

139. *Synthetic Analogues of Corticosterone.*

By WALTER C. J. ROSS.

Acetoxyacetyl derivatives of dibenzyl, $\alpha\beta$ -diethyldibenzyl, diphenyl, diphenyl ether, fluorene, and phenanthrene have been prepared for examination for corticosterone-like activity.

LINNELL and ROUSHDI (*Quart. J. Pharm.*, 1941, **14**, 270; *Nature*, 1941, **148**, 595) have reported signs of cortical hormone activity in two synthetic α -ketols. Benzoylcarbinol is stated to have 1/2500th, and 4-hydroxy-3'-hydroxyacetyl- $\alpha\beta$ -diethylstilbene 1/200th, of the activity of deoxycorticosterone in the life-maintenance test on adrenalectomised rats. The preparation of 4-methoxy-4'-hydroxyacetyl- and 4'-acetoxyacetyl- $\alpha\beta$ -diethyldibenzyl has been described (Wellcome Foundation Ltd., Brownlee and Duffin, B.P. 550,262); corticosterone-like activity is claimed for these compounds. Walker (J., 1942, 347) has prepared 4-acetoxy-4'-acetoxyacetyldiphenyl ether and 4 : 2'-diacetoxy-4'-acetoxyacetyldiphenyl ether; preliminary tests indicated that these substances were not active in increasing the liver glycogen of fasting rats but no life-maintenance tests were reported. The preparation of further α -ketol compounds to be tested for hormone-like action is now described. The acetates of α -ketols are likely to be of more clinical value than the free alcohols on account of their greater oil solubility (compare, *e.g.*, the use of deoxycorticosterone acetate); they are also more readily obtained, and it is for these two reasons that the substances now prepared are all acetoxyacetyl compounds.

Dibenzyl reacts with an excess of chloroacetyl chloride in the presence of aluminium chloride to give 4 : 4'-bischloroacetyldibenzyl, and this when heated with anhydrous potassium acetate in a mixture of acetic acid and acetic anhydride yields 4 : 4'-bisacetoxyacetyldibenzyl. Similarly, $\alpha\beta$ -diethyldibenzyl affords the two analogous $\alpha\beta$ -diethyldibenzyl compounds.

Several unsuccessful attempts were made to prepare 4 : 4'-bisacetoxyacetylstilbene. No identifiable product was obtained by treating stilbene, $\alpha\beta$ -diethylstilbene, or triphenylethylene with chloroacetyl chloride. Bromination of diacetylstilbene yielded 4 : 4'-bisbromoacetylstilbene dibromide, and this on heating with potassium acetate as described above yielded a fluorescent oil which reduced warm Fehling's solution. It had previously been shown that stilbene dibromide gave stilbene when heated with potassium acetate under these conditions. Treatment of the dibromide with sodium iodide in acetone solution gave a yellow product which was probably 4 : 4'-bisiodoacetylstilbene. The iodo-compound also gave a fluorescent oil on treatment with potassium acetate. It was hoped to prepare the required compound by the following sequence of reactions : $\cdot\text{CO}\cdot\text{CH}_3 \longrightarrow \cdot\text{CO}\cdot\text{CH}\cdot\text{NO} \longrightarrow \cdot\text{CO}\cdot\text{CH}_2\cdot\text{NH}_2 \longrightarrow \cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$, but the nitroso-ketone could not be obtained by the usual methods.

4 : 4'-Bischloroacetyldiphenyl ether was prepared by a method essentially that of Schick (*Ber.*, 1936, **69**, 242). The replacement of chlorine atoms by acetyl groups in the usual way afforded 4 : 4'-bisacetoxyacetyldiphenyl ether. 4-Acetoxyacetylacetanilide was obtained in good yield by the method of Knuckell (*Ber.*, 1900, **33**, 2644). 4 : 4'-Bisacetoxyacetyldiphenyl was readily obtained from 4 : 4'-bischloroacetyldiphenyl by the usual procedure. By the action of an excess of chloroacetyl chloride on fluorene a disubstitution product, probably 2 : 7-bischloroacetylfluorene, was obtained, and this was easily converted into 2 : 7-bisacetoxyacetylfluorene.

