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THE ROBINSON ANNULATION OF SOME MEDIUM RING SIZE 2-HYDROXYMETHYLENECYCLANONES

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Abstract—The adducts formed from methyl vinyl ketone and the 2-hydromethylene derivatives of cyclooctane and cyclodecanone can be cyclised to spiroketones containing the same number of C atoms. The spiroketone from cyclooctanone possesses a single UV maximum at 227 nm; the cyclodecanone compound has a further absorption at *ca* 246 nm. The constitution and stereochemistry of the ketols produced from the adducts under mild cyclising conditions have been investigated.

In a previous communication[1] we reported the results of cyclising the compounds **1** (R = CHO, n = 5, 6, 7, and 12). In this paper we extend the study to the medium sized ring compounds **1** (R = CHO, n = 8 and 10). Both compounds were prepared from the corresponding 2-hydroxymethylene ketones and methyl vinyl ketone. A solution of 2-formyl-2-(3-oxobutyl)cyclooctanone **1** (R = CHO, n = 8) in ether was adsorbed on to alkaline alumina (Brockmann Activity II–III). After 40 h elution with ether gave the compound **1** (R = H, n = 8) followed by a mixture which was cleanly separated by PLC into the isomeric ketols **2** (n = 8; IR, ν_{max} 3374 cm^{-1}; NMR, τ 8·1, disappears with D_2O, OH) and **3** (n = 8; IR, ν_{max} 3328 cm^{-1}; NMR, τ 7·39, disappears with D_2O, OH), τ 8·75, singlet Me). The stereochemistry of the ketol **2** (n = 8) was proved by its conversion, by way of the thioacetal (**4**) into the alcohol (**5**) identical with authentic *trans*-alcohol (**5**) synthesised by the following method. Friedel Crafts acylation of benzene with the polyanhydride of adipic acid gave[2] the keto-acid (**6**), which by Wolff Kishner reduction[3] and subsequent high dilution cyclisation[4,5] of the acid chloride of the product then produced 2,3 - benzocyclooct - 2 - en - 1 - one (**7**). A further Wolff Kishner reduction[4] now furnished 1,2-benzocyclooctene which treated with lithium in ethylamine gave[6] bicyclo[6.4.0]dodec - 1,8 - ene (**8**). This compound was identical with that obtained[7] by the formolysis of 1,5 - *trans,trans* - cyclododecadiene (**9**); the NMR and IR spectra of the two were superimposable. Compound **8** could not be induced to react with diborane. However, with *m*-chloroperbenzoic acid it readily gave the epoxide (**10**), which though resistant to the attack of LAH (less than 10% reduction after 8 h in refluxing THF), was nevertheless smoothly reduced by lithium in ethylamine to the *trans*- alcohol **5** (n = 8; 84% pure, GLC).

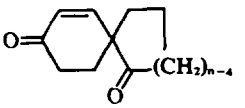
Alkaline alumina treatment of the 10-membered compound **1** (R = CHO, n = 10) gave the compound **1** (R = H, n = 10) and a ketol of structure **3** (n = 10; IR, ν_{max}3373 cm^{-1}; NMR. τ 7·91, disappears with D_2O, OH, τ 8·73, singlet Me). Careful search for a ketol of structure **2** (n = 10) proved fruitless. It is worth recording that alkaline alumina treatment of the formyl ketones (**1**) for short periods could be made to yield the deformylated ketones almost quantitatively.

From the evidence now available[1,8,9] it would appear that valence bridged ketols, i.e. of type **2**, are produced in isolable quantities only for ring sizes 6, 7, 8, and possibly 9 (the last case has not been examined). For ring size 5 no ketols of any type have been found, and for ring sizes 10 and 12 they are of the atom bridge type **3** with, in the case n = 12 retention of the aldehyde group. Furthermore the ketols **2** all posses the *trans*-stereochemistry as in **5**.

