## CHAPTER IV

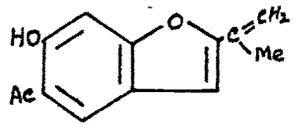
## Synthesis of some anthra-furan derivatives

### Theoretical

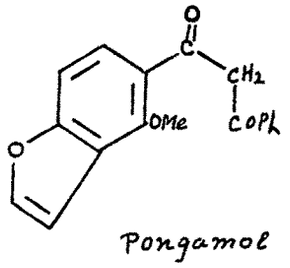
Furan, benzofuran, dibenzofuran and other furano derivatives form an important group of heterocyclic compounds.

The representatives of this class of compounds are found to occur in vegetable kingdom extensively, mostly as glycosides. Some of these may be mentioned here.

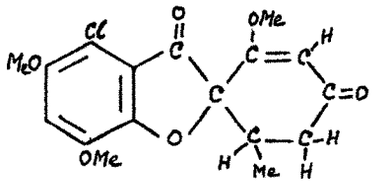
Euparin ( Kamthong and Robertson, J. Chem. Soc., 1939, 925, 933 ) ; Pongamol ( T.R.Seshadri et al., J. Chem. Soc., 1954, 1871 ; 1955, 2048 ) ; Usnic acid ( Rochleder and Heldt, Annalen, 1843, 48, 11 ; Barton et al., J. Chem. Soc., 1956, 530 ) ; Griseofulvin, one of the few natural products which contain chlorine ( Oxford, Raistrick and Simon art, Biochem, J. 1939, 33, 240 ; MacMillan et al., J. Chem. Soc., 1952, 3949, 4002 ; 1953, 1697 ; 1954, 2585 ) and Khellin ( Clarke and Robertson, J. Chem. Soc., 1949, 302 ).



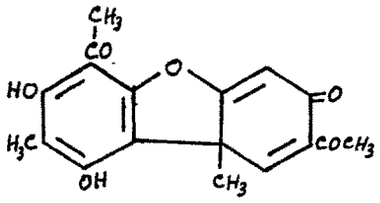

Euparin



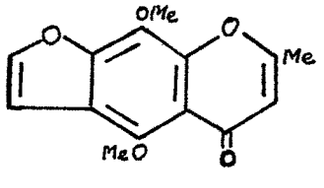

Pongamol




Griseofulvin




Usnic acid

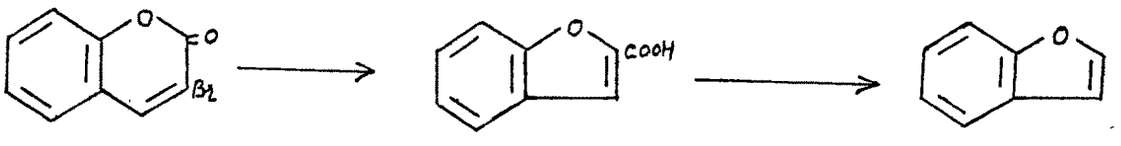



Khellin

Some of these compounds have attracted attention in recent years, because of their physiological properties and others because of their commercial importance, for example, Nitrofurazone has been reported to possess good bacteriostatic and bactericidal properties ( Dodd, et al., J. Pharmacol and Exper. Therap, 1944, 82, 11 ). Nitrofurfuryl methyl ether has been found to be decidely fungistatic to all common fungi. Nitrofurantoin ( N.N.R. 1955 ), a nitrofuran derivative, is suitable for oral use and has been found to be effective even for infections that were resistant to antibiotics. Usnic acid and Griseofulvin have been found to possess antibiotic properties. Khellin has been known for relieving spasm of uretes, kidney and gall bladder ( Ibrahim and Ali Pascha, Brit. J. Urol., 1926, I, 396 ; Ibrahim and Ali Beg, J. Roy. Egypt, Mid. Assoc., 1929, 12, 71 ).

