Synthesis of (±)-Otobain

By Iain Maclean and Robert Stevenson

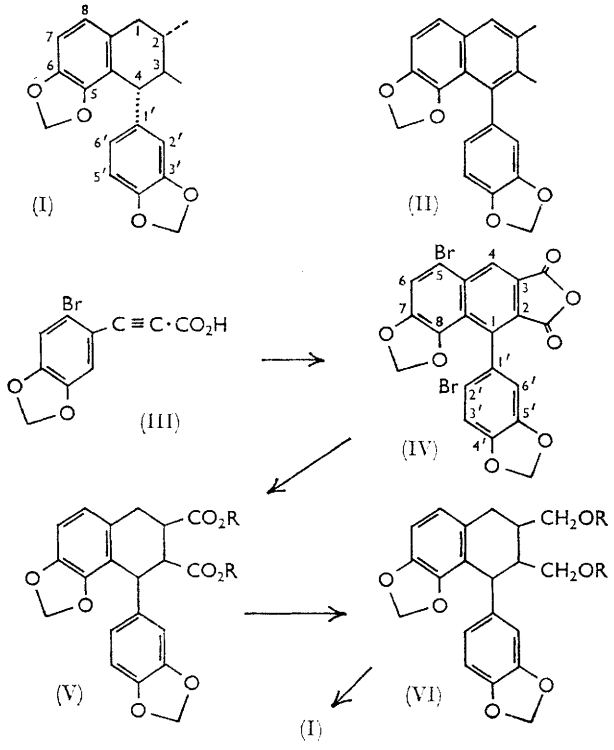
5-Bromo-1-(2-bromo-4,5-methylenedioxyphenyl)-7,8-methylenedioxynaphthalene-2,3-dicarboxylic acid anhydride, previously obtained from piperonal in three steps, was converted to (±)-otobain by consecutive treatment with sodium amalgam, lithium aluminium hydride, toluene-*p*-sulphonyl chloride, and lithium aluminium hydride.

OTOBAIN, a lignan of the aryltetralin class, first isolated in 1854 by Uricoechea,[1] was shown [2] in 1924 to have the empirical formula $C_{20}H_{20}O_4$, and recently [3,4] to have the constitution (I). The absolute configuration indicated in the formulation (I) has been assigned on the basis of optical rotatory dispersion measurements.[5] We now report a synthesis of (±)-otobain.[6]

It had been established in the synthesis [7] of dehydro-otobain (II), that 5-bromo-1-(2-bromo-4,5-methylenedioxyphenyl)-7,8-methylenedioxynaphthalene-2,3-dicarboxylic acid anhydride (IV) could be isolated from the reaction mixture obtained by treatment of 2-bromo-4,5-methylenedioxyphenylpropiolic acid (III) with *NN*-dicyclohexylcarbodi-imide. Starting from the dibromo-anhydride (IV), we sought to effect the selective reduction of ring B with sodium amalgam. The principal factor governing the choice of this reagent was the previous description of its use by Haworth and Woodcock [8] for the reduction of substituted aryl-naphthalenes to the desired aryltetralins, although these authors reported obtaining mixtures of stereo-isomeric modifications which at best required repeated and wasteful recrystallisations to yield a homogeneous

[1] E. Uricoechea, *Annalen*, 1854, **91**, 369.
[2] W. F. Baughman, G. S. Jamieson, and D. H. Brauns, *J. Amer. Chem. Soc.*, 1921, **43**, 199.
[3] N. S. Bhacca and R. Stevenson, *J. Org. Chem.*, 1963, **28**, 1638.
[4] T. Gilchrist, R. Hodges, and A. L. Porte, *J. Chem. Soc.*, 1962, 1780.
[5] W. Klyne, R. Stevenson, and R. J. Swan, *J. Chem. Soc.* (C), 1966, 893.
[6] Preliminary communication: I. Maclean and R. Stevenson, *Chem. and Ind.*, 1965, 1379.
[7] D. Brown and R. Stevenson, *J. Org. Chem.*, 1964, **30**, 1759.
[8] R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1939, 1237.

form. It was further hoped that sodium amalgam would remove the halogen atoms introduced initially as blocking groups to enforce cyclisation of the propiolic acid (III) in the desired manner to (IV), and that the methylenedioxy groups would be unaffected by the *reaction* conditions.



