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THE REACTION OF ISOPHORONE DIENAMINES WITH CERTAIN DIENOPHILES

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Abstract—Isophorone morpholine (or piperidine) dienamine exists in roughly 1:1 equilibrium of linear- and cross-conjugated forms. Each reacts with dienophiles to yield two different types of Diels-Alder adducts, *viz.*, an allylic amine and a saturated ketone. Two types of Michael adducts are also produced. The product distribution is sensitive to the variation in the combination of the reactants.

THE Diels-Alder reaction of isophorone pyrrolidine dienamine with acrylonitrile has been reported* to give an adduct with the structure A of Fig. 1, where X is a pyrrolidino group and Y is CN. In order to gain further insight on the chemistry of dienamines,[2] on which the information is slight in contrast to that of enamines,[3] we have investigated the reaction of isophorone dienamines with a variety of dienophiles and found that the reaction proceeds according to the scheme of Fig. 1. with product distribution as summarized in Table 1.

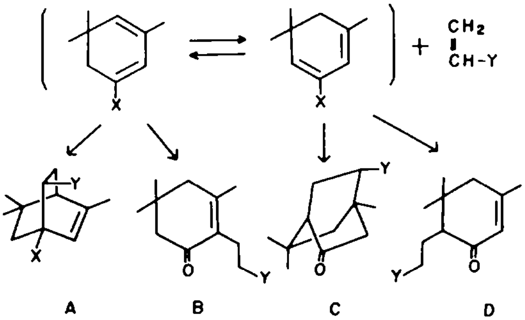

FIG. 1. The reaction scheme of dienamines and dienophiles

The morpholine and piperidine dienamines were obtained by a modification of the method of Opitz and Merz,[1] and probably exist in roughly 1:1 equilibrium mixture of the linear- and cross-conjugated isomers. This assumption is based on the NMR spectra (Fig. 2a, 2b), in which there are four peaks of equal strength in the olefinic proton region.†[4],‡

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* Opitz and Merz[1] refer to the preparation of morpholine and piperidine dienamines, but made no mention of their properties and chemical behaviour.

† All NMR spectra were taken on 60 Mc machines (Varian A60 and JEOLCO JNM-C60H) in CCl_4 soln. Chemical shifts are given in ppm from internal TMS standard. Double resonance experiments failed to afford detailed assignment because of the small differences in chemical shifts.

‡ The peak at 5·13 ppm in Fig. 2b is ascribed to the contamination of isophorone which shows an olefinic proton singlet at 5·70 ppm in the absence of the piperidine dienamine.

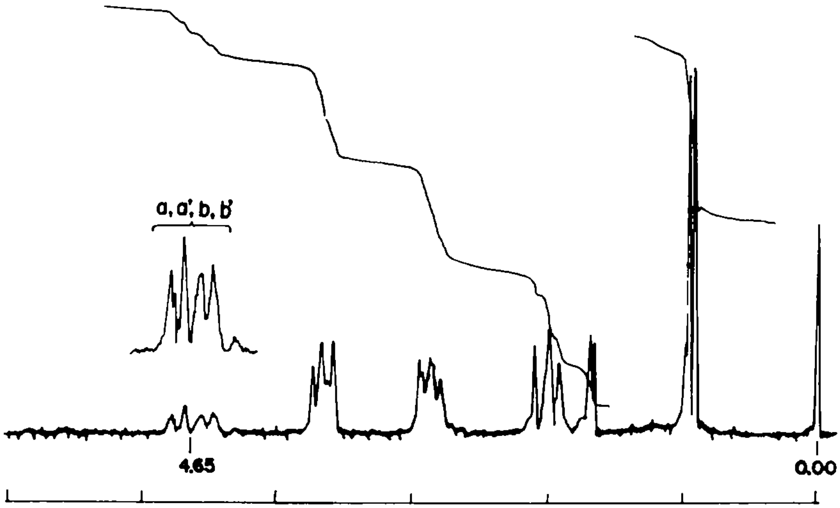


FIG. 2a. NMR spectrum of isophorone morpholine dienamine.

