187. *Studies in the Polyene Series. Part XXIV. The* C_{17} *Acid and* C_{18} *Ketone related to Vitamin A.*

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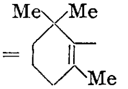
The recent publication by Arens and van Dorp (*Nature*, 1946, **157**, 190) of a description of the synthesis of " vitamin A acid " *via* the C_{17} acid and C_{18} ketone necessitates the publication of work done in our laboratory along similar lines. The crystalline C_{17} acid (II; R′ = H) is obtained in 15% yield from β-ionone by a Reformatsky reaction with γ-bromocrotonic ester and it is converted, through the acid chloride, into the C_{18} ketone (IV). Attempts to effect Reformatsky reactions with ω-bromosorbic ester and β-ionone and other ketones have been abortive.

The use of γ-halogenocrotonic esters in Reformatsky reactions was first studied by Fuson, Arnold, and Cooke (*J. Amer. Chem. Soc.*, 1938, **60**, 2272), who obtained rather poor yields of unsaturated esters in condensations of the bromo- and iodo-compounds with benzaldehyde and *cyclo*hexanone. As was noted by these authors, the usefulness of this reaction is limited by the availability of the γ-halogenocrotonates. In 1942 Ziegler *et al.* (*Annalen*, **551**, 80) described the convenient preparation of methyl γ-bromocrotonate by bromination of methyl crotonate with *N*-bromosuccinimide, and in a simultaneous paper (*ibid.*, p. 120) details of Reformatsky reactions with the bromo-ester and benzaldehyde, cinnamaldehyde, etc., were published. Cook and Schoental (*J.*, 1945, 288) have successfully condensed methyl bromocrotonate with ketotetrahydrophenanthrene, noting the many possible applications of this method in the synthesis of hydroaromatic fused-ring systems.

In the earliest synthetic work in the vitamin A field, β-ionone was condensed with ethyl bromoacetate and zinc to give, after dehydration at 170°, ethyl β-ionylideneacetate (I, R′ = Et) (Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878). This reaction is by no means as straightforward as would appear from the original description (cf. Young, Andrews, and Cristol, *J. Amer. Chem. Soc.*, 1944, **66**, 520; Sobotka, Bloch, and Glick, *ibid.*, 1943, **65**, 1961; Young, Andrews, and Lindenbaum, *ibid.*, 1944, **66**, 2131; Sobotka, Darby, Glick, and Bloch, *ibid.*, 1945, **67**, 403). Our own investigations carried out over a period of several years provide additional evidence of its complexity and will be reported in due course.

R =


(I.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2R'}$

$\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2R'}$ (II.)

(III.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$

$\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}COMe}$ (IV.)

In view of the difficulties encountered with ethyl β-ionylideneacetate, only pure β-ionone (regenerated from its semicarbazone by the method devised by Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727) was employed in Reformatsky reactions with methyl γ-bromocrotonate. Condensation proceeded normally in benzene solution and, according to spectrographic and other evidence, the crude product contained a considerable portion of the dehydrated ester (II; R′ = Me), which after distillation exhibited a broad absorption band with a maximum in the region of 3100 A. (ε = 12,500). The gummy acid obtained on hydrolysis with cold alcoholic potassium hydroxide readily crystallised in contact with ether, giving the C_{17} acid (II; R′ = H), m. p. 160°, in an overall yield of 15% from β-ionone. The structure assigned to this acid is supported by ozonolysis evidence, a 34% yield of geronic acid (isolated as semicarbazone) being obtained, and also by a quantitative hydrogenation, 3·9 moles of hydrogen being absorbed. The light-absorption properties of the acid ($\lambda_{max.}$ 3250 A., ε = 32,500) and of the pure *methyl* ester ($\lambda_{max.}$ 3230 A., ε = 33,000), prepared with diazomethane, are in accord with the structure given, being displaced towards longer wave-lengths by the expected amount when compared with the data for pure β-ionylideneacetic acid (I; R′ = H) (maxima, 2910, 2810, and 2590 A.; ε = 13,000, 13,000, and 12,000, respectively).

