

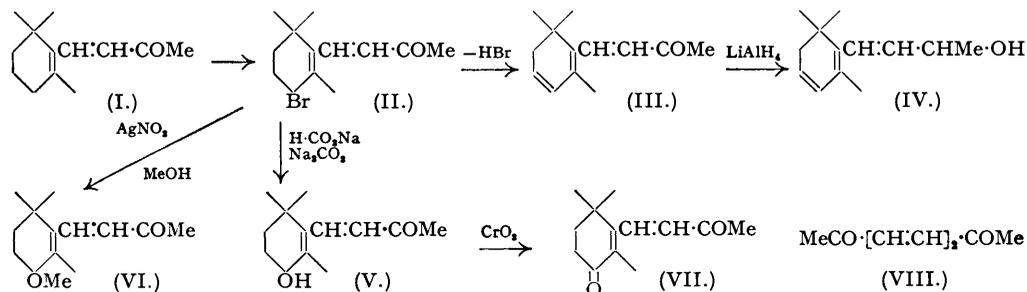
237. Studies in the Polyene Series. Part XXXVII. Preparation of 3-Dehydro- β -ionone and Some 3-Substituted β -Ionones.

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The reaction between β -ionone and *N*-bromosuccinimide yields a 3-bromo-compound, converted by dehydrobromination into 3-dehydro- β -ionone and by hydrolysis and methanolysis into 3-hydroxy- and 3-methoxy- β -ionone, respectively. Oxidation of the 3-hydroxy-compound gives 3-keto- β -ionone, identical with that prepared by Prelog and Meier (*Helv. Chim. Acta*, 1950, **33**, 1276) by a biological oxidation of β -ionone.

THE preparation of 3-dehydro- β -ionone (III), by bromination of β -ionone (I) with *N*-bromosuccinimide followed by dehydrobromination of the resulting bromo-compound with diethylaniline, was reported in a preliminary communication (Henbest, *Nature*, 1948, **161**, 481). Since that time, efforts have been directed towards improving the yield and purity of this ketone in view of the possible use of the reaction sequence for the synthesis of vitamin A₂ (cf. Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49).

However, in the meantime, two publications dealing with the bromination of β -ionone with *N*-bromosuccinimide have appeared. Karrer and Ochsner (*Helv. Chim. Acta*, 1948, **31**, 2093) describe the treatment of β -ionone with two molecular proportions of *N*-bromosuccinimide (one molecular proportion of the bromo-imide giving some unchanged β -ionone), followed by dehydrobromination with boiling diethylaniline. The products isolated were 1:2-dihydro-1:1-dimethylnaphthalene and 4-2':3':6'-trimethylphenylbutan-2-one. Büchi, Seitz, and



Jeger (*ibid.*, 1949, **32**, 39) performed the reaction with one molecular proportion of *N*-bromosuccinimide, and the dehydrobromination with silver oxide or dimethylaniline at 90°. The 3-dehydro- β -ionone (III) so formed was isolated as its crystalline phenylsemicarbazone, from which it was regenerated by steam-distillation with phthalic anhydride. Confirmation of structure (III) for the ketone was obtained by ozonolysis, whereupon $\alpha\alpha$ -dimethylsuccinic acid was isolated in 30% yield.

The method of preparing 3-dehydro- β -ionone, reported in the preliminary communication has now been considerably improved, both in yield and purity of product. The published physical constants of 3-dehydro- β -ionone and certain of its derivatives are listed in Table I, together with the constants for the best sample of the ketone now obtained by the improved procedure, and the corresponding values for pure β -ionone and its derivatives. Comparison of the second and third columns of the Table shows that, as the method of preparation has been improved, the refractive index and the value of the extinction coefficient in the 3400- μ . region have been increased.

This considerable improvement in the purity of dehydro- β -ionone has been largely brought about by ensuring that no β -ionone escapes reaction with *N*-bromosuccinimide. It has been found necessary to employ more than one molecular proportion of the bromo-imide, a 20% excess giving the best yield of final product. The excess of *N*-bromosuccinimide is probably mostly consumed by a side reaction whereby the methyl group adjacent to the carbonyl group is brominated.

