Reaction of Strained Polycyclic Ketones with Diazomethane

Ken-ichi Hirao,* Yoshimi Kajikawa, Etsuko Abe, and Osamu Yonemitsu
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

The reaction of 1,4-bishomocubanone (1) with ethereal diazomethane leads to a mixture of the homologous ketone (2) (37%) and the aldol-type dimer (3) (32%). In the presence of methanol the reaction yields predominantly the ketone (2) (70%). Other constrained ketones are shown to react with diazomethane in an analogous way. The mechanism is discussed in terms of the influence of ring strain.

We have been studying the role of the molecular strain in polycyclic cage compounds in some ring transformations involving acid-catalysed rearrangement,[1] catalytic reduction,[2] and peracid oxidation,[3] and now report another example which is concerned with the exceptional mode of reaction of constrained ketones with diazomethane.[4] Nucleophilic addition to the carbonyl carbon is one of the fundamental reactions, and is usually governed by electronic factors: the conjugation of a π system to a carbonyl group or the presence of an electron-donating group at the α-carbon of a carbonyl group generally diminishes its reactivity, whereas an electron-withdrawing group favours the reaction. In addition to these electronic factors the molecular strain affects the reactivity of the carbonyl group. When the two C–C bonds of a ketone are forced close to each other by the compression of a rigid ring system, stabilization of the carbonyl by the addition of a nucleophile would be expected. In fact it has been recognized that the constrained carbonyl is likely to form a stable hydrate,[5] and we have demonstrated the high reactivity of such ketones towards peracid (Baeyer–Villiger reaction).[3]

The reaction of ketones with diazomethane has been widely discussed and reviewed.[6] Though the reaction generally requires a long reaction period, cyclopropanone derivatives, in which the carbonyl is highly strained by the three-membered ring, have been shown to react readily with diazomethane to give cyclobutanones under very mild conditions (−77 °C).[7] Accordingly, a constrained carbonyl group on a polycyclic rigid ring system would be expected to react smoothly with diazomethane. We describe here the unusual reactivity of such ketones towards diazomethane and discuss the reaction mechanism.

Results

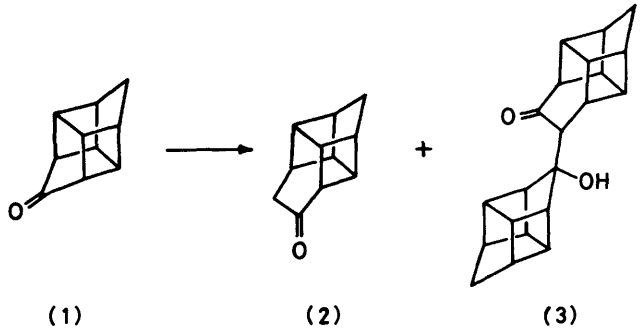
When 1,4-bishomocubanone (1)[8] was allowed to react with excess of diazomethane at 5 °C, the starting ketone was consumed within 16 h giving a ring-expanded homoketone (2) together with a novel dimeric hydroxy ketone (3) in 37 and 32% yield, respectively. The reaction of other constrained ketones proceeded in an analogous way, and the results are given in the Table. On the basis of the physical data [*m*/*z*, 306(M^+), ν(Nujol) 3 350, 1 697 cm^{-1}] the dimer (3) was deduced to have an aldol-type structure. This was substantiated by the fact that it was dehydrated fairly easily with acetic anhydride to form an α,β-unsaturated ketone (4) [$\lambda_{max.}$ (EtOH) 269 nm (ε 14 500)]. Furthermore, the dimer (3) was synthesized by the cross aldol condensation[9] of the starting ketone (1) with the enol acetate (5) derived from compound (2), confirming the assigned structure.

The ketone (6) yielded two isomeric homoketones (7) and (8), and four dimeric hydroxy ketones [(9) and (10)] which were separated by repeated silica gel chromatography. The position of the carbonyl group on the homoketones was assigned on the basis of n.m.r. spectroscopy. Thus, the

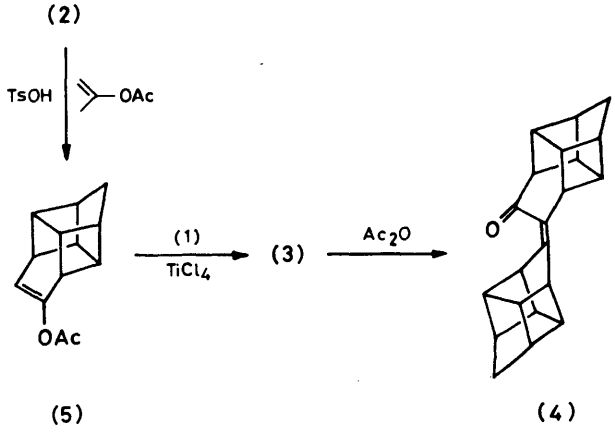
Table. Reaction of polycyclic cage ketones with diazomethane in diethyl ether at 5 °C

Substrate	Time (h)	Product and % isolated yield: Homoketones	Dimers
(1)	16	(2) 37	(3) 32
	20 [a]	(2) 70	(3) 4
(6)	24	(7) + (8) 47	(9) + (10) 43
(11) [b]	22	(12) 55	(13) 28
(14)	96 [c]	(17) 35	(18) 35
(20)	8 [a]	(22a) + (22b) + (22c) 78	
	2	(21a) + (21b) 39	

[a] Diethyl ether–MeOH (30 : 2) was used as the solvent system. [b] Ref. 10. [c] The reaction was carried out in diethyl ether–THF (1 : 15) at room temperature.