The success obtained in condensing the γ-bromocrotonate with β-ionone appeared to augur well for the extension of this type of reaction to sorbic esters, in the expectation of obtaining the C_{19} acid (III), and later, by using a methylsorbic ester, the acid corresponding to vitamin A itself. *Methyl ω-bromosorbate* was made in 65% yield by reaction between methyl sorbate and *N*-bromosuccinimide. It showed the expected light-absorption properties, and its structure was proved by the isolation of bromoacetaldehyde and the methyl ester of the half aldehyde of fumaric acid (as 2 : 4-dinitrophenylhydrazones) on ozonolysis. Numerous attempts to condense this ester, not only with β-ionone, but also with acetophenone and *cyclo*hexanone, under a great variety of conditions (use of benzene, toluene, xylene, and anisole as solvents, in the presence of activated zinc and magnesium, etc.) were entirely abortive since, although the metal usually went into solution, comparatively small amounts of high-boiling non-ketonic products were obtained from any of these experiments. [Note added in proof. Karrer and Schwyzer (*Helv. Chim. Acta*, 1946, **29**, 1191) have described the preparation of methyl ω-bromosorbate and they also report unsuccessful attempts to condense it with ketones.]

Attention was then redirected to the C_{17} acid (II; R′ = H), and the possibility of converting it to the C_{18} ketone (IV) was examined. Although on addition of the crude methyl ester to methylmagnesium iodide a crystalline complex separated rapidly, no ketonic material with the correct light-absorption properties was isolated on treatment of the product with the Girard reagent. Conversion of the acid into its chloride, followed by treatment with dimethylcadmium according to Gilman and Nelson (*Rec. Trav. chim.*, 1936, **56**, 518), was an obvious alternative, but in the case of β-ionylideneacetic acid, anomalous results have been reported (Young, Andrews, and Cristol, *loc. cit.*) when this procedure was used. It is by no means certain, however, that the method employed by Young *et al.* for the preparation of the acid chloride is free from objection. Consequently, the C_{17} acid was treated with thionyl chloride in the presence of pyridine, giving a 50% yield of the *chloride*, which not only possessed the anticipated light-absorption properties, but also furnished the crystalline C_{17} acid on hydrolysis. A preliminary condensation with dimethylcadmium yielded a ketonic product, the light-absorption properties of which were consistent with the presence of a considerable proporton of the required C_{18} ketone.

At this stage in our investigations Arens and van Dorp (*loc. cit.*) briefly reported the synthesis of " vitamin A acid " *via* the C_{17} acid mentioned above and the corresponding C_{18} ketone, the latter having been obtained by the action of methyl-lithium on the acid (cf. Gilman and van Ess, *J. Amer. Chem. Soc.*, 1933, **55**, 1258). As a result of this anticipation of our own work it seemed desirable to publish a detailed description * of our results as soon as the preparation of the C_{18} ketone by the dimethylcadmium method had been completed. Reaction with the acid chloride by this means gives a ketonic product (separated by Girard reagent P), from which the semicarbazone of the C_{18} ketone, with m. p. 191° (Arens and van Dorp, *loc. cit.*, give 189°, corr.), was isolated, the light-absorption data (maximum, 3420 A., ε = 64,500) being in agreement with those quoted

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* A preliminary account was published in *Nature* (1946, **157**, 485).

by the Dutch workers. Treatment of the semicarbazone with 3N-sulphuric acid in the presence of boiling petroleum (b. p. 80—100°) gave the C_{18} ketone (IV) which exhibited maximal light absorption in the expected region (maximum, 3350 A., ε = 38,000). [Note added in proof. A full account of the work of Arens and van Dorp has now appeared (*Rec. Trav. chim.*, 1946, **65**, 338). We have adduced additional evidence of the structure of " vitamin A acid " by an ozonolysis experiment which gave geronic acid in 15% yield.]

Our studies on this C_{18} ketone are being continued in attempts to convert it into vitamin A itself or other biologically active derivatives. Work has been in progress for some time on condensations of the acyclic C_{14} and C_{15} aldehydes and the C_{17} and C_{18} ketones (Batty, Burawoy, Heilbron, Jones, and Lowe, *J.*, 1937, 755; Barraclough, Batty, Heilbron, and Jones, *J.*, 1939, 1549) with γ-bromocrotonate and bromoacetate, respectively, in the expectation of obtaining acids of the lycopene type which, if Karrer and Bretscher's contention (*Helv. Chim. Acta*, 1943, **26**, 1758) be correct (cf. Gillam, Heilbron, Jones, and Lederer, *Biochem. J.*, 1938, **32**, 405), will be related to vitamin A_2.

EXPERIMENTAL.

(Light-absorption data determined in alcohol.)

