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AN IMPROVED PREPARATION OF *TRANS*-4,5-DIHYDROXY-4,5-DIHYDROALDRIN, A METABOLITE OF HEOD (DIELDRIN) IN MAMMALS, INSECTS, AND MICROORGANISMS.

by

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The title compound is a metabolite of HEOD (dieldrin)≠ in mammals, insects and microorganisms (for review, see Brooks[1]). It was first prepared by Korte and Arent in 1965[2]. Their method involved refluxing HEOD in 40% aqueous methanolic sulphuric acid for 17 h, and separation of the product from by-products (80%) by extensive chromatography. We report here a quicker, alternative route to this compound from HEOD which requires no chromatography, and gives a yield of 20% of recrystallized, analytically pure material.

The systematic name for this compound, which complies with the suggestions of Benson[3] concerning the nomenclature of organochlorine cyclodiene pesticides, is 1,8,9,10,11,11-hexachloro-4,5-*trans*-dihydroxy-2,3-7,6-*endo*-2,1-7,8-*exo*-tetracyclo$[6.2.1.1^{3,6}.0^{2,7}]$ dodec-9-ene (see II).

≠ Dieldrin contains not less than 85% of the compound, 1,8,9,10,11,11-hexachloro-4,5-*exo*-epoxy-2,3-7,6-*endo*-2,1-7,8-*exo*-tetracyclo$[6.2.1.1^{3,6}.0^{2,7}]$dodec-9-ene(HEOD).

Experimental

Melting points were determined on a hot-stage microscope, and are corrected. Infrared spectra were recorded as mulls (nujol) or solutions (CCl_4) on a Perkin Elmer 137 spectrophotometer. NMR spectra were recorded on a Varian HA-100spectrometer using tetramethylsilane as internal standard. Chemical shifts are reported in order of increasing τ, with multiplicities: s = singlet, d = doublet, t = triplet, b.s = broad singlet, b.d = broad doublet and m = multiplet. Mass spectra were determined on an AEI-MS9 spectrometer. Thin-layer plates (Kieselgel, *ex* Merck) were developed with system A: chloroform/acetic acid (9:1), or system B: benzene/ethyl acetate (9:1). For the detection of spots, plates were lightly sprayed with a freshly-made 0.5% solution of silver nitrate in water/2-phenoxyethanol/acetone (1:2:37), and then exposed to uv light for a few minutes. Chlorine-containing compounds gave black spots on a grey background.

Gas-liquid chromatographic analysis was carried out on a Pye 104 gas chromatograph equipped with an electron capture detector, using a glass column (1.5 m x 6 mm) containing 3% SE30 on Gas Chrom Q, with nitrogen as carrier gas (flow = 120 ml min^{-1}). The column and detector temperatures were respectively 190° and 290°.

Solvents and reagents were of analytical grade.

Acetolysis of HEOD (I)

Reflux 5 g HEOD (>99%) in a mixture of 40 ml acetic acid, 2 ml H_2O, and 2 ml c.H_2SO_4 for 1 h. Add 40 ml acetic anhydride, and reflux for 1 h. Pour the cooled reaction mixture into 100 ml hexane, and isolate the upper layer. Re-extract the lower layer with hexane

(2 x 100 ml) and wash the combined hexane extracts with water (4 x 100 ml). Dry the solution over Na_2SO_4 and evaporate the hexane *in vacuo*.

Dissolve the crude product (4.59 g) in 100 ml hot methanol and then distil off 50 ml methanol. Set aside for 16 h. Filter off the crystals (2.3 g), and recrystallize from 50 ml methanol to yield 1.9 g (30%) of pure *trans*-4,5-diacetoxy-4,5-dihydroaldrin, m.p. 159-161°, (Found:C, 39.9; H, 2.9%. Calc. for $C_{16}H_{14}O_4Cl_6$: C, 39.78; H, 2.92%); ν(nujol) = 1742, 1736, 1597, 1250 cm^{-1}; $\tau(CDCl_3)$ = 5.16 (5-CH, b.d, J ∿ 4 Hz), 5.61 (4-CH, b.s), 6.88 (7-CH, d, J8Hz), 7.19 (2-CH, d, J8Hz), 7.25 (3-CH, b.d, J ∿ 4Hz), 7.51 (6-CH, b.s), 7.87 (CH_3CO), 7.92 (CH_3CO), 8.46 (12-CH_2, b.s); tlc Rf 0.71 (A), 0.40 (B) (HEOD: Rf 0.73 (A), 0.48 (B)); glc R_t, 12.15 min, (HEOD: R_t, 3.75 min); mass spectrum, m/e 480(M^+), 445, 437, 403, 395, 385, 325, 300, 235, 167, 107, 79, 43(100%).

