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ON THE REACTION OF ACETOACETIC ESTER WITH (+)-CARVONE: AN OXABICYCLO[3.3.1]NONENE AND SOME BICYCLO[3.3.1]NONANOLONES

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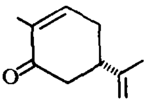
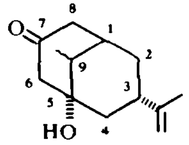
Abstract—The reaction between (+)-carvone and acetoacetic ester in the presence of sodium ethoxide is described. At 20° in the presence of small quantities of base the product is (−)-3α-isopropenyl-5α-hydroxy-7,9β-dimethyl-8-ethoxycarbonyl-6-oxabicyclo[3.3.1]non-7-ene. At 80° and in the presence of larger quantities of base, the products are isomeric 3α-isopropenyl-5α-hydroxy-9-methyl-bicyclo[3.3.1]nonan-7-ones.

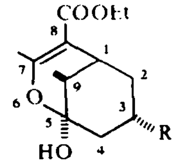
THE Michael reaction has often been used preparatively, although sometimes anomalous products are encountered.[1,2] In 1903 Rabe and Weilinger reported the synthesis of a bicyclo[3.3.1]nonanolone (shown here to be a mixture of II and III) by the Michael reaction of acetoacetic ester heated with (+)-carvone I in the presence of sodium ethoxide.[3] This paper reports *inter alia* an unexpected product from this reaction. Some modifications to the results of Rabe and Weilinger are also described.



I



II: 9α-Me
III: 9β-Me

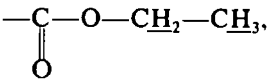


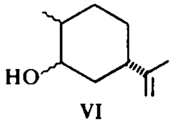
IV: R = isopropenyl
V: $R = {}^{i}Pr$

The reaction between (+)-carvone, excess acetoacetic ester and a few mmoles of sodium ethoxide in ethanol at 20° gave an unexpected product, identified as (−)-3α-isopropenyl-5α-hydroxy-7,9β-dimethyl-8-ethoxycarbonyl-6-oxabicyclo[3.3.1]non-7-ene IV (referred to in the rest of this paper as 'the adduct'). The evidence for this structure is discussed in what follows.

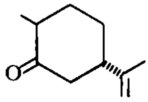
The adduct showed no enolic properties; it gave no colour with ferric chloride, and no enolic protons could be detected in the NMR spectrum at low field. The exact molecular weight found by mass spectrometry indicated the molecular formula $C_{16}H_{24}O_4$, corresponding to the addition of one molecule of carvone to one of acetoacetic ester.

The IR spectrum (in Nujol and CS_2) revealed the presence of an —OH group (band at 3410 cm^{-1}), a carbonyl doublet or two carbonyl groups (bands at 1700, 1690 cm^{-1}), a conjugated C=C (band at 1620 cm^{-1}) and an isopropenyl group (bands at 1645, 890 cm^{-1}). There were also strong bands at 1220, 1245, 1255 and 1285 cm^{-1} and at 1050, 1070 and 1090 cm^{-1}, indicative of the systems C=C—O—C and O=C—O—C. Hydrogenation of IV over Pt in ethanol converted the isopropenyl into an isopropyl group, while the conjugated C=C remained unaffected. This was shown by the IR spectra of the adduct IV (bands at 1645, 1620, 890 cm^{-1}) and the dihydro-adduct V (band at 1620 cm^{-1}), and by the UV spectra (in ethanol) of the adduct IV (λ_{max} 251 mμ, $\varepsilon = 12300$) and the dihydro-adduct V (λ_{max} 251 mμ, $\varepsilon = 11800$). These UV spectra point to the system C═C—C═O in both IV and V. Given that in (+)-carvone itself (excluding the isopropenyl group) there are two double bonds, C═C and C═O, and that in acetoacetic ester there are also two, both C═O, and given that the adduct IV (excluding the isopropenyl group) contains a non-enolic —OH group (which must be formed from a CO group) and a C═C system, it follows since the initial addition reaction must remove one double bond, that the adduct IV can contain only one CO group. The IR absorption at 1700, 1690 cm^{-1} is, therefore, a doublet, arising perhaps from Fermi resonance with the —OH absorption at 3410 cm^{-1}.

