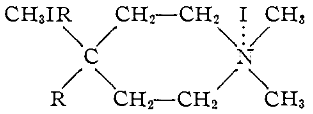
TABLE I



R'	R	Formula	M.p., °C.	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Iodine Calcd.	Iodine Found	Activity,[a] mg./kg. ED_{50}	LD_{50}
C_6H_5–	$(CH_3)_2NCH_2CH_2OCH_2$–	$C_{19}H_{34}I_2N_2O$	243.8–245.7	73	40.69	40.69	6.12	6.08	45.30	45.20	20	60 ± 2
	$(C_2H_5)_2NCH_2CH_2OCH_2$–	$C_{21}H_{38}I_2N_2O$	208.4–209.5	93	42.87	42.71	6.51	6.57	43.14	42.85	16 ± 1	32 ± 2
	$OC_4H_8NCH_2CH_2OCH_2$–	$C_{21}H_{36}I_2N_2O_2$	249–250 dec.	94	41.87	41.95	6.09	6.18	42.14	41.80	16 ± 1	62 ± 6
	$C_5H_{10}NCH_2CH_2OCH_2$–	$C_{22}H_{38}I_2N_2O$	240.0–241.6	82	44.00	43.88	6.38	6.38	42.28	41.89	8 ± 0.7	30 ± 6
	$C_5H_{10}NCH_2CH_2CH_2OCH_2$–	$C_{23}H_{40}I_2N_2O$	270.4–272.5	54	44.96	45.19	6.56	6.47	41.31	40.78	5.3 ± 0.3	14
	$C_5H_{10}NCH_2CH_2O$–	$C_{21}H_{36}I_2N_2O$	251.5–252.5	90	43.01	43.22	6.19	6.17	43.29	43.05	70 ± 7	280
H–	$C_5H_{10}NCH_2CH_2OCH_2$–	$C_{16}H_{34}I_2N_2O$	280–282 dec.	43	36.66	36.59	6.54	6.54	48.43	48.09	20 ± 2	70 ± 6
H–	$(C_2H_5)_2NCH_2CH_2OCH_2$–[b]	$C_{15}H_{34}I_2N_2O$	234.6–235.8	68	35.16	35.32	6.69	6.69	49.56	49.15	23 ± 1	60 ± 4

[a] C. J. Cavallito, A. Soria and J. Hoppe, THIS JOURNAL, **72**, 2661 (1950). Curarimimetic dose injected subcutaneously in mice. Dr. Hoppe carried out the biological screening. [b] R is on the 3-position.

solution was added 1-butanol (3.5 l.) and the combined solution distilled until the distilling vapors reached 117°. After cooling to 50°, sodium (115 g., 5 moles) was added portionwise until the violent reaction subsided. Then the remainder of the sodium was added and the mixture refluxed for an hour after all the sodium had been consumed. The reaction mixture was cooled slightly and water (100 ml.) was carefully added to the hot solution. Butanol was steam distilled from the mixture and the residual two-phase system poured into a beaker. The oil started to solidify immediately. The product was collected, dissolved in benzene, dried azeotropically and then Skelly B added to the first permanent cloud. On cooling, 185 g. (90% of theory) of product was obtained, m.p. 136.8–137.4°. An additional 10 g. was obtained on concentrating the filtrates.

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.82. Found: N, 6.73.

Ethers.—The alcohol was added to the sodamide (10% excess) suspended in dry toluene and refluxed until complete solution was effected. After cooling slightly, a second portion of sodamide (equivalent to the first portion) was added, followed by an equimolar quantity of the *t*-amino substituted alkyl halide hydrochloride. The resultant mixture was refluxed two hours, cooled and water carefully added to dissolve any unreacted sodamide and the salts that had formed. The aqueous layer was extracted with benzene which was combined with the organic layer, the solvent removed and the residual oil distilled or else converted directly to the dimethiodide.

Quaternaries.—The basic ether was dissolved in benzene and an excess of methyl iodide was added. If necessary, the solution was warmed to ensure complete reaction. The product was collected and crystallized several times from ethanol.

