A Novel Aromatisation Reaction of Derivatives of 1,2-*O*-Isopropylidene-*myo*-inositol

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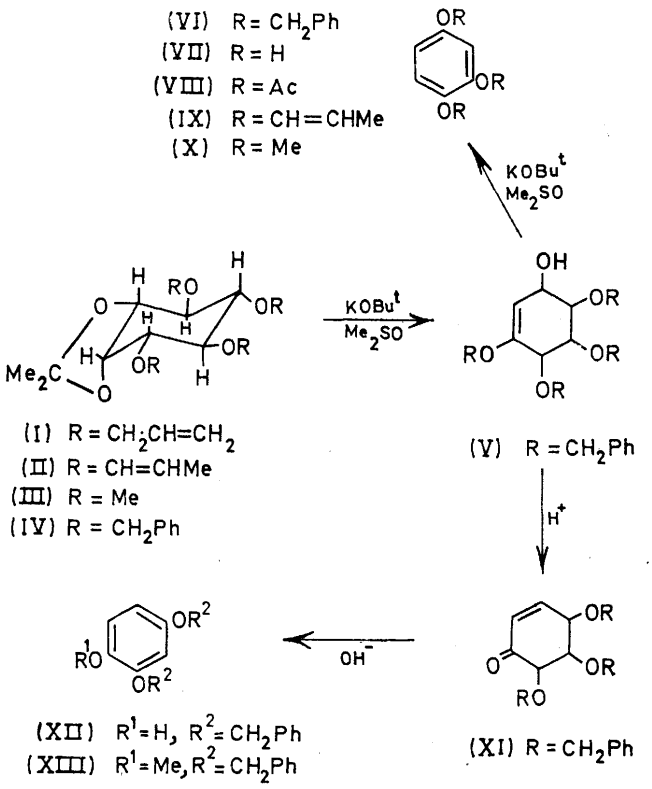
Tetra-*O*-alkyl ethers of 1,2-*O*-isopropylidene-*myo*-inositol are converted into 1,2,4-trialkoxybenzenes on treatment with potassium t-butoxide in dimethyl sulphoxide at 80°. An intermediate product in the conversion of 3,4,5,6-tetra-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol into 1,2,4-trisbenzyloxybenzene was isolated. The intermediate, 3,4,5,6-tetrakisbenzyloxycyclohex-2-enol, was converted into 4,5,6-trisbenzyloxycyclohex-2-enone on treatment with acid and the latter compound gave 2,4-bisbenzyloxyphenol after treatment with base.

In the course of investigations on the synthesis of phosphatidylinositol,[1] the isomerisation of the allyl groups in the model compound 3,4,5,6-tetra-*O*-allyl-1,2-*O*-isopropylidene-*myo*-inositol (I) when treated with potassium t-butoxide in dimethyl sulphoxide[2] was studied. Compound (I) was rapidly converted into a new product whose mobility on t.l.c. was greater than that expected for the anticipated tetra-*O*-prop-1-enyl isomer (II) and the properties of the product were those of an aromatic compound corresponding to a tris(prop-1-enyloxy)benzene. Acidic hydrolysis of the product gave (in low yield) a compound whose m.p. (141°) was similar to that of benzene-1,2,4-triol (VII).

Since the reaction was complicated by the presence of the allyl groups, the tetramethyl ether (III) and tetrabenzyl ether (IV) were treated under the same conditions and similar aromatisation reactions were observed. In the case of the benzyl ether (IV) the aromatic product was a crystalline solid whose m.p. agreed with that reported[3] for the tribenzyl ether (VI) of benzene-1,2,4-triol. Catalytic reduction of compound (VI) over palladium–charcoal and acetylation of the product gave the triacetate (VIII) of benzene-1,2,4-triol, identical (m.p., mixed m.p., and i.r. spectrum) with the compound prepared by a standard procedure.[4]

