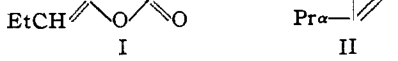
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Condensation of Acyloins with Ethyl Acetate

BY R. B. WOODWARD AND E. R. BLOUT[1]

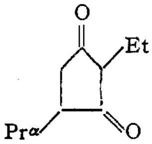
On condensation of the sodium enolate of butyroin with ethyl acetate, Bouveault and Locquin[2] obtained a *substance*, $C_{10}H_{16}O_2$, m. p. 116°,



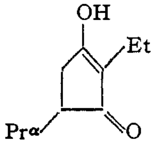
I II

to which the structure I was assigned. This formulation was supported by the observation that propionic and propylsuccinic acids were obtained on ozonization. On the other hand, the compound, on treatment with diazomethane, gave a methyl ester $C_{11}H_{18}O_2$, which could be hydrolyzed to the parent substance, or converted to an amide by the action of ammonia. Furthermore, the ester was reduced by sodium and boiling ethanol to a saturated monocyclic alcohol $C_{10}H_{20}O$. The incompatibility of these observations with formula I, and the apparently clear alternative inference that the substance contained a carboxyl group led the French investigators to the novel view that these transformations involved a reversible rearrangement of structure I into the cyclopropene derivative II under esterifying conditions.

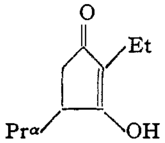
In this communication it is shown that the substance $C_{10}H_{16}O_2$ is in fact 2-ethyl-4-*n*-propylcyclopentanedione-1,3 (III).[3] The acidic char-



III

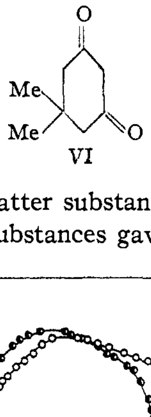


IV



V

acter of the compound was demonstrated by the *rapid* consumption of exactly one equivalent of alkali on microtitration. This observation excluded a lactonic structure (such as I) and indicated that the substance was a carboxylic acid *or* a (potentially) enolic diketone. A decision in favor of the latter alternative was strongly indicated by the observation that the substance gave a red-violet coloration with ferric chloride under carefully controlled conditions. This conclusion was fully substantiated by the examination of the ultraviolet absorption spectrum (Fig. 1) of the material ($\lambda_{\max.}$ 255 mμ, log ϵ = 4.12) which is typical of an enolized β-diketone.[4] Throughout these experiments, a comparison of the behavior of Bouveault and Locquin's compound with that of the structurally analogous (in so far as the functional group is concerned) 5,5-dimethyldihydroresorcinol (VI *or* corresponding enol) revealed striking similarities. The strong acidic character of the latter substance is well known.[5] Moreover, both substances gave red-violet ferric



VI

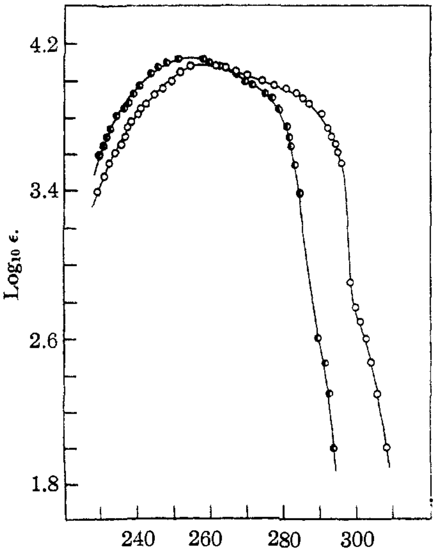


Fig. 1.—Absorption spectra in ethanol: ○, dimethyldihydroresorcinol; ◐, 2-ethyl-4-*n*-propylcyclopentanedione-1,3.

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(1) National Research Fellow in Chemistry, 1942–43.