The NMR spectrum of the adduct confirmed and supplemented these conclusions. It showed a doublet due to the system $C\underline{H}_3—CH\langle$ at 9·0, 9·1 τ (3H), almost the same position as the corresponding resonance in (+)-dihydrocarveol VI (9·0, 9·1 τ) and (−)-dihydrocarvone VII (8·95, 9·05 τ). The triplet at 8·6, 8·7, 8·8 τ (3H) and quartet at 5·6, 5·75, 5·85, 6·0 τ (2H) were attributed to the typical ethyl ester system  $—\underset{\underset{O}{\|}}{C}—O—C\underline{H}_2—C\underline{H}_3$, thus accounting for the single CO group in the adduct. Therefore, the ketonic CO groups of the carvone and acetoacetic ester presumably



VI



VII

present in the initial Michael addition product (Fig. 1), must have disappeared (with suggested formation of the hemiketal system shown in IV). The singlets at 8·3 τ (3H) and 5·25 τ (2H) were attributed to the protons in the isopropenyl group — $C(C\underline{H}_3)═C\underline{H}_2$, while that at 7·7 τ (3H) was attributed to a Me group in a system $C\underline{H}_3—C═C—C═O$, the Me and CO groups possibly being *cis*.[4] Since the dihydro-adduct V showed no olefinic proton resonance, the conjugated C═C must be tetra-substituted. The signal at 6·5 τ (1H) disappeared on washing with D_2O, confirming the presence of an alcoholic —OH group.

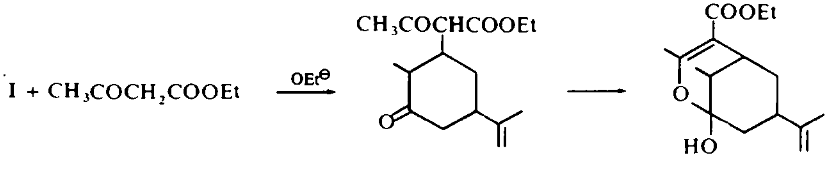
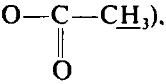


FIG. 1

Both the adduct IV and the dihydro-adduct V gave crystalline mono-acetates with isopropenyl acetate and toluene-p-sulphonic acid at 20°. The IR spectra of these acetates showed CO absorption at 1745, 1705 cm^{-1} and no absorption at 3410 cm^{-1}. The acetylation of the —OH group thus causes the CO doublet in the original compounds to collapse to a singlet. Apart from the absence of resonance at 6·5 τ

(OH) and the presence of a new singlet at 8·0 τ  $(\text{—O—C(=O)—C}\underline{\text{H}}_3)$, the NMR spectra of the acetates were almost the same as those of the adduct and dihydro-adduct. This excludes the possibility of any major skeletal rearrangement during acetylation, a conclusion supported by the fact that the UV spectra of the acetates and the parent adduct and dihydro-adduct were also similar. Since there is only one CO group in the adduct, and that in a —COOEt group, the acetates cannot have been the products of enol-acetylation, and moreover since there was no proton resonance near 5·0 τ in the NMR spectrum of the dihydro-acetate, the acetates must be tertiary, $>$C—OAc.

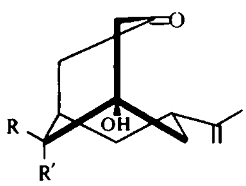
Given that the molecular formula of the adduct IV is $C_{16}H_{24}O_4$, that the oxygen functions present are —OH, COOEt and —O—, and that there are two C=C systems present, the adduct must be monocarbocyclic. And on the basis of the evidence presented, the most likely structure for the adduct is considered to be IV.

The stereochemistry is assigned on the basis of the following arguments. The results of several workers on the attack of nucleophiles at the β-position of the αβ-unsaturated CO system of cyclohexenones indicates that the incoming carbanion prefers to approach the face of the molecule which does not carry substituents. Thus Djerassi *et al.* found that the addition of CN^- to carvone occurs predominantly to the face not carrying the isopropenyl group.[5] And Allinger and Riew found that the addition of MeMgBr to 5-methylcyclohex-2-enone gave exclusively *trans*-3,5-dimethylcyclohexanone.[6] Given that the addition of acetoacetic ester carbanion to (+)-carvone follows this pattern, the stereochemistry of the adduct is most probably that shown in IV. The basic conditions of the reaction are assumed to leave the 9-Me group with the more stable 9β-equatorial orientation.