2- and 3-Acetylphenanthrene were obtained by the method of Mosettig and van der Kamp (*J. Amer. Chem. Soc.*, 1930, **52**, 3704) and converted into the corresponding bromo-ketones as described by Haworth and Mavin (J., 1933, 1012). By heating the bromo-compounds with potassium acetate in the usual way, 2- and 3-acetoxyacetylphenanthrene were prepared. 9-Bromophenanthrene on being heated with potassium cyanide and cuprous cyanide in aqueous alcohol at 200° (compare Rosenmund and Struck, *Ber.*, 1919, **52**, 1749) gave a high-melting product which was not identical with 9-phenanthroic acid. When heated with cuprous cyanide at 250—260°, the bromo-compound gave 9-cyanophenanthrene. No 9-acetylphenanthrene could be obtained by the action of methylmagnesium iodide on the nitrile. 9-Phenanthroic acid amide was prepared by heating

the nitrile with sulphuric acid : this amide gave the sodium salt of 9-phenanthroic acid on treatment with sodium hydroxide. 9-Phenanthrolyl chloride was allowed to react with diazomethane, and the product treated with acetic acid without isolation. The final product was subjected to chromatographic purification, giving 9-acetoxyacetylphenanthrene.

7-Methoxy-1-naphthoic acid was converted into its acid chloride and the diazo-ketone obtained by the action of an ethereal solution of diazomethane was decomposed with acetic acid to yield 7-methoxy-1-acetoxyacetylphenanthrene. The relative position of the substituents in this compound resembles that in corticosterone itself.

Preliminary biological tests on the new compounds now described do not indicate any marked activity in prolonging the life of an adrenalectomised rat.

EXPERIMENTAL.

4 : 4'-Bis(chloroacetyl)dibenzyl.—5 G. of dibenzyl, dissolved in 30 c.c. of carbon disulphide, were added to 10 g. of powdered aluminium chloride, and then a solution of 10 c.c. each of chloroacetyl chloride and carbon disulphide was run in slowly whilst the mixture was kept cold. After standing for $\frac{1}{2}$ hour at room temperature, the upper layer was decanted from the complex, which was then decomposed with iced water. The product was extracted with a large quantity of ether, and the extract washed with dilute hydrochloric acid, dried, and evaporated. The residue was crystallised from alcohol (charcoal) in which it was sparingly soluble. The 4 : 4'-bis(chloroacetyl)dibenzyl was finally crystallised from chloroform-methanol; it formed small plates, m. p. 142–143° (Found : C, 64.0; H, 4.8; Cl, 20.8. $C_{18}H_{16}O_2Cl_2$ requires C, 64.5; H, 4.8; Cl, 21.2%).

4 : 4'-Bis(acetoxyacetyl)dibenzyl.—2 G. of the chloro-ketone were heated under reflux for 2 hours with 2.4 g. of freshly fused potassium acetate and 20 c.c. each of acetic acid and acetic anhydride. The mixture was diluted with 40 c.c. of water, and the product separated in the form of prismatic needles. There was still some unchanged chloro-ketone present and this was readily removed by warming an alcoholic suspension of the product with a little piperidine; this formed a very soluble piperidinium compound and the pure acetoxyacetyl derivative could be filtered off from the cooled solution. After a chromatographic purification and three crystallisations from chloroform-methanol, 4 : 4'-bis(acetoxyacetyl)dibenzyl formed fine needles, m. p. 163–165° (Found : C, 69.0; H, 6.0. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%).

4 : 4'-Bis(chloroacetyl)- α -diethylidibenzyl.—8 C.c. of chloroacetyl chloride were added to 8 g. of powdered aluminium chloride in 5 c.c. of carbon disulphide, and a dark liquid complex was formed. To this was added a solution of 3 g. of diethylidibenzyl in 15 c.c. of carbon disulphide. Hydrogen chloride was immediately evolved, and after $\frac{1}{2}$ hour a solid lower layer formed. The liquor was decanted off, and the solid washed with carbon disulphide and then decomposed with iced water. The product was ground under ether-water and then filtered off. The dry solid was dissolved in hot chloroform and reprecipitated with methanol, giving 3.5 g. of the chloro-ketone, m. p. 195–196°, raised by two crystallisations from acetone to 197–198° (Found : C, 67.9; H, 6.4. $C_{22}H_{24}O_2Cl_2$ requires C, 67.6; H, 6.2%).