Condensation of β-Ionone with Methyl γ-Bromocrotonate.—The C_{17} *Acid* [1-(2′ : 6′ : 6′-*Trimethyl*-$\Delta^{1'}$-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*triene*-6-*carboxylic Acid*] (II ; R′ = H).—A solution of pure β-ionone (39 g. ; regenerated from the semicarbazone, m. p. 146° ; Heilbron, Johnson, Jones, and Spinks, *loc. cit.*) and methyl γ-bromocrotonate (36 g. ; $n_D^{12^\circ}$ 1·5022) in benzene (50 c.c.) was added in nitrogen during 1 hour to a stirred mixture of boiling benzene (350 c.c.) and zinc needles (13 g.) together with a crystal of iodine. After being stirred and refluxed for 6 hours, the cooled mixture was stirred with 5% acetic acid, and the benzene layer was separated off, washed with bicarbonate solution and water, and dried. The benzene was removed under reduced pressure in nitrogen, and distillation of the residue gave (i) β-ionone (23·5 g.) and (ii) crude methyl ester (20 g.), b. p. 120—130°/10^{-2} mm., as a pale yellow viscous oil. Two fractionations of (ii) gave material with b. p. 55° (bath temp.)/10^{-3} mm., $n_D^{19^\circ}$ 1·5632. Light absorption : Broad maximum, 2900—3240 A., ε = 12,500.

The crude ester (5 g.) was hydrolysed for 24 hours in a solution of potassium hydroxide (3 g.) in methanol (25 c.c.) in nitrogen. Acidification with phosphoric acid (20%) and isolation with ether gave a gummy acid product (3·8 g.), which partly solidified on trituration with cold ether. Crystallisation from acetone yielded the pure C_{17} acid (1·4 g.) as pale yellow plates, m. p. 160° (Found : C, 78·1 ; H, 9·15. Calc. for $C_{17}H_{24}O_2$: C, 78·4 ; H, 9·3%). On shaking with Adams's catalyst, a solution of the acid (0·26 g.) in alcohol (3 c.c.) absorbed 93·8 c.c. of hydrogen at 20° and 760 mm., equivalent to |= 3·9.

Methyl Ester.—A solution of the pure acid (2·6 g.) in ether (20 c.c.), cooled in ice-salt, was treated dropwise with diazomethane (0·4 g.) in ether. After 2 hours at −5°, the ether was removed, and distillation of the residue gave the *methyl* ester (1·4 g.) as a pale yellow liquid, b. p. 65° (bath temp.)/10^{-3} mm., $n_D^{20^\circ}$ 1·5630 (Found : C, 78·8 ; H, 9·4. $C_{18}H_{26}O_2$ requires C, 78·8 ; H, 9·55%).

Ozonolysis of the C_{17} *Acid.*—A solution of the acid (1 g.) in carbon tetrachloride (30 c.c.) was treated with a slow stream of ozonised oxygen for 24 hours. " AnalaR " acetic acid (15 c.c.) was then added to dissolve the precipitated ozonide, and the solution was ozonised for a further 24 hours. Water (200 c.c.) was added, and the mixture was heated under reflux for 1 hour and then evaporated to a syrupy consistency under diminished pressure. More water (100 c.c.) was added, and the procedure repeated. The acidic portion of the product, isolated in the usual manner, was extracted with boiling water (5 c.c.), and the filtered extract was treated with a solution of semicarbazide hydrochloride (0·6 g.) and sodium acetate (1·1 g.) in water (3 c.c.). After standing at 0° for some hours, the crude semicarbazone was filtered off and crystallised from ethyl acetate, giving pale yellow crystals (0·4 g.), m. p. 157—160°. Recrystallisation from the same solvent gave geronic acid semicarbazone (0·31 g. ; 34%), m. p. 163°, undepressed on admixture with an authentic specimen, m. p. 163°.

C_{17} *Acid Chloride* [1-(2′ : 6′ : 6′-*Trimethyl*-$\Delta^{1'}$-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*triene*-6-*carboxyl Chloride*].—The crystalline acid (13 g.) in dry ether (130 c.c.) was cooled to −5° in nitrogen and pure pyridine (7·9 g.) was gradually added. This was followed by the dropwise addition of pure thionyl chloride (5·9 g.) at such a rate that the temperature of the reaction mixture could be maintained at −5° to 0°. The mixture was then stirred at 0° for 2 hours, and finally warmed in a bath at 50° for 1 hour. After cooling in ice, dry hydrogen chloride was introduced into the stirred mixture until it became acidic, and the precipitate of pyridine hydrochloride was filtered off. Evaporation of the filtrate and distillation of the residue gave the *acid chloride* (6·7 g.), b. p. 55° (bath temp.)/10^{-3} mm., $n_D^{20^\circ}$ 1·5660 (Found: Cl, 12·5. $C_{17}H_{23}OCl$ requires Cl, 12·7%). Light absorption : Maximum, 3230 A., ε = 29,000.

Hydrolysis of the acid chloride with ice cold methyl-alcoholic potassium hydroxide gave an acidic product from which the crystalline C_{17} acid was recovered in 50% yield.