In the aromatisation reaction with the benzyl ether (IV) a more polar intermediate was observed by t.l.c., and this was isolated by chromatography. The crystalline product had an elemental analysis and i.r. and n.m.r. spectra which corresponded to the vinyl ether structure (V) and on treatment with potassium t-butoxide in dimethyl sulphoxide gave the tribenzyl ether (VI). Although the stereochemistry of compound (V) has not been established, it is likely that a *trans*-elimination occurred with abstraction of the proton from the 3-carbon atom of compound (IV) (under the strongly basic conditions of the reaction) and concomitant displacement of the axial oxygen atom of the isopropylidene group. Similar eliminations of isopropylidene groups,



[1] (*a*) R. Gigg and C. D. Warren, *J. Chem. Soc.* (*C*), 1969, 2367; (*b*) P. A. Gent, R. Gigg, and C. D. Warren, *Tetrahedron Letters*, 1970, 2575.

[2] J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82; R. Gigg and C. D. Warren, *ibid.*, 1968, 1903.

[3] J. W. Daly, J. Benigni, R. Minnis, Y. Kanaoka, and B. Witkop, *Biochemistry*, 1965, **4**, 2513.

[4] E. B. Vliet, *Org. Synth.*, 1941, Coll. Vol. I, p. 317.

under much milder basic conditions, have been observed [5] when a nitro-group is present on a carbon atom adjacent to the isopropylidene group.

The acidic hydrolysis of β-alkoxyallylic alcohols produces αβ-unsaturated ketones [6] and therefore in order to confirm the structure of compound (V) it was treated with dilute acid at room temperature. The crystalline product had properties as expected for the αβ-unsaturated ketone (XI). It has been shown [7] that compounds related to compound (XI) are readily aromatised (by β-elimination) on treatment with base; the product (XI) was therefore treated with sodium hydroxide at room temperature to give a crystalline aromatic product whose elemental analysis and m.p. agreed with those required for 2,4-bisbenzyloxyphenol (XII). Compound (XII) was also isolated by Angyal and Tate [7a] as the product from the treatment of 3,4,5,6-tetra-*O*-benzyl-1-*O*-tosyl-*myo*-inositol with base. The m.p. of its methyl ether (XIII) was identical with that reported.[7a]

Several aromatisation reactions of inositol derivatives have been described previously [7] but they all involve β-elimination from an intermediate keto-derivative and are thus unrelated to the reaction producing compound (VI) from the isopropylidene derivative (IV).

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. T.l.c. was carried out on microscope slides coated with silica gel G (unless otherwise stated) and compounds were detected by heating the plates to 200° after spraying with 50% sulphuric acid. The light petroleum used has b.p. 40—60°.

(±)-3,4,5,6-*Tetra*-O-*benzyl*-1,2,O-*isopropylidene*-myo-*inositol* (IV).—3,4,5,6-Tetra-*O*-benzyl-*myo*-inositol [1a] (10 g.) and toluene-*p*-sulphonic acid (1 g.) in dry acetone (500 ml.) were kept at room temperature for 12 hr. An excess of potassium carbonate was added to neutralise the acid and the solvent was evaporated off. The residue was extracted with ether and chromatographed on alumina in benzene–ether (3 : 1) to give the product (8 g.) as an oil which slowly crystallised. Recrystallisation from light petroleum gave *compound* (IV), m.p. 57·5—58·5° (Found: C, 76·6; H, 7·0. $C_{37}H_{40}O_6$ requires C, 76·5; H, 6·9%).

1,2,4-*Trisbenzyloxybenzene* (VI).—A solution of compound (IV) (5 g.) and potassium t-butoxide (4 g.) in dry dimethyl sulphoxide (150 ml.) was heated at 80°. After 1 hr., t.l.c. [ether–light petroleum (1 : 2)] showed unchanged starting material (R_F 0·55), a small amount of a new product (R_F 0·24), and a major product (R_F 0·9). After 8 hr., conversion into the product of R_F 0·9 was almost complete and the solution was cooled, diluted with water (150 ml.), and extracted with ether. The extract was washed with saturated potassium chloride, dried (K_2CO_3), and evaporated. The residue was chromatographed on alumina; elution with light petroleum gave the product (2 g.) as an oil which solidified. Recrystallisation from benzene–hexane gave compound (VI), m.p. 80—81° (lit.,[3] 81—82°) (Found: C, 81·8; H, 5·8. Calc. for $C_{27}H_{24}O_3$: C, 81·8; H, 6·1%).

