

255. β -Hydroxyethyl Ethers of Substituted Phenols and Related Substances.

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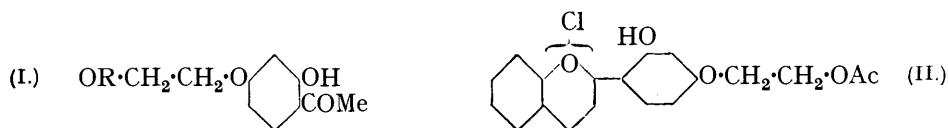
THIS investigation was undertaken with a view to synthesise substances containing fused coumaran and γ -pyrone nuclei, *i.e.*, dihydrofuranoflavones, by starting with either a coumaran or a flavone and introducing respectively either the flavone or coumaran ring. These attempts were not successful, but numerous flavone derivatives obtained are described. The starting materials were the mono- β -hydroxyethyl ethers of resacetophenone and *m*-methoxyphenol. A mono- and a di-ether of 4-ethylresorcinol were also obtained. The ethers, which may be of use as internal antiseptics, were prepared from the corresponding phenols by modifying Rindfusz's chlorohydrin reaction (*J. Amer. Chem. Soc.*, 1920, 42, 157).

The constitution of 2-hydroxy-4-(β -hydroxyethoxy)acetophenone (I; R = H) was proved by the alcoholic ferric chloride reaction and the synthesis of 7-hydroxyflavone, m. p. 240° (Robinson and Venkataraman, *J.*, 1926, 2344), by condensation with benzaldehyde, conversion of the 2-hydroxy-4-(β -hydroxyethoxy)chalkone by Feuerstein and Kostanecki's method (*Ber.*, 1898, 31, 1757) via the dicetoxychalkone dibromide into 7-(β -hydroxyethoxy)flavone, and de-ethylation of this. Direct bromination of the chalkone introduced a bromine atom into the nucleus, and the bromo-derivative when hydrolysed yielded 6-bromo-7-(β -hydroxyethoxy)flavone and not the isomeric benzylidene-coumaranone (cf. Cullinane and Philpott, *J.*, 1929, 1761). The constitution of the compound was proved by its giving a colourless solution in concentrated sulphuric acid (cf. Perkin and Everest, "The Natural Organic Colouring Matters," p. 164); on treatment with phosphorus pentabromide, it gave 6-bromo-7-(β -bromoethoxy)flavone.

Use of *p*-anisaldehyde and salicylaldehyde instead of benzaldehyde, gave the corresponding chalkones, and these, when treated by Kostanecki's method, afforded ultimately 4'-methoxy-7-(β -hydroxyethoxy)flavone and 2'-hydroxy-4'-(β -acetoxyethoxy)flavylium chloride (II), respectively. *o*-Nitrobenzaldehyde also condensed with (I; R = H).

Cyclisation of the hydroxyethyl ethers of resacetophenone and *m*-methoxyphenol and of substituted flavones by means of anhydrous zinc chloride and phosphoric oxide (Rindfusz, *loc. cit.*) could not be accomplished. Negative results were also obtained when 6-bromo-7-(β -bromoethoxy)flavone was subjected to the action of sodium in anhydrous xylene.

The phenylhydrazone, azine, anil, and benzidine derivatives of (I; R = H) were insoluble in dilute aqueous alkalis (cf. Adams, *J. Amer. Chem. Soc.*, 1919, 41, 247). The reasons for this are not clear, and the phenomena are rendered still more obscure by the observation now made that certain phenols, though insoluble in dilute alkalis, dissolve when they are suspended in 50% sodium or potassium hydroxide and then diluted with water.



EXPERIMENTAL.

2-Hydroxy-4-(β -hydroxyethoxy)acetophenone (I; R = H).—A solution of potassium hydroxide (49 g.) in water (50 c.c.) was added to a suspension of resacetophenone (66 g.) in ice-water (100 c.c.), and the mixture heated with ethylene chlorohydrin (87.5 g.) at 100° for 3 hrs. The separated oil solidified on cooling, and was repeatedly crystallised from aqueous alcohol (charcoal); needles, m. p. 106°. It was soluble in alkali, and gave a violet coloration with alcoholic ferric chloride (Found: C, 61.0; H, 6.4. $\text{C}_{10}\text{H}_{12}\text{O}_4$ requires C, 61.2; H, 6.1%). Its monoacetyl derivative (I; R = Ac) separated at once when it was treated with acetic anhydride and pyridine; it crystallises from alcohol in needles, m. p. 117°, gives a violet coloration with alco-

holic ferric chloride, and is soluble in alkali (Found: C, 60.4; H, 6.2. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%). The *diacetyl* derivative, prepared by shaking a solution of (I) in acetic anhydride and pyridine for 24 hrs., crystallised from carbon tetrachloride–light petroleum in rhombic plates, m. p. 70° (Found: C, 59.7; H, 5.7. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.7%).

