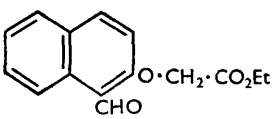
613. *Preparation of Some Naphthofurans.*

By P. Emmott and R. Livingstone.

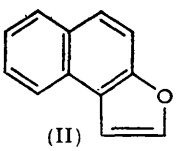
Naphtho(2′ : 1′-2 : 3)furan, naphtho(2′ : 3′-2 : 3)furan, 4-methoxynaphtho-(1′ : 2′-2 : 3)furan, and their 5-carboxylic acids have been prepared by a general method from hydroxynaphthaldehydes, similar to that used in the synthesis of coumarone.[1]

This paper records syntheses of the three possible naphthofurans (though of one only in traces) and of some derivatives.

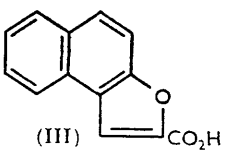
Synthesis of naphtho(2′ : 1′-2 : 3)furan started with condensation of 2-hydroxy-1-naphthaldehyde[2] and ethyl bromoacetate to give the aldehydo-ester (I). This was hydrolysed by dilute aqueous sodium hydroxide to the corresponding acid which was cyclised by acetic anhydride and sodium acetate to the furan (II) (previously[3] prepared from 1-naphthyloxyacetaldehyde). Treating the ester (I) with concentrated aqueous potassium hydroxide caused cyclisation as well as hydrolysis, the naphthofurancarboxylic acid (III) being obtained directly.



(I)



(II)

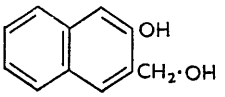


(III)

Synthesis of naphtho(2′ : 3′-2 : 3)furan required a suitable preparation of 2-hydroxy-3-naphthaldehyde; the only successful one found was reduction of 2-hydroxy-3-naphthoic acid with lithium aluminium hydride to 3-hydroxymethyl-2-naphthol (IV) followed by an

[1] Rossing, *Ber.*, 1884, **17**, 3000.
[2] Russell and Lockhart, *Org. Synth.*, **22**, 63.
[3] Stoermer, *Annalen*, 1900, **312**, 237.

Oppenauer oxidation to the aldehyde. The yield of aldehyde was not as high as that obtained by Rosenmund reduction [4] of the acid chloride (V) but the method was simpler.



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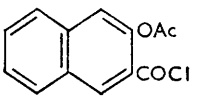

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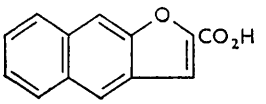
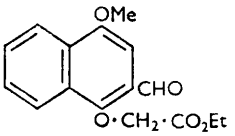


(VI)

The aldehyde was condensed with ethyl bromoacetate and the product, ethyl 3-formyl-2-naphthyloxyacetate, hydrolysed to the aldehydo-acid which with acetic anhydride and sodium acetate gave a mixture of naphtho(2′ : 3′-2 : 3)furan and its 5-carboxylic acid (VI) in good yields. This naphthofuran has been previously prepared by decarboxylation of its 5-carboxylic acid.[5]



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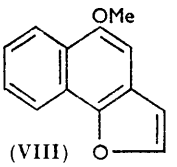
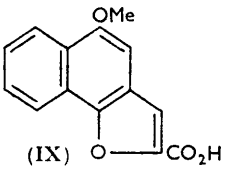


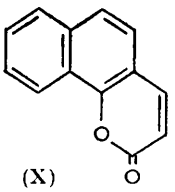
(VIII)



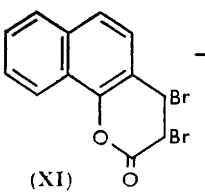
(IX)