1,2,4-*Triacetoxybenzene* (VIII).—Compound (VI) (500 mg.) in glacial acetic acid (10 ml.) was treated with hydrogen in the presence of 10% palladium–charcoal (at atmospheric pressure) until the initial rapid uptake of hydrogen had ceased (1·5 hr.). T.l.c. [chloroform–methanol (3 : 1)] indicated the presence of a major product (R_F 0·7) together with traces of slower-running material. The solution was filtered through Celite and the filtrate was evaporated. Pyridine–acetic anhydride (2 : 1) was immediately added to the residue and the solution was kept at room temperature for 1 hr. then poured into cold 2N-hydrochloric acid. The product was extracted with chloroform. The extract was washed with saturated potassium chloride and sodium hydrogen carbonate solutions and dried ($MgSO_4$). Evaporation gave a solid residue (380 mg.) which yielded compound (VIII), m.p. and mixed m.p. (with an authentic sample prepared by acetylation of quinone [4]) 95—97° [from ethanol–water (19 : 1)]. The i.r. spectra of the product and the authentic material were identical (Found: C, 56·7; H, 4·5. Calc. for $C_{12}H_{12}O_6$: C, 57·2; H, 4·8%).

(±)-3,4,5,6-*Tetrakisbenzyloxycyclohex*-2-*enol* (V).—Compound (IV) (8·5 g.) was treated with potassium t-butoxide in dimethyl sulphoxide at 80° for 1·5 hr. and the products were isolated as for the preparation of compound (VI). T.l.c. [ether–light petroleum (1 : 2)] of the residue (7·6 g.) showed the presence of compound (IV) (R_F 0·55), compound (VI) (R_F 0·9), and the new product (R_F 0·24). The residue was chromatographed on alumina; elution with ether gave compounds (IV) and (VI) and elution with ether–methanol (99 : 1) gave the required product (R_F 0·24) (930 mg.) as a solid. Recrystallisation from benzene–light petroleum gave *compound* (V), m.p. 131—132°, $\nu_{max.}$ 3160—3270 (OH) and 1660 cm.$^{-1}$ (O–CH=CH), τ ($CDCl_3$) 7·75 (s, OH, exchangeable), 6·61—5·41 (m, 5H), 5·2 (s, 8H, 4 × CH_2Ph), and 2·66, 2·69, 2·70, and 2·73 (s, 20H, 4 × Ph) (Found: C, 77·8; H, 6·5. $C_{34}H_{34}O_5$ requires C, 78·1; H, 6·6%).

On treatment with potassium t-butoxide in dimethyl sulphoxide at 80° for 4 hr., compound (V) gave 1,2,4-trisbenzyloxybenzene (VI), identical (m.p., mixed m.p., and i.r. spectrum) with the previously prepared sample.

(±)-4,5,6-*Trisbenzyloxycyclohex*-2-*enone* (XI).—A solution of compound (V) (900 mg.) in N-sulphuric acid–acetone (1 : 9; 75 ml.) was kept at room temperature for 1 hr.; t.l.c. [ether–light petroleum (1 : 1)] then showed complete conversion of the starting material (R_F 0·3) into a product (R_F 0·5). The acid was neutralised with an excess of sodium acetate and the solvent was evaporated off. The residue was extracted with ether and the extract was washed with water and dried (Na_2SO_4). Evaporation left an oil (450 mg.) which slowly crystallised and was recrystallised from benzene–light petroleum to give *compound* (XI), m.p. 71—72°, $\nu_{max.}$ 1692 cm.$^{-1}$ (C=C–C=O) (Found: C, 77·9; H, 6·1. $C_{27}H_{26}O_4$ requires C, 78·2; H, 6·3%).

