703. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part VI.*[1] *Some Investigations on the Synthesis of Tropan-2-one.*

By W. A. M. Davies, J. B. Jones, and A. R. Pinder.

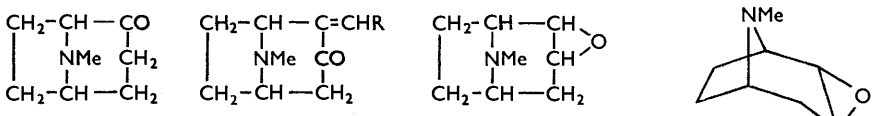
Possible routes for the synthesis of tropan-2-one have been explored. 2-Isobutyl-*NN*-dimethylcycloheptylamine has been synthesised, probably as a mixture of *cis*- and *trans*-forms. It is not identical with the fully hydrogenated Hofmann base from dioscorine.

In the previous paper[1] of this series, reasons were given for believing that the ketonic base $C_8H_{13}NO$, obtained by a degradative sequence from the alkaloid dioscorine, was tropan-2-one (I). This has now been settled beyond doubt by the synthesis[2] of (+)-tropan-2-one from (—)-ecgonine, its reduction to tropan-2α-ol,[2] and the establishment of the identity of the latter with the alcohol obtained by reduction of the base $C_8H_{13}NO$.[3] Apparently a direct comparison between the " natural " and the synthetic base $C_8H_{13}NO$ was not made: there are some slight discrepancies in the physical properties of the two products.

[1] Part V, Jones and Pinder, *J.*, 1959, 615; see also *Chem. and Ind.*, 1958, 1000.
[2] Bell and Archer, *J. Amer. Chem. Soc.*, 1958, **80**, 6147.
[3] Ayer, Büchi, Reynolds-Warnhoff, and White, *J Amer. Chem. Soc.*, 1958, **80**, 6146.

We report here some experiments begun before publication of the above work, directed towards the synthesis of tropan-2-one.

The presence of the tropane framework in the keto-base $C_8H_{13}NO$ was proved by Büchi and his co-workers,[3,4] who obtained tropane by desulphurisation of its ethylene thioketal. We have also realised this transformation by catalytic hydrogenation of the base in strongly acid solution. We placed the carbonyl group of the keto-base at position 2, because the base was not identical with synthetic tropan-6-one, and on incomplete infrared evidence.[1] We have now prepared the model compounds, 1-methyl-3-oxopyrrolidine and



(I) (II) (III) (IV)

1-methyl-3-oxopiperidine, the latter by a new route; comparison of the carbonyl stretching frequencies shows that, under the same conditions (CCl_4 solution), the value (1740 cm.$^{-1}$) for the base $C_8H_{13}NO$ is nearer to that for 1-methyl-3-oxopiperidine (1726 cm.$^{-1}$) than to that for the pyrrolidine analogue (1765 cm.$^{-1}$), confirming the view that the " natural " base is tropan-2-one. If the value 1730 cm.$^{-1}$ (in CCl_4) given by Büchi *et al.*[3] for the keto-base is adopted, the agreement is even closer.

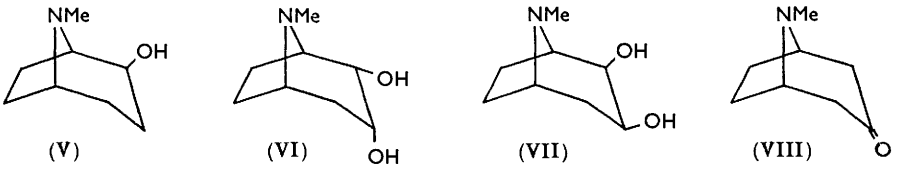
In an attempt to use tropinone as the starting material in a synthesis of tropan-2-one, we first considered 2-benzylidenetropinone (II; R = Ph) as an intermediate, but, in confirmation of Willstätter's earlier work,[5] attempts to prepare it gave only the 2,4-dibenzylidene derivative. Willstätter and Iglauer [6] described the preparation of 2-hydroxymethylenetropinone (II; R = OH); we found that this compound condensed with *N*-methylaniline,[7] but attempts to reduce the carbonyl group in the 2-methylanilinomethylenetropinone (II; R = NMePh) produced resulted in loss of the 2-substituent.

Tropidine was next considered as a starting point, the first objective being 2,3-epoxytropane (III). The more familiar per-acid epoxidising agents were found to react with tropidine to give tropidine *N*-oxide, whilst in acid solution no reaction was observed. Under the latter conditions the ethylenic bond of tropidine is deactivated by protonation of the nitrogen atom, so that epoxidation, known to be electrophilic in mechanism,[8] is inhibited. The desired epoxidation was finally achieved by the action of trifluoroperacetic acid [9] on tropidine trifluoroacetate,[10] under conditions which had to be observed carefully, owing to the sensitivity of the product to water. The epoxide was purified by distillation and characterised as its picrate. In view of Henbest and Nicholls's observations [11] on the stereochemistry of the epoxidation of bicyclo[2,2,1]hept-5-en-2α-ol (approach by the reagent on the less hindered β-side of the double bond), it seems that the epoxide is 2β,3β-epoxytropane (IV).