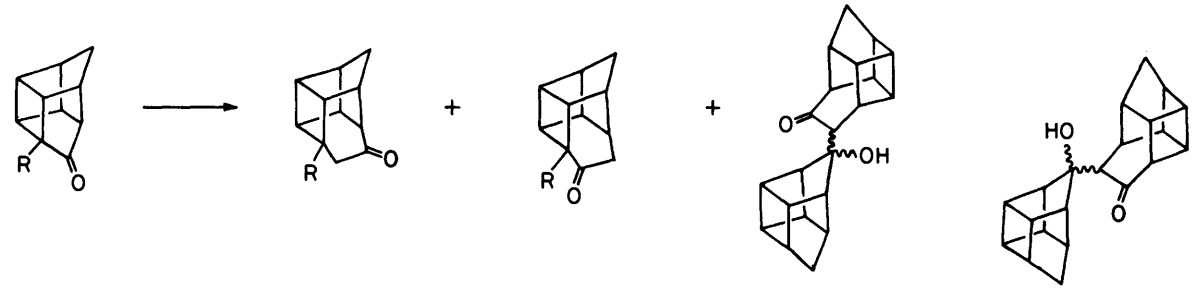


(1) (2) (3)

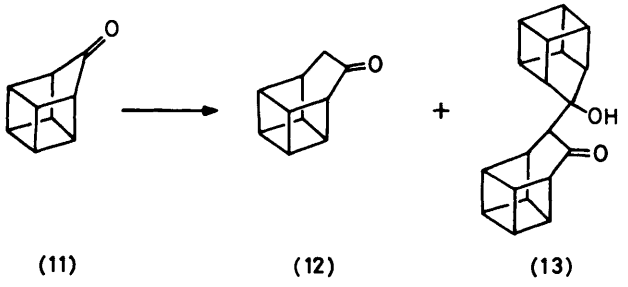


(5) (4)

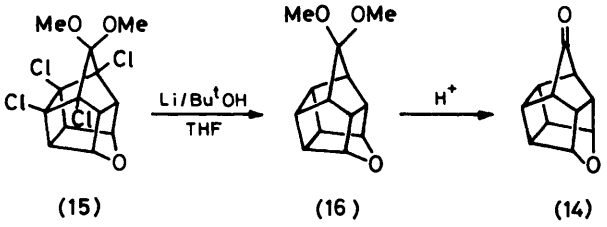
signals of the α-methylene protons of the carbonyl group were identified as the peaks at δ 1.84 (1 H, dd, *J* 20 and 2 Hz) and 2.06 (1 H, dd, *J* 20 and 2.5 Hz) and that at δ 2.24 (2 H, s), respectively, by comparing their spectra with those of the



(6; R=H) (7; R=H) (8; R=H) (9) (10)
(6a; R=D) (7a; R=D) (8a; R=D)



(11) (12) (13)



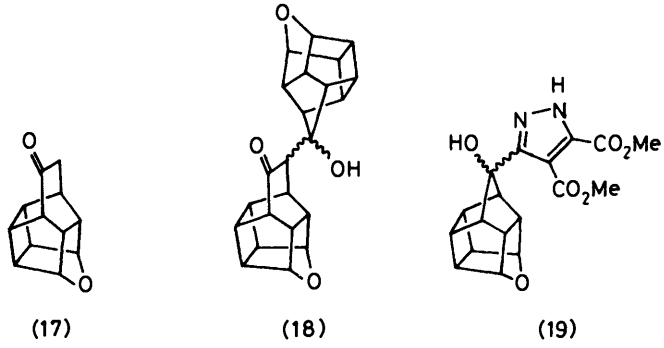
(15) (16) (14)

corresponding dideuteriated compounds which were obtained on treatment of the ketones (7) and (8) with MeOD–MeONa. In the spectrum of monodeuteriated homoketone (7a), obtained from compound (6a),[3] the double doublets at δ 1.84 and 2.06 appeared as two doublets (*J* 20 Hz), thus establishing the structure as (7). In the case of the isomer (8a), the signal at δ 2.24 was unchanged as expected.

Though the dimer from the ketone (6) theoretically has eight possible isomeric structures, four isomers were actually isolated. These isomers have the common molecular weight 306 and were again dehydrated to give the respective α,-β-unsaturated ketones. They therefore have the aldol-type skeletons (9) and (10), with uncertain stereochemistry.

The ketone (14) was prepared *via* reductive dechlorination of the tetrachloride (15)[11] with lithium in t-butyl alcohol followed by hydrolysis of the acetal group. Since the reaction mixture from compound (14) showed the band due to the diazo group at 2 030 cm^{-1} in the i.r. spectrum, it was treated with dimethyl acetylenedicarboxylate at room temperature for 30 min and a pyrazole derivative (19) was isolated, though only in 7% yield, together with a homoketone (17) and two stereoisomeric dimers (18).

The diketone (20) was treated with a large excess of diazomethane in the presence of methanol giving three isomeric bishomoketones (22a), (22b), and (22c) in 15, 34, and 15% yields, respectively. Since these are not distinguishable on the basis of their spectral data, the structures were established in the following manner. On treatment of the diketone (20) with diazomethane in diethyl ether for a short period, monohomo-



(17) (18) (19)

