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ALICYCLIC COMPOUNDS—II

ACTION OF BASE ON BICYCLIC KETOTOSYLATES— FRAGMENTATION OF A DECALONE TOSYLATE TO A CYCLODECADIENONE

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Abstract—In presence of KOBu^t in hot Bu^{t}OH the tosylate of *cis*-6,6,9-trimethyl-3-oxo-8-oxydecalin smoothly suffered fragmentation to furnish a trimethyl cyclodecadienone (XIV).†

THE action of KOBu^t in hot Bu^{t}OH on the bicyclic keto tosylates (I and II) furnished tricyclic ketones, the expected fragmentation not taking place.

Accordingly, we investigated isomeric bicyclic δ-keto tosylates of the type III where the tosylate group is in the adjacent ring. Sterically an intramolecular displacement to the cyclobutyl ketone (IV) is also possible here.

However, the rigid geometry in this syetm vis-a-vis the conformational mobility of the carbinyl tosylate in the compounds previously studied, and in particular, the presence of an ideal geometric disposition of requisite antiperiplanar bonds necessary for a one-step concerted fragmentation reaction[2] appeared to weigh in favour of the latter process in preference to intramolecular displacement.

As 2-methyldimedone (V) was available,[3] we studied the action of base on tosylate of the *cis*-hydroxydecalone (X) which could be readily obtained from V.

Synthesis of the required *cis* hydroxydecalone (X) was carried out by the two different routes shown in Fig. 1. The unambiguous synthesis proceeded through the crystalline diol (XI) which was oxidized[4] by MnO_2 to the crystalline octalone (XII) and then reduced catalytically to X.

The β-configuration of the OH group in the octalone and hence in the decalone is based on the analogy of reductions in similar systems.[5] The *cis*-configuration of the decalone (VIII) follows from its method of formation. The catalytic hydrogenations of 3-oxo-$\Delta^{4,5}$-octalins are known to give *cis*-β-decalones.[5,6] Confirmation of the *cis* ring junction was also secured by conversion of the monoketal (IX) to the crystalline ketone (XIII) found identical with an authentic specimen of *cis*-6,6,9-trimethyl-3-oxo-decalin.[3,6] The structures and configurations of the decalin dione and the hydroxydecalone were thus secured.

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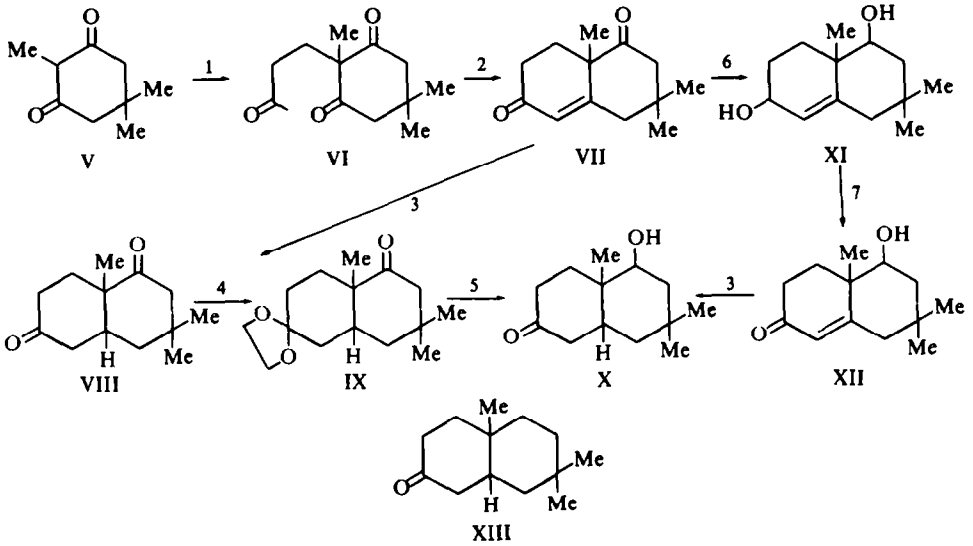


1. $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}N\,Et_2$-Py·—$C_6H_6$. 2. Et_3N—C_6H_5COOH-Xylene
3. Pd—C/H_2. 4. $(CH_2OH)_2$—H^+. 5. $NaBH_4$; $H_3\dot{O}$. 6. LAH. 7. MnO_2.

