

2-Dimethylaminoethyl and 2-Trimethylammoniumethyl Esters of D-, L-, and DL-Lactic Acids¹

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In the course of an investigation directed toward the elucidation of pharmacodynamic characteristics of psychotherapeutic agents, we became interested in examining the pharmacological properties of optically active lactylcholines. While several procedures have been reported for the preparation of lactic acid esters, none of them proved satisfactory in the synthesis of dialkylaminoalkyl and trialkylammoniumalkyl lactates. Smith and Claborn's³ method, using sulfuric acid-catalyzed esterification, gave poor yields in our hands. The procedure suggested by Hovenstein and Pählicke,⁴ involving the condensation of silver lactate and (2-bromoethyl)trimethylammonium bromide had serious limitations, including the fact that no physical constants were reported for the claimed product, DL-lactoylcholine bromide.

In our synthesis, calcium DL-lactate suspended in benzene was converted in the presence of 2-dimethylaminoethanol hydrochloride to free lactic acid. Condensation was effected by the azeotropic removal of the water of esterification in the presence of excess hydrogen chloride and a catalytic amount of *p*-toluenesulfonic acid. The dialkylaminoalkyl ester was converted to the corresponding trialkylammoniumalkyl halide by treatment with methyl iodide in ethyl ether at room temperature. The optical isomers were prepared from the corresponding calcium salts of D- and L-lactic acid.⁵ The pharmacological evaluation of these compounds is in progress.

EXPERIMENTAL⁶

2-Dimethylaminoethyl DL-lactate (I). Dry hydrogen chloride was passed into a mechanically agitated solution of 29.7

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(3) L. T. Smith and H. V. Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940).

(4) H. Hovenstein and H. Pählicke, German Patent **673,841**, March 30, 1939 [*Chem Abstr.*, **33**, 6529 (1939)], *cf. Ber.*, **71B**, 1644 (1938).

(5) The calcium lactates were dried at 120° for 6 hr. Calcium D(-)-lactate, Mann Research Laboratories; $[\alpha]_D^{25} +61.9^\circ$ [$c = 0.37$, in aqu. 10% (NH₄)₆Mo₇O₂₄]. Calcium L(+)-lactate, California Foundation for Biochemical Research; $[\alpha]_D^{25} -50.7^\circ$ [$c = 0.33$, in aqu. 10% (NH₄)₆Mo₇O₂₄].

(6) All analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England. All melting points are corrected (in sealed Corning-9530 tubes).

g. (0.333 mole) of dry 2-dimethylaminoethanol in 200 ml. of anhydrous benzene until the reaction mixture became acid to Congo red. Then, 7.2 g. (0.033 mole) of anhydrous powdered calcium DL-lactate⁵ (equivalent to 0.066 mole lactic acid) was added, and the HCl treatment was continued until the reaction mixture gave a positive Congo red test. No solid could be observed at this time, and the reaction mixture consisted of two immiscible layers. Then, 0.5 g. of *p*-toluenesulfonic acid was added and the reaction mixture was refluxed (steam bath) with vigorous mechanical agitation, until the calculated volume (1.2 ml.) of water of esterification accumulated in the attached azeotropic receiver (about 3 hr.). Upon cooling, the lower liquid layer formed a semisolid cake. The supernatant benzene layer was decanted and washed with one 100 ml. and two 50-ml. portions of aqueous saturated potassium carbonate. The semisolid cake was dispersed in 200 ml. of hot chloroform, and the resultant suspension was cooled to about 15° and treated with the combined (200 ml.) aqueous potassium carbonate washings; after suction-filtration through Celite (Johns-Manville filter aid), the contents of the filter and the aqueous layer (filtrate) were extracted first with chloroform and subsequently with ethyl ether. The benzene solution, and the chloroform and ether extracts were combined, dried over anhydrous sodium sulfate, filtered, and the solvents as well as unreacted 2-dimethylaminoethanol were removed under reduced pressure (max. pot temp. 53–54°). In order to remove residual quantities of the latter, a stream of dry nitrogen was bubbled through the residue under vacuum, at 28–30°, until the pressure dropped to 0.1-mm. Hg (about 1 hr.), and was maintained for an additional 30 minutes. Six and eight-tenths grams (63% yield) of the product remained behind. It was purified by filtering its solution in anhydrous ethyl ether through Celite and removing the solvent *in vacuo*, at 28–30°, under nitrogen. The ester was a pale-yellow liquid, $n_D^{25} 1.4491$. Its infrared absorption frequencies (5%, 0.310M soln. in CHCl₃) 2830(m), 1715(s), 1445(m), and 1125(s) cm.⁻¹ coincided with the values found for ethyl DL-lactate (5%, 0.424M soln. in CHCl₃). The compound distilled at 62–4°/0.2 mm. Hg.⁷

