314. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part III.** *Further Investigations of the Hofmann Degradation.*

By A. R. PINDER.

The base $C_{13}H_{21}N$, obtained by Hofmann degradation of dioscorine, breaks down when heated with palladised charcoal into trimethylamine, an unidentified base, and *iso*butylbenzene or ββ-dimethylstyrene, depending on the activity of the catalyst. Hofmann decomposition of the base $C_{13}H_{21}N$ gives a hydrocarbon $C_{11}H_{14}$, which is not aromatic. Spectral measurements on these degradation products and compounds derived from them are reported. The degradative work has been complicated by the formation of mixtures.

The structure (XIII) is tentatively proposed for dioscorine.

IN previous parts [1, 2] of this Series reasons were given for believing that the alkaloid occurring in the tubers of *Dioscorea hispida*, Dennst., is dioscorine, obtained by Gorter [3] from tubers of *Dioscorea hirsuta*, Blume. The present communication presents more evidence for this view, and henceforward it is assumed that the two bases are identical.

Further investigations on the structure of dioscorine are now reported. In the Hofmann degradation of the alkaloid [2] it has been found more convenient to use an ion-exchange resin for conversion of dioscorine methiodide into the methohydroxide, and this procedure has resulted in a slightly improved yield of the Hofmann base, $C_{13}H_{21}N$. A closer examination of the infrared absorption of this base confirms that it is not an aromatic amine (no bands characteristic of the benzene ring in the 1660—2000 cm.$^{-1}$ region), and strong bands at 891, 1415, and 3090 cm.$^{-1}$ confirm [4] the presence of a methylene group of the type $R_1R_2C{:}CH_2$. The general shape of the infrared curve supports the view expressed previously [2] that the base is a mixture of isomers, but attempts to separate them by adsorption methods failed.

When the base $C_{13}H_{21}N$ was heated at 210—220° with a freshly prepared palladised charcoal catalyst, it broke down smoothly into trimethylamine, a base, and a hydrocarbon, $C_{10}H_{14}$, mainly *iso*butylbenzene. The first and the last product were recognised as the picrate and *o*-aroylbenzoic acid derivative respectively. The base, b. p. 110—111°/12·5 mm. (picrate m. p. 144°), is now under investigation. If a somewhat less active catalyst was used, the basic products were the same, but a hydrocarbon $C_{10}H_{12}$ was obtained: this was mainly ββ-dimethylstyrene (*iso*but-1-enylbenzene) (I), recognised by

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* Part II, *J.*, 1953, 1825.

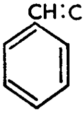
[1] Pinder, *J.*, 1952, 2236.

[2] *Idem, J.*, 1953, 1825.

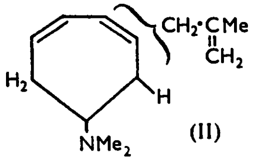
[3] Gorter, *Rec. Trav. chim.*, 1911, **30**, 161.

[4] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954.

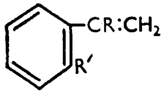
oxidation to benzaldehyde and acetone, by reduction in the presence of nickel to *iso*butylbenzene, and as its crystalline nitrosite, m. p. 124—125° (decomp.). The nitrosite of ββ-dimethylstyrene has been variously reported [5] as having a m. p. ranging from 112° to 156°. An authentic specimen of the hydrocarbon was therefore synthesised from benzaldehyde. It formed a nitrosite, m. p. 124—125° (decomp.), alone or mixed with the nitrosite of the hydrocarbon obtained from dioscorine.



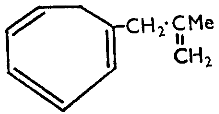
(I)



(II)



(III)



(IV)

The infrared absorption curve of the hydrocarbon $C_{10}H_{14}$ was almost identical with that of authentic *iso*butylbenzene, but it was evident that traces of other hydrocarbons were present. The ultraviolet absorption of the hydrocarbon $C_{10}H_{12}$ showed a wide maximum at 255 mμ (ε 11,850), the position and intensity of which varied somewhat with different specimens. This is at a slightly higher wavelength than that for ββ-dimethylstyrene ($\lambda_{max.}$ 240 mμ; ε 8500), and it is concluded that the hydrocarbon $C_{10}H_{12}$ is contaminated with non-aromatic, conjugated hydrocarbons, which absorb at higher wavelengths. The hydrocarbon $C_{10}H_{14}$ showed a peak at 240 mμ (ε 835), which may be due to a substituted styrene.[6]

The formation of *iso*butylbenzene and ββ-dimethylstyrene from the base $C_{13}H_{21}N$ suggests strongly that the latter has a seven-membered carbon ring, and this and earlier evidence [2] support the view put forward by Gorter [3] that the base is a mixture of *iso*butenyl-*NN*-dimethyl*cyclo*heptadienylamines of structure (II), the isomers arising from the positions of the double bonds and of the alkenyl group. A structure such as (II) might be expected to lose a carbon atom and two allylic hydrogen atoms as trimethylamine, with the simultaneous formation of aromatic hydrocarbons. The ultraviolet absorption [2] of the base $C_{13}H_{21}N$ ($\lambda_{max.}$ 270 mμ; ε 17,500) suggests that in at least one of these isomers the three double bonds are conjugated. The strong $C{:}CH_2$ band in the infrared spectrum of the base, and the failure to obtain acetone as an ozonolysis product, indicate that the base contains only small amounts of isomers with a $Me_2C{:}CH-$ side-chain. Further, the base shows no band in the 790—840 cm.$^{-1}$ region, characteristic [4] of the grouping $RR'C{:}CHR''$.