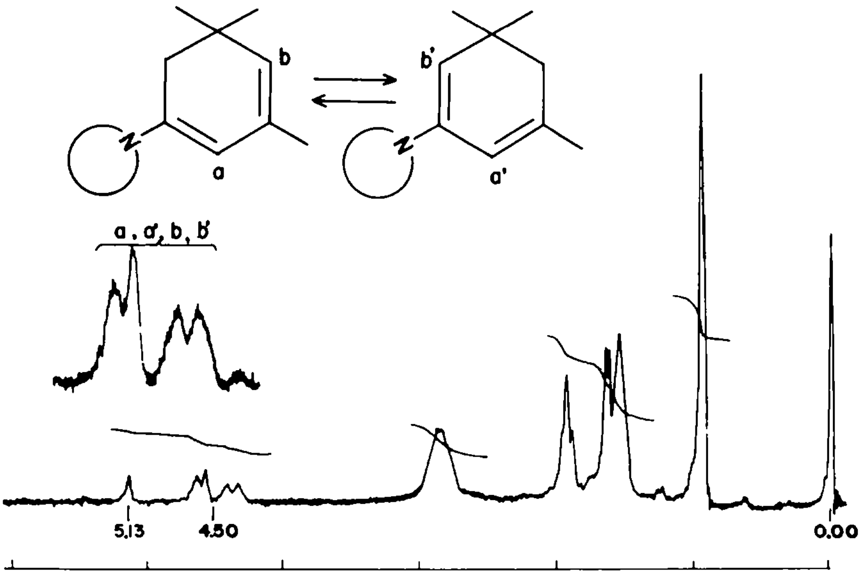


FIG. 2b. NMR spectrum of isophorone piperidine dienamine.

TABLE 1. PRODUCT DISTRIBUTION IN YIELDS (%)

X[a]	Y[b]	A[c]	B[c]	C[c]	D[c]
M	CN	I, 76	—	—	—
P	CN	II, 3·0	—	III, 10	IV, 20
M	COMe	—	V, 33	VI, 6·0	—
P	COMe	—	V, 31	VI, 7·5	—
M	COOMe	—	—	VII, 29	VIII, 23
P	COOMe	—	—	VII, 26	—

[a] M stands for morpholino and P for piperidino group, respectively.

[b] The dienophiles were arranged in the order of decreasing Q values.

[c] Formulae are given in Fig. 1.

The reaction of the dienamines with acrylonitrile. Heating an equimolar mixture of the morpholine dienamine and the dienophile gave a good yield of a crystalline allylic amine I of the type A. The NMR spectrum (Fig. 3a) clearly indicates the presence of a morpholino group and an olefinic proton. The stereochemistry of the nitrile group is deduced on the basis of the rule of maximum accumulation of multiple bonds,[5] as will be the case with other Diels-Alder adducts described below.

An analogous adduct II was also produced in a much reduced yield in the reaction of piperidine dienamine. The NMR spectrum is shown in Fig. 3b. A second Diels-Alder adduct III of the type C, also isolated in this reaction, shows carbonyl absorption at 1720 cm^{-1} (Nujol) and on methanolysis yielded VII. The third product of this reaction was isolated as an oil and was shown to be IV of the type D. Methanolysis of IV yielded VIII, as expected. The structural proof of VII and VIII will be given later.

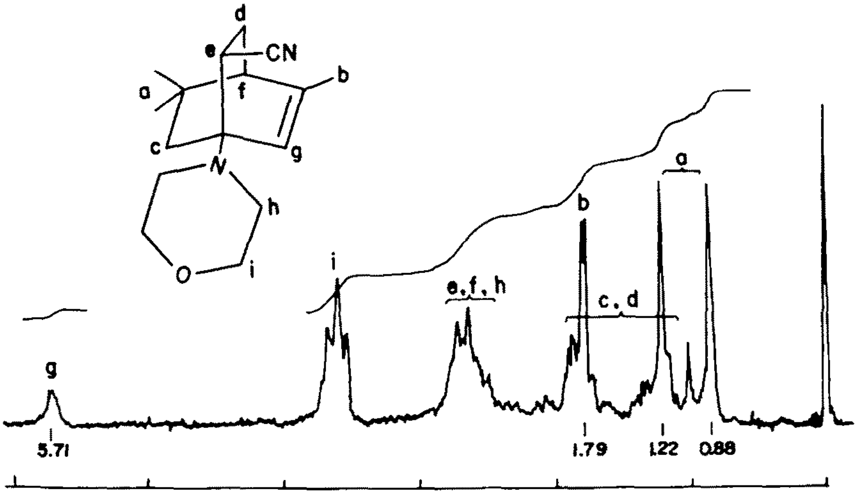


FIG. 3a. NMR spectrum of the allylic amine I.