DL-Lactoylcholine iodide (II). Treatment of freshly prepared I (4.2 g., 0.026 mole) with 4.1 g. (0.029 mole) of methyl iodide in 350 ml. of anhydrous ethyl ether, at room temperature (5 days), yielded 6.5 g. (82%) of the product. It crystallized from isopropanol-ethyl acetate in small, hygroscopic, yellow needle and prism-like structures, melting at 120.4–121.2°; its characteristic infrared absorption frequencies (1%, 0.033M concn. in KBr disk) 3500(s), 1755(s), and 1435(m) cm.⁻¹ were in agreement with the expected values.

Anal. Calcd. for C₈H₁₈INO₃: C, 31.71; H, 5.98; I, 41.88; N, 4.62. Found: C, 31.79; H, 5.86; I, 42.0; N, 4.53.

2-Dimethylaminoethyl D(-)-lactate (III). Yield 72%; $n_D^{24-5} 1.4482$; $[\alpha]_D^{25} +8.06^\circ$ ($c = 4.44$, in CH₃OH); the infrared absorption spectrum is identical with that of I.

D(-)-Lactoylcholine iodide (IV). Yield 84%; colorless plates from isopropyl alcohol-ethyl acetate melting at 89.8–90.5°; $[\alpha]_D^{24} +5.26^\circ$ ($c = 17.06$, in CH₃OH). The characteristic infrared absorption bands quoted for II were reproduced within identical frequencies; at the same time, however, some differences (*e.g.* at 1275, 1090, and 1040 cm.⁻¹) were noted in the spectra of compounds II and IV.⁸

(7) Exposure of the free dialkylaminoalkyl ester even to relatively low still pot temperatures appeared to give rise to decomposition; it was rather unstable and decomposed gradually even when stored under nitrogen. The compound was found to be stable in acidic media.

(8) In crystalline state spectra the enantiomorphs are known to differ from the racemate: (a) G. B. M. Sutherland, *Discussions of the Faraday Soc.*, **9**, 319 (1950), (b) N. Wright, *J. Biol. Chem.*, **127**, 137 (1937), (c) E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, **75**, 4585 (1953).

Anal. Calcd. for $C_8H_8INO_3$: C, 31.71; H, 5.98; I, 41.88; N, 4.62. Found: C, 31.64; H, 5.85; I, 41.6; N, 4.51.

2-Dimethylaminoethyl L(+)-lactate (V). Yield 66%; $n_D^{23.5}$ 1.4484; $[\alpha]_D^{23.5}$ -5.86° ($c = 4.27$, in CH_3OH); the infrared spectrum was identical with those of I and III.

L(+)-Lactoylcholine iodide (VI). Yield 83%; colorless plates from isopropyl alcohol-ethyl acetate melting at $90.4-91.0^\circ$; $[\alpha]_D^{23.5}$ -5.66° ($c = 11.90$, in CH_3OH); the infrared absorption spectrum was identical with that of IV.

Anal. Calcd. for $C_8H_8INO_3$: C, 31.71; H, 5.98; I, 41.88; N, 4.62. Found: C, 31.77; H, 5.78; I, 42.0; N, 4.43.

