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SYNTHESIS OF Δ^7-1-METHYLBICYCLO[5,4,0]UNDECENE-2,9-DIONE AND ITS CONDENSATION WITH ACETYLENE

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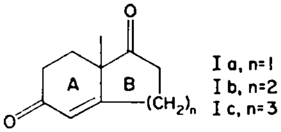
Abstract—Michael addition of methylvinyl ketone to 2-methylcycloheptane-1,3-dione (II) obtained by methylation of cycloheptane-1,3-dione furnishes 2-methyl-2-(3′-oxobutyl) cycloheptane-1,3-dione (III) which is cyclized and dehydrated in a single step to afford the title compound (Ic) in the presence of a mixture of pyrrolidine and acetic acid. A by-product isolated in this cyclization is the bridged ketol VII. Treatment of III with *p*-toluenesulphonic acid gives predominantly the acid IV and only low yields of Ic. The reaction of Ic with lithium acetylide furnishes an unexpected product formulated as IX. An explanation for the differing course of ethynylation of the analogous diones Ia, Ib and Ic is given.

THE bicyclic diones Ia and Ib have been alkylated at the α-position of the α,β-conjugated carbonyl group under suitable conditions to furnish intermediates convertible to estrone and D-homoestrone.[1,2]



I a, n=1
I b, n=2
I c, n=3

Our interest in parallel studies and other studies related to the ring enlargement reported from our laboratory previously[3] has prompted us to synthesize the bicyclic dione (Ic) incorporating a seven membered ring B and to study its reaction with acetylene. The synthesis has been achieved by application of the Robinson annelation reaction as shown on p. 950 under conditions similar to those that have been employed[4,5] for the synthesis of the analogous diones Ia and Ib.

Methylation of cycloheptane-1,3-dione[6] in methanolic solution in the presence of sodium methoxide or preferably in aqueous methanolic potassium hydroxide furnished 2-methylcycloheptane-1,3-dione (II) in 40–45% yield. The base catalysed addition of methylvinyl ketone to II gave the trione (III) in 60–65% yield based on recovered starting material. The conditions for cyclization of III to Ic were found to be critical as has been observed with similar ring enclosures.[4,7–9]

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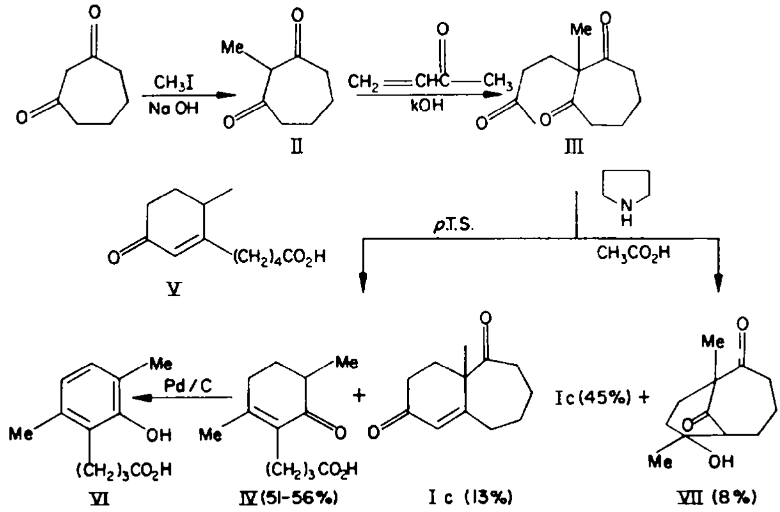
[1] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.* 5072 (1963).
[2] D. J. Crispin and J. S. Whitehurst, *Proc. Chem. Soc.* 356 (1962).
[3] S. Swaminathan, J. P. John and S. Ramachandran, *Tetrahedron Letters* 729 (1962).
[4] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.* 2022 (1959).
[5] S. Ramachandran and M. S. Newman, *Org. Syn.* **41**, 38 (1961).
[6] B. Eistert, F. Haupter and K. Schank, *Liebigs Ann.* **665**, 55 (1963).
[7] N. L. Wendler, H. L. Slates and M. Tishler, *J. Amer. Chem. Soc.* **73**, 3816 (1951).
[8] S. Swaminathan and M. S. Newman, *Tetrahedron* 88 (1958).
[9] T. A. Spencer, K. K. Schmiegel and K. Williamson, *J. Amer. Chem. Soc.* **85**, 3785 (1963).



