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SYNTHESIS OF HETEROCYCLIC STEROIDS—IV*

SYNTHESIS OF DL-B-NOR-6-OXAEQUILENIN

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Abstract—The synthesis of dl-B-nor-6-oxaequilenin starting from 7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran is described. The latter compound was prepared from the known γ-(2,4-diydroxybenzoyl)-butyric acid.

THE synthesis of dl-B-nor-6-oxaequilenin (I), the furano analogue of equilenin (II), was undertaken as a part of the work on the total synthesis of heterocyclic steroids.[1] Among the oxygen-containing steroids reported, are certain coumarino-steroids some of which are derived naturally by degradation and resynthesis.[2]

dl-B-nor-6-oxaequilenin (I) was synthesized starting from resorcinol, following the Johnson *et al.*[3] equilenin synthesis. Part of this work has been reported earlier[4] and the present paper gives details and further work.

7-Methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran (III) was prepared in a 24 per cent yield from γ-(2,4-dihydroxybenzoyl)-butyric acid[5] (IV), and in 10 per cent yield from *m*-methoxyphenol as shown in Chart 1.

Once the cyclopenteno-D-ring was built up, as in XVI the compound exhibited pronounced instability to air both in alkaline medium and neutral solutions. All subsequent reactions were, therefore, carried out in an atmosphere of nitrogen.

The 14,15-dehydro-structure was assigned to XVII by analogy with Johnson's equilenin synthesis[3] and also on the basis of spectral evidence. Johnson isolated two dehydro compounds,[3] and 14,15- and 15,16-dehydro structures XX and XXI were assigned to the higher and the lower melting compounds respectively on the basis of spectral evidence.

In the present work only one isomer (XVII) was isolated on elimination of the carbethoxy group from XVI. The product XVII is represented as the 14,15-dehydro isomer wherein the cyclopenteno double bond is in conjugation with the benzofuran chromophore and is not as the isomeric α:β-unsaturated ketone (XVIII). This was proved by a comparison of U.V. spectra of the decarboxylated product and those of 7-methoxy-1,2,3,4-tetrahydrodibenzofuran (XXII) and B-nor-6-oxaequilenin methyl ether (XIX), Fig. 1. The spectra of XXII and XIX are nearly identical, whereas in the decarboxylated product XVII the 7-methoxy-1,2,3,4-tetrahydrodibenzofurano

