Tetrahedron, 1957, Vol. 1, pp. 301–309. Pergamon Press Ltd., London

AN ALKALOID OF *DIOSCOREA HISPIDA*, DENNSTEDT—IV*

FURTHER INVESTIGATIONS ON THE LACTONE RING

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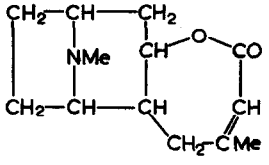
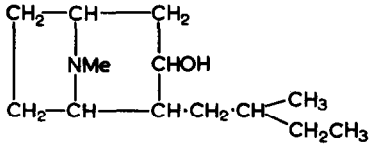
Abstract—Reductive degradation of the lactone ring of dioscorine has yielded a saturated tertiary alcohol, the formation of which means that the previously proposed formula (I) for the alkaloid is incorrect. The lactone and tropane systems are linked in a *spiro* manner, as in (VI) or (VII), of which the former is preferred for dioscorine. The behaviour of the alkaloid on Hofmann degradation can be explained on the basis of structure (VI). From infra-red studies on the above tertiary alcohol dioscorine is derived from 7α-hydroxytropane, and the (–)-base is therefore (XX) or its optical enantiomorph.

THE presence in dioscorine, an alkaloid of *Dioscorea hispida*, Dennstedt, of a tropane system linked with an αβ-unsaturated lactone ring has been established in previous parts of this series.[1,2] Infra-red absorption studies on the alkaloid and its dihydro-derivative[1] showed that the lactone ring was 6- or higher-membered, and not 5-membered, as originally proposed by Gorter.[3] On the basis of Hofmann and other degradations structure (I) has recently been proposed for dioscorine.[4] The investigations described below, which are concerned with the reductive degradation of the lactone ring, show that this formula must be modified.[5]



(I)



(II)

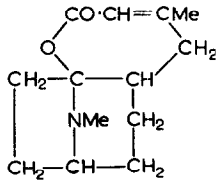
Reduction of dioscorine with lithium aluminium hydride affords *dioscorinol*, $C_{13}H_{23}O_2N$, an unsaturated glycol resulting from the reductive cleavage of the lactone ring without attack of the ethylenic bond. The presence of an ethylenic bond was confirmed by the infra-red absorption of the diol, and by ozonolysis, which gave glycollic aldehyde, identified as the *p*-nitrophenylosazone. This establishes the presence of the grouping $>C{=}CH{\cdot}CH_2OH$ in dioscorinol, and is consistent with the results of oxidative degradation of the alkaloid described earlier.[4] Accompanying

* Part III, *J. Chem. Soc.* 1577 (1956).
[1] A. R. Pinder *Nature, Lond.* **168**, 1090 (1951); *J. Chem. Soc.* 2236 (1952).
[2] A. R. Pinder *J. Chem. Soc.* 1825 (1953).
[3] M. K. Gorter *Rec. Trav. Chim. Pays-Bas* **30**, 161 (1911).
[4] A. R. Pinder *J. Chem. Soc.* 1577 (1956).
[5] For a preliminary communication, see A. R. Pinder *Chem. and Ind.* 1240 1957.

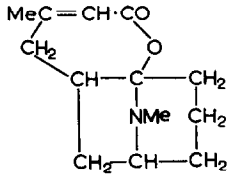
glycollic aldehyde was a basic keto-alcohol, the examination of which will be described in a future communication. This compound gives a positive iodoform reaction, and therefore contains a CH_3CO— group, which confirms the presence of a methyl group in the β-position of the lactone ring in dioscorine. On catalytic hydrogenation under mild conditions dioscorinol affords dihydrodioscorinol, identical with the product obtained by the reduction of dihydrodioscorine with lithium aluminium hydride.[2]

That dioscorinol is an allylic alcohol containing an α-hydrogen atom was confirmed by hydrogenolysis of the base. This was accomplished either by reduction with sodium and ethanol in liquid ammonia[6] or with a platinum catalyst.[7] In the former case the main product was *deoxydioscorinol*, $C_{13}H_{23}ON$, with some dihydrodioscorinol. Deoxydioscorinol on permanganate oxidation or ozonolysis afforded acetaldehyde, indicating the presence of the grouping $>C{=}CH{\cdot}CH_3$, derived by hydrogenolysis of the allylic hydroxyl group in dioscorinol. Hydrogenolysis with a platinum catalyst occurred more slowly, but the final product was the saturated base *dihydrodeoxydioscorinol*, $C_{13}H_{25}ON$, which was also readily obtained by the catalytic hydrogenation of deoxydioscorinol.

