95. *The Configuration of Heterocyclic Compounds. Part V. Thianthren and Phenoxthionine Derivatives.*

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It has been shown, on the one hand, from observations of polarisation in solution, that thianthren has a folded structure, whilst diphenylene dioxide is wholly planar (Bergmann and Tschudnowsky, *Ber.*, 1932, **65**, 458; Bennett and Glasstone, J., 1934, 128, 1179), and, on the other hand, by the isolation of optically active forms, that 10-methyl-, 10 ethyl-, and 10-phenyl-phenoxarsine-2-carboxylic acids possess dissymmetric molecules (Lesslie and Turner, J., 1934, 1170; 1935, 1268; 1936, 730). Of two alternative explanations of this dissymmetry, that involving the assumption of a folded structure is preferred to that requiring a stable "asymmetric tervalent arsenic atom," and it seems probable that the particularly high optical stability of the phenoxarsines mentioned is largely due to the very considerable difference in size of the oxygen and arsenic atoms.

It was nevertheless essential to prepare, and attempt the resolution of, suitably substituted thianthrens, in order to see if the undoubted folding was sufficiently stable to permit of optical activity. We have therefore prepared a *thianthren*-2(or 1)-*carboxylic acid* and have examined it from this point of view. Its crystalline l-α-*phenylethylamine* salt was repeatedly crystallised, but it appeared to be entirely homogeneous, and the acid liberated from it was optically inactive. Similarly, the base 2-aminothianthren (Krishna, J., 1923, **123**, 156) was found to yield a crystalline *d*-camphorsulphonate, but this could not be resolved. These negative results tend to confirm the conclusion recently reached as a result of a study of the isomeric sulphoxides of substituted thianthrens (Baw, Bennett, and Dearns, J., 1934, 680) in which none of the additional isomerides required by the stable folded configuration were, in fact, detected.

In phenoxthionine, according to our hypothesis, there might be an increased tendency to stable folding, since the sulphur atom is considerably larger than the oxygen atom. In fact, we found that neither 3-*nitro*-8-*methylphenoxthionine*-1-*carboxylic acid* nor *phenoxthionine*-2(or 1)-*carboxylic acid* could be resolved under the experimental conditions we employed. In view of the negative results of the resolution experiments, we did not regard it as necessary to orientate the phenoxthioninecarboxylic acid, but after this work had been completed, Suter, McKenzie, and Maxwell (*J. Amer. Chem. Soc.*, 1936, **58**, 717) described phenoxthionine-2-carboxylic acid as melting at 260—262°, whereas Mauthner (*Ber.*, 1906, **39**, 1340) had already described the 3-isomeride as melting at 223°. Our acid melted somewhat indefinitely at 230—238° and is almost certainly a pure substance, as it was prepared by recrystallisation of the *strychnine* salt and was itself repeatedly crystallised without showing signs of being a mixture.

Experimental.

Thianthren-2(?)-*carboxylic Acid*.—Thianthren (20 g.) was heated with phenylethylcarbamyl chloride (19 g.) and fused zinc chloride (20 g.) in an oil-bath at 160—170° for 4 hours. The mixture was boiled for 1½ hours with an aqueous-alcoholic solution of sodium hydroxide (50 g.), poured into water, heated, and filtered. Acidification of the filtrate yielded the carboxylic *acid* (average yield 1·5 g.), which was purified by dissolution in hot aqueous sodium carbonate solution and reprecipitation. It crystallised from glacial acetic acid in spherical aggregates of minute crystals, m. p. 224° (Found : C, 59·8; H, 3·1; equiv., by titration, 261·2. $C_{13}H_8O_2S_2$ requires C, 60·0; H, 3·1%; equiv., 260·2). The *amide* formed bunches of plates, m. p. 227°, from ethyl alcohol (Found : C, 60·6; H, 3·7. $C_{13}H_9ONS$ requires C, 60·2; H, 3·5%); the *anilide* separated from ethyl alcohol in radiating blade-shaped crystals, m. p. 200—201° (Found : C, 67·6; H, 4·2. $C_{19}H_{13}ONS_2$ requires C, 68·1; H, 3·9%).

