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ON MUKHARJI'S "CYCLODECADIENONE"

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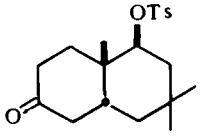
Abstract—Contrary to reports by Mukharji *et al.*, *cis*-tosyloxydecalone **1** reacts with base to yield predominately the tricyclic ketone **3**, along with minor amounts of octalone **18**, rather than cyclodecadienone **2**.

IN 1969 Mukharji and Das Gupta reported that tosyloxydecalone **1** undergoes base-catalyzed fragmentation to cyclodecadienone **2**, rather than intramolecular alkylation to tricyclic ketone **3**.[1]



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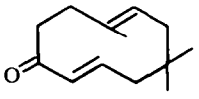

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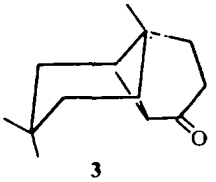
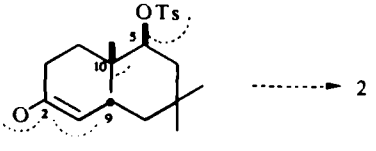


3

We were surprised by this report for two reasons. Firstly, if one examines a model of the enolate which would be required for fragmentation to occur (**1a**), it is apparent that, although the C_9—C_{10} and C_5—OTs bonds can be made perfectly *anti*-coplanar

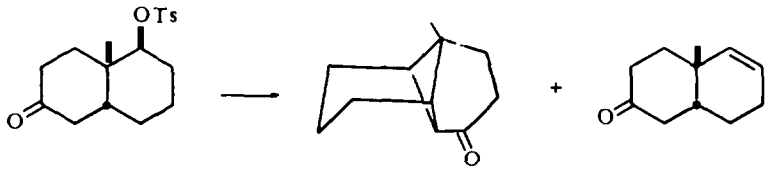


1a

(in either a rigid "steroid" conformation or a ring-**B** boat conformation), the portion of the enolate π-orbital associated with C_1 cannot become coplanar with the C_9—C_{10} bond in any reasonable conformation. For concerted fragmentation to be possible, it would be necessary to severely twist the C_1—C_2 double bond in enolate **1a** in order to force the p orbital on C_1 to be coplanar with the C_9—C_{10} bond. In such an arrangement, the p (or sp^3) unshared electrons on C_1 would be approximately orthogonal to the π orbital of the CO group.

Secondly, our previous experience with a related compound, tosyloxydecalone **4**, had revealed an alternative reaction path for such compounds. Compound **4** reacts with either potassium t-butoxide or methylsulfinyl carbanion to give the tricyclic ketone **5**, accompanied by octalone **6**.[2]

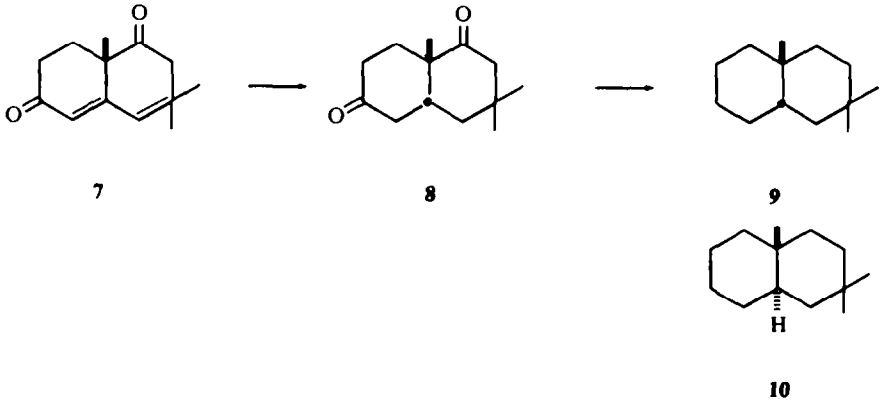
Mukharji recognized the apparent discrepancy between his results and ours,[1] and rationalized it by postulating that the *gem*-dimethyl group in compound **1**



4 5 6

hinders approach of the C_1 carbon to C_5, so that intramolecular alkylation cannot occur. Since this argument was unconvincing to us, we have repeated Mukharji's work.

