Reaction of Methyl Vinyl Ketone with 1-Pyrrolidin-1-ylisobutene

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Methyl vinyl ketone reacts with 1-pyrrolidin-1-ylisobutene to give the tricyclic diketone (2; R = Me). The reaction proceeds through the bisenamine (4; R = Me) formed by self-condensation of the intermediate dienamine (3).

FLEMING and KARGER[1] reported that the dihydropyran (1) is obtained from the reaction of methyl vinyl ketone with 1-pyrrolidin-1-ylisobutene at ambient temperature. We have found that reaction of these species in refluxing benzene solution followed by hydrolysis with acetic acid gives a crystalline product, $C_{16}H_{24}O_2$, in an overall 20% yield. The molecular formula and spectral properties of this compound indicated that it was the tricyclic diketone (2; R = Me). Its i.r. spectrum showed strong carbonyl bands at 1715 and 1727 cm^{-1}; the n.m.r. spectrum in deuteriochloroform showed four distinct methyl signals and the remaining proton signals formed a complex pattern in the region τ 6·8—8·6. Double-irradiation experiments revealed the presence of an AM quartet centred at τ 7·7 (*J* 14 Hz). In benzene solution this AM pattern showed a further fine splitting (*J* 2—3 Hz) and was consequently attributed to the geminal protons at C-10 of (2; R = Me) which would be of different chemical shift and capable of coupling with the adjacent C-1 proton. The spectrum in benzene also revealed an AA'BB' system (*J* 2·5 Hz) centred at τ 8·13 due to the four protons at C-4 and C-5.

The structure of (2; R = Me) was established by the following series of reactions. The dihydropyran (1), prepared by the method of Fleming and Karger[1] without isolation, was converted into 4,4-dimethylcyclohex-2-en-1-one on treatment with dilute hydrochloric acid at 85—90°. Reaction of this unsaturated ketone with pyrrolidine failed to produce the expected dienamine (3) but gave instead a crystalline bisenamine, $C_{24}H_{38}N_2$. This compound was formulated as (4; R = Me) on the basis of its n.m.r. spectrum and close analogy with the corresponding bisenamine (4; R = H) obtained as its diperchlorate salt from cyclohex-2-en-1-one and pyrrolidinium perchlorate by Leonard and Musliner.[2] In the n.m.r. spectrum of (4; R = Me) only one vinyl proton signal was observed. This appeared as a double doublet (*J* 7 and 2·5 Hz) and was assigned to the C-10 proton which experiences a moderately strong interaction with the proton at C-1 and a weak allylic coupling with the C-8 proton. A high field methyl resonance (τ 9·47) was also observed in the spectrum. This was attributed to one of the C-6 methyl groups which will lie over the plane of the C(9)–C(10) double bond when both 7-H and the C(1)–C(8) bridge are β.

Leonard and Musliner[2] proposed two mechanistic routes to (4; R = H), both involving the intermediate dienamine (5) which can either undergo self-condensation or

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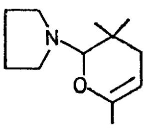
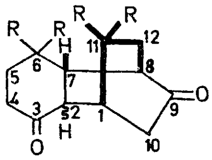
[1] I. Fleming and M. H. Karger, *J. Chem. Soc.* (*C*), **1967**, **226**.

[2] N. J. Leonard and W. J. Musliner, *J. Org. Chem.*, **1966**, **31**, 639.

reaction with cyclohex-2-en-1-one to give the enaminoketone (6; R = H) followed by further condensation with pyrrolidine. The mode of formation of (4; R = Me) is thought to be similar but it proceeds through a dienamine (3) which unlike (5) is cross-conjugated (Scheme).