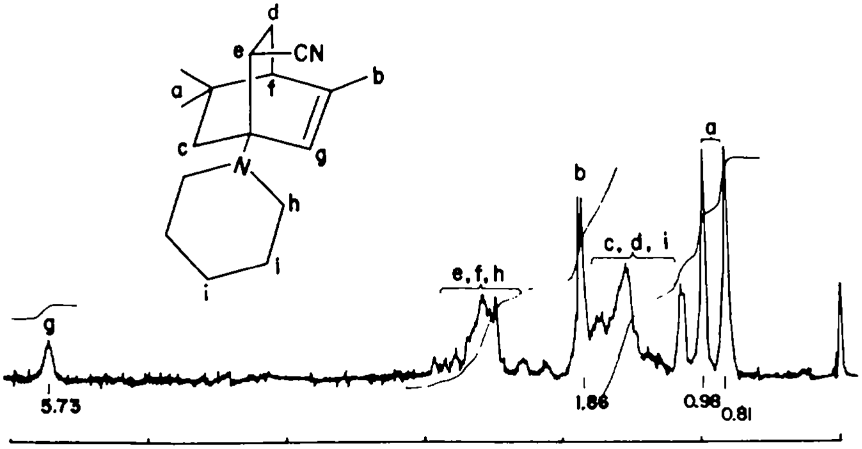


Fig. 3b. NMR spectrum of the allylic amine II.

The reaction of the dienamines with methyl vinyl ketone. The reaction of morpholine dienamine was carried out as before and gave an oily α,β-unsaturated ketone V of the type B and a solid saturated ketone VI of the type C. An authentic sample of the ketone V was prepared by the published method^6 and the identity was established by comparison of NMR spectra and GLC retention times. Negligible discrepancies in the IR spectra were observed and ascribed to a small amount of impurities in the present preparation, which could be removed by dry column chromatography.^{7}

The ketone VI shows IR absorption at 1720 cm^{-1} and gave a positive iodoform reaction. The NMR spectrum (Fig. 4) is consistent with the structure given.

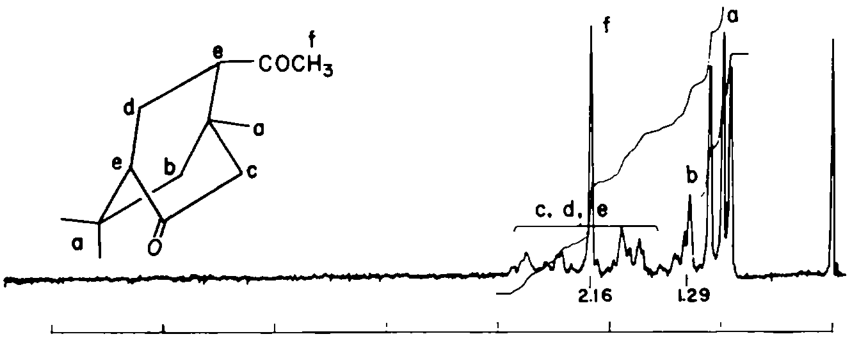
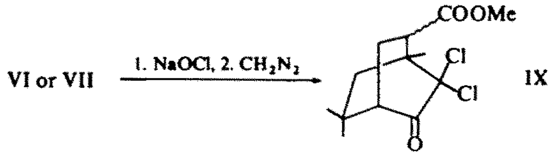


Fig. 4. NMR spectrum of VI.

Treatment of an equimolar mixture of the piperidine dienamine with methyl vinyl ketone yielded the same products (V and VI) in comparable yields.

The reaction of the dienamines with methyl acrylate. The reaction products from morpholine dienamine were found to be a solid keto ester VII and an oily ester VIII having an α,β-unsaturated keto group.