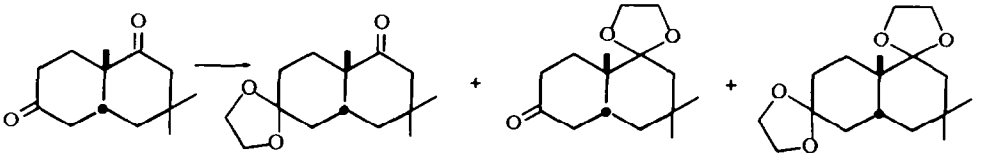
Trimethyloctalone **7** is hydrogenated in quantitative yield to a single trimethyldecalone (**8**). Previous work in these laboratories, by Mr. John Ellis, has shown that compound **8** is indeed a *cis*-decalone. The stereochemical proof, which will be communicated separately, involved conversion of **8** to a trimethyldecalin. This substance was compared with authentic samples of the *cis*- and *trans*-trimethyldecalins **9** and **10**. Thus Mukharji's initial stereochemical assumption is confirmed.



7 8 9

10

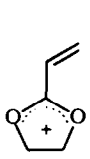
Compound **8** reacts with one equivalent of ethylene glycol in benzene, with β-naphthalenesulfonic acid, to give a mixture containing 80% of ketal **11**, 7% of ketal **12**, 7% of *bis*-ketal **13**, and 6% of unreacted starting material. The major ketal may be directly crystallized from this mixture in 40% yield. The mother liquors from this crystallization may be equilibrated with β-naphthalenesulfonic acid in refluxing



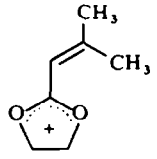
8 11 12 13

benzene. After such treatment, the mixture is again enriched in ketal **11**, and more of this material may be obtained by crystallization. Since Mukharji and Das Gupta did not succeed in crystallizing the major ketal, they were probably working with a mixture of **11**–**13**.

The structures of ketals **11–13** were unambiguously demonstrated by their mass spectra. The most prominent fragment in the spectrum of **11** is ion I *m/e* 99. Compound **12** gives a prominent fragment of *m/e* 127, corresponding to ion II *bis*-ketal **13** has major fragments of *m/e* 99 and *m/e* 127. This mode of fragmentation for ketals is well-documented.[3]

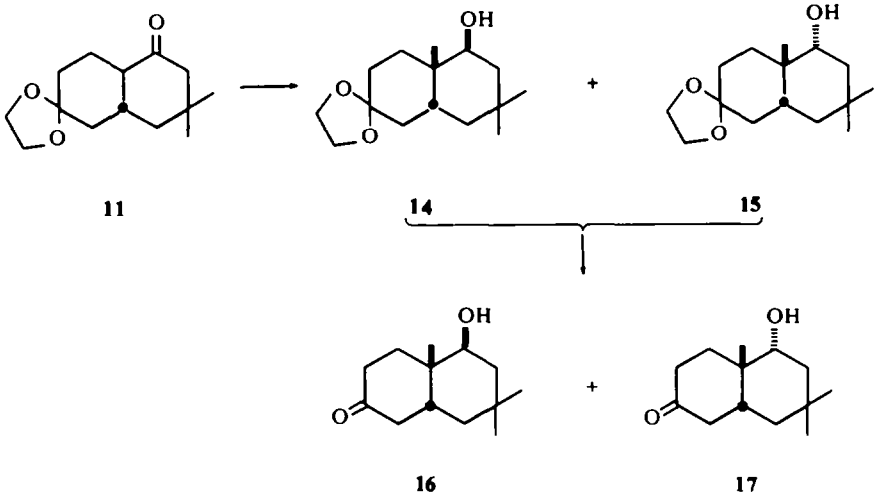


I



II

Sodium borohydride reduction of compound **11** gives a 1:1 mixture of two alcohols, subsequently identified as **14** and **15** (*vide infra*), in accord with Mukharji's second communication on the subject.[4] Although **14** and **15** could not be conveniently separated, the mixture of keto alcohols **16** and **17**, obtained by acidic hydrolysis, were separated by fractional crystallization from ethyl acetate–hexane. The less soluble isomer, compound **16**, melts at 138–139° and corresponds to the keto-alcohol used by Mukharji in his original work.[1] The more soluble isomer, compound **17**, melts at 117–118° and corresponds to Mukharji's second isomer.[4]



11 **14** **15** **16** **17**

Similar results are obtained when compound **11** is reduced with LAH in ether; compounds **16** and **17** are obtained in a ratio of 3:2 after hydrolysis. Compound **16** is obtained as the sole isomer when **11** is reduced with lithium tri-t-amyloxyaluminohydride[5] in THF. The lower melting keto alcohol, compound **17**, is produced as the major isomer (**16**:**17** = 1:10) when **11** is reduced with sodium and isopropyl alcohol in toluene.