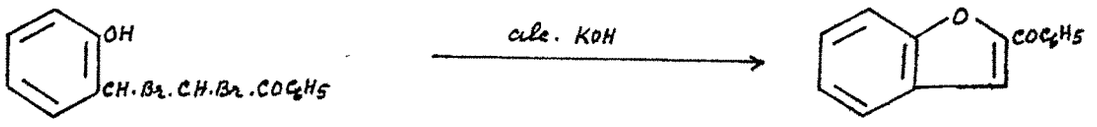
Some of the important general methods for the synthesis of benzofurans may be briefly described here as they illustrate the different ways in which a furan ring can be built up on an aromatic nucleus.

(1) When 3-halocoumarin is heated with alkali a coumarilic acid is obtained.

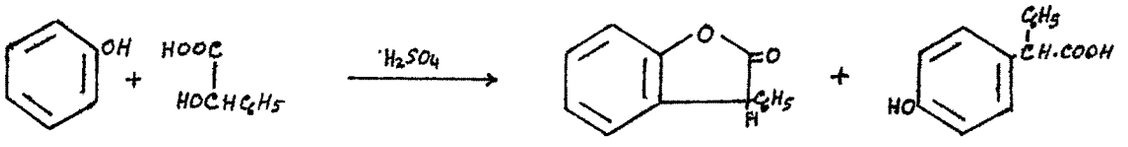



(2) Synthesis of benzofurans may be accomplished from the dibromides of α chalcones ( Kostanecki and Tambor, Ber.,

1896, 29, 237 ).




(3) o-Hydroxyphenylacetic acids readily undergo ring closure with sulphuric acid to yield benzofuran derivatives. Thus when mandelic acid is condensed with phenol, 3-phenyl-coumaran-2-one is formed ( Bistrzycki and Flataue, Ber., 1895, 28, 989 ; Bistrzycki and v.Weber, ibid., 1910, 43, 2496 ; Liebig, ibid., 1908, 41, 1644 ).

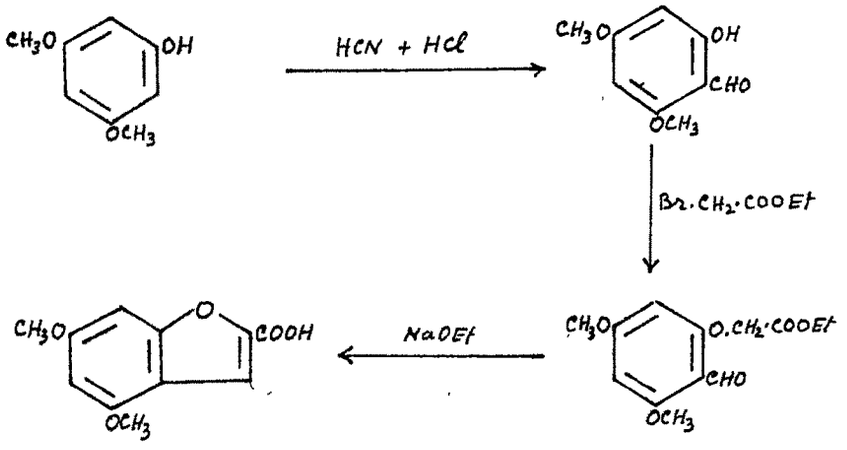



(4) By elimination of hydrogen halide from a w-halogenated acetophenone derivative, coumaran-3-one derivative can be prepared ( Friedlander and Neudorfer, Ber., 1897, 30, 1077 ; v.Auwers, ibid., 1912, 45, 976 ; 1914, 47, 3307 ).


(5) 2,3-Dihydrobenzofurans are very easily formed from o-allyl-phenols, presumably by addition and elimination of hydrogen bromide. This synthesis, originally discovered by Claisen ( Claisen and Tietze, Ann., 1926 ) is important

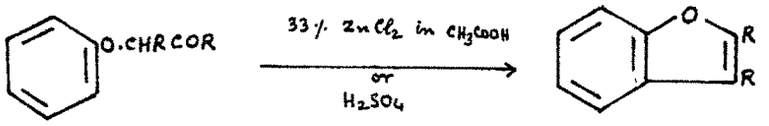
for the preparation of compounds somewhat similar to vitamin E, a chroman compound.

