330. *The Structure of Palitantin.*

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Palitantin is shown to have the structure (XV) and the probable configuration expressed in formula (XXVIII). An explanation is provided of the unusual substitution reaction between iodine and palitantin.

The neutral optically active metabolite palitantin, $C_{14}H_{22}O_4$, was isolated by Birkinshaw and Raistrick [1] from culture filtrates of *Penicillium palitans* Westling; it is also produced by strains of *P. frequentans* [2] and *P. cyclopium*.[3] Careful experimental work by the discoverers,[1] later extended by Birkinshaw,[4] revealed its principal reactions and established some of its major structural features. Because some of its reactions had a possible bearing on our other work we became interested in palitantin, and Professors Birkinshaw and Raistrick most generously encouraged us to continue their studies. We now describe additional experiments which serve to define its structure.

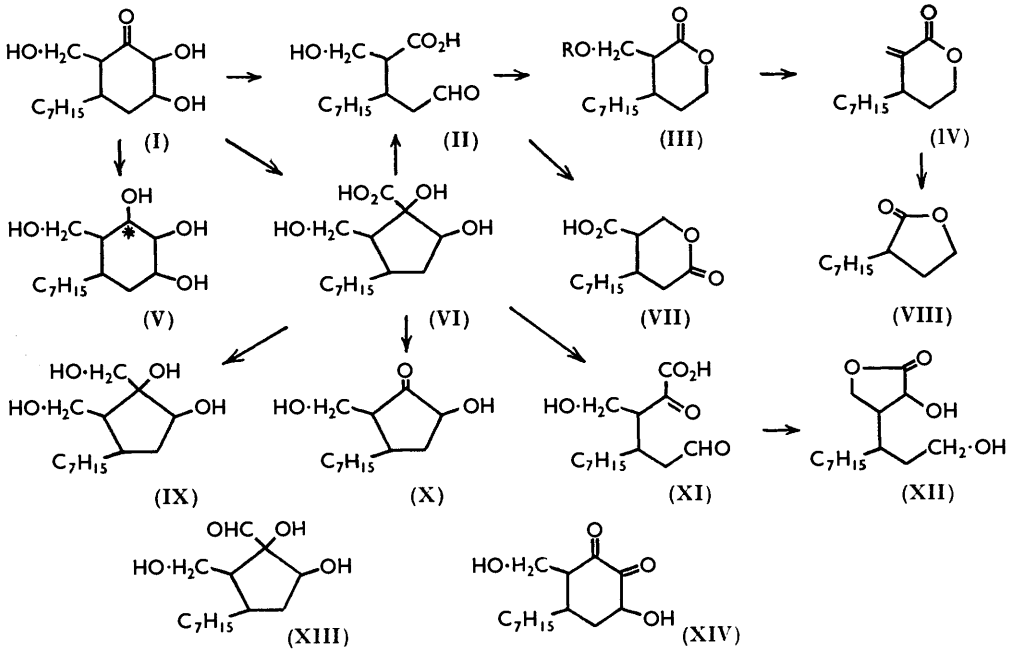
The earlier [1] work showed that palitantin contains a reactive carbonyl group, regarded as aldehydic because oxidation with Doeuvre's reagent [5] (alkaline potassium mercuri-iodide) gave palitantic acid, $C_{14}H_{22}O_5$. Palitantin formed a di-*p*-bromobenzoate, showing the presence of two hydroxyl groups; the fourth oxygen atom was not definitely characterised, but there was some evidence that it, too, was hydroxylic. This is now confirmed by the well-defined band $\nu_{max.}$ 3500 cm.$^{-1}$ shown by the di-*p*-bromobenzoate. Catalytic reduction of palitantin gave tetrahydropalitantin, which retains the original carbonyl function and was oxidised to tetrahydropalitantic acid; palitantin therefore contains two ethylenic links and one carbocyclic ring. One of the ethylenic links is present in the group $Pr^n \cdot CH{:}C<$, since ozonolysis [4] of palitantic acid gave butyraldehyde.

Birkinshaw [4] studied the behaviour of tetrahydropalitantin and tetrahydropalitantic acid towards periodate; the acid reduced only 1 mol. of oxidant, forming two new carbonyl groups. One of these was recognised as part of an α-keto-acid structure, so accounting for its resistance to further oxidation. By contrast, tetrahydropalitantin reduced 2 mols. of oxidant, giving formic acid and a syrupy aldehydo-acid. This was oxidised to a syrupy lactonic acid by Doeuvre's reagent, and then characterised as the dihydrazide of the corresponding hydroxy-dibasic acid $C_{13}H_{24}O_5$. Oxidation of the lactonic acid with nitric acid gave (+)-heptylsuccinic acid; this was identified by comparison with the synthetic racemic acid without the assistance of infrared methods; our own experiments provide an indirect confirmation that this identification is correct. Birkinshaw [4] suggested that

[1] Birkinshaw and Raistrick, *Biochem. J.*, 1936, **30**, 801.
[2] Curtis, Hemming, and Smith, *Nature*, 1951, **167**, 557.
[3] Bracken, Pocker, and Raistrick, *Biochem. J.*, 1954, **57**, 587.
[4] Birkinshaw, *ibid.*, 1952, **51**, 271.
[5] Doeuvre, *Bull. Soc. chim. France*, 1927, **41**, 1145.

palitantin contains a *cyclo*hexane ring bearing heptyl and formyl substituents, and with hydroxyl groups situated α and β to the formyl group.

