yield). The product, crystallized from 70% ethyl alcohol, melted at 197°.

2-Methyl-1,4-naphthoquinone-8-sulfonamide.—To a solution of 30 g. of pure 2-methylnaphthalene-8-sulfonamide in 300 cc. of glacial acetic acid at 80°, 60 g. of chromic acid in 120 cc. of 50% acetic acid was added dropwise within ten minutes with constant stirring. The deep green solution was refluxed for five minutes and then immediately cooled to room temperature, 1.5 liters of water was added and the mixture kept at 0° for four hours. The naphthoquinonesulfonamide which had precipitated weighed 12.4 g. after thorough washing and drying. The filtrate was evaporated to dryness *in vacuo*, the residue taken up in 400 cc. of water and subjected to a continuous ether extraction, which yielded an additional 1.9 g. of the naphthoquinonesulfonamide. The total yield corresponded to 42% of the theoretical amount. The substance crystallized in yellow plates from ethyl alcohol containing 15% of acetic acid and melted with decomposition at 231–232°.

Anal. Calcd. for $C_{11}H_9O_4NS$: C, 52.58; H, 3.61; N, 5.58; S, 12.76. Found: C, 52.44; H, 3.48; N, 5.46; S, 12.76.

This compound, and all naphthoquinone derivatives described in the following section, gave the Craven color test.[7]

2-Methyl-1,4-naphthoquinone-8-sulfonic Acid.—To 10 g. of the methylnaphthoquinonesulfonamide, suspended in a mixture of 100 cc. of glacial acetic acid, 40 cc. of water and 26 cc. of concentrated sulfuric acid, 66 cc. of a 37% aqueous sodium nitrite solution was added with constant stirring in the course of thirty minutes at 25°.[8] To the clear solution, 150 g. of barium acetate in 450 cc. of boiling water was added and the hot mixture was filtered through diatomaceous earth. One portion of the barium salt crystallized from the filtrate on cooling as yellow needles weighing 1.8 g. A larger amount (2.3 g.) was obtained when the mother liquor was concentrated *in vacuo* to 175 cc. and chilled. The total yield of 4.1 g. of barium 2-methyl-1,4-naphthoquinone-8-sulfonate corresponded to 33% of the theoretical amount.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{22}H_{14}O_{10}S_2Ba$: Ba, 21.47; volatile S, 5.01. Found: Ba, 21.32; volatile S, 5.05.

For the conversion into the potassium salt, 400 mg. of potassium sulfate was added to a solution of 1.30 g. of the barium salt in 50 cc. of hot water. The filtrate was concentrated *in vacuo* to 25 cc., saturated with potassium chloride and cooled, when 1.11 g. of potassium 2-methyl-1,4-naphthoquinone-8-sulfonate crystallized as glistening yellow plates (94% of the theoretical yield). The salt was recrystallized from saturated potassium chloride solution.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{11}H_7O_5SK$: C, 45.50; H, 2.43; S, 11.04; K, 13.47. Found: C, 45.20; H, 2.53; S, 10.96; K, 13.33.

For further characterization, thallous 2-methyl-1,4-naphthoquinone-8-sulfonate was prepared according to Gilman and Abbott.[9] The compound, several times recrystallized from water, formed yellow hexagonal plates melting with decomposition at 263–264°.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{11}H_7O_5STl$: Tl, 44.86. Found[10]: Tl, 44.75.

The authors are indebted to Mr. W. Saschek for some of the microanalyses reported.

Summary

2-Methyl-1,4-naphthoquinone-8-sulfonic acid was synthesized by way of 2-methylnaphthalene-8-sulfonamide and 2-methyl-1,4-naphthoquinone-8-sulfonamide.

(7) R. Craven, *J. Chem. Soc.*, 1605 (1931).

(8) Method based on unpublished experiments of Drs. H. T. Clarke and H. B. Gillespie on the action of nitrous acid on benzenesulfonamide.

(9) H. Gilman and R. K. Abbott, Jr., THIS JOURNAL, **65**, 123 (1943).

(10) R. J. Meyer and A. Bertheim, *Ber.*, **37**, 2051 (1904).

