 10·7; N, 9·0. Calc. for $C_9H_{17}NO$: C, 69·7; H, 11·0; N, 9·0%), $\nu_{max.}$ (in CCl_4) 1718 cm.$^{-1}$ (C=O), $[\alpha]_D^{22}$ 0° (*c* 0·5 in EtOH). The *picrate*, obtained from a freshly prepared sample of the keto-base, crystallised from methanol in yellow needles, m. p. 163° (Found: C, 47·0; H, 5·2; N, 14·4. $C_{15}H_{20}N_4O_8$ requires C, 46·9; H, 5·2; N, 14·6%).

(±)-*6-Dimethylaminomethylcyclohex-2-enone* (II).—*o*-Methoxybenzaldehyde was obtained by the methylation of salicylaldehyde with methyl sulphate.[22] It was converted into the oxime in the usual manner,[23] m. p. 91—92°. Reduction of the oxime with sodium amalgam and ethanol [23] yielded 2-methoxybenzylamine, b. p. 108°/13 mm. This amine (9·15 g.) was cooled in ice and mixed cautiously with 90% formic acid (18·0 g.). 40% Formaldehyde solution (11·0 g.) was added and the mixture refluxed on the water-bath for 3 hr.[24] The cooled solution was acidified and extracted with ether to remove neutral products. It was then rendered strongly basic with potassium hydroxide, and the liberated base isolated with ether. 2-Methoxy-*NN*-dimethylbenzylamine distilled at 103—104°/13 mm. (9·2 g.) (lit.,[25] b. p. 113°/20 mm.). This base (9·2 g.) in methanol (30 c.c.) was added dropwise gradually to stirred liquid ammonia (500 c.c.), followed by sodium metal (8·0 g.) in small pieces, during 1 hr. After a further 30 minutes' stirring, ether and water were added cautiously, and the ammonia was allowed to evaporate. The layers were separated, the aqueous layer was extracted once with ether, and the ether layers were combined and dried (K_2CO_3). Evaporation of the solvent afforded the dihydro-base (V) (8·65 g.), which was boiled with 2N-sulphuric acid (100 c.c.) under reflux under nitrogen for 1 hr. The cooled solution was extracted with ether, saturated with potassium carbonate, and extracted continuously with ether for several hours. Evaporation of the dried (Na_2SO_4) extract yielded (±)-6-dimethylaminomethylcyclohex-2-enone (II), b. p. 104—105°/14 mm. (lit.,[7] b. p. 105—106°/18 mm.) (3·65 g.) (after separation of a small

[22] Baeyer and Villiger, *Ber.*, 1902, **35**, 3023.
[23] Goldschmidt and Ernst, *Ber.*, 1890, **23**, 2740.
[24] Cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[25] Stedman, *J.*, 1927, 1904.

fore-run) (Found: C, 70·8; H, 9·9; N, 9·0. Calc. for $C_9H_{15}NO$: C, 70·6; H, 9·8; N, 9·15%), $\lambda_{max.}$ 226 mμ (ε 12,500 in MeOH). The infrared absorption curve (for a CCl_4 solution) was indistinguishable from that of the optically active Hofmann base $C_9H_{15}NO$ (also in CCl_4) described above. The picrate crystallised from methanol in golden, elongated prisms, m. p. 137—138° (lit.,[7] m. p. 130—131°) (Found: C, 46·8; H, 4·6; N, 14·5. Calc. for $C_{15}H_{18}N_4O_8$: C, 47·1; H, 4·7; N, 14·7%). The methiodide was decomposed by sodium hydrogen carbonate solution at room temperature into trimethylamine and 6-methylenecyclohex-2-enone.