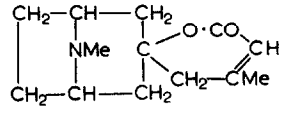
Dihydrodeoxydioscorinol was recovered unchanged when the base was heated at 65–70° for several hours with chromic acid in acetic acid solution, and it was not converted into an *O*-acetate on treatment with acetic anhydride and pyridine. Further, the base was readily dehydrated under mild conditions to *anhydrodihydrodeoxydioscorinol*, $C_{13}H_{23}N$. It is evident, therefore, that dihydrodeoxydioscorinol is a tertiary alcohol, so that dioscorine cannot be represented by (I), which would yield the secondary alcoholic dihydrodeoxy-base (II). Structures such as (III) and (IV) for the alkaloid would give tertiary alcoholic dihydrodeoxy-bases, but these formulae may be ruled out because dioscorinol, deoxydioscorinol and dihydrodeoxydioscorinol do not have the properties of an α-carbinolamine.



(III)



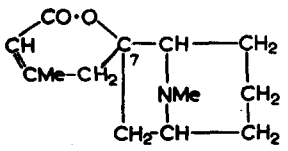
(IV)



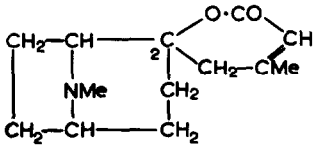
(V)

It is apparent, therefore, that in dioscorine the tropane system and lactone ring must be linked in a *spiro* manner, as in structures (V), (VI) and (VII). Of these, (V) would seem to be the most acceptable in that it is derived from tropine, the parent hydroxy-base of many well-known alkaloids.[8] This structure must, however, be rejected on the grounds that dioscorine and the transformation products described are all optically active, whereas (V) and the structures derived from it by the reactions outlined each have a plane of symmetry.

[6] A. J. Birch *J. Chem. Soc.* 809 (1945); *Quart. Rev. Chem. Soc.* **4**, 69 (1950); A. J. Birch and A. R. Murray *J. Chem. Soc.* 1888 (1951).
[7] J. Weinstock and V. Boekelheide *J. Amer. Chem. Soc.* **75**, 2546 (1953).
[8] T. A. Henry *The Plant Alkaloids* (4th Ed.) pp. 64–115. Churchill, London (1949).



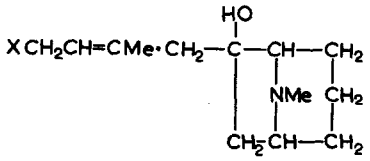
(VI)



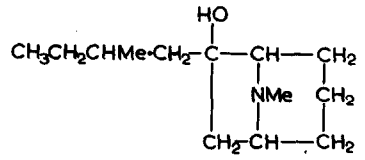
(VII)

Of the two structures (VI) and (VII), the former is more likely to represent dioscorine, on the grounds that it is derived from 7-hydroxytropane, and several familiar alkaloids are known to have structures derived from this base (*e.g.* scopolamine,[9] meteloidine[10]). On the other hand, as yet no alkaloid is known having a structure derived from 2-hydroxytropane, to which base structure (VII) is related. Formula (VI) is therefore advanced for dioscorine, and efforts are now being made to substantiate this view by synthesis.

On the basis of formula (VI) for dioscorine, dioscorinol is (VIII, X = OH), deoxydioscorinol (VIII, X = H), and dihydrodeoxydioscorinol (IX).* Anhydrodihydrodeoxydioscorinol is probably a mixture of the double-bond isomerides (X) and (XI), the third possible mode of dehydration of (IX) being ruled out by the fact

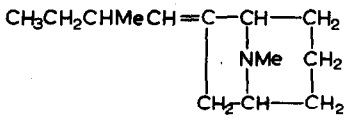


(VIII)

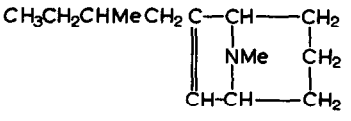


(IX)

that the anhydro-base has not the properties of a vinylamine. *Anhydrotetrahydrodeoxydioscorinol*, obtained by catalytic hydrogenation of the anhydro-base, is then

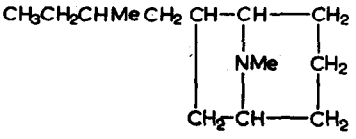


(X)



(XI)

7-(2′-methyl-*n*-butyl) tropane (XII).