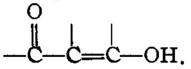
(2) Bouveault and Locquin, *Compt. rend.*, **144**, 851 (1907); *Bull. soc. chim.*, [4] **5**, 1136 (1909); *Ann. chim. phys.*, [8] **19**, 186 (1910). One of us (E. R. B.) wishes to thank Professor R. C. Elderfield of Columbia University for bringing these articles to his attention.

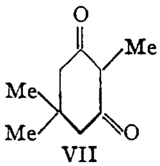
(3) It is recognized that under most conditions this substance will exist largely in the form of one or both of the corresponding enols (IV *and* V). Since, however, the factors favoring one or the other form cannot be evaluated precisely, a decision in favor of either is not possible. The structural argument in the sequel is valid throughout on the basis of either formulation.

(4) *Cf.* Gillam, Lynas-Gray, Penfold and Simonsen, *J. Chem. Soc.*, 60 (1941); Heywood and Kon, *ibid.*, 713 (1940).

(5) *I. a.*, Schwarzenbach and Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940), find pK_{enol} = 5.253.

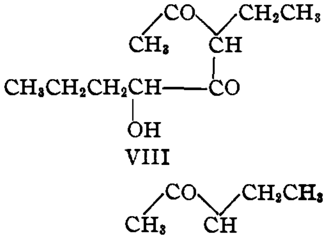
chloride colorations and, further, these colorations were destroyed (or did not appear) under identical conditions in either case. A new determination of the ultraviolet absorption spectrum of the dimethyldihydroresorcinol (Fig. 1) gave $\lambda_{max.}$ 258 mμ, log $\epsilon = 4.08$.[6] The near identity of the absorption curves needs no further comment.

We now proceed to a comparison of the reactions predicted on the basis of the above structure with those actually observed by Bouveault and Locquin. Ozonization, proceeding through the enol (IV *or* V), should, and does, give propionic and *n*-propylsuccinic acids. Those reactions previously attributed to the presence of a true carboxyl group, *viz.*, reversible esterification, and amide formation, are of course equally compatible with the vinylogous carboxyl system,  $-\overset{\overset{\textstyle O}{\|}}{C}-\overset{|}{C}=\overset{|}{C}-OH$. Furthermore, the loss of one oxygen atom through reduction by sodium and ethanol to a saturated monocyclic alcohol is readily explicable in terms of the new formula, when the behavior of other substances containing the same functional grouping is examined (*cf.* dimethyldihydroresorcinol → dimethylcyclohexanol[7]). There remains to be discussed a phenomenon observed by the earlier investigators, but not considered by them in connection with their structural proposals. On standing in air, the crystalline condensation product undergoes very facile autoxidation, with decomposition to a viscous yellow oil of penetrating and unpleasant odor. This observation is in complete accord with the assigned structure. While dimethyldihydroresorcinol itself is not attacked by oxygen on long standing, C-methyl dimethyldihydroresorcinol (VII, *or*, corresponding enol) is readily attacked, and in fact, in general *centrally alkyl-substituted cyclic β-diketones are susceptible to autoxidative decomposition*,[8] the observed phenomena in many cases corresponding very closely with those obtaining in the case of the Bouveault and Locquin condensation product.[9]

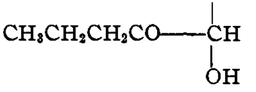


VII

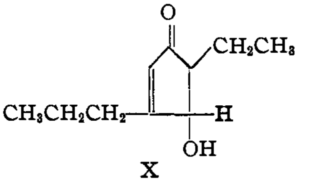
The mode of formation of 2-ethyl-4-*n*-propylcyclopentanedione-1,3, which may be envisaged as proceeding through the sequence shown below, aside from its intrinsic interest, further supports the structural argument. The reaction of the sodium enolate of butyroin with ethyl acetate gives initially, by normal ester condensation, 3-ethyl-5-hydroxyoctanedione-2,4 (VIII), which may rearrange through the common enol to the isomeric 3-ethyl-4-hydroxyoctanedione-2,5 (IX). The latter, in its character as a δ-dicarbonyl compound, condenses to the cyclopentenone derivative X, which as an α,β-unsaturated ketone establishes equilibrium, in basic media, with the corresponding β,γ-isomeride XI. Since this β,γ-form is an unstabilized enol, the shift in this case proceeds substantially irreversibly (*cf.* 3-hydroxy-6-ketocholestene-4 → 3,6-diketocholestane[10]) with the formation of the saturated β-diketone III, which of course in alkaline solution is present as the hybrid anion XII. In this connection,