Distillation of the compounds **1** (R = CHO, n = 8, 10) from a little potassium hydroxide gave the spiroketones **11** (n = 8, 10) along with unchanged and deformylated compounds. Separation from the contaminants was readily achieved by preparative GLC, the spiroketones having the longest retention times. Like the previous compounds **11** (n = 7, 12) the new spiroketones gave mono-derivatives with 2,4-dinitrophenyl hydrazine and with semicarbazide by reaction at their $\alpha\beta$-unsaturated carbonyl functions. The UV absorption spectrum of the 8-membered spiroketone **11** (n = 8) had one band (λ_{max} 228 nm, ϵ 6720); that of **11** (n = 10) had two absorptions one of them a shoulder (λ 246 nm, ϵ 4150) on the principal band (λ_{max} 224 nm, ϵ 6560). The 246 nm absorption, present as a distinct band for the spiroketone **11** (n = 5) thus disappears for ring sizes 6, 7, and 8, re-emerges as a shoulder for n = 10, and becomes fully developed once more at n = 12. The CD spectra of the optically active forms of these ketones should be interesting.

Treatment of the compound **1** (R = CHO, n = 8) with either sodium methoxide or toluene-*p*-sulphonic acid in hot benzene slowly produced the

ketone **12** (n = 8). As far as could be judged from the NMR spectra of the monitored system only little of the alternative cyclised forms (**13**) could have been present. Comparison with other cyclisations indicates that compounds of type **13** are produced principally under vigorous Brønstead-[10] and Lewis-acid[11] conditions, the more usual Robinson-type ketones being the products under basic (in particular alkali metal hydroxides and alkoxides) and mildly acidic conditions. One apparent anomaly is the behaviour of the compounds **1** (R = CHO, n = 12 and R = CO_2Et, n = 15). The former with sodium methoxide in benzene yields[1] the ketone **12** (n = 12) while the latter is stated to react with alcoholic potash[12] to give the ketone **13** (n = 15, C = C conjugated).



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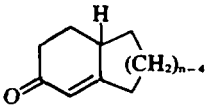

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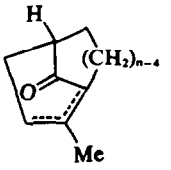

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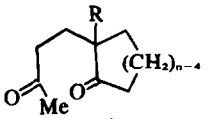

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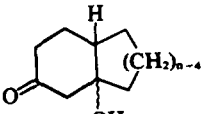

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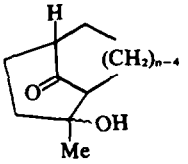

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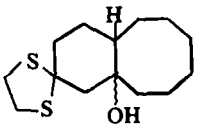

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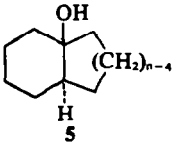

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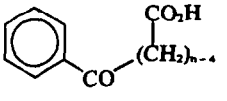

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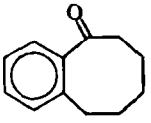

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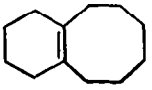
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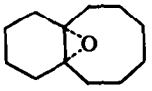

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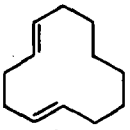
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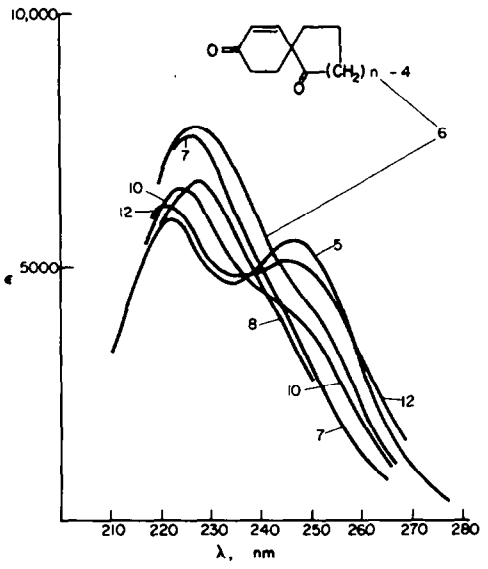

Fig 1.

EXPERIMENTAL

General directions are given in Ref 1. All compounds are racemic.

