

2-Chloroprocaine Amide and 2-Chlorothiocaine

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In connection with our investigations on the biological effect of substituting halogens on the benzene ring of procaine and related compounds, we have prepared 2-chloroprocaine amide and 2-chlorothiocaine. These were secured *via* the reaction of 2-chloro-4-nitrobenzoyl chloride with β -diethylaminoethylamine and with β -diethylaminoethanethiol, respectively, and subsequent reduction with iron.

Both, 2-chloroprocaine amide and 2-chlorothiocaine, are as active as procaine as local anesthetics. 2-Chloroprocaine amide is approximately four times as potent as procaine amide in blocking artificial fibrillation in the dog.

EXPERIMENTAL¹

N-(β -Diethylaminoethyl)-2-chloro-4-nitrobenzamide hydrochloride (I). To a solution of 0.25 mole of 2-chloro-4-nitrobenzoyl chloride, secured from the acid and thionyl chloride, in 150 ml. of dry benzene 58 g. of β -diethylaminoethylamine was added with stirring and cooling. The mixture was stirred for 20 min. at room temperature and then allowed to stand overnight at room temperature. It was stirred and heated under reflux for 1 hr., cooled, and poured into a mixture of ice and concd. hydrochloric acid (50 ml.). The aqueous layer was separated and washed with benzene. The aqueous solution was then cooled, made alkaline with sodium carbonate trihydrate (ca. 120 g.) and extracted with one 200-ml. and three 100-ml. portions of ether. The combined ether solutions were washed thoroughly with water, dried over anhydrous magnesium sulfate, and saturated with dry hydrogen chloride. The solid was removed by filtration, washed with ether, and air-dried. It weighed 70 g. and melted at 167–170°. Recrystallization from a mixture of ethanol and ether provided an analytical sample melting at 169–170°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N_2O_3$: N, 12.50. Found: N 12.53, 12.35.

N-(β -Diethylaminoethyl)-2-chloro-4-aminobenzamide(2-chloroprocaine amide) dihydrochloride (II). A suspension of 50 g. of powdered iron in 100 ml. of water was heated to 65°, and a warm solution of 20.2 g. of I in 100 ml. of water was added slowly with stirring. The mixture was then stirred and heated for 2 hr. at ca. 75° and filtered while hot. The filtrate was chilled, made alkaline with 10% sodium carbonate and extracted with one 300-ml. and three 150-ml. portions of chloroform. The chloroform solutions were combined, washed with water, and dried over anhydrous magnesium sulfate. Ethanol (100 ml.) was added and mixture was treated with dry hydrogen chloride. Ether was added to the cloud point, and after chilling overnight the solid was removed and dried. It weighed 16.2 g. and melted at 190–193°. After recrystallization from ethanol with charcoal, the white crystals melted at 193–195°.

Anal. Calcd. for $C_{13}H_{22}Cl_2ON_2$: N, 12.26; Cl, 31.04. Found: N, 12.26; Cl, 31.04.

Free base (III). An aqueous solution of 25 g. of II was made alkaline with sodium carbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the residue (18.7 g.) from ether gave white glistening crystals that melted at 79.5–80.5°.

Anal. Calcd. for $C_{13}H_{20}ClN_2O$: C, 57.86; H, 7.47. Found: C, 57.81; H, 7.50.

Monohydrochloride (IV). This was prepared by mixing a solution of II (3.06 g.) in 50 ml. of methanol and a solution of III (2.70 g.) in 5 ml. of benzene. The product melting at 139.5–141° was recrystallized from a mixture of methanol and ether to provide an analytical sample melting at 142–143°.

Anal. Calcd. for $C_{13}H_{21}Cl_2N_2O$: N, 13.72. Found: N, 13.70, 13.72.

Formate (V). A solution of III (2.70 g.) in 5 ml. of benzene was mixed with a solution of 0.46 g. of 98% formic acid in 5 ml. of isopropyl alcohol and ether was added to induce crystallization. The product weighing 2.40 g. and melting at 99.5–100° was recrystallized from a mixture of ethanol and ether to give an analytical sample melting at 100–100.5°.

