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A TRANSANNULAR REACTION DURING LITHIUM AMMONIA REDUCTION OF AN α,β-UNSATURATED KETONE

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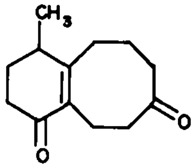
Abstract—The lithium-ammonia reduction of the α,β-unsaturated bicyclic dione 2-methyl-$\Delta^{1,6}$-bicyclo[6,4,0]cyclododecene-5,9-dione **1** has been found to give two isomeric products 2α-methyl-5-oxo-6β-tricyclo[6,4,0,$0^{1,9}$]dodecan-9-α-ol **2** and 2-β-methyl-5-oxo-6β-tricyclo[6,4,0,$0^{1,9}$]dodecan-9α-ol **3** involving a trans-annular reaction. Chemical and spectral evidence are presented to support the assigned structures. The stereochemistry of **2** and **3** is also discussed.

"Transannular Reactions" in medium ring systems is a well documented phenomenon.[1] Earlier work from our laboratory[2] led to the formation of a ring-enlarged product, 2-methyl-$\Delta^{1,6}$-bicyclo[6,4,0]dodecene-5,9-dione **1**, and it was of interest to study its reduction with lithium in liquid ammonia.



1

Silica gel chromatography of the liquid product gave two products (35% yield), one, **2**, melting at 87°C, and another, **3**, at 109°C. IR absorptions were almost identical and showed absorptions for OH at 3570 cm^{-1} and CO at 1700 cm^{-1}. NMR showed a doublet due to the CH_3 group at δ 0.95 for **2** and at δ 1.2 for **3**. Besides this a broad triplet at δ 2.8 was also seen for **3**. Exchange with D_2O was found to be rather slow, the HOD peak being weak even after 24 h. Compounds **2** and **3** were shown by mass spectrometry to have a molecular weight of 208 indicating the addition of two hydrogens and thus were isomeric. The fragmentation pattern was found to be almost identical for both the compounds. The tertiary nature of the OH function in both **2** and **3** was indicated by the failure to convert them to a mesylate or tosylate under usual conditions. However, both **2** and **3** formed a methoxalyl derivative.

The above observations indicate that the OH function results by a transannular reaction of the allyl ion radical with the CO in the 8-membered ring. This is in accordance with the 1,5-disposition of the anion radical and the CO function. The proposed mechanism is depicted in Chart 1.

The Dreiding model of **1** showed clearly the proximity of the C atoms C_1 and C_9 and prompted study of the reactions detailed in Chart 2.

The mesylate **4** showed in the NMR spectrum the characteristic downfield shift at δ 2.9 due to the CH_3 group of $-O-SO_2-CH_3$. Reduction with lithium in liquid ammonia gave a liquid product with a molecular weight of 192 as found from the mass spectrum. The NMR spectrum showed significantly the absence of the downfield CH_3 signal and also of olefinic protons. The above data again implies a transannular displacement of the mesyl group by the intermediate β-carbanion.

Two approaches were made to establish the presence

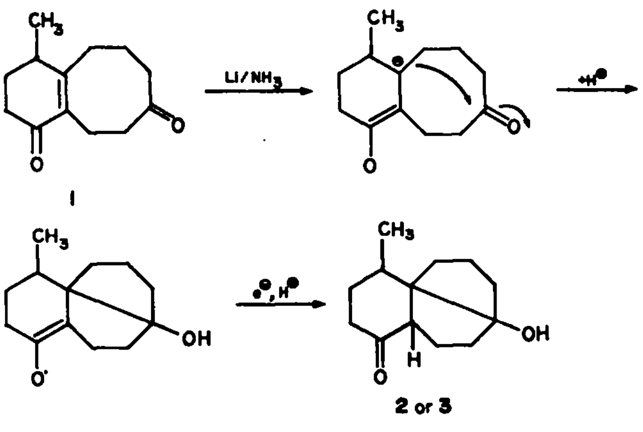


Chart 1.