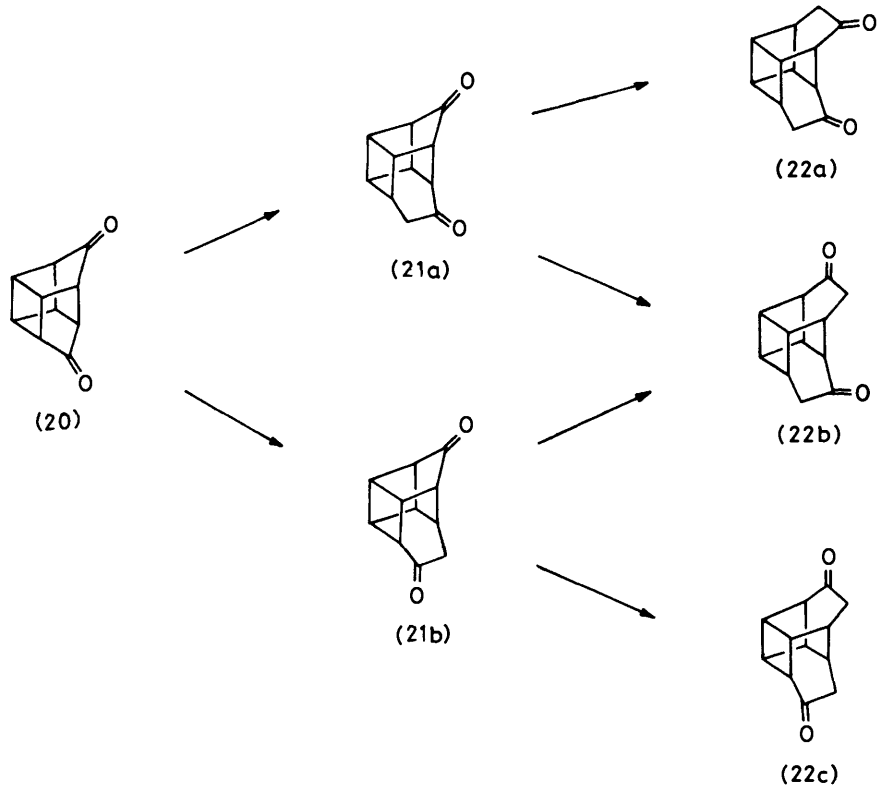
ketones (21a) (16%) and (21b) (8%) were obtained. On further treatment with an excess of diazomethane, (21a) gave isomers (22a) and (22b), whereas (21b) gave (22b) and (22c). Therefore, the common product must have the unsymmetrical structure (22b). Differentiation between (22a) and (22c), and hence between (21a) and (21b), was effected by independent preparation of the isomer (22c).[2]

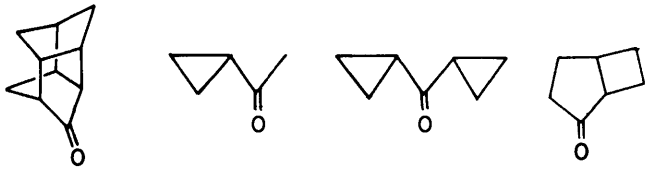
Discussion

The reaction of diazomethane with carbonyl compounds consists of the initial addition of the nucleophilic methylene of diazomethane to the carbonyl carbon forming a betaine intermediate which is stabilised either by ring closure to give epoxides or by a Wagner–Meerwein-type rearrangement to form homologous derivatives; thus the rate increases with the electrophilic character of the carbonyl component. The reaction course is generally affected by the electronic, steric, and solvent effects as well as by the added Lewis acid catalyst.

The following are characteristic of this reaction; (i) cyclopentanone derivatives usually give cycloheptanones and cyclooctanones but not cyclohexanones,[12] while the constrained five-membered ketones described here gave only the cyclohexanone derivatives; (ii) no epoxide was obtained; (iii) the reaction proceeded smoothly without any catalyst; and (iv) novel dimeric compounds with an aldol-type structure were obtained.

Since neither compound (1) nor (6) reacted with their respective homoketones (2) or (7) [or (8)] under acidic (AcOH) or basic (NaOH) conditions, it is evident that dimer formation does not result from the aldol condensation between the starting ketone and the homoketone, but is due to direct reaction of the starting ketone with diazomethane. The tetracyclic ketone (23), which can be readily obtained by the hydrogenolysis of (6) and which has a much less strained carbonyl,[2] gave no dimers under these conditions, and