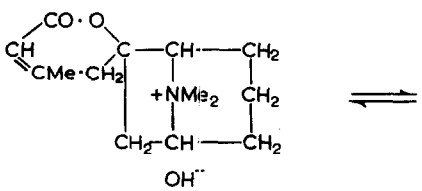


(XII)

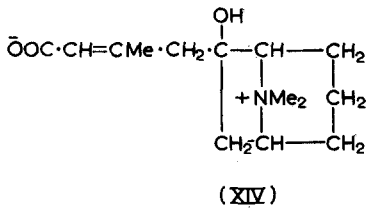
In an earlier communication[2,3] the behaviour of dioscorine on Hofmann degradation has been described. A deep-seated decomposition occurs, with the elimination of carbon dioxide and the formation of an oxygen-free base $C_{13}H_{21}N$. This

[9] T. A. Henry *The Plant Alkaloids* (4th Ed.) p. 84. Churchill, London (1949).
[10] A. Heusner *Chem. Ber.* **87**, 1032 (1954).

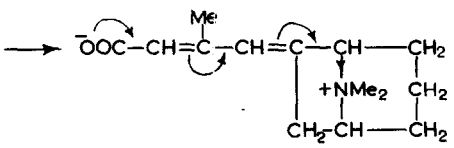
unusual mode of decomposition, which is reminiscent of the behaviour of dihydro-β-erythroidine on Hofmann degradation,[11] may possibly be explained on the basis of formula (VI) for dioscorine as follows. Dioscorine methohydroxide is probably an equilibrium mixture of the quaternary hydroxide (XIII) and the betaine (XIV); it cannot be entirely the betaine form because the compound in aqueous solution is strongly basic. The first stage in the decomposition is probably the elimination of water from the tertiary alcoholic betaine (XIV), via the side-chain methylene group,



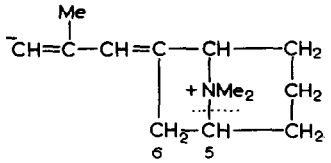
(XIII)



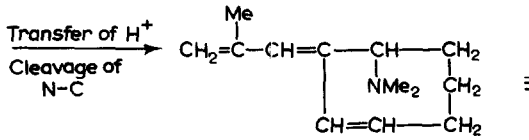
(XIV)



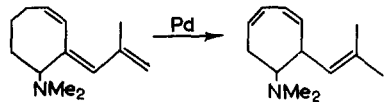
(XV)



(XVI)



(XVII)



(XVIII)

the hydrogen atoms of which are activated by conjugation with the carboxyl group, giving (XV). In this structure the strongly electron-attracting quaternary ammonium cation is now able, by the mechanism shown along the conjugated system, to facilitate the decarboxylation of the acid to the intermediate structure (XVI),[12] which is stabilised by transfer of a proton from $C_{(6)}$ to the terminal carbon atom of the side-chain, and cleavage of the N—$C_{(5)}$ bond. These stages are facilitated by the tendency to form the extended conjugated system in XVII), which therefore represents the constitution of the $C_{13}H_{21}N$ base. The chemical properties of the base, however, showed it to be a mixture,[2] and (XVII) is therefore in all probability the main constituent. It is conceivable, especially in the presence of an active catalyst at a high temperature, that double bond isomers such as (XVIII) will also be present in the base, and this

* A good *C*-methyl analysis for this compound could not be obtained [compare E. J. Eisenbraun, S. M. McElvain and B. F. Aycock *J. Amer. Chem. Soc.* **76**, 607 (1954)].

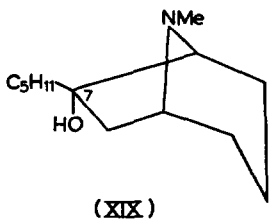
[11] V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello *J. Amer. Chem. Soc.* **75**, 2550 (1953).