The NMR spectrum (Fig. 5) of solid VII is very similar to that of VI. Conclusive evidence for the common carbon skeleton of VI and VII was obtained by chemical transformation of these compounds into IX:



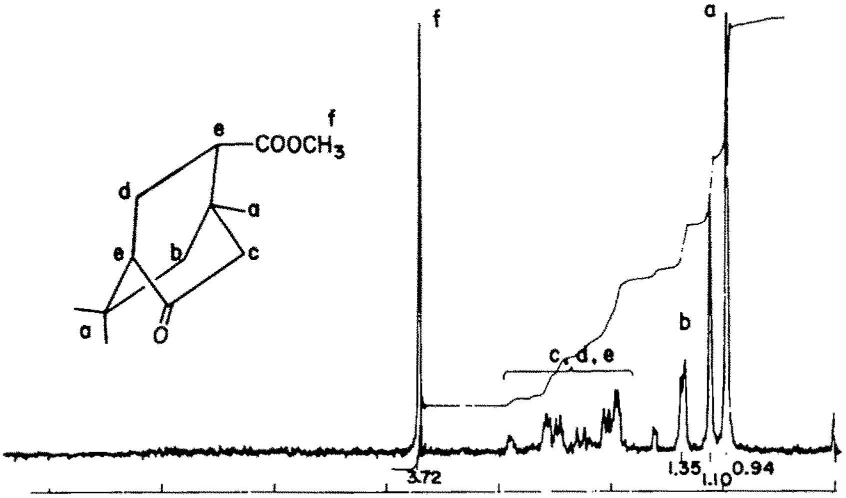


FIG. 5. NMR spectrum of VII.

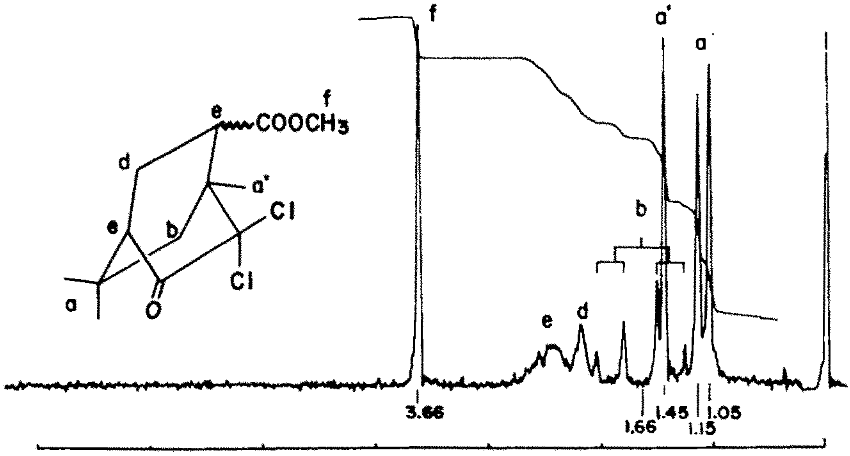


FIG. 6. NMR spectrum of IX.

The carbonyl absorption (KBr) of IX is at 1735 cm^{-1} with a shoulder at 1740 cm^{-1}. The NMR spectrum (Fig. 6) is consistent with the assigned structure. The paramagnetic shift was observed with respect to both the bridge-head methyl group (a′) and one of the β-methylene protons (b) and was ascribed to the introduction of chlorine atoms.*

The NMR spectrum (Fig. 7) of the oily unsaturated keto ester VIII indicates the presence of one olefinic proton. The IR absorption (neat) at 1750 and 1670 cm^{-1} and UV maximum (EtOH) at 236 mμ (log ε 4·09) indicates a conjugated enone system. Thus the properties of VIII are in accord with the given structure of type D and the possibility of the formulae X and XI can be excluded. The Michael adduct VIII is ascribed to the reaction of cross-conjugated dienamine.

