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RESOLUTION OF THE OPTICAL ISOMERS OF *o,p'*-DDT

William A. McBlain and Fred H. Wolfe*

Department of Zoology and Department of Food Science
University of Alberta, Edmonton, Alberta, Canada T6G 2E1

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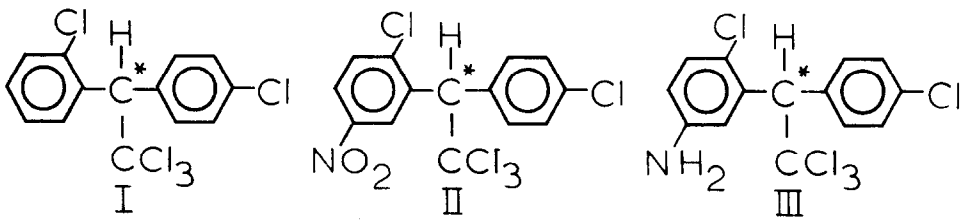
The estrogenic activity of *o,p'*-DDT[1] (I) has been amply documented by a number of workers[2]. It has not been reported, however, that the presence of a single asymmetric carbon atom (C-1) in *o,p'*-DDT and its asymmetric analogs[3] allows for their existence as enantiomeric forms. Since the reported estrogenicity of *o,p'*-DDT has recently been shown to be subject to biological stereoselectivity[4] we present here the preliminary results of the first resolution of *o,p'*-DDT.

Racemic *o,p'*-DDT (mp. 72-73°C)[5] was nitrated at 0°C with fuming nitric acid in acetic anhydride utilizing carbon tetrachloride as a cosolvent and sulfuric acid as a catalyst[6]. This reaction, monitored by TLC (silica gel G with 20% diethyl ether in hexane as the developing solvent), produced 5 compounds of which a mononitrated derivative (II) predominated. From NMR spectra the unique resonance of the strongly deshielded ortho proton on the *o*-Cl ring of *o,p'*-DDT[7] was an excellent indicator of the presence and position of substitutions on this ring. The nitration was stopped at 2 hr. so that the production of the previously described dinitro derivative[8] was not excessive and compound II (mp. 138-140°C) was crystallized from ethanol following purification on an acid-washed alumina column eluted with 20% diethyl ether in hexane (yield



39.3%). The corresponding monoamine (III) (mp. 108-111°C; mp. of the hydrochloride 184-194°C with decomposition) formed by the reduction of the nitro compound in the presence of tin, hydrochloric acid and ethanol[9] was converted to its *d*-10-camphorsulfonate salt (mp. 177-183°C with decomposition). After 5 crystallizations or 3 refluxes[10] from acetonitrile the salt (mp. 297-298°C with decomposition) yielded a levo amine whose rotation ($[\alpha]_D^{25}$ = -170.1, c = 0.55, ethanol) was unimproved by further salt crystallizations or refluxes. Although refluxing racemic or levo-enriched salts in acetonitrile had led to purification of the levo amine, refluxing of dextro-enriched salts unexpectedly led to purification of the dextro amine. Therefore the combined salts recovered from the mother liquors of the above refluxes were further refluxed 6 times and the resultant salt (mp. 288-290°C with decomposition) yielded the dextro amine ($[\alpha]_D^{25}$ = 166.4, c = 0.75, ethanol). Deamination via diazonium salts[11] gave the *o,p'*-DDT enantiomers

with specific rotations of -17.9° and 17.7° respectively ($[\alpha]_D^{25}$ = -17.9, c = 5.05, ethanol; $[\alpha]_D^{25}$ = 17.7, c = 2.22, ethanol). Both enantiomers melted at 73-75°C and gave NMR and GLC analyses typical of (±) *o,p'*-DDT. A 1% contamination of the starting material with *p,p'*-DDT, as revealed by GLC, was eliminated during the resolution process. The above technique may prove useful for the resolution of medically important *o,p'*-DDD[3].

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References and Notes

1. The commercial insecticide, DDT, is technical grade DDT, a mixture of compounds including about 80% *p,p'*-DDT (1,1'-(2,2,2-trichloroethylidene) *bis* [4-chlorobenzene]) and 15-20% *o,p'*-DDT (1-chloro-2-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]-benzene.
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3. The asymmetric analogs *o,p'*-DDD (1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]-benzene) and *o,p'*-DDA (2-chloro-α-(4-chlorophenyl)-benzeneacetic acid) as well as the related *o,m'*- and *m,p'*- derivatives are also racemates. Unresolved *o,p'*-DDD has been used as a chemotherapeutic agent in the treatment of Cushing's syndrome and adrenocortical carcinoma. See J.A. Lubitz, L. Freeman, R. Okun, J. Amer. Med. Assoc. 223, 1109 (1973); P.C. Sizonenko, A. Doret, A. Riondel, L. Paunier, Helv. Paediat. Acta 29, 195 (1974).
4. We have found that only the ℓ enantiomer of *o,p'*-DDT is a potent estrogen in immature female rats and Japanese quail (manuscript in preparation).
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