Attempted Resolution of Thianthrencarboxylic Acid.—A solution of the acid (7·7 g.) with *l*-α-phenylethylamine (3·6 g.) in hot ethyl alcohol (200 c.c.) yielded on cooling and by subsequent evaporation a succession of crops of l-α-*phenylethylamine thianthrencarboxylate*, which crystallised in rectangular plates, m. p. 286—288° (Found : C, 65·7; H, 5·0. $C_{21}H_{19}O_2NS_2$ requires C, 66·1; H, 5·0%). The first crop (5·2 g.) of this salt separated in needles which had $[\alpha]_{5791}$ − 3·4°, $[\alpha]_{5461}$ − 3·8° in methyl alcohol ($l = 2$; $c = 1·461$: $\alpha_{5791} = -0·10°$, $\alpha_{5461} = -0·11°$). The second crop (after concentration of the mother-liquors; 2·7 g.) had $[\alpha]_{5791}$ − 3·5°, and a third crop had $[\alpha]_{5791}$ − 3·3°. On recrystallisation, each crop separated in rectangular plates. The first (2·2 g.) had $[\alpha]_{5791}$ − 3·4° and the second (1·0 g.) had $[\alpha]_{5791}$ − 3·3°. The acid obtained by decomposition of these various crops was in each case optically inactive.

Attempted Resolution of 2-*Aminothianthren.*—The base, prepared from chloronitrobenzenesulphinic acid by Krishna's method (*loc. cit.*), formed a well-crystallised salt with *d*-camphor-10-sulphonic acid, which separated from hot ethyl acetate in minute plates, m. p. 278°, but no evidence was obtained of any resolution : the colour of the solutions made polarimetric observation very difficult.

Preparation of 3-*Thiol*-p-*tolyl Carbonate.*—(a) *p*-Cresol (1 kg.), sulphonated by the method of Zincke and Kempf (*Ber.*, 1911, **44**, 413), yielded potassium *p*-cresol-3-sulphonate dihydrate (1600 g., air-dried).

(b) This salt was converted into its *O*-carbethoxy-derivative following the method of Zincke and Arnold (*Ber.*, 1917, **50**, 116) except that the proportion of water used was half that recommended by these authors, as this reduced amount accelerated the condensation and facilitated the isolation of the product. Yield, 362 g. of carbethoxy-derivative from 400 g. of potassium salt without evaporation of the mother-liquor.

(c) The potassium *O*-carbethoxy-sulphonate was heated with phosphorus pentachloride at 130° for 1 hour as recommended by Prof. S. Smiles (private communication), not for 4—5 hours as described by Zincke and Arnold (*loc. cit.*), since the shorter heating improved the yield (to over 98%) and the quality of the *O*-carbethoxy-*p*-cresol-3-sulphonyl chloride obtained.

(d) The sulphonyl chloride was reduced to the cyclic carbonate by Zincke and Arnold's method (yield 40%, not 70—80% as reported by these authors).

Preparation of 3-*Nitro*-8-*methylphenoxthionine*-1-*carboxylic Acid.*—The method used was Prof. Smiles's modification of Mauthner's process (*Ber.*, 1906, **39**, 1340). A solution of the thioltolyl carbonate (16·6 g., 1 mol.) and potassium hydroxide (30 g.) in aqueous alcohol (150 c.c. of water; 100 c.c. of alcohol) was boiled under reflux for ½ hour. 2-Chloro-3 : 5-dinitrobenzoic acid (24·6 g., 1 mol.), dissolved in aqueous potassium hydroxide (7·5 g. of 82% KOH, 1 mol., in 50 c.c. of water), was then gradually added, and the mixture boiled for a further ¾ hour, cooled, and filtered. The potassium salt so obtained was suspended in much hot water and decomposed with hydrochloric acid. The liberated 3-*nitro*-8-*methylphenoxthionine*-1-*carboxylic acid* was dried at 100° (yield about 40%); it then crystallised from ethyl alcohol in orange clusters of slender needles, m. p. 253—254° (Found : C, 55·4; H, 3·1; N, 4·6. $C_{14}H_9O_5NS$ requires C, 55·4; H, 3·0; N, 4·6%). The dry acid provokes violent sneezing.

Attempted Resolution of 3-*Nitro*-8-*methylphenoxthionine*-1-*carboxylic Acid.*—To a hot solution of the acid (15 g.) in 3,500 c.c. of absolute ethyl alcohol, brucine (21·4 g.) was added. The solution, on being kept, deposited 20·6 g. of slender needles having $[\alpha]_{5791}$ − 3·4° (in chloroform). Progressive concentration of the mother-liquor gave a second crop (3·7 g.) having $[\alpha]_{5791}$ − 3·8°, and third and fourth crops having $[\alpha]_{5791}$ − 3·2° and −3·6°, respectively.

Each crop was extracted four times with 100 c.c. of boiling alcohol, and the extract allowed to cool. All the secondary crops so obtained had rotations similar to those above, and they all yielded an optically inactive acid when freed from alkaloid. The addition of less than 1 equivalent of brucine to solutions of the acid always yielded a mixture of salt with free acid and was therefore useless.