Attempted preparation of naphtho(1′ : 2′-2 : 3)furan from 1-hydroxy-2-naphthaldehyde by the above method gave only black tars, but that of the 4′-methoxy-derivative (VIII) proved successful. 1-Hydroxy-4-methoxy-2-naphthaldehyde, prepared from 1-hydroxy-4-methoxy-2-naphthoic acid,[6] was condensed with ethyl bromoacetate. The product (VII) was hydrolysed by dilute sodium hydroxide solution to its acid and cyclised in the usual way to give 4′-methoxynaphtho(1′ : 2′-2 : 3)furan (VIII) and small quantities of the 5-carboxylic acid (IX). The latter compound was also prepared by the ring closure of the ester (VII) with sodium ethoxide. Resins have often been obtained in attempts to prepare naphthofurans from substituted α-naphthols, and the yields in successful reactions are usually lower than in the β-naphthol series.

The bromination of naphtho(1′ : 2′-5 : 6)-2-pyrone having been used in the synthesis of naphtho(2′ : 1′-2 : 3)furan,[7,3] the isomeric naphthopyrone (X) was prepared from α-naphthol and malic acid in the presence of sulphuric acid,[8] and the derived dibromide (XI)



(X)



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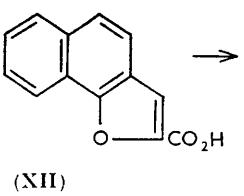
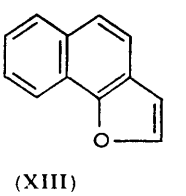


(XII)



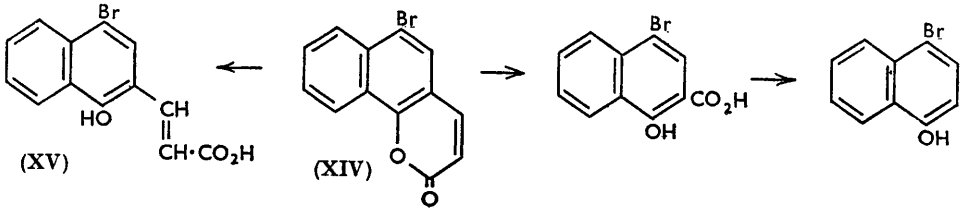
(XIII)

was treated in ethanol with aqueous potassium hydroxide, affording naphtho(1′ : 2′-2 : 3)-furan-5-carboxylic acid (XII). Attempts to decarboxylate this acid with soda lime or with copper chromite in quinoline gave only traces of the furan (XIII) (identified as the picrate).

Bromination of the naphthopyrone (X) in chloroform or acetic acid occurred in the naphthalene nucleus, giving the 4′-bromo-derivative (XIV). The yields were good, but prolonged exposure to bromine gave much tar. The structure of this compound (XIV) was verified by oxidation with potassium permanganate in acetone and decarboxylation of the resulting 1-hydroxy-4-bromo-2-naphthoic acid to 4-bromo-α-naphthol.

[4] Boehm and Profft, *Arch. Pharm.*, 1931, **269**, 25.
[5] Takeda, Shimada, and Kitahonoki, *J. Pharm. Soc. Japan*, 1950, **70**, 268.
[6] Livingstone and Watson, *J.*, 1956, 3701.
[7] Dey, Rao, and Sankaranarayanan, *J. Indian Chem. Soc.*, 1932, **9**, 281.
[8] *Idem, ibid.*, p. 71.

The bromonaphthopyrone (XIV) underwent ring fission and inversion on treatment with aqueous potassium hydroxide, to give *trans*-β-(4-bromo-1-hydroxy-2-naphthyl)-acrylic acid (XV), a reaction already observed with the chloro-analogue.[9]



Experimental

3-Hydroxymethyl-2-naphthol.—3-Hydroxy-2-naphthoic acid (6·3 g.) was refluxed in ether (70 c.c.) with lithium aluminium hydride (1·3 g.) for 4 hr. with stirring, then set aside overnight. Water was added, and the mixture poured on ice and dilute sulphuric acid, and extracted with ether. The ethereal solution was washed with sodium hydrogen carbonate solution, from which the acid (2·2 g.) was recovered. Evaporation of solvent and crystallisation of the product from ethanol gave *3-hydroxymethyl-2-naphthol* (1·6 g.), m. p. 191° (Found: C, 75·7; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·7%).

