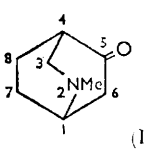
928. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part VIII.*[1] *Synthesis and Resolution of 2-Methyl-5-oxoisoquinuclidine and Synthesis of Dioscorine.*

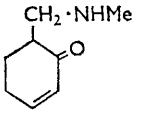
By C. B. Page and A. R. Pinder.

The synthesis and resolution of 2-methyl-5-oxoisoquinuclidine are described. Condensation of the (+)-keto-base with ethyl 4-bromo-3-methylbut-2-enoate, followed by hydrolysis and lactonisation, afforded (−)-dioscorine.

In Part VII of this Series[1] the ketonic base, $C_8H_{13}NO$, a key compound obtained by degradation of the alkaloid dioscorine,[2] was shown to be (+)-2-methyl-5-oxoisoquinuclidine (I). We now describe the synthesis of the racemic keto-base, its resolution into optically active forms, and the synthesis of (−)-dioscorine from the (+)-base.



(I)



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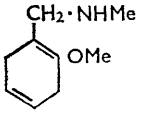

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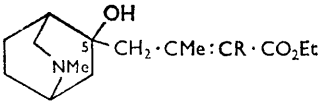


(IV)

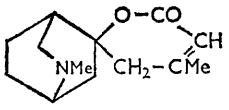
The racemic keto-base was reached by two pathways. Firstly, a Mannich reaction involving cyclohex-2-enone, formaldehyde, and methylamine led to a product which was substantially the required compound (I), possibly mixed with a small amount of the expected Mannich base, 6-methylaminomethylcyclohex-2-enone (II). Evidently the latter had undergone an intramolecular Michael addition, leading to the required bridged

[1] Part VII, Morris and Pinder, *J.*, 1963, 1841.
[2] Jones and Pinder, *J.*, 1959, 615.

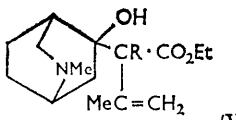
ketone. The amino-ketone (II) was detected by infrared spectroscopy; it was removed by purification of the product through its picrate, by treatment with nitrous acid, or by Hinsberg's method. The second route involved Birch reduction of 2-methoxy-*N*-methylbenzylamine, leading, in the first instance, to its dihydro-derivative (III), which, on acid hydrolysis, afforded a product which was again essentially the keto-base (I), contaminated with a small amount of (II).

The purified oxoisoquinuclidine was proved to be the racemic form of the " natural " (+)-keto-base by infrared comparison in solution, and by its chemical properties, especially the sensitivity of its methiodide to base.[1] The synthetic product was eventually resolved into optically active forms by fractional crystallisation of its hydrogen (−)-di-*p*-toluoyl-D-tartrate from 95% methanol. The first crop of crystals consisted of the salt of the (−)-base, whilst the (+)-base, identical in all respects with that derived from dioscorine, was obtained by basification of the mother-liquors.

The most obvious route to dioscorine seemed to be a Reformatsky reaction between (+)-2-methyl-5-oxoisoquinuclidine and ethyl 4-bromo-3-methylbut-2-enoate, with a view to the synthesis of the hydroxy-ester (IV; R = H). It was hoped that the latter could be hydrolysed and lactonised to dioscorine (V), but it was appreciated at the start that there would be stereochemical difficulties with this reaction. Firstly it is difficult to predict the configuration of the hydroxyl and unsaturated ester substituents in the Reformatsky product (IV; R = H) because models show that if, say, the hydroxyl group is boat-equatorial to the cyclohexane ring, it is boat-axial to the piperidine ring, and *vice versa*. The proposed relative configuration of dioscorine,[2,3] which has not yet been proved rigorously, is such that in the synthetic hydroxy-ester (IV; R = H) the hydroxyl group must be boat-axial to the cyclohexane ring, in order to lead to the correct spiro-union of the lactone ring. Secondly, ethyl 4-bromo-3-methylbut-2-enoate, as obtained by the allylic bromination of ethyl 3-methylbut-2-enoate, is presumably a mixture of *cis*- and *trans*-isomers,[4]* though inspection of models suggests that the latter isomer is considerably the less hindered sterically, and evidence has been presented [5] which suggests the ester is entirely *trans*. Models show that in compound (IV; R = H) lactonisation to yield dioscorine will be possible only if the side-chain has the *cis*-configuration. However, we were encouraged by



(V)