Lithium aluminium hydride reduced the epoxide to tropan-2β-ol (V), the configuration following since opening of epoxide rings by reaction with HX (X = H, OH, or halogen) gives products with axial substituents.[12] In the hydroxyl region, the infrared spectrum of the hydroxy-base resembled that of ψ-tropine [13] and tropan-6β-ol,[1] and differed from that

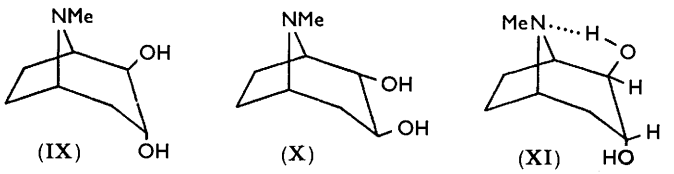
[4] Büchi, Ayer, and White, XVIth Internat. Congr. Pure Appl. Chem., Paris, July, 1957.
[5] Willstätter, *Ber.*, 1897, **30**, 731, 2716.
[6] Willstätter and Iglauer, *Ber.*, 1900, **33**, 361.
[7] Cf. Birch and Robinson, *J.*, 1944, 501; Birch, Jaeger, and Robinson, *J.*, 1945, 582.
[8] Swern, *Org. Reactions*, 1953, **7**, 385.
[9] Emmons, *J. Amer. Chem. Soc.*, 1954, **76**, 3468, 3470; Emmons, Pagano, and Freeman, *ibid.*, p. 3472; Emmons and Pagano, *ibid.*, 1955, **77**, 89.
[10] Cf. Fodor, Tóth, Koczor, Dobó, and Vincze, *Chem. and Ind.*, 1956, 764; Dobó, Fodor, Janzsó, Koczor, Tóth, and Vincze, *J.*, 1959, 3461.
[11] Henbest and Nicholls, *J.*, 1959, 221.
[12] " Progress in Stereochemistry," ed. Klyne, Butterworths, London, 1954, Vol. I, p. 74, and references there cited; Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[13] Zenitz, Martini, Priznar, and Nachod, *J. Amer. Chem. Soc.*, 1952, **74**, 5564.

of tropine,[13] in support of the view that the hydroxyl group in (V) is β-oriented and results in more extensive intramolecular hydrogen bonding.



Attempts to oxidise tropan-2β-ol to tropan-2-one (I) failed, most of the alcohol being unattacked. In one experiment a small amount of tropidine, identified as its picrate, was formed, by dehydration of the alcohol under the hot, acid conditions. The failure of this step was not altogether unexpected, in view of our experience with tropan-6β-ol, which also offered considerable resistance to oxidation.[1]

The dehydration of 1,2-glycols to ketones under acid conditions is well known.[14] Many years ago Einhorn and Fischer,[15] using dilute potassium permanganate, converted tropidine into tropan-2,3-diol in very poor yield, no attempt being made to assign a configuration to it. We were unable to improve the yield in this reaction, but obtained the same diol, in high yield, by hydroxylation with osmium tetroxide. The two hydroxylating agents used are known to react with double bonds in a *cis* manner,[16] so that the product is either tropane-2α,3α-diol (VI) or tropane-2β,3β-diol (VII). Of these, the former, having the 2-hydrogen atom and the 3-hydroxyl group *trans* to each other, and both axial, presents conditions[17] favourable for 1,2-elimination of water, with the formation of tropan-2-one. For similar reasons, the 2β,3β-isomer (VII) would be expected to yield tropinone (VIII) on dehydration. When the crystalline diol was heated with sulphuric acid tropinone (VIII) was formed, indicating that the diol is tropane-2β,3β-diol VII). Infrared measurements on the diol confirm this configuration (see below).

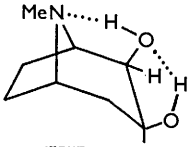


Although it was realised that the two possible *trans*-diols derivable from tropidine, *viz.*, tropane-2β,3α-diol (IX) and tropane-2α,3β-diol (X), did not present favourable conditions for the desired dehydration, we prepared one of these compounds and investigated its behaviour towards acids. Treating tropidine with trifluoroperacetic acid, in the presence of a trace of water, gave a crystalline diol; since peracids, reacting with ethylenic bonds, give first a *cis*-epoxide, which on hydrolysis yields a *trans*-diol,[16] with the two hydroxyl groups axially oriented,[12] the diol must be tropane-2β,3α-diol (IX). This configuration, and that of the *cis*-diol above, were supported by an infrared comparison (in CCl_4). Both bases showed two bands in the hydroxyl region, the former at 3628 and 3462, and the latter at 3557 and 3440 cm.$^{-1}$, the intensities of all four bands being concentration-independent. The more extensive internal hydrogen-bonding in the case of the *cis*-diol is consistent with the assignment of the 2β,3β-configuration (VII) rather than the 2α,3α (VI). The spectral observations of Nachod *et al.*[13] on tropine and ψ-tropine, and of Kuhn[18] and Cole and

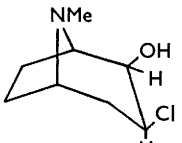
[14] *Inter al.*, Mousseron, Jacquier, and Christol, *Compt. rend.*, 1953, **236**, 927; Naves, *Helv. Chim. Acta*, 1959, **42**, 1174.
[15] Einhorn and Fischer, *Ber.*, 1893, **26**, 2008.
[16] Crombie, *Quart. Reviews*, 1952, **6**, 124; Raphael, *J.*, 1949, S44.
[17] Ref. 12, p. 64, and references there cited; Dauben and Pitzer, in "Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 48.
[18] Kuhn, *J. Amer. Chem. Soc.*, 1954, **76**, 3423.