When the trione (III) was treated with catalytic amounts of *p*-toluenesulphonic acid in refluxing benzene—conditions which have been found[4] efficient for the synthesis of Ia though not of Ib—cyclization was found to be incomplete and accompanied by the formation of an acid $C_{12}H_{18}O_3$, m.p. 86–87°. This material had UV absorption maximum at 244 mμ (ε = 11,130) and showed peaks in the IR for a conjugated carbonyl group and a carboxyl group. Based on analogy,[7] structure IV was assigned to this acid in preference to structure V and confirmed by examination of the NMR spectrum[10] which revealed two methyl peaks, one, a sharp singlet at 8·08 τ and another, a doublet centered at 8·94 τ and the absence of any olefinic proton—features consistent with structure IV but not with V. Dehydrogenation of IV with Pd–C furnished the phenolic acid VI. In another run a larger excess (0·5 equiv.) of PTS than has been employed by Boyce and Whitehurst[4] was used and the reaction mixture refluxed until no more water separated (14 hr). The predominant product was again the acid IV obtained in 51–56% yield but the neutral portion after chromatography furnished in 13% yield the desired dione Ic, m.p. 71·5–72° having the expected light absorption properties.

With a view to improve the yield of Ic from III, reagents like pyrrolidine alone or in combination with PTS and a mixture of triethyl amine-benzoic acid[11] were used to bring about cyclization selectively but these attempts led only to mixtures of products. Singularly effective among the reagents tried was a mixture of equimolar amounts of pyrrolidine and acetic acid used by Spencer *et al.*[9] for the cyclization of 2-acetoxy-2(3′-oxobutyl) cyclohexane-1,3-dione. Treatment of III first at 0° and then at room temperature with this reagent followed by chromatography of the reaction mixture gave Ic directly in 45% yield. There was also isolated in 8% yield one of the bridged ketols (VII) formulated as such on the basis of its spectral properties. Such bridged ketols have often been reported as side products in Robinson annelation reaction.[9,12]

[10] The NMR spectra referred to in this paper were obtained in the solvents specified with a Varian Model A.60 Spectrometer using tetramethylsilane as an internal standard.

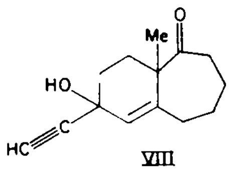
[11] P. Wieland, H. Uberwasser, G. Anner and K. Miescher, *Helv. Chem. Acta* **36**, 376 (1953).

[12] W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Amer. Chem. Soc.* **82**, 614 (1960).

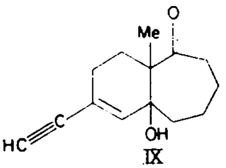
Treatment of III with pyrrolidine–acetic acid at room temperature was found vital for the successful cyclization of III to Ic; under the milder conditions of Spencer *et al.*[9] (stirring at 0° followed by chromatography) a mixture of products resulted from which the only crystalline material isolated was the bridged ketol VII. It was fortunate that the above slight modification effected cyclization and dehydration simultaneously in contrast to the experiments of Spencer *et al.*[9] which gave predominantly the normal bicyclic ketol.

The reaction of Ic with lithium acetylide (2 equivs) in liquid ammonia furnished a 67% yield of a crystalline product, m.p. 114·8–115·2°. This product had IR absorption for —OH, —C≡C—H and —C≡C— and surprisingly for an unconjugated C=O rather than for a conjugated C=O— a fact also substantiated by lack of any UV absorption maximum around 240 mμ. The NMR spectrum while confirming the presence of acetylenic and hydroxyl protons showed in addition sharp peaks for angular $C\underline{H}_3$ and a vinyl proton and also indicated that the —OH group was tertiary. It was obvious from the above evidence, that ethynylation of Ic in contrast to those of Ia and Ib had taken place at the conjugated carbonyl group. The product cannot, however, be assigned structure VIII since the observed UV maximum at 217 mμ (ε, 6294) is more in keeping with[13] structure IX formed probably from the intermediate VIII by an allylic rearrangement catalysed by the ammonium chloride added to decompose the liquid ammonia reaction mixture. Such allylic rearrangements of ethynyl alcohols have been reported.[14]

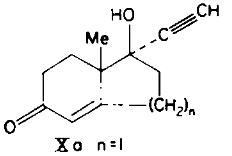
The evidence available is insufficient, however, to indicate the orientation of the hydroxyl group in IX.