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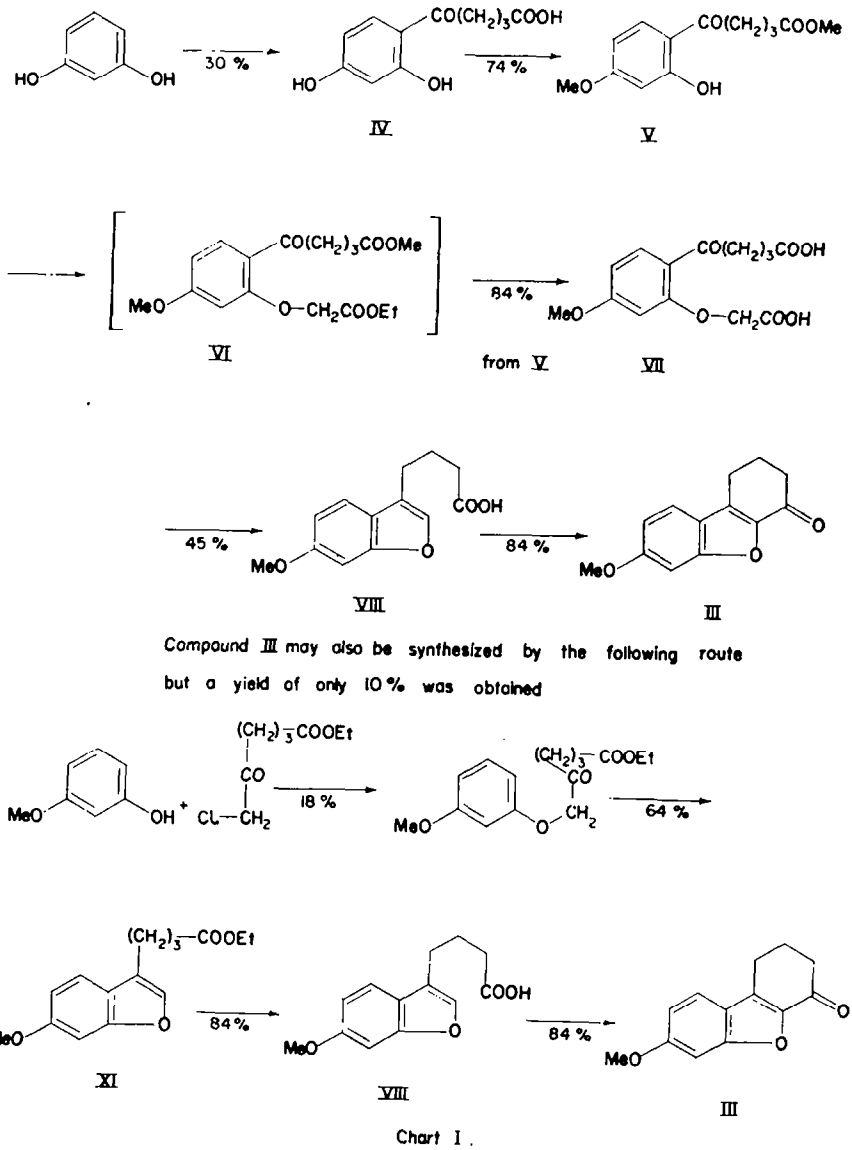
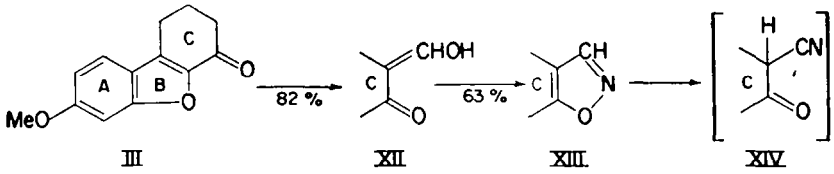
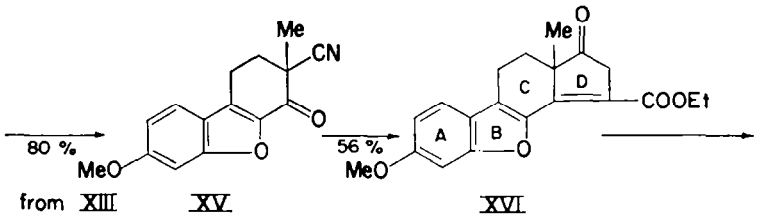


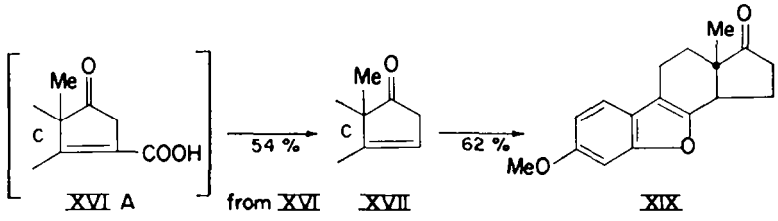
Chart I.

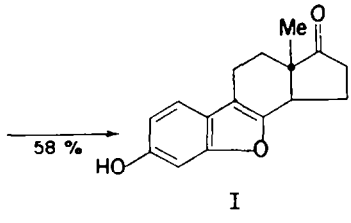
chromophore is no longer distinguishable. The increased intensity at higher wavelengths (300 mμ to 320 mμ) indicates that the cyclopenteno double bond in XVII is in conjugation with the benzofurano chromophore as shown in the structure for XVII. If the latter compound has the alternative structure XVIII, its spectrum would be similar to that of XXII and XIX since the principal maxima due to the $\alpha:\beta$-unsaturated ketonic function in XVIII would be expected to lie in the unexamined region of shorter wavelengths.[3,6] Although XVIII was not isolated, its presence in the mother liquors left after separation of XVII cannot be ruled out.

