

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

2,3-Dihydro-1H-imidazo[1.5-a]pyrroles. Condensation of Pyrroles and Formaldehyde and Primary Amines

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The reaction of pyrroles with formaldehyde and primary amines was investigated. 2,3-Dihydro-1H-imidazo[1.5-a]-pyrroles were prepared directly from 3-carbethoxy-2,4-dimethylpyrrole and also from the corresponding 2-(N-substituted aminomethyl)-pyrroles. The reactions and interrelationships of these products were studied.

The use of the Mannich reaction to introduce a substituent directly on a pyrrole ring was demonstrated by Kuhn and Stein² in the preparation of gramine (3-dimethylaminomethylindole) by the reaction of indole with formaldehyde and dimethylamine. 2-Methylgramine was obtained in an analogous manner from 2-methylindole.³ Feldman and Wagner⁴ condensed carbazole with N,N'-methylenedipiperidine to form 9-N-piperidinomethylcarbazole. Houk and Bock⁵ studied the reaction of formaldehyde and primary and secondary amines with pyrroles having a free β -position. No structure was proposed for the products, which analyzed for the condensation of equimolar proportions of the reactants. Interest in Mannich bases from pyrrole was stimulated by the work of Snyder and Smith,⁶ who found that reaction of gramine methiodide with the sodium derivative of acetaminomalonic ester resulted in an intermediate which provided a convenient synthesis of *dl*-tryptophan. In related work⁷ involving carbon alkylation, β -indoleacetic acid was prepared through the reaction of gramine methiodide with potassium silver cyanide.

Bachman and Heisey⁸ described the preparation of 2-(N-substituted-aminomethyl)-pyrroles from the condensation of pyrrole and formaldehyde with piperidine and morpholine and reported that 2,5-dimethylpyrrole formed a 3,4-bis-(N-piperidinomethyl) derivative. The related 2-dimethyl- and 2-diethylaminomethylpyrroles were reported by Herz, Dittmer and Cristol.⁹ These workers were also successful in employing primary amines in the condensation with formaldehyde and pyrrole and obtained in this way 2-methylaminomethyl- and 2-ethylaminomethylpyrroles in 15 and 27% yields.

Phenols react in a similar manner with formaldehyde and primary amines to form the analogous alkylaminomethylphenols.¹⁰ More recently¹¹ it has been shown that 1,3-benzoxazines can also be prepared directly from such systems or by further reaction of the alkylaminomethylphenols with for-

maldehyde. In view of these results the present study was undertaken in order to explore more fully the condensation of selected pyrroles with formaldehyde and primary amines.

Pyrrole reacted smoothly with equimolar proportions of formaldehyde and cyclohexylamine hydrochloride at room temperature to give a 66% yield of 2-cyclohexylaminomethylpyrrole hydrochloride from which the crystalline free base (I) was readily obtained. No monomeric products were isolated, however, when I reacted further with formaldehyde or when pyrrole, formaldehyde and cyclohexylamine hydrochloride were condensed directly in a molar ratio of 1:2:1. Only starting materials were recovered when cyclohexylamine was used in place of the hydrochloride in the above condensations at room temperature and no crystalline products were isolated from the resinous material obtained at 100°.

With a view to avoiding possible side reactions, attention was turned toward the use of substituted pyrroles. Condensation of 3-carbethoxy-2,4-dimethylpyrrole (II), formaldehyde and cyclohexylamine in a molar ratio of 1:2:1, respectively, resulted in the introduction of a heterocyclic ring with the formation of 6-carbethoxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole (III) in 66% yield. Reaction of II with equimolar quantities of formaldehyde and cyclohexylamine at 95° led to 4-carbethoxy-2-cyclohexylaminomethyl-3,5-dimethylpyrrole (IV), which upon further reaction with formaldehyde gave III. A substantially higher yield of IV was obtained at room temperature with cyclohexylamine hydrochloride in place of the free base in the equimolar condensation. Formaldehyde and IV hydrochloride in refluxing ethanol, however, yielded bis-(4-carbethoxy-3,5-dimethyl-2-pyrrolyl)-methane (V). Products analogous to III and IV were obtained when isopropyl- and *t*-butylamine were used in place of cyclohexylamine.