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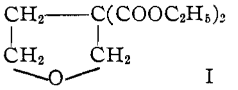
Synthesis of β,β-Dicarbethoxytetrahydrofuran

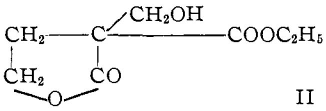
BY A. GHOSH AND C. R. RAHA

RECEIVED SEPTEMBER 29, 1953

β,β-Dicarbethoxytetrahydrofuran (I) obtained in place of α-oxymethyl-α-carbethoxy-γ-butyrolactone (II) is interesting not only because of the preferential formation of the ether to that of the ester, *i.e.*, lactone linkage but also for its antibacterial



I



II

activity. The details of this work will be published in due course.

Experimental

Four grams (0.05 mole) of ethylene chlorohydrin was added with constant shaking to the sodio salt obtained from 9.5 g. (0.05 mole) of oxymethylmalonic ester[1] and sodium ethoxide prepared from 1 g. of sodium metal (0.05 mole) and 15 ml. of absolute alcohol. The reaction mixture on keeping at 30° for 48 hr. or on refluxing for 8 hr. at steam temperature yielded a liquid b.p. 152–153° (0.6 mm.) in amounts varying between 3.6 g. (33.3%) and 4.85 g. (44.9%).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.68; H, 7.16.

The liquid on hydrolysis with 15% hydrochloric acid for 30 hr. yielded a solid acid, m.p. 115–120°, crystallizations from water raised the m.p. to constant 129–130°.

Anal. Calcd. for $C_5H_6O_3$: C, 51.72; H, 6.90; sapn. equiv., 116. Found: C, 51.95; H, 7.00; sapn. equiv., 114, 117.

Acknowledgments.—Authors' thanks are due to Dr. D. M. Bose, Director, Bose Institute, and to Dr. J. K. Chowdhury, Head of the Department of Chemistry, Bose Institute, for their kind interest in this work.

(1) S. Matsuura, *J. Pharm. Soc. Japan*, **71**, 525 (1951); *cf. C. A.*, **46**, 906 (1952).

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The Production of Tocored upon the Oxidation of *dl*-α-Tocopherol with Ferric Chloride[1]

BY VERNON L. FRAMPTON, WILFRED A. SKINNER, JR., AND PHILIP S. BAILEY

RECEIVED JUNE 30, 1952

All of the chemical methods used for the determination of tocopherols involve their oxidation. The most widely used procedure is that proposed by Emmerie and Engel,[2] which involves the rupture of the chroman ring with ferric chloride and the production of α-tocoquinone. A stoichiometric relationship is assumed, and the ferrous iron produced is determined colorimetrically as the red α,α'-bipyridyl complex.

Upon the oxidation at room temperature of *dl*-α-tocopherol (absorption maximum at 292 mμ with an extinction coefficient, $E^{1\%}_{1cm.}$ 74.2) with ferric chloride in methyl alcoholic solution, the absorption maximum at 292 mμ disappeared in about 45 seconds, and an absorption maximum which showed an

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[1] Taken from a dissertation presented by Wilfred A. Skinner, Jr., to the Graduate Faculty of The University of Texas in partial fulfillment of the requirements of the Ph.D. Degree, June, 1952.

[2] A. Emmerie and C. Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

extinction coefficient, calculated on the basis of *dl*-α-tocopherol used, of 317 appeared at 261 mμ. The extinction coefficient obtained with tocoquinone is 435.[3] In no case did the absorption maximum at 261 mμ with these solutions show an extinction coefficient as high as 435, even when the oxidation was carried out at 60° and in the presence of α,α′-bipyridyl[4]; an extinction coefficient of 435 was obtained only with the pure tocoquinone. It is evident, therefore, that the oxidation of *dl*-α-tocopherol with ferric chloride does not yield α-tocoquinone quantitatively.

The appearance of five oxidation products when *dl*-α-tocopherol, in methyl alcoholic solution, is oxidized with ferric chloride at 50° has been reported.[5] These oxidation products were resolved chromatographically on a zinc carbonate column, and they appeared, initially, as four colored bands on the column and as a colorless wax in the effluent liquid. These bands were purple, blue-grey, orange and yellow in color.[6] The yellow band-material, comprising 10% by weight of the total oxidized materials, was identified as α-tocoquinone.[5]

It has now been established that the orange band-material, comprising 42% by weight of the oxidized products obtained under the conditions used by Frampton, *et al.*,[5] is identical with tocored. Tocored, it may be recalled, is obtained upon the oxidation of α-tocopherol with nitric acid.[8] The absorption spectra of tocored and the orange band-material are identical. Both products, upon refluxing with hydrochloric acid, yield compounds[9] which also show identical absorption spectra. Both products yield phenazines which show the same fluorescence in ultraviolet light and which also show identical absorption spectra. Both substances, on reductive acetylation, yield crystalline dihydroacetates which have the same melting points, and which show no depression in melting point on mixing.