(VI)

the reported lactonisation of the product of a Reformatsky reaction between the bromo-ester and benzaldehyde,[4] and by the fact that the nuclear magnetic resonance spectrum of the bromo-ester suggested that it was composed of equal amounts of *cis*- and *trans*-isomers. Finally, the bromo-ester is known to react abnormally to some extent in Reformatsky reactions, owing to the ambident nature of the carbanion involved: [6]

$$:\bar{C}H_2\cdot CMe{:}CH\cdot CO_2Et \longleftrightarrow CH_2{:}CMe\cdot\bar{C}H\cdot CO_2Et$$

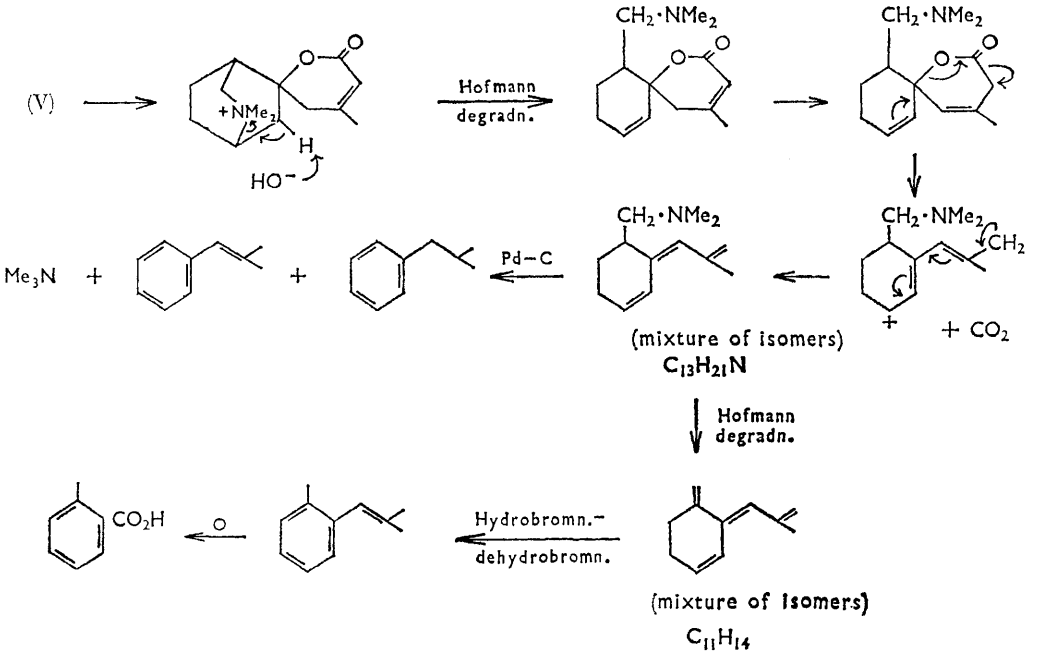
In the case under consideration the abnormal product would be the ester (VI; R = H), but it was hoped that this, if formed, would be separable from the desired ester (IV;

* The prefixes *cis* and *trans* here refer to the relative dispositions of the methyl group and hydrogen atom about the double bond.

[3] Pinder, *Tetrahedron*, 1957, **1**, 301.
[4] Harper and Oughton, *Chem. and Ind.*, 1950, 574.
[5] Halmos and Mohácsi, *J. prakt. Chem.*, 1960, **12**, 50.
[6] Wiley, Imoto, Houghton, and Veeravagu, *J. Amer. Chem. Soc.*, 1960, **82**, 1413; cf. Jones, O'Sullivan, and Whiting, *J.*, 1949, 1415; English, Gregory, and Trowbridge, *J. Amer. Chem. Soc.*, 1951, **73**, 615.

R = H) perhaps by the failure of the former to lactonise. It may be pointed out that, under the acidic conditions used for the lactonisation of the acid corresponding to (IV), if a tertiary carbonium ion at C-5 is involved, the configuration at this position in (IV) may not be relevant to the final synthesis. Similarly, base-catalysed hydrolysis of (IV) and acid-catalysed lactonisation of the acid corresponding to (IV) may result in geometrical isomerisation of the double bond. It is possible, therefore, that the reaction conditions may conspire to give dioscorine as an equilibrium-controlled product even though the Reformatsky ester may not have the favourable stereochemistry.