We commenced the present work by deducing the structure (II) for the aldehydo-acid, $C_{13}H_{24}O_4$, formed by periodate oxidation of tetrahydropalitantin. The aldehydo-acid showed no tendency to lactonise, whereas the dibasic acid obtained from it by oxidation is completely lactonic;[4] clearly the lactone ring involves the newly generated carboxyl group [structure (VII)]. Sodium borohydride reduced the aldehydo-acid to a crystalline δ-lactone (III; R = H), $\nu_{max.}$ 1718 cm.$^{-1}$; this lactonisation involved the newly generated hydroxyl function, not that which pre-existed in the aldehydo-acid. The presence of the latter hydroxyl group in the δ-lactone (III; R = H) was shown by the formation of a crystalline toluene-*p*-sulphonate. When warmed with pyridine this lost toluene-*p*-sulphonic acid, giving an αβ-unsaturated δ-lactone (IV), $\lambda_{max.}$ 212 mμ, $\nu_{max.}$ 1733 (conjugated lactonic C:O), 1631 cm.$^{-1}$ (conjugated C:C). Ozonolysis gave formaldehyde, showing that the unsaturated lactone contains an α-methylene group; it is therefore of interest that the lactone showed no C–H deformation band near 900 cm.$^{-1}$, but instead showed bands at 943 and 803 cm.$^{-1}$; similar behaviour has been recorded for 2-methylenedodecanoic acid.[6] When in the above ozonolysis the ozonide was decomposed with hydrogen peroxide–acetic acid, an optically active γ-lactone (VIII), $\nu_{max.}$ 1780 cm.$^{-1}$, was formed; after purification through the crystalline hydrazide it showed infrared absorption identical with that of synthetic (±)-α-heptyl-γ-butyrolactone.[7] The active lactone was racemised with hot ethanolic sodium ethoxide and converted into the corresponding hydrazide, which was identical with that prepared from the (±)-lactone. These reactions establish that the aldehydo-acid has the structure (II).



Only two structures for tetrahydropalitantin, (I) and (XIII), are compatible with the formation of the aldehydo-acid (II); of these, structure (XIII) represents the aldehyde corresponding to the acid (VI). There is no doubt that structure (VI) correctly represents tetrahydropalitantic acid. A Curtius degradation of this acid gave the five-membered

[6] Freeman, *J. Amer. Chem. Soc.*, 1953, **75**, 1861.
[7] Rothstein, *Bull. Soc. chim. France*, 1935, **2**, 80.

cyclic ketone (X), $\nu_{max.}$ 1742 cm.$^{-1}$. Moreover, the α-keto-acid (XI), which Birkinshaw [4] obtained by periodate oxidation of tetrahydropalitantic acid, was reduced by sodium borohydride to a γ-lactone (XII), $\nu_{max.}$ 1780 cm.$^{-1}$. Tetrahydropalitantic acid reduced 2 mols. of lead tetra-acetate, giving the aldehydo-acid (II), identified by conversion into the crystalline toluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$). Finally, lithium aluminium hydride reduced methyl tetrahydropalitantate to the tetraol (IX), which consumed 2 mols. of periodate, giving 1 mol. of formaldehyde together with the aldehydo-acid (II).

Since tetrahydropalitantic acid has the structure (VI) it would be natural to conclude that tetrahydropalitantin has the structure (XIII); however, this is untenable for the following reasons. Birkinshaw and Raistrick [1] showed, and we have confirmed, that reduction of the carbonyl function of tetrahydropalitantin with sodium amalgam gives *two* tetraols $C_{14}H_{28}O_4$, here referred to as α- and β-tetrahydropalitantol. The β-isomer, more readily obtained by reduction with sodium borohydride, has been characterised as the tetra-*p*-bromobenzoate. Neither isomer is identical with the tetraol (IX) obtained from tetrahydropalitantic acid. This acid thus has a different carbon skeleton from tetrahydropalitantin, which must be the ketone (I); the tetrahydropalitantols are clearly the diastereoisomers (V). In agreement with this, the β-isomer reduced 2 mols. of periodate, giving formic acid, but no formaldehyde.