TABLE I.

	3-Dehydro- β -ionone.			β -Ionone.
	Büchi <i>et al.</i>	Henbest (<i>loc. cit.</i>).	This paper.	This paper.
B. p.	71°/0.1 mm.	75°/1 mm.	75°/1 mm.	75°/1 mm.
<i>n</i>	<i>n</i> _D ²¹ 1.5389	<i>n</i> _D ²² 1.5497	<i>n</i> _D ²³ 1.5595	<i>n</i> _D ¹ 1.5227
Light absorption :				
Maximum; λ , μ . (ϵ)	2230 (5,600)	2210 (7,200)	2240 (5,300)	2150 (7,400)
Minimum; λ , μ . (ϵ)	—	2610 (2,700)	2640 (2,000)	2500 (1,900)
Maximum; λ , μ . (ϵ)	3430 (4,500)	3380 (9,100)	3450 (12,200)	2960 (10,400)
M. p. :				
Semicarbazone	144°	144—146°	137—142°	147—149°
2 : 4-Dinitrophenylhydrazone	—	150—151	150—151	129—130
Phenylsemicarbazone	148	—	147—150	—

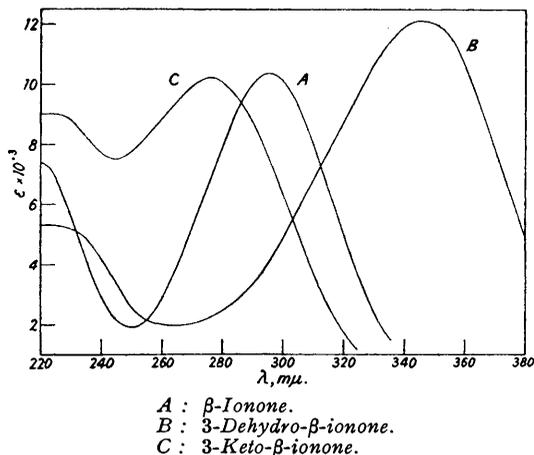
The dehydrobromination stage was effected smoothly and quickly with diethylaniline at 100°, and the crude dehydro- β -ionone so obtained was purified through its semicarbazone. Separate tests had shown that the mixed semicarbazones of β -ionone and 3-dehydro- β -ionone cannot be separated by crystallisation, mixtures of the two crystallising to give products with melting points intermediate between those of the pure derivatives. Thus it was important to have no unreacted β -ionone in the crude dehydro-ketone. On the other hand, the dehydro-ketone 2 : 4-dinitrophenylhydrazone can be purified by crystallisation; it has a higher melting point than that of the corresponding β -ionone derivative. Regeneration of the ketone from its crystalline semicarbazone was best effected by dilute acid at room temperature (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727). As already noted by Young and Linden (*J. Amer. Chem. Soc.*, 1947, 69, 2072) this method is preferable to those involving steam-distillation with phthalic or oxalic acid for the hydrolysis of polyene semicarbazones.

Crude 3-bromo- β -ionone, as obtained from the bromination of β -ionone, has been converted into a number of other 3-substituted β -ionones as outlined in the scheme above. The bromo-compound reacted readily with sodium formate at room temperature to give a 3-formoxy-compound (not isolated) which was converted by mild alkaline hydrolysis into 3-hydroxy- β -ionone (V). 3-Methoxy- β -ionone (VI) was obtained when the 3-bromo-compound was added to a solution of silver nitrate in methanol [cf. the preparation of 7-methoxy-steroids (Henbest and Jones, *J.*, 1948, 1798)].