Jefferies [19] on *cis*- and *trans*-cyclohexane-1,2-diols, indicate that in both diols the low-frequency band is characteristic of hydrogen bonding between the 2β-hydroxyl group and the nitrogen atom. The band at 3628 cm.$^{-1}$ in the spectrum of the *trans*-diol is characteristic of a free hydroxyl group (3α), and that at 3557 cm.$^{-1}$ for the *cis*-diol is ascribed to the 3β-hydroxyl group, hydrogen bonded to the 2β-hydroxyl group.[18,19] The two isomers are pictured as (XI) and (XII).

Tropane-2β,3α-diol (XI) was in the main unaffected by hot 20% sulphuric acid or potassium hydrogen sulphate. Heating it with acetic–sulphuric acid for several hours transformed it in good yield into tropane-2β,3β-diol (XII). This isomerisation, which involves the inversion at $C_{(3)}$ of a less stable (axial) to a more stable (equatorial) hydroxyl group, supports the configuration assigned to the *trans*-diol (XI). A similar inversion at $C_{(2)}$ is presumably resisted by the fairly strong hydrogen bonding, in acid solution, between the axial oxygen atom in this position and the protonated nitrogen atom. A small amount of tropinone was also formed in this reaction, the result of dehydration of the newly formed *cis*-diol (XII), referred to above.



(XII)



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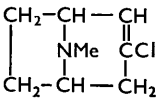
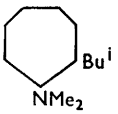


(XIV)



(XV)

An attempt was next made to prepare 3β-chlorotropan-2β-ol (XIII), which, from the known behaviour of *cis*-halogenohydrins on dehydrohalogenation,[20] would be expected to yield the required tropan-2-one on treatment with base. Replacement of hydroxyl by chlorine by the action of thionyl chloride usually involves inversion,[21] and from the behaviour of tropane-3α,6β-diol towards this reagent, resulting in replacement of the 3-hydroxyl group only,[22] it was conjectured that the *trans*-diol, tropane-2β,3α-diol, would yield the required chlorohydrin when treated with thionyl chloride. It was found, however, that under mild conditions this diol was not attacked by thionyl chloride, and under more vigorous conditions it yielded an oxygen-free product which we believe to be 3-chlorotropidine (XIV), formed by replacement of the 3-hydroxyl group, with inversion, followed by elimination of water from the 3α-hydrogen atom and the 2β-hydroxyl group (both axial).

In an attempt to prepare a cyclic sulphite from the *cis*-diol, with a view to its pyrolysis to either tropan-2-one or tropinone, the diol was unattacked under the conditions normally used for formation of the esters.[23]

In a previous part of this series,[24] the syntheses of 3- and 4-isobutyl-*NN*-dimethylcycloheptylamine were described, neither base proving identical with the saturated base $C_{13}H_{27}N$ obtained by hydrogenation of the Hofmann base of dioscorine. The 2-isomer (XV) has now been synthesised from cyclohexanone, by reaction with isopentyl-*N*-nitrosourethane, to give 2-isobutylcycloheptanone, which was converted into the required base through its oxime. Infrared comparison in solution between the base $C_{13}H_{27}N$ and the synthetic base showed they were not identical, though the curves were very similar. Again, the possibility of the synthetic product's being a *cis*- or a *trans*-isomer, or a mixture of both, complicates the comparison, and, indeed, the methiodide of the synthetic product has an unsharp, low m. p. suggesting the presence of both isomers. The lack of identity

[19] Cole and Jefferies, *J.*, 1956, 4391.
[20] Bartlett, *J. Amer. Chem. Soc.*, 1935, **57**, 224; Nickon, *ibid.*, 1955, **77**, 4094.
[21] See, for example, Archer, Lewis, and Zenitz, *J. Amer. Chem. Soc.*, 1957, **79**, 3603; 1958, **80**, 958; Archer, Bell, Lewis, Schulenberg, and Unser, *ibid.*, p. 4677.
[22] Kovacs and Banfi, quoted by Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260.
[23] Cf. Price and Berti, *J. Amer. Chem. Soc.*, 1954, **76**, 1211.
[24] Pinder, *J.*, 1956, 1577.

between the reduced Hofmann base and the three synthetic bases must be accounted for either by the complication referred to, or, in our view more probably, by the formation, in the Hofmann degradation of dioscorine, of a mixture of positional isomers.

Experimental

Dioscorinol.—This compound has now been obtained crystalline: it separated from benzene in rhombic prisms, m. p. 119—120° (lit.,[3] m. p. 121°).

2β-Acetonyltropan-2α-ol.—This base, obtained by ozonolysis of dioscorinol,[1] formed a picrate which separated from methanol in bright yellow elongated prisms, m. p. 120°, with some previous softening from 104° (lit.,[3] m. p. 120—122°) (Found: C, 47·8; H, 5·3; N, 13·4. Calc. for $C_{17}H_{22}N_4O_9$: C, 47·9; H, 5·2; N, 13·1%).