FIG. 1

Reaction of the tosylate (IIIb) in presence of a slight excess of KOBu^t in hot Bu^{t}OH furnished the unsaturated ketone (XIV). This had ν_{max}^{film} 1700, 1630, 960, 900, 765 cm^{-1} and λ_{max} 224 mμ (2500), 256 mμ (1600). On catalytic hydrogenation it absorbed exactly two mole equivalents of hydrogen confirming the presence of two double bonds. The

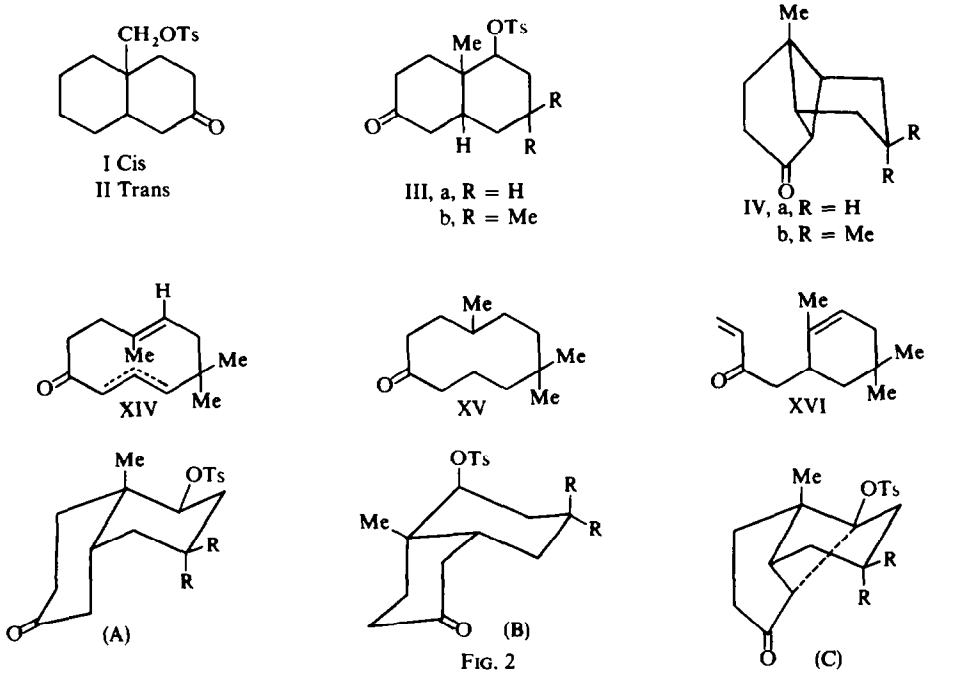


FIG. 2

tetrahydroketone (XV) had ν_{max}^{film} 1705 cm^{-1} and exhibited no UV absorption maxima between 215 and 250 mμ.

The presence of two double bonds in the ketone is thus firmly secured and the tricyclic structure IVb (R = Me) can therefore be eliminated. Formation of a diunsaturated ketone clearly, therefore, involves fragmentation of the type envisaged.[1] *A priori*, two isomeric dienones, the cyclodecadienone (XIV) and the cyclohexene (XVI) might arise through fragmentation of the tosylate (IIIb), since there are two different enolate ions derivable from this ketone.* On mechanistic grounds, from the direction of preferred enolization of a cis β-decalone[7] and the geometric requirement of bonds in a fragmentation reaction, the cylodecadienone (XIV) is the expected product. The IR and the UV spectra of the ketone which show abnormal characteristics are in agreement with the properties of medium ring unsaturated ketones. Medium ring unsaturated ketones exhibit abnormal UV and IR characteristics due to lack of effective conjugation in such systems.[8a, 8b]