C_{18} *Ketone* [1-(2′ : 6′ : 6′-*Trimethyl*-$\Delta^{1'}$-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*trien*-7-*one*] (IV).—A slight excess of methyl bromide in dry ether was added to magnesium (0·96 g.) in nitrogen, anhydrous cadmium chloride (3·68 g.) was then added to the resulting methylmagnesium bromide, and the mixture was stirred rapidly for 30 minutes. After addition of the acid chloride (6·7 g.) in ether at 20° during 30 minutes and refluxing on the steam-bath for 3 hours, the cooled mixture was poured on a stirred mixture of ice and ammonium chloride. The product isolated by means of ether was refluxed in nitrogen for 1 hour with Girard reagent P (5 g.) and acetic acid (5 c.c.) in alcohol (50 c.c.), and the crude ketonic material (2·8 g., 45%), isolated in the usual manner, was converted into the semicarbazone with a slight excess of semicarbazide acetate in methyl-alcoholic solution. After crystallisation of the derivative from ethyl acetate–methanol (1 : 1), the C_{18} ketone semicarbazone (1·6 g.) was obtained as pale yellow plates, m. p. 191° (Found : C, 72·1 ; H, 9·3. Calc. for $C_{19}H_{29}ON_3$: C, 72·3 ; H, 9·25%).

The semicarbazone (1·5 g.) was refluxed in nitrogen for 20 hours with 3N-sulphuric acid (10 c.c.) and petroleum (10 c.c. ; b. p. 80—100°). This gave the C_{18} ketone (0·8 g.) as a pale yellow viscous oil, b. p. 85° (bath temp.)/10^{-4} mm., $n_D^{16^\circ}$ 1·5670 (Found : C, 83·3 ; H, 10·1. Calc. for $C_{18}H_{26}O$: C, 83·7 ; H, 10·15%).

Methyl ω-Bromosorbate.—A mixture of powdered *N*-bromosuccinimide (178 g.) and methyl sorbate (504 g. ; m. p. 11°, b. p. 90°/35 mm., $n_D^{22^\circ}$ 1·5025, $\lambda_{\text{max.}}$ 2580 A., ε = 31,500) was stirred and heated at 120° until the bulk of the bromoimide had dissolved. After a further 15 minutes at this temperature the mixture was cooled, and the separated succinimide was filtered off and washed with carbon tetrachloride. The filtrate was washed with sodium carbonate solution and water, and then dried and evaporated, and distillation gave methyl sorbate (360 g.) and *methyl ω-bromosorbate* (133 g.), b. p. 75°/1 mm., $n_D^{20^\circ}$ 1·5456 (Found : C, 41·2 ; H, 4·45 ; Br, 38·7. $C_7H_9O_2Br$ requires C, 41·0 ; H, 4·4 ; Br, 39·0%). Light absorption : Maximum, 2650 A. ; ε = 19,000.

Ozonolysis of Methyl ω-Bromosorbate.—Ozonised oxygen was passed through a solution of the ester (2 g.) in acetic acid (15 c.c.) for 24 hours, after which zinc dust (1 g.) and water (100 c.c.) were added and the mixture was refluxed for

1 hour. On subsequent distillation, ten fractions, each of about 4 c.c., were collected and these were treated with 2 : 4-dinitrophenylhydrazine sulphate. The derivatives obtained from the later fractions were readily purified by crystallisation from 80% methanol, giving orange-yellow needles (1·4 g.; 50% yield), m. p. 195° (Found : N, 18·9. Calc. for $C_{11}H_{10}O_6N_4$: N, 19·0%). For the 2 : 4-dinitrophenylhydrazone of the aldehyde corresponding to the mono-methyl ester of fumaric acid, Heinänen (*Chem. Abs.*, 1938, **32**, 7893) gives m. p. 194°.

The derivatives obtained from the earlier fractions were extracted with hot methanol, and crystallisation of the insoluble material from alcohol–ethyl acetate (1 : 1) gave 0·87 g. (29% yield) of the 2 : 4-*dinitrophenylhydrazone* of bromo-acetaldehyde, as orange-coloured needles, m. p. 150°, undepressed on admixture with a specimen prepared from bromo-acetal (Found : N, 18·4; Br, 26·2. $C_8H_7O_4N_4Br$ requires N, 18·5; Br, 26·4%).

Note added in Proof. Ozonolysis of "Vitamin A acid."—A solution of the acid (100 mg.) in carbon tetrachloride (4 c.c.) was treated as described above for the C_{17} acid. The crude semicarbazone (20 mg.) had m. p. 153—156° and after crystallisation from ethyl acetate gave geronic acid semicarbazone (11 mg.; 15%), m. p. 163°, undepressed on admixture with an authentic specimen.

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