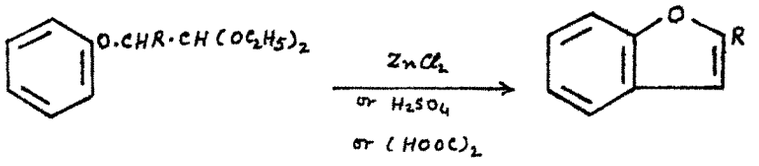
(6) An o-hydroxy-aldehyde or o-hydroxy-ketone can be condensed with α-halo-ketone or α-halogenated acid or ester in boiling acetone in presence of anhydrous potassium carbonate. The ring closure is then accomplished by (i) the Perkin reaction, which yields a non-acidic coumarone because the carboxylic group is unstable, or (ii) the familier condensation of aldehydes with esters under the influence of alkali, which effects cyclisation with retention of the carboxyl group. A typical example of this synthesis has been shown below ( Foster and Robertson, J. Chem. Soc., 1939, 921 ) :-



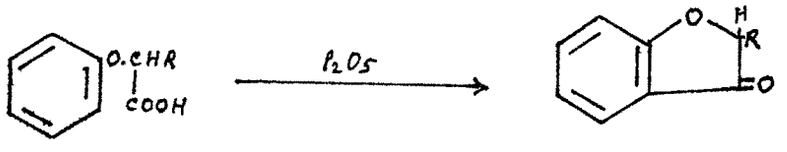

(7) Ring closure of α-phenoxy carbonyl compounds or corresponding acetals can be effected with the help of reagents like concentrated sulphuric acid or anhydrous zinc chloride to get the corresponding benzofuran derivative. ( Stoermer, Ber., 1897, 30, 1700 ; 1895, 28, 1253 ; Stoermer, Ann., 1900, 312, 237 ; Stoermer and Wehln, Ber., 1902, 35,

3549 ; Vladesco, Bull.Soc.Chim.France, 1891, 6, 807 ).



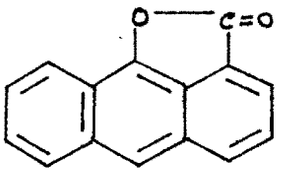




α-Phenoxyacids also undergo similar cyclisation when treated with phosphorus pentoxide to yield coumaran-3-one derivatives. ( Stoermer and Bartsch, Ber., 1900, 33, 3175 ; Stoermer and Barthelemes, ibid., 1915, 48, 62 ; Stoermer and Atenstudt, ibid., 1902, 35, 3560 ).

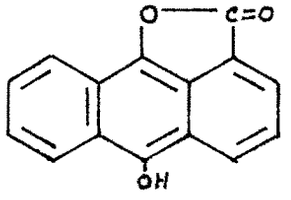



A very large number of benzofuran derivatives have been synthesised. Furan ring has also been built up on the naphthalene ring system and a number of simple as well as substituted naphtho-furans have been synthesised. A few anthra-furan-2-ones, which are actually lactones, such as 2H-anthra ( 9,1-bc ) furan-2-one ( i ) ( Barnett et al., Ber., 1924, 57, 1775 ), 2H-anthra ( 9,1-bc ) furan-2-one-6-hydroxy ( ii ) ( Scholl and Bottger, Ber., 1930, 63, 2128 ), 2H-anthra ( 9,1-bc ) furan-2-one-5-carboxylic acid ( iii )

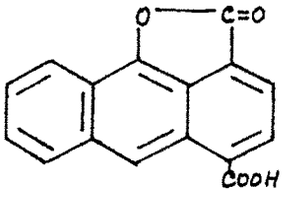
( Scholl and Bottger, Ber., 1930, 63, 2440 ) and 2H-anthra ( 9,1-bc ) furan-2-one-7-carboxylic acid ( iv ) ( Scholl and Bottger, loc.cit. ) are known. There is no reference however, in the literature, to the synthesis of simple anthra-furans.