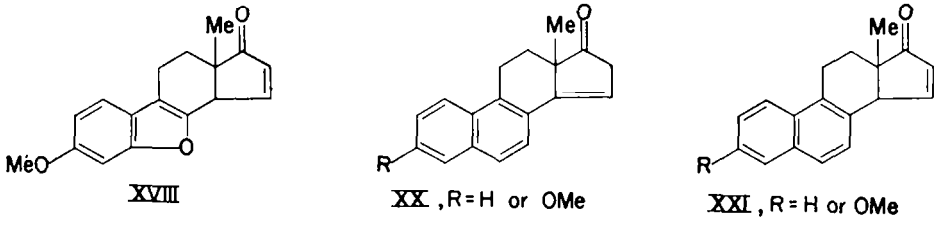
[6] A. E. Gillam and T. F. West, *J. Chem. Soc.* 486 (1942); R. B. Woodward, *J. Amer. Chem. Soc.* **64**, 76 (1942).


C
A
B
O
MeO
82 %
CHOH
C
O
63 %
CH
N
H
CN
III
XII
XIII
XIV


Me
CN
O
80 %
MeO
from XIII
XV
56 %
C
D
COOEt
A
B
XVI


Me
O
C
COOH
XVI A
54 %
from XVI
XVII
62 %
MeO
XIX


Me
O
58 %
HO
I


Me
O
MeO
XVIII
R
XX , R = H or OMe
XXI , R = H or OMe

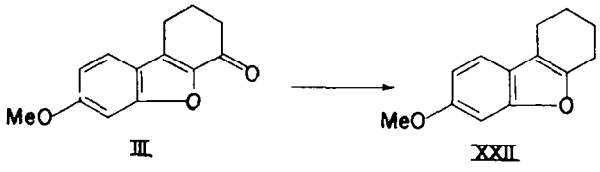

MeO
O
III
XXII

Chart II

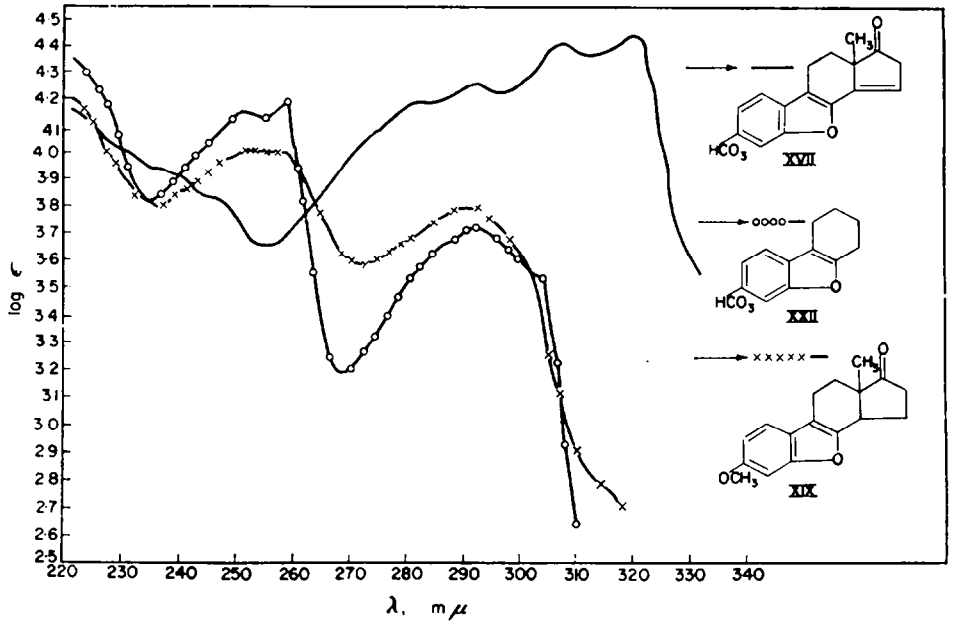


FIG. 1.