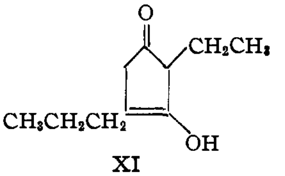
VIII



IX



X



XI

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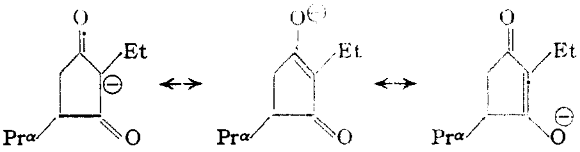
[6] Older determinations [Baly and Ewbank, *J. Chem. Soc.*, **87**, 1347 (1905), Graham and Macbeth, *ibid.*, **121**, 2603 (1922)] were not made by modern methods, and are unsuitable for comparative work, particularly in so far as intensities are concerned.

[7] Crossley and Renouf, *ibid.*, **107**, 602 (1915).

[8] The facile autoxidation of the centrally C-alkyl-substituted β-diketones, as contrasted with the inertness of the unsubstituted compounds, may be a consequence of the relatively high electron density in the unsaturated system, induced by the electron-repelling character of the substituent group.

[9] Toivonen, Lewison and Kivikoski, *Suomen Kemistilehti*, **5B**, 31 (1932); Desai, *J. Chem. Soc.*, 1079 (1932); Becker and Thorpe, *ibid.*, **121**, 1303 (1922); Vorländer and Erig, *Ann.*, **294**, 302 (1897); Fichter, Jetzer and Leepin, *ibid.*, **395**, 1 (1913).

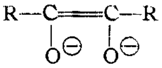
[10] Heilbron, Jones and Spring, *J. Chem. Soc.*, 801 (1937); Butenandt and Schramm, *Ber.*, **69**, 2289 (1936).



XII

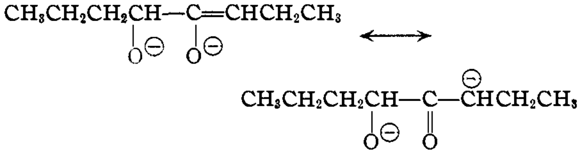
it is recognized that the above reactions actually proceed through various anions related to the neutral molecules shown (VIII–XI); the rationale of the over-all reaction, however, is readily apparent without a detailed discussion of the mechanism, for each step of which ample analogy is available in less complicated systems.

The establishment of the structure of Bouveault and Locquin's compound as 2-ethyl-4-*n*-propylcyclopentanedione-1,3 is of some consequence to the general problem of the structure of acyloin enolates. The formula usually accepted[11] for these compounds involves the dienolate anion


$$R-\underset{O^{\ominus}}{\underset{|}{C}}=\underset{O^{\ominus}}{\underset{|}{C}}-R$$

XIII

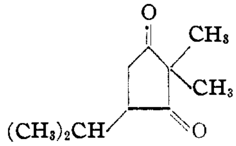
XIII; on the other hand, the considerations outlined above indicate clearly that the reacting species in the ester condensation has the structure XIV, and it seems probable that the implications


$$CH_3CH_2CH_2\underset{O^{\ominus}}{\underset{|}{CH}}-\underset{O^{\ominus}}{\underset{|}{C}}=CHCH_2CH_3 \longleftrightarrow CH_3CH_2CH_2\underset{O^{\ominus}}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-\overset{\ominus}{C}HCH_2CH_3$$