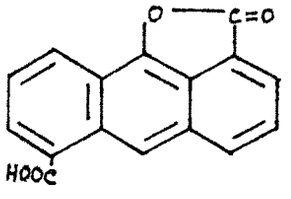

(i)




(ii)




(iii)

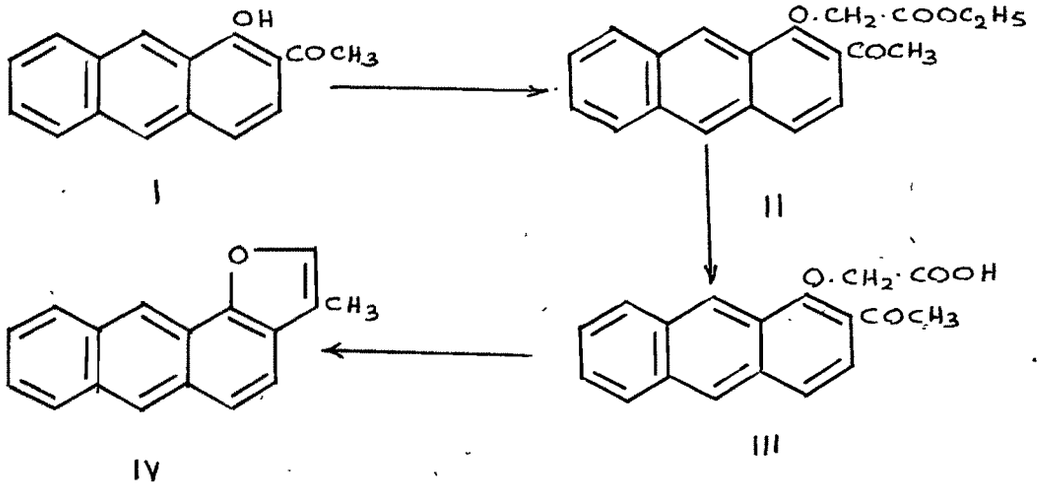



(iv)

The present work may now be described.

Synthesis of 3-methyl-anthra [ 1,2-b ] furan.

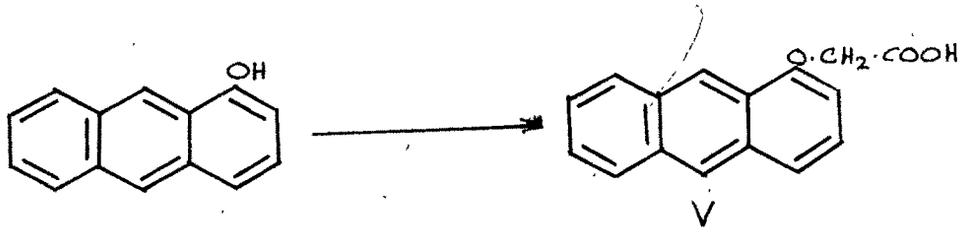
2-Acetyl-1-anthrol ( 1 ) was condensed with ethyl bromoacetate in boiling acetone in presence of anhydrous potassium carbonate when ethyl-2-acetyl-1-anthroxyacetate ( II ) was obtained. This ester was hydrolysed by treatment with alkali to 2-acetyl-1-anthroxy-acetic acid ( III ). The cyclisation of this acid was effected by refluxing it with acetic anhydride and freshly fused and powdered sodium acetate and 3-methyl-anthra [ 1,2-b ] furan ( IV ) was obtained.




The result of the analysis and the absence of a free acetyl group in the cyclised product indicate that the meso position is not involved in the ring closure.

The possibility of cyclisation in the meso position was investigated by preparing 1-anthroxyacetic acid ( XVII ) from 1-anthrol and ethyl bromoacetate. ~~but~~ The acid remained unchanged on subjecting it to the action of sodium