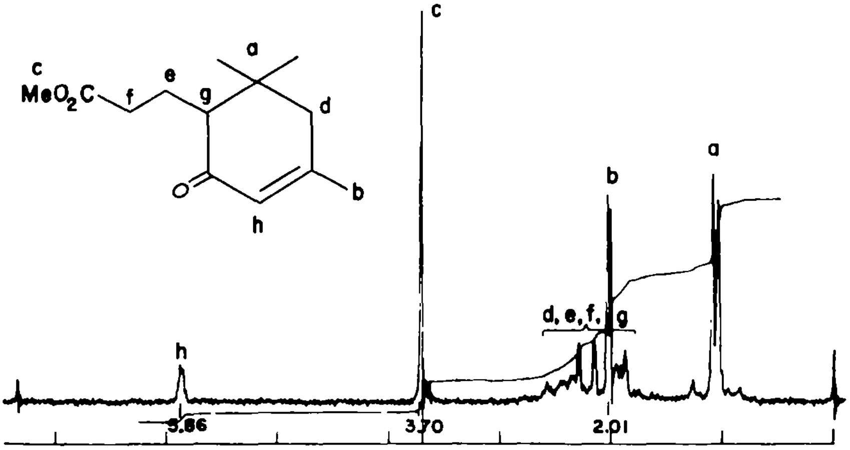
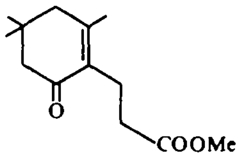
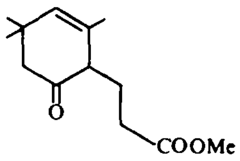


FIG. 7. NMR spectrum of VIII.



X



XI

The reaction of the piperidine dienamine with methyl acrylate yielded VII as the only isolated product (solid). The oily adduct VIII was not obtained in this case.

All these findings are explained on the assumption that the two forms of dienamines are in equilibrium and each is susceptible to attack by dienophiles. At present, the strong dependence of the product distribution on the combination of reaction components can not be accounted for.

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* Such deshielding effect of chlorine atom through space has been described.[8]

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Microanalyses were performed at the Elemental Analyses Centre of Kyôto University.

Preparation of morpholine dienamine of isophorone. A soln of isophorone (100 g, 0·72 mole), morpholine (90 g, 1·0 mole) and *p*-toluenesulphonic acid (a catalytic amount) in benzene (450 ml) was heated under reflux for 72 hr. The moisture in the condensate was trapped with a column of Molecular Sieve and returned to the still. After removal of benzene under N_2 atmosphere *in vacuo*, distillation of the residue gave a viscous yellow oil (66·7 g, 45%), b.p. 107–110° (2 mm). IR absorptions (neat) were observed at 1650, 1620, 1590 cm^{-1}, while UV (EtOH) at 288 mμ (log ε 4·15). The NMR spectrum was given in Fig. 2a. (Found: C, 75·1; H, 10·2. Calc. for $C_{13}H_{21}NO$: C, 75·3; H, 10·2%).

Preparation of piperidine dienamine of isophorone. A soln of isophorone (30 g, 0·22 mole), piperidine (25 g, 0·29 mole) and *p*-toluenesulphonic acid (a catalytic amount) in benzene (150 ml) was treated similarly as above. The dienamine was obtained as a viscous yellow oil (20 g, 45%), b.p. 105–108° (1 mm). IR absorptions (neat) were observed at 1650, 1620, 1585 cm^{-1}, while UV (EtOH) at 274 mμ (log ε 4·26). The NMR spectrum was shown in Fig. 2b. (Found: C, 82·3; H, 11·6. Calc. for $C_{14}H_{23}N$: C, 81·9; H, 11·3%).

Reaction of the dienamines with dienophiles, the general procedure. A soln of the dienamine and dienophile in dioxan (1:1:10 molar ratio) was heated under reflux for 7 hr. The residue after evaporation was heated with 1:1 aqueous MeOH (7-times the vol of dioxan) under reflux for 7-10 hr. After removal of MeOH, the residue was extracted with ether, washed, dried ($MgSO_4$) and concentrated *in vacuo*. The reaction products were fractionally distilled and purified by column chromatography or GLC.