NEW YORK, N. Y. RECEIVED MAY 17, 1943

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

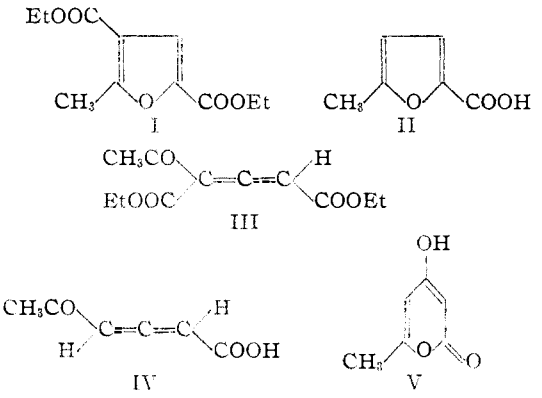
The Condensation of Ethyl α-Acetylpropionate with Ethyl Chlorofumarate

BY R. B. WOODWARD AND W. A. REED

By condensation of the sodium derivative of ethyl α-acetylpropionate with ethyl chlorofumarate, Ruhemann and Wolf[1] obtained a *compound*, m. p. 132°, to which the formula $C_{11}H_{14}O_5$ was assigned. On hydrolysis with strong acid or base, this substance was transformed, with elimination of carbon dioxide, into a new *substance*, m. p. 244° (dec.), for which analytical data indicated the formulation $C_6H_6O_3$. In the first and a later paper,[2] these substances were variously formulated as furan (I, II), allene (III, IV) and α-pyrone (V) derivatives, it being assumed in all cases that the initial condensation product had been formed from the reactants through loss of sodium chloride and *ethyl acetate*, the carbethoxyl of the latter arising from ethyl chlorofumarate, and the methyl from ethyl α-acetylpropionate. The improbability of the reaction

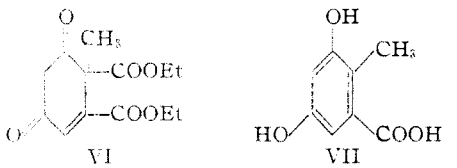
(1) Ruhemann and Wolf, *J. Chem. Soc.*, **69**, 1386 (1896).

(2) Ruhemann, *ibid.*, **71**, 325 (1897).



course, as well as our interest in compounds of the type which Ruhemann believed he had obtained, led us to reinvestigate the reaction.

In this communication it is shown that the condensation product is in fact 1-methyl-1,2,-dicarbethoxy-Δ^2-cyclohexenedione-4,6 (VI), or more accurately one of the corresponding enols, and that the hydrolysis product is cresorsellinic

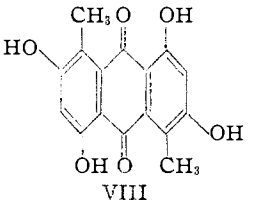


acid VII. It will be noted that this formulation necessitates a revision of the empirical formulas ascribed by the English investigators to their products. An inspection of the relevant data indicates clearly the opportunity for confusion in this case

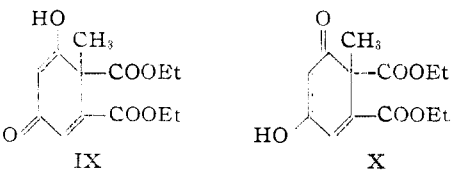
	Calcd. C	Calcd. H	Found C	Found H
$C_{11}H_{14}O_5$ (Ruhemann)	58.40	6.19		
			58.27	5.97
			58.51	6.21
$C_{18}H_{16}O_6$ (this paper)	58.20	5.97		

Obviously the analytical figures for the condensation product are acceptable for either formula. In the case of the hydrolysis product, the analytical figures are of course irrelevant to the change from $C_6H_6O_3$ to $C_8H_8O_4$, both formulas being of the type $(C_2H_2O)_x$. In this connection it is interesting to note that while the material *dried at 100°* corresponds to the latter composition, Ruhemann showed by careful titration and analyses that the *air-dried* water crystallizate had the composition $4C_6H_6O_3 \cdot 3H_2O$. It is now apparent that this material is cresorsellinic acid monohydrate, $C_8H_8O_4 \cdot H_2O$; the complicated chemical relationships proposed by Ruhemann to account for this phenomenon need no further comment.