(1)



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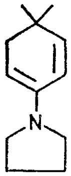
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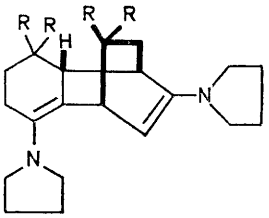

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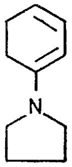
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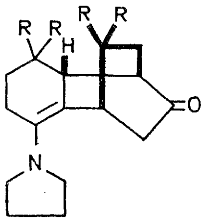
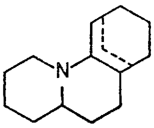
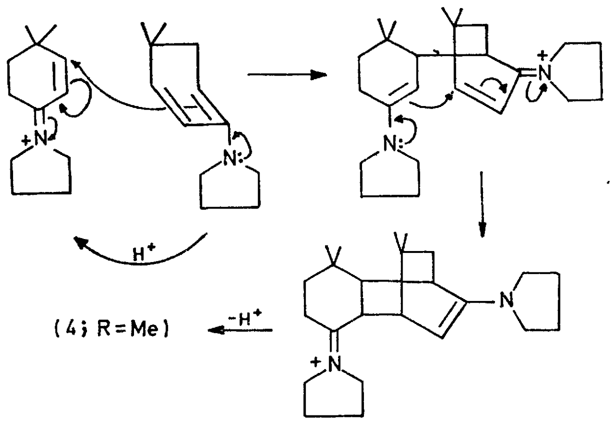


(6)



(7)



Reaction of the diketone (2; R = Me) with pyrrolidine also gave the bisenamine (4; R = Me), thereby confirming their relationship. Under less vigorous conditions this reaction afforded the enaminoketone (6; R = Me). The i.r. spectrum of this compound showed a carbonyl band at 1725 cm^{-1} indicative of a bicyclo-[2,2,2]octanone system[3] and enamine C=C absorption at 1676 cm^{-1}. Its n.m.r. spectrum showed no vinylic proton signals confirming that the enamine double bond was again tetrasubstituted and located at C(2)–C(3). Furthermore the highest-field methyl signal was at τ 9·2 now that the shielding effect of the C(9)–C(10) double bond had been removed.

The bisenamine (4; R = Me) and enaminoketone (6; R = Me) are unusual as they both contain a tetrasubstituted enamine double bond. The pyrrolidine enamine from 2-methylcyclohexanone for example is prevented from existing as the tetrasubstituted isomer by a severe steric interaction between the methyl group and the methylene groups adjacent to the nitrogen atom of the pyrrolidine ring when overlap between the electron pair of the nitrogen and double bond is maintained.[4] However, Dreiding models of (4; R = Me) and (6; R = Me) show that the steric interaction between the hydrogen atoms at C(1) and C(4) and the α-methylene groups of the pyrrolidine ring is not significantly greater than that experienced when the double bond is situated in the C(3)–C(4) trisubstituted position. Danishefsky and Feldman[5] have described a similar situation in the heterocyclic enamine (7) and found that the overriding stability of the tetrasubstituted double bond led to predominance of this isomer over the trisubstituted structure by a factor of 4 : 1.

Finally, hydrolysis of both (4; R = Me) and (6; R = Me) with acetic acid gave the diketone (2; R = Me) suggesting that this compound was formed from 1-pyrrolidin-1-ylisobutene and methyl vinyl ketone by reaction sequence (1).

$$\begin{tikzcd} (1) \arrow[r] & (3) \arrow[r] & (4;\ R = CH_3) \arrow[rr] \arrow[dr, dashed] & & (2;\ R = CH_3) \\ & & & (6;\ R = CH_3) \arrow[ur, dashed] & \end{tikzcd} \qquad (1)$$

The stereochemistry of the C(2), C(7) ring junction in (2; R = Me) could not be deduced from its n.m.r. spectrum; Leonard and Musliner[2] were similarly unable to assign stereochemistry to their diketone (2; R = H) but found that it gave mainly the *cis*-tricyclo[6,2,2,0,^{2,7}]-dodecane on Wolf–Kishner reduction.

EXPERIMENTAL

T.l.c. was carried out on Eastman Chromatogram strips. Spots were made visible with iodine vapour. M.p.s were determined on a Kofler hot-stage apparatus. Unless otherwise stated, i.r. absorption spectra were determined for potassium bromide pellets on a Perkin-Elmer 237 spectrometer and n.m.r. spectra were measured for solutions in deuteriochloroform on a Varian Associates T60 spectrometer with tetramethylsilane as internal standard. Double irradiation experiments were carried out using the frequency sweep mode.