After some exploratory work using the more plentiful racemic keto-base, ethyl 4-bromo-3-methylbut-2-enoate and (+)-2-methyl-5-oxoisoquinuclidine were condensed in the presence of zinc, using Grob's procedure,[7] in which, to avoid quaternary salt formation, the keto-base was not added until organometallic formation was complete. The product was shown by spectral examination to be a mixture of the desired (IV; R = H) and the "abnormal" ester (VI; R = H); it had $\lambda_{max.}$ (cyclohexane) 195 (wide) (ε 12,500) and 214 mμ (ε 12,000), the former being ascribed in part to an isolated ethylenic linkage [as in (VI; R = H)] and in part to the isoquinuclidine system [2-methylisoquinuclidine (I; CO replaced by CH_2) shows $\lambda_{max.}$ (cyclohexane) 202 mμ (ε 3400)]. The longer-wavelength maximum is ascribed to the αβ-unsaturated ester group in (IV; R = H). The infrared spectrum (liquid film) showed bands at 3490 and 3330 (bonded OH), 1735 (saturated ester (C=O), 1715 (αβ-unsaturated ester C=O), 1690 (isolated C=C), 1642 (conjugated C=C),



899s ($R^1R^2C{=}CH_2$), and 800 cm.$^{-1}$ ($R^1R^2C{=}CHR^3$). The nuclear magnetic resonance spectrum showed peaks at τ 8·13 (triplet, 3H) and 4·99 (quadruplet, 2H), ascribed to the grouping $H_3C{\cdot}\dot{C}{=}CH_2$, and a peak at τ 6·80 (sharp singlet, 1H), ascribed to the grouping $\cdot CH(CO_2Et){\cdot}CMe{:}CH_2$, both features of structure (VI; R = H). A peak at τ 4·25 is ascribed to the vinyl proton in (IV; R = H), the peak area being consistent with the presence of about 30% of this species.

[7] Cf. Grob and Brenneisen, *Helv. Chim. Acta*, 1958, **41**, 1184.

A similar product was obtained, in much inferior yield, by an aldol condensation between the keto-base and ethyl 3-methylbut-2-enoate, in the presence of lithamide.[8] An analogous reaction with diethyl isopropylidenemalonate, which was contemplated as a possible solution to the problem of *cis-trans* isomerism in the hydroxy-ester, referred to above, afforded in very poor yield what appeared to be a mixture of the esters (IV; R = CO_2Et) and (VI; R = CO_2Et).

The mixture of hydroxy-esters (IV; R = H) and (VI; R = H) was hydrolysed with dilute alkali and then treated with acid at 100°, to simulate conditions used earlier [9] for the hydrolysis of dioscorine and re-lactonisation of the hydroxy-acid. Careful basification of the acid solution at 0°, followed by exhaustive continuous ether extraction gave, in 15% yield, (−)-dioscorine (V), identical in all respects with the natural alkaloid. The crystalline picrate gave an *X*-ray powder photograph identical with that of the picrate of the natural base.

The exhaustive methylation of dioscorine and cognate reactions, described in detail earlier,[10] must now be re-interpreted as shown.

Experimental

(±)-2-*Methyl*-5-*oxoisoquinuclidine* (I).—Cyclohex-2-enone [11] (10·0 g., 1 mol.), methylamine hydrochloride (7·03 g., 1 mol.), trioxymethylene (10·3 g., 1·1 mol.), concentrated hydrochloric acid (6 drops), and ethanol (10 c.c.) were refluxed on a water-bath for 5 hr., by which time the system had become homogeneous.[12] The solvent was removed *in vacuo*, ice–water (50 g.) was added, and non-basic material removed with ether. The aqueous solution was cooled, basified with an excess of potassium carbonate, and subjected to continuous ether extraction for several hours. Evaporation of the dried extract gave a red oil (2·6 g.), b. p. 98—101°/12—13 mm. $\lambda_{max.}$ (cyclohexane) 207·5 (ε 3000), 215sh (ε 2650), 244 (ε 1200), and 280 mμ (ε 1300), $\nu_{max.}$ (liquid film) 1739 (saturated ketone C=O) and 1678 cm.$^{-1}$ (αβ-unsaturated ketone C=O). The product, largely (±)-2-methyl-5-oxoisoquinuclidine, was purified through the *picrate*, prepared in methanol, needles, m. p. 174—175° (decomp.) (from 50% aqueous ethanol) (Found: C, 45·8; H, 4·6; N, 15·3. $C_{14}H_{16}N_4O_8$ requires C, 45·6; H, 4·4; N, 15·2%). The picrate (0·54 g.), suspended in ether, was shaken with several portions of 50% aqueous potassium hydroxide until the aqueous later was colourless. The ether layer was dried and evaporated, and the residual pure (±)-2-*methyl*-5-*oxoisoquinuclidine* distilled, b. p. 99—101°/11 mm. (0·14 g.) (Found: C, 68·9; H, 9·1; N, 10·1. $C_8H_{13}NO$ requires C, 69·1; H, 9·3; N, 10·1%), $\nu_{max.}$ (liquid film): 1742 cm.$^{-1}$ (saturated ketone C=O), no band in 1768 cm.$^{-1}$ region. The infrared absorption curve was identical with that of (+)-2-methyl-5-oxoisoquinuclidine, obtained by degradation of dioscorine.[2] The methiodide underwent the same Hofmann-type decomposition as that of the (+)-base [1] when exposed to mild alkali.