The condensation product, in its character as a cyclic β-diketone, is strongly acidic, as evidenced by solubility in ammonia, and in soda, and gives with ferric chloride in methanol an olive-brown, and in water, a strong red coloration. The hydrolysis, which in the new formulation is merely a case of ketonic cleavage of a β-keto-ester, gives cresorsellinic acid, identical in all respects with an authentic sample, prepared by sulfonation of *o*-toluic acid, and subsequent alkali fusion of the resultant disulfonic acid.[3,4] It is worthy of note that the acid may be prepared more readily and in higher yield by the ester condensation synthesis than from *o*-toluic acid. Further proof of identity was obtained by transformation of the material by concentrated sulfuric acid into 2,4,6,8-tetrahydroxy-1,5-dimethyl anthraquinone VIII, characterized (since the compound itself is infusible) as the crystalline tetraacetate.[4]

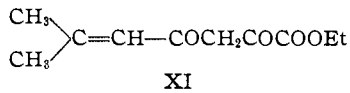


The absorption spectrum[5] of the condensation product (Fig. 1) shows a well developed maximum at 326 mμ (log ϵ = 3.68), and a subsidiary inflection indicating a maximum at ~250 mμ. The latter is undoubtedly a partial band attributable to the simple cyclic β-diketone-enol system.[6] Since no data are available on the spectra of substances containing exactly the chromophoric system present in our compound, an unequivocal decision cannot be made, but the spectrographic evidence definitely favors the enolic structure IX over that of the alternative X as



representing the preponderant species in a solution of the material. The absorbing system of α-mesityl oxide oxalic ester (XI, enol) differs from that of VI (enol) only in the transposition of

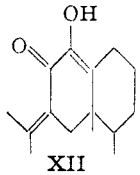
(3) Jacobsen and Wierss, *Ber.*, **16**, 1956 (1883).
(4) Liebermann, Kostanecki and Cahn, *Ann.*, **240**, 280 (1887).
(5) We are indebted to Mr. R. B. Loftfield for carrying out this determination.
(6) *Cf.* Woodward and Blout, THIS JOURNAL, **65**, 562 (1943).



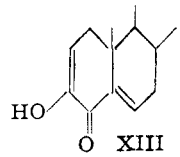
XI

terminal alkyl (non-chromophoric) and carboxyl groups, and has $\lambda_{max.}$ 312 mμ.[7]

Further, hydroxyeremophilone[8] (XII) and Δ^5-cholestenedione-3,4-enol[9] (XIII) both exhibit maximum absorption at approximately 312 mμ, and the former, at least, also manifests a subsidiary maximum at shorter wave lengths. In



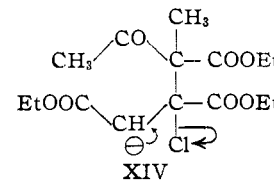
XII



XIII

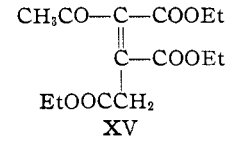
these cases, the system responsible for absorption differs from that in the Ruhemann compounds only in the absence of the terminal carbethoxyl group, and in the presence of an enolic hydroxyl on the carbon atom α- rather than β- to the carboxyl group. Generalized experience indicates that the latter difference would have little effect in the absorption,[8,10] and, further, the presence of the carbethoxyl in a system of this complexity should not result in a shift larger than that actually observed (*ca.* 15 mμ) in passing from these compounds to the Ruhemann compound. Consequently 326 mμ would seem to be a reasonable value of $\lambda_{max.}$ for the system HO—C=C—CO—C=C—COOEt contained in IX. On the other hand, the chromophore of X contains in addition to a similar absorbing system, the added geometrical feature of a conjugated cyclohexadiene system. The presence of this grouping invariably results in a shift of $\lambda_{max.}$ to longer wave lengths than that observed for the same system in a non-coannular template[11]; consequently it seems probable that X would have $\lambda_{max.}$ at a wave length considerably longer than 326 mμ.