(±)-2-*Dimethylaminomethylcyclohexanone* (IV).—(*a*) The foregoing keto-base (0·5 g.) in N-hydrochloric acid (10 c.c.) was shaken in hydrogen at room temperature and pressure with 10% palladised charcoal for 2 hr. (uptake 1 mol.). After removal of the catalyst by filtration the filtrate was basified and the product isolated with ether (continuous extraction). Evaporation of the dried extract yielded (±)-2-dimethylaminomethylcyclohexanone, b. p. 100°/15 mm. (lit.,[8] b. p. 93—94°/11·5 mm.) (Found: C, 69·6; H, 10·7; N, 9·2. Calc. for $C_9H_{17}NO$: C, 69·7; H, 11·0; N, 9·0%), $\nu_{max.}$ (in CCl_4) 1718 cm.$^{-1}$ (C=O). The picrate crystallised from methanol in needles, m. p. 140° (Found: C, 47·3; H, 5·0; N, 14·5. Calc. for $C_{15}H_{20}N_4O_8$: C, 46·9; H, 5·2; N, 14·6%) (lit.,[9] m. p. 149°).

(*b*) The same base was prepared by a Mannich reaction between cyclohexanone, dimethylamine hydrochloride, and formaldehyde,[8–10] in 79% yield. It distilled at 96°/14 mm.

The infrared absorption spectra of the two bases were identical, and identical with that of the dihydro-Hofmann keto-base $C_9H_{17}NO$ (see above; all spectra in CCl_4).

Catalytic Reduction of the Keto-base $C_8H_{13}NO$.—The hydrogenation of the base $C_8H_{13}NO$ as described earlier [1] yielded 2-methylisoquinuclidine (erroneously described as tropane in ref. 1), b. p. 96°/92 mm., identical (infrared comparison) with an authentic synthetic specimen (see below). The picrate had m. p. 284—285° (decomp.).[1]

2-*Methylisoquinuclidine* (2-*Methyl*-2-*azabicyclo*[2,2,2]*octane*) (XI).—4-Aminocyclohexanecarboxylic acid was prepared by catalytic hydrogenation of *p*-aminobenzoic acid.[11,15] Lactamisation to 3-oxoisoquinuclidine was effected thermally;[11,15] the product sublimed at 145—150° (bath)/20 mm. and separated from light petroleum (b. p. 80—100°) in elongated prisms, m. p. 194—195° (lit.,[15] m. p. 191—192°,[11] 200—202°) (Found: C, 66·9; H, 8·6; N, 11·1. Calc. for $C_7H_{11}NO$: C, 67·2; H, 8·85; N, 11·2%), $\nu_{max.}$ (in CCl_4) 1680 cm.$^{-1}$ (amide C=O). On admixture with a specimen of 3-oxoisoquinuclidine, m. p. 197—198° (kindly supplied by Dr. L. H. Werner,[11] CIBA Pharmaceutical Products, Inc.), the product had m. p. 196—196·5°; the infrared spectra of the two were identical (in CCl_4). The lactam (1·2 g.) in purified tetrahydrofuran (24 c.c.) was added to a suspension of lithium aluminium hydride (0·6 g.) in the same solvent (96 c.c.), and the mixture refluxed for 2 days. The solvent was evaporated and replaced by ether (60 c.c.), and some " Celite " added. Water was added cautiously until decomposition was complete, and the ethereal solution was decanted, dried (K_2CO_3), and evaporated. The residual isoquinuclidine sublimed at 100—110° (bath)/17 mm. (1·0 g.) (Found: C, 75·4; H, 11·6; N, 12·1. Calc. for $C_7H_{13}N$: C, 75·6; H, 11·7; N, 12·6%). Owing to the strong tendency of the base to sublime, even at room temperature and pressure, an accurate m. p. could not be ascertained. With rapid heating from 150° it had m. p. *ca.* 170° (lit.,[11] m. p. and b. p. 173—175°). The *picrate* separated from methanol in yellow plates, m. p. 245° (decomp.) (Found: C, 45·5; H, 4·9; N, 16·6. $C_{13}H_{16}N_4O_7$ requires C, 45·9; H, 4·7; N, 16·5%).