In a study of the reactivity of the imidazopyrroles, III was found to be stable to dilute acids and was recovered in high yield when treated with a refluxing ethanol solution of potassium hydroxide for one hour. Treatment of III with concentrated sulfuric acid at 25° resulted in the smooth hydrolysis of the ester group without disruption of the bicyclic ring system. Reduction of III with lithium aluminum hydride gave an 85% yield of 2-cyclohexyl-2,3-dihydro-6-hydroxymethyl-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole.

No products were isolated from the attempted condensation of 2-carbomethoxypyrrole, 2-pyrrole-carboxylic acid or 3,5-dicarbethoxy-2,4-dimethyl-

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(2) H. Kuhn and O. Stein, *Ber.*, **70**, 567 (1937).

(3) J. V. Supniewski and M. Serafin-Gajewski, *Acta Polon. Pharm.*, **2**, 125 (1938); *C. A.*, **34**, 6410 (1940).

(4) J. Feldman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(5) A. L. Houk and L. H. Bock, U. S. Patent 2,243,630 (1941).

(6) H. R. Snyder and C. W. Smith, *THIS JOURNAL*, **66**, 350 (1944).

(7) H. R. Snyder, C. W. Smith and J. M. Stewart, *ibid.*, **66**, 200 (1944).

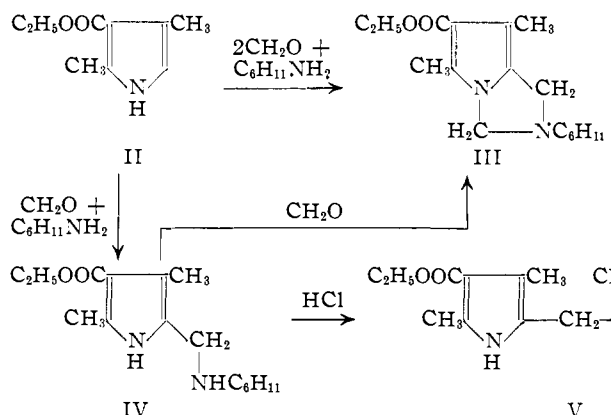
(8) G. B. Bachman and L. V. Heisey, *ibid.*, **68**, 2496 (1946).

(9) W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **69**, 1698 (1947).

(10) H. A. Bruson, *ibid.*, **58**, 1741 (1936).

(11) (a) W. J. Burke, *ibid.*, **71**, 609 (1949); (b) W. J. Burke and C. W. Stephens, *ibid.*, **74**, 1518 (1952).

pyrrole, with formaldehyde and primary amines under conditions used successfully with II. The recovery of the substituted pyrrole was high in each case. The results with 2-carbomethoxypyrrole suggested that the methyl groups present in II contributed an appreciable activating effect.



The infrared absorption in the neighborhood of 2.85μ shown by II is characteristic of an N-H bond stretching frequency. The absence of a band in this region in the spectrum for III is consistent with the imidazopyrrole structure proposed.

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Experimental

2-Cyclohexylaminomethylpyrrole.—Pyrrole (6.7 g., 0.10 mole) was added to a solution of 13.6 g. of cyclohexylamine hydrochloride (0.10 mole) in 7.5 ml. of 37% aqueous formaldehyde (0.10 mole), an equal volume of water and 10 ml. of methanol. The solution was shaken and allowed to stand one hour. Addition of 25 ml. of ether and cooling caused the crystallization of 14.2 g. of the product, which was recrystallized from methanol by the addition of ether. The hydrochloride melted at $175\text{--}176^\circ$, yield 66%.

Anal. Calcd. for $\text{C}_{11}\text{H}_{19}\text{ClN}_2$: Cl, 16.51. Found: Cl, 16.47.

The free base was obtained in 95% yield from the hydrochloride (13 g.) by treatment with 50 ml. of ether and 100 ml. of water containing 30 ml. of 2-aminoethanol. The ether solution was washed with water and dried. The solid (10.1 g.) obtained by evaporation of the ether was recrystallized from petroleum ether; m.p. $52.5\text{--}54^\circ$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2$: C, 74.11; H, 10.18. Found: C, 73.34; H, 10.14.