2,4-*Bisbenzyloxyphenol* (XII).—A solution of compound (XI) (420 mg.) in methanolic N-sodium hydroxide (25 ml.) was kept at room temperature for 20 min.; t.l.c. [ether–light petroleum (1 : 1)] then indicated complete conversion of the starting material (R_F 0·5) into a product (R_F 0·7). The solution was acidified with acetic acid and the solvent was evaporated off. The residue was extracted with ether and the extract was washed with saturated sodium hydrogen

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[6] M. Stiles and A. L. Longroy, *J. Org. Chem.*, 1967, **32**, 1095.
[7] (*a*) S. J. Angyal and M. E. Tate, *J. Chem. Soc.*, 1965, 6949. (*b*) T. Posternak and J. Deshusses, *Helv. Chim. Acta*, 1961, **44**, 2088; W. Meyer zu Reckendorf, *Chem. Ber.*, 1968, **101**, 3652; A. J. Fatiadi, *Chem. Comm.*, 1967, 441.

carbonate solution and dried (Na_2SO_4). Evaporation left a solid residue which was recrystallised from benzene–light petroleum to give compound (XII) (190 mg.), m.p. 91—92° (lit.,[7a] 93—94°), τ ($CDCl_3$) 5·02 and 4·98 (s, 4H, 2 × CH_2Ph), 4·7 (s, OH, exchangeable), 3·6—3·08 (m, 3H), and 2·67 (s, 10H, 2 × Ph) (Found: C, 78·1; H, 5·9. Calc. for $C_{20}H_{18}O_3$: C, 78·4; H, 5·9%).

2,4-*Bisbenzyloxyanisole* (XIII).—Compound (XII) (100 mg.) was methylated in benzene with methyl iodide and sodium hydroxide at reflux for 45 min. T.l.c. [alumina; ether–light petroleum (1 : 1)] showed complete conversion of the starting material (R_F 0·7) into the product (R_F 0·95). Water was added and the benzene layer was separated, dried (K_2CO_3), and evaporated to leave a crystalline residue, which was recrystallised from light petroleum to give compound (XIII) (50 mg.), m.p. 86·5—87·5° (lit.,[7a] 88—89°) (Found: C, 78·6; H, 6·3. Calc. for $C_{21}H_{20}O_3$: C, 78·7; H, 6·3%).

(±)-3,4,5,6-*Tetra*-O-*allyl*-1,2,O-*isopropylidene*-myo-*inositol* (I).—1,2,*O*-Isopropylidene-*myo*-inositol [1a] (10 g.) and allyl bromide (30 ml.) in benzene (100 ml.) were stirred with powdered sodium hydroxide (20 g.) under reflux until t.l.c. [ether–light petroleum (1 : 1)] showed almost complete conversion of the starting material (R_F 0) into the product (R_F 0·8), together with traces of partially alkylated materials (R_F 0·24, 0·42, and 0·58). Water was added and the benzene layer was separated, washed with water, and dried (K_2CO_3). Evaporation of the solvent left an oil which was chromatographed on alumina. Elution with ether–light petrolum (1 : 2) gave the *product* (I) (15 g.). For analysis a portion was distilled, b.p. 138—139°/1 mm. (Found: C, 66·1; H, 8·4. $C_{21}H_{32}O_6$ requires C, 66·2; H, 8·5%). Acidic hydrolysis of a portion gave 3,4,5,6-*tetra*-O-*allyl*-myo-*inositol* as an oil, b.p. 150—155° (bath)/0·1 mm. (Found: C, 63·4; H, 8·0. $C_{18}H_{28}O_6$ requires C, 63·5; H, 8·3%),