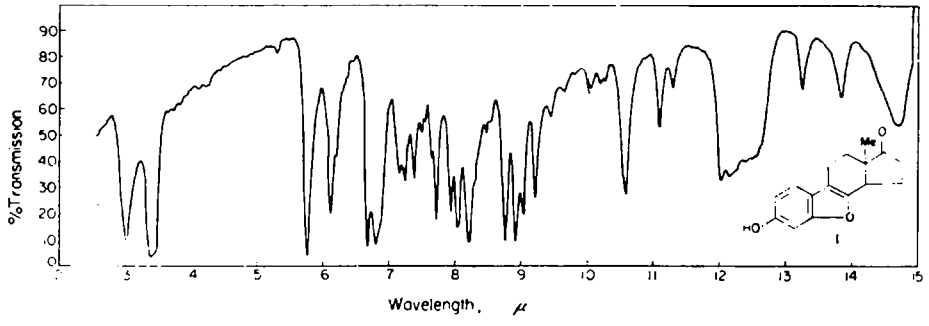


FIG. 2.

7-Methoxy-1,2,3,4-tetrahydrodibenzofuran (XXII) was prepared from the ketone (III) by Clemmensen reduction for the purpose of spectral examination.

In B-nor-6-oxaequilenin methyl ether (XIX) the C/D rings are *trans*-fused and the angular C-18-methyl group is represented by the β-configuration. This structure is suggested by analogy with Johnson's observation that catalytic hydrogenation of 14,15-dehydroequilenin methyl ether (XX, R = OCH_3) under neutral conditions leads predominantly to C/D *trans*-fusion. It is, however, necessary to provide unambiguous proof since stereochemical analogy between natural steroids and their heterocyclic analogues has not been experimentally established. The ultra-violet absorption spectra of XIX and XXII are similar and showed a maximum at 292 mμ characteristic of the benzofuran chromophore. Demethylation of the XIX gives dl-B-nor-6-oxaequilenin (I). The infra-red spectrum (Nujol mull) shows the bands at 3,311 cm^{-1} (3·02 μ) and 1730 cm^{-1} (5·78 μ) indicating the presence of the 3-hydroxy group and the cyclopentano-keto group, respectively (Fig. 2). The ultra-violet absorption spectra of I

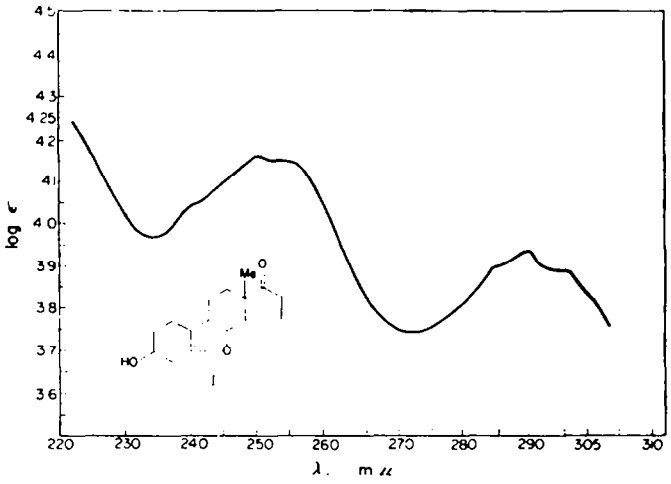


FIG. 3.

and XIX are similar and they show a maximum at 292 mμ characteristic of the benzofuran chromophore (Figs. 1 and 3).

The overall yield of I from the ketone III was 3·5%. The estrogenic and carcinogenic activity of dl-B-nor-6-oxa-equilenin (I), will be examined. The optical resolution of the compound could not be undertaken due to lack of the material.

EXPERIMENTAL

Methyl γ-(2-hydroxy-4-methoxybenzoyl)-butyrate (V). To a solution of γ-(2,4-dihydroxybenzoyl)-butyric acid[5] (IV, 3·6 g) and dimethyl sulphate (3 cc) in dry acetone (50 cc), anhydrous potassium carbonate (15–18 g) was added. The mixture was refluxed for 6 hr, acetone distilled off and the residue diluted with water and crystallized from n-hexane as white needles, m.p. 58°, yield 3 g. (Found: C, 61·5; H, 6.5. $C_{13}H_{16}O_5$ requires: C, 61·9; H, 6·4%).