Compound **16** gives a *p*-toluenesulfonate ester (**1**), which reacts with either potassium t-butoxide in t-butyl alcohol or methylsulfinyl carbanion in DMSO to give a mixture of two products, identified as tricyclic ketone **3** and octalone **18**.

Quantitative GLPC analysis indicates that compound **3** is formed in 43% yield. Octalone **18** is produced in approximately 10% yield. No other volatile products are formed.

The NMR spectra of compounds **3** and **18** (isolated by preparative GLPC) are shown in Fig. 1. Mukharji reports that his "cyclodecadienone" (**2**) has NMR bands at 9·04 τ (singlet), 8·85 τ (singlet), 8·15 τ (singlet) and "absorption between 4·7 and

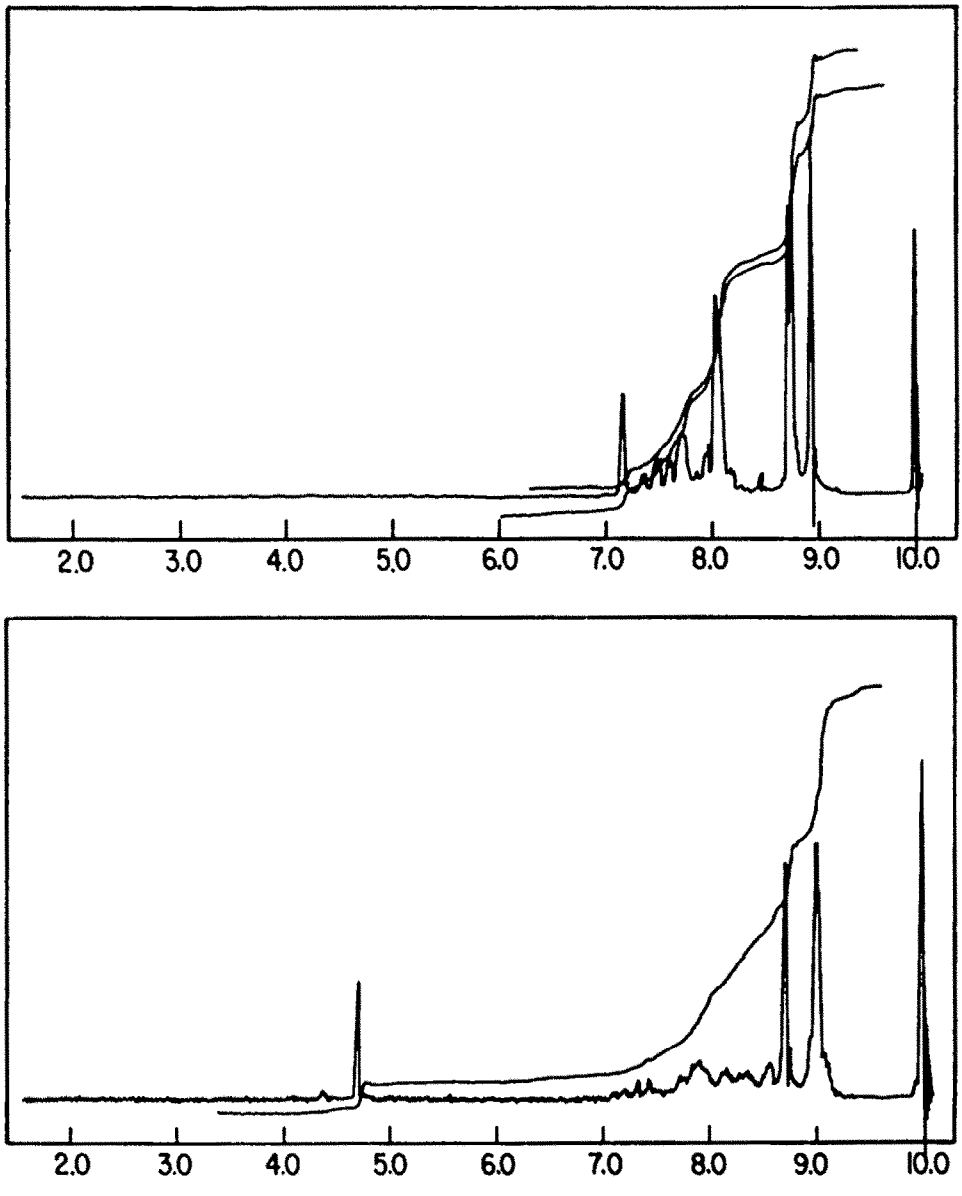
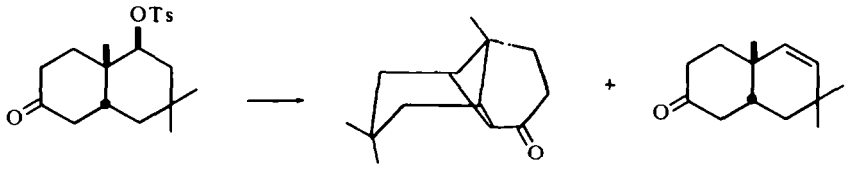


