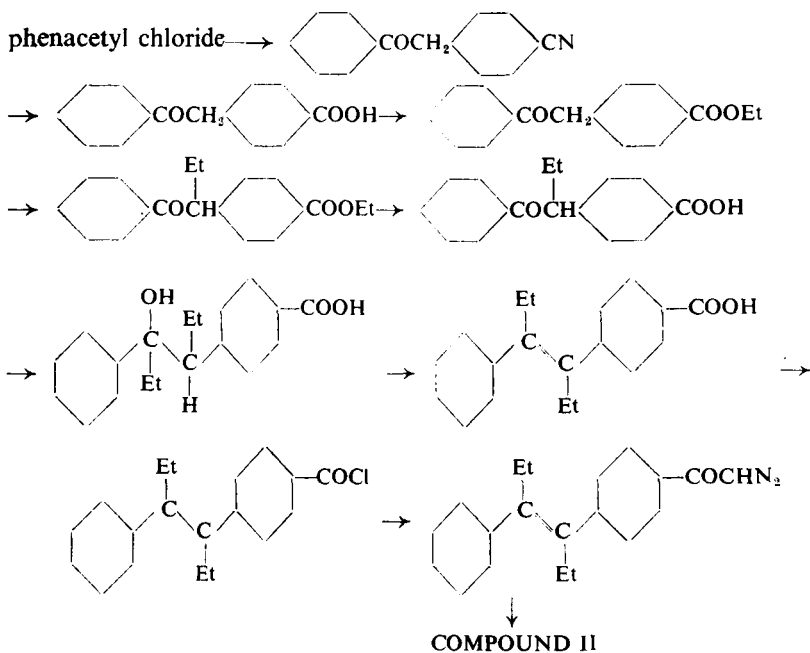


CORTICOSTERONE-LIKE COMPOUNDS

Benzyl cyanide → *p*-nitrobenzyl cyanide → *p*-nitrophenylacetic acid
 → *p*-aminophenylacetic acid → *p*-cyanophenylacetic acid → *p*-cyano-



β -Naphthaleneacetyl carbinol was prepared by a similar method from β -naphthaleneacetic acid and was obtained as a low-melting solid, soluble in boiling water.

Preliminary pharmacological tests, for which we are indebted to Professor Buttle and Dr. Dyer of the Pharmacological Department of this School, indicate that 4-(ω -hydroxyaceto): β -diethylstilbene (II) is less active than its corresponding 4'-hydroxy derivative. The naphthaleneacetyl carbinol was found to be inactive at the dose levels used.

This work is being extended to cover other derivatives of naphthalene and hydroxyaceto derivatives of such other systems as may be in any way considered as fragments of the cyclopentenophenanthrene nucleus, including a thorough exploration of the indene skeleton from this point of view.

EXPERIMENTAL

4-Cyanodesoxybenzoïn.— $C_6H_5.CO.CH_2.C_6H_4.CN$

p-Nitrobenzyl cyanide was obtained in 57 per cent. yield, converted into the corresponding acid (yield 90 per cent.) which was then reduced to *p*-aminophenylacetic acid (yield 85 per cent.) according to the method of Robertson^{4,5,6}. This compound was converted into *p*-cyanophenylacetic acid by following the process of Jaeger and Robinson⁷ when a 59 per cent. yield was realised. 5 g. of phosphorus trichloride was added to 10 g. of dry *p*-cyanophenylacetic acid and the mixture heated on a water-bath till completely liquid. While still warm, 50 ml. of dry benzene

was added and the benzene solution decanted on to 10 g. of anhydrous aluminium chloride. When the spontaneous reaction had subsided the mixture was refluxed for 1 hour, cooled and poured into a solution of 25 ml. of concentrated hydrochloric acid in 500 ml. of cold water. The benzene layer was separated, the aqueous portion was washed with benzene and the washings combined with the benzene solution. The solvent was removed by distillation and the yellow sticky residue was crystallised from a small quantity of alcohol (97 per cent.) when 4'-cyanodesoxybenzoin was obtained as light yellow crystals melting at 105° to 106°C. Yield 5.7 g. (41 per cent.). Found : C, 80.1 ; H, 5.0 ; N, 6.33 per cent. ; $C_{15}H_{11}OH$ requires C, 81.4 ; H, 4.9 ; N, 6.35 per cent.

