pared by dehydration[33] of (III), yield 75%, b. p. 75–78°. (XIV)[34] was prepared by adding bromine diluted with petroleum ether to a solution of (XIII) in the same solvent until color persisted, keeping the temperature at about −15° (below this temperature the reaction rate was slow). After removal of solvent *in vacuo*, (XIV) remained as an almost colorless oil, yield 92%.

Ethanol solutions of (XIV) and of thioformamide were mixed at −50°, allowed to warm slowly to 5° and kept at this temperature for three days; a substantial crystalline deposit had formed. The basic products were taken up in acid, liberated with potassium carbonate and converted directly to picrates; no halogen containing picrate could be detected. The products[35] were not identified;

derivative was formed. When acrolein dibromide was mixed with an equimolar amount of thiourea in the presence of absolute alcohol, no reaction (other than acetal formation) took place at room temperature. However, on warming on the steam-bath an apparently crystalline precipitate formed, only sparingly soluble in water, m. p. 235° dec. from aqueous ethanol (Found: C, .18.05; H, 2.65; N, 14.96). On treatment with aqueous potassium carbonate this solid was converted to an amorphous material insoluble in the usual solvents but soluble in acids. Hubacher (*Ann.*, **259**, 243 (1890)) had reported that acrolein dibromide does not react with thiourea.

(33) Décombe, *Compt. rend.*, **202**, 1685 (1936); compare ref. 14b.

(34) Schlotterbeck, *Ber.*, **42**, 2563 (1909).

(35) One condensation (carried out at 5°) gave 9.0 g. (from 40 g. of (XIV) and 17 g. of thioformamide) of viscous ether-soluble oily bases.

however, it seems reasonably certain that (XV) (see above) was not formed by this reaction.

Summary

The preparation of 4-methyl-5-(hydroxymethyl)-thiazole by several different methods has been investigated. A convenient two-step synthesis starting from chloroacetone has been developed.

On fractionation, 0.3 g. of material b. p. *ca.* 70° at 2 mm. was obtained which gave a halogen-free picrate, m. p. 154.5–154.8° from ethanol; the rest was considerably higher boiling. Another condensation carried out at room temperature gave a product which behaved in a similar fashion on distillation. The picrate however (also halogen-free) melted at 184.0–184.5° from water. *Anal.* (154° picrate): C, 35.97; H, 2.93; N, 14.71; S, 19.99. *Anal.* (184° picrate): C, 36.23; H, 2.78; N, 14.86; S, 19.94.

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Studies on Ionone. III. Structure of Ethyl Ionylidene-acetates[1]

BY HARRY SOBOTKA, HUGH H. DARBY, DAVID GLICK AND EDITH BLOCH

It has been reported in a preceding publication[2] that the important ionylidene acetaldehyde cannot be obtained by dry distillation of the mixed barium salts of ionylidene acetic acid and formic acid, but that ionone is obtained. It has also been stated that dry distillation of barium ionylidene-acetate leads invariably to α-ionone regardless of whether the ionylidene-acetic acid was prepared from α- or β-ionone in the Reformatsky condensation. Since both series thus converge, the question arises whether the transition from the β- to the α-series takes place in the course of the Reformatsky reaction or during the ensuing dry distillation. As has been indicated in the first paper of this series, spectrographic evidence points to the occurrence of this rearrangement during the synthetic reaction. The study of the ultraviolet absorption spectra of ethyl ionylidene-acetate forms the subject of the present communication.

The double bond of the carbethoxy group in ethyl α-ionylidene-acetate is conjugated with two ethylene bonds, whereas the cyclic double bond is not conjugated with this system and is not expected to influence the position of the main absorption band. Conversely, the C=O— bond

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and the Mount Sinai Hospital. Original manuscript received November 12, 1943.