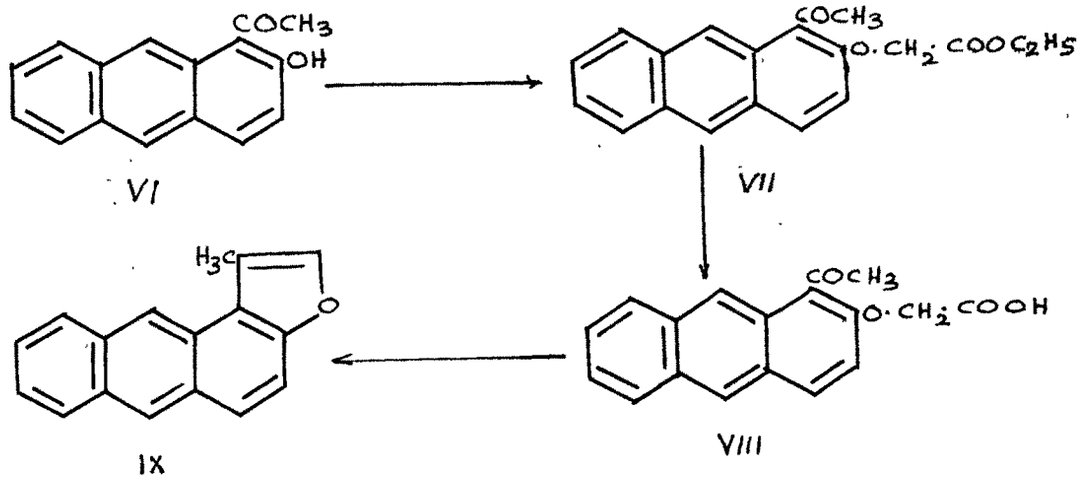
acetate and acetic anhydride.




V

Synthesis of 1-methyl-anthra [2,1-b] furan.

Similarly 1-acetyl-2-anthrol ( VI ) on condensation with ethyl bromoacetate, under the same conditions, gave ethyl-1-acetyl-2-anthroxyacetate ( VII ). The ester was hydrolysed with alkali to 1-acetyl-2-anthroxyacetic acid ( VIII ). 1-Methyl-anthra [2,1-b] furan ( IX ) was obtained on heating the acid with sodium acetate and acetic anhydride.

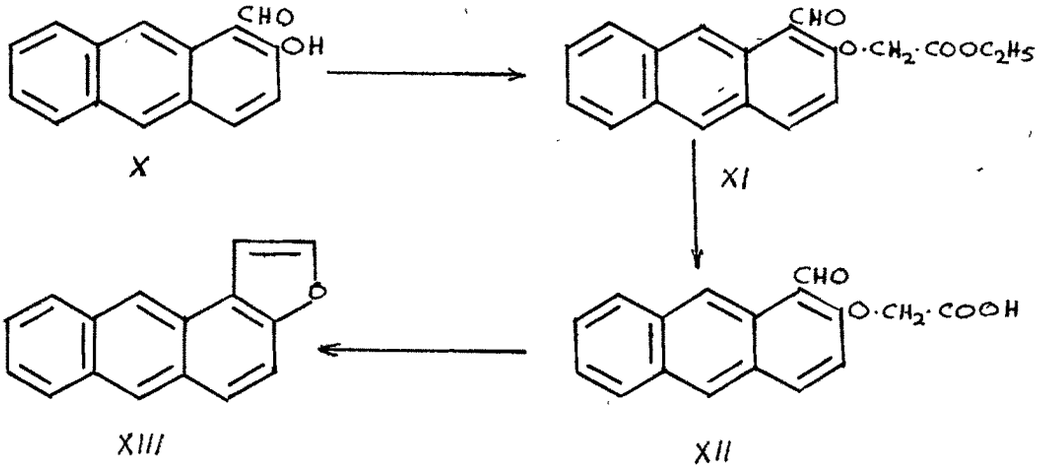



VI VII VIII IX

Synthesis of anthra [2,1-b] furan.

The simple, unsubstituted, anthra [2,1-b] furan

( XIII ) was synthesised by condensation of 1-formyl-2-anthrol ( X ) with ethyl bromoacetate to get ethyl-1-formyl-2-anthroxyacetate ( XI ), hydrolysis of this ester to 1-formyl-2-anthroxyacetic acid ( XII ) and ring closure of this acid to the anthra [2,1-b] furan.



## EXPERIMENTAL

Condensation of 2-acetyl-1-anthrol with ethyl bromoacetate : Ethyl-2-acetyl-1-anthroxyacetate.

