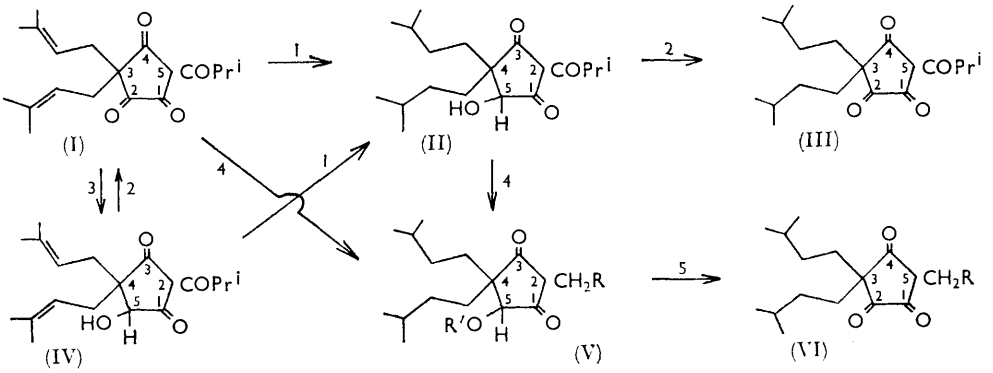
839. *Chemistry of Hop Constituents. Part XVII.*[1] *Hydrogenation of the Hulupones.*

By J. S. Burton and R. Stevens.

Hydrogenation of cohulupone gives (*a*) a hexahydro-derivative, 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione, and (*b*) the corresponding 2-isobutyl-1,3-dione. The analogous second reduction product of hulupone, 5-hydroxy-2,4,4-tri-isopentylcyclopentane-1,3-dione, is identical with hexahydrolupulenol. Reduction of cohulupone with sodium borohydride affords 5-hydroxy-2-isobutyryl-4,4-di-(3-methylbut-2-enyl)cyclopentane-1,3-dione.

The hydrogenation of humulone,[2] lupulone,[2] and isohumulone [3] provided helpful information regarding their structures. It was therefore of interest to examine the behaviour on hydrogenation of hulupones, a newly recognised group of resins.[1,4,5] Spetsig and Steninger [4] briefly reported that hulupone was reduced by sodium borohydride and hydrogenated in the presence of Adams catalyst to a hexahydro-derivative. Wright [1] described the hydrogenation of the sodium salt of cohulupone in methanol in presence of Adams catalyst to a product having light absorption similar to that of oxyhumulinic acid. This product was not characterized further apart from noting that its oxidation with bismuth oxide gave tetrahydrocohulupone.

We first examined the hydrogenation of cohulupone (I) using palladium chloride as catalyst: 5·0 mol. of hydrogen were absorbed and two products formed. One of these distilled as a syrup from which an amorphous copper salt was obtained. This compound, $C_{19}H_{32}O_4$, is seemingly the hexahydro-derivative reported earlier.[1,4] It had light absorption both in the ultraviolet and the infrared region identical with that of compound (II) obtained by a different route from hexahydrocolupulone [5] and its structure was confirmed by the smooth oxidation of the product to tetrahydrocohulupone (III). The second product, $C_{19}H_{34}O_3$, of the hydrogenation was isolated by crystallization from the distillation residue. The infrared spectrum showed hydroxyl and carbonyl absorption, and both this and the



Reagents: 1, H_2–Pd–$BaSO_4$. 2, Bi_2O_3. 3, $NaBH_4$. 4, H_2–PtO_2–MeOH. 5, Bi_2O_3 or MnO_2.

ultraviolet spectrum indicated that the 1,2,4-triketone grouping present in cohulupone had been replaced by a cyclopentane-1,3-dione structure. This "abnormal" reduction product is analogous to those reported earlier from the hydrogenation of isohumulone A[3]

[1] Part XVI, Wright, *J.*, 1963, 1769.
[2] Wöllmer, *Ber.*, 1916, **49**, 750, 780; 1925, **58**, 672.
[3] Brown, Howard, and Tatchell, *J.*, 1959, 545.
[4] Spetsig and Steninger, *J. Inst. Brewing*, 1960, **65**, 413.
[5] Stevens and Wright, *J.*, 1963, 1763.

and cohumulinic acid [6] and is accordingly assigned the structure (V; R = Pr^i, R′ = H). Similar "abnormal" reductions have recently been observed with callophyllolide and 5,7-dihydroxy-8-isopentenyl-6-isovaleryl-4-phenylcoumarin.[7]

Hydrogenation of cohulupone with Adams catalyst in methanol afforded the hexahydro-derivative (II) in only 1% yield and gave principally the "abnormal" reduction product (V; R = Pr^i, R′ = H). With acetic acid as solvent the hexahydro-derivative (II) was obtained in 25% yield. We therefore repeated the hydrogenation of the sodium salt of cohulupone with Adams catalyst in methanol as described by Wright,[1] for it seemed that, under these conditions, the triketone system is not reduced when chelated as in the sodium salt, so that only the sodium salt of the hexahydro-derivative (II) is formed.