γ-(2-Carboxymethoxy-4-methoxybenzoyl)-butyric acid (VII). The ester V (5·04 g) was dissolved in dry ethyl methyl ketone (100 cc) and ethyl bromacetate (2·8 cc) and anhydrous potassium carbonate (11·6 g) added. The mixture was refluxed for 7 hr, ethyl methyl ketone removed and water added. The intermediate product (VI) was hydrolysed by boiling with 10% aqueous sodium hydroxide (45 cc) and ethanol (35 cc) under reflux for 2 hr. Ethanol was distilled off and the residual solution acidified. The precipitated acid, on crystallization from water gave VII as white needles, m.p. 155°, yield 5·1 g. (Found: C, 56·8; H, 5·1. $C_{14}H_{16}O_7$ requires: C, 56·7; H, 5·4%).

3-ω-Carboxypropyl-6-methoxybenzofuran (VIII). A mixture of VII (3·8 g), fused sodium acetate (12 g) and acetic anhydride (40 cc) was heated under reflux for 5 hr, at 160–70° (oil bath) with evolution of carbon dioxide. The reaction mixture was diluted with hot water and kept overnight. The product was filtered washed acid-free and extracted with sodium bicarbonate solution, leaving an insoluble portion which crystallized from ethanol in needles, m.p. 129°, identical with III. Acidification of the sodium bicarbonate extract gave VIII which crystallized from water in white needles, m.p. 106°, yield 1·2 g. (Found: C, 66·6; H, 5·9. $C_{13}H_{14}O_4$ requires: C, 66·6; H, 6·0%)

7-Methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran (III). A mixture of VIII (7·1 g), acetic anhydride (125 cc) and glacial acetic acid (65 cc) was added to a solution of zinc chloride in acetic acid (20%, 65 cc). The mixture was refluxed for 4 hr at 160–70° (oil bath) under nitrogen atmosphere. Acetic acid and acetic anhydride were removed (reduced press) and the residue was filtered washed and then treated with sodium bicarbonate solution to remove unchanged VIII. Crystallization of the product from ethanol, gave III as pale orange needles, m.p. 129°, yield 5·4 g. (Found: C, 77·2; H, 5·6. $C_{13}H_{12}O_3$ requires: C, 77·2; H, 5·6%). The *semicarbazone* crystallized in shining white silky needles, m.p. 235° (decomp). (Found: C, 61·9; H, 5·3; N, 15·3. $C_{14}H_{15}O_3N_3$ requires: C, 61·5; H, 5·5; N, 15·3%).

Ethyl 6-(m-*methoxyphenoxy*)-5-*oxo-caproate* (X). Resorcinol mono-methyl ether (1·24 g) was refluxed for 3 hr with anhydrous potassium carbonate (4·5 g) in presence of ethyl methyl ketone (25 cc). To this ethyl 6-chloro-5-oxo-caproate IX (2·3 g) was added and the mixture refluxed for 4 hr, the solvent removed, water added and the mixture extracted with ether and the extract washed with 10% aqueous sodium hydroxide and water. The product was distilled, unreacted IX was removed at 100–120°/1·2 mm and X was collected at 155–160°/0·01 mm as a colourless liquid, yield 0·2 g. (Found: C, 64·6; H, 7·0. $C_{15}H_{20}O_6$ requires: C, 64·2; H, 7·2%).

3-*ω-Carbethoxypropyl-methoxybenzofuran* (XI). A solution of X (0·2 g) in dry benzene (20 cc) was added to polyphosphoric acid (mixture of 0·6 g of P_2O_5 and 0·6 g of H_3PO_4) and the deep blue coloured mixture refluxed for 3 hr. The benzene layer was decanted and the residue extracted twice with 15 cc portions of benzene. The polyphosphoric acid residue was diluted with ice water and the mixture extracted with ether and benzene. The total ether-benzene extracts were washed with aqueous sodium bicarbonate and water. Removal of the solvents gave XI which distilled at 120–125°/0·01 mm, as a pale yellow viscous liquid, yield 0·125 g. (Found: C, 69·0; H, 6·9. $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%).

3-*ω-Carboxypropyl-6-methoxybenzofuran* (VIII). Finely powdered barium hydroxide octahydrate (0·085 g) was added to a solution of XI (0·08 g) in 80% aqueous ethanol (10 cc) and the mixture refluxed for 3 hr. After removal of ethanol the mixture was diluted with water and acidified with HCl and the ether extract treated with aqueous sodium bicarbonate. Acidification gave VIII m.p. 106°. A mixed m.p. with the authentic specimen (prepared earlier) was not depressed.