Purification of the product was also effected by treatment with cold nitrous acid or with toluene-*p*-sulphonyl chloride (Hinsberg separation), the impurity evidently being the Mannich secondary base.

2-*Methoxy*-N-*methylbenzylamine*.—*o*-Methoxybenzaldehyde [13] was oximated,[14] and the oxime reduced with sodium amalgam to 2-methoxybenzylamine.[14] The amine (19·5 g., 1 mol.) and freshly distilled benzaldehyde (15·1 g., 1 mol.) were mixed and kept at room temperature for 48 hr.[15] The water was removed *in vacuo*, the residue taken up in ether, and the solution dried (Na_2SO_4) and filtered. The oily residue was mixed with methyl iodide (50·5 g., 2·5 mol.) and refluxed for 10 min., then kept at room temperature for 24 hr. The excess of methyl iodide was removed *in vacuo* and the yellow crystalline residue treated with 90% ethanol (120 c.c.), and

[8] Cf. Dunnavant and Hauser, *J. Org. Chem.*, 1960, **25**, 1693.
[9] Pinder, *J.*, 1952, 2236.
[10] Pinder, *J.*, 1953, 1825; 1956, 1577.
[11] Braude and Evans, *J.*, 1954, 607.
[12] Cf. Jacquier, Mousseron, and Boyer, *Bull. Soc. chim. France*, 1956, 1653.
[13] Baeyer and Villiger, *Ber.*, 1902, **35**, 3023.
[14] Goldschmidt and Ernst, *Ber.*, 1890, **23**, 2740.
[15] Cf. Decker and Becker, *Annalen*, 1913, **395**, 333; Buck, *J. Amer. Chem. Soc.*, 1930, **52**, 4120.

refluxed for 1 hr. The ethanol was evaporated *in vacuo* and water added, the liberated benzaldehyde being removed with ether. The aqueous solution was basified with potassium hydroxide. Ether extraction gave 2-methoxy-*N*-methylbenzylamine (19·2 g.), b. p. 101—102°/9 mm. (lit.,[16] 103°/10 mm.).

Birch Reduction of 2-*Methoxy*-N-*methylbenzylamine.**—The base (5·0 g.) in dry ether (20 c.c.) was added to stirred liquid ammonia (75 c.c.), followed by lithium metal (1·15 g., 5 atoms) in small pieces,[17] during several minutes. After stirring for a further 10 min., ethanol (10 c.c.) was added gradually during 20 min., and when the blue colour had vanished the ammonia was allowed to evaporate, and replaced gradually with ether. Water was added, and the ether layer separated, dried (Na_2SO_4), and evaporated. The crude dihydro-base (4·83 g.) remaining was refluxed with 2N-hydrochloric acid (50 c.c.) under nitrogen for 1½ hr. Basification of the solution with potassium carbonate, and continuous ether extraction yielded an oil (1·47 g.), b. p. 93—95°/10 mm. which was substantially (±)-2-methyl-5-oxoisoquinuclidine. The infrared absorption curve was identical with that of the product obtained using the Mannich reaction, there being evidence of the presence of a small amount of αβ-unsaturated ketone.