The Hofmann degradation of the base $C_{13}H_{21}N$, already described by Gorter,[3] was next re-investigated. The base formed a partly crystalline methiodide,[2] which was converted by anion-exchange resin into a foamy methohydroxide. Decomposition of the latter gave trimethylamine and a highly unsaturated hydrocarbon $C_{11}H_{14}$, which corresponded exactly in properties with the hydrocarbon obtained by Gorter, although he gave no analytical figures. The hydrocarbon polymerised in a few hours, and on catalytic hydrogenation absorbed 4 mols. of hydrogen readily, to give a saturated hydrocarbon, $C_{11}H_{22}$. Gorter's statement that oxidation of the unsaturated hydrocarbon with permanganate gave only formic acid and no aromatic acid has been confirmed; a careful search did not reveal an aromatic acid. Ozonolysis gave formaldehyde, but no acetone. Gorter has described the hydrobromination, dehydrobromination, and oxidation of the hydrocarbon to *o*-toluic acid.

The infrared absorption of the hydrocarbon $C_{11}H_{14}$ suggested that it contained traces of aromatic hydrocarbons, weak bands in the 1600—2000 cm.$^{-1}$ region indicating the presence of a 1 : 2- or 1 : 3-di- or 1 : 2 : 3-tri-substituted benzene system, the 1 : 2-disubstitution being preferred. Bands at 890, 1633, 1785, and 3070 cm.$^{-1}$ confirm the presence of a $C{:}CH_2$ group, which is evidently of the type $RR'C{:}CH_2$. These observations could be explained by the presence of small amounts of *o* : α-dialkylstyrenes (III; R =

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[5] Angeli, *Ber.*, 1892, **25**, 1956; Blaise and Herman, *Ann. Chim.* (*France*), 1911, **23**, 522; Kishner, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 863; Tiffeneau and Orékhoff, *Bull. Soc. chim.* (*France*), 1921, **29**, 809; Haller and Ramart, *Compt. rend.*, 1922, **174**, 1212.

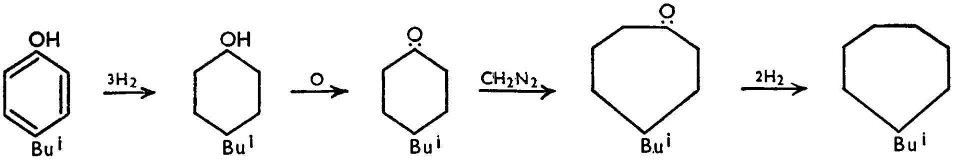
[6] Hirschberg, *J. Amer. Chem. Soc.*, 1949, **71**, 3241.

Me, R′ = Et, or *vice versa*). The ultraviolet absorption of the hydrocarbon $C_{11}H_{14}$ is, however, not in agreement with this. The product has two maxima, at 230 (ε 8500) and 278 mμ (ε 8500) (wide), the former being possibly an inflexion. The ultraviolet absorption of substituted styrenes of type (III) has been examined recently by Hirschberg.[6] *o* : α-Dimethylstyrene (III; R = R′ = Me), for example, shows no maximum absorption between 210 and 300 mμ, owing to steric hindrance between the *o*-substituents.

The most satisfactory explanation of the behaviour of the hydrocarbon $C_{11}H_{14}$ appears to be that it is a mixture, possibly containing a very small proportion of an *o* : α-dialkylstyrene, but is mainly an alkenyl*cyclo*heptatriene of possible structure (IV), which could be degraded by Gorter's procedure to *o*-toluic acid, and in which the positions of the double bonds are not fixed though at least three must be in conjugation. The strong evidence for the presence of a $C{:}CH_2$ group suggests that this bond may be fixed. *cyclo*Heptatriene [7] itself absorbs maximally at 260 mμ (ε not quoted), and a typical conjugated tetraene, decatetraenol,[8] at 299 mμ (ε 64,000).

The saturated hydrocarbon $C_{11}H_{22}$ shows infrared bands at 1154, 1170, 1366, and 1380 cm.$^{-1}$, characteristic of a $>CMe_2$ group. If the reasoning regarding the structure of the hydrocarbon $C_{11}H_{14}$ is correct, the infrared absorption curve of the saturated hydrocarbon should resemble that of *iso*butyl*cyclo*hexane,[9] and, indeed, a comparison of the two curves shows that they are very similar. An authentic specimen of *iso*butyl*cyclo*heptane (IX) was synthesised from *p*-*iso*butylphenol (V) by the route shown. The infrared absorption curves of the product (IX) and the hydrocarbon $C_{11}H_{22}$ were very similar, but not identical. A *C*-methyl estimation for the hydrocarbon $C_{11}H_{22}$ gave a value of 0·66 per molecule, which is more in agreement with structure (IX) than with structures derived by the total hydrogenation of the benzene derivative (III).