The *benzoyl* derivative (I; R = Bz), prepared by the pyridine method at 100°, separated from the usual solvents as a gel. The gel from acetic acid passed, when treated with dilute hydrochloric acid, into a white powder, m. p. 100° (Found: C, 67.9; H, 5.4. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). It gives a violet coloration with alcoholic ferric chloride and is soluble in alkali. The *oxime* crystallised from aqueous alcohol in silky needles, m. p. 144° (Found: N, 6.8. $C_{10}H_{13}O_4N$ requires N, 6.6%). The *hydrazone*, prepared by warming an alcoholic solution with 50% hydrazine hydrate and diluting after 30 mins., formed colourless needles, m. p. 123° (Found: N, 13.5. $C_{10}H_{14}O_3N_2$ requires N, 13.3%), from aqueous alcohol.

The *azine* was obtained either by treatment with hydrazine hydrate in glacial acetic acid or by heating the hydrazone with glacial acetic acid. Insoluble in the usual solvents, it crystallised from boiling nitrobenzene in golden-yellow, woolly needles which gave an opaque liquid at 253°, becoming transparent at 263° (Found: N, 7.4. $C_{20}H_{24}O_6N_2$ requires N, 7.2%). The *phenylhydrazone* crystallised from rectified spirit in thin, yellowish plates, m. p. 148–149° (Found: N, 9.9. $C_{16}H_{18}O_3N_2$ requires N, 9.8%). Both this and the azine exhibited unusual behaviour towards aqueous alkali. The latter was insoluble in 8% alkali, but dissolved to a yellow solution on addition of alkali to an alcoholic suspension; considerable dilution of its suspension in 50% alkali caused dissolution to a colourless solution, whereas addition of alcohol gave a yellow solution which became colourless on addition of water. The phenylhydrazone behaved similarly except that it did not dissolve on dilution of its suspension in sodium hydroxide.

The *anil*, from boiling aniline (2 hrs.), crystallised from aqueous alcohol in thin, shining plates, m. p. 173° (Found: N, 5.5. $C_{16}H_{17}O_3N$ requires N, 5.2%). It was insoluble in aqueous alkali, but dissolved when alkali was added to its suspension in dilute alcohol.

The second hydroxyl group of resacetophenone did not react with ethylene chlorohydrin.

The *benzidine* condensation product, $OH \cdot C_2H_4 \cdot O \cdot C_6H_3(OH) \cdot CMe \cdot N \cdot C_6H_4 \cdot NH_2$, was obtained by refluxing a solution of the compound (I; R = H) (4 g.) and benzidine (12 g.) in alcohol (50 c.c.) for 2 hours. The solid (1.7 g.) was filtered from the hot liquid and repeatedly washed with boiling alcohol. It was insoluble in the usual solvents. Hot nitrobenzene gave microscopic yellow needles, which softened at 153° and melted at 288–290° (Found: N, 7.7, 7.8. $C_{22}H_{22}O_3N_2$ requires N, 7.7%). It was insoluble in aqueous alkali and did not form a salt with 50% alkali. It separated unchanged from its solution in hydrochloric acid on basification. With alkaline β -naphthol the diazotised acid solution gave a red dye-stuff.

2-Hydroxy-4-(β -hydroxyethoxy)ethylbenzene.—Zinc amalgam (Robinson and Shah, J., 1934, 1497), hydrochloric acid (1:1; 100 c.c.), and (I; R = H) (6 g.) were heated at 100°, with gradual addition of concentrated hydrochloric acid (50 c.c.), till the mixture failed to give a violet coloration with ferric chloride; it was then saturated with salt and left over-night. The solid (5 g.) crystallised from dilute alcohol in silky needles, m. p. 99–100° (Found: C, 65.8; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%). The aqueous solution gave a blue-black coloration with ferric chloride.