Isoquinuclidine (1·0 g.) was mixed cautiously, with cooling, with 90% formic acid (1·15 g.). 40% Formaldehyde solution (0·7 g.) was added and the mixture heated under reflux on the water-bath until the evolution of carbon dioxide had ceased (2 hr.),[24] cooled, diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The aqueous layer was cooled and basified with solid potassium hydroxide, and the liberated base was isolated with ether. Evaporation of the dried (K_2CO_3) extract through a Vigreux column yielded 2-*methylisoquinuclidine*, b. p. 86°/66 mm. (0·46 g.) (Found: C, 76·7; H, 12·2; N, 10·9. $C_8H_{15}N$ requires C, 76·7; H, 12·1; N, 11·2%). The infrared absorption curve of this base was identical with that of the reduction product of the keto-base $C_8H_{13}NO$ (see above). The picrate crystallised from water in yellow needles, m. p. 283—284° (decomp.) (Found: C, 47·7; H, 5·0; N, 15·6. Calc. for $C_{14}H_{18}N_4O_7$: C, 47·5; H, 5·1; N, 15·8%). The *methiodide* separated from methanol in needles, m. p. 338—339° (Found: C, 40·7; H, 6·8; N, 5·05. $C_9H_{18}IN$ requires C, 40·4; H, 6·7; N, 5·2%). This salt was identical (mixed m. p. comparison) with the methiodide (m. p. 338—338·5°) afforded by the reduction product of the keto-base $C_8H_{13}NO$ (see above).

Ethyl β-5-*Ethoxycarbonyl*-2-*pyridylpyruvate* (XIV; X = $CO{\cdot}CO_2Et$).—Ethyl 6-methylnicotinate was obtained by oxidation of 5-ethyl-2-methylpyridine ("aldehydecollidine"), followed by esterification;[26] the ester had b. p. 120—122°/13 mm. (lit.,[26] b. p. 116—118°/11 mm.). The *picrate* crystallised from ethanol in yellow needles, m. p. 169° (Found: C, 45·7; H, 3·4; N, 14·2. $C_{15}H_{14}N_4O_9$ requires C, 45·6; H, 3·55; N, 14·2%). The ester (3·3 g.) in dry ether (10 c.c.) was mixed with a suspension of finely powdered, ethanol-free sodium ethoxide (from 0·46 g. of sodium) in dry ether (15 c.c.).[27] After 30 min. diethyl oxalate (2·92 g.) in dry ether (10 c.c.) was added. After 16 hr. (occasional shaking), dilute acetic acid was added until the solution was just acid. The ether layer was separated, washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and concentrated. The residual *pyruvate ester* (4·4 g.) crystallised from light petroleum (b. p. 60—80°) in yellow needles, m. p. 102° (Found: C, 58·8; H, 5·4; N, 5·2. $C_{13}H_{15}NO_5$ requires C, 58·9; H, 5·7; N, 5·3%), $\nu_{max.}$ (in CCl_4) 1740 (aryl ester C=O) and 1746 $cm.^{-1}$ (α-keto-ester).[5] With alcoholic ferric chloride the product gave an intense green colour. The *copper complex* separated from 2-ethoxyethyl acetate in brown crystals, m. p. 220° (Found: C, 52·8; H, 4·7; N, 4·7. $C_{26}H_{28}CuN_2O_{10}$ requires C, 52·75; H, 4·7; N, 4·7%).

Attempts to decarbonylate the ester by heating it with powdered glass or toluene-*p*-sulphonic acid resulted in deep-seated decomposition.