The ketonic structure (I) agrees well with the infrared absorption of tetrahydropalitantin, which shows $\nu_{max.}$ 1706 cm.$^{-1}$ but no aldehydic band near 2800 cm.$^{-1}$. A molecular rearrangement analogous to the benzilic acid change must occur in the formation of tetrahydropalitantic acid. It is possible that the α-diketone (XIV) may be an intermediate, although under similar conditions Doeuvre's reagent converted adipoin only into *cyclo*hexane-1 : 2-dione, which requires more vigorous alkaline treatment for rearrangement [8] to 1-hydroxy*cyclo*pentanecarboxylic acid. The palitantic acid rearrangement is stereospecific, only one of the two possible diastereoisomers being isolated.

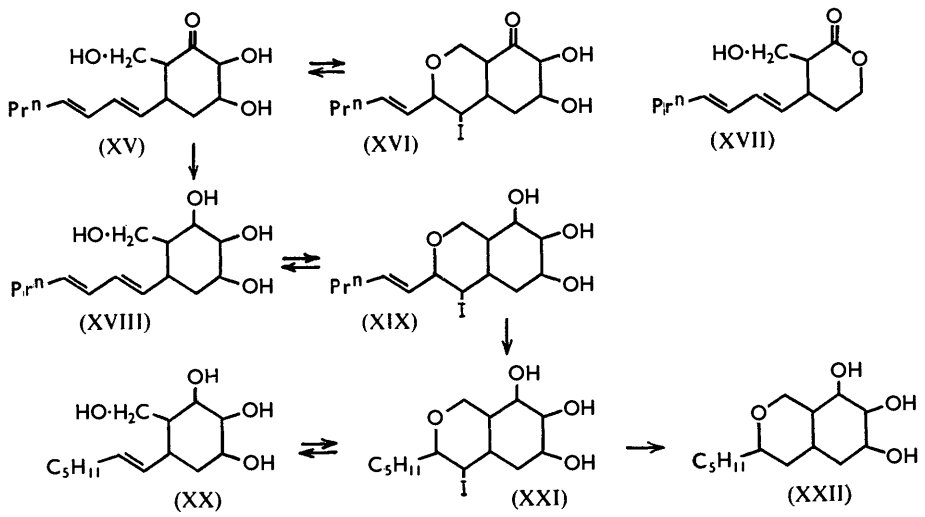
Turning now from the saturated to unsaturated compounds, we note that palitantin has $\lambda_{max.}$ 232 mμ (ε 34,000). Palitantol, the tetraol obtained from it by reduction with sodium amalgam [9] or, better, with sodium borohydride, shows similar absorption, which is thus dienoid. In view of the earlier isolation [4] of butyraldehyde on ozonolysis of palitantic acid, palitantin therefore contains the system $Pr^n{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}$ and has the structure (XV). Palitantin and its dienoid relatives show $\nu_{max.}$ 990 (conjugated *trans*-CH:CH) and 942 cm.$^{-1}$; a band of the latter frequency is present [10] in the spectra of dienes with one *cis*- and one *trans*-double bond, but the corresponding saturated compounds of the palitantin series also showed a similar band, so this type of diene system is not necessarily present in palitantin; indeed we regard it as improbable in view of the high intensity of the 232 mμ absorption.

Birkinshaw [4] showed that palitantin and palitantic acid are substituted by iodine, giving monoiodo-compounds. We have studied this unusual reaction, which we found to take place also with palitantol (XVIII) and with the diunsaturated δ-lactone (XVII) obtained from palitantin by periodate oxidation followed by reduction with sodium borohydride. During the reaction the dienoid light absorption was lost and a hydroxyl group was masked; for example, the product from the δ-lactone (XVII) contained no free hydroxyl group. The reaction is therefore a cyclisation between one of the double bonds and the hydroxymethyl group, and iodopalitantin has the cyclic iodo-ether structure (XVI). In agreement with this, it was reconverted into palitantin by zinc and acetic acid. Addition of the elements of an alkyl hypoiodite to a double bond is not normally possible, and the present example illustrates the favourable effect on reaction velocity often observed when two reacting groups occupy sterically suitable positions within the same molecule.

In further confirmation of the proposed structures iodopalitantol (XIX) absorbed 1 mol.