Light petroleum refers to the fraction of b.p. 60—80°.

6,6,11,11-*Tetramethyltricyclo*[6,2,2,0,^{2,7}]*dodecane*-3,9-*dione* (2; R = Me).—Methyl vinyl ketone (105 g) was added to a stirred solution of 1-pyrrolidin-1-ylisobutene (150 g) in dry benzene (150 ml) at 0° under nitrogen. The

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[3] R. Zbinden and H. K. Hall, jun., *J. Amer. Chem. Soc.*, 1960, **82**, 1215.

[4] G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

[5] S. Danishefsky and M. Feldman, *Tetrahedron Letters*, 1965, 1131.

resulting solution was allowed to warm to room temperature during 15 min and then heated under reflux for 15 h. The solution was cooled to 0°, acetic acid (80 g) was added, and the mixture was heated under reflux for a further 4 h. The benzene layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with dilute hydrochloric acid and water, and dried. Removal of the solvent gave a solid which was washed well with ethanol and dried. Recrystallisation from ethanol gave the *diketone* (2; R = Me) (28·1 g) as needles, m.p. 167—168° (Found: C, 77·1; H, 10·0. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%); $\nu_{max.}$ 1727 (sh) and 1715 (C=O) cm^{-1}; τ 9·02, 8·96, 8·90, and 8·78 (all s, 3H, Me), and 6·98 (half of an AMq centred at τ 7·7, 1H, *J* 14 Hz, 10-H; on double irradiation at τ 8·33, this signal collapsed to a broad singlet), τ (C_6H_6) 9·37 (s, 3H, Me), 9·21 (s, 9H, 3 × Me), 8·60 (d, 2H, *J* 2·5 Hz, 4-CH_2), 7·69 (d, 2H, *J* 2·5 Hz, 5-CH_2; on double irradiation at τ 7·69, the signal at τ 8·60 collapsed to a singlet), and 7·39 (dd, 1H, *J* 14 and 2—3 Hz, 10-H).

4,4-*Dimethylcyclohex*-2-*en*-1-*one*.[1]—Methyl vinyl ketone (82 g) was added to a stirred solution of 1-pyrrolidin-1-ylisobutene (90 g) during 30 min at 0°. The mixture was stirred for 18 h at room temperature and then 2N-hydrochloric acid (500 ml) was added during 30 min (temperature rose to 70—80°). The temperature was maintained at 85—90° for 4 h, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and dried and solvent was removed *in vacuo*. The residue was distilled to give 4,4-dimethylcyclohex-2-en-1-one (20·7 g), b.p. 71—76° at 15 mmHg (lit.,[6] b.p. 60—74° at 3 mmHg). Redistillation of a higher-boiling fraction (27 g) gave a further quantity of product (10·5 g), b.p. 68—76° at 15 mmHg (Found: C, 77·8; H, 9·6. Calc. for $C_8H_{12}O$: C, 77·5; H, 9·75%); $\nu_{max.}$ (film) 1680 (C=O) and 1620 (C=C) cm^{-1}; τ 8·87 (s, 6H, 2 × Me), 8·19 (m, 2H, 5-CH_2), 7·65 (m, 2H, 6-CH_2), 4·31 (d, 1H, *J* 10 Hz, 2-H), and 3·40 (dd, 1H, *J* 10 and 0·5 Hz). On double irradiation at τ 3·40, the signal at τ 4·31 collapsed to a singlet and resonances at τ 8·19 and τ 7·65 simplified into two completely symmetrical multiplets. This suggests a small coupling between 3-H and the protons at C-5 and C-6.