VIII



IX



Xa n=1
Xb n=2

The differing course of ethynylation of the diones Ia and Ib on the one hand which yield[15–18] Xa and Xb respectively as the sole products and that of Ic on the other hand requires comment. In the case of Ia and Ib, it seems reasonable that attack by the acetylide ion should occur preferentially at the carbon atom of the unconjugated carbonyl group by virtue of its more positive nature as compared to that of the

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[13] Both *cis* and *trans* 3-methylpent-3-en-1-yn-5-ols have λ_{max}^{EtOH} 223 mμ (ε, 11,000) and 224 mμ (ε, 13,100) respectively [W. Oroshnik, *J. Amer. Chem. Soc.* **78**, 2651 (1956)] while 5,5-dimethylpent-3-en-1-yn-5-ol has λ_{max}^{EtOH} 223·5 mμ (ε, 10,000) (A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy* p. 101. E. Arnold, London (1957)). By comparison with these acyclic compounds, the observed absorption for IX is seen to be low. A more appropriate comparison will be with a cyclic compound analogous to IX; however, such a compound does not seem to have been reported.

[14] J. Cymerman, I. M. Heilbron and E. R. H. Jones, *J. Chem. Soc.* **90** (1945).

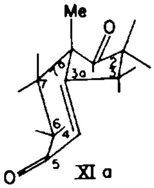
[15] I. N. Nazarov and I. A. Gurvich, *Zh. Obsch. Khim.* **25**, 956 (1955).

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

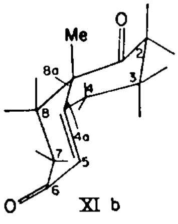
[17] S. Swaminathan, S. Ramachandran and S. K. Sankarappa, *Tetrahedron* **20**, 1119 (1964).

[18] S. Swaminathan, J. P. John, P. S. Venkatramani and K. Viswanathan, *Proc. Ind. Acad. Sci.* LVII-A, 44 (1963).

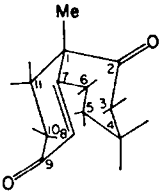
conjugated carbonyl group. Assuming that XIa and XIb represent the most stable[19] conformations for Ia and Ib, this attack seems to take place from the less hindered α-side containing only quasi-axial or axial hydrogen atoms at C_3 and C_6 in XIa and at C_3 and C_7 in XIb rather than from the more hindered β-side having 1:3 interactions in ring B between an axial CH_3 and quasi-axial (XIa) or axial (XIb) hydrogen atoms. The fact that only monoethynylated products have been obtained in these cases even with excess lithium acetylide may be due to the insolubility in the reaction medium of the initially formed lithium salts. In the case of the dione Ic an examination of a model shows that while the β-side is inaccessible for the same reasons as before for attack at the unconjugated carbonyl, attack from the α-side should also be hindered irrespective of which conformation XIc or XId is preferred. In the former case there is interaction between the C_{10} methylene group and quasi-axial hydrogens at C_3 and C_5 while in XId, the interaction is between the same methylene group and C_4 and C_8 quasi-axial hydrogen atoms. This hindrance to attack from the α-side no doubt results from a deformed chair conformation for the seven membered ring. Under these circumstances attack of the conjugated carbonyl seems to take precedence leading via VIII to IX.



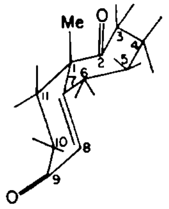
XI a



XI b



XI c



XI d

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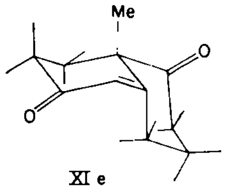
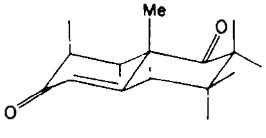
[19] Actually three conformations are possible for Ib, viz., XIb, XIe and XIf. XIf has three CH_3:H



XI e



XI f

axial interactions, XIb has two such interactions plus two interactions of axial trigonal carbon atoms with a hydrogen atom while XIe has one CH_3:H interaction and two additional interactions between a hydrogen atom and a cyclic methylene group. Since according to A. S. Dreiding, *Chem. & Ind.* 1419 (1954) an axial trigonal carbon atom has less interaction than a similarly placed tetrahedral carbon atom, conformation XIb is likely to be preferred. Conformations XIa, XIc and XId are assumed to be the most stable by analogy.