Anal. Calcd. for $C_{14}H_{22}ClN_2O_2$: N, 13.31. Found: N, 13.34, 13.37.

N-(β -Diethylaminoethyl)-2-chloro-4-nitrothiolbenzoate hydrochloride (VI). To a solution of 2-chloro-4-nitrobenzoyl chloride, prepared from 12.1 g. of acid and 14.3 g. of thionyl chloride, in 25 ml. of dry benzene a solution of 7.98 g. of β -diethylaminoethanethiol² in 20 ml. of dry benzene was added with stirring and cooling. The mixture was stirred 0.5 hr. longer and then allowed to stand overnight at room temperature. It was transferred to a mixture of 150 ml. of water and 50 g. of ice. Ether (50 ml.) and benzene (50 ml.) were added, and mixture was made alkaline with ammonium hydroxide. The organic layer was separated, and the aqueous solution was washed twice with 50 ml. of ether. The combined organic solutions were washed with one 100-ml. and four 50-ml. portions of water, dried over anhydrous magnesium sulfate, and treated with dry hydrogen chloride. The hydrochloride was removed and dried. It weighed 11.85 g. and melted at 120.5–122.5°. After recrystallization from a mixture of ethanol and ether, the melting point was raised to 125–126°.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_3S$: N, 7.93. Found: N, 8.00.

N-(β -Diethylaminoethyl) 2-chloro-4-aminothiolbenzoate (2-chlorothiocaine) hydrochloride (VII). A solution of 2.7 g. of VI (m.p. 120.5–122.5°) in 20 ml. of distilled water was added with stirring to a mixture of 7.5 g. of iron powder and 10 ml. of distilled water preheated to 45°. The resulting mixture was stirred and heated for 1 hr. at 45° and then allowed to stand for 1 hr. at room temperature. While cooling, the pH was adjusted to 11 with concd. ammonium hydroxide, and the mixture was filtered. The filtrate was extracted with 50 ml. of ethyl acetate and the sludge was washed with 200 ml. of hot ethyl acetate. The combined ethyl acetate solutions were washed with three 100-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. Absolute ethanol (10 ml.) and anhydrous ether (50 ml.) were added and solution was charged with dry hydrogen chloride. The crude hydrochloride weighed 1.4 g. An analytical sample, after recrystallization from aqueous ethanol, melted at 218–219°.

Anal. Calcd. for $C_{13}H_{20}Cl_2N_2OS$: N, 8.67; Cl, 21.93. Found: N, 8.60; Cl, 21.82.

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(1) All melting points are uncorrected.

(2) N. F. Albertson and R. O. Clinton, *J. Am. Chem. Soc.*, 67, 1222 (1945).

Chromium Trichloride Tetrahydrofuranate¹

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The reaction of anhydrous chromium trichloride and phenylmagnesium bromide in ether² or in tetrahydrofuran³ is necessarily a heterogeneous one owing to the extreme insolubility of this metallic halide in organic solvents. Inorganic salts of chromium are in fact generally insoluble in all non-hydroxylic solvents; and this property presents difficulties in promoting their reactions in organic solvents with organic reagents. We have now found that the trichloride may be made soluble by complexing it with tetrahydrofuran and that its reactions with Grignard reagents proceed rapidly, quantitatively, and homogeneously in this form.

The conversion of anhydrous chromium trichloride into its tetrahydrofuranate is achieved by the continuous extraction with anhydrous tetrahydrofuran of its solid form admixed with catalytic amounts of zinc dust. In this manner the halide is quantitatively extracted by the solvent from which the violet tetrahydrofuranate is crystallized. The zinc metal which is recovered unchanged is considered to behave as a reducing agent, solubilizing chromium in its divalent form, followed by subsequent reduction itself and concurrent formation of $\text{CrCl}_2(\text{THF})_3$.⁴ The coordinating tetrahydrofuran molecules are very tightly bound in the complex, for they are not lost even upon heating of the complex to 100° at 20 mm., and the tetrahydrofuranate may be kept in the open air several hours without appreciable hydrolysis, since the crystals are only slightly hygroscopic and deliquesce quite slowly to a green hydrate. Consequently, as a reagent it may be stored indefinitely without decomposition so long as it is kept dry.