The mode of formation of the condensation product may now be depicted in reasonable terms. Attack by the ethyl α-acetylpropionate anion on ethyl chlorofumarate gives the intermediary anion XIV, which subsequently loses chloride ion, and undergoes internal ester condensation to give



XIV

the product (VI). The first step is comparable to the Michael reaction, while the second needs no further comment. It is worthy of note that the condensation of acetoacetic ester itself with ethyl chlorofumarate[12] parallels the first steps of the above condensation, in that acetylaconitic ester (XV, or a tautomer) is obtained. The initial



XV

reaction, however, is not followed in this case by internal cyclization, presumably in consequence of the negligible proton release from the methyl group when the very acidic hydrogen of the acetylaconitate system is available.

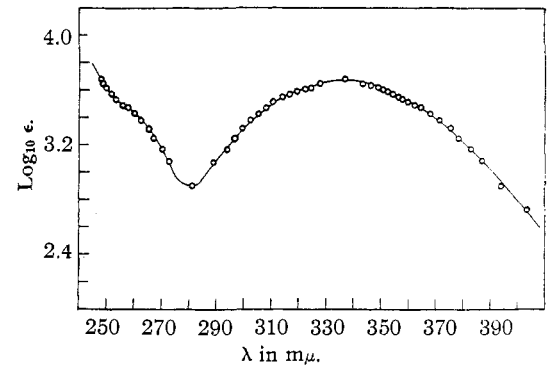


Fig. 1.—Absorption spectrum of 1-methyl-1,2-dicarbethoxy-Δ^2-cyclohexenedione-4,6 (enol) in ethanol.

Experimental

Ethyl Chlorofumarate.—The method is a modification of that used by Perkin.[13] Two hundred and twenty-five grams of granular phosphorus pentachloride was placed in a 250-cc. distilling flask, and 38 g. of well-dried (twenty-four hours *in vacuo*) tartaric acid was added and the two mixed by shaking. The sidearm of the flask was corked and the neck fitted with a calcium chloride tube. The reaction mixture rapidly became warm, and in five to ten minutes the reaction proceeded so vigorously that it was necessary to shake the flask to prevent frothing over. After about twenty minutes the initial vigorous reaction had subsided, and the reaction flask was placed on the steam-bath. After an hour a clear yellow solution was ob-

(7) Morton and Rogers, *J. Chem. Soc.*, 717 (1926).

(8) Gillam, Lynas-Gray, Penfold and Simonsen, *ibid.*, 60 (1941).

(9) Inhoffen, *Ber.*, **69**, 1705 (1936).

(10) *Cf.* Heywood and Kon, *J. Chem. Soc.*, 713 (1940), and Morton, Hassan and Calloway, *ibid.*, 883 (1934).

(11) Booker, Evans and Gillam, *ibid.*, 1453 (1940); Heilbron, Jackson, Jones and Spring, *ibid.*, 102 (1938); Woodward, THIS JOURNAL, **64**, 72 (1942).

(12) Ruhemann and Tyler, *J. Chem. Soc.*, **69**, 532 (1896), **71**, 323 (1897); Ruhemann and Stapleton, *ibid.*, **77**, 804 (1900).

(13) Perkin, *ibid.*, **53**, 695 (1888).

tained; heating was then continued two hours, the reaction mixture was allowed to stand overnight and heating was resumed for three hours more. After attaching a condenser, the phosphorus oxychloride was distilled off from an oil-bath, heating being continued until the temperature of the vapor reached 140°. The residual dark acid chloride was transferred to a 50-cc. Claisen flask and distilled at 14 mm., the portion boiling at 80–90° being collected. This material was added, with cooling, to 50 cc. of absolute ethanol. In order to remove most of the hydrogen chloride formed, carbon dioxide was bubbled through the reaction mixture for several hours. Then the excess alcohol was removed on the steam-bath, and the residual oil distilled *in vacuo*. The fraction, b. p. 135–142° (15 mm.) weighed 31 g. (59%) and was substantially pure **ethyl chlorofumarate.**

1-Methyl-1,2-dicarbethoxy-Δ^2-cyclohexanedione-4,6 (enol).—In preparing this substance, the method of Ruhemann and Wolf[1] was followed closely. The crude product was washed thoroughly with benzene, recrystallized once from this solvent, and then thrice from aqueous alcohol; it then had m. p. 137–138° and weighed (from 0.078 mole of the reactants) 4.5 g. The absorption spectrum was observed in absolute ethanol: $\lambda_{max.}$ 326 mμ, log ϵ = 3.68, infl. ~250 mμ, log ϵ ~3.4.