EXPERIMENTAL

2-*Methylcycloheptane*-1,3-*dione* (II)

A solution of cycloheptane-1,3-dione[6] (43 g, 0·34 mole) in 300 ml 1:1 methanolic KOHaq (19·5 g, 0·34 mole) was refluxed for 4 hr with MeI (49 g, 0·35 mole) and the solvent then removed under suction. The residual deep red liquid was treated with 300 ml NaOHaq (14 g), cooled and extracted with ether to remove alkali insoluble by-products. The alkaline solution was acidified to pH 2 with 4N HCl under cooling, saturated with $(NH_4)_2SO_4$ and extracted thrice with ether. The combined ether extracts were stripped of solvent and the residual liquid distilled *in vacuo* to give II, b.p. 102–108°/5 mm, (20–22 g, 40–65%), $\lambda_{max}^{CHCl_3}$ 5·8 and 5·9 μ. The dione II furnished a dioxime, crystallized from aqueous MeOH m.p. 196·5–198°. (Found: C, 56·8; H, 8·4; N, 16·4. $C_{18}H_{14}N_2O_2$ requires: C, 56·5; H, 8·2; N, 16·5%.)

An unidentified higher boiling fraction (9·5 g) was collected at 130–140°/5 mm. When the methylation was done in abs MeOH in the presence of MeONa, the yield of II was about 35 to 40%.

2-*Methyl*-2-(3′-*oxobutyl*)*cycloheptane*-1,3-*dione* (III)

A mixture of II (18 g, 0·13 mole), abs MeOH (100 ml), 85% methylvinyl ketone (9 g, 0·13 mole) and KOH (2 pellets) was *stirred* for 1 hr at 50–60° and then for 3 hr at reflux temp. The mixture was freed of solvent *in vacuo* and the residual liquid extracted with $CHCl_3$. After washing with a small amount of water, the organic layer was dried and solvent removed. Fractional distillation of the residual liquid gave a forerun consisting mainly of II (4·5 g, b.p. 96–156°/5 mm) followed by the main fraction (15–16 g, b.p. 150–160°/4·5 mm). Redistillation of this main fraction afforded III, b.p. 134–136°/1·5 mm (12–13 g, 44–48%). (Found: C, 68·5; H, 8·6. $C_{12}H_{18}O_3$ requires: C, 68·6; H, 8·6%.) $\lambda_{max}^{CHCl_3}$ 5·81, 5·85 and 5·9 μ and no —OH absorption.

Δ^7-1-*Methylbicyclo*[5,4,0]*undecene*-2,9-*dione* (Ic)

(a) *Cyclization of* III *with* p-*toluenesulphonic acid.* A solution of III (21 g, 0·1 mole) in dry benzene (500 ml) was refluxed with *p*TS (3 g) in a flask fitted with a Dean-Stork water separator. Three additional portions (2 g each) of *p*TS were added at intervals of 3 hr and the mixture refluxed for a total period of 14 hr when the theoretical amount of water (1·8 ml) separated. The dark reaction mixture was diluted with benzene (250 ml) and washed repeatedly with a sat $NaHCO_3$aq. The organic layer was freed of solvent and residue mixed with 50 ml 1:1 benzene–petrol (40–60°) mixture and cooled. Pale yellow crystals (2·6 g, 13%) separated and were collected and recrystallized from the same mixture of solvents to furnish colourless crystals of Ic, m.p. 71·5–72°. (Found: C, 75·3; H, 8·6. $C_{12}H_{16}O_2$ requires: C, 75·0; H, 8·3%.) $\lambda_{max}^{CHCl_3}$ 5·865, 6·01 and 6·175 μ. λ_{max}^{EtOH} 238 mμ (ε, 12,200). The NMR spectrum (CCl_4) showed sharp singlets at 4·15 τ (C_8 proton) and 8·72 τ (angular methyl protons).

The diketone (Ic) furnished when treated with a mixture of pyridine and hydroxylamine, a dioxime, m.p. 204–205° (aq. EtOH). (Found: C, 65·2; H, 8·0. $C_{12}H_{18}N_2O_2$ requires: C, 64·9; H, 8·2%.) The diketone Ic also furnished a monosemicarbazone formed in presence also of more than two equivs of semicarbazide; m.p. 219–222° (EtOH). (Found: C, 62·9; H, 7·7; N, 16·7. $C_{13}H_{19}N_3O_2$ requires: C, 62·6; $\underline{H}$, 7·7; N, 16·9%.)

The bicarbonate washings when acidified furnished 12 to 13 g (51–56%) of IV, m.p. 86–87° (benzene–petrol). (Found: C, 68·2; H, 8·6. $C_{12}H_{18}O_3$ requires: C, 68·6; H, 8·6%.) $\lambda_{max}^{CHCl_3}$ 5·85, 6·025 and 6·15 μ. λ_{max}^{EtOH} 244 mμ (ε, 11,130). The NMR spectrum (CCl_4) showed a singlet at 8·08 τ ($C\underline{H}_3$ at C_2) and a doublet centred at 8·94 τ ($C\underline{H}_3$ at C_5) and no olefinic proton absorption.