The condensation of ethylene chlorohydrin (8 g.) with a solution of *m*-methoxyphenol (10 g.) in 40% potassium hydroxide (12 c.c.) was carried out as above. The ethereal extract was washed with 40% potassium hydroxide until the washings were colourless. The residue on distillation gave *m*-(β -hydroxyethoxy)anisole (8 g.), b. p. 160°/2 mm. (Found: C, 64.1; H, 7.3. $C_9H_{12}O_3$ requires C, 64.3; H, 7.1%); *acetyl* derivative, b. p. 140°/7 mm. (Found: C, 62.7; H, 6.8. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7%); *benzoyl* derivative, fleecy needles, m. p. 91–92° (Found: C, 70.4; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%), from alcohol.

The *chloro-ether*, obtained on treatment with phosphorus pentachloride, distilled at 130°/5 mm. (Found: Cl, 18.9. $C_9H_{11}O_2Cl$ requires Cl, 19.0%).

Condensation of Ethylene Chlorohydrin with 4-Ethylresorcinol.—4-Ethylresorcinol (13 g.), 40% alkali (25 c.c.), and ethylene chlorohydrin (16 g.), treated as before, gave a liquid mixture of the mono- and the di-ether. They were separated by washing the ethereal extract with 40% alkali. *2-Hydroxy-4-(β -hydroxyethoxy)ethylbenzene* (12 g.) collected at 200–210°/5 mm., soon solidified and was found to be identical with the reduction product of (I; R = H). The alkali-insoluble extract gave 1–2 c.c. of *2:4-di-(β -hydroxyethoxy)ethylbenzene* which solidified after long keeping. It crystallised from carbon tetrachloride–light petroleum in needles, m. p. 66° (Found: C, 63.4; H, 8.1. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%). The *benzoyl* derivative of

the mono-ether was soluble in alkali, and crystallised from alcohol in thin, pinkish needles, m. p. 109—110° (Found: C, 71.0; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).

2-Hydroxy-4-(β -hydroxyethoxy)chalkone.—Benzaldehyde (13.6 g.) and 40% potassium hydroxide (70 c.c.) were added to a solution of (I; R = H) (25 g.) in alcohol (250 c.c.); after 24 hrs., during which the chalkone separated as its potassium salt, the whole was diluted and acidified with concentrated hydrochloric acid. The precipitated chalkone (26 g.) was collected; it crystallised from alcohol in yellow, woolly needles, m. p. 123—124° (Found: C, 71.7; H, 5.9. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%).

7-(β -Hydroxyethoxy)flavanone.—A solution of the above chalkone (5 g.) in alcohol (300 c.c.) was refluxed with 10% sulphuric acid (250 c.c.) for 30 hrs., then left over-night in an evaporating dish, freed from tarry matter, and diluted. The mixture of the flavanone and the chalkone was filtered off, and washed with very dilute alcohol and then with 2% sodium hydroxide. The solid recovered from the alcoholic washings on dilution was treated in the same way. The two crops of the almost pure flavanone crystallised from very dilute alcohol in white needles, m. p. 113° [Found (micro): C, 72.1; H, 5.9. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%]; it gave a colourless solution in concentrated sulphuric acid, which changed to yellow owing to conversion of the substance into the chalkone.

2-Hydroxy-4-(β -acetoxyethoxy)chalkone crystallised from alcohol in thin, golden-yellow plates, m. p. 139° (softening at 135°). It gave a violet coloration with alcoholic ferric chloride and was soluble in alkali (Found: C, 69.8; H, 5.7. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.5%). Its diacetyl derivative (3.9 g. from 3 g.), obtained as for (I; R = H), crystallised from dilute alcohol in thin, bluish needles, m. p. 68° [Found (micro): C, 68.8; H, 5.8. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.4%]; and when this (9 g. in 150 c.c. of carbon disulphide) was treated with bromine (3.9 g. in 15 c.c. of the disulphide) the dibromo-derivative was formed; after 7 hrs. it was collected and crystallised from alcohol; needles (11 g.), m. p. 122° (Found: Br, 30.3. $C_{21}H_{20}O_6Br_2$ requires Br, 30.3%).