Reaction of morpholine dienamine of isophorone with acrylonitrile. The reaction of morpholine dienamine (12·5 g, 60 mmoles) and acrylonitrile (3·2 g, 60 mmoles) in dioxan (50 ml) yielded *7-cyano-1-morpholino-3,5,5-trimethylbicyclo-*[2.2.2]*oct-2-ene* (I) as colourless fine needles (11·8 g, 76%), m.p. 95–98° (from hexane–benzene). IR absorptions (Nujol) were observed at 2230, 1120 cm^{-1}. The mass spectrum consisted of peaks at *m/e* 260 (P, 20·0%), 245 (43·8%), 207 (32·2%), 192 (71·5%), 82 (100%), 53 (43·2%). The NMR spectrum was given in Fig. 3a. (Found: C, 74·1; H, 9·4. $C_{16}H_{24}N_2O$ requires: C, 73·8; H, 9·3%).

Reaction of piperidine dienamine of isophorone with acrylonitrile. The reaction of the piperidine dienamine (8 g, 39 mmoles) and acrylonitrile (2·1 g, 40 mmoles) in dioxan (50 ml) gave a yellow oil (5·5 g), b.p. 90–102° (3 mm). Chromatographic separation on a Florisil column afforded *7-cyano-1-piperidino-3,5,5-trimethylbicyclo*[2.2.2]*oct-2-ene* (II; 3%), *8-cyano-4,6,6-trimethylbicyclo*[2.2.2]*octan-2-one* (III; 10%) and *6-(2-cyanoethyl)3,5,5-trimethyl-2-cyclohexen-1-one* (IV; 20%). Yields of each product were determined by GLC. II formed colourless needles, m.p. 108–110° (from hexane). IR absorptions (Nujol) were observed at 2230, 1110 cm^{-1}. The NMR spectrum was shown in Fig. 3b. (Found: C, 78·9; H, 10·2. $C_{17}H_{26}N_2$ requires: C, 79·0; H, 10·1%). III formed colourless fine needles, m.p. 87–88° (from hexane). IR absorption (Nujol) was observed at 1720 cm^{-1}. (Found: C, 75·1; H, 9·1. $C_{12}H_{17}NO$ requires: C, 75·3; H, 9·0%). IV formed a yellow oil, b.p. 150–163° (4 mm). IR absorptions (neat) were observed at 2250, 1670, 1635 cm^{-1}. Correct analyses have not yet been obtained.

Reaction of morpholine dienamine of isophorone with methyl vinyl ketone. The reaction of the morpholine dienamine (74 g, 0·36 mole) with methyl vinyl ketone (25 g, 0·36 mole) in dioxan (350 ml) gave a yellow oil (29·6 g), b.p. 109–112° (1 mm), which solidified gradually on standing in a refrigerator. The solid was collected by filtration and recrystallized from hexane to give *8-acetyl-4,6,6-trimethylbicyclo*[2.2.2]*octan-2-one* (VI; 4·4 g, 6%), m.p. 71–72°. The carbonyl absorption (Nujol) was observed at 1720 cm^{-1}. The mass spectrum consisted of peaks at *m/e* 208 (P, 22·3%), 138 (36·9%), 123 (100%), 43 (78·5%). The NMR spectrum was given in Fig. 4. (Found: C, 75·0; H, 9·9. $C_{13}H_{20}O_2$ requires: C, 75·0; H, 9·7%). The mother liquor was purified by chromatography on a Silicagel column to afford V (24·4 g, 33%) as a yellow oil, b.p. 112–116° (1 mm) (lit.[8] b.p. 115–116° (0·5 mm)). Certain negligible discrepancies were observed upon comparison of the IR spectrum of this preparation with that of an authentic sample prepared by the published method.[8] In addition, the present preparation gave a bis-2,4-dinitrophenylhydrazone instead of the mono-2,4-dinitrophenylhydrazone previously recorded. The bis-2,4-dinitrophenylhydrazone of V melted at 216–217°. UV (EtOH): 255 mμ (log ε 3·58), 438 mμ (log ε 3·98). (Found: C, 52·5; H, 5·2. $C_{25}H_{28}N_8O_8$ requires: C, 52·8; H, 5·0%). The monosemicarbazone of V melted at 234–235° (from EtOH). (Found: C, 63·1; H, 8·8. $C_{14}H_{23}N_3O_2$ requires: C, 63·4; H, 8·7%). Upon chromatography of V on a dry column of alumina with hexane-benzene-EtOAc (5:10:2) as an eluant, a pure sample of V was obtained, which showed an IR spectrum completely superimposable on that of the authentic V. The purified V gave the mono-2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 163–165° (lit.[6] 164–166°). The nature of the impurity is not clear yet.