Resolution of (±)-2-*Methyl*-5-*oxoisoquinuclidine.*—The hydrogen (+)-tartrate and (+)-α-bromocamphor-π-sulphonate of the (±)-base could not be obtained crystalline. The (+)-*camphor*-10-*sulphonate*, prepared by mixing equivalent proportions of base and acid in ethanol, crystallised from ethanol–ether in needles, m. p. 146—148° (decomp., with previous softening at *ca.* 90°), $[\alpha]_D^{18}$ +9·5° (*c* 2·0 in H_2O) (Found, on specimen dried to constant weight: C, 55·5; H, 8·3; N, 3·9. $C_{18}H_{29}NO_5S,H_2O$ requires C, 55·5; H, 8·0; N, 3·6%). The salt could not be resolved by fractional crystallisation, even when solutions were seeded with (+)-2-*methyl*-5-*oxoisoquinuclidine* (+)-*camphor*-10-*sulphonate*, prepared in ethanol from the (+)-base, as above. This salt crystallised from ethanol–ether in needles, m. p. 143—145° (decomp.), $[\alpha]_D^{18}$ +19·8° (*c* 2·04 in H_2O) (Found: C, 56·1; H, 7·7; N, 3·8%). The *hydrogen di*-p-*toluoyl*-D-*tartrate* of the (±)-base, formed from equimolecular quantities of the base and (−)-acid in 95% methanol, crystallised from the same solvent in needles, m. p. 154—156° (decomp.), $[\alpha]_D^{25}$ −86·5° (*c* 1·9 in EtOH) (Found: C, 62·8; H, 6·2; N, 2·7. $C_{28}H_{31}NO_9,CH_3OH$ requires C, 62·5; H, 6·3; N, 2·5%). The hydrogen di-*p*-toluoyl-D-tartrate of the "natural" (+)-base, prepared in an analogous manner, separated in needles, m. p. 149—151° (decomp.) (lit.,[18] 149—151°), $[\alpha]_D^{22}$ −99·0° (*c* 2·0 in EtOH) (Found: C, 62·7; H, 6·2; N, 2·7%). A warm solution of the racemic base (1·75 g.) and (−)-di-*p*-toluoyl-D-tartaric acid (4·86 g.) in 95% methanol (15 c.c.) was seeded with the corresponding salt of the (+)-base, and kept at room temperature for some hours. When about half the material in the original solution had crystallised the *salt* was collected (3·18 g.), m. p. 147—149° (decomp.), $[\alpha]_D^{23}$ −92·2° (*c* 2·0 in EtOH) (Found: C, 62·1; H, 6·2; N, 2·7%). The salt was suspended in water, basified with potassium carbonate, and the whole subjected to continuous ether extraction for several hours. Evaporation of the dried extract gave (−)-2-methyl-5-oxoisoquinuclidine (0·30 g.), b. p. 105—106°/18 mm. $[\alpha]_D^{21·5}$ −10·9° (*c* 1·47 in H_2O), the infrared absorption curve of which was identical with that of (+)-2-methyl-5-oxoisoquinuclidine obtained from dioscorine. A second fraction (1·54 g.) had m. p. 143—146° (decomp.), $[\alpha]_D^{21·5}$ −86·1° (*c* 2·0 in ethanol). Basification and extraction yielded a keto-base with $[\alpha]_D^{22}$ +6·5° (*c* 1·45 in H_2O), evidently largely the (+)-isomer. The mother-liquors from the fractional crystallisation were basified and extracted as above, affording an oil not completely miscible with water. This was shaken with dilute hydrochloric acid, and neutral matter (methyl *p*-toluate) removed with ether. The aqueous layer was basified and extracted with ether continuously. Evaporation of the dried extract yielded (+)-2-methyl-5-oxoisoquinuclidine (0·19 g.), b. p. 104—106°/18 mm. $[\alpha]_D^{21·5}$ +9·9° (*c* 1·5 in H_2O). The infrared absorption curve was identical with that of the (+)-keto-base obtained by degradation of dioscorine.[2] A freshly-prepared sample of the latter had $[\alpha]_D^{18·5}$ +9·5° (*c* 1·46 in H_2O).

Reformatsky Reaction between (+)-2-*Methyl*-5-*oxoisoquinuclidine and Ethyl* 4-*Bromo*-3-*methylbut*-2-*enoate.*—Zinc wool was cut into small pieces and washed with dilute hydrochloric acid, water, acetone, and ether, and dried *in vacuo*. A suspension of the metal (1·76 g., 2·5 atoms) in anhydrous benzene–ether (1 : 1; 60 c.c.), containing a crystal of iodine, was stirred mechanically

* This experiment was first carried out by Dr. I. G. Morris, in this laboratory.