The hydroxymethyleneketones were made by published methods[13] and converted into their methyl vinyl ketone adducts as in other cases.[1]

2-*Formyl*-2-(3-*oxobutyl*)*cyclooctanone* (1, R = CHO, n = 8) was a colourless crystalline solid (91% yield), m.p. 49–50° (from petrol, b.p. < 40°); IR, ν_{max} (liquid paraffin) 1715 1712 cm^{-1}; NMR, τ (CCl_4) 0·21 (1H, s, CHO) and 7·91 (3H, s, $COCH_3$). (Found: C, 70·13; H, 9·33. $C_{13}H_{20}O_3$ requires: C, 69·61; H, 8·99%) (mass spectrum, highest mass number 196·2, loss of CO).

2-*Formyl*-2-(3-*oxobutyl*)*cyclodecanone* (1, R = CHO, n = 10) crystallised from petrol (b.p. < 40°) in colourless needles (60% yield), m.p. 44–45°; IR, ν_{max} (liquid paraffin) 1716, 1691 cm^{-1}. (Found: C, 71·82; H, 9·83; $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

trans-8-*Hydroxybicyclo*[6.4.0]*dodecan*-10-*one* (2, n = 8, trans-) and 8 - *hydroxy* - 8 - *methyl*[5.3.1]*undecan* - 11 - *one* (3, n = 8). Hopkin and Williams alkaline alumina, Brockmann Activity I (240 g) was treated with water (12 ml') and shaken for 4 h at room temp before being made up into a column with ether. A soln of 1 (R = CHO, n = 8; 4 g) in ether (15 ml) was run onto the column and transfer to the adsorbent completed with more solvent (15 ml'). After 40 h elution with ether gave, from the early fractions, a colourless oil (3·2 g) which was virtually pure (TLC) deformylated material 1 (R = H, n = 8); IR, no OH; NMR, no CHO, τ 7·88 (3H, s, $COCH_3$), proton count agreeing with the formula. The later fractions gave a colourless oil (0·50 g) which was preparatively plate-chromatographed with benzene–ether (1 : 1) on silica gel. The band at R_f 0·81 gave (*ca* 0·25 g) ketone 1 (R = H, n = 8); the band at R_f 0·59 gave an oily solid which was crystallised from petrol (b.p. 60–80°)—chloroform to produce the *ketol* 2 (n = 8, *trans*-; 80 mg), m.p. 129°, IR, ν_{max} (liquid paraffin) 3374, 1723, 1703 cm^{-1}; NMR, τ ($CDCl_3$), 8·1 (1H, s, exchanges with D_2O), OH). (Found: C, 73·80; H, 10·71. $C_{12}H_{20}O_2$ requires: C, 73·43; H, 10·27%) (M^+ 196·3). A band at R_f 0·47 gave a solid which was recrystallised from petrol (b.p. 60–80°) containing a few drops of chloroform and gave the bridged *ketol* 3 (n = 8; 60 mg), m.p. 120–121°; IR, ν_{max} (liquid paraffin) 3328, 1702 cm^{-1}; NMR, τ ($CDCl_3$) 7·39 (1H, s, exchanges with D_2O, OH), 8·75 (3H, s, CH_3). (Found: C, 73·48; H, 10·43. $C_{12}H_{20}O_2$ requires: C, 73·43; H, 10·27%).

trans-*Bicyclo*[6.4.0]*dodecan*-1-*ol* (5, n = 8). (a) To a stirred mixture of 2 (n = 8, *trans*-; 75 mg), dioxane (1·5 ml, freshly distilled from LAH), and finely powdered anhyd $ZnCl_2$ (100 mg) was added a soln of 1,2-ethanedithiol (0·4 ml) in dioxane (1 ml) followed by powdered anhyd Na_2SO_4 (100 mg). The mixture was stirred for 2 days at room temp and then poured into chloroform. After being washed with water the organic layer was dried and evaporated. The colourless crystalline solid was recrystallised from petrol (b.p. 40–60°) containing a little ether. The *thioacetal* 4 (*trans*-) formed colourless needles, m.p. 98° (65 mg); IR, ν_{max} (liquid paraffin) 3463 cm^{-1}. (Found: C, 61·82; H, 8·97. $C_{14}H_{24}OS_2$ requires: C, 61·74; H, 8·88%) (M^+ 272·3).