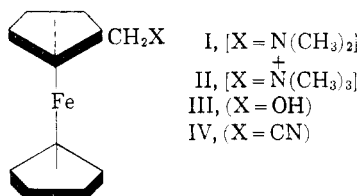
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The Benzal Derivative of Ferrocenylacetonitrile¹

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It has previously been shown in this laboratory that ferrocene can be aminomethylated readily to form dimethylaminomethylferrocene (I),² and that the methiodide of this tertiary amine (II) is a useful intermediate for the synthesis of a number of monosubstituted ferrocene derivatives.²⁻⁶ For example, II undergoes the S_N2 displacement reaction with aqueous sodium hydroxide and potassium cyanide to give excellent yields of alcohol III² and nitrile IV,^{5,6} respectively.



Since the S_N2' type of displacement was possible,⁷

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957). For an earlier communication, see C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1956).

(3) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 906 (1957).

(4) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 1246 (1957).

(5) C. R. Hauser, J. K. Lindsay, and D. Lednicer, *J. Org. Chem.*, **23**, 358 (1958).

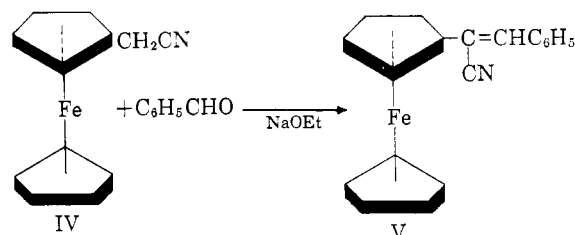
(6) D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958).

(7) In a preliminary communication [C. R. Hauser, J. K. Lindsay, D. Lednicer, and C. E. Cain, *J. Org. Chem.*, **22**, 717 (1957)] the S_N2' displacement was assumed to occur with the cyanide ion to form the 2-methylecyano structure but this structure was soon discarded in favor of structure IV; see refs. 5 and 6. Evidence for the latter structure has been independently obtained by J. M. Osgerby and P. L. Pauson, see ref. 8.

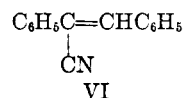
definite proof for structures III and IV was desirable. This was readily accomplished with the alcohol III which produced the corresponding aldehyde on oxidation,² but the structure of nitrile IV was more difficult to establish with certainty.⁷ The nitrile gave on hydrolysis an acid, the infrared absorption spectrum of which was identical with that of ferrocenylacetic acid prepared from acetylferrocene by the Willgerodt rearrangement.^{6,8} However, the yields of this acid from the latter reaction have been low (10–20%),⁸⁻¹⁰ and the melting points have varied somewhat, 161° ,⁸ $150-152^\circ$,⁹ and $135-140^\circ$.¹⁰

Confirmation⁵ for the two-carbon side chain of structure IV was obtained by reducing the nitrile to the corresponding primary amine, which was exhaustively methylated. The resulting quaternary ammonium ion underwent β -elimination with potassium amide to form vinylferrocene.⁵

Still further evidence for structure IV has now been obtained by showing the presence of the two methylenic hydrogen atoms in the nitrile. Thus, like phenylacetonitrile,¹¹ ferrocenylacetonitrile IV underwent with benzaldehyde in the presence of alkali an aldol type condensation accompanied by the elimination of water to form the benzal derivative V in 80% yield.



The product exhibited an infrared absorption spectrum that was similar to that of the benzal derivative of phenylacetonitrile (VI). In Table I are listed some of the more significant infrared absorption bands for nitriles V and VI.



The bands at 4.5 and 4.46 μ are ascribed to the nitrile group since Bellamy¹² gives 4.45–4.5 μ for the nitrile group in α,β -unsaturated alkyl nitriles. The bands at 14.32 and 14.33 μ are evidently due

(8) J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 656 (1958); see also J. M. Osgerby and P. L. Pauson, *Chem. and Ind.*, 196 (1958).

(9) P. L. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

(10) K. L. Rinehart, Jr., Ronald J. Curby, Jr., and Phillip E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957).

(11) See H. M. Crawford, *J. Am. Chem. Soc.*, **56**, 139 (1934).

(12) See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.