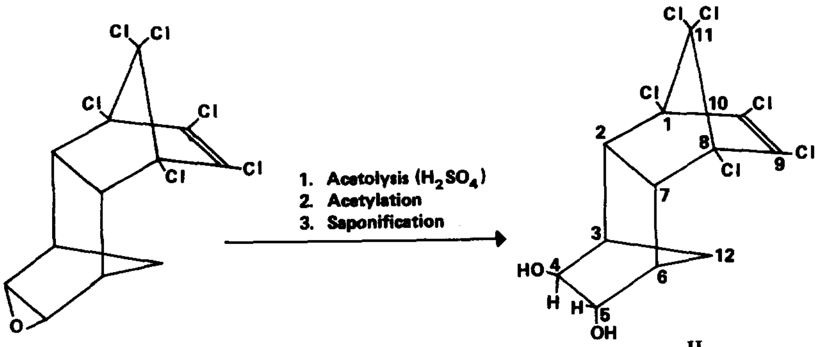
Saponification

Reflux 1.9 g of the diacetate in 50 ml 90% methanolic 1M KOH for 0.5 h. Cool and dilute with 200 ml ice-water. Extract with 3 x 100 ml diethyl ether, and wash the combined extracts with 50 ml 1N H_2SO_4, and 50 ml water. Dry the extract over Na_2SO_4. Evaporate the solvent and dissolve the residue in 10 ml methanol. Add decolourizing charcoal, boil, filter, and evaporate to a clear gum. Crystallize and recrystallize from CH_2Cl_2/hexane to yield 1.2 g of pure *trans*-4,5-dihydroxy-4,5-dihydroaldrin, (II) m.p. 134-136°, (Found: C, 36.1; H, 2.5%. Calc for $C_{12}H_{10}O_2Cl_6$: C, 36.12; H, 2.5%); ν (CCl_4) = 3610 cm^{-1},

ν(nujol) = 3225, 1600 cm^{-1}; τ ($CDCl_3$) = 6.14 (5-CH, b.d, J ∿ 4.5 Hz), 6.63 (4-CH, b.s), 6.69 (7-CH, d, J8Hz), 7.23 (4,5-COH,s), 7.37((2-CH, d, J8Hz), 7.51 (3-CH, b.d, J4.5Hz), 7.71 (6-CH, b.s), 8.52 (12-CH_2, b.s); tlc Rf 0.26(A), 0.025(B); mass spectrum, m/e 396(M^+), 361, 325, 300, 125, 107, 85, 83, 79, 67(100%).

DISCUSSION

The method we have employed for the improved preparation of trans-4,5-dihydroxy-4,5-dihydroaldrin is a three-step sequence involving (i) sulphuric acid-catalyzed acetolysis of HEOD (I) in aqueous acetic acid at 110-115°, (ii) acetylation of the crude product to give the diacetate of the required diol, and (iii) saponification of the purified diacetate to the diol (II).



I

II

Fig 1

We were guided in our choice of conditions by some previous reports of acid treatment of HEOD. A 70% yield of α-bromohydrin was obtained with HBr in dry dioxan [4], and an unrecorded yield of the corresponding bromoacetate with HBr/acetic acid/acetic anhydride [5]. BF_3 in benzene converted HEOD into an isomeric ketone, 4-keto-4,5-dihydroaldrin [6]. Reaction with H_2SO_4/acetic anhydride yielded the orthoacetate of the same ketone [7,8], *cis*-4,5-diacetoxy-4,5-dihydroaldrin [9], and two novel skeletal rearrangement products (a monoacetate and a diacetate) of partly determined structures [10]; interestingly no *trans*-4,5-diacetoxy-4,5-dihydroaldrin was found [10]. We thus considered that acetolysis in neat acetic acid might favour the formation of undesired rearrangement products. In the event, the choice of acetic acid/water (20:1) proved to be a felicitous one, for with a reaction temperature 50-60° higher than that attained by Korte and Arent complete solvolysis of HEOD was effected within 1.5 h, and after *in situ* acetylation of the solvolysis mixture with acetic anhydride the diacetate of the required *trans*-diol was formed in 58% yield. Two fractional crystallizations from methanol yielded the pure diacetate, which had m.p. 159-161°, in agreement with the value (161°) cited by Korte and Kochen [11]. Saponification of the *trans*-diacetate was quantitative, and *trans*-4,5-dihydroxy-4,5-dihydroaldrin, m.p. 134-136°, was obtained pure after one recrystallization in 20% overall yield. Full physical data (mass spectrum, ir, nmr and tlc), with assignments as appropriate, are recorded in the experimental section for both these compounds.

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