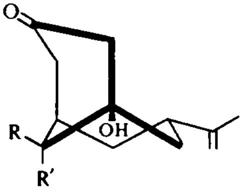
None of the crystalline adduct was isolated when the reaction described between (+)-carvone, excess acetoacetic ester and a few mmoles of sodium ethoxide was carried out under reflux. The product here was a viscous oil in low yield (ca. 10%) which was not characterized, but which when refluxed with potassium hydroxide in aqueous ethanol, gave a mixture of the ketols II and III described below. It is of interest that no analogous adduct was isolated from the reaction between (+)-carvone and ethyl methylacetoacetate under the same conditions as those leading to the isolation of the adduct IV.

The oily product of the reaction between (+)-carvone, excess acetoacetic ester and 1 mole of sodium ethoxide in ethanol at 80° gave, on heating with potassium hydroxide in aqueous ethanol, a mixture of the isomeric ketols II and III, $C_{13}H_{20}O_2$, in ca. 33% yield. These ketols were separated by crystallization and chromatography. The mixture of ketols was also obtained by heating the adduct IV with potassium hydroxide in aqueous ethanol. The basic structure of these ketols was suggested by Rabe and Weilinger[3] in 1903 on the basis of the analysis, molecular weight and molecular refraction determined for the mixture. Their conclusions are supported and amplified by the work described here. The analyses and mol wts confirmed the formula $C_{13}H_{20}O_2$ for these isomeric ketols, whose IR and NMR spectra were almost identical. The IR spectra revealed an —OH group (3400 cm^{-1}), a ketonic CO (1705 cm^{-1}) and a methylene system $>$C=CH_2 (890 cm^{-1}). The NMR spectra confirmed the —OH group (6·75 τ; 1H; signal disappeared on washing with D_2O), and showed an isopropenyl group (8·38 τ; 3H; 5·35 τ; 2H), the system $>CH—CH_3$ (8·80, 8·95 τ; 3H) and approximately four H atoms α to a CO (7·55–7·7 τ). If as before the reaction involves the attack of the acetoacetic ester carbanion on the face of the carvone molecule not carrying the isopropenyl group, then the ketols most likely differ only in the configuration of the $C_{(9)}$-Me group. (An attack of the acetoacetic ester carbanion on the face carrying the isopropenyl group would give an initial product unlikely to cyclize since the conformational inversion necessary would bring the newly introduced side-chain and the isopropenyl group into a 1,3-diaxial relationship.) It seems reasonable to assume that the crystalline ketol, m.p. 84–85°, which is the minor product, is the 9α-Me isomer, while the major product, the oily ketol, is the 9β-Me isomer, since the basic conditions of the Michael reaction would undoubtedly leave the 9-Me group predominantly equatorial.

If this is so, then the ketols II and III can have two conformations, IX or XI and VIII or X respectively. Models show that for the 9β-Me isomer III, the conformation



VIII: R = Me; R′ = H
IX: R = H; R′ = Me



X: R = Me; R′ = H
XI: R = H; R′ = Me

VIII is more favourable than X on steric grounds; for although the interactions between the $C_{(7)}$-CO and the $C_{(3)}$-βH or the $C_{(9)}$-βCH_3 in VIII or X respectively do not appear to be very different, in X there are the usual unfavourable eclipsing interactions associated with boat forms of cyclohexane. This conclusion in favour of VIII is supported by the fact that the resonance of the $C_{(9)}$-CH_3 protons (8·85, 8·95 τ; 3H) is at almost the same position as that in (—)-dihydrocarvone VII (8·95, 9·05 τ), suggesting that the 9β-Me group is not appreciably shielded by the $C_{(7)}$-CO group. Moreover, reduction of the $C_{(7)}$-CO with sodium in ethanol resulted in practically no change in the position of this resonance. Since in X the $C_{(9)}$-β-Me group falls well within the shielding cone of the $C_{(7)}$-CO group, a shift in the Me resonance of ca. 20 c/s to low field would be expected on reduction of the CO, had conformation X obtained.[7]

