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AN UNUSUAL 1,4-BRIDGING IN A CYCLOHEXANE RING VIA AN ACETYLENIC FUNCTION

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Abstract—A new structure (IV) containing a bicyclo[2,2,2]octane skeleton is discussed for an isomeric compound first reported by Nazarov during an attempted hydration of the ethynyl alcohol (I).

NAZAROV and Gurvich[1] reported that treatment of the ethynyl carbinol I, m.p. 172–173°, with mercuric sulphate in methanol furnished in 25% yield an isomeric compound, m.p. 122–123°, for which they assigned structure III.

Authentic III (m.p. 97–98°) has however been synthesized[2] via a Rupe reaction on I or better on either of the diacetates of I or II. This communication presents evidence in favour of a new structure IV for Nazarov's compound.

Using borontrifluoride–mercuric oxide catalyst[3] we have improved the yield of Nazarov's compound to 55–60% from I.[4]

Treatment of I with borontrifluoride etherate in the *absence* of mercuric oxide does not furnish the above product but only a mixture of epimers I and II. In the preparation of Nazarov's compound, anhydrous potassium carbonate is used to neutralize the medium at the end of the reaction; it was suspected that this reagent

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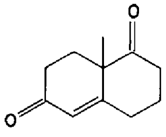
[1] I. N. Nazarov and I. A. Gurvich, *Zh. Obsch. Khim.* **25**, 1723 (1955).

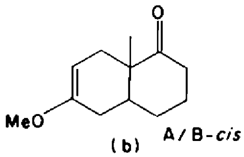
[2] M. S. Newman, S. Ramachandran, S. K. Sankarappa and S. Swaminathan, *J. Org. Chem.* **26**, 727 (1961).

[3] G. F. Hennion, D. B. Kilian, T. H. Vaughn and J. A. Nieuwland, *J. Amer. Chem. Soc.* **56**, 1130, 1384 (1934).

[4] I. N. Nazarov and I. A. Gurvich [*Zh. Obsch. Khim.* **25**, 956 (1955)] have assigned the α-hydroxy structure to the ethynyl carbinol, m.p. 172–173°, but we prefer the β-hydroxy structure I for the following reasons: The —OH peaks in the NMR spectra for I and II occur respectively at 7·44 and 7·55τ at room temperature and 7·50 and 7·61τ when heated to 50–60° and spectrum run while cooling for a 5% solution in chloroform. This evidence indicates that the —OH in II is subject to greater steric hindrance, is axial and hence α (*trans* to the angular methyl group). A further factor in favour of our assignment is the position of the angular methyl group which occurs at 8·689τ (±0·003) in I and at 8·603τ (±0·003) in II. The methyl *cis* to —C≡CH may be expected to show up at lower fields due to paramagnetic anisotropy alongside the triple bond. Nazarov's assignment is based on a reported difference in the mode of addition of metal acetylides to the ketones (a) and (b).

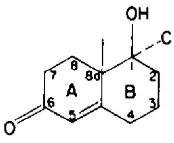


(a)



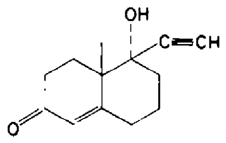
(b)

While we agree that the mode of addition is obviously opposed to each other in the case of (a) and (b), we believe (b) may have given the α-hydroxyethynyl alcohol and not the β-hydroxy compound as is assumed by Nazarov.