Cresorsellinic Acid.—One gram of the condensation product (VI) was heated under reflux for two hours with 9 cc. of concentrated hydrochloric acid. The crystalline material which separated on cooling was collected and combined with a second crop obtained on further evaporation of the filtrate. The combined material (0.4–0.5 g.), on recrystallization from water (decolorizing charcoal), separated in large clear crystals which became opaque on drying at 100°, m. p. 245–246°, mixed with an authentic sample, m. p. 245–246°. (Since the fusion in this case is accompanied by some browning at *ca.* 230°, and extensive decomposition at the melting point, the mixed melting point is probably of no great significance.)

2,4,6,8-Tetrahydroxy-1,5-dimethylanthraquinone Tetraacetate.[4]—The hydrolysis product (0.2 g.) was dissolved in 2 g. of concentrated sulfuric acid by heating on the steam bath for ten to fifteen minutes. The resultant deep red solution was poured into 15 cc. of water; the flocculent orange precipitate was collected, washed well with water, dissolved in saturated baryta, and reprecipitated by hydrochloric acid. After filtration and washing, the product was dissolved in hot alcohol (*ca.* 15 cc.). On cooling, the orange microcrystalline quinone separated (*ca.* 0.1 g.), m. p. >300°. This material was boiled for two hours with 2 cc. of acetic anhydride and 0.3 g. of anhydrous sodium acetate. The reaction mixture was poured into water, the precipitated yellow product was collected, washed with water, and recrystallized first from alcohol and then from benzene: fine yellow needles, m. p. 231–232°, mixed with a sample prepared similarly from authentic cresorsellinic acid, m. p. 231–232°.

Summary

The condensation of ethyl α-acetylpropionate with ethyl chlorofumarate gives 1-methyl-1,2-dicarbethoxy-Δ^2-cyclohexanedione-4,6. The latter, on hydrolysis, is converted into cresorsellinic acid.

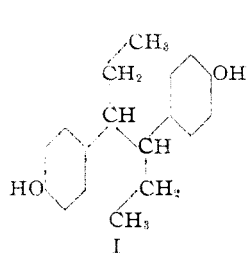
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 12, 1943

[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

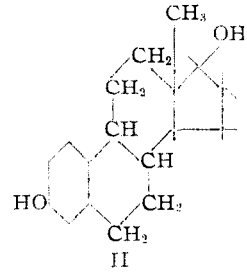
Some Analogs of Hexestrol

BY B. R. BAKER

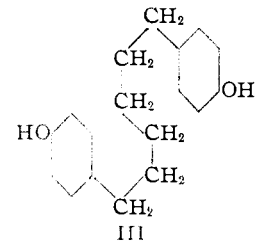
It has been postulated[1] that hexestrol (I) owes its estrogenic activity to its geometrical relationship to estradiol (II). To test this theory 1,6-bis-(*p*-hydroxyphenyl)-hexane (III),[2] 1,3-bis-(*p*-hydroxyphenyl)-hexane (IV), and 1,2-bis-(2-ethyl-4-hydroxyphenyl)-ethane (V) were synthesized



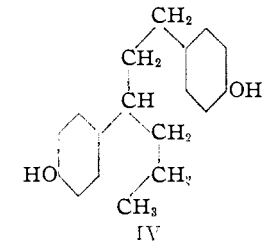
I



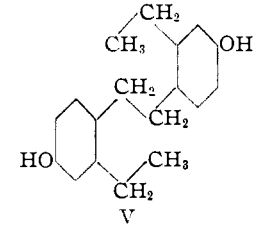
II



III



IV



V

(1) Dodds, Golberg, Lawson and Robertson, *Proc. Roy. Soc.* (London), **127**, 140 (1939); Dodds, *Lancet*, **2**, 953 (1939); Golberg, *J. S. African Chem. Inst.*, **23**, No. 2, 41 (1940); Plentl and Bogert, THIS JOURNAL, **63**, 989 (1941).

(2) Prepared by modifications of the method of Richardson and Reid, THIS JOURNAL, **62**, 413 (1940).