The above thioacetal (50 mg) in pure MeOH (5 ml) was refluxed with freshly made Raney Ni (W 2, 3 g) for 3 h. Filtration followed by evaporation gave a colourless camphoraceous smelling oil (37 mg) easily purified by PLC. This compound, trans-*bicyclo*[6.4.0]*dodecan*-1-*ol* 5 (n = 8) (M^+ 182·3) was identical with that made by method (b) below; GLC, 15% Carbowax 20 M on Universal B support, column temp 140°, injection temp 180°, gas flow (argon) 27 cm^3/min—retention time 36·0 min. (b) Bicyclo[6.4.0]dodec - 1(8) - ene (8) was prepared from 7 (= H_2 in place of = O) by the published method except that it was found better to use 50% more Li than that stated.[6] The compound, NMR, τ ($CDCl_3$) 8·0 (m, 8H, allylic protons), 8·5 (12H, m), IR, ν_{max} (CCl_4) 1444, 1465 cm^{-1} (M^+ 164) was identical with that obtained[7] from 1,5-*trans,trans*-9 (we thank Drs. Erman and Kretschmar for sending us copies of their IR and NMR spectra of this compound).

To a stirred soln of the above olefine (1·15 g) in $CHCl_3$ (5 ml)) was added a soln of *m*-chloroperbenzoic acid (2·0 g) in $CHCl_3$ (15 ml) during 30 min. After 12 h the mixture was diluted with $CHCl_3$ (75 ml) and then washed with Na_2SO_3 aq, Na_2CO_3 aq, and finally water. The dried organic layer furnished the colourless *epoxide* which was purified by PLC; IR, ν_{max} (film) 1404, 1460 cm^{-1}; NMR, τ (CCl_4) 8·5 (broad singlet—all protons). The above epoxide 10 (440 mg) in stirred ethylamine (40 ml) was treated with Li (500 mg) and after 3 h the mixture was worked up by extraction into ether, washing with HCl, drying, and evaporation. The product (400 mg) was purified by PLC (3 : 1 benzene–ether/silica gel, R_f 0·60) and gave (260 mg) the trans-*alcohol* 5 (n = 8), solid at −20°; IR, ν_{max} (film) 3480 cm^{-1}; GLC (experiment sequential to that given above), retention time 36·2 min (M^+ 182·3). (Found: C, 79·15; H, 11·86. $C_{12}H_{22}O$ requires: C, 79·06; H, 12·16%).

10 - *Hydroxy* - 10 - *methylbicyclo*[7.3.1]*tridecan* - 13 - *one* (3, n = 10). The experiment was conducted as for 3 (n = 8). The first eluates gave 1 (R = H, n = 10; 65%); τ ($CDCl_3$) 7·88 (3H, s, $COCH_3$) followed by the *ketol* 3 (n = 10; 23%) which crystallised from petrol (b.p. 60–80°) containing a few drops of $CHCl_3$ in colourless rosettes, m.p. 124–127°; IR, ν_{max} (liquid paraffin) 3373 cm^{-1}; NMR, τ ($CDCl_3$) 7·91 (1H, s, exchanges with D_2O, OH), 8·73 (3H, s, CH_3). (Found: C, 75·20; H, 10·85. $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%).

Cyclooctanespirocyclohex - 2' - *ene* - 2,4' - *dione* (11,

n = 8) and *cyclodecanespirocyclohex - 2' - ene - 2,4' - dione* **11** (n = 10). These compounds were made by the general method given earlier.[1] They were the highest boiling components in the mixtures and on preparative GLC they had the longest retention times.