2-Acetyl-1-anthrol ( 0.5 g. ) was dissolved in dry acetone ( 50 ml. ). To the clear solution, anhydrous potassium carbonate ( 3 g. ) and ethyl bromoacetate ( 0.5 ml. ) were added and the reaction mixture heated under reflux on a steam bath for 4 hours. The solution was then filtered hot and the residue obtained on removal of acetone crystallised from dilute alcohol (charcoal) in fine yellow needles, m.p.108-109°. Yield 0.35 g.

Analysis :

9.04 mg. of the substance gave 24.80 mg. of carbon dioxide and 4.26 mg. of water.

Found : C, 74.86 % ; H, 5.27 %.

$C_{20}H_{18}O_4$ requires : C, 74.50 % ; H, 5.59 %.

2-Acetyl-1-anthroxyacetic acid.

The above ester ( 0.5 g. ) was heated with sodium hydroxide solution ( 50 ml. ; 2 % ) at 50° in a water bath till the ester dissolved. The solution was then filtered hot, cooled and acidified with dilute hydrochloric acid. The product obtained was further purified by sodium bicarbonate treatment and crystallised from dilute acetic acid (charcoal) in yellow needles, m.p.161-162°. Yield 0.4 g.

Analysis :

3.202 mg. of the substance gave 8.574 mg. of carbon dioxide and 1.290 mg. of water.

Found : C, 73.10 % ; H, 4.50 %.

$C_{18}H_{14}O_4$ requires : C, 73.50 % ; H, 4.80 %.

3-Methyl-anthra [1,2-b] furan.

A mixture of 2-acetyl-1-anthroxyacetic acid ( 0.3 g. ), acetic anhydride ( 12.0 ml. ) and freshly fused and powdered sodium acetate ( 1.2 g. ) was boiled for 30 minutes. The reaction mixture was then added to cold water. The product which separated was filtered and crystallised from dilute alcohol ( charcoal ) in pale greenish yellow plates, m.p. 105°. Yield 0.15 g.

Analysis :

13.34 mg. of the substance gave 42.68 mg. of carbon dioxide and 6.70 mg. of water.

Found : C, 87.31 % ; H, 5.62 %.

$C_{17}H_{12}O$ requires : C, 87.92 % ; H, 5.17 %.

Attempted cyclisation of 1-anthroxyacetic acid.

1-Anthroxyacetic acid. A mixture of 1-anthrol ( 1 g. ), ethyl bromoacetate ( 1 ml. ) and anhydrous potassium carbonate ( 3 g. ) was refluxed in acetone solution for 7 hours. An oil was obtained on removal of acetone. This was hydrolysed in alcoholic solution with potassium hydroxide ( 2 g. in 5 ml. water ) by heating on a steam bath for 2 hours. It was then filtered and the filtrate diluted with water and acidified. The product

obtained was purified through sodium bicarbonate treatment and crystallised first from dilute alcohol ( charcoal ) and then from benzene in colourless needles, m.p. 190-191°.

Analysis :

10.42 mg. of the substance gave 29.12 mg. of carbon dioxide and 4.60 mg. of water.

Found : C, 76.25 % ; H, 4.94 %.

$C_{16}H_{12}O_3$ requires : C, 76.19 % ; H, 4.76 %.

The above acid ( 0.1 g. ) was refluxed with sodium acetate ( 0.3 g. ) and acetic anhydride ( 2 ml. ) for 30 minutes. The original acid was obtained on working up the reaction mixture.

Condensation of 1-formyl-2-anthrol with ethyl bromoacetate : Ethyl-1-formyl-2-anthroxyacetate.

1-Formyl-2-anthrol ( 0.5 g. ) was dissolved in dry acetone ( 50 ml. ) and refluxed on a steam bath with anhydrous potassium carbonate ( 3 g. ) and ethyl bromoacetate ( 0.5 ml. ) for 3 hours. The solution was filtered hot and the residue obtained on removal of acetone crystallised from alcohol ( charcoal ) in yellow needles, m.p. 140°. Yield 0.4 g.