This oxidation with ferric chloride involves the elimination of a methyl group from an aromatic ring.

Experimental

Considering that most of the products used in this study are oils, heavy reliance was necessarily placed upon chromatographic techniques for fractionation and upon the ultraviolet absorption spectra as criteria in establishing purity and identity.

Purification of *dl*-α-Tocopherol.—A solution containing 1 g. of synthetic commercial *dl*-α-tocopherol (Hoffman-La-Roche, Inc.) per 15 ml. of anhydrous methanol was precooled to −6° for 1 hr., and then chilled in a CO_2–acetone-bath. Only the crystalline material (appearing after the container was scratched with a glass rod) was used which showed a single absorption maximum at 292 mμ, in methanol solution, with an extinction coefficient, $E^{1\%}_{1\,\text{cm.}}$ 74.2.[11]

Oxidation of *dl*-α-Tocopherol.—Ten grams of C.P. grade ferric chloride was added to 50 ml. of a methanolic solution which contained 1 g. of *dl*-α-tocopherol, and the mixture was heated at 50° for 2 hr.; water was then added, and the resulting mixture was extracted with successive portions of diethyl ether. A red-brown oil was obtained upon the concentration of the combined and dried extracts. This oil, in a minimum quantity of petroleum ether (boiling range 60–75°), was chromatographed on a zinc carbonate column (made up of 2 parts diatomaceous earth and 1 part zinc carbonate). The orange band[5] was removed from the column, and the red oil obtained upon elution with diethyl ether was subjected to repeated chromatographic fractionation, *vide supra*, until the ultraviolet absorption spectrum became and remained constant in all of its characteristics. Absorption maxima appeared at 262, 269 and 460 mμ.

Preparation of Tocored.—Forty ml. of concentrated nitric acid was added to 0.5 g. of *dl*-α-tocopherol in 200 ml. of methanol, and the solution was then heated on a steam-bath for 10 minutes. The solution, which turned bright red in color, was then poured into water, and the aqueous solution was extracted with successive portions of diethyl ether. The combined, dried and concentrated ethereal extracts were chromatographed on the zinc carbonate column. Two colored bands developed: a purple one,[12] which remained near the top, and an orange one which moved rapidly down the column. The oil recovered from the orange band showed the absorption characteristics previously recorded by Smith[8] for α-tocored; absorption maxima appeared at 262, 269 and 460 mμ. This absorption spectrum was identical with that determined with the orange band material from the ferric chloride oxidation.

Preparation of a Phenazine of the Orange Band Material and of α-Tocored.—A solution made up of 100 mg. of the oil from the orange band, 10 ml. of glacial acetic acid and 50 mg. of *o*-phenylenediamine, was heated on a water-bath for 15 minutes, and then poured into water. This mixture was extracted with successive portions of diethyl ether, which were then combined, dried and concentrated. Four colored bands appeared when the concentrate was chromatographed on the zinc carbonate column, a purple (absorption maximum at 305 mμ), an orange (absorption maxima at 262, 269 and 460 mμ), a rose (absorption maximum at 270 mμ) and a yellow band. The oil from the yellow band showed absorption maxima at 265 and 355 mμ, and it also showed the strong yellow-green fluorescence in ultraviolet

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(3) H. M. Evans, O. H. Emerson and G. A. Emerson, *J. Biol. Chem.*, **113**, 319 (1936); M. Tishler and H. L. Wendler, THIS JOURNAL, **63**, 1532 (1941); P. Karrer and A. Geiger, *Helv. Chim. Acta*, **23**, 455 (1940).

(4) According to Emmerie and Engel[2] the conversion of α-tocopherol to α-tocoquinone is quantitative in the presence of α,α′-bipyridyl.

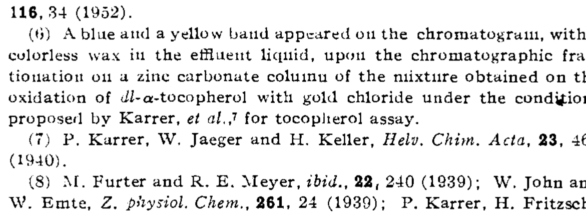
(5) V. L. Frampton, W. A. Skinner, Jr., and P. S. Bailey, *Science*, **116**, 34 (1952).