[8] Wallach, *Annalen*, 1924, **437**, 148.
[9] Curtis and Duncanson, *Biochem. J.*, 1952, **51**, 276.
[10] Cf. Crombie, *J.*, 1955, 1007.

of hydrogen (palladium), giving the saturated iodo-ether (XXI); further hydrogenation in the presence of aqueous alkali gave the iodine-free cyclic ether (XXII); iodopalitantin



underwent similar reactions. Zinc and acetic acid converted the iodo-ether (XXI) into the monounsaturated compound (XX), which on treatment with iodine gave back the iodo-ether (XXI); the cyclisation does not require a diene system for its success. The structure of the product (XX) was shown by ozonolysis, which gave hexanal. These reactions provided means of studying the component double bonds of the diene system of palitantin in isolation from each other. The compounds (XVI) and (XIX) showed very strong bands near 960 cm.$^{-1}$, which disappeared on hydrogenation, so that the double bond remote from the ring in palitantin undoubtedly has the *trans*-configuration. The monounsaturated tetraol (XX) gave a somewhat less clear picture; it showed a band of moderate intensity at 959 cm.$^{-1}$; we conclude that the double bond proximate to the ring in palitantin is probably of the *trans*-type.

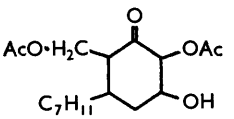
It was of interest to prepare partially protected derivatives of palitantin; acetylation readily gave a diacetate, but no well-defined triacetate. The diacetate probably has the structure (XXIII), since it failed to undergo the cyclic iodo-ether reaction, and was recovered after treatment with periodate. The resistance of the third hydroxyl group to acylation is connected with the presence of the keto-group in palitantin and tetrahydropalitantin; in tetrahydropalitantol all four hydroxyl groups are reactive. Palitantin, tetrahydropalitantin, iodopalitantin, and iodopalitantic acid (XXIV) readily formed crystalline *iso*propylidene derivatives; it may be inferred that the reaction giving *iso*propylidenepalitantin (XXV) does not involve the primary hydroxyl group.

Although we have not attempted a detailed study of the stereochemistry of palitantin, some of our observations are relevant to it, and we point out the conclusions which may, with due reserve, be drawn from them. It is probable that (+)-heptylsuccinic acid belongs to the same configurational series as *D*(+)-methylsuccinic acid (XXVI) and *D*(+)-*iso*propylsuccinic acid;[11] this defines the absolute configuration at the carbon atom bearing the heptadienyl group. Iodopalitantin semicarbazone gave back iodopalitantin on treatment with pyruvic acid, so that the two six-membered rings in the iodo-compound probably have the stable *trans*-fusion; *i.e.*, the hydroxymethyl and the heptadienyl group of palitantin are *trans*-related. The non-primary hydroxyl groups of

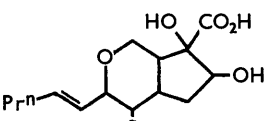
[11] Fredga, *Arkiv Kemi Min. Geol.*, 1942, **15**, *B*, No. 23.

palitantin and palitantic acid, which react with acetone, are almost certainly *cis*-related. Since palitantic acid shows no tendency to lactone formation its carboxyl and hydroxymethyl groups are probably *trans*-related. These considerations lead to the complete stereostructures (XXVII) and (XXVIII) for palitantic acid and palitantin respectively.

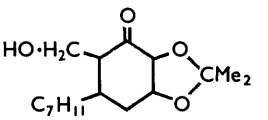
It may be noted that the structure (XV) for palitantin could readily be derived biogenetically from acetate residues, as are many other mould metabolites.[12]



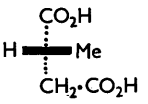
(XXIII)



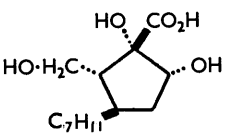
(XXIV)



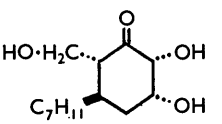
(XXV)



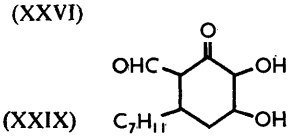
(XXVI)



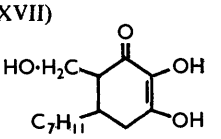
(XXVII)



(XXVIII)



(XXIX)



(XXX)

Finally, mention must be made of the acidic (enolic) compound frequentin, $C_{14}H_{20}O_4$, first isolated from *P. palitans* [1] and later from *P. frequentans*.[2] Curtis and Duncanson [9] showed that frequentin, $\nu_{max.}$ 1732, shoulder at 1720 cm.$^{-1}$, is reduced by sodium amalgam to " dihydropalitantin," *i.e.*, palitantol. Frequentin is clearly an enolised α- or β-dicarbonyl compound, and in the light of the present work two structures (XXIX) and (XXX) are possible; of these we prefer the latter.

Experimental

Ultraviolet spectra were taken in ethanol.

Palitantin.—Culture filtrates from a strain of *P. cyclopium* (freshly isolated from soil), grown [3] at 24° for 14 days on Czapek–Dox medium, were extracted with chloroform, the chloroform evaporated, and the residue crystallised first from benzene and then from water, giving palitantin (250 mg./l. of medium), m. p. 164—165° (lit.,[1] 165°) (Found: C, 66·0; H, 8·6. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7%), $\lambda_{max.}$ 232 mμ (ε 34,000), $\nu_{max.}$ (in KCl) 3333, 1715, 984, 956 cm.$^{-1}$.