(+)-*Tropan-2-one* (I).—The following are improved conditions for the cleavage of the aldol base.[1] 2β-Acetonyltropan-2α-ol (1·0 g.) was mixed with 0·1N-aqueous sodium hydroxide (65 c.c.) and kept for 24 hr., then cooled in ice, saturated with potassium carbonate, and subjected to continuous ether-extraction for 16 hr. Evaporation of the dried (K_2CO_3) extract gave (+)-tropan-2-one (0·55 g.), b. p. 98°/14 mm., 105—106°/17 mm., $[\alpha]_D^{24}$ +15·0° (*c* 1·43 in H_2O), (lit.,[3] +17°). The keto-base was purified *via* its crystalline picrate,[1] which was suspended in ether and cooled in ice during addition of an excess of cold 50% aqueous potassium hydroxide, followed by powdered potassium hydroxide. The ethereal solution was decanted and concentrated, and the residual (+)-tropan-2-one distilled; it had b. p. 100°/14·5 mm.

Catalytic Hydrogenation of (+)-*Tropan-2-one.*—Adams platinum oxide (50 mg.) was pre-reduced in suspension in 2N-hydrochloric acid (10 c.c.). The keto-base (0·30 g.) in 2N-hydrochloric acid (15 c.c.) was added, followed by concentrated hydrochloric acid (2 c.c.), and the mixture shaken in hydrogen at room temperature and pressure for 18 hr. (uptake 2 mols.). The solution was freed from catalyst, basified with potassium hydroxide, and extracted with ether several times. The dried (K_2CO_3) extracts were concentrated *via* a short Vigreux column, and the residual oil distilled (b. p. 96°/92 mm.; 0·25 g.). The picrate, prepared in methanol, separated from water in yellow needles, m. p. 284—285° (decomp.) (Found: C, 47·55; H, 5·1; N, 15·8. Calc. for $C_{14}H_{18}N_4O_7$: C, 47·5; H, 5·1; N, 15·8%), alone or mixed with an authentic specimen of tropane picrate, prepared by reduction of tropidine.[25] The infrared spectra (in Nujol) of the two picrates were identical.

Ethyl N-*Ethoxycarbonylmethyl-γ-methylaminocrotonate.*—Ethyl α-bromocrotonate [26] (5·0 g., 1 mol.) was added dropwise with swirling and ice-cooling to ethyl methylaminoacetate (6·07 g., 2 mols.) during 15 min. The mixture became viscous and solid material separated. After being kept overnight at room temperature the mixture was treated with ether, and the ether decanted, dried, and evaporated. The residue was distilled *in vacuo* through a short Vigreux column. After a small fore-run, the *ester* distilled at 95—96°/0·1 mm. (4·3 g.) (Found: C, 57·5; H, 8·35; N, 6·1. $C_{11}H_{19}NO_4$ requires C, 57·6; H, 8·35; N, 6·1%). The product reacted with cold aqueous potassium permanganate immediately.

Ethyl N-*Ethoxycarbonylmethyl-γ-methylamino-n-butyrate.*—The above unsaturated diester (1·56 g.) in ethanol (15 c.c.) was shaken with pre-reduced Adams platinum oxide in hydrogen at room temperature and pressure. After 1 hr. absorption (1·8 mols.) ceased and the solution was filtered and concentrated under reduced pressure, and the residual liquid distilled *in vacuo*. After a fore-run consisting of ethyl methylaminoacetate, the required ester distilled at 130°/9 mm. (0·2 g.) (Found: C, 56·9; H, 8·9. Calc. for $C_{11}H_{21}NO_4$: C, 57·1; H, 9·2%). Prill and McElvain [27] give b. p. 134—135°/10 mm. The alcoholic distillate contained ethyl butyrate, isolated by dilution with a large volume of water and ether-extraction.

A similar result attended an attempt to effect the hydrogenation in the presence of 5% palladised charcoal.

1-*Methyl*-3-*oxopiperidine.*—Dieckmann cyclisation of the above diester, essentially as described by Prill and McElvain,[27] followed by acid-hydrolysis and decarboxylation, afforded 1-methyl-3-oxopiperidine. The base had b. p. 56—58°/11 mm.; $\nu_{max.}$ 1726 cm.$^{-1}$ (C=O) (in CCl_4). The *methiodide*, obtained by mixing the base with an excess of methyl iodide, crystallised

[25] Archer, Cavallito, and Gray, *J. Amer. Chem. Soc.*, 1956, **78**, 1227.
[26] Ziegler, Späth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 109.
[27] Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233.

from ethanol in elongated prisms, m. p. 200—202° (decomp.) (Found: C, 33·6; H, 5·6; N, 5·7. $C_7H_{14}NOI$ requires C, 33·0; H, 5·5; N, 5·5%), carbonyl band at 1736 cm.$^{-1}$ (in Nujol).

1-*Methyl*-3-*oxopyrrolidine*.—β-Methylaminopropionitrile was prepared from methylamine and acrylonitrile.[28] Alcoholysis gave ethyl β-methylaminopropionate.[28] The ester (17·4 g., 2 mols.) and ethyl bromoacetate (11·1 g., 1 mol.) were mixed and kept at room temperature overnight. Ether was added and the solution decanted from methylamine hydrobromide and evaporated. The residual *N*-β-ethoxycarbonylethyl-*N*-ethoxycarbonylmethylmethylamine distilled at 74°/0·15 mm. (lit.,[27] b. p. 124—125°/10 mm.) (12·4 g.) (Found: N, 6·5. Calc. for $C_{10}H_{19}NO_4$: N, 6·45%). Cyclisation of the diester essentially as described by Prill and McElvain [27] gave 1-methyl-3-oxopyrrolidine, b. p. 48—49°/21 mm. (lit.,[27] b. p. 46—47°/18 mm.), carbonyl band at 1765 cm.$^{-1}$ (in CCl_4). The *methiodide* crystallised from ethanol in elongated needles, m. p. 234° (decomp.) (Found, on specimen dried at 100° *in vacuo*: C, 30·2; H, 4·95. $C_6H_{12}NOI$ requires C, 29·9; H, 5·0%), carbonyl band at 1761 cm.$^{-1}$ (in Nujol).