3-*Hydroxymethylene-7-methoxy-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XII). A mixture of dry sodium methoxide (from 0·07 g sodium), ethyl formate (0·07 cc), the ketone III (0·216 g) and benzene (20 cc) was shaken mechanically under nitrogen atmosphere for 6 hr. The mixture was ether extracted and the product isolated with aqueous sodium hydroxide. Acidification gave XII (0·2 g) which crystallized from aqueous ethanol in pale yellow micro-crystalline flakes, m.p. 184–186°. (Found: C, 69·0; H, 5·1. $C_{14}H_{12}O_4$ requires: C, 68·8; H, 4·9%).

9,10-*Dihydro-6-methoxydibenzofurano*-(2,1-*d*)-*isoxazole* (XIII). Dry finely powdered hydroxylamine hydrochloride (0·14 g) was added to a solution of XII (0·32 g) in glacial acetic acid (7 cc) and the mixture was refluxed for 12 min at 170–175° (oil bath). After dilution with hot water (20–30 cc) and cooling the solid product was dissolved in ether and washed with aqueous sodium hydroxide (2%). The dark yellowish orange product was distilled at 190–210°/0·03–0·05 mm and the distillate crystallized from acetone (0·2 g) as pale yellow needles, m.p. 211–212°. (Found: C, 69·5; H, 4·9; N, 6·2. $C_{14}H_{11}O_3N$ requires: C, 69·7; H, 4·6; N, 5·8%).

3-*Cyano-7-methoxy-3-methyl-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XV). To a solution of potassium (0·78 g) in t-butanol (70 cc), XIII (1·6 g) was added and the mixture refluxed for 2 hr with separation of the yellowish green potassium salt of XIV. The solution was cooled, methyl iodide (1 cc) added and the mixture kept at room temp for 2 hr, and then refluxed gently at 120–125° (oil bath) for a further 2 hr. After cooling methyl iodide (1·5 cc) was added and the mixture refluxed for 2 hr cooled and again methyl iodide (1 cc) added and the mixture kept overnight at room temp. The next day, the mixture was refluxed for 2 hr, cooled and the last lot of methyl iodide (1·5 cc) added and refluxed vigorously for 4 hr and t-butanol removed (reduced press). The residue was extracted with ether and washed with aqueous sodium hydroxide (2%, extract A) to remove the unreacted XIV. Removal of ether gave XV (1·35 g) which crystallized from aqueous ethanol in white needles, m.p. 121°. (Found: C, 70·7; H, 5·2; N, 5·4; OMe, 13·2%. $C_{15}H_{13}O_3N$ requires: C, 70·6; H, 5·1; N, 5·5; OMe, 12·2%).

3-*Cyano-7-methoxy-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XIV). The alkaline extract (A) from the above experiment was acidified giving a pale greyish white solid (0·1 g), which crystallized from aqueous methanol XIV as pale yellow needles, m.p. 221–222°. (Found: C, 70·2; H, 4·6; N, 6·0. $C_{14}H_{11}O_3N$ requires: C, 69·6; H, 4·9; N, 6·2%).

15-*Carbethoxy*-14,15-*dehydro*-B-*nor-6-oxaequilenin methyl ether* (XVI). To a solution of potassium (0·341 g) in t-butanol, diethyl succinate (2·9 cc) and XV (1 g) were added. The mixture was mechanically shaken at room temp for 7 hr in nitrogen atmosphere. The reddish solution containing an orange precipitate was cooled and carefully acidified with HCl with evolution of carbon dioxide. t-Butanol was removed (reduced press) and the residue ether extracted washed with aqueous sodium hydroxide (2%) and water. The product, on crystallization from ethanol, gave XVI (0·75 g) as pale violet prisms, m.p. 135°. (Found: C, 70·9; H, 5·8. $C_{20}H_{20}O_5$ requires: C, 70·6; H, 5·9%).