(2) H. Sobotka, E. Bloch and E. Glick, THIS JOURNAL, **65**, 1961 (1943).

of ethyl β-ionylidene-acetate is conjugated with three ethylene bonds; this should produce a difference, at the very least, of 25 mμ and up to 45 mμ, between the main absorption band of the two compounds.
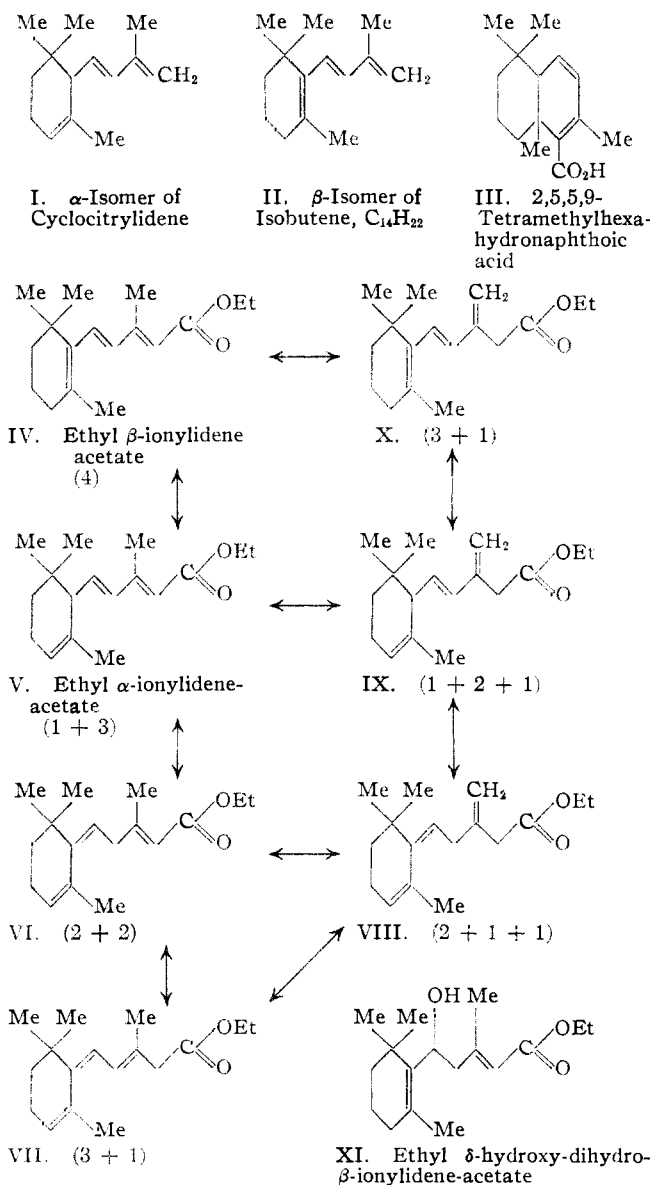
Table I gives the absorption bands for the pair α-ionone–β-ionone and also for the pair of isomeric hydrocarbons $C_{14}H_{22}$ (formulas I and II) which we have prepared according to Kipping and Wild.[3]

TABLE I

ABSORPTION MAXIMA OF ETHYL IONYLIDENE-ACETATES AND RELATED COMPOUNDS

Graph	Compound (mol. wt.)	Max. wave length, mμ	Mol. extinction coefficient, ϵ_{max}
	Ionone (192.3)		
..	α-Isomer	228	15,550
..	β-Isomer	296	12,700
	Cyclocitrylidene-isobutene (190.3)		
1	α-Isomer	230	30,100
2	β-Isomer	281.5	21,900
	Ethyl ionylidene-acetate (262.4)		
3	Prepn. A	271	10,750
4	Prepn. B	284.5	12,550
5	Prepn. B (purified)	281.5	34,000
6	Prepn. C	269	27,200
7	Prepn. D	275	17,400

(3) Kipping and Wild, *J. Chem. Soc.*, 1239 (1940).