2-*Methylanilinomethylenetropinone* (II; R = NMePh).—The sodium salt of 2-hydroxymethylenetropinone was prepared as described by Willstätter and Iglauer.[6] The salt (2·0 g.) was heated with glacial acetic acid (10 c.c.) and freshly distilled *N*-methylaniline (1·1 g.) under reflux on the water-bath for 10 min. Water was added to the cooled mixture, followed by an excess of concentrated aqueous potassium hydroxide. Ether-extraction gave 2-*methylanilinomethylenetropinone* (1·4 g.), which crystallised from acetone in pale yellow rhombic prisms, m. p. 121—122° (Found: C, 75·0; H, 7·8; N, 11·25. $C_{16}H_{20}N_2O$ requires C, 75·0; H, 7·8; N, 10·9%). Attempts to reduce this ketone to 2-methylanilinomethylenetropane or 2-methylanilinomethylenetropine under a variety of conditions (lithium aluminium hydride, sodium borohydride, Wolff–Kishner) were unsuccessful.

(±)-2β,3β-*Epoxytropane* (IV).—Tropidine was obtained by dehydration of tropine with acetic–sulphuric acid.[25] Trifluoroperacetic acid was prepared as follows.[9] Trifluoracetic anhydride (40 g., 0·19 mol.), obtained by the dehydration of trifluoroacetic acid with phosphorus pentoxide,[29] was added dropwise during 15 min., with stirring and ice-cooling, to 86% hydrogen peroxide (5·6 g., 0·14 mol.) dissolved in dry methylene chloride (83 c.c.). The homogeneous solution was stirred for a further 15 min. at 0°, then dried over " Drierite " for 30 min. and filtered through glass wool.

A solution of tropidine trifluoroacetate was prepared by adding to tropidine (5·0 g., 0·041 mol.) a solution of trifluoroacetic acid (9·45 g., 0·083 mol.) in dry acetonitrile (33 c.c.). To this solution the above per-acid solution was added, during 10 min., and the mixture kept at 0° for 4 days.[10] The solvents were then evaporated *in vacuo* from a bath at 60°, leaving a yellow oil. This was dissolved in dry methylene chloride (30 c.c.) and treated with anhydrous sodium sulphate (5 g.), followed by anhydrous potassium carbonate (30 g.) portionwise, with vigorous stirring and ice-cooling. The stirring was continued for a further 4 hr., the solution decanted, and the residue washed repeatedly by decantation with methylene chloride. Evaporation of the combined washings gave a reddish-brown oil (4·86 g.), which when fractionated *in vacuo* gave tropidine (0·3 g., b. p. 53—54°/16 mm.), followed by 2β,3β-*epoxytropane*, b. p. 93—94°/16 mm. (1·63 g.) (Found: C, 68·7; H, 9·5; N, 10·1. $C_8H_{13}NO$ requires C, 69·0; H, 9·4; N, 10·1%), $\nu_{max.}$ (in CCl_4) 834 and 1247 cm.$^{-1}$ (epoxide [30]); weak OH band, possibly due to the presence of a trace of glycol. A considerable amount of involatile residue, probably mainly undecomposed 2β,3β-epoxytropane trifluoroacetate, remained in the distillation flask. Attempts to liberate the epoxy-base from its salt by using triethylamine or " Amberlite " IRA-400 (OH) anion-exchange resin were unsuccessful. The *picrate* crystallised from ethanol in sheaves of yellow needles, m. p. 255° (decomp., rapid heating) (lit.,[3] m. p. 248—254°) (Found: C, 45·4; H, 4·1; N, 15·1. $C_{14}H_{16}N_4O_8$ requires C, 45·65; H, 4·4; N, 15·2%).

Attempts to prepare the epoxy-base by treatment of tropidine or tropidine trifluoroacetate with trifluoroperacetic acid in the presence of anhydrous sodium carbonate gave tropidine *N*-oxide, the *picrate* of which separated from methanol in yellow needles, m. p. 255—255·5° (decomp.) (Found: C, 45·95; H, 4·0; N, 15·3. $C_{14}H_{16}N_4O_8$ requires C, 45·65; H, 4·4; N, 15·2%). Reduction of the oxide with sulphur dioxide gave tropidine [picrate, m. p. 285° (decomp.); lit.,[31] m. p. 285° (decomp.)], and on catalytic reduction (uptake $2H_2$) gave tropane

[28] Cook and Reed, *J.*, 1945, 399.
[29] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976.
[30] Jones and Sandorfy, in " Technique of Organic Chemistry," ed. Weissberger, Interscience Publ., Inc., New York, 1956, Vol. IX, p. 436.
[31] Willstätter, *Annalen*, 1901, **317**, 362.