Attempted Condensation of Ethyl 6-*Methylnicotinate with Diethyl Carbonate.*—The nicotinate (3·3 g.) and diethyl carbonate (11·8 g.) were mixed and added to ethanol-free sodium ethoxide (from 0·46 g. of sodium). The mixture was slowly distilled at 200 mm. from an oil-bath, through a Vigreux column, during 3 hr. The cooled residue was acidified with dilute acetic acid and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and concentrated. The residue (1·7 g.), considered to be *ethyl* 6-[2-(6-*methyl*-3-*pyridyl*)-2-*oxoethyl*]*nicotinate* (XV), separated from light petroleum (b. p. 60—80°) in bright yellow crystals, m. p. 97—98° (Found: C, 67·5; H, 5·6; N, 9·85; *C*-Me, 6·7; OEt, 18·4. $C_{16}H_{16}N_2O_3$ requires C, 67·6; H, 5·6; N, 9·9; 1*C*-Me, 5·3; 1OEt, 15·85%), $\nu_{max.}$ (in CCl_4) 1724 (aryl ester C=O) and 1681 $cm.^{-1}$ (aryl ketone C=O). The product gave a deep green colour with alcoholic ferric chloride.

5-*Ethoxycarbonyl*-2-*methylpyridine* 1-*Oxide.*—Ethyl 6-methylnicotinate (14·9 g.), glacial acetic acid (60 c.c.), and 30% hydrogen peroxide (21·5 c.c.) were heated together at 70—80° for 16 hr. The residual liquid was concentrated somewhat *in vacuo*, water (20 c.c.) was added, and the solution re-concentrated. The syrupy residue was dissolved in chloroform and washed with potassium carbonate solution until neutral, dried, (K_2CO_3) and recovered. The N-*oxide* remaining (13·6 g.) distilled at 104°/0·05 mm. It crystallised in needles, m. p. 42—43° (Found: C, 60·3; H, 6·3; N, 7·6. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%), $\nu_{max.}$ (in CCl_4) 1235 $cm.^{-1}$ (*N*-oxide). The *picrate* crystallised from ethanol in bright yellow needles, m. p. 87—88° (Found: C, 44·5; H, 3·4; N, 13·9. $C_{15}H_{14}N_4O_{10}$ requires C, 43·9; H, 3·4; N, 13·7%).

Ethyl 2-*Chloro*-6-*methylnicotinate* (XVII; X = Cl).—Phosphorus pentachloride (1·15 g.), the foregoing *N*-oxide (1·0 g.), and dry chloroform (10 c.c.) were refluxed on the water-bath for 1 hr. Ice was added to the cooled solution, which was then basified with potassium carbonate. The chloroform layer was separated, dried ($CaCl_2$), and concentrated. The solid residue (0·8 g.) of the 2-*chloro-ester* sublimed at 90—100° (bath)/0·3 mm. in needles, m. p. 34° (Found: C, 53·6; H, 5·6; N, 7·1; Cl, 18·1. $C_9H_{10}ClNO_2$ requires C, 54·2; H, 5·0; N, 7·0; Cl, 17·8%), $\nu_{max.}$ (Nujol mull) 1600 (C=N) and 1730 $cm.^{-1}$ (aryl ester C=O). Mild alkaline hydrolysis afforded the hydroxypyridine (XVII; X = OH) (see below).

Ethyl 6-*Acetoxymethylnicotinate* (XIV; X = OAc).—The above *N*-oxide (15·2 g.) in acetic anhydride (16·4 g.) was cautiously warmed to 80°, whereupon a vigorous reaction occurred. The mixture was boiled under reflux for 2 hr., and the excess of anhydride removed *in vacuo*. The residual dark oil was distilled fractionally through a short column. After a small fore-run *ethyl* 6-*acetoxymethylnicotinate* distilled at 138°/0·5 mm. (11·5 g.); it solidified at 0° to needles, m. p. 25° (Found: C, 59·1; H, 6·0; N, 6·2. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·8; N, 6·3%), $\nu_{max.}$ (in CCl_4) 1600 (C=N), 1730 (aryl ester C=O), and 1761 $cm.^{-1}$ (saturated ester C=O). The *picrate* crystallised from ethanol in yellow needles, m. p. 109—111° (Found: C, 45·5; H, 3·6; N, 12·3. $C_{17}H_{16}N_4O_{11}$ requires C, 45·1; H, 3·5; N, 12·4%).