[12] B. R. Brown *Quart. Rev. Chem. Soc.* **5**, 131 (1951).

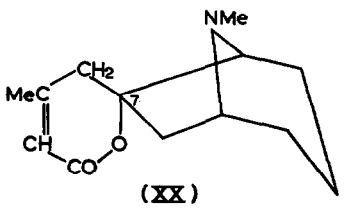
accounts for the ready formation of $\beta\beta$-dimethylstyrene and *iso*butylbenzene when the base $C_{13}H_{21}N$ is heated with palladised charcoal, as explained earlier.[4]

It is interesting to note that dihydrodioscorine, when subjected to Hofmann degradation, yields a normal *des*-base; this would be expected because the γ-methylene group is not activated by conjugation with the carbonyl group as in dioscorine, and the mechanism described above cannot operate.

A careful study, under high resolution conditions, of the infra-red absorption spectrum of dihydrodeoxydioscorinol (IX) in carbon tetrachloride solution showed a single band at 3651 cm^{-1}, with no internal hydrogen bonding; under the same conditions tropine showed a similar band at 3653 cm^{-1}, again with no intramolecular hydrogen bonding.[13] It is concluded that dihydrodeoxydioscorinol has an α-oriented hydroxyl group, and is therefore more accurately represented by (XIX). It is to be expected that the lithium aluminium hydride reduction of dioscorine, which involves



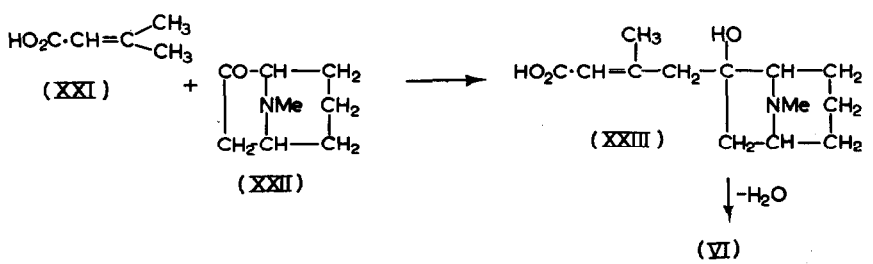
(XIX)



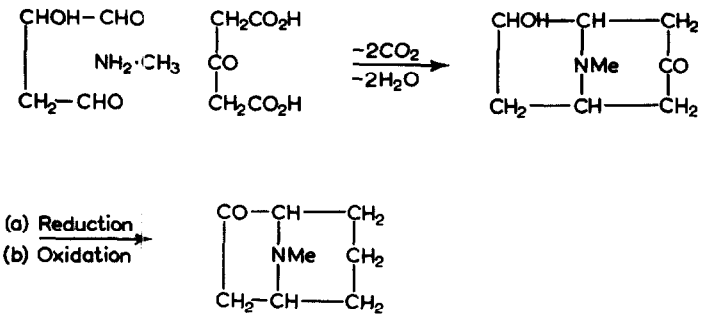
(XX)

the cleavage of the carbonyl-oxygen bond, will not disturb the stereochemistry at $C_{(7)}$, so that dioscorine is represented by (XX).

From the biogenetic point of view it would seem reasonable that dioscorine is formed by an aldol-type condensation between 7-ketotropane (XXII) and senecioic acid (XXI), which occurs in nature,[14] to give the hydroxy-acid (XXIII), the methyl groups of senecioic acid being activated by conjugation with the carbonxyl group. Lactonisation of the hydroxy-acid affords dioscorine (VI). The view that senecioic acid is involved in the biosynthesis of dioscorine is strengthened by the fact that tropine senecioate has recently been found to occur to a small extent in the tubers of *D. hispida*. The biosynthesis of (XXII) presents a problem, there being as yet no knowledge of the way in which hydroxytropanes, other than tropine, are formed in the plant.[15] The ketone may arise from malic dialdehyde via a Robinson tropinone synthesis, [16] with subsequent reduction and oxidation:—



[13] B. L. Zenitz, C. M. Martini, M. Priznar and F. C. Nachod *J. Amer. Chem. Soc.* **74**, 5564 (1952).
[14] Y. Asahina *Arch. Pharm.* **251**, 355 (1913).
[15] Sir R. Robinson *The Structural Relations of Natural Products* p. 63. Oxford University Press (1955).
[16] Sir R. Robinson *J. Chem. Soc.* **111**, 762 (1917); J. C. Sheehan, and B. M. Bloom *J. Amer. Chem. Soc.* **74**, 3825 (1952); A. Stoll, B. Becker and E. Jucker *Helv. Chim. Acta* **35**, 1263 (1952).



