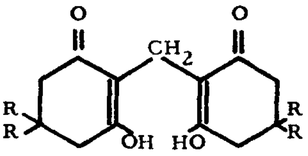
Tetrahedron Letters No.20, pp. 1855–1858, 1967. Pergamon Press Ltd. Printed in Great Britain.

FORMATION OF CYCLOPROPANE AND DIHYDROBENSOFURAN DERIVATIVES THROUGH OXIDATIVE COUPLING OF METHYLENE-BIS-1,3-CYCLOHEXANEDIONES

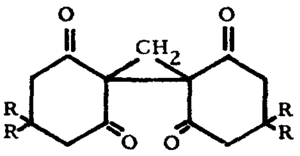
Ove H. Mattsson and Carl Axel Wachtmeister
Department of Organic Chemistry, University of Stockholm
Stockholm Va, Sweden

(Received 9 March 1967)

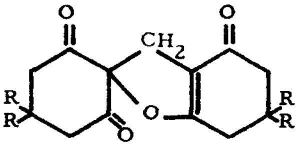
In phenol chemistry, carbon-carbon and carbon-oxygen oxidative coupling have received considerable attention from a biogenetic and purely synthetic viewpoint.(1) The present paper describes analogous reactions involving cyclisations of enolisable β-dicarbonyl compounds, as exemplified by methylene-bis-dimedone (Ia) and methylene-bis-1,3-cyclohexanedione (Ib).



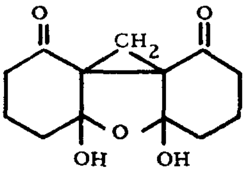
Ia R = CH_3
Ib R = H



IIa R = CH_3
IIb R = H



IIIa R = CH_3
IIIb R = H



IV

The dimedone derivative (Ia) has been studied by Radulescu and Georgescu(2) who treated the sodium salt with iodine, then isolated a neutral ketone $C_{17}H_{22}O_4$, m.p. 212–213°C, formulated as a cyclopropane derivative (IIa). Recently, Kondratéva, Kogan and Zav´yalov(3) obtained the same compound by treating Ia with bromine in chloroform but ascribed structure IIIa to it on the basis of ultraviolet and infrared spectra.

In seeking a suitable one electron acceptor, advantage was taken of the properties of an aqueous equimolar solution of iron (III) chloride and potassium hexacyano ferrat (III), which has been recommended as a spraying reagent in paper chromatography$^{(4)}$. In contrast to either component, such a solution reacts readily under neutral or weakly acidic conditions with a number of enolisable cyclic β-diketones and related compounds. This behaviour evidently reflects the formation of iron (III) hexacyanoferrate (III), a soluble complex the existence and properties of which has recently been discussed in some detail by de Wet and Rolle$^{(5)}$. It is readily reduced with formation of the stable complex

$Fe^{III}K\ [Fe^{II}(CN)_6]$, "Berlin Blue".

Treatment of enols Ia and Ib with iron hexacyanoferrate induced carbon-oxygen coupling in both cases with the formation of cyclic enol ethers, IIIa and IIIb respectively; however, with enol Ib a second reaction product IIb containing a cyclopropane ring was isolated, evidently formed by intramolecular carbon-carbon coupling.

A saturated solution of methylene-bis-dimedone (Ia) (10 mmol) in 50 % aqueous acetic acid was treated for 6 hr at 20°C with an aqueous solution of iron (III) chloride (40 mmol) and potassium hexacyanoferrate (III) (40 mmol). The main reaction product, m.p. 214-215°C, isolated in 28 % yield, gave analytical values and ultraviolet and infrared absorption spectra in agreement with values expected and previously reported $^{(3)}$ for enol ether IIIa. Structure IIIa is in agreement with the n.m.r. spectrum of the compound in a $CDCl_3$-solution which shows a signal at τ 6.83 (2H, triplet, J 1.6 cps) assigned to the bridge methylene group, homoallylically coupled to the CH_2-group at τ 7.52 (2H, triplet, J 1.6 cps). The remaining protons appear at τ 7.23 (4H), τ 7.77 (2H), τ 8.84 (3H), τ 8.88 (6H) and τ 9.01 (3H).

Methylene-bis-1,3-cyclohexandione (Ib) (7.1 g, 30 mmol) was treated for 3 hr at 20°C with iron (III) chloride (90 mmol) and potassium hexacyanoferrate (III) (90 mmol) using 45 % aqueous ethanol (4500 ml) as solvent. Extraction with chloroform, then evaporation afforded an oil, but one component (A, 1.5 g) crystallised from acetonitrile. Recrystallisation from dimethyl sulphoxide - chloroform gave pure A as plates, m.p. 148-150°C (dec.). After drying in vacuo at 90°C, analytical values in accordance with the composition $C_{13}H_{16}O_5$ (252.3) were obtained. The mass spectrum, however, showed a molecular ion $M^+ = 234$. (λ_{max}^{EtOH} 275 mμ (broad), ε 300; end absorption.
ν_{max}^{KBr} 3435, 3098, 1700(s), 1050(s), 1017 cm^{-1}).