EXPERIMENTAL

Chromium trichloride tri-tetrahydrofuranate. The tetrahydrofuran (Mathieson, Coleman and Bell, b.p. 64–66°) used in this preparation was purified and dried by refluxing over sodium ribbon with fresh ribbon being added until new ribbon maintained a clean surface after 5 hr. of refluxing. Just prior to use the THF was distilled, treated with fresh sodium ribbon and with lithium aluminum hydride, and then redis-

(1) Paper VI, " π -Complexes of the Transition Metals"; Paper V, H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.*, **80**, 2913 (1958).

(2) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **79**, 3062 (1957).

(3) W. Herwig and H. H. Zeiss, *J. Am. Chem. Soc.*, **79**, 5959 (1957).

(4) This phenomenon has been observed previously in that chromous chloride will cause the trichloride to dissolve in ether: N. V. Sidgwick, *The Chemical Elements and Their Compounds*, Oxford Univ. Press, New York, N. Y., 1950, p. 1012.

tilled in a stream of dry, oxygen-free nitrogen (GE lamp grade is suitable for this purpose without further drying and/or purification).

Anhydrous chromium trichloride (Fisher), 12.21 g., mixed with 0.15 g. of zinc dust, is placed in the thimble of a Soxhlet extraction apparatus and then extracted overnight with 140 ml. of boiling THF or until no further color is observable in the cycling liquid (10–15 hr.). After complete extraction only zinc dust remains in the extraction thimble, while the pot flask contains the solution of the tetrahydrofuranate (2.8 g./100 ml. of hot THF) together with the crystalline chromium trichloride tri-tetrahydrofuranate which has crystallized during extraction. Concentration, cooling, and filtration are employed to isolate the crystalline form in essentially quantitative yield.

Anal. Calcd. for $\text{CrCl}_3(\text{C}_4\text{H}_8\text{O})_3$: Cr, 13.88; Cl, 28.39. Found: Cr, 13.42; Cl, 28.57, 28.19.

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Preparation of a New Class of Steroids with Unnatural Configuration. The 19-Nor-5 α ,10 α Series

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There are four possible steric arrangements of the A/B rings of the 19-nordihydrosteroid nucleus (the *trans-syn-trans* conformation requires a boat form for ring B), all other centers of asymmetry being kept constant. The allo configurational series (5 α ,10 β) was reported by Bowers, Ringold, and Dorfman¹ while the normal series (5 β ,10 β) was described recently from this Laboratory.²

This communication reports the synthesis of a third and hitherto unknown series of 19-norsteroids, and evidence is presented which permits assignment of structure and classification as 19-nor-5 α ,10 α -dihydrosteroids.

Hydrogenation of 17 α - ethinyl - or 17 α - ethyl-17 β - estradiol with ruthenium dioxide catalyst at elevated pressures afforded a crystalline product, 17 α -ethyl-5 α ,10 α -estrane-3 β ,17 β -diol (Ia) (m.p. 143–145°; $[\alpha]_D^{25}$ –20.9° (CHCl₃). Found for C₂₀H₃₄O₂ · C, 78.11; H, 11.27) in excellent yield. Oxidation of this diol with chromic anhydride - pyridine gave 17 α -ethyl-5 α ,10 α -estrane-17 β -ol-3-one (IIa) (m.p. 205–207°; $[\alpha]_D^{25}$ –66.4°. Found for C₂₀H₃₂O₂: C, 78.67; H, 10.99).³ Sodium and pro-

(1) A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957).

(2) R. T. Rapala and E. Farkas, *J. Am. Chem. Soc.*, **80**, 1008 (1958).

(3) All melting points are uncorrected. We gratefully acknowledge valuable technical assistance by Messrs. W. Scanlon, hydrogenation experiments; Messrs. G. M. Maciak, W. L. Brown, and H. L. Hunter, elemental analysis. All rotations are done in methanol unless otherwise specified.