It is concluded from the investigations on the hydrocarbons derived from dioscorine that, as first postulated by Gorter,[3] the alkaloid is an unsymmetrical derivative of tropane, and that the mixtures of products obtained are the result of the ability of the primary Hofmann degradation to take place in more than one direction. It is rather surprising that the final Hofmann product, the hydrocarbon, $C_{11}H_{14}$, is not aromatic.



(V) (VI) (VII) (VIII) (IX)

The saturated base $C_{13}H_{27}N$, obtained [2] by hydrogenation of the Hofmann base $C_{13}H_{21}N$, has also been further examined. Its infrared absorption curve shows strong bands at 1156, 1179, 1364, and 1379 cm.$^{-1}$, characteristic of a $>CMe_2$ group. If the partial structure (II) assigned to the Hofmann base is correct, the base $C_{13}H_{27}N$ would be one of three possible *iso*butyl-*NN*-dimethyl*cyclo*heptylamines. Two of these, (X) and (XI), have been synthesised for comparison. 4-*iso*Butyl-*NN*-dimethyl*cyclo*heptylamine (X) was obtained from the ketone (VIII) by reduction of its oxime, followed by methylation. The 3-isomer (XI) was obtained by a similar method from 3-*iso*butyl*cyclo*heptanone (XII), which was synthesised *via* the appropriate adipic and suberic acids (see Experimental section). The two bases had physical properties very similar to those of the base $C_{13}H_{27}N$, and the infrared absorption curves of all three bore a striking similarity. It was not possible to say, however, that the unknown base was identical with either of the synthetic bases. The synthetic bases formed crystalline methiodides, m. p. respectively 271° (decomp.) and 207°, neither of which appeared to be identical with the methiodide (m. p.

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[7] Dryden, *J. Amer. Chem. Soc.*, 1954, **76**, 2841.

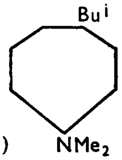
[8] Braude, *Ann. Reports*, 1945, **42**, 116, and references there cited.

[9] American Petroleum Institute, infrared curve no. 557.

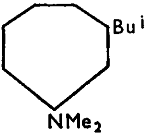
182—183°) of the base $C_{13}H_{27}N$, although neither showed a m. p. depression on admixture with the unknown methiodide. It is not unexpected that isomers of such similar structure should have closely similar infrared absorption curves. The comparison may also be complicated by the fact that the structures (X) and (XI) can exist in *cis*- and *trans*-forms.

The oxidation of dioscorine with potassium permanganate has been investigated, the lactone ring being first opened by pre-treatment with alkali. The only non-nitrogenous product isolated was oxalic acid. No basic, ketonic material has been obtained, and efforts to isolate an amino-acid have so far proved unsuccessful. The isolation of oxalic acid is consistent with the view that the lactone ring in dioscorine contains the grouping $-O\cdot CO\cdot CH{:}C{<}$. The ultraviolet absorption of the alkaloid is also consistent with the presence of this grouping ($\lambda_{max.}$ 217 mμ) (cf. ethyl β-methylcrotonate, $Me_2C{:}CH\cdot CO_2Et$,[10] $\lambda_{max.}$ 217 mμ), as pointed out previously.[2]

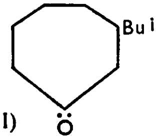
(X)

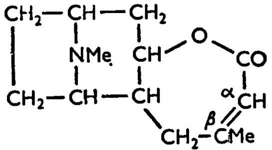


(XI)

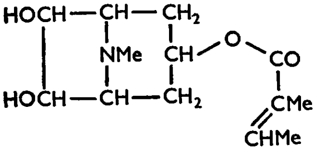


(XII)





(XIII)



(XIV)

If it is assumed that dioscorine is a tropane alkaloid, and that the lactone ring is attached to the tropane system *via* the tropine (3-)hydroxyl group, the structure which explains the reactions described most satisfactorily appears to be (XIII). It is conceivable that this structure would break down on Hofmann degradation to give structures of the type (II), by elimination of water and carbon dioxide. The formation of oxalic acid on oxidation indicates that $C_{(\alpha)}$ is unsubstituted, and the ultraviolet absorption of the alkaloid, and the nature of the base $C_{13}H_{27}N$ and the hydrocarbons, suggest that a methyl group is at $C_{(\beta)}$. The structure is closely related to that of meteloidine[11] (XIV). It is interesting that the nitrogen atom is situated relatively to the carbonyl group in a very similar position to that which is found in dihydro-β-erythroidine,[12] and it will be recalled that the latter compound undergoes a similar type of Hofmann degradation.

Tests kindly carried out by Mr. A. W. Patterson, of the Heriot-Watt College, Edinburgh, have shown that dioscorine, in common with other lactones, has anthelmintic properties. Against *Ascaris lumbricoides* and *Fasciola hepatica* the alkaloid produced a marked depression, with slow recovery, at a dilution of 1 in 2000. There was no activity at a dilution of 1 in 4000.