While the gross cyclodecadienone structure (XIV) for the ketone is confirmed, it is difficult to assign a more refined formulation. The *trans*-configuration for the non-conjugated double bond is anticipated on the basis of concerted fragmentation of the tosylate (IIIb), where the angular Me and the Ts groups are *cis* and this has several well documented analogies.[9] However, the position and configuration of the double bond adjacent to the CO group is less certain. Mechanistically a *trans* bond will be formed. But the inversion to the *cis*-configuration or migration to the non-conjugated βγ-position through enolization is possible under the strongly basic conditions employed as well as during isolation of the product. It is established that a *cis* cyclodecene is thermodynamically more stable than the *trans* isomer.[10, 11] Cyclodecenone prepared by pyrolysis of acetoxy cyclodecanone is a mixture of conjugated and non-conjugated isomers[8b] with both *cis* and *trans* double bonds. The presence of two *trans* linkages in the ketone (XIV) would therefore involve considerable strain, and inversion to the less strained geometric configuration will occur. The UV and IR spectra indicate that the ketone (XIV) is a mixture of both αβ- and βγ-isomers with *cis*/*trans* bonds. No conclusive evidence as to the stereochemistry of the double bond and the relative proportion of αβ–βγ isomers has been possible.

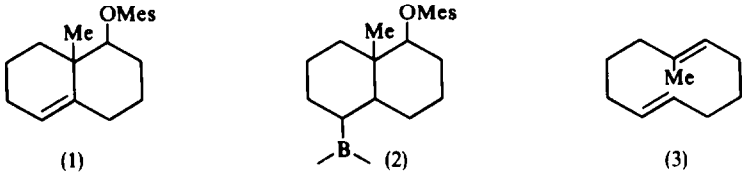
Heathcock[12] has described the conversion of the *cis* decalone tosylate (IIIa) to the tricyclic ketone (IVa) through an intramolecular displacement. No evidence of fragmentation was obtained and the results therefore contradict our observations. However, if an intramolecular displacement occurs, the decalone tosylate must react in the steroidal conformation (A) (Fig. 2), and in the transition state the ring bearing the CO group must fold to the extent that the C_4 carbon atom can reach the proximate position for the intramolecular SN_2 displacement of the tosylate group (C). In the decalone tosylate (IIIa) of Heathcock and other examples,[13] there is no steric hindrance to attain the required transition state geometry (C) for the displacement. In the keto-tosylate (IIIb), the presence of an axial Me group introduces intense 1,3-diaxial

* Formation of the Cyclohexene (XVI) would indeed be unlikely. Since the C_8OTs bond is not anti-periplanar to the C_1—C_9 bond, the dihedral angle ca. 60°, the steric requirement[2] of a concerted fragmentation cannot be fulfilled. On the other hand the C_8—OTs bond, the C_9—C_{10} Bond and the C_4-equatorial Hydrogen bond are in perfect anti-periplanar juxtaposition.

interaction with the methylene group in the adjacent ring in the steroid conformation.* Any geometric change that would tend to bring the methylene group closer to the axial Me would accentuate the interaction and would be resisted. As the decalone (IIIb) cannot attain the required transition state geometry (C) for an intramolecular displacement it suffers facile fragmentation to the cyclodecadienone (XIV).†

This therefore constitutes a new synthetic route to medium ring unsaturated ketones and we are currently engaged in exploring this method for the synthesis of natural compounds of this class.

An analogous fragmentation has been described by Marshall[15] who achieved a facile synthesis of the *trans–trans*-cyclodecadiene (3) from the octalinmesylate (1).



(1) (2) (3)

FIG. 3

EXPERIMENTAL

The m.ps and b.ps are uncorrected. Solvent extracts were dried over Na_2SO_4. Alumina used for chromatography was E.Merck aluminium oxide standardized according to Brockmann. Pet. ether indicates fraction b.p. 40–60°. The UV spectra were taken in 95% EtOH, unless otherwise stated on Unicam Spectrophotometer Model S.P.500. The IR spectra were taken in thin films or in $CHCl_3$ soln in Perkin–Elmer Infrachord Recording Spectrophotometer Model 137.