3-Hydroxy- β -ionone was easily oxidised in acetone solution with chromic acid (cf. Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) to give the crystalline 3-keto- β -ionone (VII). A compound, to which a 3-keto- β -ionone structure was assigned, has recently been isolated from the urine of rabbits which had been fed on a diet containing β -ionone (Prelog and Meier, *loc. cit.*). The physical constants of the diketone obtained by this biological oxidation of β -ionone agreed well with those of our compound, and a mixed-m. p. determination confirmed their identity. The Swiss workers also obtained a hydroxy-ketone from the same experiment, the analysis and ultra-violet light absorption properties of which indicated the structure either of a 3-keto- β -ionol or a 3-hydroxy- β -ionone, the former structure being preferred on the basis of infra-red spectroscopic data. A comparison of the phenylsemicarbazone of Prelog and Meier's hydroxy-ketone (m. p. 174—175°) with the phenylsemicarbazone of 3-hydroxy- β -ionone (m. p. 153—154°) prepared in this work showed that the higher-melting compound was indeed a

derivative of 3-keto- β -ionol, the non-identity of the two compounds being further confirmed by a marked depression in a mixed-m. p. determination. These mixed-m. p. determinations were kindly carried out by Professor Prelog.

3-Keto- β -ionone is of further interest in that it may be possible to insert another keto-group in the 4-position, thus yielding a compound with a ring structure identical with the



terminal ring systems in the carotenoid, astacene (Karrer *et al.*, *Helv. Chim. Acta*, 1936, **19**, 479, and earlier papers).

The light-absorption properties of the compounds prepared in this work are listed in Table II. It is evident that these substituted β -ionones exhibit "anomalous" light-absorption properties similar in character to that shown by β -ionone itself. For instance, the main absorption band of dehydro- β -ionone is located in a position similar to where a triply unsaturated ketone of this type would be expected to display maximal absorption, but the intensity of absorption is very much reduced. Moreover, dehydro- β -ionone, like β -ionone (see figure),

TABLE II.

	Compound.			Semicarbazone.			2 : 4-Dinitrophenyl-hydrazone.		
	Max.	Min.	ϵ .	Max.	Min.	ϵ .	Max.	Min.	ϵ .
β -Ionone	2150		3,400	2150		8,100	2150		17,100
		2500	1,900		2350	2,900	2900	2820	11,300
								3230	11,600
3-Dehydro- β -ionone	2960		10,400	2810		22,200	3860		5,600
		2240	5,300		2280	5,900	2150		29,200
					2590	12,200		2330	15,600
3-Hydroxy- β -ionone	3450		12,200	3250		18,700	3980		14,400
		2500	4,200		2350	6,900	2190		11,600
								2820	11,500
3-Methoxy- β -ionone	2870		8,000	2775		22,800	3815		11,600
		2180	9,800		2170	8,200	2170		28,600
								3180	18,000
3-Dehydro- β -ionol	2500		4,000	2340		6,700	2880		11,700
		2840	8,000		2760	23,800	3820		5,100
								3180	29,200
3-Keto- β -ionone	2200		8,900						
		2450	7,500						
2 : 7-Diketo-octa-3 : 5-diene *	2770		10,200						
		2760	33,200						

Wave-lengths are in \AA .

* Karrer, Eugster, and Perl, *Helv. Chim. Acta*, 1949, **32**, 1013.

shows a subsidiary absorption band in the 2200-A. region, which is not found in acyclic unsaturated ketones. The deviation from "normal" behaviour of the light-absorption properties of these substituted β -ionones and their derivatives can be explained, as for β -ionone and its derivatives, by steric inhibition of resonance (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). According to these authors, the unsaturated side-chain is displaced out of the plane of the ring by the neighbouring methyl groups, thus severely restricting resonance and leading to diminished absorption intensities, and also to the appearance of bands due to partial chromophores. Similarly, the position of the main absorption band of 3-keto- β -ionone is close to that of the analogous acyclic compound, 2 : 7-diketoocta-3 : 5-diene (VIII), but the intensity is very much reduced.

EXPERIMENTAL.

(M. p.s were determined on a Kofler block and are corrected; the light-absorption data were determined in ethanol solution with a Beckman spectrophotometer.)