EXPERIMENTAL

Ultraviolet absorptions were measured in MeOH solution.

Hofmann Degradation of Dioscorine.—The following are improved conditions for this degradation.[13] Dioscorine methiodide (3·3 g.) in water (25 c.c.) was passed down a column, about 20 cm. long, containing Amberlite IRA-400(OH) anion-exchange resin (10 g.). The column was eluted with water (30 c.c.), and the combined aqueous solutions were evaporated to dryness *in vacuo*. The methohydroxide so obtained was decomposed as previously described.[2] The crude distillate was taken up in ether and shaken several times with dilute hydrochloric acid.

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[10] Ungnade and Ortega, *J. Amer. Chem. Soc.*, 1951, **73**, 1564.

[11] Heusner, *Chem. Ber.*, 1954, **87**, 1032.

[12] Boekelheide, Weinstock, Grundon, Sauvage, and Agnello, *J. Amer. Chem. Soc.*, 1953, **75**, 2550

[13] Cf. Weinstock and Boekelheide, *ibid.*, p. 2546.

The combined acid extracts were rendered strongly alkaline with potassium hydroxide, and the solution was heated on the water-bath for 1 hr. The cooled solution was thoroughly extracted with ether, and the extracts were dried and evaporated. The Hofmann base distilled at 114—115°/10 mm. (0·7 g.) (Found: C, 81·5, 81·5; H, 10·7, 10·7; N, 7·1, 7·4. Calc. for $C_{13}H_{21}N$: C, 81·7; H, 11·0; N, 7·3%). Infrared absorption (liquid film): no benzene-ring bands in the 1600—2000 cm.$^{-1}$ region; $C{:}CH_2$ bands at 890, 1415, and 3090 cm.$^{-1}$.

Decomposition of the Base $C_{13}H_{21}N$ *with Palladised Charcoal.*—(*a*) The pure base (2·0 g.) and freshly prepared palladised charcoal [14] (30%; 0·6 g.) were heated gradually under reflux in an oil-bath to 210—220°, the gases evolved being absorbed in cooled methanol. At 170—175° a brisk effervescence occurred; after 3 hr. at 210—220° the mixture was cooled, treated with ether, and filtered. The filtrate was washed twice with dilute hydrochloric acid, then with sodium hydrogen carbonate solution, and dried. The ether was evaporated through a short Vigreux column. The residue (1·3 g.) distilled mainly at 180—190°/769 mm. (0·5 g.); a smaller fraction (0·2 g.) had b. p. 190—200°/769 mm., and there was a residual, involatile tar (0·6 g.).

The main fraction, twice distilled through a micro-Vigreux column, had b. p. 124—125°/100 mm., n_D^{25} 1·4840 (Found: C, 89·6, 89·6; H, 10·3, 10·4. Calc. for $C_{10}H_{14}$: C, 89·6; H, 10·4%). Ultraviolet max.: 240 mμ (ε 835) (wide) and strong "end-absorption" at *ca.* 200 mμ. Infrared absorption (liquid film): almost identical with that of *iso*butylbenzene; [15] principal bands at 699, 740, 1170, 1370, and 1380 cm.$^{-1}$; weak bands in 890 and 1750—1800 cm.$^{-1}$ regions, due to impurities.

The hydrocarbon was stable to cold, acid potassium permanganate for several hours. It was converted into its *o-aroylbenzoic acid derivative*; the hydrocarbon (0·2 g.), powdered anhydrous aluminium chloride (0·4 g.), phthalic anhydride (0·2 g.), and dry carbon disulphide (10 c.c.) were refluxed on the water-bath for 1½ hr. The solvent was decanted and the residue decomposed with ice-cold 5N-hydrochloric acid (15 c.c.). The crude acid was collected and washed with water; it was dissolved in dilute aqueous ammonia (10 c.c.) and water (10 c.c.), and the solution boiled for a minute with a little charcoal. The filtered solution was cooled and acidified with 5N-hydrochloric acid, and the solid collected, washed with water, and dried. After two crystallisations from 60% ethanol the acid was obtained as rhombic prisms, m. p. 124·5° (Found: C, 76·5; H, 6·6. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). The m. p. was undepressed on admixture with an authentic specimen of *o*-(*p*-*iso*butylbenzoyl)benzoic acid (see below).

An authentic specimen of *iso*butylbenzene was prepared by Clemmensen reduction of *iso*butyrophenone.[16] It had b. p. 125°/100 mm. n_D^{20} 1·4865. It was converted into *o*-(*p*-*iso*butylbenzoyl)benzoic acid as described for the hydrocarbon $C_{10}H_{14}$. The acid separated from 60% ethanol in rhombic prisms, m. p. and mixed m. p. 124·5° (Found: C, 76·4; H, 6·3%).

The methanolic solution of the evolved vapours was mixed with an excess of methanolic picric acid, and the crystalline precipitate collected and recrystallised from ethanol. It formed yellow, elongated prisms, m. p. 221°, alone or admixed with trimethylamine picrate, m. p. 221°.