The conformation of the 9α-Me isomer II is more difficult to define. For models show no clear preference for either conformation IX or XI. In XI there is a negligible interaction between the $C_{(7)}$-CO and the $C_{(9)}$-βH, whereas in IX there is some interaction likely between the $C_{(7)}$-CO and the $C_{(3)}$-βH; in XI, however, there are the usual eclipsing interactions of a boat form of cyclohexane. Since the 9α-methyl group in XI is not significantly shielded by the $C_{(7)}$-CO group, no inference can be drawn from a comparison of the $C_{(9)}$-Me resonance in the ketol and its reduction product. In fact on reduction the $C_{(9)}$-Me resonance shifted about 6 c/s to higher field. So no decision is possible on the conformation of the ketol II.

Oxidation of the Na/EtOH reduction products of the ketols II and III with chromic acid in acetone regenerated the ketols. This eliminates the possibility of a retroaldol reaction preceding the reduction. This point was confirmed by the NMR spectra of the reduction products.

EXPERIMENTAL

M.ps are uncorrected. Specific rotations were determined for $CHCl_3$ solns at 20°. IR spectra were measured with Perkin-Elmer spectrophotometers PE-21 and Infracord 137 with NaCl optics. NMR spectra were obtained using a Perkin–Elmer R10 at 60 Mc/s. Mass spectra were measured on an AEI MS-902 instrument. UV spectra were measured on a Hilger–Watts Ultrascan.

Peter Spence's Grade H alumina, deactivated with 5% of 10% AcOH was used for chromatography. Pet. ether refers to the fraction, b.p. 60–80°, unless otherwise stated.

The reaction between (+)-carvone and excess acetoacetic ester at 20°

(+)-Carvone purified *via* its oxime (m.p. 75–76°; $[\alpha]_D$ + 40·2° (*c*, 8·6)) had b.p. 108–110°/20 mm; $[\alpha]_D$ + 57·4° (*c*, 9·0); n_D^{20} 1·4993. Lit. records[8]: 111–112°/18 mm; $[\alpha]_D$ + 50° (*c*, 2·9); n_D^{23} 1·4970.

A soln of (+)-carvone (30 g) and ethyl acetoacetate (65 g) in EtOH (150 ml) containing NaOEt (from 340 mg Na) was kept at 20° for 16 hr. Addition of water and extraction with ether gave an oil (85 g). Unchanged reagents were removed by distillation and the viscous residue mixed with pet. ether. The solid ppt (9 g) was collected and recrystallized from pet. ether to give (−)-3α-*isopropenyl*-α-*hydroxy*-7,9β-*dimethyl*-8-*ethoxycarbonyl*-6-*oxabicyclo*[3.3.1]*non*-7-*ene* (IV) as soft needles (7 g), m.p. 110–111°; $[\alpha]_D$ −8·0° (*c*, 13·1); IR spectrum (in CS_2): ν_{max} 3410, 1700, 1690, 1645, 1620, 1370, 1305, 1285, 1255, 1245, 1220, 1150, 1090, 1075, 1050, 995, 900, 890, 850, 780 cm^{-1}; UV spectrum (in EtOH): λ_{max} 251 mμ (ε 12300); (in hexane): λ_{max} 243 mμ (ε 11500); NMR spectrum in $CDCl_3/SiMe_4$): τ 9·0, 9·1 (D, 3H); 8·6, 8·7, 8·8 (T, 3H); 8·3 (S, 3H); 7·7 (S, 3H); 6·5 (S, 1H); 5·6, 5·75, 5·85, 6·0 (Q, 2H); 5·25 (S, 2H). Exact MW by mass spectrometry 280·1695; $C_{16}H_{24}O_4$ requires 280·1674. (Found: C, 68·6; H, 8·2. $C_{16}H_{24}O_4$ requires: C, 68·6; H, 8·6%).