4-2' : 6' : 6'-Trimethylcyclohexa-1' : 3'-dienylbut-3-en-2-one (3-Dehydro- β -ionone) (III).—A solution of β -ionone (96 g.) in carbon tetrachloride (250 c.c.) was warmed until boiling commenced, in a flask fitted with a reflux condenser. Finely powdered *N*-bromosuccinimide (110 g.) (recrystallised from water and dried) was added in eleven equal portions, each addition being made when the exothermic reaction caused by the previous portion had subsided. When the reaction resulting from the addition of the last portion had finished, the pale-brown solution suddenly became dark brown. The mixture was immediately cooled to 30°, and light petroleum (100 c.c.; b. p. 40–60°) added to complete the precipitation of succinimide. The latter (62 g.) was filtered off, the filtrate being added directly to diethylaniline (150 c.c.). Owing to the instability of the bromo-compound(s), these last operations were carried out as quickly as possible. The deep-brown solution was warmed under reduced pressure (water-pump) to remove the light petroleum and most of the carbon tetrachloride, and the residue was heated (internal temperature 96°) on a steam-bath for 45 minutes. Diethylaniline hydrobromide crystallised out either during the heating or when the mixture was seeded. Dry pyridine (50 c.c.) was added and the mixture was heated for a further 30 minutes. The product was isolated by the addition of light petroleum (b. p. 40–60°) and sufficient 5*N*-hydrochloric acid to extract the organic bases. The petroleum solution was processed in the usual manner and the residue distilled from a Claisen flask with a low wide, water-jacketed side arm. The golden-yellow product (55–60 g.) had b. p. 97–100°/2 mm., n_D^{25} 1.553. For purification, it was dissolved in a solution of semicarbazide acetate [from semicarbazide hydrochloride (40 g.) and potassium acetate (40 g.)] in 80% methanol. After being kept overnight, the product was recrystallised from 80% methanol and gave the pure semicarbazone (54–58 g.), m. p. 137–142° (Found : C, 67.7; H, 8.65. $C_{14}H_{21}ON_3$ requires C, 68.0; H, 8.55%).

The finely powdered semicarbazone (41 g.) was shaken with light petroleum (150 c.c.; b. p. 40–60°) and 3*N*-sulphuric acid (150 c.c.) for two days in nitrogen and shielded from light. The mixture was filtered and the recovered semicarbazone was again powdered and shaken with petroleum (100 c.c.) and 3*N*-sulphuric acid (100 c.c.) for three days. Unchanged semicarbazone (5.2 g.) was then recovered; concentration of the petroleum extracts followed by distillation gave 3-dehydro- β -ionone (24.5 g.) as a yellow liquid with an odour similar to but sweeter than that of β -ionone; it had b. p. 75°/mm., n_D^{19} 1.5595 (Found : C, 82.15; H, 9.75. $C_{13}H_{18}O$ requires C, 82.1; H, 9.55%).

Pyridine was added at the end of the dehydrobromination stage to quaternise (and render water soluble) unreacted bromo-compounds (probably of the α -bromo-ketone type mentioned in the theoretical section), pyridine being more reactive in this way than diethylaniline. If the pyridine treatment was omitted, the unreacted bromo-compounds present in the crude 3-dehydro- β -ionone decomposed violently with evolution of hydrogen bromide before all the ketone had distilled over. This hazard could also be avoided by isolating the ketone by steam-distillation, a more tedious process.

The 2 : 4-dinitrophenylhydrazone prepared at room temperature crystallised from ethanol or ethyl acetate-methanol in dark-red needles, m. p. 150–151° (Found : C, 61.3; H, 6.15. $C_{19}H_{22}O_4N_4$ requires C, 61.6; H, 6.0%).

The phenylsemicarbazone, prepared in ethanol containing a little acetic acid, crystallised from methanol in plates, m. p. 147–150° (Büchi, Seitz, and Jeger, *loc. cit.*, give m. p. 148°). Light absorption : Maxima, 2380, 2750, and 3200 Å.; $\epsilon = 16,500, 15,900,$ and $16,400$; Minima, 2520 and 3000 Å.; $\epsilon = 12,500$ and $15,500$.