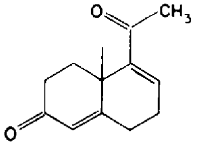
I

(m.p. 172–173°)

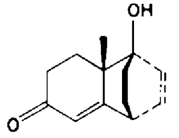


II

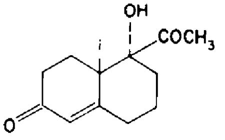
(m.p. 184–185°)



III



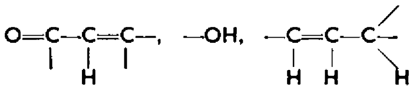
IV



V

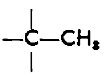
might have caused side reactions of the type encountered[5] with vinylogous β-hydroxyketones of the type I or II. However, the compound could be obtained by omitting the neutralization step during work-up. Nazarov's compound is unaffected by treatment with (i) aqueous alcoholic potassium hydroxide; (ii) sodium ethoxide in ethanol; (iii) palladized charcoal in refluxing *p*-cymene; (iv) *p*-toluenesulphonic acid in benzene; (v) hydrogen bromide in acetic acid and (vi) chromic acid—the starting material being recovered in all the cases. The compound furnishes a monoacetyl and a monobromoacetyl derivative,[6] while reduction with lithium in liquid ammonia affords a dihydro compound. Two tetrahydro derivatives have been obtained[1] under other conditions by Nazarov who has formulated them on the basis of the erroneous structure III. As reported earlier,[2] Nazarov's compound has $\lambda_{\max}^{\mathrm{EtOH}}$ 257 mμ (ϵ, 11,000) indicative of the presence of an α,β-unsaturated carbonyl unit, even though the shift in $\lambda_{\max}$ from 242 mμ—characteristic of the starting material I—is significant. The IR absorptions indicate absence of —C≡C— and while confirming the presence of $O{=}\overset{|}{C}{-}\overset{|}{C}{=}\overset{|}{C}{-}$, reveal the presence of an —OH group. This is substantiated by the preparation of the acetyl derivatives which do not show, as expected, hydroxyl absorption in the IR but retain the UV absorption at 257 mμ characteristic of the parent compound. However, the formation of only a *monoacetyl* derivative is in sharp contrast to the behaviour of I and II which under identical acid catalysed acetylating conditions give[2] the corresponding diacetates inclusive of an enol acetate function. This difference in behaviour is probably because of hindrance to enolization of the enone moiety in ring A.

The NMR data[7] require the presence of the following groups:



$$O{=}\underset{|}{C}{-}\underset{\underset{H}{|}}{C}{=}\underset{|}{C}{-},\quad -OH,\quad -\underset{\underset{H}{|}}{C}{=}\underset{\underset{H}{|}}{C}{-}C\begin{smallmatrix}/\\ -\\ \diagdown H\end{smallmatrix}$$

and



$$-\overset{|}{\underset{|}{C}}{-}CH_3$$

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[5] S. Swaminathan, J. P. John and S. Ramachandran, *Tetrahedron Letters* 729 (1962).

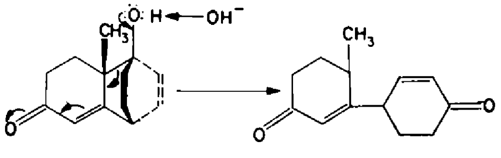
[6] X-ray structure studies on this derivative have been undertaken by Dr. K. Venkatesan, Dept. of Physics, University of Madras.

and also confirm that the —OH group is tertiary as indicated by its stability to chromic acid. Interpretation of the evidence summarized so far points to structure IV[8] for Nazarov's compound. The proximity of the two double bonds and the fact that the double bond in ring A is exocyclic to two rings may possibly account for the shift in the UV maximum to 257 mμ. Structure IV represents the first instance known to us of a bicyclo[2,2,2]octane derivative formed by internal bridging of 1,4-carbon atoms of a cyclohexane ring via an acetylenic linkage.