(*b*) The use of an older and less active specimen of palladised charcoal led to slightly different results. The two basic products appeared to be the same, but the hydrocarbon product, isolated in the same manner, had b. p. 76—77°/14 mm., 186°/760 mm., n_D^{20} 1·5415 (Found: C, 90·8; H, 9·0. Calc. for $C_{10}H_{12}$: C, 90·85; H, 9·15%). Ultraviolet max.: 255 mμ (ε 11,850) (wide) and strong "end-absorption" at *ca.* 200 mμ. The compound was oxidised readily to benzaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 237°) and acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°) by acid permanganate. When shaken in hydrogen in solution in ethanol at atmospheric pressure and temperature with "W2" Raney nickel [17] it absorbed 1 mol. of hydrogen, giving *iso*butylbenzene, b. p. 174—175°, n_D^{20} 1·4866, which reacted with phthalic anhydride to give the corresponding *o*-aroylbenzoic acid (see above), m. p. and mixed m. p. 124—125°. The *nitrosite* was prepared [18] by shaking the hydrocarbon (0·1 g.), sodium nitrite (0·2 g.), water (3 c.c.), and glacial acetic acid (0·2 g.) for several hours at 0°. The crystalline precipitate was collected, washed with water, and dried; it crystallised from benzene in needles, m. p. 124—125° (decomp.) (Found: C, 57·4; H, 5·4; N, 13·4. Calc. for $C_{10}H_{12}O_3N_2$: C, 57·7; H, 5·8; N, 13·5%). An authentic specimen of ββ-dimethylstyrene

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[14] Linstead and Thomas, *J.*, 1940, 1127.

[15] American Petroleum Institute, infrared curves nos. 188, 412.

[16] Hennion and Auspos, *J. Amer. Chem. Soc.*, **1943**, **65**, **1603**.

[17] *Org. Synth.*, Coll. Vol. III, p. 181; *Chem. Abs.*, 1953, **47**, 3098.

[18] Cf. Baeyer, *Annalen*, 1893, **278**, 88.

(I) was prepared from 2-methyl-1-phenylpropan-1-ol [19] by dehydration with oxalic acid.[20] The hydrocarbon, b. p. 185—186°, n_D^{20} 1·5410, was converted into its nitrosite as described above, giving needles (from benzene), m. p. 124—125° (decomp.) alone or mixed with the nitrosite from the hydrocarbon $C_{10}H_{12}$ (Found: C, 57·5; H, 5·5%).

Hofmann Degradation of the Base $C_{13}H_{21}N$.—A mixture of the base (3·75 g.), methanol (10 c.c.), and methyl iodide (6 c.c.) was kept overnight at room temperature, then evaporated to dryness *in vacuo*. The methiodide was partly crystalline and partly a glass; it was dissolved in water (60 c.c.) and passed down a column (about 15 cm.) containing Amberlite IRA-400(OH) anion-exchange resin (20 g.). After elution with water (50 c.c.) the aqueous solution was evaporated to dryness at 11 mm. from a bath at 40—45°. The foamy residue, which smelled strongly of trimethylamine, was decomposed by gentle heating with a free flame at 10—11 mm., the receiver being cooled to −10°. The crude distillate (1·6 g.) was taken up in ether and washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The ether was evaporated through a Vigreux column, leaving an oil which distilled at 83—84°/10·5 mm. (0·8 g.) (Found: C, 90·25, 90·3; H, 9·3, 9·4. $C_{11}H_{14}$ requires C, 90·4; H, 9·6%). Ultraviolet max.: 230 (inflexion, ε 8500) and 278 mμ (ε 8500). Infrared absorption (liquid film): bands at 741, 890, 1170, 1376, 1633, 1785, 2980, and 3070 cm.$^{-1}$. The *hydrocarbon* was very unstable, and polymerised in a few hours to a white gum, insoluble in ether. With a drop of concentrated sulphuric acid it polymerised vigorously to a dark, plastic mass. The hydrocarbon (0·67 g.) in glacial acetic acid (10 c.c.) was shaken with pre-reduced Adams platinum oxide in hydrogen. The uptake was 441 c.c. at 17°/755·7 mm. (theor. for $4H_2$: 439 c.c.). The solution was filtered, the filtrate diluted with a large volume of water, and the hydrocarbon isolated with ether. The ethereal extract was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated *via* a 30 cm. Vigreux column. The residual *hydrocarbon*, distilled at 68·5—69°/11 mm. (0·6 g.), had n_D^{17} 1·4480 (Found: C, 85·4, 85·6; H, 14·0, 14·1; *C*-Me, 6·4. $C_{11}H_{22}$ requires C, 85·7; H, 14·3; 1 *C*-Me, 9·7%). Infrared absorption (liquid film): bands at 1380, 1366, 1170 and 1154 cm.$^{-1}$; curve very similar to those of *iso*butyl*cyclo*hexane and *iso*butyl*cyclo*heptane. On oxidation of the hydrocarbon $C_{11}H_{14}$ with potassium permanganate only formic acid (*p*-bromophenacyl ester, m. p. and mixed m. p. 140°) was isolated.[3] Ozonolysis of the hydrocarbon (0·35 g.) in glacial acetic acid (25 c.c.) gave formaldehyde only (dimedone derivative, m. p. and mixed m. p. 190°).