Both in the ionone pair, and in the cyclocitrylidene–isobutene pair, one deals with the difference between conjugated double systems of two and three double bonds; hence, the difference between the wave lengths of the absorption peaks is larger than the difference one would anticipate between α- and β-ethyl ionylidene-acetate with three and four double bonds, respectively.

I. α-Isomer of Cyclocitrylidene

II. β-Isomer of Isobutene, $C_{14}H_{22}$

III. 2,5,5,9-Tetramethylhexahydronaphthoic acid

IV. Ethyl β-ionylidene acetate (4)

X. (3 + 1)

V. Ethyl α-ionylidene-acetate (1 + 3)

IX. (1 + 2 + 1)

VI. (2 + 2)

VIII. (2 + 1 + 1)

VII. (3 + 1)

XI. Ethyl δ-hydroxy-dihydro-β-ionylidene-acetate

Note to Formulas IV–X: The figures in parentheses indicate the number of double bonds in conjugated groups.

The Reformatsky condensation of α- and of β-ionone with zinc and ethyl bromoacetate yielded two products A and B with absorption maxima at 271 and 284.5 mμ, respectively (Fig. 2, curves 3 and 4), the spectrum of product B showing a minute hump at 271 mμ which cannot be dis-

cerned in the figure. The ester B was saponified and the resulting acid re-esterified with ethanol; a product of high purity with a sharp peak at 281.5 mμ was obtained (Fig. 2, curve 5). The difference of 10.5–13.5 mμ between the absorption peaks of A and B seems to exclude the presence of an additional conjugated double bond in B. The wave length of either maximum is at least 20 mμ below the value expected for a system of 4 conjugated double bonds as in ethyl β-ionylidene-acetate (formula IV).

Since a rearrangement of the β-form must thus have occurred during the Reformatsky reaction, we attempted to synthesize authentic ethyl β-ionylidene-acetate by a different procedure. We undertook a Barbier–Grignard condensation of β-ionone with the Grignard compound of ethyl bromoacetate in nascent state. In the hope of clarifying the observed differences between A and B, we performed a parallel Barbier–Grignard synthesis with α-ionone. The resulting pair of ethyl ionylidene-acetates were designated "C" from α-ionone and "D" from β-ionone. The absorption maxima of both products fell in the same range with a value of 269 mμ for C and 275 mμ for D (Fig. 2, curves 6 and 7).

The use of lithium instead of magnesium, which had proved of value in the preparation of another authentic β-ionone derivative,[3] gave too poor a yield for further investigation.

Besides the spectroscopic evidence, neither the differences in boiling range, nor in refractive index, favor the assumption that any of the 4 esters be ethyl β-ionylidene-acetate. Saponification with 0.1 N alcoholic potassium hydroxide indicates differences in stability amongst these esters. Saponification proceeds approximately twice as rapidly with the products of the Reformatsky reaction, A and B, than with the products of the Barbier–Grignard reaction, C and D. This difference may be caused by cis–trans-isomerism, but ring closure resulting in the formation of a 2,5,5,9 - tetramethyl - hexahydronaphthoic acid (III) had also to be considered, in which the carboxyl group may be conceivably hindered. The possibility of the formation of a bicyclic derivative was disproved by catalytic hydrogenation of A and C in alcoholic solution with platinum oxide (Adams); both compounds took up slightly over three molecules of hydrogen. The free acid, obtained from C, likewise consumed three moles of hydrogen to form a saturated compound. The perhydroionylidene-acetic acids thus obtained from A and from C showed the required elementary composition $C_{15}H_{28}O_2$ and an identical refractive index $n^{24}D$ 1.4710. Furthermore, major
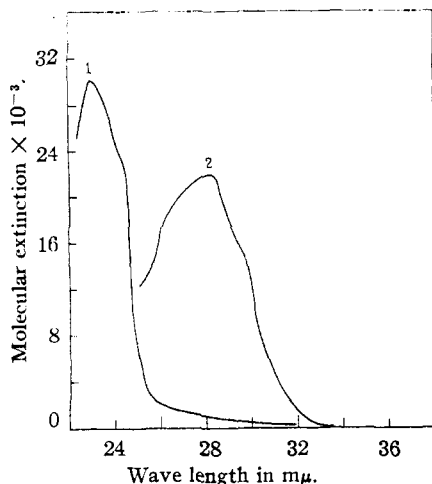
Fig. 1.—Ultraviolet absorption spectra of the cyclocitrylidene isobutenes: Curve 1, α-isomer; Curve 2, β-isomer.
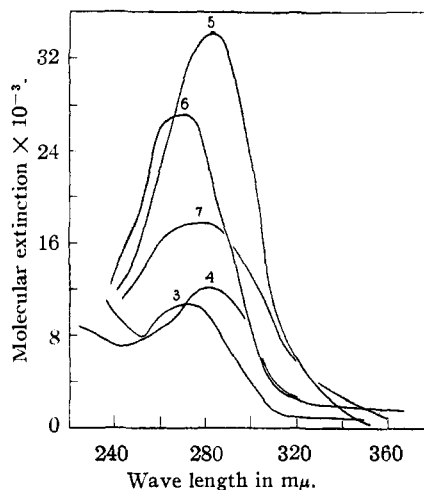