14,15-*Dehydro*-B-*nor*-6-*oxaequilenin methyl ether* (XVII). To a solution of XVI (0·72 g) in ethanol (20 cc) and water (10 cc), barium hydroxide octahydrate (0·735 g) was added and the mixture refluxed for 2½ hr in nitrogen atmosphere. Ethanol was removed under a current of nitrogen and the residue decomposed by treatment with HCl. The acid was filtered, washed, dried (crude yield 0·7 g) and then dissolved in pyridine (5·6 cc). Under nitrogen atmosphere, conc HCl (11·2 cc) was added in 3 lots at 5 min intervals with evolution of carbon dioxide. The mixture was refluxed for 30 min under nitrogen at 140–150° (oil bath) and extracted with ether and the extract washed successively with dil HCl, aqueous NaOH and water. The product distilled at 165–175°/0·02–0·04 mm giving a pale yellow liquid which on solidification and keeping developed a pale violet colour. On crystallization from ethyl acetate under nitrogen, pale violet needles of XVII m.p. 161° (0·3 g) were obtained (Found: C, 75·6; H, 5·6. $C_{17}H_{16}O_3$ requires: C, 76·1; H, 5·9%). The U.V. absorption spectrum of XVII (ethanol) revealed the following principal absorption maxima: λ_{max} 292, 308, 320 mμ (log ε = 4·262, 4·423, 5·456).

B-*nor*-6-*oxaequilenin methyl ether* (XIX). Compound XVII (0·268 g) was added to a suspension of 30% palladium charcoal catalyst (0·08 g) in ethyl acetate (25 cc) previously saturated with hydrogen. Hydrogenation was carried out at room temp and atm press. The required quantity of hydrogen (for one double bond) was absorbed in 10 hr. The mixture was filtered, ethyl acetate removed and the residue distilled at 145–150°/0·015 mm yielding a colourless viscous semisolid (0·24 g). The product crystallized from benzene, as white needles m.p. 78°, yield 0·170 g. (Found: C, 75·3; H, 6·7. $C_{17}H_{18}O_3$ requires: C, 75·5; H, 6·7%). The U.V. absorption spectrum of XIX (ethanol) revealed the following principal absorption maxima: λ_{max} 252, 292 mμ (log ε = 3·784, 3·564).

dl-B-*nor*-6-*oxaequilenim* (I). The methyl ether XIX (0·27 g) was dissolved in glacial acetic acid (25 cc) and hydrobromic acid (2 cc, sp. gr. 1·4) was added and the solution refluxed for 6 hr in nitrogen atmosphere. Refluxing was continued for 21 hr after addition of HBr in 6 lots of 2 cc at intervals of 3 hr. Acetic acid was removed, (reduced press) the residue ether extracted and I isolated from the extract by aqueous sodium hydroxide (3%). The alkali-insoluble product in the ether extract gave unreacted methyl ether XIX (0·12 g). The alkaline extract was acidified and the product redissolved in ether–benzene and washed acid free and crystallized from benzene, yielding I as pale brown needles, m.p. 190° (previous shrinking at 187°), yield 0·06 g. (Found: C, 75·4; H, 6·0. $C_{16}H_{16}O_3$ requires: C, 75·0; H, 6·3%). The yield of I was 58% based on the recovery of unreacted XIX (alkali-insoluble product). The U.V. absorption spectrum of I (ethanol) revealed the following principal maxima: λ_{max} 250, 292 mμ (log ε = 4·146, 3·929).

7-*Methoxy*-1,2,3,4-*tetrahydrodibenzofuran* (XXII). Amalgamated zinc was prepared by shaking for 5 min mossy zinc (3 g), mercuric chloride (0·3 g) water (10 cc) and conc HCl (1–2 cc). The supernatant solution was decanted and III (0·2 g) dissolved in toluene (20 cc) added with conc HCl (3 cc). The mixture was refluxed for 21 hr with further additions of 3 cc lots of conc HCl at intervals of 3 hr. The reduction product isolated by ether extraction, on distillation at 128–132°/1·5 mm gave XXII as a colourless liquid 0·06 g, yield 32%). (Found: C, 76·9; H, 6·9. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 6·9%). The U.V. absorption spectrum of XXII (ethanol) revealed the following principal absorption maxima: λ_{max} 258, 292 mμ (log ε = 4·138, 3·722).

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