4-iso*Butyl*cyclo*hexanol* (VI).—Phenyl *iso*butyrate was converted by Fries rearrangement into *p*-*iso*butyrylphenol,[21] which on Clemmensen reduction [22] gave *p*-*iso*butylphenol, m. p. 50—51°. The latter (10 g.) in ethanol (10 c.c.) was hydrogenated at 110—120°/90 atm. in the presence of "W7" Raney nickel [23] and sodium hydroxide (1 pellet) for 6 hr. The filtered solution was evaporated, and the residue taken up in ether and washed twice with dilute sodium hydroxide solution, then with water. The dried extract was evaporated. The residue of 4-iso*butyl*cyclo*hexanol* distilled at 110—112°/13 mm. (9·3 g.) (Found: C, 76·8; H, 12·9. $C_{10}H_{20}O$ requires C, 76·9; H, 12·8%). The 3 : 5-*dinitrobenzoate* separated from methanol in plates, m. p. 125—126° (Found: C, 58·4; H, 6·4. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%).

4-iso*Butyl*cyclo*hexanone* (VII).—The above alcohol (30 g.) in glacial acetic acid (60 c.c.) was added during 30 min. to a stirred solution of chromic acid (14 g.) in water (12 c.c.) and glacial acetic acid (24 c.c.), at <20°. After being kept overnight, the solution was diluted with much water and extracted several times with ether. The combined extracts were washed thoroughly with dilute sodium hydroxide solution and water, dried, and evaporated. The residual 4-iso*butyl*cyclo*hexanone* distilled at 94°/11 mm. (21 g.) (Found: C, 78·0; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange-yellow plates, m. p. 105° (Found: C, 57·75; H, 6·9. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6%).

4-iso*Butyl*cyclo*heptanone* [24] (VIII).—*N*-Nitrosomethylurethane (10·0 g.) was added dropwise to a stirred mixture of 4-*iso*butyl*cyclo*hexanone (11·3 g.), methanol (25 c.c.), and powdered anhydrous potassium carbonate (1·4 g.) during 20 min., at <25° (ice-cooling). After a further 12 hours' stirring the mixture was filtered, the methanol evaporated, water added, and the organic material isolated with ether. Evaporation of the ether gave an oil which distilled at 105—110°/9 mm. (10·6 g.). It was shaken for 24 hr. with saturated sodium hydrogen sulphite

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[19] Grignard, *Ann. Chim.* (*France*), 1901, **24**, 433.

[20] Conant and Blatt, *J. Amer. Chem. Soc.*, 1928, **50**, 551.

[21] Cf. Hartung, Munch, Miller, and Crossley, *ibid.*, 1931, **53**, 4149.

[22] Barber and Haslewood, *Biochem. J.*, 1945, **39**, 285.

[23] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

[24] Cf. Cook, Raphael, and Scott, *J.*, 1951, 695.

solution (200 c.c.). The crystalline bisulphite compound was collected, washed with ether, dried, and shaken with 20% sodium carbonate solution (150 c.c.) and ether (100 c.c.). The ether layer was separated, washed with sodium hydrogen carbonate solution, dried, and evaporated. The residual 4-iso*butyl*cyclo*heptanone* distilled at 106°/10 mm. (5·3 g.) (Found : C, 78·5; H, 12·0. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%). Infrared absorption (liquid film) : CO band at 1704 cm.$^{-1}$, $>CMe_2$ bands at 1363, 1379, and 1169 (not split) cm.$^{-1}$. The *semicarbazone* crystallised from methanol in prisms, m. p. 163° (Found : C, 63·8; H, 10·1. $C_{12}H_{23}ON_3$ requires C, 64·0; H, 10·2%).

4-iso*Butyl*cyclo*heptylamine*.—Anhydrous potassium acetate (7 g.) in hot methanol (30 c.c.) was mixed with hydroxylamine hydrochloride (4·2 g.) in the minimum amount of water. The cooled mixture was filtered, and the filtrate mixed with 4-*iso*butyl*cyclo*heptanone (5 g.), and refluxed on the water-bath for 3 hr. The methanol was evaporated and the residue treated with water and extracted with ether. Evaporation of the dried extract gave 4-iso*butyl*cyclo*heptanone oxime* as a syrup which distilled at 159° (bath)/9 mm. (5·3 g.) (Found : C, 72·3; H, 11·6. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%). The oxime (4·8 g.) in dry ether (40 c.c.) was added dropwise, during 10 min., to a stirred suspension of lithium aluminium hydride (2·5 g.) in dry ether (75 c.c.). The mixture was refluxed on the water-bath for 2 hr., then decomposed with water in the presence of " Celite " (0·5 g.). The ether layer was decanted, dried, and evaporated. The residual 4-iso*butyl*cyclo*heptylamine* distilled at 117—118° (bath)/9 mm. (3·7 g.) (Found : C, 78·0; H, 13·5. $C_{11}H_{23}N$ requires C, 78·1; H, 13·6%).