Hydrogenation of cohulupone in methanol with palladium–barium sulphate afforded the hexahydro-derivative (II) in 87% yield, so that this is the best route to this substance. Hydrogenation of this product in methanol with Adams catalyst converted it into the abnormal reduction product (V; R = Pr^i, R′ = H). It is noteworthy that conditions have not been found in which cohulupone is converted into tetrahydrocohulupone directly and in no case has hydrogenolysis of an isoprene group, such as occurs in the humulone and lupulone series,[2] been observed.

Attempts to oxidize the "abnormal" reduction product (V; R = Pr^i, R′ = H) to the related triketone (VI; R = Pr^i) with bismuth oxide in glacial acetic acid (5 hr.) led to the acetate (V; R = Pr^i, R′ = Ac). Hydrolysis afforded the parent compound (V; R = Pr^i, R′ = H) which was reconverted into the acetate (V; R = Pr^i, R′ = Ac) by acetic anhydride–pyridine. The triketone (VI; R = Pr^i) was obtained by oxidation of the alcohol (V; R = Pr^i, R′ = H) with manganese dioxide in chloroform during 20 minutes or by carrying out the reaction with bismuth oxide for 24 hr.

Oxidation of colupulone by means of alkaline hydrogen peroxide gives lupuloxinic acid which is readily decarboxylated to lupulenol.[8] Hexahydrolupulenol was assigned [9] the structure 5-hydroxy-2,4,4-tri-isopentylcyclopentane-1,3-dione and was oxidized with bismuth oxide to 3,3,5-tri-isopentylcyclopentane-1,2,4-trione. It follows therefore that the "abnormal" reduction product of hulupone (V; R = Bu^i, R′ = H) should be identical with hexahydrolupulenol if the assigned structures are correct. Hydrogenation of hulupone (I; Bu^i in place of Pr^i) in the presence of Adams catalyst in methanol did give hexahydrolupulenol,[8] confirming the structures assigned to this compound and the abnormal reduction products and relating two oxidative degradations of lupulone. Hexahydrolupulenol (V; R = Bu^i, R′ = H) was smoothly oxidized to the triketone (VI; R = Bu^i) by manganese dioxide in chloroform.

Reduction of cohulupone with sodium borohydride gave a dihydro-derivative which had light absorption similar to that of the hexahydro-derivative (II) and is accordingly regarded as (IV). In agreement with this structure iodine uptake shows the presence of two double bonds and hydrogenation with palladium–barium sulphate gives the hexahydro-derivative (II). Further, the dihydro-compound is readily oxidized back to cohulupone (I) in presence of bismuth oxide. The reduction of cohulupone with lithium aluminium hydride was more drastic and the products, which only showed end-absorption in the ultraviolet spectrum, have not yet been completely characterized.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°. Infrared spectra have been deposited with the D.M.S. and allocated numbers after 11,600. Evaporations were carried out under

[6] Howard and Tatchell, *J.*, 1954, 2400.
[7] Polonsky and Rondest, *Bull. Soc. chim. France*, 1962, 1560.
[8] Howard and Pollock, *J.*, 1952, 1902.
[9] Howard, Pollock, and Tatchell, *J.*, 1955, 174.

nitrogen. Cohulupone was prepared from colupulone in the presence of sodium sulphite;[1] it had b. p. 115° (bath)/10^{-4} mm. and formed a *copper salt*, m. p. 104—106° (Found: C, 65·3; H, 7·7. $C_{38}H_{50}CuO_8$ requires C, 65·5; H, 7·3%). Hulupone was prepared from 3-isovaleryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione and had the reported[1] light absorption (Found: C, 71·9; H, 8·75. Calc. for $C_{20}H_{28}O_4$: C, 72·3; H, 8·45%).