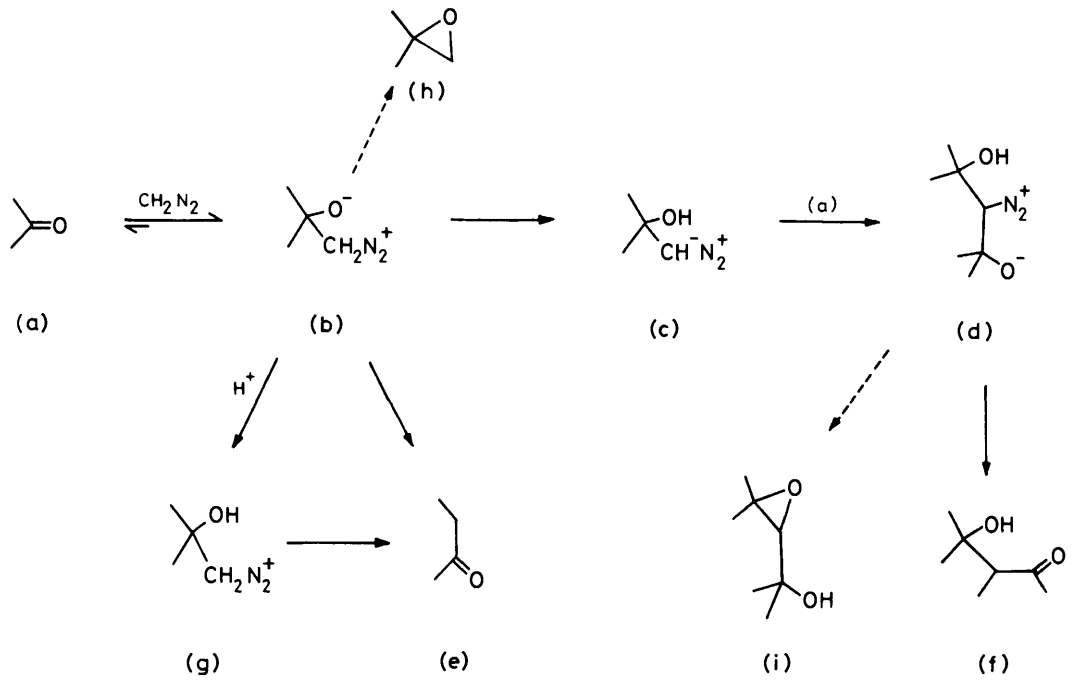


therefore we wondered if the presence of a strained small ring adjacent to the carbonyl group was one of the factors leading to dimer formation. However, this possibility was excluded by the fact that ketones (24), (25), and (26) do not give any dimer from the reaction with diazomethane, and it is probably the strain added to the carbonyl group itself that is necessary for the dimer formation. The ketone (1) was therefore used as a representative substrate in an investigation of the reaction mechanism. After compound (1) had been allowed to react with excess of diazomethane for 10 min, the i.r. spectrum of the whole reaction mixture showed that the intensity of the carbonyl group absorption at 1 755 cm^{-1} had diminished by *ca.* 95%. Direct analysis of this reaction mixture by silica gel t.l.c. (proton-catalyst, see below) revealed the almost complete formation of compound (2) together with a trace amount of recovered (1). On the other hand, after removal of diazomethane from the same reaction mixture only the starting ketone (1) was detected by t.l.c. These results show that the reaction of the constrained ketone with diazomethane proceeds as illustrated in the Scheme. A constrained, highly electrophilic ketone (a) reacts rapidly with diazomethane to give a betaine (b), and in the initial stage of the reaction an equilibrium between (a) and (b), which lies well over towards (b) [in the case of (1), 5 : 95], is established. Since the direct conversion of the resultant betaine (b) into a homoketone (e) is slow without an acid catalyst, prototropy occurs, converting (b) into a more stable diazo intermediate (c). The reactive starting ketone (a) which is present in the reaction medium then reacts with (c) to give a dimer (f) *via* a dimeric betaine (d).

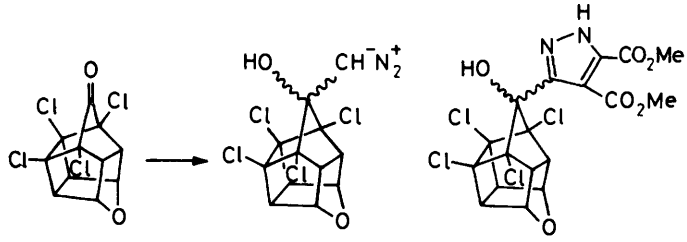
The formation of analogous dimers has been observed in the reaction of some aldehydes having a strong electron-withdrawing group such as trichloromethyl,[13] nitrophenyl, and a heterocycle, benzofuran.[14] Thus the essential feature for the dimer formation is not only that the carbonyl group reactivity toward diazomethane is increased but also that the conversion of the resultant betaine (b) into the homoketone (e) or to the epoxide (h) is retarded so that a high concentration of (b) can be attained. In the case of the constrained ketones, the reactivity towards diazomethane is enhanced, while the conversion of the intermediary betaine (b) into the epoxide (h) may be unfavourable owing to the angle strain of the five-membered ring.

We obtained further evidence which bears out the validity of this mechanism. First, when methanol was added to the reaction medium of the ketone (1) as a proton donor, the yield of the homoketone (2) was increased to 70%, whereas that of the dimer (3) decreased to 4%, because the protonation of betaine (b) [(b) ⟶ (g)] overcomes the prototropy [(b) ⟶ (c)]. This indicates that the step involving the direct rearrangement of the betaine (b) to the homoketone (e) is very slow in the absence of a proton catalyst. Secondly, when compound (27), with electron-withdrawing and bulky chlorine atoms adjacent to the carbonyl group, was subjected to the same reaction, both steps (b) ⟶ (e) and (c) ⟶ (d) were retarded, and a rather unstable diazo intermediate (28) was isolated as a yellow oil. The i.r. spectrum of this oil has a diazo band at 2 100 cm^{-1}, but no carbonyl bands. On treatment with dimethyl acetylenedicarboxylate, compound (28) gave a pyrazole (29).

If the mechanism illustrated in the Scheme is operative with all constrained ketones, cyclopropanone derivatives are also expected to give the dimers. However, such experimental results do not appear in the literature. The carbonyl carbon of cyclopropanone is strongly electrophilic, and is certainly



Scheme.



susceptible to the reaction with diazomethane, giving the betaine (b) quite rapidly. However, because the cyclopropane ring itself is very strained the direct rearrangement of (b) to the homoketone (e) is much accelerated as this reduces the angle strain, and hence cyclopropanones give no dimer. Finally, for the reaction of the less strained ketone (14), a longer reaction time and a rather higher temperature were required as expected from the proposed mechanism.

It can be concluded that, besides electronic and steric factors, the strain actually plays a role in determining the reaction course. In the reaction discussed here there are two aspects of the strain effect. The one is the strain which is added to the carbonyl group increasing its electrophilicity, and the other is the angle strain decreasing the efficiency of the direct conversion of the betaine intermediate into the epoxide and the homologous ketone.

Experimental

Preparation of Ethereal Diazomethane.—To a mixture of 50% KOH (25 ml) solution and diethyl ether (75 ml), cooled to 0 °C, was added in portions *N*-methyl-*N*-nitrosourea (5 g) with stirring. After 30 min, the resulting yellow ethereal layer was separated and dried (KOH).