FIG 1. PMR spectra of compound 3 (top) and 18 (bottom)

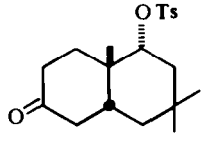
3·95 τ for vinyl hydrogens."[4] In all likelihood, these workers are referring to the NMR spectrum of a *mixture* of compounds **3** and **18**. The 2,4-dinitrophenylhydrazone (m.p. 174–175°) and the semicarbazone (m.p. 210–212°) of compound **3** correspond closely with the corresponding derivatives of Mukharji's "cyclodedecadienone" (reported, m.p. 178° and 218°, respectively).[1] The other evidence for structure **3**



3 **18**

reported by Mukharji (hydrogenation to 4,7,7-trimethylcyclodecanone,[1] oxidation to levulinic acid and β,β-dimethylgluraric acid[4]) remains obscure.

As expected, and as reported by Mukharji,[4] *p*-toluenesulfonate ester **19** is recovered unchanged after treatment with potassium t-butoxide or methylsulfinyl carbanion. The observed cyclization of compound **1** and the unreactivity of compound **19** argues well for the stereochemistry assigned to these isomers.



19

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on Perkin–Elmer 137 and 237 spectrophotometers. PMR spectra were taken on a Varian T-60 spectrometer. Chemical shifts are relative to internal TMS. Mass spectra were taken on either a Consolidated 21-103c or a Varian M-66 mass spectrometer. High resolution mol wt determinations were done on a Consolidated 21-110 spectrometer. Elemental analyses were performed by the microanalytical laboratory, operated by the Department of Chemistry, University of California, Berkeley, California 94720.

4a,7,7-Trimethyl-4,4a,7,8-tetrahydronapthalen-2(3H), 5(6H)-dione (**7**)

To a stirring soln of NaOMe in MeOH (15·8 g of Na dissolved in 220 ml abs MeOH) 5,5-dimethyl-1,3-cyclohexanedione (90 g, 0·64 mole) was slowly added. The mixture was stirred for 20 min, cooled to 0° and treated with iodomethane (190 g, 1·33 moles). Addition took 30 min after which the mixture was refluxed for 4 hr. The major portion of MeOH was removed under reduced press and the residue diluted with water and extracted with ether. The ether extract was extracted with 10% K_2CO_3 aq and the extract acidified to precipitate 2,5,5-trimethyl-1,3-cyclohexanedione. The dione was isolated by filtration, washed with water, dried and recrystallized from EtOAc–light petroleum to afford 27 g (28%) of product, m.p. 159–160°.