[16] Holly and Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 1875.
[17] Cf. Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360.
[18] Ayer, Büchi, Reynolds-Warnhoff, and White, *J. Amer. Chem. Soc.*, 1958, **80**, 6146.

on a water-bath during the gradual addition (1 hr.) of ethyl 4-bromo-3-methylbut-2-enoate [19] (5·58 g., 2·5 mol.) in the same solvent (5 c.c.).[7] After the elapse of 40 min. from the start a further quantity (0·88 g., 1·25 atom) of zinc wool was added, then a similar quantity towards the end. After stirring for a further 30 min. at reflux much of the metal had dissolved to give a green solution. At this point (+)-2-methyl-5-oxoisoquinuclidine (1·50 g., 1 mol.) in benzene–ether (1 : 1, 10 c.c.) was added during 10 min., with continued rapid stirring and refluxing. The mixture was stirred and refluxed for a further 6 hr., cooled, and decomposed with 50% acetic acid (40 c.c.). The liquids were decanted and separated, and the organic layer washed with 0·2N-hydrochloric acid. The combined aqueous layer and washings were basified at 0° with potassium carbonate and continuously extracted with ether. Evaporation of the dried (Na_2SO_4) extract and fractionation yielded the pale yellow *ester* (IV) b. p. 107—113°/0·5 mm. (Found: C, 67·1; H, 9·3; N, 5·3. $C_{15}H_{25}NO_3$ requires C, 67·4; H, 9·4; N, 5·2%), $\nu_{max.}$ (liquid film) 3490, 3330 (bonded OH), 1715 (αβ-ester C=O), 1735sh (saturated ester C=O), 1690sh (isolated C=O), 1642 (conjugated C=C), 899 (C=CH_2), and 800 cm.$^{-1}$ (R^1R^2C=CHR^3), $\lambda_{max.}$ (cyclohexane) 195 (ε 12,500) and 214 mμ (ε 12,000). The *picrate* separated from aqueous methanol in irregular yellow plates, m. p. 134—136° (Found: C, 51·0; H, 5·6; N, 11·0. $C_{21}H_{28}N_4O_{10}$ requires C, 50·8; H, 5·6; N, 11·3%). The *methiodide*, prepared in ether, separated from methanol–ether in pale yellow microcrystals, m. p. 150—155° (Found: C, 46·5; H, 6·8; N, 3·6. $C_{16}H_{28}INO_3$ requires C, 46·9; H, 6·8; N, 3·4%).

The same product was obtained, in inferior yield, by condensation of the keto-base with ethyl 3-methylbut-2-enoate, in the presence of lithamide [8] or sodamide. The lower yield was partly explained by the formation of 3-methylbut-2-enamide in a side-reaction between lithamide and the ester.

(−)-*Dioscorine* (V).—The foregoing mixture of hydroxy-esters (2·0 g.) and 0·5N-aqueous potassium hydroxide (60 c.c.) were heated on a water-bath for 1½ hr. The nearly homogeneous system was filtered and non-acidic matter removed with ether. The aqueous layer was rendered acidic with 2N-hydrochloric acid, heated on a water-bath for 1 hr., cooled to 0°, saturated with potassium carbonate, and subjected to continuous ether extraction. The dried extract was evaporated, leaving a reddish oil (0·65 g.), which, on fractionation, afforded a small fore-run, b. p. 80° (bath)/0·1 mm., of 2-methyl-5-oxoisoquinuclidine, identified by infrared comparison and as the picrate, followed by a pale yellow syrup, b. p. 114—117°/0·09 mm. (0·25 g.), which crystallised on keeping, $[\alpha]_D^{19\cdot5}$ −22·6° (*c* 3·05 in $CHCl_3$). A freshly prepared specimen of natural dioscorine had $[\alpha]_D^{19\cdot5}$ −23·5° (*c* 3·05 in $CHCl_3$). The infrared absorption curve of the product was identical with that of natural (−)-dioscorine. The picrate separated from acetone in prisms, m. p. 188·5°, undepressed by admixture with authentic (−)-dioscorine picrate,[9] m. p. 188·5°. The *X*-ray powder photographs of the two picrates were identical.

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Department of Chemistry, University College, Cardiff. [*Received, February 5th*, 1964.]

[19] Huisman, Smit, Uromen, and Fisscher, *Rec. Trav. chim.*, 1952, **71**, 899.