[26] Graf, *J. prakt. Chem.*, 1932, **133**, 19; Plattner, Keller, and Boller, *Helv. Chim. Acta*, 1954, **37**, 1379.

[27] Cf. Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 3168.

Ethyl 6-Hydroxymethylnicotinate (XIV; X = OH).—The foregoing acetoxymethylpyridine (4·6 g.) in dry chloroform (23 c.c.) was mixed with ethanolic sodium ethoxide, prepared from sodium (0·46 g.) and ethanol (11·5 c.c.). After 2 hr. at room temperature the solution was poured into water (60 c.c.) containing glacial acetic acid (3 c.c.). The chloroform layer was separated, dried (Na_2SO_4), and evaporated, leaving a dark syrup containing crystalline material. This was shaken with cold carbon tetrachloride and filtered. The filtrate was concentrated and distilled, affording *ethyl 6-hydroxymethylnicotinate*, b. p. 86°/0·05 mm. (2·6 g.), hexagonal plates, m. p. 67° (Found: C, 59·8; H, 6·2; N, 8·0. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%), $\nu_{max.}$ (in CCl_4) 1600 (C=N), 1730 (aryl ester C=O), and 3600 cm.$^{-1}$ (OH). The *picrate* separated from ethanol in yellow plates, m. p. 108—109° (Found: C, 44·5; H, 3·5; N, 13·4. $C_{15}H_{14}N_4O_{10}$ requires C, 43·9; H, 3·4; N, 13·7%). The crystalline residue obtained during the above filtration, *ethyl 6-hydroxy-2-methylnicotinate* (XVII; X = OH) (0·5 g.), separated from ethanol–light petroleum (b. p. 60—80°) in needles, m. p. 201—202° (Found: C, 59·6; H, 6·0; N, 7·7. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%), $\nu_{max.}$ (Nujol mull) 1718 cm.$^{-1}$ (aromatic ester C=O), no amide C=O band.

Ethyl 6-Chloromethylnicotinate (XIV; X = Cl).—Phosphorus pentachloride (4·6 g.) was added gradually to a solution of the above hydroxymethyl-ester (4·0 g.) in dry chloroform so that gentle reflux was maintained. After a further 16 hr. water was added, followed by solid potassium carbonate. The chloroform layer was separated, dried ($CaCl_2$), and evaporated, furnishing *ethyl 6-chloromethylnicotinate*, b. p. 94°/0·1 mm. (3·5 g.), as an unstable oil (Found: C, 54·6; H, 5·5; N, 7·0; Cl, 16·2. $C_9H_{10}ClNO_2$ requires C, 54·2; H, 5·0; N, 7·0; Cl, 17·8%), $\nu_{max.}$ (in CCl_4) 1600 (C=N) and 1730 cm.$^{-1}$ (aryl ester C=O). The *picrate* crystallised from ethanol in bright yellow needles, m. p. 117—118° (Found: C, 42·1; H, 4·4; N, 13·0. $C_{15}H_{13}ClN_4O_9$ requires C, 42·0; H, 4·3; N, 13·0%).

Ethyl 6-Cyanomethylnicotinate (XIV; X = CN).—The foregoing chloromethyl-ester (1·75 g.) in absolute ethanol (4·0 c.c.) was added to a refluxing solution of sodium cyanide (1·3 g.) in absolute ethanol (19·4 c.c.) and water (0·8 c.c.). After being refluxed for 23 min. the liquid was cooled and poured into water (65 c.c.) and glacial acetic acid (2·1 c.c.), and the whole was extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract afforded *ethyl 2-cyanomethylnicotinate* (1·2 g.), b. p. 110°/0·1 mm., plates, m. p. 50—52° (Found: C, 63·3; H, 5·7; N, 14·6. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·7%), $\nu_{max.}$ (in CCl_4) 2290w (C≡N), 1736 (ester C=O), and 1605 cm.$^{-1}$ (pyridine C=N). The *picrate* separated from ethanol in brown crystals, m. p. 106—107° (Found: C, 46·3; H, 3·4; N, 16·4. $C_{16}H_{13}N_5O_9$ requires C, 45·8; H, 3·1; N, 16·7%).