[picrate m. p. 285° (decomp.); lit.,[25] m. p. 284—285° (Found: C, 47·8; H, 5·2. Calc. for $C_{14}H_{18}N_4O_7$: C, 47·5; H, 5·1%)]. The action of performic acid on tropidine formate gave principally the unchanged base, accompanied by a small amount of tropane-2β,3α-diol (see below).

(±)-*Tropan*-2β-*ol* (V).—2β,3β-Epoxytropane (2·08 g., 0·015 mol.) in anhydrous ether (30 c.c.) was added, with swirling, to an ice-cooled solution of lithium aluminium hydride (0·28 g., 0·0074 mol.) in dry ether (30 c.c.) during 15 min. After 16 hr. at room temperature the mixture was decomposed by cautious addition of the minimum quantity of ice-water, in the presence of " Celite." The ethereal solution was decanted, and the inorganic residue extracted several times with methylene chloride. The combined solutions were dried (Na_2SO_4) and the solvents evaporated *via* a short Vigreux column. The residual (±)-*tropan*-2β-*ol* distilled at 94—95°/18 mm. (1·62 g.) (Found: C, 68·0; H, 10·0; N, 9·5. $C_8H_{15}NO$ requires C, 68·05; H, 10·7; N, 9·9%), $\nu_{max.}$ (in CCl_4) 3610 cm.$^{-1}$ (OH). The picrate, prepared from ethereal solution, crystallised from water in yellow needles, m. p. 263—263·5° (decomp., rapid heating; lit.,[3] m. p. 263—265°) (Found: C, 46·0; H, 4·7; N, 14·9. Calc. for $C_{14}H_{18}N_4O_8$: C, 45·4; H, 4·9; N, 15·1%).

Attempts to oxidise the hydroxy-base to (±)-tropan-2-one (I) with chromic acid were unsuccessful, most of the starting material being recovered [OH band at 3620 cm.$^{-1}$ (in CCl_4); no C=O band]. In one or two experiments a small yield of a crystalline *substance* was obtained. This separated from benzene in needles, m. p. 140° (Found: C, 60·7; H, 8·7; N, 7·1. $C_{10}H_{17}NO_3$ requires C, 60·2; H, 8·6; N, 7·0%), $\nu_{max.}$ (in CCl_4) 1721 (ester C=O) and 3160 cm.$^{-1}$ (wide, OH). On hydrolysis with sodium methoxide in methanol, at room temperature for 2 days, (±)-tropane-2β,3α-diol (see below) was obtained (comparison by mixed m. p. and infrared absorption). It is concluded that this product is either 2β-acetoxytropan-3α-ol or 3α-acetoxytropan-2β-ol. In one experiment tropidine [(picrate m. p. and mixed m. p. 285—286° (decomp.)] was detected in the product.

(±)-*Tropane*-2β,3α-*diol* (IX).—Trifluoroacetic anhydride (6·3 g., 0·03 mol.) was added during 10 min. to a cooled (0°) solution of 86% hydrogen peroxide (1·0 g., 0·73 c.c., 0·025 mol.) in dry methylene chloride (40 c.c.), and the mixture was stirred at 0° for a further 15 min. This solution of the per-acid was added during 10 min. to a stirred solution of tropidine trifluoroacetate from tropidine (2·5 g., 0·02 mol.) and trifluoroacetic acid (2·3 g., 0·02 mol.) in acetonitrile (20 c.c.). An exothermic reaction ensued; after being refluxed for 30 min. the mixture was set aside overnight. Removal of the solvents *in vacuo* gave a syrup, which was dissolved in water (50 c.c.). The solution was saturated with potassium carbonate and subjected to continuous ether-extraction for 24 hr. Evaporation of the dried (Na_2SO_4) ethereal solution afforded a semicrystalline mass of (±)-*tropane*-2β,3α-*diol*, which crystallised from benzene in rhombic prisms, m. p. 101° (1·3 g.) (Found: C, 60·4; H, 9·4; N, 8·9. $C_8H_{15}NO_2$ requires C, 61·1; H, 9·6; N, 8·9%), hydroxyl bands (in $CHCl_3$) at 3462 and 3628 cm.$^{-1}$. The *methiodide* separated from ethanol in rhombic prisms, m. p. >320° (Found: C, 36·4; H, 5·7; N, 4·6. $C_9H_{18}NO_2I$ requires C, 36·1; H, 6·1; N, 4·7%). The *picrate* crystallised from benzene–methanol in yellow needles, m. p. 208—210° (decomp.) (Found: C, 43·7; H, 4·8; N, 14·7. $C_{14}H_{18}N_4O_9$ requires C, 43·5; H, 4·7; N, 14·5%).

Attempts to dehydrate the diol with 20% sulphuric acid or potassium hydrogen sulphate resulted in the main in recovery of the starting material. The diol (1·93 g.) was mixed with glacial acetic acid (0·7 c.c.) and concentrated sulphuric acid (1·5 c.c.) with cooling, and the mixture heated at 165° for 5 hr. Cooling, followed by dilution with water, basification with potassium carbonate, and continuous ether-extraction, gave a pale yellow oil (1·52 g.) which crystallised on trituration with light petroleum (b. p. 60—80°). It separated from the same solvent in prisms, m. p. 103·5—105° (Found: C, 61·2; H, 9·3; N, 9·0. Calc. for $C_8H_{15}NO_2$: C, 61·1; H, 9·6; N, 8·9%), alone or mixed with (±)-tropane-2β,3β-diol prepared by oxidation of tropidine with potassium permanganate or osmium tetroxide (see below). A small yield of tropinone was also obtained (picrate, m. p. and mixed m. p. 219°) (see below).