2,5,5-*Trimethyl*-1,3-*dioxo-cyclohexane* (V). Dimedone (56 g), was added with stirring to NaOMe (from 10·12 g, Na and 110 ml MeOH followed by MeI (44 ml) at 5° during 30 min. After reflux (4 hr) MeOH was removed and the residue diluted with water and extracted with ether. The ethereal soln was extracted with 10% K_2CO_3 aq and the extract acidified to precipitate V which was washed with water, dried and used directly in the next step, yield 34 g (55%). Specimen crystallized from EtOH had m.p. 160° (Lit.[3,8] 160°).

6.6.9-*Trimethyl*-3,8-*dioxo*-$\Delta^{4,10}$-*octalin* (VII). The dione V (14·4 g), 4-diethylaminobutanone-2 (16·5 g), pyridine (10·5 ml) and benzene (150 ml) were refluxed (15 hr) using a Dean–Stark apparatus.[16] Usual work up gave VI (17·8 g) as a viscous oil, b.p. 135–138°/0·6 mm.

The triketone (13·0 g), Et_3N (7·5 ml), benzoic acid (8·8 g) and xylene (75 ml) were refluxed using a Dean–Stark apparatus, till no more water separated[17] (20 hr). Usual work up gave, after fractionation, the desired product as a pale yellow oil which solidified. It was crystallized from ether and pet. ether, m.p. 94°, λ_{max} 243 mμ (ε, 18,000), $\lambda_{max}^{CHCl_3}$ 5·84, 6·0, 6·18 μ. (Found: C, 75·33; H, 8·49. $C_{13}H_{18}O_2$ requires: C, 75·73; H, 8·76%). The 2,4-*dinitrophenylhydrazone* was crystallized from EtOH and $CHCl_3$: orange-red; m.p. 204°, $\lambda_{max}^{CHCl_3}$ 385 mμ (ε, 17,000). (Found: N, 14·70. $C_{19}H_{22}O_5N_4$ requires: N, 14·50%).

The cyclodehydration appeared to be rather sluggish presumably due to the *gem*-dimethyl groups which introduce intense 1,3-diaxial interaction in the intermediate aldol.

* For tosylate (IIIb, R = Me), the steroid conformation (A) would appear to be favoured over the "non-steroid" conformation (B), since in the latter conformation the axial tosylate group is subject to serve 1,3-diaxial interaction with the axial Me group. After cancelling common 1,3-axial interactions in the two conformations of the *cis*-hydroxydecalone (X) there are left a CH_3/CH_2 interaction of 3·6 KCal/mole for the steroid conformation against a CH_3/H (0·9 KCal/mole), a HO/CH_3 (ca. 2·4 KCal/mole) and a 3-alkyl-ketone interaction (ca. 0·9 KCal/mole) totalling 4·2 KCal/mole in the non-steroid conformation.[14]

† Evidence in support of the directive influence of an axial Me in promoting fragmentation vis-a-vis intramolecular displacement has been obtained in other systems (P. C. Mukharji, D. P. Ghosh and T. K. Das Gupta, Unpublished work). The results will be communicated in the future.

cis-6,6,9-*Trimethyl*-3,8-*dioxo-decalin* (VIII). The above octalone (10 g) in EtOH (50 ml) over 10% Pd on C (0·2 g) absorbed 1270 ml (1·016 mole equiv) H_2 during 6 hr at 30°/754 mm, when further absorption stopped. It was worked up in the usual manner and on crystallization from ether and pet. ether furnished needles, m.p. 112°, $\lambda_{max}^{CHCl_3}$ 5·85 μ. (Found: C, 75·27; H, 9·70. $C_{13}H_{20}O_2$ requires: C, 75·00; H, 9·60%). The 2,4-*dinitrophenylhydrazone* was crystallized from EtOH and $CHCl_3$: yellow, m.p. 230°, $\lambda_{max}^{CHCl_3}$ 368 mμ (ε, 17,500). (Found: N, 20·36; $C_{25}H_{28}O_8N_8$ requires N, 19·70%).

cis-6,6,9-*Trimethyl*-8-*hydroxy*-3-*oxo-decalin* (X). The above VIII (10 g), ethylene glycol (3·3 g), *p*-toluenesulphonic acid (0·5 g) and benzene (120 ml) were refluxed using a Dean–Stark apparatus, till no more water separated (3 hr). Usual work up furnished after fractionation, IX b.p. 130°/0·2 mm, 11 g (90%), which was used directly in the next step.