Compound IV results apparently by a buckling of the C_4 methylene in I to give the boat configuration for ring B followed by its linking with the two-carbon unit at C_1—present either as an acetylenic linkage or suitably transformed. This process, if correct, means that the angular methyl must be on the side opposite to that containing the olefinic bridge and pointing away from it as indicated in IV. Interestingly enough, the epimer II when treated with Nieuwland's catalyst does not lead to any similar isomeric product but only to the normal product (V) of hydration of the triple bond. An examination of a model shows that the formation of an olefin bridge is conceivable also in the case of II; a buckling of C_1 in II can make ring B take up the boat configuration and simultaneously bring the equatorial two-carbon unit within reach of the C_4 methylene to make linking possible—the angular methyl now becoming *cis* to the olefin bridge. The isolation of only V probably means that while the catalyst,[9] $Hg(OCH_3 \cdot BF_3)_2$ effects normal hydration of the equatorial triple bond in II, its action on the less readily accessible axial triple bond in I is different and leads to the abnormal product IV.

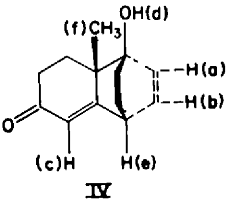
As for the actual mechanism of formation of IV, two routes seem possible; one involving an abnormal hydration of I to a β-hydroxy aldehyde followed by an aldol condensation with the active methylene at C_4 and subsequent dehydration. The difference in behaviour between I and II seems however to favour a direct nucleophilic attack (catalysed by Hg^{2+}) of the terminal carbon of the acetylenic bond by the C_4 methylene which no doubt is activated vinylogously by the co-ordination of the oxygen of the carbonyl group at 6 with borontrifluoride or Hg^{2+}.

The surprising stability to alkali of Nazarov's compound requires comment, especially since the vinyl alcohols obtained by the selective reduction of the triple bonds in I and II have been shown[5] to undergo cleavage of ring B followed by recyclization. The conversion of IV to VI pictured below seems *a priori* plausible:



IV VI

The NMR proton signals ($CHCl_3$) are as follows:



IV

a, 4·00; b, 3·65; c, 4·40; d, 6·15; e, 6·80; f, 8·70τ.

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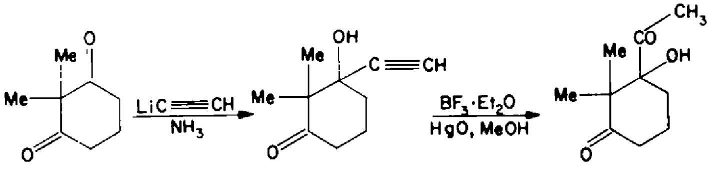
[8] This structure was originally suggested to us by Dr. K. Nagarajan.

[9] L. A. O'Leary and H. H. Wenzke, *J. Amer. Chem. Soc.* **55**, 2117 (1933).

However for this fragmentation reaction to occur, the atoms involved would be required to be coplanar which is obviously impossible in structure IV.

With a view to determine the structural requirements for the unusual reaction leading to Nazarov's product, it was of interest to study the reaction of VIII with Nieuwland's catalyst.



VII VIII IX

There was no evidence of formation of any bicyclooctane derivative similar to IV and only the normal hydrated product IX was obtained. Apparently, the eneone unit in I plays an important part in the formation of IV. Work on degradation and an unequivocal synthesis of IV is in progress.

EXPERIMENTAL

Nazarov's compound

*1β-Hydroxy-6-oxo-*8a-*methyl-*1,2,3,4,6,7,8,8a-*octahydro-*1α,4α-*ethenonaphthalene* (IV). A solution of I (10 g) in methanol (75 ml) was stirred at 60° for 6 hr with Nieuwland's catalyst prepared from red mercuric oxide (1·3 g), borontrifluoride etherate (1·5 ml) and methanol (1·5 ml). The mixture was cooled, treated with anhydrous K_2CO_3 (10 g) and decanted from the sludge of mercury and undissolved matter. The methanol was removed, the residue treated with water (15 ml) and extracted with two successive portions of ether and chloroform. The combined extract was dried ($MgSO_4$) and concentrated to dryness. Trituration with ether furnished a colourless solid (5·5–6·1 g), m.p. 116–120°. Two crystallizations from ether afforded pure IV, m.p. 124·5–126°. The material had IR absorptions identical with those of a sample prepared by the method of Nazarov.[1] $\lambda_{\max}^{\mathrm{EtOH}}$ 257 mμ (ε, 11,000). IR peaks (KBr) at 2·86 (s), 3·33 (w), 6·1 (s), 6·25 (m), 7·35 (m), 7·5 (m), 8·22 (s), 8·7 (s), 11·82 (s) and 14·0 μ (s). No absorptions for acetylenic hydrogen and —C≡C—