4 : 4'-Bis(acetoxyacetyl)- α -diethylidibenzyl.—The chloro-ketone was treated with fused potassium acetate as described above, and the product was purified by removing the unchanged starting material as the soluble piperidinium salt. The acetoxyacetyl compound formed small plates from chloroform-methanol, m. p. 205–210° (decomp.) (Found : C, 71.0; H, 7.0. $C_{26}H_{30}O_6$ requires C, 71.2; H, 6.9%).

Attempted Preparation of Bis(acetoxyacetyl)stilbene.—1.3 G. of 4 : 4'-diacetylstilbene were dissolved in 50 c.c. of chloroform, and an excess (about 1.4 c.c.) of bromine in chloroform added to the warmed solution. 25 C.c. of the chloroform were then evaporated off, and 25 c.c. of ethanol added : this caused the formation of a microcrystalline precipitate, m. p. 205–207° (decomp.) (Found : Br, 55.9. $C_{18}H_{14}O_2Br_4$ requires Br, 55.0%). 1 G. of the bromo-compound was dissolved in acetone and treated with an acetone solution of 1.5 g. of sodium iodide. Iodine was liberated, and sodium bromide precipitated. Dilution of the mixture with water gave a yellow solid, decomp. 180–190° (Found : I, 48.0. $C_{18}H_{14}O_2I_2$ requires I, 49.2%). Fluorescent oils were obtained when the bromo- or the iodo-compound was treated with potassium acetate as previously described.

Stilbene dibromide was refluxed with its own weight of fused potassium acetate in 10 times its weight of acetic acid for 3 hours. Careful dilution of the mixture with water gave a crystalline precipitate, m. p. 123–124°, not depressed by admixture with stilbene, m. p. 124°.

4 : 4'-Bis(acetoxyacetyl)diphenyl Ether.—8.3 G. of diphenyl ether, 15 g. of powdered aluminium chloride, and 50 c.c. of carbon disulphide were treated with 8.0 c.c. of chloroacetyl chloride. The solid complex which formed was worked up in the usual way. The product was resinous and could not be improved by chromatography, but after an alcoholic solution had been heated with charcoal for a short time and filtered, a crystalline solid was obtained. After recrystallisation from alcohol, the m. p. was 100° (2.2 g.); Schick (*loc. cit.*) gives 102°. The chloro-ketone was refluxed with potassium acetate in acetic acid-anhydride for 3 hours, and the product isolated in the manner already described. The 4 : 4'-bis(acetoxyacetyl)diphenyl ether formed fine needles from chloroform-alcohol, m. p. 149–150° after three recrystallisations (Found : C, 64.7; H, 4.8. $C_{20}H_{18}O_7$ requires C, 64.8; H, 4.9%).

4 : 4'-Bis(acetoxyacetyl)diphenyl.—Diphenyl was treated with chloroacetyl chloride as described above. The product, which was sparingly soluble in most solvents, was best purified by grinding it with charcoal and then extracting the mixture with acetone (Soxhlet). The boiling acetone extract deposited a yellow solid which, after recrystallisation from cyclohexanone, had m. p. 220–225°; Carpenter and Turner (J., 1934, 869) give 226–227°. 1.1 G. of the chloro-ketone were heated under reflux with 1.6 g. of fused potassium acetate and 15 c.c. each of acetic acid and acetic anhydride for 3 hours. The product, which formed plates from alcohol, had m. p. 184–189° (Found : C, 67.7; H, 4.95. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%).

2 : 7-Bis(chloroacetyl)fluorene.—5 G. of fluorene were treated with chloroacetyl chloride exactly as in the previous example. The product was also very sparingly soluble and was purified by extracting a mixture with charcoal by acetone (Soxhlet). The extract, which showed a yellow fluorescence, deposited the chloro-ketone as a granular solid. After several crystallisations from cyclohexanone, it formed fine needles, m. p. 280° (decomp.) (Found : C, 64.5; H, 4.0. $C_{17}H_{12}O_2Cl_2$ requires C, 64.1; H, 3.8%).

2 : 7-Bis(acetoxyacetyl)fluorene.—This was formed in the usual way but the product did not crystallise well. Accordingly, it was dissolved in a large quantity of benzene, and the solution percolated through a column of alumina. The impurities formed a broad orange band at the top of the column, whereas the early eluates afforded the pure acetoxyacetyl compound. It formed small colourless plates from alcohol, m. p. 185–190° (Found : C, 69.0; H, 4.8. $C_{21}H_{18}O_6$ requires C, 68.9; H, 4.9%).