Its identity was confirmed by conversion [1] into tetrahydropalitantin, m. p. 116° (lit.,[1] 116°) and palitantic acid, m. p. 146° (lit.,[1] 146—148°), $\lambda_{max.}$ 232 mμ (ε 29,000).

Degradation of Tetrahydropalitantin to the δ-Lactone (III; R = H).—Tetrahydropalitantin (1 g.) in ethanol (50 c.c.) was kept for 18 hr. with aqueous 0·1M-sodium metaperiodate (120 c.c.). Extraction with ether gave the crude syrupy aldehydo-acid, which required for neutralisation at 18° 0·94 equiv. of 0·02N-sodium hydroxide. The aldehydo-acid was reduced at 20° with sodium borohydride (1 g.) in methanol (20 c.c.). The solution was diluted with water and extracted with ether, and the aqueous phase acidified and extracted with chloroform. Evaporation of the chloroform and crystallisation from light petroleum (b. p. 60—80°) gave the *δ-lactone* as plates (500 mg.), m. p. 46°, $[\alpha]_D^{18}$ −19° (in alcohol), $\nu_{max.}$ (in Nujol) 3460, 1723 cm.$^{-1}$ (Found: C, 68·1; H, 10·4. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%). At 18° the lactone did not react in aqueous alcohol with 0·02N-sodium hydroxide; titration at 80° gave neutralisation equivalent 231 ($C_{13}H_{24}O_3$ requires 228).

[12] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360; and later papers by Birch and his co-workers.

Degradation of the δ-Lactone to (−)-α-Heptylbutyrolactone.—The δ-lactone (150 mg.), toluene-*p*-sulphonyl chloride (250 mg.), pyridine (0·2 c.c.), and chloroform (5 c.c.) were kept together at 18° for 18 hr. and the mixture worked up in the usual manner, giving the *toluene*-p-*sulphonate* (170 mg.) as plates [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 76° (Found: C, 62·7; H, 7·8. $C_{20}H_{30}O_5S$ requires C, 62·8; H, 7·9%). A portion (120 mg.) was kept at 80° in pyridine (5 c.c.) for 2 hr., and the cooled solution diluted with ether and washed with dilute hydrochloric acid and with water. Evaporation gave the crude α-methylene-δ-lactone as an oil (61 mg.), $\lambda_{max.}$ 212 mμ (ε 6000), which absorbed 0·85 mol. of hydrogen (palladised charcoal). Ozonolysis at 0° of this oil (230 mg.) in glacial acetic acid (6 c.c.) and ethyl acetate (4 c.c.), followed by steam-distillation and treatment of the distillate with dimedone gave formaldehyde dimethone (125 mg.), m. p. and mixed m. p. 189°.

The α-methylene-δ-lactone (200 mg.) was similarly ozonised at −25°, and the solution then heated under reflux for 2 hr. with water (2 c.c.) and 30% hydrogen peroxide (1 c.c.). The cooled solution was diluted with water and extracted with chloroform, and the extract washed with aqueous sodium thiosulphate, aqueous sodium carbonate, and water, then dried and evaporated. The neutral oil (140 mg.) and ethanolic hydrazine hydrate gave the *hydrazide* of (−)-α-heptyl-γ-hydroxybutyric acid (140 mg.) as needles (from dilute alcohol), m. p. 138°, $[\alpha]_D^{18}$ −21° (in pyridine) (Found: C, 61·0; H, 11·0; N, 13·4. $C_{11}H_{24}O_2N_2$ requires C, 61·1; H, 11·2; N, 12·95%). The hydrazide was kept at 100° for 30 min. with 8N-sulphuric acid; extraction with chloroform gave (−)-α-heptylbutyrolactone as an oil, $[\alpha]_D^{18}$ −12° (in chloroform); its infrared spectrum was identical with that of synthetic (±)-α-heptylbutyrolactone.[7]

The (−)-lactone (120 mg.) and N-ethanolic sodium ethoxide (2·5 c.c.) were heated under reflux for 2 hr.; acidification and extraction with ether gave the racemic lactone, $[\alpha]_D^{18}$ 0° ± 0·2° (in chloroform). It was converted into the (±)-*hydrazide* which separated from aqueous alcohol as needles, m. p. 127—127·5° (Found: C, 60·7; H, 10·95; N, 13·15%), undepressed on admixture with material of m. p. 127—127·5° prepared from the synthetic (±)-lactone.