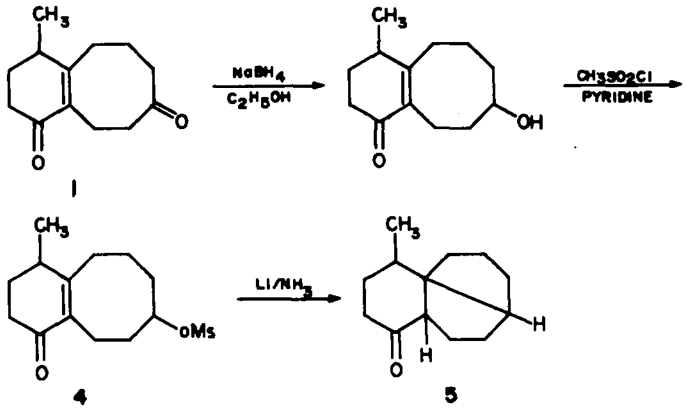


Chart 2.

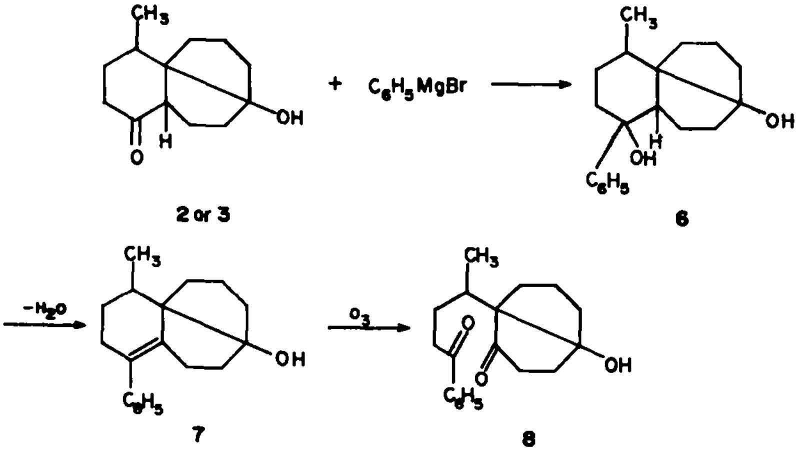


Chart 3.

of a bicyclo[3,3,0]octane system in the products. The first is the second order Beckmann transformation of the oximes of 2 and 3. The reaction, however, failed to give a nitrile but lactams were obtained as evidenced by IR spectra.

The second approach involved the cleavage of ring A as depicted in Chart 3.

The formation of a product of the type 8, it was expected should be readily identified. Compound 2 underwent this sequence of reactions and the final product 8 showed a CO frequency at 1740 cm^{-1} thereby confirming the presence of a bicyclo[3,3,0]octane system. Compound 3 however failed to undergo the Grignard reaction probably due to structural features which will be apparent from a discussion of the stereochemistry of compounds 2 and 3.

Treatment of either of the compounds 2 and 3 with base or acid under equilibrating conditions resulted only in the respective starting materials being recovered indicating that the compounds do not differ in the orientation of the methine hydrogen at C_6. Since the most stable mode of fusion of a 6-membered ring with a 5-membered ring is *cis*, the hydrogen at C_6 and the C_1–C_{12} bond must be *cis* to each other. Since the compounds are not epimeric at C_6, they can differ in stereochemistry only at C_1, C_2 and C_9. It is known that *cis* fusion of two 5-membered rings represents a very stable arrangement as compared to a *trans* fusion. In both compounds 2 and 3 rings B and C must therefore be *cis* fused with the C_9–OH group and the C_1–C_2 bond on the same side of a common plane—both above or below. In other words, the compounds probably do not differ in stereochemistry at C_1 and C_9 and are epimeric only at C_2.

From the known mode of protonation of an enolate ion, the proton at C_6 must necessarily occupy an axial position. The overall stereochemistry of the compounds could be represented as follows:

Table 1.