6,6,11,11-*Tetramethyl*-3,9-*dipyrrolidin*-1-*yltricyclo*-[6,2,2,0,^{2,7}]*dodec*-2,9-*diene* (4; R = Me).—*From* 4,4-*dimethylcyclohex*-2-*en*-1-*one*. The ketone (5 g) and pyrrolidine (3·2 g) in benzene (40 ml) were heated under reflux for 18 h with removal of water. Solvent was removed and the residue was triturated with acetone to give the *bisenamine* (4; R = Me) (1·68 g) which crystallised from acetone or ether–light petroleum in needles, m.p. 116—119° (Found: C, 81·3; H, 10·9; N, 7·7. $C_{24}H_{38}N_2$ requires C, 81·3; H, 10·8; N, 7·9%); $\nu_{max.}$ 1675 and 1608 (C=C) cm^{-1}; τ 9·47 (s, 3H, 6-Me), 9·1 (s, 3H, Me), 9·03 (s, 6H, 2 × Me), and 5·54 (dd, 1H, *J* 7 and 2·5 Hz, 10-H). On double irradiation at τ 7·95, the signal at τ 5·54 collapsed to a simple doublet (*J* 6—7 Hz), while on irradiation at τ 6·89, it collapsed to a broad singlet. The signals at τ 7·95 and τ 6·89 collapsed into singlets on reverse irradiation at τ 5·54 and were consequently assigned to the protons at C-8 and C-1 respectively.

From the diketone (2; R = Me). The diketone (2; R = Me) (5 g), pyrrolidine (5 g) and a trace of toluene-*p*-sulphonic acid in dry toluene (120 ml) were heated under reflux until the theoretical quantity of water had been evolved (3—4 days). Solvent was removed and the residue was triturated with acetone to give the bisenamine (4; R = Me) (4·10 g) which after crystallisation from acetone was identical (m.p., and i.r. and n.m.r. spectra) with the foregoing specimen.

6,6,11,11-*Tetramethyl*-9-*pyrrolidin*-1-*yltricyclo*-[6,2,2,0,^{2,7}]-*dodec*-2-*en*-3-*one* (6; R = Me).—The diketone (2; R = Me) (2·5 g), pyrrolidine (1·25 g), and a trace of toluene-*p*-sulphonic acid in dry toluene (50 ml) were heated until the theoretical quantity of water had been evolved (12—18 h). Solvent was removed and the residue was triturated with acetone to give the enaminoketone (6; R = Me) (1·20 g); $\nu_{max.}$ 1725 (C=O) and 1676 (C=C) cm^{-1}; τ 9·2 (s, 12H, 4 × Me) and 6·8—8·9 (19H, 8 × CH_2, 3 × CH). Reaction of (6; R = Me) (1·1 g) with hydrogen chloride–ether gave the *hydrochloride salt* which crystallised from ethanol–ether as prisms m.p. 122—125° (Found: C, 67·9; H, 10·1; Cl, 10·0, N, 3·5. $C_{20}H_{32}ClNO,H_2O$ requires C, 67·5; H, 9·65; Cl, 10·0; N, 3·95%); $\nu_{max.}$ 3500, 3410 (H_2O), 1730 (C=O), and 1620 (C=C) cm^{-1}.

Hydrolysis of (4; R = Me) *and* (6; R = Me) *to the Diketone* (2; R = Me).—The bisenamine (4; R = Me) (100 mg) in benzene (40 ml) was heated under reflux with glacial acetic acid (0·25 ml) for 2 h. The benzene solution was washed with dilute hydrochloric acid and water, and dried. The crystalline residue (29 mg) after removal of benzene was recrystallised from ethanol and identified as the diketone (2; R = Me) by comparison of its m.p. and i.r. spectrum with that of the specimen obtained earlier.

Similar hydrolysis of the hydrochloride salt (100 mg) of (6; R = Me) gave a crystalline product (68 mg) which after recrystallisation from ethanol was identified (m.p. and i.r. spectrum) as the diketone (2; R = Me).

[0/1266 *Received, July 23rd*, 1970]

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[6] E. J. Eliel and C. A. Likach, *J. Amer. Chem. Soc.*, 1957, **79**, 5986.