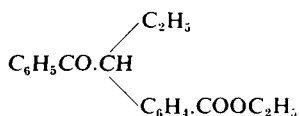
4'-Carboxydesoxybenzoin.— $C_6H_5.CO.CH_2.C_6H_4.COCH$

1 g. of 4'-cyanodesoxybenzoin was refluxed with 25 ml. of glacial acetic acid, 25 ml. of water and 25 ml. of concentrated sulphuric acid for 5 hours and poured into an equal volume of cold water. The thick white precipitate was collected, washed with cold water and crystallised from 60 per cent. acetic acid. After purification by animal charcoal and recrystallisation from 60 per cent. acetic acid, 4'-carboxy-desoxybenzoin was obtained as shining white flakes melting at 209°C. (decomp.). Yield 0.75 g. (63 per cent.). Found : C, 74.3 ; H, 5.1 ; per cent. $C_{15}H_{12}O_3$ requires C, 75.0 ; H, 5.0 per cent.

4'-Carbethoxydesoxybenzoin.— $C_6H_5.CO.CH_2.C_6H_7.COOC_2H_5$

4'-Carboxydesoxybenzoin was esterified by bubbling hydrogen chloride through an alcoholic solution of 3 g. of the acid and refluxing the mixture at the same time when a quantitative yield of 4'-carbethoxydesoxybenzoin was obtained as pale shining flakes melting at 106°C. Found C, 75.1 ; H, 6.02 per cent. ; $C_{17}H_{16}O_3$ requires C, 76.1 ; H, 5.97 per cent.

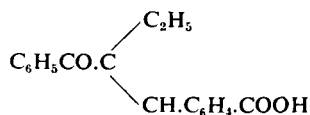
4'-Carbethoxy- α -ethyl-desoxybenzoin.—



2.5 g. of 4'-carbethoxydesoxybenzoin was dissolved in 10 ml. of boiling absolute alcohol and to the boiling solution 0.5 g. of sodium in 5 ml. of absolute alcohol and 3.3 g. of ethyl iodide were added ; the mixture being heated until neutral to litmus. A further quantity of 0.5 g. of sodium in 5 ml. of absolute alcohol and 3.3 g. of ethyl iodide was added and the mixture again refluxed until neutral. After cooling and dilution with water, the alcohol was removed under reduced pressure. The oily suspension was extracted with ether and the ethereal solution well washed with water, 5 per cent. sodium thiosulphate solution and water. After drying overnight the ether was removed by distillation and 4'-carbethoxy-ethyl-desoxybenzoin was obtained as a bright yellow oil which solidified to a glassy substance. Yield 2.1 g. (90 per cent.). Found : C, 77.0 ; H, 6.79 per cent. ; $C_{19}H_{20}O_3$ requires C, 77.02 ; H, 6.75 per cent.

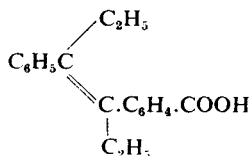
CORTICOSTERONE-LIKE COMPOUNDS

4'-Carboxy- α -ethyl-desoxybenzoin.—



2.1 g. of 4'-carbethoxy- α -ethyl-desoxybenzoin was saponified with 110 ml. of N/10 alcoholic potassium hydroxide solution. The crude oily substance was crystallised from 70 per cent. acetic acid, when fine white crystals of 4'-carboxy- α -ethyl-desoxybenzoin melting at 126° to 127°C. were obtained. Yield 1.42 g. (75 per cent.). Found : C, 75.98 ; H, 5.95 per cent. : $\text{C}_{17}\text{H}_{16}\text{O}_3$ requires C, 76.11 ; H, 5.97 per cent.