Treatment of compound (IV) with 4% sodium amalgam in aqueous sodium hydroxide gave an acid, isolated as a solid, which gave a negative Beilstein test but melted over a wide range. It was apparent from the ultraviolet spectrum [λ 235 (ε 7000) and 288 mμ (ε 5600)], which was typical of that reported for the otobain system,[3] that reduction of ring B had occurred. Without further purification, this acid (V; R = H) was esterified with diazomethane to give the ester (V; R = Me), which although not obtained in crystalline form, gave no evidence of inhomogeneity on thin-layer chromatographic examination. Reduction of either the acid or ester with lithium aluminium hydride yielded a fraction, showing hydroxyl absorption and lacking carbonyl absorption in the infrared (i.r.) spectrum, considered to be the diol (VI; R = H). Conversion of the hydroxymethyl groups of compound (VI; R = H) to methyl groups as in otobain was attempted by the route used by Carnmalm [9] and by Schrecker and Hartwell [10] in the synthesis of galbulin. Thus, treatment of the diol fraction with toluene-*p*-sulphonyl chloride in pyridine gave a mixture (at least three components were detected by thin-layer chromatography), which by preparative thin-layer chromatography yielded a major fraction whose i.r. spectrum showed absence of hydroxyl and presence of sulphonate ester absorption. This fraction was identified as the ditoluene-*p*-sulphonate (VI; R = Ts) by reduction with lithium aluminium hydride in tetrahydrofuran solution to yield the crystalline product, (±)-otobain (I) whose i.r. spectrum in chloroform solution was identical to that of naturally occurring (−)-otobain. It was further characterised by nitration to yield (±)-dinitro-otobain with i.r. and ultraviolet solution spectra identical to those of the dinitro-derivative obtained in the same manner from natural otobain.

A second synthesis of (±)-otobain employing a tetralone route has recently been reported.[11]

EXPERIMENTAL

Ultraviolet spectra were recorded in 95% ethanol solution using a Cary spectrophotometer, and infrared spectra using a Perkin-Elmer Infracord spectrophotometer.

5-Bromo-1-(2-bromo-4,5-methylenedioxyphenyl)-7,8-methylenedioxynaphthalene-2,3-dicarboxylic Acid Anhydride (IV).—To a solution of 2-bromo-4,5-methylenedioxyphenylpropiolic acid [7] (III) (33·0 g.) in dimethoxyethane (450 ml.) at −5° was added a solution of dicyclohexylcarbodi-imide (19·0 g.) in the same solvent (300 ml.) at the same temperature. The mixture was set aside at 0° for 72 hr., the precipitated dicyclohexylurea (12·4 g.) removed by filtration, and the filtrate evaporated under reduced pressure. The residue was crystallised once from benzene to give a yellow solid (8·0 g.), which was dissolved in a minimum volume of chloroform, diluted with benzene, and filtered through a column of silica (210 g., Grace, desiccant activated). Elution with benzene (4·5 l.) gave the anhydride (IV) as yellow needles (6·05 g.), m. p. 252—254°, ν (KBr) 1847 and 1775 (anhydride) and 1610 cm.$^{-1}$ (aromatic ring). M. p. 255—258° for analytical sample.[7]

Action of Sodium Amalgam on the Arylnaphthalene Anhydride (IV).—The anhydride (2·19 g.) was added to a solution of sodium hydroxide (0·4 g.) in water (40 ml.), followed by sodium amalgam (12·4 g.; 4%). The mixture was then heated on a steam-bath for 9 hr. under an atmosphere of carbon dioxide, diluted, filtered, and acidified with hydrochloric acid. The resultant white precipitate was extracted by shaking the aqueous suspension with ether, the extracts washed, dried ($MgSO_4$) and evaporated to give a solid (1·25 g.), m. p. 140—170° (dec.); negative Beilstein test; ν (KBr) 3600—2400 (carboxyl-OH) and 1710—1705 cm.$^{-1}$ (carboxyl-C=O); λ 235 (ε 7800) and 288 mμ (ε 5600). This product, regarded as crude 1,2,3,4-tetrahydro-7,8-methylenedioxy-1-(3,4-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic acid (V; R = H), was not further purified.

A solution of the crude dicarboxylic acid (245 mg.) in ether was treated with ethereal diazomethane at room temperature overnight; the mixture was then washed with sodium carbonate solution and water, dried ($MgSO_4$), and evaporated to yield a glassy solid (246 mg.), ν (KBr) 1745 cm.$^{-1}$ (ester), λ 232 (ε 8300) and 289 mμ (ε 6000), regarded as the dimethyl ester (V; R = Me). No indic-

[9] B. Carnmalm, *Acta Chem. Scand.*, 1954, **8**, 1827.
[10] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.
[11] T. B. H. McMurry and H. K. Kennedy-Skipton, *Tetrahedron Letters*, 1966, 975.

ation of inhomogeneity of this product was apparent from thin-layer chromatographic examination on silica gel.