Ethyl 6-Ethoxycarbonylmethylnicotinate (XIV; X = CO_2Et).—A solution of the above nitrile (1·3 g.) in absolute ethanol (40 c.c.) was saturated with dry hydrogen chloride at 0°, and then kept overnight at room temperature. The excess of ethanol was evaporated under reduced pressure, and the residue diluted with ice–water and basified with potassium carbonate. The required *diester*, isolated with chloroform, distilled at 106—108°/0·1 mm. (1·4 g.) (Found: C, 60·4; H, 6·4; N, 6·1. $C_{12}H_{15}NO_4$ requires C, 60·7; H, 6·3; N, 5·9%) and had $\nu_{max.}$ (in CCl_4) 1750 (saturated ester C=O) and 1730 cm.$^{-1}$ (aromatic ester C=O). The *picrate* crystallised from ethanol in yellow needles, m. p. 106—107° (Found: C, 46·6; H, 3·9; N, 12·3. $C_{18}H_{18}N_4O_{11}$ requires C, 46·4; H, 3·9; N, 12·3%).

Ethyl 5-Ethoxycarbonyl-2-piperidylacetate (XII; R = H).—The foregoing pyridine diester (14·1 g.) in glacial acetic acid (150 c.c.) was hydrogenated at room temperature and pressure over 5% rhodium–alumina during 10 hr. (uptake 3 mol.). The solution was filtered, concentrated, diluted with water, cooled, and basified with aqueous potassium carbonate. The *piperidine diester*, isolated with ether, distilled, after separation of a small fore-run, at 96°/0·1 mm.; it was presumably a mixture of *cis*- and *trans*-isomers, with the latter predominant (Found: C, 59·4; H, 8·7; N, 5·8. $C_{12}H_{21}NO_4$ requires C, 59·3; H, 8·6; N, 5·8%), $\nu_{max.}$ (in CCl_4) 3500 (secondary amine >NH) and 1749 cm.$^{-1}$ (saturated ester C=O). The product formed a yellow nitrosamine on treatment with nitrous acid.

Ethyl 5-Ethoxycarbonyl-1-methyl-1-piperidyl acetate (XII; R = Me).—The foregoing secondary base (5·1 g.) was mixed cautiously with 90% formic acid (2·4 g.) and 40% formaldehyde (2·0 g.), and the whole heated on the water-bath for ¾ hr.[24] (longer heating caused extensive hydrolysis of the diester). The mixture was cooled, then diluted with water, and the neutral matter removed by ether-extraction. The aqueous layer was cooled, basified with aqueous potassium carbonate, and extracted several times with ether. Evaporation of the

dried (Na_2SO_4) extract gave the 1-*methyl-ester* (4·6 g.), b. p. 110°/0·3 mm. (Found: C, 61·4; H, 9·1; N, 5·4. $C_{13}H_{23}NO_4$ requires C, 60·7; H, 8·95; N, 5·45%), $\nu_{max.}$ (in CCl_4) 1748 cm.$^{-1}$ (saturated ester C=O), no NH absorption. The product did not react with nitrous acid.

Attempts to effect the Dieckmann cyclisation of this diester, by using powdered sodium or potassium, or sodium or potassium ethoxide, were unsuccessful. Pyrolysis of the barium or magnesium salt of the corresponding diacid was equally ineffective. There was evidence in both methods of *N*-demethylation.

We thank Dr. J. M. Pryce (Imperial Chemical Industries Limited, Pharmaceuticals Division) and Mr. G. Phillips for spectral measurements, and Mr. C. B. Page, B.Sc., for preparing the bridged ketone (X). One of us (I. G. M.) thanks the D.S.I.R. for a maintenance grant.

Department of Chemistry, University College, Cardiff. [*Received, October 17th*, 1962.]