XIV

of this observation may be extended to include acyloin enolates in general. This conclusion is not surprising in view of the unfavorable charge distribution in molecules of type XIII.[12]

In addition to the condensation product described above, Bouveault and Locquin obtained analogous compounds from other acyloins, *viz.*, propionoin, isobutyroin, isovaleroin, and caproin. There is no doubt that all of these products have cyclopentanedione structures. The product from isobutyroin, however, deserves special mention, in that the presence, in the anticipated structure (XV), of two methyl groups on the carbon



XV

between the carbonyl groups effectively prevents enolization. The product should therefore be non-acidic, and it is significant in this connection that the compound is the only one of the series from which the French investigators failed to obtain a methyl ester.[2b]

It is noteworthy that very few 1,3-cyclopentanediones have been described previously. While 1,3-cyclohexanediones are easily obtained by internal condensation from δ-keto-esters, the corresponding five-membered diketones can be prepared similarly only in the event that highly substituted γ-keto-esters are used,[13] and then in poor yield; for example, all attempts to obtain the parent compound of the series, cyclopentanedione-1,3, by internal cyclization of ethyl levulinate have failed.[13b,c,14] The elucidation in this communication of the correct course of the acyloin enolate–ethyl acetate condensations opens a new and quite possibly general route to this hitherto very difficultly accessible class of compounds.

Experimental

2-Ethyl-4-*n*-propylcyclopentanedione-1,3.—Freshly distilled ethyl butyrate (b. p. 121–121.6°, 81.4 g.) was added in portions (0.1 mole) over a period of two and one-half hours to 400 cc. of anhydrous ether in which 32.2 g. of sodium wire was suspended. The reaction, which set in immediately, was complete in about eighteen hours (complete solution of sodium). To the resultant thick yellow paste, 61 g. of dry ethyl acetate was added in one portion. After removal of ether on the steam-bath, heating was continued for four hours, during which time the reaction mixture became red and translucent. After cooling, the mass was dissolved in water, acidified with hydrochloric acid, and the aqueous solution extracted with ether. The extract was washed with 5% sodium hydroxide solution; after acidification of the latter, the material was again taken up in ether, dried over anhydrous sodium sulfate, and the ether removed. The residual yellow oil was fractionated *in vacuo;* the fraction, b. p. 172–176° (1 mm.), was practically pure **2-ethyl-4-*n*-propylcyclopentanedione-1,3**; it crystallized on cooling and weighed

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[11] First suggested by Bouveault and Locquin, *Bull. soc. chim.*, [3] **35**, 633 (1906).

[12] Salt formation in cases of this sort ordinarily involves the generation of the most weakly basic of the possible anions. The anion XIII, in consequence of the like charge interaction through the double bond, will be very strongly basic. Considered in another way, the ordinary stabilization of an enolate anion, through resonance contributions of forms which in this case are of the type


$$R-\overset{\ominus}{\underset{O^{\ominus}}{\underset{|}{C}}}-\underset{O}{\underset{\|}{C}}-R \longleftrightarrow R-\underset{O}{\underset{\|}{C}}-\overset{\ominus}{\underset{O^{\ominus}}{\underset{|}{C}}}-R$$

will be greatly diminished.

[13] Farmer, Ingold and Thorpe, *J. Chem. Soc.*, **121**, 128 (1922); De Rosambo, *Ann. chim.*, [9], **19**, 327 (1923); Rothstein and Thorpe, *J. Chem. Soc.*, 2011 (1926); Kandiah, *ibid.*, 952 (1931).

[14] Duden and Freydag, *Ber.*, **36**, 947 (1903).

18.7 g. (32%). After washing with petroleum ether, recrystallization from hot water gave plates, m. p. 118.7–120.5°, and a further recrystallization from ethyl acetate gave clusters of glistening colorless plates, m. p. 119.4–120.5°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.40; H, 9.57. Found: C, 71.28; H, 9.55.