Hydrogenation of the adduct (IV)

The adduct IV took up 1 mole H_2 over Pt in EtOH to give the *dihydro-adduct* (V) which crystallized from pentane at 0° as needles, m.p. 80–81°; $[\alpha]_D$ −3·0° (*c*, 15·2); IR spectrum (in Nujol): ν_{max} 3400, 1700, 1690, 1610, 1370, 1300, 1285, 1255, 1245, 1220, 1150, 1090, 1075, 1050, 995, 900, 845, 780 cm^{-1}: UV spectrum (in EtOH): λ_{max} 251 mμ (ε 11800); NMR spectrum (in $CCl_4/SiMe_4$): τ 9·1–9·25 (M, 9H); 8·65, 8·75, 8·85 (T, 3H); 7·75 (S, 3H); 6·2 (S, 1H); 5·7. 5·85, 5·95, 6·1 (Q, 2H). (Found: C, 68·3; H, 9·1. $C_{16}H_{26}O_4$ requires: C, 68·1; H, 9·2%).

Acetylation of the adduct (IV)

A soln of IV (300 mg) in isopropenyl acetate (20 ml) containing toluene-*p*-sulphonic (75 mg) was kept at 20° for 24 hr. Recovery by the addition of $NaHCO_3$aq and extraction with ether gave a solid (280 mg). This was filtered through alumina (10 g) in pet. ether–ether (7 : 1) to give the *adduct acetate* which crystallized from Me_2COaq as needles (220 mg), m.p. 92–93°; $[\alpha]_D$ −6·6° (*c*, 19·2); IR spectrum (in Nujol): ν_{max} 1745, 1705, 1645, 1625, 1305, 1290, 1260, 1240, 1220, 1160, 1085, 1075, 1050, 900 cm^{-1}; UV spectrum (in EtOH): λ_{max} 251 mμ (ε 10200): NMR spectrum (in $CCl_4/SiMe_4$): τ 9·15, 9·25 (D, 3H); 8·6, 8·7, 8·8 (T, 3H); 8·3 (S, 3H); 7·95 (S, 3H); 7·7 (S, 3H); 5·7, 5·8, 5·95, 6·05 (Q, 2H); 5·15 (S, 2H). (Found: C, 67·1; H, 8·0. $C_{18}H_{26}O_5$ requires: C, 67·1; H, 8·1%).

Acetylation of the dihydro-adduct (V)

The dihydro-adduct was acetylated as described for the adduct, and the *dihydro-adduct acetate* obtained crystallized from Me_2COaq as needles, m.p. 36–37°; $[\alpha]_D$ −0·9° (*c*, 21·3); IR spectrum (in Nujol): ν_{max} 1745, 1705, 1620, 1300, 1280, 1260, 1230, 1215, 1160, 1085, 1070, 1040 cm^{-1}; UV spectrum (in EtOH): λ_{max} 250·5 mμ (ε 12100); NMR spectrum (in $CCl_4/SiMe_4$): τ 9·1–9·3 (M, 9H); 8·75, 8·85, 8·90 (T, 3H); 8·0 (S, 3H); 7·75 (S, 3H); 5·75, 5·85, 6·0, 6·1 (Q, 2H). (Found: C, 66·7; H, 8·3. $C_{18}H_{28}O_5$ requires: C, 66·7; H, 8·6%).

The reaction between (+)-carvone and excess acetoacetic ester at 80°

A soln of (+)-carvone (37·5 g), acetoacetic ester (75 g) and NaOEt (from 5·6 g Na) in EtOH (275 ml) was refluxed for 48 hr. A soln of KOH (70 g) in water (350 ml) was then added and the reflux continued for a further 24 hr. The product was recovered as a brown oil by dilution with water and extraction with ether. This oil (35 g) was fractionated to give (i) mainly unchanged (+)-carvone (7 g), b.p. 100–115°/12 mm, and (ii) an oil (20 g), b.p. 170–195°/12 mm. This latter was refractionated and the fraction b.p. 180–185°/12 mm, n_D^{20} 1·5100, $[\alpha]_D$ + 15°(*c*, 5·4) was collected. This partly crystallized on standing to give (+)-3α-*isopropenyl-5α-hydroxy-9α-methyl-bicyclo*[3.3.1]*nonan-7-one* (II) as blades (4 g), m.p. 84–85° (from pet. ether); $[\alpha]_D$ + 26° (*c*, 10·3); IR spectrum (in Nujol): ν_{max} 3400, 1705, 1645, 1370, 1330, 1225, 1075, 1060, 1000, 890 cm^{-1}; NMR spectrum (in $CCl_4/SiMe_4$): τ8·80, 8·95 (D, 3H); 8·38 (S, 3H); 7·55–7·7 (M, 4H); 6·75 (S, 1H, disappears on washing with D_2O); 5·35 (S, 2H). (Found: C, 75·1; H, 9·6; MW 219·5. $C_{13}H_{20}O_2$ requires: C, 75·0; H, 9·6%; MW 208).