Ketalization of the dione in the absence of excess glycol preferentially involves the less hindered CO group since ketalization of the other centre introduces severe 1,3-diaxial interaction with the *gem*-dimethyl groups.

A soln of IX (10 g) in EtOH (100 ml) was added dropwise to $NaBH_4$ (4·5 g) in EtOH (200 ml) at room temp and the mixture was left overnight. It was acidified with gl. AcOH (15 ml), EtOH removed, then diluted with water (200 ml), and extracted with ether. The residue, after removal of ether, was refluxed with 65% MeOH aq (96 ml) containing conc HCl (8 ml) for 3 hr, then diluted with water (400 ml) and extracted with ether. Usual work up afforded X (7·5 g) which on crystallization from ether and pet. ether had m.p. 134°, $\lambda_{max}^{CHCl_3}$ 2·8 (broad), 5·85 μ. (Found: C, 73·70; H, 10·21. $C_{13}H_{22}O_2$ requires: C, 74·30; H, 10·50%). The 2,4-*dinitrophenyl hydrazone* was crystallized from EtOH and $CHCl_3$: yellow needles, m.p. 158°, $\lambda_{max}^{CHCl_3}$ 368 mμ (ε, 13,500). (Found: C, 58·50; H, 6·55. $C_{19}H_{26}O_5N_4$ requires: C, 58·46; H, 6·66%). The acetate was crystallized from pet. ether as colourless needles, m.p. 88°. (Found: C, 71·00; H, 9·62. $C_{15}H_{24}O_3$ requires: C, 71·43; H, 9·52%).

6,6,9-*Trimethyl*-3,8-*dihydroxy*-$\Delta^{4,10}$-*octalin* (XI). A soln of VII (1 g) in ether (10 ml) was added slowly (15 min) to a well stirred suspension of LAH (0·4 g) in ether (10 ml) at room temp. After stirring at room temp (1·5 hr) it was decomposed at 5° (ice-bath) with sat Na_2SO_4 aq. Usual work up furnished the diol as a colourless solid which was crystallized from ether and pet. ether as needles, m.p. 180°. (Found: C, 74·05; H, 10·83. $C_{13}H_{22}O_2$ requires: C, 74·30; H, 10·50%). The compound did not show any UV absorption characteristic of αβ-unsaturated ketones.

6,6,9-*Trimethyl*-8-*hydroxy*-$\Delta^{4,10}$-*octalin* (XII). A soln of XI (1 g) in $CHCl_3$ (100 ml) and active MnO_2 (9 g) were stirred at room temp for 14 hr. The mixture was then filtered, the inorganic residue washed with hot $CHCl_3$ (50 ml × 5) and the combined filtrates dried and concentrated. Sublimation of the residue furnished a viscous oil which solidified and after crystallization from acetone-pet. ether had m.p. 121°, λ_{max} 243 mμ (ε, 18,000), λ_{max}^{Nujol} 2·9 and 6·0 μ. (Found: C, 74·68; H, 9·38. $C_{13}H_{20}O_2$ requires: C, 75·00; H, 9·60%).

The above hydroxyenone (0·5 g) in EtOH (10 ml) over 10% Pd on C (0·19) absorbed 70 ml (1·1 mole equiv) H_2 during 1 hr at 30°/755 mm to give after usual work up and crystallization the hydroxydecalone, m.p. 134°, undepressed on admixture with X. The 2,4-*dinitrophenylhydrazone* had m.p. 158°, undepressed on admixture with the specimen described.