The above experiment was carried out without mercuric oxide. A mixture of solids (m.p. 128–145°) separable by chromatography into I and II was recovered in 70% yield. Compound IV could also be obtained if the treatment with K_2CO_3 was omitted.

Acetyl derivative of IV. A mixture of IV (1 g), acetic anhydride (7 ml) and *p*-toluenesulphonic acid (catalytic amount) was left overnight at room temp. On pouring the mixture into ice, an oil separated which solidified on standing. It was crystallized from ethanol m.p. 122–123°; $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (ε, 15,000). Analytical and IR data reported earlier.[2]

Bromoacetyl derivative of IV. A mixture of IV (2 g), bromoacetyl bromide (2 ml), pyridine (0·8 ml) and dry benzene (50 ml) was refluxed for 2 hr. The mixture was cooled, treated with dil. HCl (20 ml) and the benzene layer separated, washed ($NaHCO_3$ aq.) and concentrated to give 2·4 g solid. Three crystallizations from a mixture of ethyl acetate and ether furnished crystals, m.p. 132–133°. (Found: C, 55·8; H, 5·4; Br, 25·3. $C_{15}H_{17}O_3Br$ requires: C, 55·4; H, 5·3; Br, 24·6%.) $\lambda_{\max}^{\mathrm{EtOH}}$ 254 mμ (ε, 17,300). IR peaks ($CHCl_3$) at 5·75 (m), 6·01 (s), (7·25 μ (w) and no —OH absorption.

1α-*Hydroxy-*1β-*acetyl-6-oxo-*8a-*methyl-*1,2,3,4,6,7,8,8a-*octahydronaphthalene* (V). Treatment of II (1 g) with Nieuwland's catalyst, as described for I, furnished 0·33 g crude solid, m.p. 118–122°. The analytical sample was obtained after 5 crystallizations from ether, m.p. 133–133·5°. (Found: C, 69·8; H, 7·9. $C_{13}H_{18}O_3$ requires: C, 70·2; H, 8·2%), $\lambda_{\max}^{\mathrm{EtOH}}$ 239 mμ (ε, 15,620); IR peaks ($CHCl_3$) at 2·85 (m), 5·86 (m), 6·0 (s) and 7·35 μ (m). Compound V gave a positive iodoform test.

Reduction of IV *with lithium–ammonia.* To a solution of lithium (0·7 g) in liquid ammonia (ca. 150 ml), a solution of IV (2 g) in dry ether (200 ml) was added during 15 min. The mixture was stirred 1 hr, decomposed (sat. NH_4Cl aq.) and the organic layer separated. The aqueous layer was extracted with successive portions of ether and chloroform. The extracts were combined, washed with water, and 5% HCl, dried and solvents removed. The viscous residue solidified when triturated with ether and was crystallized from ether; 1·2 g, m.p. 66–68°. Two further crystallizations gave the analytical sample, m.p. 68–69°. (Found: C, 76·0; H, 8·7. $C_{13}H_{18}O_2$ requires: C, 75·7; H, 8·8%). No UV maximum between 220 and 325 mμ; IR peaks ($CHCl_3$) at 2·75 (m), 3·33 (w) and 5·85 μ (s). On the basis of analogy to similar reductions of α,β-eneones, the above dihydro product may be expected to have *trans* A/B junction; however the olefinic bridge at C_4 may have affected the course of reduction.