Compound	C_2	C_4	C_5	C_9	C_1	C_6	C_{13}
2	—	43.602 (t)	213.81 (s)	91.237 (s)	61.037 (s)	61.037 (d)	16.689 (q)
3	36.63 (d)	42.284 (t)	212.54 (s)	90.229 (s)	60.037 (s)	60.637 (d)	16.113 (q)

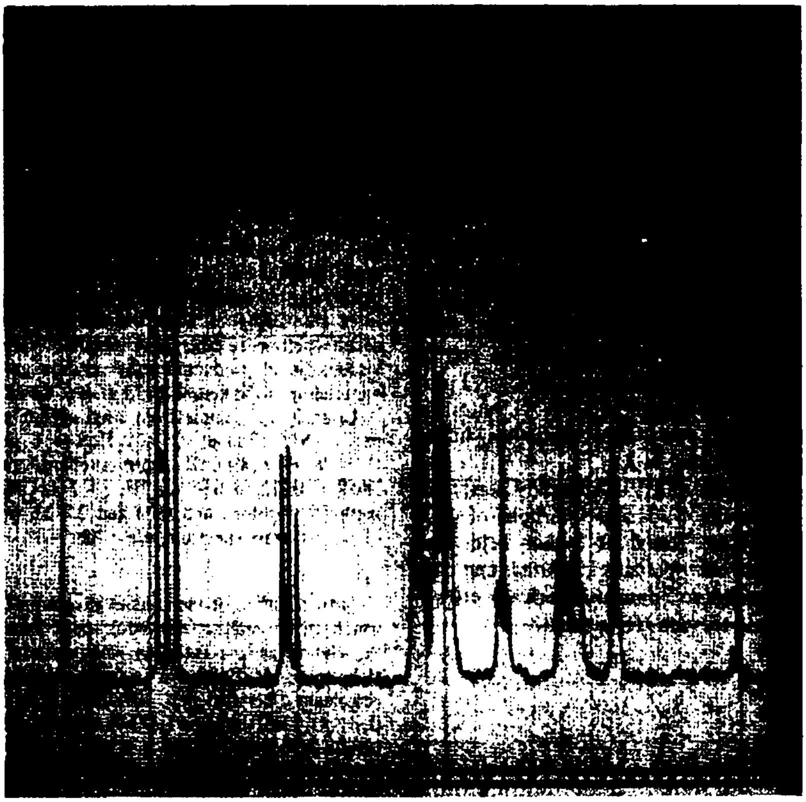


Fig. 1. Compound 2.

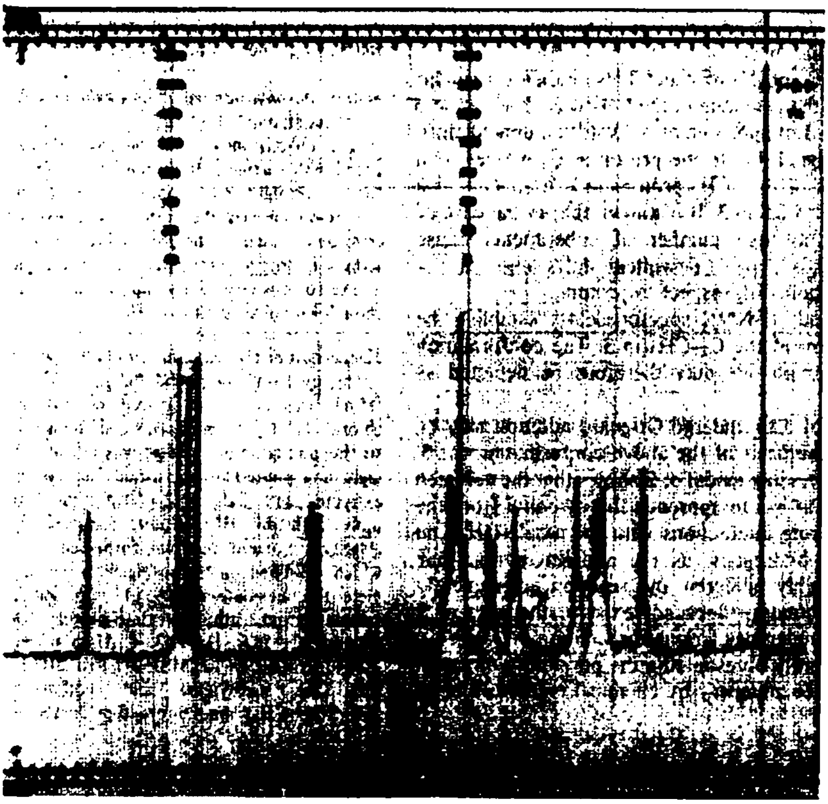
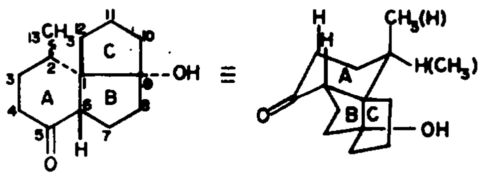