When cyclohexylamine was used in the above condensation in place of the hydrochloride, only starting materials were recovered at room temperature. Use of cyclohexylamine at 100° led to a resinous material from which no monomeric products were isolated.

6-Carbethoxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole (III). Procedure A.—Cyclohexylamine (4.95 g., 0.05 mole) was added slowly and with cooling to 100 ml. of 1,4-dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.10 mole). After addition of 16.7 g. of 3-carbomethoxy-2,4-dimethylpyrrole (0.10 mole), the solution was heated at 95° in a closed system for one hour. The solvent was removed by distillation under reduced pressure and the residue taken up in 40 ml. of acetone and an equal volume of ether. The solution was then saturated with hydrogen chloride and allowed to stand at -10° . The hydrochloride (11.5 g.) which separated was recrystallized from 95% ethanol; m.p. $183\text{--}185^\circ$, yield 70%.

Anal. Calcd. for $\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}_2$: Cl, 10.85. Found: Cl, 11.00.

The free base (95% yield) melted at $88.5\text{--}89^\circ$ after recrystallization from acetone-water. The infrared absorption spectrum showed maxima at 5.90, 7.88, 8.90, 11.53 and 12.75μ .

Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_2$: C, 70.30; H, 9.02; N, 9.65; mol. wt., 290.4. Found: C, 69.67; H, 8.97; N, 9.79; mol. wt., 290.

Procedure B.—Cyclohexylamine (4.95 g., 0.05 mole) was added slowly and with cooling to 50 ml. of 1,4-dioxane containing 15 ml. of 37% aqueous formaldehyde (0.20 mole). After addition of 8.35 g. of 3-carbomethoxy-2,4-dimethylpyrrole (0.05 mole) the mixture was heated at 95° in a closed system for one hour. The solvent was removed by distillation under reduced pressure and the residue dissolved in 50 ml. of ether, washed twice with 50-ml. portions of water and dried over sodium sulfate. The ether was evaporated and 30 ml. of acetone was added to the residue. The acetone solution was then saturated with hydrogen chloride and cooled. The hydrochloride (7.2 g.) was recrystallized from 95% ethanol; m.p. $183\text{--}185^\circ$, yield 44%.

Anal. Calcd. for $\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}_2$: Cl, 10.85. Found: Cl, 10.69.

The free base melted at $88.5\text{--}89^\circ$ and did not depress the melting point of the compound from procedure A. Similar results were obtained when procedure B was repeated except that only 0.1 mole of formaldehyde was used.

4-Carbethoxy-2-cyclohexylaminomethyl-3,5-dimethylpyrrole (IV). Procedure A.—3-Carbomethoxy-2,4-dimethylpyrrole (16.7 g., 0.10 mole) was dissolved in 40 ml. of methanol and added to a solution of cyclohexylamine hydrochloride (13.6 g., 0.10 mole) in 7.5 ml. of 37% aqueous formaldehyde (0.10 mole), an equal volume of water and 10 ml. of methanol. After standing for one hour, 25 ml. of ether was added and the mixture cooled. The product (23.5 g.) was recrystallized by the addition of 10 volumes of ether to a solution of the hydrochloride in methanol; m.p. $154\text{--}155^\circ$, yield 75%.

Anal. Calcd. for $\text{C}_{16}\text{H}_{27}\text{ClN}_2\text{O}_2$: Cl, 11.26. Found: Cl, 11.25.

The free base, obtained by treatment of the hydrochloride with 2-aminoethanol, was recrystallized from petroleum ether; m.p. $82\text{--}82.5^\circ$. The infrared absorption spectrum showed maxima at 2.85, 6.02, 7.88, 8.80, 9.15 and 12.75μ .

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_2$: C, 69.02; H, 9.42. Found: C, 69.36; H, 9.46.

Procedure B.—Cyclohexylamine (4.95 g., 0.05 mole) was added slowly with cooling to 25 ml. of 1,4-dioxane containing 3.75 ml. of 37% aqueous formaldehyde (0.05 mole). After the addition of 8.35 g. of 3-carbomethoxy-2,4-dimethylpyrrole (0.05 mole), the solution was refluxed for one-half hour. The solvent was removed by distillation under reduced pressure and the residue dissolved in 50 ml. of petroleum ether (b.p. $65\text{--}110^\circ$) from which it crystallized on cooling; m.p. $82\text{--}82.5^\circ$, yield 30%. The m.p. of a mixture of the products from procedures A and B was not depressed.