3-*Chlorotropidine* (XIV).—Thionyl chloride (2 c.c.) was added dropwise, with ice-cooling and stirring, to the foregoing *trans*-diol (0·61 g.), with stirring for a further 30 min. at room temperature. After being heated under reflux on the water-bath for 18 hr., the mixture was freed from volatile material under reduced pressure. The residual gum was dissolved in water, and the solution filtered, saturated with potassium carbonate, and extracted six times with ether–methylene chloride (1 : 1). The combined, dried (K_2CO_3) extracts were evaporated,

leaving 3-*chlorotropidine*, b. p. 52—54°/0·1 mm. (0·33 g.) (Found: C, 60·6; H, 8·0; N, 8·9; Cl, 21·4. $C_8H_{12}NCl$ requires C, 60·9; H, 7·7; N, 8·9; Cl, 22·5%), $\nu_{max.}$ (liquid film) 1639s cm.$^{-1}$ (C=C), no carbonyl band. Under milder conditions (thionyl chloride in chloroform at 20°) the diol was recovered.

(±)-*Tropane*-2β,3β-*diol* (VII).—(*a*) [15] To a solution of tropidine (5 g.) in water (50 c.c.), at 0°, was added a solution of potassium permanganate (4·35 g.) and magnesium sulphate heptahydrate (8·7 g.) in water (435 c.c.) during 5 hr., with continuous stirring, at 0°. After a further hour's stirring, the solution was cooled during the addition of solid potassium hydroxide (*ca.* 500 g.), and then subjected to continuous ether-extraction for 30 hr. The dried (Drierite) extract was concentrated and unchanged tropidine removed by heating the residual oil for 30 min. at 100°/18 mm. The remaining oil was extracted several times with boiling light petroleum (b. p. 60—80°), leaving an appreciable amount of insoluble gum. On partial evaporation and cooling, the petroleum extract afforded (±)-tropane-2β,3β-diol (0·40 g.), which crystallised from light petroleum (b. p. 60—80°) in regular prisms, m. p. 104·5—105° after careful drying (lit.,[15] m. p. 105°), hydroxyl bands (in CCl_4) at 3440 and 3557 cm.$^{-1}$. The *picrate* separated from methanol in yellow rhombs, m. p. 239·5—240·5° (decomp., rapid heating) (Found: C, 43·1; H, 4·7; N, 14·5. $C_{14}H_{18}N_4O_9$ requires C, 43·5; H, 4·7; N, 14·5%). The yield of the diol was not improved by addition of a catalytic amount of osmium tetroxide.

(*b*) To a solution of osmium tetroxide (1·0 g.) in dry ether (20 c.c.) was added gradually, during 15 min., with ice-cooling and shaking, a solution of tropidine (0·47 g.) in dry ether (10 c.c.). After 2 days at room temperature the dark brown osmic ester which had separated was collected, dissolved in water (50 c.c.), and mixed with a solution of sodium sulphite (6·0 g.) in the minimum amount of water. The solution was refluxed for 30 min., cooled, saturated with potassium carbonate, and subjected to continuous ether-extraction for 48 hr. Evaporation of the dried extract gave (±)-tropane-2β,3β-diol (0·5 g.), which separated from light petroleum (b. p. 60—80°) in irregular prisms, m. p. 104·5—105°, alone or mixed with the product obtained as in (*a*).

Dehydration of (±)-*Tropane*-2β,3β-*diol*.—The foregoing diol (0·36 g.) was mixed with concentrated sulphuric acid (3 c.c.), with ice-cooling, and then heated at 120° (internal temperature) for 6 hr. The mixture was cooled, diluted with water (20 c.c.), basified with potassium carbonate and potassium hydroxide, and extracted continuously with ether for 14 hr. Evaporation of the dried (K_2CO_3) extract gave a semicrystalline syrup (0·18 g.) which distilled at 104° (bath)/18 mm. The distillate solidified on ice-cooling; its infrared absorption curve was indistinguishable from that of tropinone. The picrate crystallised from water in yellow needles, m. p. 219° (decomp.), alone or mixed with tropinone picrate [lit.,[32] m. p. 220° (decomp.)].

Isopentyl-N-*nitrosourethane*.—Isovaleronitrile was obtained by refluxing isobutyl bromide, potassium cyanide, and 60% ethanol, essentially as described by Rosenmund *et al.*[33] The yield was much improved by concentration of the ethereal extract *via* a metre Vigreux column. The nitrile (20 g.; b. p. 128°) was mixed with ethanol (350 c.c.) and refluxed gently during addition of sodium (33 g.) in small pieces during 45 min. The cooled solution was rendered acid with 5N-hydrochloric acid (370 c.c.), and the ethanol removed under reduced pressure. The residual aqueous solution was cooled, basified with potassium hydroxide, and extracted with ether. The dried (K_2CO_3) extract was evaporated *via* a Vigreux column, and the residual isopentylamine distilled (b. p. 96—97°; 14 g.; lit.,[34] b. p. 95—97°). Isopentylurethane was prepared by condensation of the amine and ethyl chloroformate,[35] in quantitative yield; it distilled at 106—107°/14 mm. (lit.,[34] b. p. 101—102°/14 mm.) (Found: C, 60·3; H, 10·8. Calc. for $C_8H_{17}NO_2$: C, 60·4; H, 10·7%). The urethane (40 g.), ether (100 c.c.), sodium nitrite (100 g.), ice (30 g.), and water (140 c.c.) were mixed, cooled in ice, and shaken during the gradual addition (1 hr.) at below 15° of a mixture of concentrated nitric acid (66 c.c.) and water (100 c.c.). The ether layer was separated, washed with potassium carbonate solution until neutral, and dried (K_2CO_3). The ether was evaporated under reduced pressure from a bath at 40°, leaving isopentyl-*N*-nitrosourethane as a pink oil (46 g.), which was used without purification.