Hydrogenation of Cohulupone.—(i) *With palladium chloride.* Cohulupone (0·62 g.) in methanol (20 ml.) was hydrogenated in the presence of a suspension of palladium chloride (70 mg.) in water (2 ml.), hydrogen absorption (220 ml.) being complete in 3 hr. After the removal of catalyst and solvent, the residue (0·61 g.) was distilled, giving 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione (II) as a pale yellow syrup, b. p. 145° (bath)/5×10^{-3} mm. (Found: C, 70·85; H, 10·1. $C_{19}H_{32}O_4$ requires C, 70·5; H, 9·9%), $\lambda_{max.}$ 245 ($E^{1\%}_{1\,cm.}$ 598), 275 ($E^{1\%}_{1\,cm.}$ 444), $\lambda_{min.}$ 260 mμ in acidified ethanol, and $\lambda_{max.}$ 250 ($E^{1\%}_{1\,cm.}$ 629), 267 infl., $\lambda_{min.}$ 272 mμ in alkaline ethanol, identical in infrared spectrum with the sample obtained earlier.[5] The *copper salt*, precipitated from aqueous methanol, had m. p. 122—125° (Found: C, 64·1; H, 8·8; Cu, 8·7. $C_{38}H_{62}CuO_8$ requires C, 64·2; H, 8·75; Cu, 9·0%).

The structure of the reduction product was confirmed by oxidation with bismuth oxide to tetrahydrocohulupone[5] (III) the sodium salt of which after crystallization from ether–light petroleum had m. p. 226° (lit.,[5] m. p. 227°) (Found: C, 64·2; H, 8·5. Calc. for $C_{19}H_{29}NaO_4$, 0·5 H_2O: C, 64·5; H, 8·5%) and the reported[5] light absorption.

The residue from the distillation of the hydrogenation product recrystallized from ether–light petroleum and then aqueous methanol as needles of *5-hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione* (V; R = Pr^i, R′ = H) (0·11 g.), m. p. 183—184° (Found: C, 73·1; H, 10·9. $C_{19}H_{34}O_3$ requires C, 73·5; H, 11·0%), $\lambda_{max.}$ 250 mμ ($E^{1\%}_{1\,cm.}$ 456) in acidified ethanol, $\lambda_{max.}$ 275 ($E^{1\%}_{1\,cm.}$ 773), $\lambda_{min.}$ 235 mμ in alkaline ethanol, $\nu_{max.}$ 3490, 2940, 2700, and 1560 $cm.^{-1}$.

(ii) *With Adams catalyst.* Cohulupone (0·52 g.) in methanol (40 ml.) containing Adams catalyst (70 mg.) was hydrogenated, absorption being complete in 2 hr. Distillation of the residue after removal of catalyst and solvent afforded 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione (50 mg.), b. p. 140° (bath)/10^{-2} mm., identical in infrared spectrum with the sample obtained as above. Oxidation with bismuth oxide gave tetrahydrocohulupone whose sodium salt had m. p. and mixed m. p. 227°.

From the distillation residue, by recrystallization from ether–light petroleum and then aqueous methanol, 5-hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (0·21 g.), m. p. and mixed m. p. 183—184°, was obtained.

(iii) In a similar manner cohulupone (0·43 g.) in glacial acetic acid (10 ml.) with Adams catalyst (30 mg.) gave the hexahydro-derivative (II) (110 mg.) and 5-hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (30 mg.), m. p. and mixed m. p. 183—184°.

(iv) *With palladium–barium sulphate.* Cohulupone (0·24 g.) in methanol (30 ml.) was hydrogenated in the presence of 5% palladium–barium sulphate (80 mg.). Working up in the usual manner afforded 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione, b. p. 140° (bath)/6×10^{-3} mm. (0·21 g., 87%), with none of the abnormal reduction product.

Hydrogenation of the Sodium Salt of Cohulupone.—The sodium salt (0·37 g.), of cohulupone, m. p. 118—120°, in methanol (50 ml.) was hydrogenated in the presence of Adams catalyst (0·03 g.), hydrogen absorption being complete in 90 min. After removal of catalyst and solvent the residual gum was triturated with ether, to give the amorphous pale yellow *sodium salt* of 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione (II) (0·10 g.), m. p. 157—160° (Found: C, 62·4; H, 8·25. $C_{19}H_{31}NaO_4$ requires C, 62·6; H, 9·05%).

5-Hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (V; R = Pr^i, R′ = H).—5-Hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione (0·16 g.) in methanol (10 ml.) was hydrogenated in the presence of Adams catalyst. When hydrogen absorption (26 ml.) was complete, and catalyst and solvent had been removed, the residue was heated at 140°/4×10^{-3} mm., but only a trace of material distilled. The residue then crystallized (0·06 g.) and after recrystallization had m. p. 180—183° alone or mixed with sample obtained as above.