Conversion of IV to III with Formaldehyde.—Ten grams of IV (0.036 mole) was added to 100 ml. of 1,4-dioxane containing 5 ml. of 37% aqueous formaldehyde (0.067 mole). After the solution was refluxed gently for two hours, the solvent was removed by distillation under reduced pressure and the residue dissolved in 70 ml. of acetone. The product (8.0 g.) which precipitated on addition of hydrogen chloride was recrystallized from 95% ethanol; m.p. $184\text{--}186^\circ$, yield 68%.

Anal. Calcd. for $\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}_2$: Cl, 10.85. Found: Cl, 10.77.

The free base from the above hydrochloride melted at $88.5\text{--}89^\circ$ after recrystallization from acetone-water and did not depress the melting point of III, prepared directly from II as described above.

Bis-(4-carbomethoxy-3,5-dimethyl-2-pyrrolyl)-methane.—A mixture of 1.83 g. of IV hydrochloride (0.0058 mole) and 0.45 ml. of 37% aqueous formaldehyde (0.006 mole) in 45 ml. of ethanol was heated under reflux for one hour. The crystalline product (quantitative yield of crude) obtained upon removal of solvent was washed with ether and dried; m.p. $227\text{--}228^\circ$. V was prepared earlier¹² from II and formaldehyde; m.p. 223.5° .

(12) O. Piloty, W. Krannich and H. Will, *Ber.*, **47**, 2544 (1914).

Anal. Calcd. for $C_{19}H_{25}N_2O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.21; H, 7.66; N, 8.21.

The same product (m.p. 228°) was obtained in 72% yield when II, formaldehyde and cyclohexylamine hydrochloride in molar proportions of 1:2:1, were refluxed in ethanol for 15 minutes.

6-Carboethoxy-2,3-dihydro-2-isopropyl-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole.—Isopropylamine was treated with formaldehyde and II essentially as described in the direct preparation of III by procedure A above. The product was isolated as the hydrochloride, which was recrystallized from 95% ethanol; m.p. 159–160°, yield 32%.

Anal. Calcd. for $C_{14}H_{23}ClN_2O_2$: Cl, 12.36. Found: Cl, 12.39.

The free base, obtained by treatment with 2-aminoethanol, was recrystallized from acetone–water (5:1 by volume); m.p. 86.5–87.5°.

Anal. Calcd. for $C_{14}H_{22}N_2O_2$: C, 67.16; H, 8.86; mol. wt., 250.3. Found: C, 67.33; H, 9.04; mol. wt., 247 (cryoscopic in benzene).

2-*t*-Butyl-6-carboethoxy-2,3-dihydro-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole.—*t*-Butylamine was condensed with formaldehyde and II essentially as described in the direct preparation of III by procedure A. The product was isolated as the hydrochloride, which was recrystallized from methanol–ether; m.p. 187–189°, yield 40%.

Anal. Calcd. for $C_{15}H_{25}ClN_2O_2$: Cl, 11.79. Found: Cl, 11.84.

The free base melted at 92–94°, after recrystallization from an acetone solution to which water was added.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.14; H, 9.15; mol. wt., 264.4. Found: C, 68.46; H, 9.04; mol. wt., 256 (cryoscopic in benzene).

4-Carboethoxy-2-isopropylaminomethyl-3,5-dimethylpyrrole Hydrochloride.—Equimolar quantities of isopropylamine, formaldehyde and II in dioxane solution were heated at 95° in a closed system for one hour. The product was isolated as the hydrochloride, which melted at 172°, after recrystallization from methanol–ether; yield 39%.

Anal. Calcd. for $C_{13}H_{23}ClN_2O_2$: Cl, 12.90. Found: Cl, 12.23.