(XXII)

EXPERIMENTAL

Lithium aluminium hydride reduction of dioscorine. A suspension of powdered lithium aluminium hydride (0·6 g) in dry ether (150 cm³) was added during 30 min at room temperature with shaking to dioscorine (2·0 g) in dry ether (50 cm³). After keeping for 18 hr the reaction mixture was decomposed by the careful addition of water, in the presence of "Celite". The ethereal solution was decanted, dried (potassium carbonate) and evaporated. The residual thick syrup was distilled in a bulb-tube, giving *dioscorinol* (VIII, X = OH) (1·7 g), b.p. 175° (bath)/1 mm, 155–160° (bath)/0·2 mm, 150° (bath)/0·05 mm, $[\alpha]_D^{20}$ + 1·9° (c 6·2 in chloroform) (Found: C, 69·6, 69·5; H, 10·4, 10·2. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2 per cent) as a glassy solid. Infra-red absorption (in carbon tetrachloride): broad band at 3360 (associated OH), band at 1653 (C=C), and at 805 cm^{-1} (R_1R_2C=CHR_3). Dioscorinol is readily soluble in water, giving a strongly alkaline solution; it is sparingly soluble in ether and moderately so in chloroform. The *picrate* separated from methanol in yellow nodules, m.p. 159-160° (decomp.) (Found: C, 50·2; H, 5·8. $C_{19}H_{26}O_9N_4$ requires C, 50·2; H, 5·8 per cent). The *picrolonate* crystallised from ethanol in clusters of pale yellow prisms, m.p. 212° (decomp.) (Found, on material dried at 100° *in vacuo*, C, 56·4; H, 6·3. $C_{23}H_{31}O_7N_5$ requires C, 56·4; H, 6·3 per cent). Attempts to make the hydrochloride, hydrobromide, and methiodide gave oily products.

Ozonolysis of dioscorinol. A solution of dioscorinol (4·0 g) in glacial acetic acid (15 cm³) was cooled to 10° and ozonised at this temperature for 4 hr. The solution was diluted with ether (100 cm³) and shaken with zinc dust (6·0 g) for 3 hr, after which time the starch-iodide test was negative. The ether was removed under reduced pressure at 15–20°, and the residue treated with water (30 cm³), filtered, and mixed with a concentrated ethanolic solution of *p*-nitrophenylhydrazine (4·0 g). After warming the solution on the water-bath for 30 min the precipitate was collected, washed with water and dried. Crystallisation from nitrobenzene gave wine-red needles (0·65 g), m.p. 310–311° (decomp.) alone or mixed with an authentic specimen of glyoxal bis-*p*-nitrophenylhydrazone (m.p. 311°),[17] obtained from glycollic aldehyde prepared by the ozonolysis of allyl alcohol.[18]

Reduction of dioscorinol. (a) Dioscorinol (0·5 g) in ethanol (10 cm³) was shaken in hydrogen at room temperature and pressure with 5 per cent palladised charcoal

[17] A. Wohl and C. Neuberg *Ber. Dtsch. Chem. Ges.* **33**, 3107 (1900).
[18] H. O. L. Fischer and L. Feldman *Ber. Dtsch. Chem. Ges.* **62**, 854 (1929).