4-iso*Butyl*-NN-*dimethyl*cyclo*heptylamine* [25] (X).—The foregoing base (1·7 g.) was mixed with 90% formic acid (2·6 g.), with shaking and ice-cooling. Formaldehyde (2·0 g. of 40%) was added, and the mixture heated under reflux on the water-bath for 3 hr. It was then acidified with dilute hydrochloric acid, and neutral matter removed with ether. The aqueous layer was basified with potassium hydroxide, and the basic product isolated with ether. Evaporation of the dried extract gave 4-iso*butyl*-NN-*dimethyl*cyclo*heptylamine*, b. p. 123° (bath)/9—10 mm. (1·5 g.) (Found : C, 79·2; H, 13·8. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7%). Infrared absorption (liquid film) : bands at 1379, 1365, 1153 (not split) cm.$^{-1}$.

The *methiodide*, obtained in warm methanol, crystallised from acetone in needles, m. p. 271° (decomp.) (Found : C, 49·4; H, 8·7. $C_{14}H_{30}NI$ requires C, 49·6; H, 8·8%).

iso*Butyl*cyclo*heptane* (IX).—4-*iso*Butyl*cyclo*heptanone (4 g.), powdered potassium hydroxide (4 g.), diethylene glycol (30 c.c.), and 100% hydrazine hydrate (4 c.c.) were boiled gently under reflux for 1½ hr.[26] The mixture was then distilled until the b. p. of the liquid reached 175—178°, and finally boiled under reflux for a further 3 hr. The cooled mixture was diluted and extracted with ether, and the extract washed with water and dilute hydrochloric acid, dried, and evaporated *via* a Vigreux column. The residual iso*butyl*cyclo*heptane* distilled at 80—81°/13 mm. (Found : C, 85·5; H, 14·0. $C_{11}H_{22}$ requires C, 85·7; H, 14·3%), and had n_D^{25} 1·4490. Infrared absorption (liquid film) : bands at 1364, 1382, and 1168 (not split) cm.$^{-1}$

Permanganate Oxidation of Dioscorine.—The alkaloid (2 g.), potassium hydroxide (5 g.), and water (50 c.c.) were heated on the water-bath for 3 hr. The clear solution was cooled to 0° and kept at this temperature during addition of 4% potassium permanganate solution (250 c.c) during 30 min., with shaking. The excess of permanganate was destroyed with sulphur dioxide, and the solution acidified with concentrated hydrochloric acid and subjected to continuous ether-extraction for several hours. Evaporation of the ethereal extract gave a semi-crystalline mass of oxalic acid; the crystals (0·05 g.), collected and washed with a little ether, had m. p. about 100°. After drying at 100° the m. p. was 189° (sealed tube), alone or mixed with anhydrous oxalic acid. The bis-*p*-nitrobenzyl ester had m. p. and mixed m. p. 204°.

The acid aqueous solution was rendered alkaline with potassium hydroxide and subjected to further continuous ether extraction. No basic product was obtained. Neutralisation of the aqueous liquid to pH 7, evaporation to dryness, and thorough extraction with methanol also gave nothing save a trace of intractable gum.

*Diethyl 3-Bromopropyl*iso*butylmalonate*.[27]—Sodium metal (2·4 g.) was powdered and suspended in dry benzene (20 c.c.). Diethyl *iso*butylmalonate [28] (21·6 g.) was added, with shaking and cooling, during 10 min. The mixture was heated for a further 10 min. on the water-bath, by which time all the sodium had disappeared. The cooled solution was added slowly to trimethylene bromide (40·5 g.), with shaking. After refluxing on the water-bath for

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[25] Cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.

[26] Cf. Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[27] Cf. Franke and co-workers, *Sitzungsber. Akad. Wiss. Wien*, 1932, **141**, 881; 1936, **145**, 788.

[28] Fischer and Schmidt, *Ber.*, 1906, **39**, 351.

1 hr., the solution was cooled, treated with water and ether, and the organic layer separated, dried, and evaporated. The residual *bromo-ester* distilled at 160—165°/9—10 mm. (16·3 g.) (Found : C, 50·2; H, 7·5. $C_{14}H_{25}O_4Br$ requires C, 49·9; H, 7·4%). A fore-run, b. p. up to 150°/9—10 mm. (6·8 g.), consisted of unchanged reactants.

Diethyl iso*Butyl-*3-*cyanopropylmalonate.*[27]—The foregoing bromo-ester (16·2 g.), potassium cyanide (15 g.), water (15 c.c.), and ethanol (35 c.c.) were boiled under reflux for 8 hr. The ethanol was distilled off under reduced pressure, and the residue diluted with water. The product was isolated with ether; *diethyl* iso*butyl-*3-*cyanopropylmalonate* distilled at 144—148°/1·5 mm. (11·4 g.) (Found : C, 63·7; H, 8·6. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·8%).