Fig. 2. Compound 3.

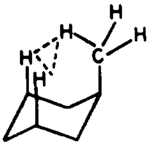


2 or 3

It was found very difficult to establish the stereochemistry at C_2 by chemical methods; so the completely decoupled and off-resonance ^{13}C-NMR spectra of both the compounds were analysed. The ^{13}C-chemical shifts for 2 and 3 are given in Table 1 (see also Figs. 1 and 2).

It is difficult to assign the chemical shift of C_2 in 2 as it merges with a group of multiplets (Fig. 1) but it is significant that the doublet due to this carbon has shifted downfield as compared to that in 3.

It is known that chemical shifts of sterically perturbed carbon atoms (such as the 1-, 3- and 5-carbons of axial methyl cyclohexanes) are found at higher field than similar carbon atoms not spatially crowded and this upfield difference amounts to 5 ppm. All sterically crowded groups can give rise to such steric shifts.



The small chemical shift difference (1 ppm) is significant and may be assumed to indicate an *axial* orientation of the CH_3 group in 3. The chemical shift of carbon atom C_{13} in 3 itself is 0.57 ppm upfield as compared to that in 2.

The ^1H-NMR spectra of 2 and 3 also indicate a similar situation. In 2 the peak due to the CH_3 was observed at δ 1.12 (d) and in 3, it appeared at δ 0.95(d) an upfield shift. Further, the signal due to the proton at C_6 merges with the broad peak of the $-CH_2$ protons in 2, it appears as a broad triplet at δ 2.8 in 3. It is known that in the case of cyclohexanes, a large number of substituents cause pronounced (0.3–0.5 ppm) downfield shifts when in 1,3-diaxial orientation with respect to protons.

Both ^{13}C- and ^1H-NMR spectra clearly establish the axial orientation of the C_2–CH_3 in 3. The conformation of the two compounds may therefore be depicted as indicated.

The failure of 3 to undergo Grignard addition may be explained on the basis of the above conformation for 3. A study of a Dreiding model of 3 shows that the solvated Grignard reagent has to approach the carbonyl from the top side involving interactions with the axial $-CH_3$ and the two axial hydrogens, as the alternative rear side approach is highly hindered and reaction consequently fails. Such a situation does not exist in the case of 2 which readily undergoes Grignard reaction.

We are currently investigating the possibility of establishing the stereochemistry by chemical methods and by X-ray analysis.

EXPERIMENTAL

Lithium-ammonia reduction of 2-methyl-$\Delta^{1,6}$-bicyclo[6.4.0]dodecene-5,9-dione 1

(a) *At* −33°C. In a 1 l. 3-necked flask fitted with a mechanical stirrer, a gas inlet tube and an outlet tube protected from atmospheric moisture, ammonia (300 ml) was collected. Lithium metal (1.4 g, 0.2 g atom) was added in the form of foils during 30 min with stirring. A solution of the bicyclic enedione 1 (20.6 g, 0.1 mole) in dry ether (100 ml) was added slowly with stirring during 20 min and stirring continued for another 45 min. The reaction mixture was quenched with solid NH_4Cl (5 g). The solution was poured into a large dish and ammonia allowed to evaporate. To the residue, water (50 ml) was added and extracted with ether (3 × 75 ml). The combined ether extract was washed with water and dried ($MgSO_4$). Solvent removal yielded a viscous liquid product (19 g), tlc analysis (silica gel 20% ethyl acetate-petrol) showed four spots. This liquid was chromatographed over silica gel (20 g/g of liquid material). Elution with 20% ethyl acetate–petroleum ether gave initially a very small amount of a viscous liquid product. Further elution gave a colorless solid material, tricyclic ketone 2 (3.1 g) m.p. 82–84°C.