Reaction of Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]*decan-5-one* (1) *with Diazomethane.*—(*a*) To a solution of the ketone (1) (200 mg) in diethyl ether (3 ml) was added the ethereal diazomethane (10 ml). The solution was allowed to stand at 0—5 °C for 16 h. Removal of the solvent and diazomethane under reduced pressure afforded a colourless oil. Purification by column chromatography on silica gel (n-hexane–acetone, 30 : 1 v/v) gave two fractions. The first fraction (80 mg, 37%) gave, after recrystallisation from n-hexane–ethyl acetate, pure *pentacyclo*[5.4.0.0^{2,6}.0^{3,9}.0^{4,8}]*undecan-10-one* (2) as needles, m.p. 53—55 °C; $\nu_{max.}$ (Nujol) 1 700 cm^{-1}; *m/z* 160(M^+), 117, and 95; δ ($CDCl_3$) 1.37 (2 H, s), 2.18 (2 H, d, *J* 3 Hz), 2.42 (2 H, m), 2.66 (2 H, m), 2.99 (3 H, m), and 3.17 (1 H, m) (Found: C, 82.7; H, 7.6. $C_{11}H_{12}O$ requires C, 82.46; H, 7.55%). The second fraction (70 mg, 32%) gave, after recrystallisation from n-hexane–ethyl acetate, pure 11-(*5-hydroxypentacyclo*-[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]*decan-5-yl*)*pentacyclo*[5.4.0.0^{2,6}.0^{3,9}.0^{4,8}]-*undecan-10-one* (3), m.p. 149—150 °C (needles); $\nu_{max.}$ (Nujol) 3 350 and 1 697 cm^{-1}; *m/z* 306(M^+), 240, 222, 156, and 66; δ ($CDCl_3$) 1.36 (2 H, s), 1.44 (2 H, t, *J* 8 Hz), 2.08 (1 H, d, *J* 3 Hz), and 2.3—3.6 (17 H, m) (Found: C, 82.05; H, 7.2. $C_{21}H_{22}O_2$ requires C, 82.32; H, 7.24%).

(*b*) To a solution of the ketone (1) (150 mg) in MeOH (0.3 ml) was added the ethereal diazomethane (5 ml). The solution was allowed to stand at 0—5 °C for 20 h. Work-up of the reaction mixture as described above gave the homoketone (2) (115 mg, 70%) and the dimer (3) (6 mg, 4%).

(*c*) To a solution of (1) (10 mg) in $CHCl_3$ (2 ml) was added ethereal diazomethane (2 ml). After 10 min the transmission at 1 750 cm^{-1} in the i.r. spectrum of this solution was 2%, whereas that of the standard solution [20 mg of (1) in 8 ml of $CHCl_3$–diethyl ether, 1 : 1 v/v] was 42%.

Dehydration of the Dimer (3).—A solution of the dimer (3) (40 mg) in acetic anhydride (40 ml) was refluxed for 1.5 h. Removal of the solvent under reduced pressure gave a solid. Recrystallisation from n-hexane–ethyl acetate afforded colourless needles of the enone (4) (24 mg, 64%), m.p. 232—233 °C; $\nu_{max.}$ (Nujol) 1 685 cm^{-1}; $\lambda_{max.}$ (EtOH) 269 nm (ε 14 500); δ ($CDCl_3$) 1.34 (2 H, s), 1.52 (2 H, s), 2.30—2.64 (4 H, m), 2.64—2.84 (4 H, m), 2.88—3.24 (5 H, m), and 3.26—

3.64 (3 H, m) (Found: C, 86.9; H, 7.0. $C_{21}H_{20}O$ requires C, 86.92; H, 7.29%).

Synthesis of the Dimer (3).—A solution of the homoketone (2) (140 mg), isopropenyl acetate (3.5 ml), and a trace of toluene-*p*-sulphonic acid was stirred at 50 °C for 3 h. Concentration of the reaction mixture under reduced pressure followed by column chromatography on silica gel (n-hexane–acetone, 30 : 1 v/v) gave the enol acetate (5) (153 mg, 87%) as an oil; $\nu_{max.}$ (neat) 1 758 cm^{-1}. To a solution of this oil and the ketone (1) (144 mg) in methylene dichloride (9 ml) was added dropwise a solution of $TiCl_4$ (135 mg) in methylene dichloride (5 ml) at −20 °C under N_2. The mixture was stirred at this temperature for an hour, and then at −5 °C for 24 h. The resulting mixture was poured into 50 ml of ice-cooled saturated aqueous $NaHCO_3$ and extracted with methylene dichloride. The combined extracts were dried over Na_2SO_4. Concentration of the solvent under reduced pressure gave crude material which was chromatographed on silica gel to give the dimer (3) (72 mg, 31%). This was identical in all respects (m.p., i.r., n.m.r.) with the dimer (3) obtained by the reaction of (1) with diazomethane.

Reaction of Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan-6-one* (6) *with Diazomethane*.—A sample of the ketone (6) (2.27 g) was treated with ethereal diazomethane (105 ml) at 0—5 °C for 24 h. The mixture was concentrated under reduced pressure to give a residue which afforded two fractions upon silica gel chromatography (n-hexane–ethyl acetate, 20 : 1 v/v).

Repeated chromatography on silica gel of the first fraction (1.16 g, 47%) gave pure *pentacyclo*[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecan-11-one* (7) (316 mg) and *pentacyclo*[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecan-10-one* (8) (164 mg). Compound (7) boiled at 140—145 °C (needles), m.p. 98 °C; $\nu_{max.}$ (Nujol) 1 718 cm^{-1}; *m/z* 160(M^+), 117, 95, and 66; δ (CCl_4) 1.53 (2 H, s), 1.84 (1 H, dd, *J* 20, 2 Hz), 2.06 (1 H, dd, *J* 20 and 2.5 Hz), 2.22 (1 H, s), 2.78 (6 H, br s), and 3.08 (1 H, br s); semicarbazone, m.p. 206—208 °C (from EtOH; fine needles) (Found: C, 64.95; H, 7.55; N, 17.5. $C_{12}H_{15}N_3O1/2EtOH$ requires C, 64.62; H, 7.37; N, 17.57%). Compound (8) boiled at 130—140 °C (needles, m.p. 66—67 °C; $\nu_{max.}$ (Nujol) 1 718 cm^{-1}; *m/z* 160(M^+), 117, 95, and 66; δ (CCl_4) 1.40 (1 H, d, *J* 10.5 Hz), 1.68 (1 H, d, *J* 10.5 Hz), 2.24 (2 H, s), 2.27 (1 H, br s), and 2.40—3.16 (7 H, m); semicarbazone, m.p. 202—203 °C (from EtOH; fine needles) (Found: C, 66.4; H, 6.95; N, 19.2. $C_{12}H_{15}N_3O$ requires C, 66.34; H, 6.96; N, 19.34%).