Fig. 2.—Spectra of ethyl ionylidene-acetates: Curve 3, A; Curve 4 and 5, B; Curve 6, C; Curve 7, D. The right half of curve 4 overlaps with curve 6.

structural differences between the preparations obtained with zinc and those with magnesium, might be betrayed by their behavior in monomolecular layers.[4] The unsaturated esters or acids themselves could hardly be expected to form such layers, nor could one expect the formation of a monomolecular film from a saturated bicyclic compound, a formulation which was already eliminated on analytical grounds. The maximum extension of a molecule of perhydroionylidene-acetic acid, δ-(2,2,6-trimethylcyclohexyl)-β-methylvaleric acid is ca. 9.6 Å. The perhydro derivatives both of the A and C acids on a barium buffer substratum of pH 9.0 form monomolecular films, stable to lateral pressures up to 12 dynes/cm. When built up on a metal plate with staggered layers of barium stearate,[5] the thickness of three successive double layers was the same in both instances and definitely surpassed the thickness of one double layer of barium stearate, which is 49 Å. This leads to an estimate of 60 Å. for six layers and 10 Å. for the thickness of a single layer of barium perhydroionylidene-acetate, both in the case of product A and C. If one considers the increment for the metal atom on one hand, and the correction for the probably slant of the molecule on the other hand, these data support the monocyclic formulation and the structural identity of the carbon skeletons of the products obtained with zinc and with magnesium.

In the subjoined tabulation of the seven structural possibilities, obtainable by shifting double bonds in ethyl ionylidene-acetate, IV, with four conjugated double bonds, and formulas VI, VIII and IX, with less than three conjugated double bonds, are excluded by spectroscopic evidence. This leaves possibilities V, VII and X for closer scrutiny. V, the authentic α-form, and X with the improbable methylene group are obtainable

from the β-form IV by the shift of merely one double bond. VII is related only to the α-form, namely, by a rearrangement involving two double bonds. An analogous rearrangement of both α- and β-forms of citrylideneisobutyraldehyde has been demonstrated by Heilbron and co-workers.[6] A similar shift in the present case in, or via, the α-form, is not beyond the realm of possibility. The starting material is at present too expensive to explore the possibility of formulations X and VII by oxidative degradation. In view of the formation of α-ionone by dry distillation, we believe that we are dealing in all instances with the α-ester of formula V and that the slight differences amongst the four products in wave length and extinction coefficients of the ultraviolet absorption spectra as well as the reported differences in the rate of saponification, may be ascribed to geometric isomerisms of the two double bonds in the side chain.

Since all rearrangements of the α-ester (formula V) involve the center of asymmetry except in the case of formula IX, the availability of optically active α-ionone[7] may be of aid in the further investigation of this question.