α-iso*Butyladipic Acid.*[27]—The above nitrile (11·4 g.), potassium hydroxide (13 g.), water (26 c.c.), and ethanol (26 c.c.) were boiled under reflux for 10 hr. The alcohol was removed *in vacuo* and the solution diluted, acidified with hydrochloric acid, and extracted with ether. Evaporation of the dried extract gave crystalline α-iso*butyl-α-carboxyadipic acid* (9·6 g.), which was heated at 180—190° for 30 min. The liquid product, α-*iso*butyladipic acid, distilled at 205—210° (bath)/0·05 mm. (7·2 g.). The product solidified; it separated from benzene–light petroleum (b. p. 40—60°) in hexagonal prisms, m. p. 60° (Found : C, 59·25; H, 8·5%; equiv., 99·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%; equiv., 101).

β-iso*Butylsuberic Acid.*[29, 30]—α-*iso*Butyladipic acid (11·1 g.) and purified thionyl chloride (20 c.c.) were heated gently on the water-bath for 1 hr. Excess of thionyl chloride was evaporated *in vacuo* and the residual *acid chloride* distilled (b. p. 130—132°/10 mm.; 10 g.) (Found : Cl, 30·0. $C_{10}H_{16}O_2Cl_2$ requires Cl, 29·7%). The acid chloride (10 g.) in dry ether (80 c.c.) was added slowly, with swirling and ice-cooling, during 15 min., to ethereal diazomethane (8·4 g. in 300 c.c.; from 30 g. of nitrosomethylurea). After 12 hr., the ether and excess of diazomethane were removed *in vacuo*. The residual bis-diazoketone (11·0 g.) was dissolved in dioxan (100 c.c.) and added portionwise to a suspension of silver oxide (from 17 g. of silver nitrate) in water (350 c.c.) containing sodium thiosulphate (16·5 g.), with shaking. After being heated at 70—75° for 1½ hr. the solution was cooled and filtered, and the filtrate acidified with nitric acid and extracted with ether. Evaporation of the dried extract gave β-iso*butylsuberic acid,* b. p. 170—172° (bath)/0·05 mm. (7·6 g.) (Found : C, 62·4; H, 9·55%; equiv., 114·1. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%; equiv., 115).

3-iso*Butyl*cyclo*heptanone* (XII).[30]—The foregoing acid (31 g.), iron filings (31 g.), and powdered barium hydroxide (1·7 g.) were heated to 350° during 2 hr., and kept thereat until distillation was complete. The distillate was mixed with ether, and the solution washed with sodium hydrogen carbonate solution and water, dried, and evaporated *via* a Vigreux column. The residual 3-iso*butyl*cyclo*heptanone* distilled at 100°/10—11 mm. (11·7 g.) (Found : C, 78·4; H, 11·8. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%). The *semicarbazone* separated from methanol in rhombic prisms, m. p. 171·5° (Found : C, 64·2; H, 10·0. $C_{12}H_{23}ON_3$ requires C, 64·0; H, 10·2%).

3-iso*Butyl*cyclo*heptylamine.*[31]—The above ketone (5·6 g.), hydroxylamine hydrochloride (5·0 g.), anhydrous potassium acetate (8 g.), methanol (35 c.c.), and water (5 c.c.) were heated on the water-bath for 3½ hr. The methanol was evaporated, the residue diluted with water, and the product isolated with ether. 3-iso*Butyl*cyclo*heptanone oxime* distilled at 150—156° (bath)/9—10 mm. (5·9 g.) (Found : C, 72·2; H, 11·4. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%). The oxime (5·9 g.) in dry ether (30 c.c.) was added slowly, with swirling and cooling, to a suspension of lithium aluminium hydride (2·7 g.) in dry ether (80 c.c.). After refluxing on the water-bath for 20 hr., the mixture was decomposed in the usual manner in the presence of "Celite." The *base* distilled at 121—122° (bath)/9—10 mm. (3·8 g.) (Found : C, 78·0; H, 13·6. $C_{11}H_{23}N$ requires C, 78·1; H, 13·6%).

3-iso*Butyl*-NN-*dimethyl*cyclo*heptylamine* (XI).[25]—The above primary amine (3·0 g.), formic acid (4·6 g. of 90%), and formaldehyde (3·35 g. of 40%) were mixed, with cooling, and heated on the water-bath for 16 hr. The solution was cooled, diluted, and acidified, and neutral matter was removed with ether. The tertiary amine was isolated by basification and ether extraction; 3-iso*butyl*-NN-*dimethyl*cyclo*heptylamine* distilled at 113° (bath)/8 mm. (2·0 g.) (Found : C, 79·1; H, 13·8; *C*-Me, 6·9. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7; 1 *C*-Me, 7·6%). Infrared absorption (liquid film) : bands at 1379, 1362, 1166, and 1152 cm.$^{-1}$. The *methiodide* crystallised from acetone in minute prisms, m. p. 207° (Found : C, 49·8; H, 8·6. $C_{14}H_{30}NI$ requires C, 49·6; H, 8·8%).

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[29] "Organic Reactions," Vol. I, p. 51.

[30] Nozoe *et al.*, *Proc. Japan Acad.*, 1950, **26**, (7), 43.

[31] Cf. Walter, *J. Amer. Chem. Soc.*, 1952, **74**, 5185.

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