Microtitration with 0.01 *N* sodium hydroxide (phenolphthalein) gave equivalent weight: 167.9, 168.3. Calcd. 168.2.

Determination of the absorption spectrum in ethanol solution gave $\lambda_{max.}$ 255 mμ, log ϵ = 4.12.

The Ferric Chloride Test.—As a result of the insolubility of the dione in cold water (the solid is waxy, and is not wetted under these conditions), no color appeared on addition of aqueous ferric chloride to a suspension of the substance. If, however, the hot aqueous solution of the dione was cooled and filtered, the filtrate gave a strong red-violet color with one drop of 1% aqueous ferric chloride solution.[15]

Summary

The condensation of acyloin enolates with ethyl acetate leads to the formation of 1,3-cyclopentanediones.

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[15] *Cf.* Blaise and Maire, *Bull. soc. chim.*, [4] **3**, 427 (1908).

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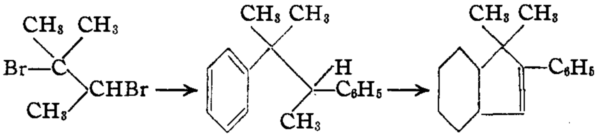
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Action of Methylmagnesium Iodide on Methyl α-Phenylcinnamate and a Synthesis of 1,1-Dimethyl-2-phenylindene

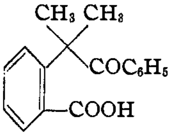
BY C. F. KOELSCH AND PAUL R. JOHNSON

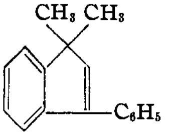
In connection with an investigation on the pyrolysis of indene derivatives[1] a sample of 1,1-dimethyl-2-phenylindene was required. It had been reported that this hydrocarbon was formed[2] by the action of trimethylethylene bromide on benzene in the presence of aluminum bromide.

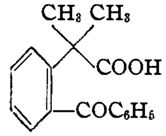

I

The hydrocarbon so obtained melted at 50–51°, gave an acidic oxidation product that melted at 198° (formulated as II), and gave a nitro derivative that melted at 140°. But these properties are in exact agreement with those of 1,1-dimethyl-3-phenylindene,[1] and it was therefore believed that the Friedel–Crafts reaction involved a rearrangement and that the product was really the isomer (III) of I.

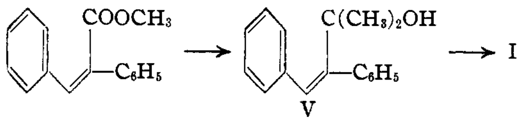
This belief was confirmed by the results of the work described in the present paper, in which it is shown that I has properties different from those previously ascribed to it. The 198° acidic oxidation product is therefore IV, and the 142° nitro derivative is 1,1-dimethyl-2(?)-nitro-3-phenylindene.


II


III


IV

The synthesis of I first attempted involved the reactions


V

But no solid product could be obtained by the action of acids on V. Oxidation of the oils produced by dehydrating agents gave only benzoic acid, indicating that no indene had been formed.

If the product of the reaction between methylmagnesium iodide and methyl α-phenylcinnamate were a ketone, formed by 1,2- and 1,4-additions, it would not yield an indene. The Grignard product had been studied previously[3] and its structure had been based on the formation of benzoic and acetic acids from it by oxidation. Since these acids might also result from the oxidation of a 1,4-addition product, it became necessary to secure new evidence regarding the structure.

Reduction with sodium and alcohol gave a carbinol, and this carbinol was identical with the product (VI) obtained from methylmagnesium

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[1] Koelsch and Johnson, THIS JOURNAL, **65**, 567 (1943).

[2] Earl and Smythe, *J. Proc. Roy. Soc. N. S. Wales*, **44**, 90 (1930). *Brit. Chem. Abstracts*, A, 340 (1931).

[3] Kohler and Heritage, *Am. Chem. J.*, **33**, 153 (1905).