2-*Isobutylcycloheptanone*.—Cyclohexanone (25·5 g.), dry methanol (30 c.c.), and powdered anhydrous sodium carbonate (0·6 g.) were stirred mechanically during the gradual addition

[32] Willstätter, *Ber.*, 1896, **29**, 396.
[33] Rosenmund, Luxat, and Tiedemann, *Ber.*, 1923, **56**, 1956.
[34] Jaeger, *Z. anorg. Chem.*, 1917, **101**, 93.
[35] Schmidt, *Ber.*, 1903, **36**, 2476; *Z. phys. Chem.*, 1907, **58**, 516.

of isopentyl-*N*-nitrosourethane (46 g.) during 1½ hr. Ice-cooling was applied from time to time to keep the temperature at 20—25°. After 16 hr. at room temperature the sodium carbonate was removed and the methanol distilled off under reduced pressure *via* a short fractionating column. The residual liquid distilled at 102—106°/13—14 mm. (27·3 g.) and contained some *N*-isopentylurethane (infrared absorption spectrum). It was purified by dissolution in methanol (35 c.c.) and treatment with methanolic semicarbazide acetate [from semicarbazide hydrochloride (30 g.) in the minimum volume of water, and anhydrous potassium acetate (30 g.) in methanol (150 c.c.)]. After evaporation of some of the methanol, the solution was set aside overnight at 0°. The *semicarbazone* (25·5 g.) which separated was collected; a small portion separated from 50% aqueous methanol in plates, m. p. 131—132° (Found: C, 64·0; H, 10·15. $C_{12}H_{23}NO_3$ requires C, 64·0; H, 10·2%). Hydrolysis of the main bulk of the semicarbazone by heating with strong aqueous oxalic acid in the usual manner furnished 2-*isobutylcycloheptanone*, b. p. 104—105°/12—13 mm. (16·5 g.) (Found: C, 78·6; H, 11·4. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%), C=O band (liquid film) at 1715, $>CMe_2$ bands [36] at 1389, 172, 1176, 1156, and 784 cm.$^{-1}$. The 2,4-*dinitrophenylhydrazone* separated from ethanol in orange hexagonal plates, m. p. 76° (Found: C, 58·4; H, 6·9. $C_{17}H_{24}N_4O_4$ requires C, 58·6; H, 6·9%).

2-*Isobutylcycloheptanone Oxime*.—The above ketone (15 g.) in methanol (20 c.c.) was mixed with hydroxylamine acetate [from hydroxylamine hydrochloride (30 g.) in the minimum amount of water, and anhydrous potassium acetate (45 g.) in methanol (250 c.c.)] and the solution refluxed on the water-bath for 30 min. The methanol was removed *in vacuo*, water was added, and the oil taken up in ether. The ethereal solution was washed with sodium hydrogen carbonate, dried, and concentrated. The residual *oxime* distilled at 140—141°/11—12 mm., 146—147°/14 mm. (14·6 g.) (Found: C, 72·1; H, 11·2; N, 7·3. $C_{11}H_{21}NO$ requires C, 72·1; H, 11·5; N, 7·65%).

2-*Isobutyl*-NN-*dimethylcycloheptylamine* (XV).—The foregoing oxime (6·8 g.) in dry ether (100 c.c.) was added during 30 min. to a suspension of lithium aluminium hydride (2·5 g.) in dry ether (150 c.c.), with continual agitation. After 24 hr. at room temperature, the mixture was refluxed on the water-bath for 3 hr., then cooled and decomposed with ice-water in the presence of "Celite." The dried, ethereal solution was concentrated *via* a fractionating column; the residual 2-*isobutylcycloheptylamine* distilled at 124°/15 mm. (5·1 g.) (Found: N, 8·0. $C_{11}H_{23}N$ requires N, 8·3%). The amine (2·0 g.), 90% formic acid (3·0 g.), and 40% aqueous formaldehyde (3·0 g.) were mixed in the cold and heated on the water-bath for 3 hr., by which time evolution of carbon dioxide was complete. To the cooled solution dilute hydrochloric acid (15 c.c.) was added, and neutral matter was removed with ether. The aqueous layer was basified with potassium hydroxide. 2-*Isobutyl*-NN-*dimethylcycloheptylamine*, isolated with ether, distilled at 114°/15 mm. (2·0 g.) (Found: C, 78·9; H, 13·8; N, 7·3. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7; N, 7·1%). The tertiary base reacted with methyl iodide to give a product which, after several recrystallisations from acetone–ether, melted over a wide range, softening at *ca.* 85°, melting being complete at 102—105°.

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[36] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 2nd Ed., 1958, Chapter 1.