5-Acetoxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (V; R = Pr^i, R′ = Ac).—(i) 5-Hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (V; R = Pr^i, R′ = H) (0·21 g.) was set aside with acetic anhydride (1·5 ml.) and pyridine (2 ml.) for 24 hr. After dilution with water and extraction with ether a syrup was obtained which slowly crystallized; recrystallized from aqueous methanol it gave the *acetate* (V; R = Pr^i, R′ = Ac), m. p. 123—124° (Found: C, 71·4; H, 10·2. $C_{21}H_{36}O_4$ requires C, 71·5; H, 10·2%), $\lambda_{max.}$ 250 mμ ($E^{1\%}_{1\,cm.}$ 395)

in ethanol, $\lambda_{max.}$ 275 mμ ($E^{1\%}_{1\,cm.}$ 643) in alkaline ethanol, $\nu_{max.}$ (in Nujol) 2910, 1750, and 1575 cm.$^{-1}$.

(ii) 5-Hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (V; R = Pr^i, R′ = H) (0·13 g.) in glacial acetic acid (10 ml.) was heated under reflux with bismuth oxide (0·27 g.) for 5 hr. The mixture was poured into 2N-hydrochloric acid (20 ml.) and extracted with ether, and the extract washed twice with water and dried ($MgSO_4$). The yellow syrup (0·12 g.) obtained on evaporation was distilled [b. p. 150° (bath)/3 × 10^{-3} mm.; 0·09 g.]; it slowly crystallized. Recrystallization afforded the acetate (V; R = Pr^i, R′ = Ac), m. p. 123—124° alone or mixed with sample obtained as above.

5-Isobutyl-3,3-di-isopentylcyclopentane-1,2,4-trione (VI; R = Pr^i).—(i) The abnormal reduction product (V; R = Pr^i, R′ = H) (0·55 g.) in chloroform (50 ml.) was stirred with manganese dioxide (2·70 g.) for 20 min. (cf. the oxidation of allethrolone [10]). After filtration and evaporation of the filtrate and washings, the residue was extracted with ether, and the soluble portion distilled to give a pale yellow syrup, b. p. 130° (bath)/3 × 10^{-3} mm. (0·62 g.) This crystallized, and recrystallization from aqueous methanol gave the *triketone* (VI; R = Pr^i), m. p. 69—71° (Found: C, 74·3; H, 10·4. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·4%), $\lambda_{max.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 133), $\lambda_{min.}$ 240 mμ in acidified ethanol, and $\lambda_{max.}$ 230 ($E^{1\%}_{1\,cm.}$ 140), 330 ($E^{1\%}_{1\,cm.}$ 116), $\lambda_{min.}$ 255 mμ in alkaline ethanol, $\nu_{max.}$ (in Nujol) 2970, 1740, 1680, and 1645 cm.$^{-1}$.

A solution of triketone (VI; R = Pr^i) (0·1 g.) in light petroleum (2 ml.) was shaken with a saturated solution of sodium hydrogen carbonate (4 ml.). The insoluble material formed at the interface was extracted with ether, and the ethereal solution evaporated to afford the *sodium salt*, m. p. 230—231° (Found: C, 69·7; H, 9·7. $C_{19}H_{31}NaO_3$ requires C, 69·2; H, 9·4%).

No crystalline compound was obtained by treating the triketone (VI; R = Pr^i) with *o*-phenylenediamine or naphthalene-2,3-diamine.

(ii) 5-Hydroxy-2-isobutyl-4,4-di-isopentylcyclopentane-1,3-dione (0·1 g.) in glacial acetic acid (5 ml.) was heated under reflux with bismuth oxide (0·2 g.) for 24 hr. Dilution with 2N-hydrochloric acid (20 ml.) and extraction with ether afforded a yellow syrup (0·07 g.), b. p. 130° (bath)/5 × 10^{-4} mm., which crystallized. Recrystallization from aqueous methanol gave the triketone, m. p. and mixed m. p. 69—71°.