2-Hydroxy-3-naphthaldehyde.—A solution of aluminium *tert.*-butoxide (1·4 g.) in dry benzene (30 c.c.) was added to one of 3-hydroxymethyl-2-naphthol (2·1 g.) and *p*-benzoquinone (4 g.) in dry benzene (60 c.c.). The solution was refluxed for 1½ hr. and the excess of benzene and *p*-benzoquinone was then removed by steam-distillation. The mixture was cooled, treated with concentrated sulphuric acid (1 c.c.), and steam-distilled. The solid in the distillate was purified by decomposing the bisulphite derivative with hot dilute sulphuric acid, giving 3-hydroxy-2-naphthaldehyde (0·3 g.) as yellow needles, m. p. and mixed m. p. 98°.

3-Formyl-2-naphthyloxyacetic Acid.—Ethyl bromoacetate (0·4 c.c.), potassium carbonate (0·8 g.), and 3-hydroxy-2-naphthaldehyde (0·4 g.) in acetone (10 c.c.) were refluxed for 3 hr. and set aside overnight. After filtration, evaporation and crystallisation of the product from ethanol gave ethyl 3-formyl-2-naphthyloxyacetate (0·5 g.), m. p. 91—92°. The ester was refluxed for ½ hr. with 5% sodium hydroxide solution (20 c.c.), then poured into dilute hydrochloric acid, to give 3-formyl-2-naphthyloxyacetic acid (0·4 g.), m. p. 173—174°. Takeda, Shimada, and Kitahonoki [5] give m. p. 174°.

Naphtho(2′ : 3′-2 : 3)*furan.*—3-Formyl-2-naphthyloxyacetic acid (0·4 g.), acetic anhydride (10 c.c.), and fused sodium acetate (1 g.) were heated under reflux for 2 hr., then poured into water and set aside overnight. The solid was dissolved in ether, washed with sodium hydrogen carbonate solution, then water, and dried. Removal of solvent, chromatography from benzene, and crystallisation from aqueous ethanol gave the naphthofuran (0·1 g.), m. p. 120° (lit., m. p. 121°) (Found: C, 85·4; H, 4·6. Calc. for $C_{12}H_8O$: C, 85·7; H, 4·8%). A picrate, prepared from methanolic solution, formed orange needles, m. p. 134°. Acidification of the sodium hydrogen carbonate extract with dilute hydrochloric acid, and recrystallisation of the product from ethanol, gave naphtho(2′ : 3′-2 : 3)furan-5-carboxylic acid (VI) as needles, (0·1 g.), m. p. 285° (lit., m. p. 291°) (Found: C, 73·8; H, 4·1. Calc. for $C_{13}H_8O_3$: C, 73·6; H, 3·8%).

Ethyl 1-Formyl-2-naphthyloxyacetate.—Ethyl bromoacetate (1·6 c.c.), potassium carbonate (4 g.), and 2-hydroxy-1-naphthaldehyde (2 g.) in acetone (50 c.c.) gave, as for the isomer, *ethyl 1-formyl-2-naphthyloxyacetate* (2·5 g.), m. p. 92° (Found: C, 69·4; H, 5·2. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

1-Formyl-2-naphthyloxyacetic Acid.—The foregoing ester (2 g.) and 5% sodium hydroxide solution (80 c.c.) were refluxed for ½ hr. The mixture was cooled and poured into dilute hydrochloric acid. Filtration and recrystallisation from light petroleum (b. p. 80—100°) gave the *acid* (1·5 g.) as needles, m. p. 176—177° (Found: C, 67·1; H, 4·0. $C_{13}H_{10}O_4$ requires C, 67·6; H, 4·3%).