Reaction of piperidine dienamine of isophorone with methyl vinyl ketone. The reaction of the piperidine dienamine (6 g, 29 mmoles) and methyl vinyl ketone (2·0 g, 29 mmoles) yielded V (1·8 g, 31%) and VI (0·45 g, 7·5%).

Reaction of morpholine dienamine of isophorone with methyl acrylate. The reaction of the morpholine dienamine (6 g, 29 mmoles) and methyl acrylate (2·5 g, 29 mmoles) in dioxan (25 ml) gave a yellow oil (3·4 g), b.p. 140–150° (3 mm). Chromatographic separation on a Florisil-Silicagel (1:1) column afforded *8-carbomethoxy-4,6,6-trimethylbicyclo*[2.2.2]*octan-2-one* (VII; 1·9 g, 29%) and *6-(2-carbomethoxyethyl) 3,5,5-trimethyl-2-cyclohexen-1-one* (VIII; 1·5 g, 23%). VII formed colourless fine needles, m.p. 54·5–55·5° (from hexane). IR absorption (Nujol) was observed at 1720 cm^{-1}. The mass spectrum consisted of peaks at *m/e* 224 (P, 8·3%), 138 (45%), 123 (100%), 41 (32%). The NMR spectrum was shown in Fig. 5. (Found: C, 69·4; H, 9·0. $C_{13}H_{20}O_3$ requires: C, 69·6; H, 9·0%). VIII formed a yellow oil, b.p. 125–127° (1 mm). IR absorptions (neat) were observed at 1750, 1670, 1635 cm^{-1}, while UV (EtOH) at 236 mμ (log ε 4·09). The mass spectrum consisted of peaks at *m/e* 224 (P, 31%), 151 (36%), 135 (100%), 109 (51%), 95 (43%), 41 (47%). The NMR spectrum was shown in Fig. 7. (Found: C, 69·3; H, 9·3. $C_{13}H_{20}O_3$ requires: C, 69·6; H, 9·0%).

Methanolysis of III *and* IV was carried out by heating a mixture of 2 mmoles each of the nitriles, MeOH (5 ml) and conc H_2SO_4 (1 ml) for 4 hr under reflux to give VII and VIII, respectively, both in ca. 50% yield.

Reaction of the piperidine dienamine of isophorone with methyl acrylate. The reaction of the piperidine dienamine (10 g, 49 mmoles) and methyl acrylate (5·0 g, 58 mmoles) yielded a viscous oil which crystallized gradually on standing. Recrystallizations from hexane afforded VII (3·1 g, 28%).

Preparation of 8-carbomethoxy-3,3-dichloro-4,6,6-trimethylbicyclo[2.2.2]*octan-2-one* (IX). To a mixture of NaOClaq (10 ml, effective Cl_2 10%) and 10% NaOHaq (6 ml) was added dropwise at 55° a soln of VI (0·3 g, 1·4 mmoles) in dioxan (2 ml). The mixture was stirred for 2 hr. After excess hypochlorite was destroyed by adding $NaHSO_3$aq, the mixture was cooled to room temp and acidified with HCl. Colourless ppt (300 mg) was treated with excess diazomethane in ethereal soln to give IX as colourless fine needles (250 mg, 62%), m.p. 90–92° (from hexane). IR absorptions (KBr) were observed at 1740 (sh), 1735 cm^{-1}. The NMR spectrum was shown in Fig. 6. (Found: C, 53·2; H, 6·4. $C_{13}H_{18}Cl_2O_3$ requires: C, 53·3; H, 6·2%).

The hypochlorite treatment of VII in an analogous manner gave IX. Remethylation with diazomethane was required, as partial hydrolysis occurred in the halogenation step.

The geometry of the carbomethoxy group of IX has not yet been clarified.

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