5-Hydroxy-2,4,4-tri-isopentylcyclopentane-1,3-dione (*Hexahydrolupulenol*) (V; R = Bu^i).—A solution of hulupone (I; Bu^i in place of Pr^i) in methanol (50 ml.) was hydrogenated in the presence of Adams catalyst (0·10 g.), absorption being complete in 90 min. The residue, after removal of catalyst and solvent, was heated at 110°/2 × 10^{-3} mm.; a small amount of material distilled. The residue then crystallized and recrystallization from ether–light petroleum and then aqueous methanol gave needles of 5-hydroxy-2,4,4-tri-isopentylcyclopentane-1,3-dione (V; R = Bu^i), m. p. 177—178° alone or mixed with hexahydrolupulenol [8] (Found: C, 73·6; H, 10·9. Calc. for $C_{20}H_{36}O_3$; C, 74·1; H, 11·1%), $\lambda_{max.}$ 250 mμ ($E^{1\%}_{1\,cm.}$ 433) in acidified ethanol, $\lambda_{max.}$ 275 mμ ($E^{1\%}_{1\,cm.}$ 768) in basic ethanol, $\nu_{max.}$ (in Nujol) 3500, 2960, 2700, and 1560 cm.$^{-1}$.

3,3,5-Tri-isopentylcyclopentane-1,2,4-trione (VI; R = Bu^i).—Hexahydrolupulenol (V; R = Bu^i) (0·25 g.) in chloroform (25 ml.) was stirred with manganese dioxide (1·3 g.) for 20 min. After filtration and removal of solvent the residue distilled as a yellow syrup, b. p. 120° (bath)/5 × 10^{-3} mm., which solidified to afford the triketone (VI; R = Bu^i), m. p. 32—33° (lit., 34°), with the reported [9] ultraviolet light absorption and $\nu_{max.}$ (film) 2980, 1740, 1685, and 1645 cm.$^{-1}$

The triketone (VI; R = Bu^i) (0·10 g.) in light petroleum (1 ml.) was treated with a saturated solution of sodium hydrogen carbonate, giving a *sodium salt* which after recrystallization from ether–light petroleum had m. p. 212—213° (Found: C, 71·2; H, 10·0. Calc. for $C_{40}H_{67}NaO_6$: C, 72·0; H, 10·1%). Howard, Pollock, and Tatchell [9] give similar analysis but do not record the m. p.

5-Hydroxy-2-isobutyryl-4,4-di-(3-methylbut-2-enyl)cyclopentane-1,3-dione (IV).—Cohulupone (1·01 g.) in ethanol (50 ml.) was added with stirring at room temperature during 30 min. to a solution of sodium borohydride (0·80 g.) in water (15 ml.), and the mixture was stirred for a further 2 hr. The excess of reagent was decomposed with 2N-hydrochloric acid, and the mixture was diluted with water (120 ml.) and extracted with ether (3 × 50 ml.). The combined ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated to a syrup which distilled [b. p. 145—150° (bath)/10^{-3} mm.], to give the *dione* (IV) (0·56 g.) (Found: C, 71·3; H, 8·7%; I no., 163, 169. $C_{19}H_{28}O_4$ requires C, 71·3; H, 8·75%; I no., 159), $\lambda_{max.}$ 260 mμ

[10] Elliott, personal communication.

($E^{1\%}_{1\,cm.}$ 258) in acidified ethanol, $\lambda_{max.}$ 270 ($E^{1\%}_{1\,cm.}$ 392), 260sh mμ ($E^{1\%}_{1\,cm.}$ 367), $\lambda_{min.}$ 235 mμ ($E^{1\%}_{1\,cm.}$ 266) in alkaline ethanol, $\nu_{max.}$ (film) 3450, 1690, 1626, and 1587 $cm.^{-1}$.

This compound (IV) (210 mg.) in methanol (30 ml.) was hydrogenated in the presence of 5% palladium–barium sulphate. Absorption (27 ml.) ($2H_2$ = 30 ml.) was complete in 48 hr. After removal of catalyst and solvent the residue was distilled to afford 5-hydroxy-2-isobutyryl-4,4-di-isopentylcyclopentane-1,3-dione, b. p. 145—150° (bath)/4×10^{-3} mm., identical in infrared absorption with the sample obtained as above.

The reduction product (IV) (0·56 g.) and bismuth oxide (1·1 g.) in glacial acetic acid (30 ml.) were heated under reflux during 18 hr. The mixture was diluted with 2N-hydrochloric acid and extracted with ether. The ethereal extract on evaporation afforded with sodium hydrogen carbonate a crude sodium salt. This was acidified, to give cohulupone, b. p. 125° (bath)/$2{\cdot}2 \times 10^{-3}$ mm. (57 mg.), having ultraviolet and infrared absorption identical with those of an authentic sample.[1]

We thank Dr. A. H. Cook, F.R.S., for his encouragement and Dr. M. Elliott for details of the oxidation of allethrolone before publication.

BREWING INDUSTRY RESEARCH FOUNDATION,
NUTFIELD, SURREY.

[*Received, April 3rd,* 1963.]