The oily residue was adsorbed on alumina (500 g). Pet. ether–ether (1:2) initially eluted a small quantity of II. Further elution gave the 9β-*methyl isomer* (III) as an oil (13 g), b.p. 178–179°/10 mm: n_D^{20} 1·5095; $[\alpha]_D$ + 11° (*c*, 9·2); IR spectrum (film): ν_{max} 3410, 1705, 1645, 1370, 1330, 1225, 1080, 1060, 1010, 895 cm^{-1}; NMR spectrum (in $CCl_4/SiMe_4$): τ 8·80, 8·95 (D, 3H); 8·35 (S, 3H); 7·55–7·75 (M, 4H); 6·7 (S, 1H, disappears on washing with D_2O); 5·3 (S, 2H). (Found: C, 74·8; H, 9·8. $C_{13}H_{20}O_2$ requires: C, 75·0; H, 9·6%). Lit. records for a mixture of II and III[3]: b.p. 182–183°/12–15 mm; n_D^{20} 1·4992; $[\alpha]_D$ + 18·8° (*c*, 7·074 in 99% EtOH).

This mixture of ketols was also obtained by heating IV with aqueous ethanolic KOH.

Reduction of the ketols II *and* III with Na *in* EtOH

The 9β-*methyl isomer* (III). Sodium (5 g) was added to a boiling soln of III (2 g) in EtOH (50 ml). When the Na had dissolved, the mixture was poured into water and the oily product (1·9 g) isolated in ether. The oil partly crystallized on the addition benzene to give a crystalline diol (3·0 mg), m.p. 172–173°; $[\alpha]_D$ − 18° (*c*, 6·3); IR spectrum (in Nujol): ν_{max} 3300, 1645, 1025, 1015, 885 cm^{-1}; NMR spectrum (in $CDCl_3/SiMe_4$): τ 8·95, 9·05 (D, 3H); 8·3 (S, 3H); 5·3 (S, 2H). Lit. records[3]: m.p. 172–173°; $[\alpha]_D$ − 19·35° (*c*, 7·88 in 99% EtOH).

The mother liquors were evaporated and the oil adsorbed on alumina (60 g). Pet. ether–ether (1:5) eluted an oily diol (1·3 g), b.p. 190–193°/12 mm; $[\alpha]_D$ + 14° (*c*, 5·9); IR spectrum (film): ν_{max} 3300, 1645, 1020, 1010, 895 cm^{-1}; NMR spectrum (in $CHCl_3/SiMe_4$): τ 8·9, 9·0 (D, 3H); 8·35 (S, 3H); 5·3 (S, 2H). Lit. records[3]: b.p. 198°/15 mm; $[\alpha]_D$ + 11·75° (*c*, 7·425 in 99% EtOH). These diols were not further characterized.

The 9α-*methyl isomer* (II). Na (2·5 g) was added to a boiling soln of the ketol (1 g) in EtOH (40 ml). Recovery of the product by dilution with water and extraction with ether gave an oily mixture of *epimeric diols* (890 mg), b.p. 189–192°/15 mm; $[\alpha]_D$ + 32° (*c*, 7·6); IR spectrum (film): ν_{max} 3350, 1645, 1020, 1010, 890 cm^{-1}; NMR spectrum ($CHCl_3/SiMe_4$): τ 8·9, 9·0 (D, 3H); 8·3 (S, 3H); 5·35 (S, 2H). This diol mixture was not further characterized.

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