4'-Carboxy- α : β -diethylstilbene.—



A cold ethereal solution of ethyl magnesium iodide (prepared by adding 1.65 g. of ethyl iodide to 0.25 g. of dry magnesium in ether) was added slowly with frequent shaking to a solution of 2.7 g. of 4'-carboxy- α -ethyl-desoxybenzoin in dry ether. The reaction mixture, protected from moisture, was left overnight and then refluxed for 3 hours. The resulting product was decomposed with ice and dilute sulphuric acid, and the product worked up in the usual way after which the oily residue was heated on a water-bath with 1 to 2 per cent. of iodine under an air condenser for 1 hour. The residue, dissolved in ether, was washed with water and 5 per cent. sodium thiosulphate solution and dried overnight. The solvent was removed by distillation and 2 g. of a dark brown oil was obtained. From boiling 90 per cent. acetic acid, on scratching the sides of the vessel and standing, it gave a white powder melting at 95° to 100°C. Titration with N/125 sodium hydroxide indicated a purity of 96.1 per cent. Its acid chloride prepared as described below gave a crystalline 4-amido-derivative melting at 94°C. Found : N, 4.79 per cent. ; $\text{C}_{19}\text{H}_{11}\text{ON}$ requires N, 5.01 per cent.

4-(*o*-Hydroxyaceto)- α : β -diethylstilbene.— $\text{C}_{18}\text{H}_{19}\cdot\text{COCH}_2\text{OH}$

1.5 g. of 4-carboxy- α : β -diethylstilbene was converted into its acid chloride by boiling with 5 ml. of dry benzene and 5 ml. of thionyl chloride. The acid chloride in dry ether was treated with an ethereal solution of diazomethane (prepared from 10 g. of nitrosomethylurea) and the mixture kept at 6°C. for 1 hour and then allowed to stand overnight at room temperature. After removing the excess of diazomethane and the solvent, the diazoketone, obtained as a dark oil, was dissolved in 10 ml. of dioxan and, on addition of 15 ml. of 2N sulphuric acid, nitrogen was liberated during about half an hour, after which the reaction mixture was warmed to 40° to 45°C. when no more gas was evolved. It was then diluted with water and extracted with ether. The ethereal solution was washed

with water and a small quantity of 1 per cent. sodium bicarbonate solution. After drying the ethereal solution, ether was removed by distillation and the dark oil distilled under vacuum. 4-(*o*-Hydroxyaceto)- α : β -diethylstilbene was obtained as a yellow oil boiling at 175 to 180°C. 5 mm.Hg. Yield 0.8 g. (40 per cent.). Found C, 78.8; H, 7.5 per cent.: $C_{20}H_{22}O_2$ requires C, 81.2; H, 7.6 per cent. It was soluble in ether, alcohol, acetone, benzene, chloroform and toluene, but insoluble in water. It reduced cold ammoniacal silver nitrate solution and gave an osazone with 2:4-dinitrophenylhydrazine, which, on recrystallisation from toluene, melted at 115°C. Found: N, 17.5 per cent.: $C_{32}H_{28}O_8N_8$ requires N, 17.18 per cent.

β -Naphthaleneacetyl carbinol.— $C_{10}H_7 \cdot CH_2 \cdot CO \cdot CH_2 \cdot OH$

An ethereal solution of β -naphthaleneacetyl chloride obtained from 1 g. of β -naphthaleneacetic acid was treated with diazomethane as described earlier. The resulting diazoketone was dissolved in 10 ml. of dioxan, decomposed with 5 ml. of 2N sulphuric and worked up as stated previously to give 0.71 g. (63 per cent.) of β -naphthaleneacetyl carbinol melting at 90 to 93°C. as light yellow crystals from 97 per cent. alcohol. Found: C, 75.32; H, 5.91 per cent.: $C_{13}H_{12}O_2$ requires C, 78.00; H, 6.00 per cent.

It was soluble in most organic solvents and also in boiling water. It reduced ammoniacal silver nitrate solution in the cold. With 2:4-dinitrophenylhydrazine it gave the corresponding hydrazone melting at 24°C. The hydrazone on analysis gave N, 14.0 per cent.: $C_{19}H_{16}O_5$ requires N, 14.7 per cent.

REFERENCES

1. Linnell and Roushdi, *Quart. J. Pharm. Pharmacol.*, 1941, **14**, 270.
2. Allen and Barker, " *Organic Syntheses*," Wiley, 1935, **12**, 16.
3. Steiger and Reichstein, *Helv. chim. Acta*, 1937, **20**, 1040.
4. Robertson, " *Organic Syntheses*," Wiley, 1932, Coll. Vol. 1, 389.
5. Robertson, *ibid.*, 1932, Coll. Vol. 1, 398.
6. Robertson, *ibid.*, 1932, Coll. Vol. 1, 44.
7. Jaeger and Robinson, *J. chem. Soc.*, 1941, 744.