Analysis :

3.260 mg. of the substance gave 8.832 mg. of carbon dioxide and 1.472 mg. of water.

Found : C, 73.93 % ; H, 5.05 %.

$C_{19}H_{16}O_4$ requires : C, 74.01 % ; H, 5.19 %.

1-Formyl-2-anthroxyacetic acid.

Ethyl-1-formyl-2-anthroxyacetate ( 0.5 g. ) was hydrolysed by heating it with sodium hydroxide solution ( 2 % ; 50 ml. ) at 50-60° for 6 hours. The product obtained on acidification with hydrochloric acid crystallised from dilute acetone (charcoal) in pale reddish yellow shining needles, m.p.222-223°. Yield 0.2 g.

Analysis :

3.390 mg. of the substance gave 8.992 mg. of carbon dioxide and 1.26 mg. of water.

Found : C, 72.38 % ; H, 4.16 %.

$C_{17}H_{12}O_4$ requires : C, 72.85 % ; H, 4.29 %.

Anthra [2,1-b] furan.

A mixture of 1-formyl-2-anthroxyacetic acid ( 0.1 g. ), acetic anhydride ( 2 ml. ) and freshly fused and powdered sodium acetate ( 0.3 g. ) was boiled for 30 minutes. The mixture was then cooled, added to cold water and kept overnight. The solid obtained was filtered, washed with a dilute solution of sodium hydroxide and crystallised from dilute acetic acid (charcoal). It was recrystallised from dilute alcohol when shining greenish yellow plates were obtained, m.p.177-178°.

Analysis :

3.610 mg. of the substance gave 11.648 mg. of carbon dioxide and 1.508 mg. of water.

Found : C, 88.07 % ; H, 4.67 %.

$C_{16}H_{10}O$ requires : C, 88.06 % ; H, 4.59 %.

Condensation of 1-acetyl-2-anthrol with ethyl bromoacetate : Ethyl-1-acetyl-2-anthroxyacetate.

1-Acetyl-2-anthrol ( 0.5 g. ), ethyl bromoacetate ( 0.5 ml. ) and anhydrous potassium carbonate ( 3 g. ) were refluxed on a steam bath in dry acetone ( 50 ml. ) for 3 hours. The solution was then filtered hot and the product obtained on removal of acetone was washed with water and crystallised from alcohol (charcoal) in greenish yellow needles, m.p.127-128°. Yield 0.3 g.

Analysis :

3.718 mg. of the substance gave 10.182 mg. of carbon dioxide and 1.880 mg. of water.

Found : C, 74.74 % ; H, 5.66 %.

$C_{20}H_{18}O_4$ requires : C, 74.50 % ; H, 5.59 %.

1-Acetyl-2-anthroxyacetic acid.

1-Acetyl-2-anthroxyacetate ( 0.5 g. ) was hydrolysed by keeping it with sodium hydroxide solution ( 4 % ; 20 ml. ) overnight at room temperature. The solution was then filtered and the product obtained on acidification of the alkaline filtrate with dilute hydrochloric acid, crystallised from dilute acetic acid (charcoal) in greenish yellow needles, m.p.190°. Yield 0.4 g.

Analysis :

3.270 mg. of the substance gave 8.802 mg. of carbon dioxide and 1.286 mg. of water.

Found : C, 73.46 % ; H, 4.40 %.

$C_{18}H_{14}O_4$ requires : C, 73.48 % ; H, 4.76 %.

1-Methyl-anthra [ 2,1-b ] furan.

A mixture of 1-acetyl-2-anthroxyacetic acid ( 0.1 g. ), acetic anhydride ( 2 ml. ) and freshly fused and powdered sodium acetate ( 0.3 g. ) was boiled for 30 minutes. It was then cooled and added to cold water. The product obtained was crystallised first from dilute acetic acid ( charcoal ) and then from alcohol in needles, m.p. 139-140°.

Analysis :

4.408 mg. of the substance gave 14.126 mg. of carbon dioxide and 2.120 mg. of water.

Found : C, 87.45 % ; H, 5.38 %.

$C_{17}H_{12}O$ requires : C, 87.92 % ; H, 5.17 %.