The above dione, (27 g, 0·18 mole), was added to a soln of methyl vinyl ketone (18·9, 0·27 mole) in abs methanol (200 ml). One pellet of KOH was added and the mixture stirred under reflux for 2 hr. The mixture was allowed to stand at room temp overnight after which excess methylvinyl ketone and the major portion of MeOH were removed under reduced pressure. The concentrate was dissolved in benzene, β-naphthalene-sulfonic acid (8 g) added, and this mixture refluxed until no more water was given off (Dean–Stark

apparatus). Water was added and the benzene layer separated and washed with dil $NaHCO_3$ aq, water, and brine and dried with $MgSO_4$. Removal of benzene followed by distillation at reduced pressure gave 27·2 g of product, b.p. 118–125°/0·3 mm, which was recrystallized from EtOAc–hexane to afford **7** (20 g, 54%) m.p. 91–92°; IR ($CHCl_3$) 1719, 1669, 1618, 1453, 1410, 969, 870 cm^{-1}; PMR (CCl_4) τ 9·21 (s, 3, Me), 8·85 (s, 3, Me), 8·55 (s, 3, angular Me), 4·20 (d, 1, vinyl H).

4aβ,7,7-*Trimethyl*-3,4,4a,7,8,8aβ-*hexahydronaphthalen*-2(1H), 5(6H)-*dione* (**8**)

In a typical preparation of **7** (10 g) in EtOAc (100 ml) over 10% Pd/C (0·2 g) was hydrogenated at room temp and atm press to afford, after recrystallization from EtOAc–hexane, **8** (9·6 g) m.p. 109–110°. The disappearance of IR bands ($CHCl_3$) at 1618, 969 and 870 cm^{-1} and PMR resonance at 4·20 τ is consistent with the conversion of **7** to **8**.

4aβ,7,7-*Trimethyl*-3,4,4a,7,8aβ-*hexahydronaphthalen*-2(1H), 5(6H)-*dione*, 2-*ethylene ketal* (**11**)

A mixture of **8** (9·5 g, 46 mmoles) ethylene glycol (3·2 g) and β-naphthalenesulfonic acid (0·5 g) in benzene (120 ml) was refluxed until no more water was given off, about 3 hr. The mixture was cooled and poured into a slurry of ice–10% $NaHCO_3$ aq. The organic layer was separated, washed with water and brine and dried with $MgSO_4$. Removal of benzene under reduced pressure afforded 11 g of a viscous oil. GLPC analysis (10′ × ¼″ SE-30 column operated at 220° with helium flow of 86 ml/min) showed that it contained four components in a ratio of 6:80:7:7 (order of elution). A sample of each material was collected and subjected to analysis. The first material to elute, 5 min, was identified as starting material, **8**. The second component (9 min) was identified as the desired ketal, **11**, m.p. 76–77°, by its fragmentation pattern in the mass spectrometer (see Text). The third material (11 min), m.p. 63·5–65° and fourth material (17 min), m.p. 88·5–90° were identified as **12** and **13**, respectively, through their fragmentation patterns in the mass spectrometer: Compound **12** exhibits an intense peak at *m/e* 127 and compound **13** at *m/e* 99 and *m/e* 127.

The desired ketal, **11**, was crystallized from light petroleum in about 40% yield. The mother liquor was then concentrated, dissolved in benzene containing β-naphthalenesulfonic acid (0·1 g) and refluxed for 1 hr. Work-up in the usual way gave a mixture enriched in **11** from which more of this ketal could be obtained; PMR (CCl_4) τ 9·18 (s, 3, Me), 8·95 (s, 3, Me), 8·30 (s, 3, angular Me), 6·12 (m, 4, ketal Hs). Calcd. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59%. (Found: C, 71·42; H, 9·58.)

5β-*Hydroxy*-4aβ,7,7-*trimethyl*-3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-2(1H)-*one* (**16**) *and* 5α-*hydroxy*-4aβ,7,7-*trimethyl*-3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-2(1H)-*one* (**17**)