2,2-*Dimethyl*-1,3-*cyclohexanedione* (VII). This could be obtained as a by-product, as described by Nazarov *et al.*[10] during the monomethylation of 1,3-cyclohexanedione or preferably by methylation of 2-methyl-1,3-cyclohexanedione as follows:

To a solution of potassium methoxide (prepared from 0·4 g K) in dry methanol (50 ml), 2-methyl-1,3-cyclohexanedione (12·6 g) and methyl iodide (14·2 g) was added. The mixture was refluxed for 3 hours when an additional amount (5 g) of methyl iodide was introduced and refluxing continued for further 3 hours. The mixture was cooled, filtered from potassium iodide and freed of solvent to give crude liquid (13 g). Distillation (b.p. 103–105°/11 mm) gave pure VII (11·5 g, 82%) which when cooled solidified; m.p. 39–40°; IR peaks ($CHCl_3$) at 5·75 (m) and 5·875 μ (s). The product furnished[11] a dioxime (pyridine–hydroxylamine method) m.p. 195–195·5° (ethanol). (Found: C, 56·4; H, 7·8. $C_8H_{14}N_2O_2$ requires: C, 56·5; H, 8·0%).

The yield of VII was of the same order when methyl iodide was reacted with the anhydrous potassium salt of 2-methyl-1,3-cyclohexanedione in acetone medium.

1-*Ethynyl*-1-*hydroxy*-2,2-*dimethyl*-3-*oxocyclohexane* (VIII). A solution of lithium acetylide from lithium wire (1·6 g) in liquid ammonia (500 ml) was prepared as usual in a one litre 3-necked flask provided with a stirrer, dropping funnel and inlet for acetylene. The flask was then cooled in a dry ice–acetone mixture and a solution of VII (31·8 g) in dry ether (200 ml) added rapidly over 5 to 10 min. During this addition and subsequently for 20 min, the stream of acetylene was maintained with stirring. The reaction mixture was decomposed (solid NH_4Cl), excess ammonia evaporated and the product extracted successively with ether and chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue (26 g) solidified. A portion was crystallized twice from petrol (40–60°) m.p. 91–91·5°. (Found: C, 72·0; H, 8·5. $C_{10}H_{14}O_2$ requires: C, 72·3; H, 8·5%). No absorption maxima in the region 225–320 mμ; IR peaks (KBr) at 2·97 (s), 3·03 (s), 3·07 (s), 4·72 (m), 5·82 (s) and 5·88 μ (s); IR peaks ($CHCl_3$) at 2·90 (w), 3·0 (m), 5·83 (s) and only a shoulder (w) at 5·93 μ. Apparently there is hydrogen bonding involved in the KBr spectrum.

1-*Acetyl*-1-*hydroxy*-2,2-*dimethyl*-3-*oxocyclohexane* (IX). Treatment of VIII (2 g) with Nieuwland's catalyst furnished after the usual work-up 1 g of IX; m.p. 123–124° (from ether–pet ether mixture). The analytical sample had m.p. 124–125°. (Found: C, 65·0; H, 8·7. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%). There was no absorption maxima in the region 225–300 mμ; IR peaks (KBr) at 2·85 (s) 5·83 (s) and 5·89 μ (s). Compound IX gave a positive iodoform test.

Acknowledgements—The authors are grateful to Dr. G. V. D. Tiers and Dr. K. Nagarajan for providing the NMR spectra and their interpretation and to Mr. R. Balasubramanian for analyses and IR data. One of the authors (S. K. S.) is thankful to the Lady Tata Trust, Bombay for the award of a fellowship and another (S. R.) to the C.S.I.R., New Delhi for financial support.

[10] I. N. Nazarov, S. I. Zavyalov, M. S. Burmistrova, I. A. Gurvich and L. I. Shmonina, *Zh. Obsch. Khim.* **26**, 441 (1956).

[11] We thank Mr. P. S. Venkataramani for preparing this derivative.