(6) A blue and a yellow band appeared on the chromatogram, with a colorless wax in the effluent liquid, upon the chromatographic fractionation on a zinc carbonate column of the mixture obtained on the oxidation of *dl*-α-tocopherol with gold chloride under the conditions proposed by Karrer, *et al.*,[7] for tocopherol assay.

(7) P. Karrer, W. Jaeger and H. Keller, *Helv. Chim. Acta*, **23**, 464 (1940).

(8) M. Furter and R. E. Meyer, *ibid.*, **22**, 240 (1939); W. John and W. Emte, *Z. physiol. Chem.*, **261**, 24 (1939); P. Karrer, H. Fritzsche and R. Escher, *Helv. Chim. Acta*, **22**, 661 (1939); L. I. Smith, W. B. Irwin and H. E. Ungnade, THIS JOURNAL, **61**, 2424 (1939).

(9) One of the compounds obtained upon the refluxing of α-tocored with hydrochloric acid is the purple oil which appears among the oxidation products of α-tocopherol. This purple oil, as will be shown later, is an hydroxyparaquinone. The second compound is a yellow oil which is only slightly soluble in methyl alcohol and which gives an orange coloration in glacial acetic acid. It is felt, because of its chromatographic behavior, its color, and its ultraviolet absorption spectrum, that this yellow oil is a paraquinone analogous to some obtained by John and Emte[10] upon the isomerization of *o*-quinones and tocoquinone-like substances, *e.g.*



(10) W. John and W. Emte, *Z. physiol. Chem.*, **268**, 85 (1941).

(11) E. Fernholz, THIS JOURNAL, **60**, 700 (1938); J. G. Baxter, C. O. Robeson, J. O. Taylor and R. W. Lehman, *ibid.*, **65**, 918 (1943).

(12) The purple oil recovered on elution with methanol showed indicator properties, being yellow in acid and purple in basic media. It is not identical with the purple band material found upon the oxidation of *dl*-α-tocopherol with ferric chloride, however, since this oil showed a single absorption maximum at 268 mμ, whereas the product from the ferric chloride oxidation absorbs at 305 mμ.[5]

light that is characteristic of the phenazines of *o*-quinones.[13] The same results were obtained with α-tocored.[14]

Isomerization of the Orange Band Material and of Tocored.—A yellow solution, with a yellowish-brown oil floating on top, was produced when a mixture of 35 mg. of the red oil from the orange band and 20 ml. of 6 *N* hydrochloric acid was refluxed for 2 hr. The concentrated and dried ethereal extract of this mixture was chromatographed on the zinc carbonate column; three colored bands appeared, a purple (absorbing at 305 mμ) an orange (absorbing at 260, 270 and 460 mμ) and a yellow band (absorption maximum at 289 and a minimum at 255 mμ). The oil from the yellow band was only slightly soluble in methanol, and it gave an orange coloration in glacial acetic acid. Identical results were obtained with α-tocored.

Reductive Acetylation of the Orange Band Material and of Tocored.—The red color faded to a pale yellow when a mixture composed of 50 mg. of the red oil from the orange band, 10 ml. of pyridine, 10 ml. of acetic anhydride and 1.5 g. of powdered zinc was stirred for 1 hr. Cold water was then added and the resulting mixture was extracted with successive portions of diethyl ether. A pale-yellow, sweet-smelling oil (absorption maximum at 240 mμ) was recovered from the combined ethereal extracts. This oil was only slightly soluble in methanol, but was very soluble in ether. White needles, m.p. 70°, appeared when a solution of the oil in diethyl ether-methanol was chilled to −5°.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.38; H, 10.14. Found: C, 74.20; H, 10.49.

The oily acetate from a comparable treatment of tocored showed an absorption maximum at 240 mμ, and the white needles obtained in the manner indicated above melted at 69–70° and did not depress the melting point of the above diacetate.

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[13] S. C. Hooker, This Journal, **58**, 1163, 1168, 1181, 1198 (1936).

[14] W. John and W. Emte,[10] report absorption maxima for this phenazine at 270 and 365 mμ.

