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THE SYNTHESIS OF DIACYL-L-1-GLYCEROL BROMOHYDRINS (INTERMEDIATES IN THE SYNTHESIS OF PHOSPHATIDIC ACIDS)

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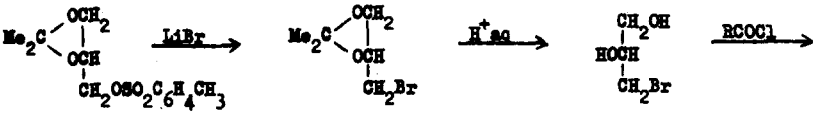
A convenient procedure for the synthesis of L-1-phosphatidic acids (VI) is that of Stanacev and Kates[1], based upon the methods of Verkade et al.[2,3,4,5] entailing condensation of silver dibenzyl phosphate with a diacyl-L-1-glycerol iodohydrin to yield the dibenzyl ester of a phosphatidic acid (V), which can be catalytically hydrogenolysed to the L-1-phosphatidic acid. A disadvantage of the procedure in that diacyl glycerol iodohydrins, and the iodine containing compounds used as intermediates in the synthesis, are light sensitive and hence difficult to handle and store.

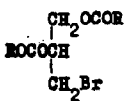
We now report the synthesis of the light stable diacyl-L-1-glycerol bromohydrins (IV), which can be used with advantage in the synthesis of phosphatidic acids.

A modification[6] of the procedure developed by Baer[7] was used to prepare D-1,2:5,6-di-isopropylidene mannitol, which was then converted, via D-isopropylidene glycerol[8], to 1-tosyl D-isopropylidene glycerol (I). This was then converted in three stages to the desired diacyl-L-1-glycerol

bromohydrin (IV), thus:-



I II III



IV

R = (a)$C_{17}H_{33}$ (b)$C_{13}H_{27}$ (c)$C_{17}H_{35}$

Overall yield. ~ 70%

The nucleophilic displacement of the tosyl group was effected in excellent yield by refluxing an anhydrous acetone solution of (I) with three moles of dried lithium bromide for twenty hours under anhydrous conditions; after filtration, the acetone solution was carefully evaporated in vacuo, and the residue freed from inorganic salts by dissolving in ether and washing with water. Fractional distillation gave an excellent yield of pure 1-bromo-D-isopropylidene glycerol (II) as a colourless liquid, B.Pt.65°C/12 mm., n_D^{20} 1.4597, d_4^{20} 1.381, $[\alpha]_D^{20}$ + 49.2° in substance. (Found: C, 37.2; H, 5.8: $C_6H_{11}O_2Br$ requires: C,36.9; H,5.7%).

(II) was hydrolysed by allowing to stand for one day in an N/6 solution of sulphuric acid in 80% alcohol, followed by three minutes refluxing to complete the reaction. After neutralisation with Amberlite

IR-45(OH) and evaporation in vacuo, fractional distillation of the residue gave an excellent yield of L-1-glycerol bromohydrin (III) as a colourless oil, B.Pt. 78°C/0.4 mm., n_D^{20} 1.5179, d_4^{20} 1.756, $[\alpha]_D^{20}$ - 0.9° in substance and - 5.7° in ethanol, c 17. (Found: C, 23.4; H, 4.7: $C_3H_7O_2Br$ requires: C, 23.2; H, 4.5%).

The L-1-glycerol bromohydrin (III) was acylated by slow addition of the appropriate fatty acid chloride (10% excess) at 0°C to a solution of (III) in dry benzene with pyridine (50% excess), followed by stirring at room temperature for two days under anhydrous conditions. After washing with ice-cold $^N/_5$ sulphuric acid, then with water, the benzene solution was dried and rapidly percolated through a short column of neutral alumina to remove excess free fatty acid. After eluting the column with dry benzene, and then a little ether, the combined eluents were evaporated in vacuo to give the pure diacyl-L-1-glycerol bromohydrins (IV) as colourless solids (saturated long chain analogues) or liquids (unsaturated analogues) in excellent yields. Thus:-

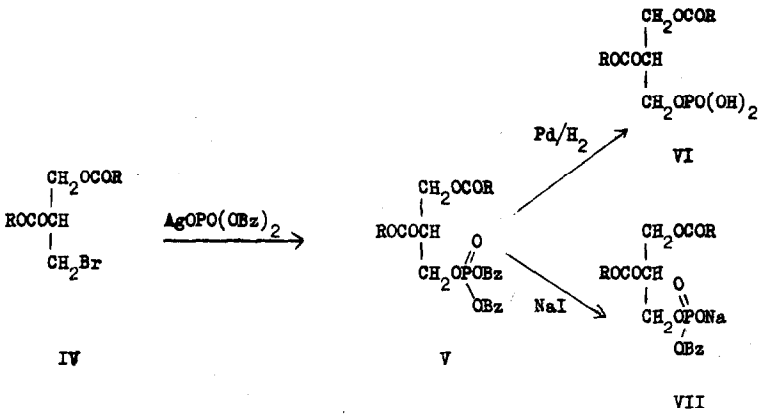
IVa, Dioleoyl-L-1-glycerol bromohydrin, $[\alpha]_D^{20}$ + 2.9° in chloroform, c 10 (Found: C, 68.5; H, 10.2: $C_{39}H_{71}O_4Br$ requires: C, 68.5; H, 10.4%).

IVb, Dimyristoyl-L-1-glycerol bromohydrin, m.p. 42°, $[\alpha]_D^{20}$ + 3.7° in chloroform, c 10 (Found: C, 65.0; H, 10.2: $C_{31}H_{59}O_4Br$ requires: C, 64.7; H, 10.3%).

IVc, Distearoyl-L-1-glycerol bromohydrin, m.p. 60°, $[\alpha]_D^{25}$ + 3.2° in chloroform, c 10 (Found: C, 68.4; H, 11.0: $C_{39}H_{75}O_4Br$ requires: C, 68.1; H, 10.9%).

These compounds had an Rf value of 0.8 by T.L.C. on silica gel G using hexane/ether 3:1 as eluent. For the diacyl-L-1-glycerol bromohydrins (M_D = 21, average value), the optical purity was proven by the complete hydrolysis of VII to its lyso compound by the stereo - specific enzyme, Phospholipase A.

Condensation of IV with silver dibenzyl phosphate[9], by four hours refluxing in the dark in a minimum volume of dry acetonitrile afforded excellent yields of the dibenzyl esters of the L-1-phosphatidic acid (V), which could be converted to the L-1-phosphatidic acids (VI) or their monobenzyl esters (VII) by standard procedures[1,3].



L-1-lecithins and cephalins can also be prepared from VII[10].

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6. D-mannitol was stirred at 35-37°C for 90 minutes in an acetone solution of anhydrous zinc chloride, filtered from unreacted mannitol (about 2% of starting material) and poured rapidly into cold potassium carbonate aqueous solution covered with ether (as in the Baer method[7]). The combined ether-acetone extracts were concentrated to a low bulk and the resulting aqueous solution cooled to 0°C, upon which the diisopropylidene mannitol crystallised out; and after filtering and drying by suction, washing with hexane gave the desired product in 55% yield (purity shown by T.L.C. on silica gel G using chloroform/methanol/conc. ammonia, 65:16:2 as eluent).

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point to 270°C, and gives a product with the correct silver content.

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