4-2' : 6' : 6'-Trimethylcyclohexa-1' : 3'-dienylbut-3-en-2-ol (3-Dehydro- β -ionol) (IV).—A mixture of 3-dehydro- β -ionone (1 g.) and dry ether (10 c.c.) was cooled to –40°, and an ethereal solution of lithium aluminium hydride (0.34*M.*; 5 c.c.) was added dropwise with stirring during fifteen minutes, the internal temperature being maintained at –40°. After a further fifteen minutes at this temperature, the solution was allowed to warm to 10°. A few drops of ethyl acetate were added to decompose the excess of lithium aluminium hydride, and the product was isolated with ether. Distillation gave the carbinol (0.65 g.), b. p. 75°/0.01 mm., n_D^{17} 1.5381 (Found : C, 80.95; H, 10.3. $C_{13}H_{20}O$ requires C, 81.2; H, 10.5%).

4-3'-Hydroxy-2' : 6' : 6'-trimethylcyclohex-1'-enylbut-3-en-2-one (3-Hydroxy- β -ionone) (V).—Pure, finely powdered *N*-bromosuccinimide (20 g.) was added to a solution of β -ionone (19.2 g.) in chloroform (50 c.c.; $CaCl_2$ -dried) in a flask fitted with a reflux condenser, and the mixture warmed with gentle swirling until the reaction started. As soon as the exothermic reaction had subsided, the mixture was cooled, light petroleum (50 c.c.; b. p. 40–60°) was added, and the mixture filtered directly into a solution of sodium formate (9 g.) in 90% formic acid (50 c.c.), the succinimide being washed with more light petroleum. The reaction mixture (now in two layers) was evaporated under reduced pressure (water-pump)

at 30° or below to remove the light petroleum and most of the chloroform. Dioxan (25 c.c.) was added and the still slightly heterogeneous mixture vigorously stirred at room temperature for 2 hours. The formoxy-compound was isolated with ether, and then dissolved in methanol (200 c.c.) and added to a solution of anhydrous sodium carbonate (15 g.) in water (200 c.c.), the mixture being shaken overnight. Light petroleum (30 c.c.; b. p. 40—60°) was added and the mixture shaken. The petroleum layer, containing most of the dark colour, was separated and rejected. The hydroxy- β -ionone was then isolated from the aqueous methanol layer with ether. The crude pale-brown syrup (16.0 g.) was chromatographed on a column of alumina (Peter Spence, Grade H; 40 × 3.6 cm.). Development with light petroleum (b. p. 40—60°)—benzene (2 : 1) gave a chromatogram with the following appearance : (a) a small dark-brown band at the top, (b) a large pale-brown zone in the middle, and (c) two brown bands and a yellow band at the bottom. The column was allowed to drain and zones (a) and (c) were removed and rejected. The alumina of zone (b) was eluted with ether-methanol (9 : 1) to give a fairly pure product (12.2 g.), n_D^{18} 1.5315. Regeneration from the powdered semicarbazone (0.75 g.) (see below) by shaking it with benzene (15 c.c.) and 3N-sulphuric acid (10 c.c.) for four hours at room temperature in an atmosphere of nitrogen gave the pure ketone (0.46 g.) as a nearly odourless, viscous liquid, b. p. 131—132°/0.02 mm., n_D^{18} 1.5358 (Found : C, 75.0; H, 9.95. $C_{13}H_{20}O_2$ requires C, 74.95; H, 9.7%).

The semicarbazone was prepared from the crude ketone and semicarbazide acetate in methanol-water (1 : 1) at room temperature for two hours, the solution being finally cooled to 0° to obtain a better yield. Recrystallisation from methanol-water (5 : 2) or nitromethane gave the semicarbazone as a very pale yellow, granular solid, m. p. 182—183.5° (Found : C, 62.75; H, 8.65; N, 16.0. $C_{14}H_{23}O_2N_3$ requires C, 63.45; H, 8.75; N, 15.85%). This semicarbazone crystallised very slowly from supersaturated solutions.

The phenylsemicarbazone, prepared in ethanol containing a little acetic acid, was crystallised from methanol and then from benzene giving fine needles. To obtain consistent values for the melting point it was necessary to dry the samples at 80°/10⁻³ mm. for 2 hours. The pure derivative had m. p. 153—154° (Found : C, 70.7; H, 7.35. $C_{20}H_{27}O_2N_3$ requires C, 70.35; H, 7.95%). Light absorption : Maxima, 2340 and 2870 Å.; ϵ = 16,300 and 27,400 : Minima, 2120 and 2510 Å.; ϵ = 10,900 and 10,300. On admixture with 3-keto- β -ionol phenylsemicarbazone (m. p. 174—175°) the melting point was depressed to 134—135°.