Naphtho(2′ : 1′-2 : 3)*furan* (II).—The foregoing acid (1 g.), acetic anhydride (30 c.c.), and fused sodium acetate (3 g.) were heated under reflux for 2 hr., then poured into water and set

[9] Chakravarti and Bagchi, *J. Indian Chem. Soc.*, 1936, **13**, 649.

aside overnight. The solid was dissolved in ether and washed with sodium hydrogen carbonate solution, then water, and dried. Evaporation of solvent and crystallisation from light petroleum (b. p. 80—100°) gave the naphthofuran (0·6 g.), m. p. 60—61° (lit.,[3] m. p. 60—61°) (Found: C, 86·0; H, 4·7. Calc. for $C_{12}H_8O$: C, 85·7; H, 4·8%). Acidification of the sodium hydrogen carbonate extract gave a mixture of acids, presumably the 5-carboxylic acid and unchanged aldehydo-acid.

Naphtho(2′ : 1′-2 : 3)*furan-5-carboxylic Acid* (III).—Ethyl 1-formyl-2-naphthyloxyacetate (2·5 g.) was refluxed for 5 hr. with water (30 c.c.) and potassium hydroxide (30 g.). Acidification and crystallisation from benzene gave the naphthofuran-5-carboxylic acid (2 g.), m. p. 192° (lit.,[3] m. p. 191—192°) (Found: C, 73·2; H, 3·6. Calc. for $C_{13}H_8O_3$: C, 73·6; H, 3·8%).

Ethyl 2-Formyl-4-methoxy-1-naphthyloxyacetate.—Ethyl bromoacetate (2·4 c.c.), potassium carbonate (6 g.), and 1-hydroxy-4-methoxy-2-naphthaldehyde (3 g.) in acetone (75 c.c.) gave, as above, *ethyl 2-formyl-4-methoxy-1-naphthyloxyacetate* (4 g.), m. p. 89—90° (Found: C, 66·2; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%). This (1 g.) was hydrolysed by 5% sodium hydroxide solution (20 c.c.) to the *aldehydo-acid* (0·7 g.), m. p. 179—180° (Found: C, 63·9; H, 5·1. $C_{14}H_{12}O_5$ requires C, 64·2; H, 4·6%).

4′-*Methoxynaphtho*(1′ : 2′-2 : 3)*furan.*—The methoxy-acid (0·6 g.), acetic anhydride (20 c.c.), and fused sodium acetate (2 g.) were heated under reflux for 2 hr., poured into water, and set aside overnight. The solid was dissolved in ether and washed with sodium hydrogen carbonate solution, then water, and dried. Evaporation and chromatography from benzene gave 4′-methoxynaphtho(1′ : 2′-2 : 3)furan (0·3 g.), b. p. 135°/760 mm., n_D^{20} 1·5749. A *picrate*, prepared in methanol, formed red needles, m. p. 183—184° (Found: C, 53·9; H, 2·9. $C_{19}H_{13}O_9N_3$ requires C, 53·4; H, 3·0%). Acidification of the sodium hydrogen carbonate washings gave the 5-carboxylic acid (0·03 g.), m. p. 278° (see below).

4′-*Methoxynaphtho*(1′ : 2′-2 : 3)*furan-5-carboxylic Acid.*—A solution from sodium (0·2 g.) in dry ethanol (5 c.c.) was added to ethyl 2-formyl-4-methoxy-1-naphthyloxyacetate (1 g.) in dry ethanol (10 c.c.), and the mixture refluxed for 5 min., cooled, taken up in ether, and extracted with sodium hydrogen carbonate solution. Acidification of the extract followed by crystallisation from acetic acid gave the *5-carboxylic acid* (0·3 g.), m. p. 278° (Found: C, 69·0; H, 4·2. $C_{14}H_{10}O_4$ requires C, 69·5; H, 4·1%).