(a) *Sodium borohydride reduction.* To compound **11** (2·4 g, 95 mmoles) in EtOH (50 ml) was added dropwise $NaBH_4$ (1·1 g) in EtOH (100 ml). The mixture was stirred at room temp overnight and then acidified with glacial AcOH (10 ml). Most of the EtOH was removed under reduced press and the residue diluted with water and extracted with ether. The ether extract was washed with water, dil $NaHCO_3$ aq, water and brine and dried with $MgSO_4$. The ether was removed under reduced press and the residue dissolved in methanolic–HCl (100 ml of 65% MeOH containing 8 ml conc HCl) and refluxed for about 3 hr. The mixture was diluted with water and extracted with ether. Work-up in the usual way gave 2 g of an oily product. GLPC analysis (3′ × ¼″ 10% Hyprose on 60/80 chromosorb P at 175°, helium flow about 200 ml/min) showed the presence of two components in approximately equal amount. Fractional crystallization from EtOAc–hexane gave two keto alcohols. The less soluble melted at 138–139°, and the more soluble at 117–118°. The higher melting epimer, compound **16**, has the shorter retention time, 12 min (by co-injection experiments); PMR ($CHCl_3$) τ 9·08 (s, 3, Me), 8·89 (s, 3, Me), 8·70 (s, 3, angular Me), 6·28 (m, 1, C<u>H</u>-OH). (Found: C, 74·32; H, 10·61. Calcd for $C_{13}H_{22}O_2$: C, 74·24; H, 10·54%).

The lower melting epimer, compound **17**, has a retention time of 14 min; PMR ($CHCl_3$) τ 9·10 (s, 6, HC(<u>Me</u>)$_2$), 8·69 (s, 3, angular Me), 6·31 (m, 1, C<u>H</u>OH). (Found: C, 74·62; H, 10·34. Calcd for $C_{13}H_{22}O_2$: C, 74·24; H, 10·54%).

(b) *Lithium aluminum hydride reduction.* To a stirred suspension of LAH (0·22 g) in ether (15 ml) **11** (1·5 g, 5·95 mmoles) in ether (25 ml) was slowly added. The mixture was stirred for 3 hr at room temp. Excess hydride was destroyed by the slow addition of methanolic–HCl to the mixture. Deketalization was then accomplished by refluxing the mixture for 1 hr. Work-up in the usual way gave 1 g of product which was found by GLPC to consist of epimers **16** and **17** in a ratio of 3:2.

(c) *Lithium tri-t-amyloxyaluminohydride*[5] *reduction.* To **11** (5 g, 19·7 mmoles) in THF (50 ml) was added dropwise lithium tri-*t*-amyloxyaluminohydride (10 g) in THF (150 ml). The mixture was stirred at room

temp overnight and worked up as in part (b). Gas chromatographic analysis of the crude material showed compound **16** to be the sole product. Crystallization from EtOAc–hexane gave pure **16** (2·5 g, 60%).

(d) *Dissolving metal reduction.* To a stirred refluxing mixture of toluene (100 ml) and Na (5 g), **11** (5 g) in isopropyl alcohol (40 ml) was added. The mixture was refluxed for 3 hr and the major portion of toluene removed by distillation. Excess Na was removed by filtration and the mixture extracted with ether. The ether extract was washed with dil $NaHCO_3$ aq, water and brine and dried with $MgSO_4$. Removal of the solvent under vacuum gave an oil which crystallized on standing. The IR spectrum of the crude product showed the absence of CO absorption. Deketalization and work-up gave product which was shown by GLPC to consist of **16** and **17** in a ratio of 1:10. Crystallization from EtOAc–hexane gave pure **17** (1·5 g, 36%).

4aβ,7,7-*Trimethyl*-5β-p-*toluenesulfonyloxy*-3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-2(1H)-*one* (**1**)

To **16** (2 g, 9·54 mmoles) in dry pyridine (20 ml) cooled to 0° was added slowly with stirring freshly recrystallized *p*-toluenesulfonyl chloride (1·9 g). The mixture was allowed to warm to room temp and was then stirred at this temp for 2 days. Excess *p*-toluenesulfonyl chloride was hydrolyzed by the addition of a few drops water, after which the mixture was stirred for several min. The mixture was then poured into a slurry of ice-conc HCl (20 ml HCl and about 20 g ice) and extracted with chloroform. The chloroform extract was washed with dil HCl, water, dilute $NaHCO_3$ aq, water and brine and dried with $MgSO_4$. Concentration under reduced pressure gave crude tosylate which was crystallized from EtOAc–hexane to afford **1** (2·3 g, 67%) m.p. 142–143°; PMR ($CDCl_3$) τ 9·19 (s, 3, Me), 9·04 (s, 3, Me), 8·82 (s, 3, angular Me), 7·58 (s, 3, aryl Me), 5·51 (t, 1, C-5H), 2·51 (A_2B_2 with τA 2·32 and τB 2·74, 4, aryl Hs). (Found: C, 65·65; H, 7·77. Calcd for $C_{20}H_{28}O_4S$: C, 65·92; H, 7·74%).