The second fraction (1.01 g, 43%) gave four pure isomeric dimers A (164 mg), B (141 mg), C (485 mg), and D (14 mg), 10- or 11-(6-*hydroxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan-6-yl*)-*pentacyclo*[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecan*-11- or -10-*one* respectively on repeated chromatography (n-hexane–ethyl acetate, 20 : 1 v/v). Dimer A; fine needles from n-hexane–ethyl acetate; m.p. 179—180.5 °C; $\nu_{max.}$ (Nujol) 3 400 and 1 690 cm^{-1}; *m/z* 306(M^+), 282, 222, 156, 117, and 66; δ ($CDCl_3$) 1.44 (2 H, d, *J* 5 Hz), 1.60 (2 H, d, *J* 5 Hz), 1.94 (1 H, s), 2.28 (1 H, m), 2.36 (2 H, m), 2.5—2.7 (4 H, m), 2.7—2.9 (4 H, m), and 2.9—3.2 (6 H, m) (Found: C, 82.35; H, 7.25. $C_{21}H_{22}O_2$ requires C, 82.32; H, 7.27%). Dimer B; fine needles from n-hexane–ethyl acetate; m.p. 176—177 °C; $\nu_{max.}$ (Nujol) 3 500, 3 400, and 1 695 cm^{-1}; *m/z* 306(M^+), 288, 222, 156, 117, and 66; δ ($CDCl_3$) 1.44 (2 H, dd, *J* 6 and 2 Hz), 1.66 (2 H, dd, *J* 6 and 3 Hz), 2.12 (1 H, s), and 2.5—3.3 (16 H, m) (Found: C, 82.15; H, 7.15. $C_{21}H_{22}O_2$ requires C, 82.32; H, 7.27%). Dimer C; fine needles from ethyl acetate; m.p. 199—201 °C; $\nu_{max.}$ (Nujol) 3 400 and 1 690 cm^{-1}; *m/z* 306(M^+), 288, 222, 156, 117, and 66; δ ($CDCl_3$) 1.52 (4 H, br s), 2.24 (2 H, br s), and 2.5—3.2 (16 H, m) (Found: C, 82.45; H, 7.25. $C_{21}H_{22}O_2$ requires C, 82.32; H, 7.27%). Dimer D; prisms from n-hexane–ethyl acetate; m.p. 183—186 °C; $\nu_{max.}$ (Nujol) 3 400 and 1 690 cm^{-1}; *m/z* 306(M^+), 288, 222, 156, 118, 117, and 66 (Found: C, 82.45; H, 7.2. $C_{21}H_{22}O_2$ requires C, 82.32; H, 7.27%).

Dehydration of the Dimers A, B, C, and D [(9) *and* (10)].—A solution of the dimer in acetic anhydride was refluxed for 2 h. The solution was concentrated under reduced pressure to give a solid which was recrystallised from n-hexane–ethyl acetate. The dimer A (52.3 mg) gave the enone A (31 mg) as colourless fine prisms; m.p. 176—176.5 °C; $\nu_{max.}$ (Nujol) 1 700 and 1 645 cm^{-1}; *m/z* 288(M^+); $\lambda_{max.}$ (EtOH) 263 nm (ε 13 500) (Found: C, 87.25; H, 7.0. $C_{21}H_{20}O$ requires C, 87.46; H, 6.99%). The dimer B (18.8 mg) gave the enone B (16.8 mg) as a colourless powder; m.p. 179—182 °C; $\nu_{max.}$ (Nujol) 1 700 and 1 640 cm^{-1}; *m/z* 288(M^+); $\lambda_{max.}$ (EtOH) 264 nm (ε 13 700) (Found: C, 87.6; H, 7.05. $C_{21}H_{20}O$ requires C, 87.46; H, 6.99%). The dimer C (687.0 mg) gave the enone C (656.0 mg) as prisms; m.p. 231—233 °C; $\nu_{max.}$ (Nujol) 1 690 and 1 640 cm^{-1}; *m/z* 288(M^+); $\lambda_{max.}$ (EtOH) 262.5 nm (ε 13 800) (Found: C, 87.35; H, 6.95. $C_{21}H_{20}O$ requires C, 87.46; H, 6.99%). The dimer D (12.0 mg) gave the enone D (5.2 mg) as fine prisms; $\nu_{max.}$ (Nujol) 1 700 and 1 640 cm^{-1}; $\lambda_{max.}$ (EtOH) 264 nm (ε 14 000); *m/z* 288(M^+).

Reaction of Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]*nonan-9-one* (11) *with Diazomethane*.—The ketone (11) (100 mg) was treated with excess of diazomethane at 0—5 °C for 22 h. Concentration of the mixture under reduced pressure gave crude material which was purified by chromatography on silica gel (n-hexane–acetone, 30 : 1 v/v) to give two fractions. The first fraction (61 mg, 55%) gave, after recrystallisation from n-hexane, pure *pentacyclo*[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]*decan-9-one* (12) as prisms; m.p. 92—94 °C; $\nu_{max.}$ (Nujol) 1 724 and 1 700 cm^{-1}; *m/z* 146(M^+), 104, and 78; δ ($CDCl_3$) 2.20 (2 H, s), and 3.1—3.7 (8 H, m) (Found: C, 81.95; H, 6.85. $C_{10}H_{10}O$ requires C, 82.16; H, 6.90%). The second fraction (29 mg, 28%) gave, after recrystallisation from n-hexane–ethyl acetate, pure 10-(9-*hydroxypentacyclo*[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]*nonan-9-yl*)*pentacyclo*[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]*decan-9-one* (13) as needles; m.p. 207—209 °C; $\nu_{max.}$ (Nujol) 3 380 and 1 682 cm^{-1}; *m/z* 277($M^+ - 1$), 115, 104, 91, 78, and 77; δ ($CDCl_3$) 3.2—3.5 (10 H, br s), 3.5—3.7 (6 H, br s), and 3.7—3.9 (2 H, br s) (Found: C, 81.75; H, 6.6. $C_{19}H_{18}O_2$ requires C, 81.98; H, 6.52%).