Addendum.—After this paper had been submitted for publication, there appeared an article by Young and co-workers[8] on the same subject. The ultraviolet absorption data of these authors for the two ethyl ionylidene-acetates agree closely with our findings: the difference of the maxima between the products obtained from α- and from β-ionone are 11 mμ for the esters (our difference 10.5–13.5 mμ), 16 mμ for the free acids, and 6.5 mμ for the nitriles. Their data for the two ionylideneacetones show no difference in wave length.

(4) H. Sobotka, in "Handbook of Medical Physics," Year Book Publishers, Chicago, 1944, p. 763.

(5) H. Sobotka and E. Bloch, J. Phys. Chem., **45**, 9 (1941).

(6) I. M. Heilbron, A. W. Johnson, E. R. H. Jones and A. Spinks, J. Chem. Soc., 727 (1942).

(7) Sobotka, Bloch, Cahnmann, Feldbau and Rosen, THIS JOURNAL, **65**, 2061 (1943).

(8) Young, Andrews and Cristol, ibid., **66**, 520 (1944).

This is in striking contrast to the difference of 69 mμ for the ionones, of 51.5 mμ for the cyclocitrylideneisobutenes, pairs with two and three double bonds, respectively, and also to the difference of 46 mμ for the ionylidene-cyanoacetic acids and 60.5 mμ for their methyl esters, pairs with three and four double bonds, respectively. There is no compound known, containing a chromophoric system of four double bonds, with a maximum below 296 mμ. The principle, laid down by Woodward,[9] regarding the influence on absorption maxima in α,β-unsaturated ketones of substitution

$$R-\underset{\underset{O}{\|}}{C}-\underset{\underset{a}{|}}{C}=C\underset{b}{\overset{b}{\diagup}}$$
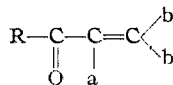
in positions a, b and b, when applied to ethyl ionylidene-acetate with only one substituent, would place both its β- and α-isomer amongst the group with lowest values, without, however, affecting the expected difference between the two isomers. The same holds for the observation by Zechmeister,[10] that cis-linkages in long polyene chains produce a shift of the absorption spectrum toward shorter wave lengths as compared to all-trans compounds. On the basis of the available spectroscopic evidence and of the above considerations, we hesitate to ascribe β-structure to our condensation product of β-ionone with ethyl bromoacetate.

There remains a conflict between the spectroscopic evidence on one hand, and the chemical evidence, adduced by Young, on the other hand, especially the following three points, namely, that β-ionylidene-acetic acid preparations of coinciding chemical and physical properties are obtained from β-ionone, both by the Reformatsky reaction and via ionylidenecyanoacetic acid, decarboxylation and hydrolysis of the nitrile; that α- and β-ionylideneacetone may be prepared from the respective ionylidene-acetic acids; and by the evidence of ozonolysis, yielding small but significant yields of geronic acid from the β-isomers, but isogeronic acid from the α-isomers.[7,11] The first curve in Young, Andrews and Cristol's[8] Fig. 1 (—·—, β, solid) displays a second maximum at 294 mμ, i. e., 27 mμ higher than that of the α-form; moreover, a secondary maximum is given for the β-ionylideneacetonitrile at 300 mμ, i. e., 37.5 mμ higher than for the α-nitrile. These data, in conjunction with the chemical observations, may suggest that the experimental conditions during condensation, dehydration and distillation cause rearrangement to varying degrees with preservation of considerable quantities of β-form, especially in the cyanoacetic ester variant of the synthesis. This assumption seems more satisfactory than to postulate an unprecedented

deviation from spectroscopic experience. An ultimate clarification of this conflict is desirable, as it will determine the amount of reliance that may be placed on spectroscopic regularities and, at the same time, shed light on the degree of lability and the mechanism of isomerization in the trimethylcyclohexene ring.