Curtius Degradation of Tetrahydropalitantic Acid.—Tetrahydropalitantic acid [1] (250 mg.) was suspended in 0·01N-ethereal diazomethane (100 c.c.); after 5 min. the solvent was removed and the residue crystallised from benzene–light petroleum (b. p. 60—80°), giving the *methyl ester monohydrate* (220 mg.), m. p. 80—81° (Found: C, 58·5; H, 9·7. $C_{15}H_{28}O_5,H_2O$ requires C, 58·8; H, 9·9%). Sublimation at 75°/10^{-4} mm. gave anhydrous material, m. p. 83—84° (Found: C, 62·9; H, 9·7. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·8%). The *hydrazide*, obtained from the methyl ester in the usual way, separated from methanol as needles, m. p. 207—208° (Found: C, 58·8; H, 9·7; N, 9·4. $C_{14}H_{28}O_4N_2$ requires C, 58·3; H, 9·8; N, 9·7%). A portion (170 mg.) in N-hydrochloric acid was shaken with ether (10 c.c.) and aqueous sodium nitrite (700 mg. in 4 c.c.) at 0°. The ethereal layer was separated, the aqueous layer was re-extracted with ether, and the united ethereal layers were washed with aqueous sodium hydrogen carbonate and water, and dried. Alcohol (20 c.c.) was added, the ether was evaporated, and the solution heated under reflux for 2 hr. Evaporation and crystallisation from benzene gave a *substance* (36 mg.), m. p. 172° (Found: C, 61·8; H, 9·7; N, 5·0. $C_{14}H_{25}O_4N$ requires C, 62·0; H, 9·3; N, 5·2%). The mother-liquors were diluted with light petroleum (b. p. 60—80°), and the product recrystallised from that solvent, giving the *ketone* (X) as plates (44 mg.), m. p. 69° (Found: C, 68·1; H, 10·4. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%).

Oxidative Degradation of Tetrahydropalitantic Acid.—(*a*) The acid (274 mg.) and 0·05M-chloroformic lead tetra-acetate (50 c.c.) were kept for 24 hr. (uptake 1·9 mol.), and the solution was washed with water and freed from precipitated lead dioxide. It was extracted with aqueous sodium hydrogen carbonate, which was then acidified, and the product extracted with chloroform and reduced in methanol (15 c.c.) with sodium borohydride (0·4 g.). The diluted solution was extracted with ether, then acidified and extracted with chloroform. Evaporation of the chloroform and crystallisation from light petroleum (b. p. 60—80°) gave the δ-lactone (III; R = H) (70 mg.), m. p. 43°, $[\alpha]_D^{18}$ −19° (in alcohol). It was further identified by conversion into the toluene-*p*-sulphonate, m. p. and mixed m. p. 76°.

(*b*) The acid (1 g.) was oxidised [4] with sodium metaperiodate (uptake 1 mol.), the product isolated with ether, and a portion (240 mg.) reduced in methanol (20 c.c.) with sodium borohydride (500 mg.). Isolation in the usual manner gave a neutral oily lactone (200 mg.), $\nu_{max.}$ 1783 $cm.^{-1}$.

The Tetraol (IX).—Methyl tetrahydropalitantate (500 mg.) in ether (50 c.c.) was added

slowly with stirring to lithium aluminium hydride (1·5 g.) in ether (100 c.c.). The stirred mixture was heated under reflux for 3 hr., then cooled, and the excess of hydride was destroyed cautiously with ethyl acetate (10 c.c.) followed by saturated aqueous ammonium chloride (12 c.c.). The mixture was filtered and the filtrate evaporated; it left no residue. The precipitate was dissolved in dilute hydrochloric acid and the product isolated with chloroform. Crystallisation from benzene–*cyclo*hexane gave the *tetraol* (180 mg.) as needles, m. p. 46°, $[\alpha]_D^{18}$ −78° (in alcohol) (Found: C, 64·6; H, 10·5. $C_{14}H_{28}O_4$ requires C, 64·6; H, 10·8%).

The tetraol (160 mg.) was kept for 4 hr. with 0·1M-sodium metaperiodate (25 c.c.) (uptake, 2·0 mol.), and an aliquot part (10 c.c.) treated with sodium acetate and dimedone, giving formaldehyde dimethone (0·9 mol.), m. p. and mixed m. p. 189—190°. The remainder of the solution was extracted with ether, giving an oil (120 mg.) which was reduced in methanol (5 c.c.) with sodium borohydride (200 mg.). Isolation in the usual manner gave the δ-lactone (III; R = H) (80 mg.), m. p. and mixed m. p. 45°, $[\alpha]_D^{20}$ −19° (in chloroform).