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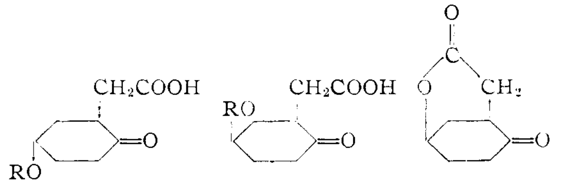
Epimeric 5-Hydroxy-2-ketocyclohexaneacetic Acids

By E. M. Fry

Received August 13, 1953

The stabilities of isomeric substituted cyclohexane derivatives are now related to the idea of a chair form for the ring with substituents occupying either equatorial or polar positions. In systems in which the interaction of groups is mainly of a steric nature the equatorially substituted compounds are considered to be the more stable. Thus in a disubstituted compound the more stable forms are *trans*-1,2,*trans*-1,4 and *cis*-1,3 since the substituents can assume an equatorial position, whereas the *cis*-1,2,-*cis*-1,4 and *trans*-1,3 forms are less stable because one of the substituents is polar oriented.[1] In support of this concept evidence is here presented that in an equilibrating solution of the epimeric 5-hydroxy-2-ketocyclohexaneacetic acids Ia and IIa, the *cis* form is the more favored.

The preparations of the epimeric benzyl ethers Ib and IIb have been described.[2] When the liquid isomer IIb was dissolved in 9 *N* hydrochloric acid an oil began to separate within a few seconds. This oil readily crystallized to yield the epimeric benzyl ether Ib.



Ia, R = H, m.p. 120°   IIa, R = H, m.p. 150°   III
b, R = $C_6H_5CH_2$, m.p. 110°   b, R = $C_6H_5CH_2$, liquid

This separation of oil indicates that in the liquid as well as in the crystalline state Ib is much less soluble in the acid than its precursor IIb. The solid isomer was dissolved in the large volume of hydrochloric acid necessitated by its low solubility and then removed with chloroform in which it is very soluble. After several chloroform extractions 37% of the solid isomer was recovered along with an oil which was identified as the liquid isomer by converting it to the solid in the usual manner. This material accounted for an additional 36% of the starting material for a total recovery of 73%.

It is evident that this combination of high solubility in chloroform and low solubility in 9 *N* hydrochloric acid favored removal of the solid isomer from the acid solution, and that 37% is probably a higher value than is actually present, since rapid equilibrating forces during and between extractions would favor formation of the isomer more easily removed by chloroform. Hence it may be concluded that the liquid benzyl ether IIb is the more stable of the two.

Proof of structure depended on finding which of the debenzylated products Ia and IIa yields the lactone III. The benzyl ethers readily underwent hydrogenolysis to give crystalline alcohols. That from the solid (less stable) benzyl ether was obtained with more difficulty owing to the ease with which it isomerized on the palladium-carbon catalyst during hydrogenolysis to give a mixture which was difficult to separate into its component epimeric alcohols. This circumstance together with the recovery in an impure state after acid equilibration of the alcohols of slightly over 50% of epimer IIa indicates that the order of stability for the alcohols is the same as that of the benzyl ethers, but this point is not yet firmly established.

The lactone was obtained in poor yield (13–21%) from both epimers after prolonged heating at 130°. As alkaline hydrolysis of the ketolactone III might lead to epimerization (and indeed gave an impure product), the position adjacent to the ketone function was made less sensitive to anionic attack by converting the lactone to its semicarbazone before hydrolysis. Hydrolysis yielded the semicarbazone of the compound IIa derived from the liquid benzyl ether IIb, thus establishing the *cis* orientation of its groups. The semicarbazone of the isomeric compound Ia was unaltered by the alkaline conditions used to hydrolyze the lactone, hence there is no question of epimerization occurring in this sequence. As the melting points of the semicarbazones were close together and that of a mixture was not depressed, identifications were based on the

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[1] For an excellent review with the pertinent references see D. H. R. Barton, The Tilden Lecture, *J. Chem. Soc.*, 1027 (1953). Papers which were in press at the time of that lecture are: H. L. Goering and C. Serres, This Journal, **74**, 5908 (1952); D. S. Noyce and D. B. Denny, *ibid.*, **74**, 5912 (1952); and J. A. Mills, *J. Chem. Soc.*, 260 (1953). Also see S. Siegel, This Journal, **75**, 1317 (1953); G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 408 (1953); and L. H. Darling, A. K. Macbeth and J. A. Mills, *ibid.*, 1364 (1953).

[2] E. M. Fry, *J. Org. Chem.*, **17**, 1484 (1952).