Experimental

Preparation of A- and B-forms of Ethyl Ionylidene-acetate.—The synthesis of these two esters was carried out according to Karrer,[12] as described in paper I of this series.[2]

Analysis of B-ester. Calculated for $C_{17}H_{26}O_2$: C, 77.8; H, 10.0. Found: C, 77.7; H, 10.0.

Preparation of C- and D-forms of Ethyl Ionylideneacetate.—19.2 g. of α-ionone and the equivalent amount (16.7 g.) ethyl bromoacetate were dissolved in 100 ml. of dry benzene and the solution was added dropwise to 2.43 g. of magnesium in 100 ml. of dry benzene under reflux. The reaction did not appear to commence until all the reactants were added. After two hours of further refluxing, almost all the magnesium had disappeared. The reaction product was decomposed with cold saturated ammonium chloride solution and, after washing and drying, fractionated under 0.2 mm. pressure. The main fraction distilling between 122 and 123° weighed 10 g. The product was free from carbonyl compounds, when tested with dinitrophenylhydrazine, and free of hydroxy acid. *Analysis* of ester C. Calcd. for $C_{17}H_{26}O_2$ (262.4): C, 77.8; H, 10.0. Found: C, 77.4; H, 10.1; saponification equivalent, 261; n^{22}D 1.5203.

Ester D was similarly prepared from β-ionone: b. p. 127–130° at 0.6 mm. *Anal.* Found: C, 77.1; H, 9.9; sap. equivalent, 261; n^{22}D 1.5218.

Ethyl δ-Hydroxydihydro-β-ionylidene-acetate (XI).—(By Martin Rubin). As an alternative route for the synthesis of ethyl β-ionylidene-acetate, a modified Reformatsky condensation was attempted with β-cyclocitral[13] and ethyl γ-bromo-β-methylcrotonate, the preparation of which will be described elsewhere. For an analogous reaction with γ-iodocrotonic ester cf. Fuson.[14] After decomposition with 10% acetic acid, the product was fractionated *in vacuo* under a current of nitrogen. The elementary analysis showed that no dehydration had occurred under these conditions. Calcd. for $C_{17}H_{28}O_3$ (280.4): C, 72.85; H, 10.05. Found: C, 72.4; H, 9.4; sap. equivalent, 274. The yield was too scanty for further attempts at dehydration.

Ultraviolet Absorption Spectra.—These were taken with a medium Hilger quartz spectrograph with a constant hydrogen source and a Spekker photometer. All spectra were obtained from observation of approximately 0.0013 molar solutions in absolute alcohol in a 1-cm. cell.

Summary

Rearrangement during the condensation of β-ionone with ethyl bromoacetate leads presumably to ethyl α-ionylidene-acetate. The presence of the expected β-isomer is excluded on grounds of ultraviolet spectroscopy. Minor differences in the absorption spectra and in the rate of saponification of four preparations obtained by two different methods from α- and from β-ionone are most probably due to geometric isomerism of the double bonds in the side chain.

(9) Woodward, THIS JOURNAL, 63, 1123 (1941).

(10) Zechmeister and Polgár, *ibid.*, 66, 137 and 186 (1944); Zechmeister, *Chem. Rev.*, 34, 267 (1944).

(11) Lindenbaum, Andrews and Young, THIS JOURNAL, 66, 2130 (1944).

(12) Karrer, Salomon, Morf and Walker, *Helv. Chim. Acta*, 15, 878 (1932); Karrer, Morf and Schoepp, *ibid.*, 16, 557 (1933); Karrer, Ruegger and Solmssen, *ibid.*, 21, 448 (1938).

(13) H. Sobotka and E. Bloch, *Chem. Rev.*, 35, 435 (1944).

(14) R. C. Fuson, R. T. Arnold and H. G. Cooke, THIS JOURNAL, 60, 2272 (1938); R. C. Fuson and P. L. Southwick, *ibid.*, 66, 679 (1944).