An analytical sample from ethyl acetate-petroleum ether had m.p. 86–87°C (Found: C, 75.01; H, 9.34. $C_{13}H_{20}O_2$ (208) requires: C, 74.96; H, 9.68%). IR spectrum (chloroform): 3570, 1700 cm^{-1}; NMR ($CDCl_3$): δ 0.95 (d, 3H, J = 7 Hz CH_3), 1.4–2.2 (m, 13H, methylene protons and OH) and 2.3–2.6 (m, 4H, methine and $-\underset{\overset{\|}{O}}{C}-CH_2$); mass spectrum *m/e* = 208.

Further elution of the column gave a pale yellow liquid (12 g) which on tlc analysis showed 3 spots. Proceeding further with the elution gave a colorless solid material, tricyclic ketone 3 (3.2 g) m.p. 104–106°C. An analytical sample from ethyl acetate-petroleum ether had m.p. 108–109°C (Found: C, 74.85; H, 9.4. $C_{13}H_{20}O_2$ (208) requires: C, 74.96; H, 9.68). IR Spectrum (chloroform): 3570 and 1700 cm^{-1}; NMR($CDCl_3$/TMS): δ 1.1 (d, 3H, J = 7 Hz CH_3), 1.2–2.6 (m, 17H), mass spectrum *m/e* = 208. Further elution with the same solvent did not yield any material.

(b) *At* −78°C. The bicyclic enedione 1 (4.12 g, 0.02 mole) was treated with lithium metal (280 mg) dissolved in ammonia (200 ml). The solution was cooled to −78° and stirring continued for 45 min at this temperature. Workup of the reaction mixture as before gave a viscous liquid product (3.8 g). Chromatography of this liquid over silica gel afforded the tricyclic ketones 2 (0.6 g) and 3 (0.7 g) and a liquid product (2.2 g).

Sodium borohydride reduction of the bicyclic enedione 1

The compound 1 (4.12 g, 0.02 mole) was dissolved in 95% ethanol (50 ml) and sodium borohydride (0.33 g, 0.01 mole) was added with stirring at 0° during 20 min. The reaction mixture was stirred overnight and decomposed with acetic acid (2 ml). Solvent was removed and the residue was extracted with methylene chloride (2 × 50 ml). The organic layer was washed with saturated sodium hydrogen carbonate, water and dried ($MgSO_4$). Evaporation of solvent yielded a syrupy liquid product (3.8 g), found pure enough for subsequent reactions.

Conversion of the reduction product to the mesylate 4

The hydroxy compound (6.9 g, 0.033 mole) in dry pyridine (15 ml) was cooled in a freezing mixture. Methane sulfonyl chloride (11.4 g, 0.1 mole) was added during 20 min with magnetic stirring and reaction mixture was left at room temperature overnight and poured onto crushed ice. The aqueous solution was extracted with CH_2Cl_2 (2 × 50 ml), the extract washed sequentially with dil. HCl, water, bicarbonate solution and dried ($MgSO_4$). Solvent removal furnished a glassy liquid product which solidified on triturating with petrol under ice cooling to yield the mesylate 4 (4.95 g), m.p. 105–107°C. An analytical sample from ethyl acetate–petrol had m.p. 113–114°C (Found: C, 58.6, H, 7.43. $C_{14}H_{22}SO_4$ requires: C, 58.73; H, 7.74%). NMR($CDCl_3$/TMS): δ 1.1 (d, 3H, J = 7 Hz, CH_3), 1.4–2.8 (m, 15H, methylenes and methine protons), 2.95 (s, 3H—SO_2—CH_3) and 4.6 (broad peak, 1H, $-\underset{\underset{H}{|}}{C}-O-SO_2-CH_3$).

