82. *A New Synthesis of Olivetol.*

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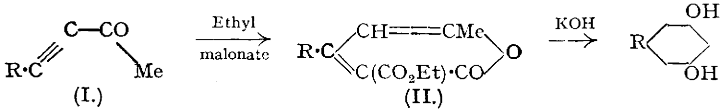
A convenient synthesis of orcinol starting from ethyl crotonate and ethyl acetoacetate is described; a similar series of reactions from methyl Δ^{α}-octenoate provides an improved route to olivetol.

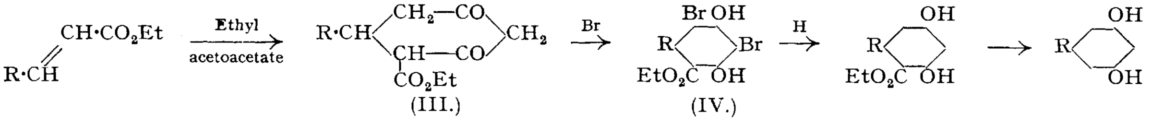
OLIVETOL (5-*n*-amylresorcinol) was first obtained (Asahina and Asano, *Ber.*, 1932, **65**, 475) by degrading the lichen acid, olivetonic acid. This constitution was verified by condensing ethyl *n*-hexoylacetate with ethyl acetonedicarboxylate; the product, presumably ethyl dihydro-olivetoldicarboxylate, was, without isolation, hydrolysed, decarboxylated and apparently oxidised by fusion with alkali. Asahina and Nogami (*Ber.*, 1935, **68**, 1500) described a more rational synthesis *via* 3 : 5-dimethoxyvalerophenone, itself obtained by propylation of the rather difficultly accessible ethyl 3 : 5-dimethoxybenzoylacetate, followed by hydrolysis. Disadvantages were partly overcome (Asahina, *Ber.*, 1936, **69**, 1643) by preparing 3 : 4 : 5-trimethoxyvalerophenone, which is directly reducible with sodium and alcohol to olivetol dimethyl ether. The method of Suter and Weston (*J. Amer. Chem. Soc.*, 1939, **61**, 232) by which dimethoxyvalerophenone is reduced is made tedious by the sulphonation of benzoic acid, alkali fusion, etc.

Having need of olivetol, we first considered a synthesis by the following route :



(I.) (II.)

The initial step is comparable with the addition of ethyl malonate to benzoylphenylacetylene (Kohler, *J. Amer. Chem. Soc.*, 1922, **44**, 379) and the second with the conversion of dehydracetic acid into orcinol (Collie and Myers, J., 1893, **63**, 122). In model experiments hexynyl methyl ketone (I, R = Bu) was submitted to the Michael reaction, and the resulting *lactone* (II, R = Bu) hydrolysed to a product apparently identical with 5-n-butylresorcinol but this approach was abandoned because of the relatively difficult accessibility of the required acetylenic ketone. The series (R = Me) does not appear to have been used as a synthesis of orcinol,



yet each of the individual reactions has been effected at different times. The series does indeed provide a very convenient synthesis of orcinol, particularly when the reduction of the bromo-compound (IV, R = Me) is carried out over palladium on a colloidal carrier (Rampino and Nord, *J. Amer. Chem. Soc.*, 1941, **63**, 2745). Hydrolysis and decarboxylation of (III, R = Me) and oxidation of the resulting dihydro-orcinol were less satisfactory; dihydro-orcinol was not oxidised to orcinol by selenium dioxide in ethanol at 80° and the bromination procedure of Merling (*Annalen*, 1894, **278**, 44) was troublesome as a preparative method. Addition of ethyl acetoacetate to the readily available methyl Δ^{α}-octenoate gave *ethyl dihydro-olivetolcarboxylate* (III, R = C_5H_{11}) in good yield and this was smoothly converted into *ethyl dibromo-olivetolcarboxylate* (IV, R = C_5H_{11}). Reduction of the bromo-ester over palladium on polyvinyl alcohol led to *ethyl olivetolcarboxylate*, which was hydrolysed and decarboxylated in the usual way. The overall yield from the octenoate to olivetol was more than 30% of the theoretical; whereas previous preparations were described as glasses, the present material readily crystallised, though it could only be recrystallised in a solvated form. Its identity was established by its colour reactions and by comparison of its hydrate and tribromo-derivative (Asahina, *loc. cit.*) with those of authentic olivetol which was kindly furnished by Dr. F. Bergel of Roche Products Ltd.

EXPERIMENTAL.

Oct-3-yn-2-one (15 g.) was added to ethyl sodiomalonate prepared from ethanol (20 c.c.), sodium (0·4 g.), and ethyl malonate (19·5 g.), and the red solution heated at 90° for 1 hour. Addition of water (3 vols.) and excess of acetic acid gave the *lactone* (II, R = C_4H_9), which was extracted with chloroform and distilled eventually in a vacuum; it was an oil, b. p. 157°/5 mm. (yield, 17 g. or 50%) (Found: C, 65·4; H, 7·4. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). Hydrolysis and decarboxylation of the lactone by successive treatment with sodium hydroxide and hydrochloric acid (cf. Kohler, *loc. cit.*), extraction of the acid with chloroform, and fusion for 25 mins. at 250° with a 1 : 1 mixture of sodium and potassium hydroxides, followed by acidification and extraction with chloroform, gave a small quantity of 5-n-butylresorcinol, m. p. 79° (lit., m. p. 82°).