Preparation of Phenoxthioninecarboxylic Acid.—*Phenoxthionine.* The preparation of phenoxthionine was improved as follows : diphenyl ether (340 g.) was heated to 80—90°, and sulphur (64 g.) added with stirring. Anhydrous aluminium chloride (134 g.) was then added in three lots at 70°, and, after the vigorous reaction had subsided, the temperature was raised to 100° and stirring continued until no further evolution of hydrogen sulphide was observed (4 hours). The mixture was treated with dilute hydrochloric acid and extracted with chloroform, the extract dried over calcium chloride and distilled. Unchanged diphenyl ether was recovered, and 176 g. of crude phenoxthionine (yield 88% from 170 g. of diphenyl ether) obtained of b. p. 183—184°/12 mm. After two crystallisations from ethyl alcohol, it melted at 57—58° (129 g.). Suter and co-workers (*loc. cit.*) obtained 119 g. of crude phenoxthionine from 340 c.c. of diphenyl ether, and 115—116 g. of pure product.

Phenoxthioninecarboxylic acid. A mixture of 100 g. of phenoxthionine and 90 g. of phenylethylcarbamyl chloride was heated at 100°, and powdered anhydrous zinc chloride (1 mol.) added. The mixture was heated at 190—200° for 2 days, and then extracted with hot dilute hydrochloric acid. The residual tar was boiled with alcoholic potassium hydroxide, the mixture diluted, and the solution decanted from the oil. This process was repeated, and the combined alkaline solutions, on acidification, yielded the crude acid. This was dissolved in very dilute aqueous sodium bicarbonate (the sodium salt of the acid being very sparingly soluble in water), the solution filtered, and acidified. The *phenoxthioninecarboxylic acid* (yield 20 g.) crystallised from xylene or from aqueous alcohol in needles (11 g.), m. p. 230—238° (Found: C, 64·3; H, 3·4. $C_{13}H_8O_3S$ requires C, 63·9; H, 3·3%).

When this acid was converted into its strychnine salt, the latter recrystallised from alcohol, the acid regenerated, and itself recrystallised from dilute alcohol, the acid (8·2 g.) so obtained had m. p. 230—238°.

Attempted Resolution of Phenoxthioninecarboxylic Acid.—(a) *With strychnine.* The acid (3·1 g.) was dissolved in hot alcohol, and strychnine (1·3 g.; $\frac{1}{3}$ mol.) added. On cooling, 1·25 g. of the salt crystallised, which had $[\alpha]_{5791}$ − 8·4°, $[\alpha]_{5461}$ − 10·3° in chloroform ($l = 2$; $[\alpha]_{5791} = -0{\cdot}35°$, $[\alpha]_{5461}$ − 0·43°, *c*, 2·087). To the heated mother-liquor a second portion of strychnine was added (1·3 g.). The crop of salt (3·1 g.) which subsequently separated had $[\alpha]_{5791}$ − 9·4°, $[\alpha]_{5461}$ − 11·5°. A third similar addition of the base to the mother-liquor gave rise to a further 1·85 g. of salt having $[\alpha]_{5791}$ − 9·3°, $[\alpha]_{5461}$ − 11·4°.

Recrystallisation of these three crops from ethyl alcohol yielded salts with approximately the same rotations, *viz.*, $[\alpha]_{5791}$ − 9·1°, $[\alpha]_{5461}$ − 10·9°. *Strychnine phenoxthioninecarboxylate* formed leaflets, m. p. 178—179° (Found: C, 69·9; H, 5·7. $C_{34}H_{30}O_5N_2S,\frac{1}{2}EtOH$ requires C, 69·9; H, 5·5%). The presence of ethyl alcohol in the dry crystals was confirmed by direct test.

(b) *With* l-α-*phenylethylamine.* The acid (15 g.) and the base (7·5 g.) were dissolved in 100 c.c. of hot ethyl alcohol. On cooling, a salt separated which had $[\alpha]_{5791}$ − 3·1°, $[\alpha]_{5461}$ − 4·1° ($l = 2$; $c = 1{\cdot}472$; α_{5791} − 0·09°, α_{5461} − 0·12°) in methyl alcohol. Concentration of the mother-liquor gave successive crops with $[\alpha]_{5791}$ − 3·4°, − 4·2°, − 4·6°, and − 4·3°. Recrystallisation of the first crop gave fractions with $[\alpha]_{5791}$ varying from − 4·0° to − 4·8°. After repeated crystallisation, crops were obtained with rotations ranging from − 3·25° to − 4·6°, but the extreme specimens when decomposed gave an acid the rotatory power of which was negligible. The l-α-*phenylethylamine* salt crystallised from ethyl alcohol in needles, m. p. 188—189° (Found: C, 68·9; H, 5·3. $C_{21}H_{19}O_3NS$ requires C, 69·0; H, 5·2%).

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