7-(β -Hydroxyethoxy)flavone.—A suspension of this dibromide (2 g.) in alcohol (20 c.c.) was shaken with 40 c.c. of 8% sodium hydroxide. A bright yellow solution was obtained, and the flavone began to separate. After $\frac{3}{4}$ hour, the whole was diluted, and the flavone (1 g.) filtered off. It crystallised from alcohol in fleecy needles, m. p. 166° (Found: C, 72.1; H, 5.1. $C_{17}H_{14}O_4$ requires C, 72.2; H, 5.0%). Its colourless solution in concentrated sulphuric acid showed blue fluorescence. The acetyl derivative crystallised from alcohol in microscopic needles, m. p. 130° (Found: C, 70.2; H, 5.0. $C_{19}H_{16}O_5$ requires C, 70.4; H, 4.9%).

De-ethylation of the flavone. A solution of the flavone (1 g.) in phenol (6 g.) was boiled with hydriodic acid (20 c.c.; b. p. 128—130°) for 1 hr. in an atmosphere of carbon dioxide. The solid obtained after dilution was dissolved in alcohol and shaken with mercury to remove iodine. The solid crystallised from ethyl acetate (charcoal) in pinkish needles, m. p. 238—240°, not depressed when mixed with an authentic specimen of 7-hydroxyflavone.

5-Bromo-2-hydroxy-4-(β -hydroxyethoxy)chalkone Dibromide.—Bromine (5 g.) in chloroform (7 c.c.) was slowly added to a solution of the chalkone (4.4 g.) in chloroform (20 c.c.). The precipitated dibromo-compound (3 g.) crystallised from boiling alcohol in woolly needles, m. p. 204° (efferv.) (Found: Br, 45.9. $C_{17}H_{15}O_4Br_3$ requires Br, 45.9%).

6-Bromo-7-(β -Hydroxyethoxy)flavone.—The above dibromide (1.5 g.) yielded the corresponding flavone (1.05 g.) on hydrolysis with 8% sodium hydroxide (30 c.c.) in alcoholic (30 c.c.) suspension. It crystallised from boiling alcohol in woolly needles, m. p. 206.5°, depressed (180—198°) on admixture with the dibromide [Found (micro): C, 56.4; H, 4.0; Br, 22.5. $C_{17}H_{13}O_4Br$ requires C, 56.4; H, 3.6; Br, 22.2%].

6-Bromo-7-(β -bromoethoxy)flavone.—A solution of the preceding flavone (2 g.) in anhydrous toluene (25 c.c.) was refluxed with phosphorus pentabromide (2 g.) for $\frac{3}{4}$ hr. After cooling, the solvent was decanted, and the residue (2 g.) extracted with water and finally crystallised twice from acetic acid (charcoal); thin, pale yellow needles, m. p. 199° (Found: Br, 37.6. $C_{17}H_{12}O_3Br_2$ requires Br, 37.7%).

2-Hydroxy-4-(β -hydroxyethoxy)-4'-methoxychalkone.—A solution of (I; R = H) (8.7 g.) in alcohol (100 c.c.), together with *p*-anisaldehyde (6 g.) in presence of 40% potassium hydroxide (30 c.c.), gave the corresponding chalkone (11 g.) after 30 hrs. It was twice crystallised from alcohol, forming woolly, yellow needles, m. p. 134° (Found: C, 68.8; H, 5.8. $C_{18}H_{16}O_5$ requires C, 68.8; H, 5.7%). The monoacetyl derivative, which was soluble in alkali and gave a violet coloration with alcoholic ferric chloride, crystallised from boiling alcohol in spongy, yellow needles, m. p. 134—135°, depressed (116—124°) on admixture with the chalkone (Found: C, 67.3; H, 5.7. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.6%). The diacetyl derivative crystallised

from carbon tetrachloride–light petroleum in pale yellow needles, m. p. 87–88° [Found (micro) : C, 66.2; H, 5.5. $C_{22}H_{22}O_7$ requires C, 66.3; H, 5.5%].

Bromine (2 g.) and the diacetoxy-chalkone (4.98 g.) in carbon disulphide (150 c.c.) gave the *dibromo-compound* (4 g.) after slow evaporation of the solvent. It crystallised from the above mixed solvent in clusters of needles, m. p. 105–107° (efferv.) (Found : Br, 28.4. $C_{22}H_{22}O_7Br_2$ requires Br, 28.7%). The compound is stable when exposed to the atmosphere, but in a closed bottle it evolves bromine and hydrogen bromide and becomes pasty.