(0·5 g; Baker Platinum Co.). After 2 hr absorption had ceased (1 mol absorbed), and the solution was filtered and evaporated. The residue distilled at 160–165° (bath)/0·05 mm (0·5 g). The picrate had m.p. 144°, with previous softening at 138°, alone or mixed with the picrate of dihydrodioscorinol, obtained by the lithium aluminium hydride reduction of dihydrodioscorine.[2]

(b) Dioscorinol (2·6 g) in ethanol (15 cm^3) was added to liquid ammonia (300 cm^3), and the solution stirred vigorously during the gradual addition of sodium (3·0 g) in small pieces over 30 min. After stirring for a further 30 min, 75 cm^3 of water was added cautiously, dropwise, and the ammonia allowed to evaporate overnight. A few pellets of potassium hydroxide were added, the solution extracted thoroughly with ether, and the extract dried with potassium carbonate. Evaporation of the solvent gave a syrup, which was separated by distillation into two fractions. The main fraction, distilling at 123–125° (bath)/0·3 mm, 97–98° (bath)/0·1 mm, 87–88° (bath)/0·04 mm (1·6 g) $[\alpha]_D^{24} + 23{\cdot}0°$ (*c* 2·3 in chloroform) (Found: C, 74·3; H, 11·4; N, 6·9. $C_{13}H_{23}ON$ requires C, 74·6; H, 11·0; N, 6·7 per cent) was *deoxydioscorinol* (VIII, X = H). Infra-red absorption (in carbon disulphide): bands at 3598 (non-bonded hydroxyl), 2804 (*N*-methyl), 823, 806, and 754 cm^{-1} (trisubstituted ethylenic bond). Deoxydioscorinol is a strong base, slightly soluble in water. The *methiodide*, prepared by mixing the base with an excess of methyl iodide, was formed very readily and crystallised from a large volume of acetone in clusters of elongated prisms, m.p. 191·5–192° (Found: C, 48·2; H, 7·6. $C_{14}H_{26}ONI$ requires C, 47·9; H, 7·4). The *picrate* separated from methanol in glistening yellow elongated prisms, m.p. 112·5° (Found: C, 51·8; H, 6·0; N, 12·7. $C_{19}H_{26}O_8N_4$ requires C, 52·05; H, 5·9; N, 12·8 per cent).

A higher-boiling fraction distilled at 160–165° (bath)/0·05 mm (0·75 g). It was converted to its picrate, which crystallised from methanol in yellow prisms, m.p. 144°, with previous softening at 138°, alone or mixed with a specimen of dihydrodioscorinol picrate.[2]

Dihydrodeoxydioscorinol (IX). (a) Dioscorinol (2·55 g) dissolved in *N* hydrochloric acid (40 cm^3) was shaken in hydrogen at room temperature and pressure with pre-reduced platinic oxide catalyst (0·4 g) (Baker Platinum Co.) until absorption ceased (about 6 hr; 2 mols. absorbed). The solution was filtered, basified with potassium hydroxide and extracted with ether. Evaporation of the dried (potassium carbonate) extract gave *dihydrodeoxydioscorinol* (IX), which distilled at 104–105° (bath)/0·15 mm (2·45 g), $[\alpha]_D^{20} + 21{\cdot}3°$ (*c*, 2·35 in chloroform) (Found: C, 73·6; H, 11·7; N, 6·3, CMe, 5·1. $C_{13}H_{25}ON$ requires C, 73·9; H, 11·8; N, 6·6; 2CMe, 14·2 per cent). Infra-red absorption (in carbon tetrachloride): single hydroxyl band at 3651 cm^{-1}, with no internal hydrogen bonding. Dihydrodeoxydioscorinol is a strong base, slightly soluble in water. The *methiodide*, obtained by mixing the base with methyl iodide, separated from acetone-light petroleum (b.p. 80–100°) in clusters of prisms, m.p. 162° (Found, on material dried at 100° *in vacuo*: C, 47·4; H, 7·7; N, 3·9. $C_{14}H_{28}ONI$ requires C, 47·6; H, 7·9; N, 4·0 per cent). The *picrate*, prepared in methanol solution, crystallised from methanol in glistening yellow plates, m.p. 107·5–108° (Found, on material dried at 78° *in vacuo*: C, 51·8; H, 6·7; N, 12·9. $C_{19}H_{28}O_8N_4$ requires C, 51·8; H, 6·4; N, 12·7 per cent).