When III (5·25 g) was refluxed for 4 hr with *p*TS (0·4 g) and the reaction mixture worked up as above, the acid IV (1·4 g) was isolated. The neutral portion after chromatography gave only oily fractions showing two unconjugated and one conjugated C═O absorptions in the IR.

(b) *Cyclization of* III *with a mixture of equivalents of pyrrolidine and acetic acid.* To a stirred solution of III (6·3 g, 0·03 mole) in dry ether (100 ml) cooled to 0°, pyrrolidine (2·4 ml, 0·03 mole) was added dropwise followed by acetic acid (1·8 ml, 0·03 mole). The reaction mixture was kept stirred at 0° for 2 hr and then at room temp for 3 hr. The solvent was removed and the residual brown liquid taken up in 20 ml ether and transferred to a column of Al_2O_3. Elution initially with a mixture of benzene and petrol (40–60°) and then with benzene alone furnished 2·6 g (45%) of crystalline material, m.p. and mixed m.p. with Ic described above, 71–72°.

Further elutions with a 1:1 mixture of ethyl acetate and benzene followed by benzene alone gave colourless crystals of VII (490 mg, 8%) which were recrystallized from a mixture of ethyl acetate and petroleum; m.p. 120·5–121·5°. (Found: C, 68·6; H, 8·6. $C_{12}H_{18}O_3$ requires: C, 68·8; H, 8·7%.) $\lambda_{max}^{CHCl_3}$ 2·75, 5·81 μ. NMR: ($CDCl_3$) 7·7 τ ($—\overset{|}{\underset{|}{C}}—O\underline{H}$, singlet), 8·7 τ ($—\overset{|}{\underset{|}{C}}—C\underline{H}_3$) and 8·85 τ ($C\underline{H}_3—\overset{|}{\underset{|}{C}}—OH$). UV: no intense absorption.

γ (2,5-*Dimethyl-6-hydroxyphenyl) butyric acid* (VI)

Acid IV (1 g) was heated at 250° for 1½ hr with 10% Pd–C (0·25 g) cooled and extracted with ether. The organic layer furnished a viscous liquid which solidified partially on standing. Trituration with 1:1 benzene–petrol mixture furnished solid (300 mg) which was twice recrystallized from the same solvent mixture, m.p. 126·5–127·5°. (Found: C, 69·6; H, 8·0. $C_{12}H_{16}O_3$ requires: C, 69·2; H, 7·7%.) $\lambda_{max}^{CHCl_3}$ 2·75, 5·875 and 6·35 μ. λ_{max}^{EtOH} 280 mμ (ε, 1248).

Δ^8-1-*Methyl-7-hydroxy-9-ethynyl-bicyclo*[5,4,0]*undecene-2-one* (IX)

A solution of Ic (3·84 g, 0·02 mole) in dry ether (50 ml) was added over 5 min to a stirred solution of lithium acetylide (prepared from 0·3 g Li in liquid ammonia (150 ml) kept cooled in a dry ice–acetone bath while bubbling in a slow stream of acetylene through the reaction mixture. Stirring was continued for another 20 min and the reaction mixture then decomposed with solid NH_4Cl (6 g). The ammonia and ether were removed, water (20 ml) added and the precipitated solid (2·7 g) collected. A further crop (0·7 g) of the same solid was obtained by extraction with $CHCl_3$ of the filtrate. Recrystallization of the combined crops from a mixture of ethylacetate and petroleum (40–60°) furnished 2·8 g (67%) of IX, m.p. 109–111°. The analytical sample obtained by a further crystallization had m.p. 114·8–115·2°. (Found: C, 77·4; H, 8·5. $C_{14}H_{18}O_2$ requires: C, 77·0; H, 8·3%.) λ_{max}^{EtOH} 217 mμ (ε, 6294), 290 mμ (ε, 210). λ_{max}^{KBr} 2·9 (s), 3·08 (s), 4·7 (w), 5·92 (s), 6·05 (m) μ; NMR: ($CDCl_3$), 4·3 τ ($—\overset{|}{\underset{|}{C}}=\underset{\underline{H}}{C}—\overset{|}{\underset{|}{C}}—$, singlet), 7·4 τ ($—\overset{|}{\underset{|}{C}}—O\underline{H}$, singlet), 7·42 τ ($—C\equiv C—\underline{H}$, singlet) and 8·76 τ ($—\overset{|}{\underset{|}{C}}—C\underline{H}_3$, singlet).

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