4aβ,7,7-*Trimethyl*-5α-p-*toluenesulfonyloxy*-3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-2(1H)-*one* (**19**)

In a typical preparation (as described above) **17** (1·5 g, 7·3 mmoles) in dry pyridine (20 ml) was treated with *p*-toluenesulfonyl chloride (1·5 g) to afford **19** (1·7 g, 64%), m.p. 168–169° (dec); PMR ($CDCl_3$) τ 9·18 (s, 3, Me), 9·11 (s, 3, Me) 8·98 (s, 3, angular Me), 7·57 (s, 3, aryl Me), 5·38 (t, 1, C-5 H), 2·38 (A_2B_2 τA 2·15 and τB 2·63, 4, aryl Hs). (Found: C, 65·68; H, 8·01. Calcd for $C_{20}H_{28}O_4S$: C, 65·92; H, 7·74%).

1,4,4-*Trimethyltricyclo*[4.4.0.$0^{2,7}$]*decan*-8-*one* (**3**)

(a) *Sodium hydride in dimethyl sulfoxide.* A soln of methylsulfinyl carbanion in DMSO was prepared from 38·2 mg, 56·8% NaH emulsion (washed with pentane) and DMSO (7 ml). To the stirred soln, under N_2 at 75°, was added in one portion a warm soln of 330 mg of **1** in DMSO (10 ml). The orange soln was stirred at 75° for 3 hr, cooled, poured into 100 ml ice–water and extracted with ether. The ether extract was washed with water and dried with $MgSO_4$. Removal of the ether gave an oil which was found by GLPC (5' × ¼" FFAP on 60/80 chromosorb P operated at 158°, helium flow 60 ml/min) to consist of two components. A sample of each was collected and analyzed (the PMR spectra of the collected material and crude material was the same, indicating that secondary reactions on the column had not occurred). The first material to elute (5 min) had spectra (PMR and IR) consistent for compound **18**: PMR ($CDCl_3$) (Fig I); IR (film) 1718, 1645, 1460, 1412, 1355, 1221, 769 cm^{-1}. The second component (8 min) was identified as compound **3** by its PMR spectrum which is quite similar to that of the related tricyclic ketone **5**;[2] PMR ($CDCl_3$) τ (Fig I); IR (film) 1724, 1468, 1445, 1370, 1250, 1163, 1086, 1029, 961, 900 cm^{-1}. (Found: 192·15 (mass spectrum). Calcd for $C_{13}H_{20}O$; mol wt 192·29).

The 2,4-dinitrophenylhydrazone derivative of **3** melted at 174–175° after two recrystallizations from EtOH–chloroform. (Found: C, 61·07; H, 6·50; N, 14·93. Calcd for $C_{19}H_{24}N_4O_4$: C, 62·9; H, 6·45; N, 15·06%).

The semicarbazone of **3** melted at 210–212° after recrystallization from 95% EtOH.

Quantitative GLPC analysis (after continuous extraction of the reaction products (from another run) with ether for 18 hr using propiophenone as the internal standard and employing the cutting and weighing method indicated **3** was produced in 43% yield and **18** in approximately 10% yield.

(b) *Potassium* t-*butoxide in* t-*butyl alcohol.* To K (78 mg, 2 mmoles) dissolved in t-BuOH (20 ml) under N_2 was added a warm soln of **1** (750 mg, 2·1 mmoles) in t-BuOH. The soln was stirred at 90° for 4 hr, cooled, poured into water (120 ml) and extracted with ether. The ether extract was washed several times with water, brine and dried with $MgSO_4$. Evaporation of the ether under reduced press afforded an orange oil (400 mg) which on gas chromatographic analysis revealed the presence of **18** and **3**.

Reaction of tosylate **19** *with base.* Compound **19** when treated, as described above with either methylsulfinyl carbanion or t-butoxide was recovered unchanged.

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