(b) Deoxydioscorinol (0·5 g) in *N* hydrochloric acid (15 cm^3) was shaken with pre-reduced platinic oxide catalyst (0·1 g) in hydrogen at room temperature and

pressure. After 2 hr absorption (1 mol) had ceased. The solution was filtered, basified, and extracted with ether. Evaporation of the dried extract gave dihydrodeoxydioscorinol, b.p. 100–101° (bath)/0·1 mm (0·5 g), picrate m.p. 107·5–108° and methiodide m.p. 162°, both alone or mixed with the respective derivatives obtained as in (a) above. Identity was confirmed by comparison of the infra-red curves of the two bases.

Dihydrodeoxydioscorinol was recovered unchanged when heated at 65–70° in glacial acetic acid solution for 2½ hr with chromic acid, and also when warmed with acetic anhydride in the presence of pyridine.

Oxidation of deoxydioscorinol (a) Deoxydioscorinol (0·1 g) in 5 per cent sulphuric acid (50 cm^3) was heated to boiling and a 1·5 per cent aqueous solution of potassium permanganate (80 cm^3) added dropwise during 5 min, the boiling being maintained whilst about 35 cm^3 of distillate were collected in an ice-cooled receiver.[19] The distillate was mixed with an excess of a saturated solution of 2:4-dinitrophenylhydrazine in dilute sulphuric acid and kept for several hours. The yellow precipitate was collected, washed with water, dried, and crystallised from ethanol, from which it separated in orange-yellow needles m.p. 167–168°, alone or mixed with an authentic specimen of acetaldehyde 2:4-dinitrophenylhydrazone (m.p. 168°). Later fractions of the distillate gave formaldehyde 2:4-dinitrophenylhydrazone, identified as previously,[1] arising from oxidation of the *N*-methyl group.

(b) Deoxydioscorinol (2·0 g) in glacial acetic acid (15 cm^3) was ozonised at 0–5° for 3 hr. Water (10 cm^3) was added, followed by zinc dust (4·0 g), and the mixture shaken for 2–3 hr. The filtered solution was mixed with excess of a saturated solution of 2:4-dinitrophenylhydrazine in dilute sulphuric acid and kept for several hours. The precipitate was collected and identified as acetaldehyde 2:4-dinitrophenylhydrazone as in (a).

Anhydrodihydrodeoxydioscorinol (X) or (XI). A solution of dihydrodeoxydioscorinol (0·5 g) in dry ether (5 cm^3) was added dropwise to thionyl chloride (1 g) in dry ether (5 cm^3), the reaction being conducted at 0–10° during 10 min, with continuous shaking. Finally the mixture was heated under reflux in a bath at 45–50° for 30 min. The solvent was evaporated, the excess thionyl chloride removed *in vacuo*, and the syrupy residue taken up in water, a neutral turbidity being removed with ether. Evaporation of the dried extract gave the *anhydro-base*, b.p. 124°/18 mm, 128°/21 mm (0·35 g) (Found: C, 80·5; H, 11·5; N, 7·3. $C_{13}H_{23}N$ requires C, 80·8; H, 11·9; N, 7·25 per cent). Infra-red absorption (liquid film): probably at least two types of C=C bond present; bands at 1635 and 1665 cm^{-1} The *picrate* crystallised from 50 per cent ethanol in glistening, yellow needles, m.p. 118° (Found: C, 54·1; H, 6·1. $C_{19}H_{26}O_7N_4$ requires C, 54·0; H, 6·2 per cent).

Anhydrotetrahydrodeoxydioscorinol (XII). The foregoing anhydro-base (0·35 g) in glacial acetic acid (15 cm^3) was shaken with pre-reduced platinic oxide catalyst (50 mg) in hydrogen at room temperature and pressure for 12 hr. The absorption (1 mol) had then ceased. The solution was filtered, basified, and extracted with ether. Evaporation of the dried extract gave *anhydrotetrahydrodeoxydioscorinol*, b.p. 135°/24–25 mm (0·35 g). (Found: C, 80·1; H, 7·7. $C_{13}H_{25}N$ requires C, 80·0; H, 7·8 per cent). The base was stable to cold, acid potassium permanganate. The *picrate* separated from 50 per cent methanol in glistening yellow needles, m.p. 116° (Found: C, 53·5; H, 6·7; N, 13·0. $C_{19}H_{28}O_7N_4$ requires C, 53·8; H, 6·6; N, 13·2 per cent).

[19] T. M. Reynolds and R. Robinson *J. Chem. Soc.* 594 (1934).

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