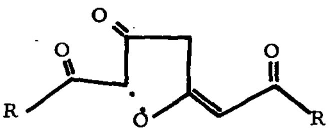
Cautious destillation at 1.5×10^{-4} mm Hg, 135-145°C, of compound A gave a viscous oil containing unchanged A and a ketone as a main component which crystallised from chloroform - hexane, $C_{13}H_{14}O_4$ (234.3), m.p. 97-99°C (dec.) (Molecular ion $M^+ = 234$. λ_{max}^{EtOH} 275 mμ (broad), ε 500; end absorption. ν_{max}^{KBr} 3081, 1748, 1715(s), 1020, 1010 cm^{-1}).

The spectral values found are in agreement with a formulation of the ketone as dispiro [5.0.5.1.] -trideca-1,5,8,12-tetraone (IIb). The n.m.r. spectrum showed a sharp signal at τ 7.71 (2H), ascribed to the cyclopropane methylene protons. Typical cyclopropane carbon-hydrogen stretching vibration was observed at 3081 cm^{-1}, accompanied by a band at 1020 cm^{-1}. In the carbonyl region, the ketone exhibited two bands at 1748 and 1715 cm^{-1}, which are characteristic for 2,2-disubstituted 1,3-cyclohexandiones(3).

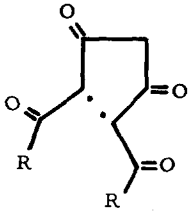
When crystallised from aqueous acetonitrile, the ketone (IIb) was transformed back to compound A which likewise showed a sharp carbon-hydrogen stretching band at 3098 cm^{-1} as well as a pronounced hydroxyl band at 3435 cm^{-1}. Hence, compound A is considered to be a hydrate of IIb, either a cyclic ether (IV) containing two semiketal hydroxyl groups or, less likely, a gem-diol. Contrary to structure IIb and in accordance with a structure IV, compound A exhibited only a single band in the carbonyl region. A strong band at 1050 cm^{-1} possibly indicated the presence of a strained tetrahydrofuran ring.

The mother liquor from isolation of compound A contained a second compound (B, 2.1 g) which crystallised as a semiketal with methanol from methanol-isopropanol (1:1). Sublimation of B at 10^{-3} mm Hg, 130°C gave a compound $C_{13}H_{14}O_4$, m.p. 138-139°C, formulated as 4,5,6,7-tetrahydro-spiro [bensofuran-2 (3H), 1′-cyclohexane] - 2′,4,6′-trione (IIIb) [Molecular ion $M^+ = 234$. λ_{max}^{EtOH} 267 mμ, ε 9400. $\nu_{max}^{CHCl_3}$ 1750, 1720, 1640(s), 1230 (broad)]. The n.m.r. spectrum showed a signal at τ 6.81 (2H, triplet, J 1.8 cps) assigned to the bridge methylene group coupled to a methylene group centered at τ 7.33.

The two most simple reaction mechanisms by which compounds A and B are formed may be construed as involving the intermediate formation of resonance stabilised radicals from enolate ions. A hypotetical precursor of more obvious biogenetic interest than cyclic dienols like Ia or Ib, could form a mesomeric diradical (Va ↔ Vb) which would undergo cyclisation and subsequent changes to form a furan or, alternatively, a cyclopentane derivative.



Va



Vb

An example of biosynthesis by carbon-oxygen coupling essentially of this type may possibly be provided by 8-(5-hexyl-2-furyl)-octanoic acid(6) recently isolated from *Exocarpus cupressiformus* Labill. Carbon-carbon coupling might be exemplified by the even-numbered acids of the Chaulmoogric Acid type, as proposed by Richards and Hendrickson(7).

Most fatty acids of natural origin containing a cyclopropane ring, e.g. Sterculic Acid, posses an odd number of carbon atoms and are apparently formed along other routes(8).

A full account of this work, which is supported by the Swedish Natural Science Research Council, will be published elsewhere.

REFERENCES

1. D.H.R. Barton and T. Cohen, in *Festschrift Arthur Stoll*, Basel 1957, p. 117 H. Erdtman and C.A. Wachtmeister, ibid. p. 144; A.I. Scott, *Quaterly Reviews* **10**, 1 (1965)
2. D. Radulescu and V. Georgescu, *Bull.Soc.Chim.* **37**, 187 (1925)
3. G.V. Kondrat'eva, A.G. Kogan and S.I. Zav'yalov, *Izv.Akad.Nauk.SSSR, Otd. Khim. Nauk* (1962) 1441
4. G.M. Barton, R.S. Evand and J.A.F. Gardner, *Nature* **170**, 249 (1952)
5. J.F. de Wet and R. Rolle, *Z.anorg. allg. Chem.* **336**, 96 (1965)
6. L.J. Morris, M.O. Marshall and W. Kelly, *Tetrahedron Letters* **No 36**, 4249, (1966) J.A. Elix and M.W. Sargent, *Chem.Comm.* (1966) 823
7. J.H. Richards and J.B. Hendrickson, *Biosynthesis of Terpenes, Steroids and Acetogenins*, W.A. Benjamin Inc., New York 1964; p. 97
8. K. Hofman and T.Y. Liu, *Biochem. Biophys. Acta* **2**, 80 (1960).