and Ermolayeva[1] obtained two waves with this aldehyde in buffers of *p*H 4–7, the height of the first wave decreasing and that of the second increasing with increase in *p*H. This behavior is unusual. The two acidic waves of simple carbonyl compounds are usually of about equal height and merge as the *p*H is increased. The half-wave potentials reported by these workers also are considerably more negative than those reported by Tachi,[2] who found only one wave over the *p*H range 1–13. Likewise the potentials reported by Tachi are slightly more negative than those found by MacKenney and Temmer[3,4] in the *p*H range 3–7.

The behavior of furfural upon polarographic reduction would be expected to be similar to that of benzaldehyde and of simple aromatic ketones, such as benzophenone. The principal difference would be that the metal ketyl produced in the first step of reduction in basic solutions should dimerize more strongly than the corresponding ketyl from benzophenone, since the aldehyde contains a hydrogen atom in place of a phenyl group.[5–7] Likewise the ketyl produced from furfural should dimerize more strongly than that from benzaldehyde, since a furyl group, from both steric and resonance considerations, should stabilize the dimer to a greater extent than a phenyl group.

The polarography of furfural was studied in 25% ethanol–water media in buffered solutions of *p*H 1–13. The aldehyde concentration was 0.001 *M*. In acid solution two waves of about equal height were observed only at a *p*H of 5.0.[8] Below a *p*H of 4.0 the single wave was about half the height of the wave at *p*H 6 and 7, the second wave being masked by decomposition of the supporting electrolyte. The half-wave potentials were in good agreement with those reported by Tachi.[2] The values reported by MacKenney and Temmer[3] in this region were obtained in aqueous solution. Somewhat more negative values would be expected in alcohol solutions.[6]

The unusual behavior reported by Korshunov and Ermolayeva[1] in this region was probably caused by insufficient buffering. These results were obtained with about 0.01 *M* aldehyde and at such a concentration it is difficult to have sufficiently high buffer concentration to maintain constant *p*H at the mercury drop. Several runs were made with 0.01 *M* furfural which indicated that this was true. Increasing the concentration of a citrate–phosphate buffer of *p*H 5.5 to the saturation point consistently shifted the half-wave potentials to more positive values. These values were still more negative, however, than those obtained with 0.001 *M* aldehyde in well buffered solutions. The unusual behavior reported for benzaldehyde in acid solution[9] is also probably caused by insufficient buffering.

As the *p*H was increased in basic solutions the current decreased slowly, falling to about half-value in 0.01 and 0.1 *M* sodium hydroxide. The second wave is again masked by decomposition of the supporting electrolyte. Ashworth[5] has shown that a second wave can be obtained with benzaldehyde in basic media by addition of calcium and tetraalkylammonium ions. This was found to be true also for furfural in a calcium chloride–calcium hydroxide buffer of *p*H 12.1.[10] With benzaldehyde in this same buffer the two waves were actually merged. In 0.01 *M* tetramethylammonium hydroxide the second wave of benzaldehyde is observed, but that of furfural is still masked. This indicates that the dimer produced from furfural is more stable than that produced from benzaldehyde, as was expected.

Furfural also produces two waves in solutions of calcium chloride and tetramethylammonium bromide as has been reported for benzaldehyde.[11] The half-wave potentials observed in these salt solutions correspond to those obtained in basic media. In such unbuffered solutions a local decrease in hydrogen ion concentration at the mercury drop would lead to this behavior.

Experimental

The procedure and apparatus were the same as previously described.[6,7] Both furfural and benzaldehyde were freshly distilled under vacuum before use.

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(1) I. A. Korshunov and S. A. Ermolayeva, *J. Gen. Chem. U.S.S.R.*, **17**, 181 (1947).

(2) T. I. Tachi, *Bull. Agr. Chem. Soc. Japan*, **14**, 1371 (1938).

(3) G. MacKenney and O. Temmer, THIS JOURNAL, **70**, 3586 (1948).

(4) I. M. Kolthoff and J. J. Lingane, "Polarography," Second Ed., Vol. II, Interscience Publishers, Inc., New York, N. Y., 1952, p. 796.

(5) M. Ashworth, *Collection Czechoslov. Chem. Communs.*, **13**, 229 (1948).

(6) R. A. Day, Jr., S. R. Milliken and W. D. Shults, THIS JOURNAL, **74**, 2741 (1952).

(7) R. A. Day, Jr., and R. E. Biggers, *ibid.*, **75**, 738 (1953).

(8) All *p*H values herein are of the aqueous buffer.

(9) I. A. Korshunov and T. N. Saznova, *Zhur. Fiz. Khim.*, **23**, 202 (1949).

(10) W. M. Tuddenham and D. H. Anderson, *Anal. Chem.*, **22**, 1146 (1950).

(11) M. Tokuoka, *Collection Czechoslov. Chem. Communs.*, **7**, 392 (1935).

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Basic Ethers of Some Piperidine Alcohols

BY BILL ELPERN

RECEIVED SEPTEMBER 3, 1953

This note reports one of the attempts to prepare compounds having pure curariform activity. The ethers were synthesized by treating the hydroxy substituted piperidines with sodamide and *t*-amino substituted alkyl halides. The resultant dibasic ethers were quaternized with methyl iodide in an inert solvent.

Experimental[1]

Alcohols.—4-Hydroxymethyl-1-methylpiperidine,[2] 3-hydroxymethyl-1-methylpiperidine[2] and 4-hydroxy-1-methyl-4-phenylpiperidine[3] were prepared by published procedures.

4-Hydroxymethyl-1-methyl-4-phenylpiperidine.[4]—Isonipecaine (284 g., 1 mole) was dissolved in water (500 ml.), made strongly alkaline with 35% sodium hydroxide solution and the free base extracted with benzene. To the benzene

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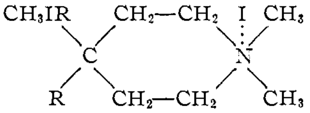
(1) All melting points are corrected. Analyses were carried out by Messrs. M. E. Auerbach, K. D. Fleischer and staff.

(2) R. F. Feldkamp, John Faust and Anna Cushman, THIS JOURNAL, **74**, 3831 (1952).

(3) Aktieselkabet "Ferrosan," Danish Patent 60592; *C. A.*, **40**, 4086 (1946).

(4) S. Schauman, *Arch. Exptl. Path. Pharmakol.*, **196**, 109 (1940). The procedure given was supplied by Dr. S. Archer of this Laboratory.

TABLE I



R′	R	Formula	M.p., °C.	Yield, %	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

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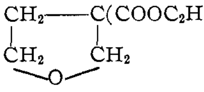
β,β-Dicarbethoxytetrahydrofuran (I) obtained in place of α-oxymethyl-α-carbethoxy-γ-butyrolactone (II) is interesting not only because of the preferential formation of the ether to that of the ester, *i.e.*, lactone linkage but also for its antibacterial activity. The details of this work will be published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



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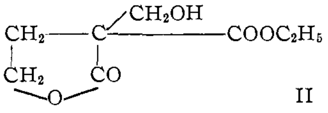

II

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 $C_5H_8O_3$: 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, $E^{1\%}_{1\text{cm.}}$ 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).