cis-6,6,9-*Trimethyl*-3-*oxo-decalin* (XIII). A soln of IX (1 g) in digol (30 ml) was refluxed with 98% hydrazine hydrate (3 ml) and solid KOH (3 g) for 2 hr at 198° on the oil-bath. The water formed was removed by distillation and the mixture refluxed for another 4 hr. It was then poured into water (100 ml) and the oil extracted with ether. The residue left after removal of ether was refluxed for 3 hr with 65% MeOH aq (12 ml) containing conc HCl (1 ml). Usual work and crystallization from MeOH aq furnished XIII (0·49 g) in needle-shaped crystals, m.p. 70°, undepressed on admixture with authentic specimen of *cis*-6,6,9-trimethyl-3-oxodecalin.[3,8]

cis-6,6,9-*Trimethyl*-8-*tosyloxy*-3-*oxo-decalin* (IIIb). A soln of *p*-toluenesulphonyl-chloride (5 g) in pyridine (10 ml) was added to a cooled (below −10°) soln of VIII (5 g) in pyridine (10 ml) and the mixture was kept at 0° for 48 hr. The soln was poured into conc HCl containing crushed ice and then extracted with $CHCl_3$. Usual work up finished the tosylate which on crystallization from MeOH aq had m.p. 145°. (Found: C, 66·11; H, 7·42. $C_{20}H_{28}O_4S$ requires: C, 65·93; H, 7·69%).

7,7,10-*Trimethyl*-3-*oxo*-4,9-*cyclodecadiene* (XIV). A soln of IIIb (5·5 g) in Bu^{t}OH (100 ml) was added dropwise to warm KOBu^t (from 0·7 g, K and 150 ml Bu^{t}OH) on steam-bath, with stirring under N_2. The soln gradually turned brown and KOTs began to separate. Stirring under reflux was continued for another 4 hr. The mixture was then cooled to room temp, KOTs allowed to settle and the supernatant soln carefully decanted into ether (500 ml) in a separatory funnel. The ether–Bu^{t}OH mixture was washed repeatedly with water (200 ml × 10) and the soln dried and concentrated at 40–45°. The residue (2·2 g) was dissolved in pet. ether (5 ml) and left at 5° overnight. Next day, the supernatant soln was separated from the ppt (0·2 g) and

concentrated under diminished press at room temp to give a brown residue (2 g) which was absorbed over a column of alumina (25 g); elution with pet. ether containing 10% ether furnished a pale yellow oil (1·4 g) having a characteristic smell. It was sublimed at bath temp 110°/0·4 mm to give the pure ketone (1·29) as a colourless mobile liquid λ_{max} 224 mμ (ε, 2600); 256 mμ (ε, 1600); ν_{max}^{film} 1700, 1630, 960, 900, 765 cm^{-1}. The *2,4-dinitrophenylhydrazone* was crystallized from EtOH and $CHCl_3$: orange-red; m.p. 178°, $\lambda_{max}^{CHCl_3}$ 374 mμ (ε, 23,000). (Found: C, 60·85; H, 7·00; N, 14·92. $C_{19}H_{24}O_4N_4$ requires: C, 61·29; H, 6·45; N, 15·06). The *semicarbazone* crystallized from MeOH aq had m.p. 218°, λ_{max} 232 mμ (ε, 22,000). (Found: C, 67·70; H, 9·32; N, 16·74. $C_{14}H_{23}ON_3$ requires: C, 67·47; H, 9·23; N, 16·87%).

7,7,10-*Trimethyl*-3-*oxo*-*cyclodecane* (XV). The above XIV (0·4 g) in EtOH (10 ml) over 10% Pd on C (0·1 g) absorbed 104 ml (2 mole equiv) H_2 during 1 hr at 25°/765 mm. The reaction mixture was worked up in the usual way to give XV, b.p. 110° (bath)/0·5 mm, ν_{max}^{film} 1705 cm^{-1}. The *2,4-dinitrophenylhydrazone* was crystallized from EtOH aq; yellow, m.p. 136°, $\lambda_{max}^{CHCl_3}$ 374 mμ (ε, 23,000). (Found: C, 60·57; H, 7·66. $C_{19}H_{28}O_4N_4$ requires: C, 60·63; H, 7·45). The *semicarbazone* crystallized from MeOH; m.p. 230°, λ_{max} 229–230 mμ (ε, 20,000). (Found: C, 66·86; H, 10·26. $C_{14}H_{27}ON_3$ requires: C, 66·40; H, 10·67%).

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