1,2,4-*Tris*(*prop*-1-*enyloxy*)*benzene* (IX).—Compound (I) (7 g.) and potassium t-butoxide (10 g.) in dry dimethyl sulphoxide (200 ml.) were heated at 80° for 5 hr.; t.l.c. [ether–light petroleum (1 : 7) then showed conversion of the starting material (R_F 0) into a product (R_F 0·86), with traces of slower-running material. The solution was diluted with water (200 ml.) and extracted with ether. The extract was dried (K_2CO_3) and evaporated, and the oily residue was chromatographed on alumina. Elution with light petroleum gave the *product* (IX) (3·6 g.), b.p. 100° (bath)/0·5 mm., $\nu_{max.}$ 1670 (O–CH=CH), 1600, and 1500 cm.$^{-1}$ (aromatic), $\lambda_{max.}$ (EtOH) 220, 237, and 287 nm. (Found: C, 72·8; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·4%). A portion of the product was reduced with hydrogen over palladium–charcoal until uptake was complete, to give 1,2,4-trispropyloxybenzene, b.p. 130°/1 mm. (Found: C, 71·6; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

Benzene-1,2,4-*triol* (VII).—Compound (IX) (2 g.) in 2N-hydrochloric acid–methanol (1 : 4) was refluxed under nitrogen for 30 min.; t.l.c. [chloroform–methanol (3 : 1)] then showed conversion into a new product (R_F 0·7) which gave a red colour with the sulphuric acid spray on heating the t.l.c. plate [*cf.* phloroglucinol (R_F 0·7; yellow colour); pyrogallol (R_F 0·75; brown-mauve colour)]. When the thin-layer plate was sprayed with a ferric chloride spray the compound gave a yellow-brown colour immediately which turned black after 3 hr. [*cf.* phloroglucinol (colour appears slowly to give a light brown colour in a few hr.); pyrogallol (immediate brown colour turning black in 3 hr.)]. The solvents were evaporated off and the product was extracted with ether. A solution of the product in ether–chloroform gave small crystals of benzene-1,2,4-triol, m.p. and mixed m.p. 141°.

(±)-3,4,5,6-*Tetra*-O-*methyl*-1,2,O-*isopropylidene*-myo-*inositol* (III).—1,2,*O*-Isopropylidene-*myo*-inositol [1a] was methylated with methyl iodide and sodium hydride in dry tetrahydrofuran until t.l.c. (ether) showed almost complete conversion into the fully methylated derivative (R_F 0·9). Methanol was added to decompose the excess of sodium hydride and the solvents were evaporated off. The residue was chromatographed on alumina; elution with ether–light petroleum (1 : 10) gave the product (III) as an oil, b.p. 150° (bath)/1 mm. (Found: C, 56·4; H, 8·7. Calc. for $C_{13}H_{24}O_6$: C, 56·5; H, 8·8%). Acidic hydrolysis of a portion and recrystallisation of the product from cyclohexane gave 3,4,5,6-tetra-*O*-methyl-*myo*-inositol as needles, m.p. 102—104° (lit.,[7a] 105—106°) (Found: C, 50·8; H, 8·5. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5%).

1,2,4-*Trimethoxybenzene* (X).—3,4,5,6-Tetra-*O*-methyl-1,2,*O*-isopropylidene-*myo*-inositol (III) was treated with potassium t-butoxide in dry dimethyl sulphoxide at 80° as already described. T.l.c. [ether–light petroleum (1 : 1)] showed conversion of the starting material (R_F 0·3) into the product (R_F 0·7). The product was isolated as described before and chromatographed on alumina. Elution with ether–light petroleum (1 : 20) gave compound (X), b.p. 100° (bath)/0·5 mm., $\nu_{max.}$ 1500 and 1600 cm.$^{-1}$ (aromatic) (Found: C, 64·0; H, 7·0. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2%).

We thank Mr. R. Conant for much of the preparative work and Dr. R. Ferrier for the n.m.r. spectra.

[0/588 *Received, April 15th,* 1970]