4,4-*Dimethoxy*-12-*oxahexacyclo*[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]-*dodecane* (16).—To a solution of the tetrachloride (15) (1.9 g) in a mixture of THF (30 ml) and Bu^{t}OH (4.8 ml) under N_2 was added in portions, sodium turnings (3.2 g). The mixture was refluxed for 5 h, and to this MeOH (30 ml) was added. The ether extracts were washed with water and brine, dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (n-hexane–ethyl acetate, 20 : 1 v/v) to give pure (16) (580 mg, 50%), as colourless prisms from light petroleum; m.p. 71—72 °C; $\nu_{max.}$ (Nujol) 1 142, 1 119, and 1 100 cm^{-1}; *m/z* 220(M^+), 205, 191, 189, and 152; δ ($CDCl_3$) 2.40 (2 H, m), 2.75 (6 H, m), 3.20 (3 H, 3), 3.25 (3 H, s), and 4.85 (2 H, m) (Found: C, 70.8; H, 7.35. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%).

12-*Oxahexacyclo*[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]*dodecan-4-one* (14).—To a solution of (16) (1.3 g) in methylene dichloride (1 ml) was added concentrated sulphuric acid (8 ml). The mixture was stirred at room temperature for 6 h, poured onto ice–water, and extracted with diethyl ether. The ether extracts were washed with 10% $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the ether gave a crude material which was purified by silica gel chromatography (n-hexane–ethyl acetate)

to give a solid fraction. This solid was dissolved in benzene and the solution was refluxed for 1 h using a Dean–Stark apparatus. The benzene was evaporated under reduced pressure to give (14) (720 mg, 70%) as needles (from n-hexane), m.p. 239—240 °C; $\nu_{max.}$ (Nujol) 1 750 cm^{-1}; *m/z* 174(M^+), 146, 145, 130, and 117; δ ($CDCl_3$) 2.28 (2 H, m), 2.74 (2 H, m), 2.88 (4 H, m), and 5.06 (2 H, m) (Found: C, 75.4; H, 5.75. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%).

Reaction of 12-*Oxahexacyclo*[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]-*dodecan-4-one* (14) *with Diazomethane*.—To a solution of (14) (400 mg) in tetrahydrofuran (THF) (1 ml) was added ethereal diazomethane (15 ml). After the solution had been left at room temperature for 96 h, the solvent and diazomethane were removed under reduced pressure to give a yellow oil. To this in THF (1 ml) was added dimethyl acetylenedicarboxylate (163 mg). The solution was stirred at 0—5 °C for 30 min and concentrated under reduced pressure to give crude material which was purified by silica gel chromatography (n-hexane–acetone). The first fraction was the starting material (9 mg). The second fraction (150 mg, 35%) gave, after recrystallisation from n-hexane–acetone, pure 13-*oxahexacyclo*-[6.4.1.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$.$0^{9,12}$]*tridecan-4-one* (17) as needles; m.p. 241—243 °C; $\nu_{max.}$ (Nujol) 1 715 cm^{-1}; *m/z* 188(M^+), 160, 146, 121, 117, 115, 110, 91, 78, and 68; δ ($CDCl_3$) 2.10—3.18 (10 H, m) and 4.89 (2 H, m) (Found: C, 76.4; H, 6.4. $C_{12}H_{12}O_2$ requires C, 76.57; H, 6.43%).

The third fraction (144 mg, 35%) gave, after final purification by chromatography on silica gel, two stereoisomers of the dimer (18). Dimer A; needles from n-hexane–acetone; m.p. 241—243 °C; $\nu_{max.}$ (Nujol) 3 400 and 1 702 cm^{-1}; *m/z* 362(M^+) and 344; δ ($CDCl_3$) 2.20 (1 H, d, *J* 2 Hz), 2.41 (4 H, m), 2.3—3.0 (13 H, m), and 4.91 (4 H, m) (Found: C, 76.3; H, 6.05. $C_{23}H_{22}O_4$ requires C, 76.22; H, 6.12%). Dimer B; needles from n-hexane–acetone; m.p. 239—243 °C; $\nu_{max.}$ (Nujol) 3 400 and 1 702 cm^{-1}; *m/z* 362(M^+) and 344; δ ($CDCl_3$) 1.94 (1 H, d, 2 H), 2.03 (1 H, m), 2.19 (1 H, m), 2.35 (2 H, m), 2.40—2.90 (11 H, m), 2.98 (2 H, m), and 4.90 (4 H, m) (Found: C, 76.1; H, 6.15. $C_{23}H_{22}O_4$ requires C, 76.22; H, 6.12%).

The fourth fraction (65 mg, 7%) gave, after recrystallisation from n-hexane–ethyl acetate, a mixture of two stereoisomers of the pyrazolyl derivative (19) as needles; m.p. 204—214 °C; $\nu_{max.}$ (Nujol) 3 360, 3 200, and 1 733 cm^{-1}; *m/z* 358(M^+), 340, 326, 211, 175, 117, and 115; δ ($CDCl_3$) 2.68 (6 H, m), 3.22 (2 H, br s), 3.92, 3.93, and 3.94 (all s, 6 H), and 4.92 (3 H, br s) (Found: C, 60.1; H, 5.0; N, 7.8. $C_{18}H_{18}N_2O_6$ requires C, 60.33; H, 5.06; N, 7.82%).