β-*Tetrahydropalitantol.*—To tetrahydropalitantin (500 mg.) in methanol (15 c.c.) sodium borohydride (200 mg.) was added during ½ hr. The product, isolated in the usual way, separated from ether as plates (400 mg.), m. p. 96° (lit.,[1] 98—99°) (Found: C, 64·4; H, 10·6. Calc. for $C_{14}H_{28}O_4$: C, 64·6; H, 10·8%). The *tetra*-p-*bromobenzoate* separated from dilute alcohol as needles, m. p. 151—152° (Found: C, 50·9; H, 4·0; Br, 32·3. $C_{42}H_{40}O_8Br_4$ requires C, 50·8; H, 4·0; Br, 32·2%).

β-Tetrahydropalitantol reduced 1·9 mols. of sodium metaperiodate in 48 hr., giving a neutral oil and 0·5 equiv. of formic acid. When lead tetra-acetate was the oxidant 2·0 mols. were reduced rapidly, giving as the product a neutral oil.

Palitantol.—Reduction with sodium borohydride in methanol in the usual way converted palitantin (500 mg.) into palitantol (400 mg.) which separated from water as plates, m. p. 171—172° (lit.,[9] 170—171°), $[\alpha]_D^{18}$ −53° (in alcohol) (Found: C, 65·6; H, 9·3. Calc. for $C_{14}H_{24}O_4$: C, 65·6; H, 9·4%), $\lambda_{max.}$ 231 mμ (ε 32,000), $\nu_{max.}$ (in KCl), 3280, 992, 960 cm.$^{-1}$. Hydrogenation (uptake 2·0 mols.) in alcohol (palladised charcoal) gave β-tetrahydropalitantol, m. p. and mixed m. p. 96°.

Reactions of Iodopalitantin.—Prepared by Birkinshaw's [4] method, iodopalitantin had m. p. 136° (decomp.), $[\alpha]_D^{18}$ −28° (in chloroform) (Found: C, 44·1; H, 5·5. Calc. for $C_{14}H_{21}O_4I$: C, 44·2; H, 5·6%), $\lambda_{max.}$ 262 mμ (ε 900), $\nu_{max.}$ (in Nujol) 3413, 1724, 959 cm.$^{-1}$.

Iodopalitantin (100 mg.), zinc dust (1 g.), acetic acid (1 c.c.), and alcohol (5 c.c.) were kept under reflux for 1 hr. and filtered. The filtrate was diluted with chloroform, washed with aqueous sodium carbonate, dried, and evaporated. Crystallisation from water gave palitantin (55 mg.), m. p. and mixed m. p. 163°.

Iodopalitantin semicarbazone (41 mg.), m. p. 228° (decomp.) (Found: C, 41·3; H, 5·4; N, 9·5. $C_{15}H_{24}O_4N_3I$ requires C, 41·2; H, 5·4; N, 9·6%), and pyruvic acid (300 mg.) in glacial acetic acid (5 c.c.) and water (0·5 c.c.) were kept at 80° for 45 min., the cooled mixture extracted with chloroform, and the extract washed with aqueous sodium hydrogen carbonate and water, and evaporated. Crystallisation from water gave iodopalitantin, m. p. 136° (decomp.), $[\alpha]_D^{18}$ −29° (in chloroform). In one experiment a second crystalline form, m. p. 151° (decomp.), was obtained; it had the same optical rotation and furnished on hydrogenation the dihydro-compound, m. p. 147—148° (see below).

Hydrogenation (uptake 1·0 mol.) of iodopalitantin in ethyl acetate (5% palladised charcoal) gave quantitatively the *dihydro-compound.* It separated from dilute alcohol as plates, m. p. 147—148°, $[\alpha]_D^{20}$ −23° (in alcohol) (Found: C, 44·2; H, 6·0. $C_{14}H_{23}O_4I$ requires C, 44·0; H, 6·1%), $\lambda_{max.}$ 259 mμ (ε 900), no $\nu_{max.}$ near 950 cm.$^{-1}$. Hydrogenation (uptake 1·0 mol.) of a portion (35 mg.) in alcohol containing 1 equiv. of aqueous sodium hydroxide with the same catalyst gave the *deiodo-compound* (20 mg.) as needles (from dilute alcohol), m. p. 129° (Found: C, 65·6; H, 9·6. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%).

Iodopalitantol.—Prepared similarly to iodopalitantin, from palitantol (500 mg.), *iodopalitantol* (350 mg.) formed hydrated plates (from dilute alcohol), m. p. 145° (decomp.), $[\alpha]_D^{18}$ −101° (in chloroform) (Found: C, 42·1; H, 6·2. $C_{14}H_{23}O_4I,H_2O$ requires C, 42·0; H, 6·3%), $\lambda_{max.}$ 260 mμ (ε 800) $\nu_{max.}$ (in Nujol) 960 cm.$^{-1}$. The *dihydro-compound* formed hydrated needles (from dilute alcohol), m. p. 126° (Found: C, 41·4; H, 6·7. $C_{14}H_{25}O_4I,H_2O$ requires C, 41·8; H, 6·8%). Further hydrogenation in the presence of alkali gave the *deiodo-compound* which separated from benzene as hydrated needles, m. p. 112° (Found, in material dried at 80°/0·1 mm.: C, 65·3; H, 9·5. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%).