4'-Methoxy-7-(β-hydroxyethoxy)flavone.—Hydrolysis of the foregoing dibromide (2 g.) yielded the *flavone* (1 g.), which crystallised from alcohol in lemon-yellow needles, m. p. 155° (Found : C, 69.1; H, 5.2. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%), giving a pale yellow solution with blue fluorescence in sulphuric acid. The *acetyl* derivative crystallised from alcohol in greyish needles, m. p. 141° (efferv.) (Found : C, 67.7; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%).

2'-Nitro-2-hydroxy-4-(β-hydroxyethoxy)chalkone.—An alcoholic solution of *o*-nitrobenzaldehyde (8.5 g.) was mixed with an alcoholic solution (100 c.c.) of (I; R = H) (11 g.) in an amber-coloured bottle; 40% potassium hydroxide (40 c.c.) was added, and the whole kept under running water for 1 hr. After 3 hrs. the reaction mixture was slowly poured with stirring into very dilute, ice-cold hydrochloric acid. The yellow *chalkone* (9 g.), which became green on exposure to light, was crystallised from nitrobenzene; green needles, m. p. 183° [Found (micro) : N, 4.1, 4.09. $C_{17}H_{15}O_6N$ requires N, 4.25%].

The *diacetyl* derivative separated from carbon tetrachloride–light petroleum in pale yellow, woolly needles, m. p. 155° [Found (micro) : N, 3.41. $C_{21}H_{18}O_8N$ requires N, 3.39%]. On saponification, this yielded the starting substance, proving that the original substance cannot be the lactyl-ketone, which would have formed a triacetyl derivative or would have lost a molecule of water and given a diacetyl derivative hydrolysable to a chalkone (cf. Claisen, *Ber.*, 1881, 14, 2470; Baeyer and Drewsen, *Ber.*, 1882, 15, 2856; Price and Bogert *J. Amer. Chem. Soc.*, 1934, 56, 2443).

2 : 2'-Dihydroxy-4-(β-hydroxyethoxy)chalkone.—Condensation of (I; R = H) with salicylaldehyde and alcoholic alkali at 60° for 24 hrs., followed by dilution and acidification with acetic acid, yielded an oil which soon solidified; the solid *chalkone* crystallised from methyl alcohol in yellow, woolly needles, m. p. 177° (darkening at 171°) (Found : C, 67.9; H, 5.5. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

2'-Hydroxy-4'-(β-acetoxyethoxy)flavylium Chloride.—Dry hydrogen chloride was passed through a solution of the preceding chalkone (2 g.) in glacial acetic acid (40 c.c.) during 2 hrs.; the solution became red, and after 24 hrs. the *flavylium chloride* (2 g.) was precipitated by addition of much ether. It crystallised from boiling methyl alcohol, previously saturated with hydrogen chloride, in red, woolly needles, m. p. 212–213° (darkening at 190°) (Found : Cl, 9.8. $C_{19}H_{17}O_5Cl$ requires Cl, 9.9%). Amyl alcohol extracts the chloride from its solution in dilute hydrochloric acid. Its yellow solution in concentrated sulphuric acid shows a green fluorescence. The chloride and its salts are sternutatory.

The violet colour *base*, obtained by the action of concentrated sodium acetate on the chloride, could not be crystallised; after being washed with water, it melted at 180° (Found : C, 67.9; H, 5.0. $C_{19}H_{18}O_6$ requires C, 66.6; H, 5.3%). The *ferrichloride* crystallised from methyl alcohol saturated with hydrogen chloride in shining, orange, tiny needles, m. p. 214° (195°)* (Found : C, 43.3; H, 3.5. $C_{19}H_{17}O_5Cl_4Fe$ requires C, 43.6; H, 3.3%). The *mercurichloride* formed brick-red, fleecy needles, m. p. 215° (188–197°)* (Found : Hg, 33.9. $C_{19}H_{17}O_5Cl_3Hg$ requires Hg, 31.7%); the *perchlorate* in brick-red needles, m. p. 201–203° (188–191°)* (Found : Cl, 8.5. $C_{19}H_{17}O_6Cl$ requires Cl, 8.4%), and the *picrate* in thin, shining, red plates, which become pale at 150° and melt at 211–213° (190–195°)* (Found : N, 7.8. $C_{25}H_{19}O_{12}N_3$ requires N, 7.6%).

The authors are grateful to Dr. J. N. Rây for having carried out the micro-analyses, and also to Dr. R. C. Shah and Dr. M. S. Shah for their valuable suggestions.

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[Received, May 1st, 1935.]

* M. p.'s in parentheses are mixed m. p.'s with the flavylium chloride.