2-Acetoxyacetylphenanthrene.—2.5 G. of 2-bromoacetylphenanthrene (Haworth and Mavin, *loc. cit.*) were treated with potassium acetate in acetic acid-anhydride in the usual way. The product formed prismatic needles, m. p. 116–118°, from ethanol (Found : C, 78.2; H, 5.2. $C_{18}H_{14}O_3$ requires C, 77.7; H, 5.1%).

3-Acetoxyacetylphenanthrene.—3-Bromoacetylphenanthrene (Haworth and Mavin, *loc. cit.*) was treated with potassium acetate as before. The *acetoxyacetyl* compound formed prismatic needles, m. p. 124–125°, from acetone-methanol (Found: C, 77.9; H, 5.2%).

9-Acetoxyacetylphenanthrene.—30 G. of phenanthrene, dissolved in 420 c.c. of acetic acid, were treated with a solution of 18.5 c.c. of bromine in acetic acid. After standing for 1 hour the insoluble dibromide was filtered off. The solid was heated in a large flask on a water-bath and hydrogen bromide was liberated and 9-bromophenanthrene formed. 20 G. of bromo-compound, recrystallised from alcohol, were heated with 9 g. of cuprous cyanide in a distilling flask at 250–260° for 4½ hours. The product, which was distilled straight out of the reaction flask at 10 mm., was crystallised several times from ethanol; yield 7.5 g., m. p. 103–104°. 4 G. of the nitrile were warmed with 60 c.c. of 60% sulphuric acid, and a crop of fine needles was soon deposited. This proved to be the amide, m. p. 238–240°, and when this was heated with 10% aqueous-alcoholic sodium hydroxide and the mixture acidified, 9-phenanthroic acid was obtained. 2.5 G. of the acid were suspended in 10 c.c. of dry benzene and treated with 2 c.c. of thionyl chloride in the presence of 2 drops of pyridine. After warming on a water bath for ¼ hour, the benzene was distilled off and replaced by a further 10 c.c. of benzene which was also removed. The crystalline residue was dissolved in 100 c.c. of benzene and treated with an ethereal solution of diazomethane formed from 4 g. of nitrosomethylurea. The mixture was left for 2 days at room temperature, and after addition of an excess of acetic acid, the solvents were removed under reduced pressure. The residue was heated with acetic acid for a short time, a considerable evolution of gas occurring. An ethereal solution of the product was washed with dilute alkali, dried, and then evaporated. The material was dissolved in benzene, and the solution percolated through a column of alumina. The solid obtained by evaporation of the eluates was crystallised from benzene-light petroleum and finally from light petroleum (b. p. 60–80°). The 9-acetoxyacetylphenanthrene had m. p. 121–123° (Found: C, 77.7; H, 5.2%).

Attempted Conversion of 9-Bromophenanthrene into 9-Phenanthroic Acid.—2 G. of 9-bromophenanthrene, 2 g. of potassium cyanide, 0.5 g. of cuprous cyanide, and 10 c.c. each of water and alcohol were heated together in a sealed tube at 200° for 2 hours. The mixture was then diluted with water and extracted with ether. On acidification, the aqueous layer yielded a white solid which was readily soluble in alkali. This acid product had m. p. >280°, whereas 9-phenanthroic acid melts at 250°. The high-melting compound was probably a copper complex, since it dissolved in dilute ammonium hydroxide to give a blue solution and left a residue of copper oxide on ignition.

7-Methoxy-1-acetoxyacetylnaphthalene.—2 G. of 7-methoxynaphthoic acid were converted into the acid chloride as described above, and the product dissolved in 20 c.c. of benzene. This solution was treated with diazomethane (from 4 g. of nitrosomethylurea) in ethereal solution. After standing at room temperature for 4 hours, the product was decomposed with acetic acid as previously described. The resin was dissolved in benzene, and the solution allowed to percolate through a column of alumina. A light yellow oil was obtained from the early eluates, and this solidified after standing for 2 days. Crystallisation was difficult, but by dissolving the compound in ether, adding light petroleum (b. p. 40–60°), and then allowing the ether to evaporate off slowly, long lemon-coloured needles of 7-methoxy-1-acetoxyacetylnaphthalene, m. p. 61°, were obtained (Found: C, 69.8; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%).

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RESEARCH DEPARTMENT, ORGANON LABORATORIES LTD., LONDON.

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