(±)-*Otobain*.—(i) *Reduction of dicarboxylic acid* (V; R = H). A solution of the dicarboxylic acid (490 mg.) in ether (25 ml.) was heated under reflux with lithium aluminium hydride (1·05 g.) for 3·5 hr. Ice was added to the cooled mixture, which was then acidified with hydrochloric acid and extracted with ether. Evaporation of the washed and dried extract gave a brown oil (279 mg.) which was dissolved in chloroform and chromatographed on silica gel (10 g.) After elution with chloroform (220 ml.) had given a coloured oil, elution with 2% methanol in chloroform (110 ml.), yielded a glass (254 mg.), ν (KBr) 3350 cm.$^{-1}$ (hydroxyl), carbonyl absorption absent, λ 236 (ε 7300) and 288 mμ (ε 5500), considered to be the diol (VI; R = H). A similar reduction of the ester (V; R = Me) (1·075 g.) in tetrahydrofuran solution yielded the same product (510 mg.)

(ii) *Action of toluene*-p-*sulphony chloride on the diol* (VI; R = H). Freshly recrystallised toluene-*p*-sulphonyl chloride (1·20 g.) was added to a solution of the diol (226 mg.) in dry pyridine (25 ml.); the mixture was set aside at 20° for 1 day, diluted with water, and then extracted with chloroform. The extracts were washed successively with dilute hydrochloric acid, water, dilute sodium carbonate solution, and water, dried, and evaporated to yield a residual brown oil (293 mg.). Thin-layer chromatographic examination on silica gel G (0·025 cm.) with 5% ethyl acetate in chloroform as eluent indicated two major (R_F 0·78, 0·55) and one minor (R_F 0·83) constituents, located by spraying with 3% aqueous perchloric acid solution. The oil (210 mg.) was fractionated by preparative thin-layer chromatography (0·1 cm.) using the same solvent system, the fraction corresponding to R_F 0·78 extracted with chloroform and the extract evaporated to give the ditoluene-*p*-sulphonate (VI; R = Ts) as a colourless oil (141 mg.), ν ($CHCl_3$) 1605, 1370, and 1180 cm.$^{-1}$ (aromatic sulphonate ester), hydroxyl absorption absent; λ 227 (ε 23,900) and 289 mμ (ε 5500).

(iii) *Action of lithium aluminium hydride on the ditoluene-sulphonate* (VI; R = Ts). A solution of the ditoluene-sulphonate (210 mg.) in tetrahydrofuran (10 ml.) was added to a suspension of lithium aluminium hydride (245 mg.) in tetrahydrofuran (5 ml.); the mixture was heated under reflux for 2·5 hr., and worked up in the usual way *via* ether. Evaporation of the washed and dried ether extract yielded an oil (170 mg.) which was dissolved in light petroleum and chromatographed on alumina. Elution with benzene gave a solid (94 mg.) which was recrystallised from methylene chloride–methanol to give (±)-otobain as needles, m. p. 171—173°, λ 237 (ε 9500) and 288 mμ (ε 6800) (Found: C, 74·05; H, 6·2. $C_{20}H_{20}O_4$ requires C, 74·05; H, 6·2%). The i.r. spectrum (chloroform solution) was identical to that of an authentic sample of natural otobain (m. p. 137—138°, $[\alpha]_D$ −40°).

(±)-8,6′-*Dinitro-otobain*.* (±)-Otobain (24 mg.) was dissolved in acetic acid (*ca.* 4 ml.); nitric acid (0·5 ml.) was added, and the mixture heated on the steam-bath for 1 min., then set aside at room temperature for 30 min. Dilution with water yielded a precipitate which was collected, washed with methanol, and recrystallised from chloroform–methanol to give (±)-8,6′-*dinitro-otobain* as yellow needles, m. p. 246—248°, λ 249 (ε 17,200) and 347 mμ (ε 10,900) and i.r. spectrum (chloroform solution) identical with that obtained from a sample (m. p. 234—236°, $[\alpha]_D$ −170°) similarly obtained from (−)-otobain (Found: C, 58·1; H, 4·6. $C_{20}H_{18}O_8N_2$ requires C, 57·95; H, 4·4%).

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* Lignan aryl 1,2,3,4-tetrahydronaphthalenes are numbered as 4-aryltetralins (see ref. 5 for discussion of nomenclature).