Lithium-ammonia reduction of mesylate 4

The mesylate 4 (3.53 g, 0.0125 mole) in dry THF (30 ml) was added in portions with stirring to a solution of lithium metal

(150 mg) in liquid ammonia (300 ml) during 20 min. The reaction mixture was stirred for a further period of 1 h and quenched with NH$_4$Cl (2 g). Ammonia was allowed to evaporate, residue treated with water and extracted with ether (2 × 75 ml). The ether layer was once washed with water and dried (MgSO$_4$). Solvent was distilled to give a viscous liquid (2 g) which on tlc (silica gel, 20% ethyl acetate–petrol) showed 4 spots. This was chromatographed on silica gel, elution with petrol gave a clear viscous liquid **5** (1.1 g), found to be homogeneous on tlc. IR(Chloroform): 1700 cm^{-1}; NMR(CDCl$_3$/TMS): δ 1.0 (d, 3H, J = 7 Hz, CH$_3$), 1.2–2.0 (broad m, 13H, methylene protons) and 2.2–2.7 (broad m, 4H, $-\underset{\underset{O}{\|}}{C}-CH_2$ and methine protons); mass spectrum $m/e = 192$.

Addition of phenylmagnesium bromide to compound **2**

To a solution of phenylmagnesium bromide in ether (from 0.19 g of Mg and 1.36 g of bromobenzene) was added the tricyclic ketone **2** (0.624 g) in ether in portions during 15 min with magnetic stirring. The reaction mixture was stirred overnight and decomposed with saturated ammonium chloride. Ether layer was separated and aqueous solution was extracted with ether. The combined ether extracts were worked up to yield a solid phenyl carbinol **6** (0.367 g) m.p. 194–196°C (ethyl acetate-petrol). (Found: C, 79.37; H, 9.48. C$_{19}$H$_{26}$O$_2$ requires: C, 79.72, H, 9.01%). Mass spectrum $m/e = 286$.

Dehydration of phenyl carbinol **6** *to the olefin* **7**

The phenyl carbinol **6** (0.2 g) was refluxed with toluene-*p*-sulfonic acid (20 mg) in dry benzene for 30 min using a Dean–Stark trap. The reaction mixture was cooled, washed with water and dried (MgSO$_4$). Benzene was removed by distillation to give the olefin **7** (0.14 g) as a clear brown liquid. The liquid was found to be pure on tlc analysis and was used as such for subsequent reactions.

Ozonolysis of the olefin **7**

A solution of the olefin **7** (0.14 g) in dry ethyl acetate (50 ml) was cooled to 0° and ozonised oxygen was bubbled for 25 min. Solvent was distilled under reduced pressure, water (10 ml) was added and heated on a steam bath for 30 min. The reaction mixture was cooled and extracted with CH$_2$Cl$_2$ (25 ml), dried (MgSO$_4$) and concentrated to yield a viscous liquid (0.1 g). Trituration with ether gave the hydroxy diketone **8** (90 mg) m.p. 192–193°C (ethyl acetate–petroleum ether). (Found: C, 76.15; H, 7.93. C$_{19}$H$_{24}$O$_3$ requires: C, 76.0; H, 8.0%). IR(KBr): 1740, 1670 cm^{-1}; NMR(CDCl$_3$/TMS): δ 0.6 (d, 3H, J = 7 Hz, CH$_3$), 1.0–2.0 (broad multiplet, 10H-methylenes and OH), 2.0–2.5 (a narrow multiplet, 4H, $-\underset{\underset{O}{\|}}{C}-CH_2$), (a broad multiplet centred at 3.6, 1H, methine proton), (a narrow multiplet centred at 7.5, 3H, ArH), (multiplet centred at 8.0, 2H, two protons ortho to $-\underset{\underset{O}{\|}}{C}-$group).

The mass spectrum had m/e at 300.

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