3 : 4-*Dibromo*-3 : 4-*dihydronaphtho*(2′ : 1′-5 : 6)-2-*pyrone.*—Naphtho(2′ : 1′-5 : 6)-2-pyrone (2 g.) was refluxed with carbon disulphide (80 c.c.), and cooled. The undissolved pyrone (0·2 g.) was separated and bromine (1 c.c.) in carbon disulphide (10 c.c.) added to the solution which was set aside for 2 days; more unchanged naphthopyrone (0·3 g.) was precipitated. After filtration, part of the solvent was removed and orange crystals of the *dibromide* separated. Recrystallisation from benzene and light petroleum (b. p. 80—100°) gave white needles (1·5 g.), m. p. 113° (Found: C, 43·3; H, 2·3; Br, 44·6. $C_{13}H_8O_2Br_2$ requires C, 43·8; H, 2·2; Br, 44·8%).

4′-*Bromonaphtho*(2′ : 1′-5 : 6)-2-*pyrone.*—(i) To a solution of the naphthopyrone (10 g.) in chloroform (100 c.c.) was added bromine (5 c.c.) in chloroform (20 c.c.). Hydrogen bromide was evolved and the mixture was left for 3 hr. Removal of the solvent gave a red gum which following crystallisation from ethanol gave the *4′-bromo-derivative* (10·7 g.) as needles, m. p. 170—171°. (ii) The naphthopyrone (1 g.) in glacial acetic acid (10 c.c.) was treated with bromine (0·6 c.c.) in acetic acid (2 c.c.). Evaporation and crystallisation from ethanol gave the 4′-bromo-derivative (0·8 g.), m. p. 170—171° (Found: C, 56·7; H, 2·5; Br, 29·0. $C_{13}H_7O_2Br$ requires C, 56·7; H, 2·6; Br, 27·8%).

Naphtho(1′ : 2′-2 : 3)*furan-5-carboxylic Acid.*—Ethanol (10 c.c.) was added to potassium hydroxide (1 g.) in the minimum amount of water. This solution was added to the preceding dibromide (0·5 g.) in ethanol (10 c.c.). The mixture was refluxed for ½ hr. and set aside for a further 2 hr. The potassium salt of the *naphthofurancarboxylic acid* was precipitated by the addition of solid potassium hydroxide, separated by filtration, dissolved in water, and acidified with hydrochloric acid, to afford the acid (0·2 g.), m. p. 250° (decomp.) (Found: C, 73·6; H, 3·7. $C_{13}H_8O_3$ requires C, 73·2; H, 3·4%).

trans-β-(4-*Bromo*-1-*hydroxy*-2-*naphthyl*)*acrylic Acid.*—The 4′-bromonaphthopyrone (5 g.) was refluxed for 1 hr. with 5% potassium hydroxide solution (100 c.c.). 70 c.c. of the water were removed by evaporation, and the potassium salt of the acid precipitated by solid potassium hydroxide, separated, dissolved in water, and acidified with hydrochloric acid, to afford the *acrylic acid* (1 g.), m. p. 290—291° (Found: C, 53·8; H, 2·7. $C_{13}H_9O_3Br$ requires C, 53·3; H, 3·1%).

Degradation of 4'-Bromonaphtho(1' : 2'-2 : 3)pyrone.—The bromonaphthopyrone (1·9 g.) was refluxed and stirred for 6 hr. with potassium permanganate (6·5 g.) in acetone (70 c.c.). The solid was filtered off and sulphur dioxide bubbled through its suspension in water (100 c.c.) until all the inorganic matter had dissolved. The residue crystallised from toluene, to give 4-bromo-1-hydroxy-2-naphthoic acid (0·5 g.), m. p. and mixed m. p. 237—238°.

This acid (0·4 g.) was heated for several minutes just above its m. p. It darkened and evolved carbon dioxide. The residue was extracted with ether, and the extract washed with sodium hydrogen carbonate solution and then sodium hydroxide solution. The sodium hydroxide extract on acidification and crystallisation from aqueous ethanol gave 4-bromo-1-naphthol (0·2 g.), m. p. 121°.

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