Cyclooctanespirocyclohex - 2' - ene - 2,4' - dione **11** (n = 8) yield (30%) was a colourless liquid, b.p. 120°/0·09 mm; UV, λ_{max} (EtOH) 228 nm (ϵ 6720); IR, ν_{max} (film) 1694, 1685 cm^{-1}; NMR, τ (CCl_4), 3·16 (1H, d, *J* 10·5 Hz) and 4·08 (1H, d, *J* 10·5 Hz) (CH=CH). (Found: C, 75·55; H, 8·90. $C_{13}H_{18}O_2$ requires: C, 75·69; H, 8·80%). The red *mono - 2,4 - dinitrophenylhydrazone* had m.p. 167–169° (from EtOAc); UV, λ_{max} ($CHCl_3$) 380 nm (ϵ 26540). (Found: C, 59·44; H, 5·62; N, 14·64. $C_{19}H_{22}N_4O_5$ requires: C, 59·06; H, 5·74; N, 14·50%). The *mono-semicarbazone* had m.p. 207–209° (from MeOH); UV, λ_{max} (MeOH) 270 nm (ϵ 27880). (Found: C, 63·60; H, 8·35; N, 15·76. $C_{14}H_{21}N_3O_2$ requires: C, 63·85; H, 8·04; N, 15·96%).

Catalytic hydrogenation of the above spiroenedione (95% EtOH–Pd-$CaCO_3$) gave *cyclooctanespirocyclohexane - 2,4' - dione*, m.p. 65–66° (from b.p. 40–60° petrol; 58% yield); UV, no selective absorption; IR, ν_{max} (liquid paraffin) 1696 (broad), 1682 cm^{-1}. (Found: C, 75·30; H, 9·86. $C_{13}H_{20}O_2$ requires: C, 74·96; H, 9·68%).

Cyclodecanespirocyclohex-2'-ene-2,4'-dione **11** (n = 10; 42% yield) was a colourless liquid, b.p. 132°/0·1 mm; IR, ν_{max} (film) 1685 cm^{-1} (broad); UV, λ_{max} (EtOH) 224 nm (ϵ 6560), λ 246 nm (shoulder) (ϵ 4150); NMR, τ (CCl_4) 3·05 (1H, d, *J* 10·5 Hz) and 4·10 (1H, d, *J* 10·5 Hz) (CH=CH) (M^+ 234·3). It gave an orange *mono - 2,4 - dinitrophenylhydrazone*, m.p. 159° (from MeOH); UV, λ_{max} ($CHCl_3$) 382 nm (ϵ 27740). (Found: C, 60·39; H, 5·80; N, 13·75. $C_{21}H_{26}N_4O_5$ requires: C, 60·80; H, 6·30; N, 13·54%). The spiroketone was not stable to storage.

Bicyclo[6.4.0]*dodec - 8 - en - 10 - one* **12** (n = 8). (a) A mixture of **1** (R = CHO, n = 8: 2 g), Na-dried benzene (50 ml) and toluene-*p*-sulphonic acid (0·4 g) was refluxed for 3 h. The soln was then cooled, washed with water, dried, and evaporated. Distillation (b.p. 96–98°/0·06 mm) gave a colourless liquid (1·6 g) TLC of which showed two closely spaced spots and NMR confirmed the presence of **1** (R = H, n = 8) (τ 7·88, singlet Me) (absence of starting material–no CHO) and the ketone **12** (n = 8; τ 4·02, CH = singlet). Preparative layer chromatography gave an oil (500 mg) (NMR τ 4·02 with very slight absorption at τ 7·88) which was nearly pure *bicyclo*[6.4.0]*dodec - 8 - en - 10 - one* **12** (n = 8), UV, λ_{max} 249 nm (ϵ 14200). This gave an almost quantitative yield of the 2,4-*dinitrophenylhydrazone*, m.p. 190° (from $CHCl_3$–EtOH); UV, λ_{max} ($CHCl_3$) 395 nm (ϵ 28500); NMR, τ 3·79 (1H, s, CH=). (Found: C, 60·52; H, 6·36; N, 15·79. $C_{18}H_{22}N_4O_4$ requires: C, 60·32; H, 6·19; N, 15·63%). Prelog[10] prepared the corresponding semicarbzone. (b) Compound **1** (R = CHO, n = 8; 0·3 g), Na-dried benzene (3·0 ml) and NaOMe (0·1 g) were stirred together under N_2 with rigorous exclusion of moisture for 24 h. Work-up gave material similar to that in (a) above.

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