The 2 : 4-dinitrophenylhydrazone crystallised in dark-red needles, m. p. 137—138°, from methanol-ethyl acetate (3 : 1) (Found : C, 58.5; H, 6.65. $C_{19}H_{24}O_6N_4$ requires C, 58.75; H, 6.25%).

4-3'-Keto-2' : 6' : 6'-trimethylcyclohex-1'-enylbut-3-en-2-one (3-Keto- β -ionone) (VII).—A solution of chromic acid (3.5 c.c.) [prepared by dissolving chromic acid (10 g.) in a mixture of concentrated sulphuric acid (9 c.c.) and water (40 c.c.)] was added with stirring at 0° to a solution of 3-hydroxy- β -ionone (2.08 g.) in dry (K_2CO_3) AnalaR acetone (30 c.c.) during five minutes. The oxidation was very rapid, and after a further two minutes, water was added and the organic product isolated with ether. The oily product was dissolved in methanol-water (20 c.c.; 5 : 2) and cooled to -30°, whereupon a granular solid separated. This was recrystallised from light petroleum (b. p. 40—60°) (solution at 25° cooled to -25°) and methanol-water (1 : 1) (solution at 35° cooled to -10°) and gave the diketone (0.44 g.) in lustrous plates, m. p. 51—52° (Found : C, 75.3; H, 8.75. Calc. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8%). On admixture with Prelog and Meier's diketone (m. p. 52—53°) the melting point was 52—53°.

4-3'-Methoxy-2' : 6' : 6'-trimethylcyclohex-1'-enylbut-3-en-2-one (3-Methoxy- β -ionone) (VI).— β -Ionone (9.6 g.) was brominated as described for the preparation of 3-hydroxy- β -ionone, and the mixture, after being cooled to 25°, was filtered into a methanolic solution of silver nitrate, prepared by dissolving silver nitrate (12 g.) in the minimum quantity of warm water and adding this solution to methanol (400 c.c.) at 25°. There was an immediate precipitation of silver bromide, and, after being gently stirred for 5 minutes, the mixture was filtered, and the silver bromide washed with light petroleum (b. p. 40—60°). The filtrate was diluted with water, and the product isolated with light petroleum (b. p. 40—60°). After concentration, the petroleum solution was passed down a column of alumina (200 g.; Peter Spence, Grade O), the column being developed with light petroleum (b. p. 40—60°). This treatment removed any hydroxy-compounds present as well as some coloured impurities. The petroleum eluate was concentrated under reduced pressure (water-pump), and the residue dissolved in aqueous methanol containing semicarbazide acetate. This solution was then kept at -8° for several days, during which time a solid product slowly separated. The collected solid was recrystallised from ethanol, giving the crystalline semicarbazone (3.5 g.), m. p. 165—167° (Found : C, 64.25; N, 9.55. $C_{15}H_{25}O_2N_3$ requires C, 64.5; H, 9.0%).

Pure 3-methoxy- β -ionone (0.17 g.) was obtained by shaking the powdered semicarbazone (0.25 g.) with light petroleum (10 c.c.; b. p. 40—60°) and 2N-sulphuric acid (10 c.c.) for 4 hours. The ketone was obtained as a liquid with an odour similar to, but much fainter than, that of β -ionone; it had b.p. 95°/0.02 mm., n_D^{17} 1.5161 (Found : C, 75.6; H, 10.1. $C_{14}H_{22}O_2$ requires C, 75.65; H, 10.25%).

The 2 : 4-dinitrophenylhydrazone, prepared by adding the semicarbazone to a warm solution of 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid, crystallised from methanol-ethyl acetate (1 : 1) in fine, dark-red needles, m. p. 140—141° (Found : C, 59.85; H, 6.25. $C_{20}H_{26}O_6N_4$ requires C, 59.7; H, 6.5%).

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