Treatment of iodopalitantol with zinc dust in ethanol–acetic acid, as described for iodopalitantin, gave palitantol, m. p. and mixed m. p. 171°, $\lambda_{max.}$ 231 mμ (ε 31,000). Similar treatment of the dihydro-compound (m. p. 126°) gave the *product* (XIX) as plates (from ethyl acetate), m. p. 154—156° (Found: C, 65·0; H, 10·0. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%), $\nu_{max.}$ (in $CHCl_3$) 959 cm.$^{-1}$. Ozonolysis of this product (80 mg.) gave hexanal, isolated as the 2 : 4-dinitrophenylhydrazone (30 mg.), m. p. and mixed m. p. 106° (Found: C, 51·5; H, 6·0. Calc. for $C_{12}H_{16}O_4N_4$: C, 51·4; H, 5·8%).

The Iodo-derivative of the δ-Lactone (XVII).—The *δ-lactone* (250 mg.), prepared from palitantin (500 mg.) as described for the saturated analogue, separated from ether–light petroleum (b. p. 60—80°) as needles, m. p. 78°, $[\alpha]_D^{18}$ −25° (in alcohol) (Found: C, 69·1; H, 8·8. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%), $\lambda_{max.}$ 231 mμ (ε 29,000), $\nu_{max.}$ (in Nujol) 3378, 1706, 983 cm.$^{-1}$. The *toluene-p-sulphonate*, plates [from ether–light petroleum (b. p. 40—60°)], had m. p. 94° (Found: C, 63·6; H, 6·8. $C_{20}H_{26}O_5S$ requires C, 63·5; H, 6·9%).

The δ-lactone (200 mg.) gave in the usual way an *iodo-derivative* (80 mg.) which separated from ether as plates, m. p. 78°, $[\alpha]_D^{18}$ −55° (in chloroform) (Found: C, 44·9; H, 5·5. $C_{13}H_{19}O_3I$ requires C, 44·6; H, 5·5%), $\lambda_{max.}$ 258 mμ (ε 840), no hydroxyl band near 3500 cm.$^{-1}$, $\nu_{max.}$ (in Nujol) 1733, 983 cm.$^{-1}$. The *dihydro-compound* separated from light petroleum (b. p. 40—60°) as needles, m. p. 53—54° (Found: C, 44·9; H, 6·0. $C_{13}H_{21}O_3I$ requires C, 44·3; H, 6·0%).

Palitantin Diacetate.—Palitantin (250 mg.), acetic anhydride (0·6 c.c.), pyridine (0·3 c.c.), and chloroform (5 c.c.) were kept together at room temperature for 18 hr. and the product was isolated in the usual way, giving the *diacetate* (200 mg.) as plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 157—158° (Found: C, 64·0; H, 7·75. $C_{18}H_{26}O_6$ requires C, 63·9; H, 7·7%), $\lambda_{max.}$ 232 mμ (ε 34,000), $\nu_{max.}$ (in Nujol) 3546, 1733, 1718, 988 cm.$^{-1}$. Prepared similarly, *tetrahydropalitantin diacetate* had m. p. 120—121° (Found: C, 62·8; H, 8·2. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

iso*Propylidene Derivatives.*—(*a*) Tetrahydropalitantin (100 mg.) and freshly fused zinc chloride (400 mg.) were heated for 10 min. under reflux with dry acetone (50 c.c.) and enough glacial acetic acid to give homogeneity. The cooled mixture was diluted with water, extracted with chloroform, and the extract washed, dried, and evaporated. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *product* (90 mg.) as needles, m. p. 79° (Found: C, 68·5; H, 10·3. $C_{17}H_{30}O_4$ requires C, 68·4; H, 10·1%).

(*b*) Similarly prepared, OO-iso*propylidenepalitantin* formed needles, m. p. 108° (Found: C, 69·0; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%), $\lambda_{max.}$ 228 mμ (ε 34,500), $\nu_{max.}$ (in Nujol) 3460, 1727, 980 cm.$^{-1}$.

(*c*) Iodopalitantin similarly gave an iso*propylidene derivative*, m. p. 117—118°, $[\alpha]_D^{20}$ −38° (in alcohol) (Found: C, 48·45; H, 6·15. $C_{17}H_{25}O_4I$ requires C, 48·6; H, 6·0%).

(*d*) The iso*propylidene derivative* of iodopalitantic acid formed cubes [from light petroleum (b. p. 40—60°)], m. p. 154—155° (Found: C, 46·8; H, 5·9. $C_{17}H_{25}O_5I$ requires C, 46·8; H, 5·8%).

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