Preparation of Orcinol.—Ethyl crotonate (115 g.) was added slowly to a solution prepared from ethanol (300 c.c.), sodium (23 g.), and ethyl acetoacetate (140 g.). After refluxing for 5 hours, the solution was cooled to 0°, and the sodio-compound (180 g. or 82%) collected. Decomposition with acid gave ethyl dihydro-orcinolcarboxylate, which crystallised on standing (yield, 97%) (cf. Schilling and Vorländer, *Annalen*, 1898, **308**, 195). The ester (140 g.) in acetic acid (450 c.c.) was treated with bromine (105 c.c.) in acetic acid at ~40°, and the mixture stirred overnight; ethyl dibromo-orcinolcarboxylate was then collected and recrystallised from ethanol (yield, 195 g. or 80%, a further quantity being obtained from the filtrates and mother-liquor); it had m. p. 144° (cf. Sonn, *Ber.*, 1928, **61**, 926). The bromo-ester (80 g.) in N-sodium hydroxide (700 c.c.) was rapidly hydrogenated over 2% palladium (from 0·5 g. of palladium chloride) on polyvinyl alcohol (Rampino and Nord, *loc. cit.*). Addition of sodium chloride (120 g.) precipitated the catalyst and acidification and extraction with chloroform gave ethyl orcinolcarboxylate, m. p. 132—133° (yield, 35 g. or 80%) (cf. Sonn, *loc. cit.*). The ester (17 g.) was warmed for 2 hours at 90° with sodium hydroxide (40 g.) in water (150 c.c.), and the acidified solution heated to boiling for 3 mins. and cooled. Extraction with ether and distillation gave orcinol (8·6 g. or 80%), m. p. 106—108°, b. p. 147°/5 mm. Its m. p. was not depressed by an authentic specimen and on bromination it gave pentabromo-orcinol, m. p. 125°.

Preparation of Olivetol.—n-Hexaldehyde (*Org. Syn.*, 1936, **16**, 41) (150 g.), malonic acid (80 g.), and pyridine (280 g.) were heated at 40—54° for 20 hours, the cooled solution treated with 50% (by vol.) sulphuric acid (220 c.c.), and the Δ^{α}-octenoic acid extracted with ether and distilled. Hexaldehyde (10 g.) was recovered, and Δ^{α}-octenoic acid (160 g. or 75%), $n_D^{20°}$ 1·4588, collected at 102°/5 mm. (cf. Bachmann, *J. Amer. Chem. Soc.*, 1933, **55**, 4281). The acid was converted into its methyl ester, b. p. 97°/18 mm. (yield, 160 g. or 91%) by diazomethane in ether. A boiling solution of ethyl acetoacetate (115 g.) in ethanol (260 c.c.) in which sodium (20 g.) had been dissolved was treated dropwise with methyl Δ^{α}-octenoate (114 g.), and the whole refluxed for 4 hours. The cold product was collected, the filtrate refluxed for a further 5 hours, and, after cooling, a further quantity of sodio-compound collected. The combined precipitates of sodio-compound (180 g.) were dissolved in water (1 l.) and treated with concentrated hydrochloric acid (100 c.c.). Crude *ethyl dihydro-olivetolcarboxylate* (145 g. or 71%) soon solidified and was recrystallised from light petroleum, separating in microscopic prisms, m. p. 64—65° (Found: C, 66·3; H, 8·85. $C_{14}H_{22}O_4$ requires C, 66·15; H, 8·75%). The filtrates from the sodio-compound gave no considerable amount of the desired ester and the yield was depressed under other conditions or by the use of sodamide in toluene. The ester (158 g.) in acetic acid (400 c.c.) was slowly treated, with stirring but without cooling, with bromine (104 c.c.) in acetic acid (400 c.c.), and the solution finally heated at 60° until evolution of hydrogen bromide ceased. Cooling to 0° overnight gave *ethyl dibromo-olivetolcarboxylate*, more being obtained by evaporating the filtrate in a vacuum and cooling (total yield, 140 g. or 55%); it separated from light petroleum in microscopic prisms, m. p. 67° (Found: C, 41·05; H, 4·2; Br, 39·7. $C_{14}H_{18}O_4Br_2$ requires C, 41·0; H, 4·4; Br, 39·0%). The dibromo-ester (70 g.) in N-sodium hydroxide (500 c.c.) was hydrogenated at room temperature and 1 atm. over palladium on polyvinyl alcohol (0·5 g. of $PdCl_2$). Almost 90% of the theoretical quantity of hydrogen was rapidly taken up; *ethyl olivetolcarboxylate* and the catalyst were then salted out from the acidified solution, and the ester extracted with ether and crystallised from light petroleum; it formed prisms, m. p. 69° (yield 34 g. or 80%) and sublimed very slowly at 50° in a high vacuum (Found: C, 66·65; H, 8·05. $C_{14}H_{20}O_4$ requires C, 66·65; H, 8·0%). The crude ester (31 g.) was hydrolysed and decarboxylated by boiling with sodium hydroxide (40 g.) in water (150 c.c.) for 2 hours, acidifying, boiling again for 3 minutes, and extracting with ether. Olivetol prepared by this route (yield, 20·5 g. or 92%) distilled at 145° in a high vacuum and solidified to an almost colourless, crystalline mass, m. p. 49°. It could be recrystallised from benzene–light petroleum, but separated in solvated form. It gave all the colour reactions of olivetol prepared by other processes (see Asahina and Nogami, *loc. cit.*) and in addition gave a green-brown coloration with ethanolic ferric chloride; on hydration the hydrate, m. p. 40—41°, was obtained, which depressed the m. p. of the unhydrated olivetol. The hydrate was identical with that of authentic olivetol, and the tribromo-compounds, m. p. 84°, prepared from the present material and from authentic olivetol, were identical.

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