Reaction of Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*dodecane-6,10-dione* (20) *with Diazomethane*.—(*a*) A solution of compound (20) (388 mg) in ethereal diazomethane (30 ml) and MeOH (2 ml) was left at 0—5 °C for 8 h. After concentration of the solution, the resultant residue was chromatographed on silica gel (benzene–ethyl acetate, 20 : 1 v/v) to give four fractions. The first fraction (71 mg 15%) gave, after recrystallisation from diethyl ether, *pentacyclo*[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]*dodecane-7,10-dione* (22a) as prisms; m.p. 200—205 °C; $\nu_{max.}$ (Nujol) 1 720 cm^{-1}; *m/z* 188(M^+), 146, 118, 117, and 94; δ ($CDCl_3$) 2.20 (2 H, dd, *J* 10 and 2 Hz), 2.46 (2 H, dd, *J* 10 and 1.5 Hz), 2.86 (6 H, br s), and 3.10 (2 H, br s) (Found: C, 76.35; H, 6.45. $C_{12}H_{12}O_2$ requires C, 76.57; H, 6.43%).

The second fraction (63 mg, 14%) was a mixture of isomers (22a) and (22b). The third fraction (154 mg, 34%) gave, after recrystallisation from diethyl ether, *pentacyclo*-[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]*dodecane-7,11-dione* (22b) as prisms; m.p. 90—92 °C; $\nu_{max.}$ (Nujol) 1 715 cm^{-1}; *m/z* 188(M^+), 146, 118, 117, and 94; δ ($CDCl_3$) 2.0—2.5 (5 H, m), 2.76 (2 H, br s), and 2.9—3.2 (5 H, m) (Found: C, 76.65; H, 6.45. $C_{12}H_{12}O_2$ requires C, 76.57; H, 6.43%).

The fourth fraction (68 mg, 15%) gave, after recrystallisation from Bu^{n}OH, *pentacyclo*[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]*dodecane-6,11-dione* (22c) as prisms. This was identical in all respects (m.p., i.r., n.m.r.) with the compound (22c) obtained by the reported synthesis.[2]

(*b*) A solution of compound (20) (2.25 g) in ethereal diazomethane (40 ml) was allowed to stand at 0—5 °C for 2 h. After concentration of the solution, the residue was chromatographed on silica gel (benzene–ethyl acetate, 20 : 1 (v/v) to give (20) (304 mg) and a mixture of (21a) and (21b) (947 mg, 39%). The latter was purified by silica gel chromatography (benzene–ethyl acetate, 5 : 1 v/v) to afford two fractions. The first fraction (379 mg) gave, after recrystallisation from n-hexane–ethyl acetate, *pentacyclo*[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecane-6,11-dione* (21a) as needles: m.p. 156—159 °C; $\nu_{max.}$ (Nujol) 1 755, 1 720, and 1 710 cm^{-1}; *m/z* 174(M^+), 132, 131, 104, 91, and 78; δ ($CDCl_3$) 2.24 (2 H, m), 2.68 (1 H, s), 2.88 (2 H, br s), and 3.16 (5 H, br s) (Found: C, 75.55; H, 6.2. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%). The second fraction (202 mg) gave, after recrystallisation from n-hexane–ethyl acetate, *pentacyclo*[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecane-6,10-dione* (21b) as needles; m.p. 166—171 °C; $\nu_{max.}$ (Nujol) 1 760, 1 725, and 1 710 cm^{-1}; *m/z* 174(M^+), 132, 131, 104, 93, 91, and 78; δ($CDCl_3$) 2.34 (1 H, d, *J* 2 Hz), 2.45 (1 H, d, *J* 2 Hz), 2.47 (1 H, s), 2.90 (3 H, m), and 3.20 (4 H, m) (Found: C, 75.45; H, 5.75. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%).

Reaction of Pentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecane-6,11-dione* (21a) *with Diazomethane*.—A mixture of compound (21a) (3.7 mg) and excess of ethereal diazomethane was left at 0—5 °C for 5 h. The yields, which were determined by g.l.c. using a column of 3% SE-52 (2 m × 4 mm; 150 °C), of (22a) and (22b) were 16 and 15%, respectively.

Reaction of Pentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]*undecane-6,10-dione* (21b) *with Diazomethane*.—Compound (21b) (3.4 mg) was treated in a manner identical with that described for (21a). The yields of (22b) and (22c) were 19 and 24%, respectively.

Reaction of 3,5,9,10-*Tetrachloro*-12-*oxahexacyclo*-[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]*dodecan-4-one* (27) *with Diazomethane*.—A sample of (27) (170 mg) was treated with excess of diazomethane at 0—5 °C for 24 h. Concentration of the solution under reduced pressure gave a yellow oil whose i.r. spectrum showed a band at 2 100 cm^{-1} but no carbonyl band. To a solution of this oil in benzene (5 ml) was added dimethyl acetylenedicarboxylate (69 mg). The solution was left at 5 °C overnight, and a precipitated solid was filtered off. The filtrate was recrystallised from n-hexane–ethyl acetate to give 4-(4,5-*dimethoxycarbonylpyrazol-3-yl*)-3,5,9,10-*tetrachloro*-12-*oxahexacyclo*[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]*dodecan-4-ol* (29) (201 mg, 75%) as prisms; m.p. 212—215 °C; $\nu_{max.}$ (Nujol) 3 270, 1 744, 1 680, 1 565, and 1 550 cm^{-1}; *m/z* 498, 496, 494(M^+), 463, 461, 459, 431, 429, and 427; δ ($CDCl_3$) 3.32 (2 H, m), 3.66 (2 H, m), 3.95 (6 H, s), 5.30 (2 H, m), 7.72 (1 H, s), and 11.20 (1 H, br s) (Found: C, 43.75; H, 2.8; Cl, 28.65; N, 5.75. $C_{18}H_{14}Cl_4N_2O_6$ requires C, 43.57; H, 2.84; Cl, 28.59; N, 5.65%).

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