2-*t*-Butyl-4-carboethoxy-3,5-dimethylpyrrole Hydrochloride.—*t*-Butylamine (0.10 mole) reacted with formaldehyde (0.10 mole) and II (0.05 mole) in dioxane at 95° for one hour in a closed system. The product (54% yield), isolated

as the hydrochloride, melted at 162–164°, after recrystallization from methanol–ether.

Anal. Calcd. for $C_{14}H_{25}ClN_2O_2$: Cl, 12.28. Found: Cl, 12.24.

6-Carboxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole.—Three grams of III (0.0103 mole) was added with cooling to 11 ml. of concentrated sulfuric acid and was stirred occasionally over a period of two hours. The mixture was then poured into 100 g. of ice and sodium hydroxide was added until the pH was 7. The resulting solid (2.15 g.) was removed by filtration and washed with water. The product, after recrystallization from acetone turned yellow at 155° and melted at 183°, yield 80%.

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.54; H, 8.44.

2-Cyclohexyl-2,3-dihydro-6-hydroxymethyl-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole.—Lithium aluminum hydride (0.35 g., 0.0092 mole) was stirred in dry ether for 15 minutes. III (2.9 g., 0.01 mole) dissolved in 75 ml. of dry ether was added to the hydride suspension. The mixture was stirred for one hour and water was slowly added to decompose the complex. The ether layer was washed three times with 100-ml. portions of water, dried over anhydrous sodium sulfate and evaporated. The oily residue crystallized from petroleum ether. The product (2.1 g.) was recrystallized from ethyl acetate–petroleum ether (1:5 by volume); m.p. 94.5–95.5°, yield 85%.

Anal. Calcd. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74. Found: C, 72.35; H, 9.63.

Treatment of III with Potassium Hydroxide.—A solution of 6-carboethoxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1H-imidazo[1.5-a]pyrrole (2.9 g., 0.01 mole) and 0.65 g. of 85% potassium hydroxide (0.01 mole) in 30 ml. of 95% ethanol was refluxed for one hour. On evaporation of the solvent there remained a sticky oil that crystallized on standing. The crystalline mass was dissolved in 30 ml. of acetone and saturated with hydrogen chloride. The resulting hydrochloride (2.5 g., 77% recovery) was recrystallized from 95% ethanol; m.p. 184–186°.

Anal. Calcd. for $C_{17}H_{27}ClN_2O_2$: Cl, 10.85. Found: Cl, 10.83.

Infrared Absorption Spectra.—The infrared absorption spectra were determined with a Perkin–Elmer recording infrared spectrophotometer model 12 C equipped with sodium chloride prisms. Nujol mulls of the samples were used.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some New 2,6-Disubstituted- ω -dialkylaminoacetanilides

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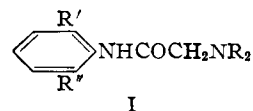
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Twelve new 2,6-disubstituted- ω -dialkylaminoacetanilides have been prepared along with their corresponding hydrochlorides and their physical properties described. Preliminary pharmacological testing of these compounds indicates they all possess anesthetic properties of varying degrees of strength but are too irritating to permit clinical use.

Since the discovery of Xylocaine, 2,6-Me₂C₆H₃NHCOCH₂N(C₂H₅)₂, by Löfgren¹ in 1946, many compounds of the ω -dialkylaminoacetanilide type have been synthesized and tested for their local anesthetic properties. Much of the work done on compounds of this general type has been aptly reviewed by Löfgren² in 1948.

In this work we have synthesized twelve compounds of the general type I and their corresponding hydrochlorides with various arrangements of alkyl, alkoxy and halogen groups in the 2,6-positions.

(1) N. Löfgren, *Arkiv. Kemi Mineral. Geol.*, **22A**, No. 18 (1946).
(2) N. Löfgren, "Studies on Local Anesthetics, Xylocaine, A New Synthetic Drug," Inaugural Dissertation for the Doctor of Philosophy, Univ. of Stockholm, Stockholm, 1948.



tions. Since no compounds of the type I with alkoxy or halogen substituents in the 2,6-positions had been synthesized until the recent work of Löfgren and Ekstrand,³ it was decided to limit our work to these types of compounds.

2-Methoxy-6-methylaniline and 2,6-dimethoxyaniline were first converted to the corresponding chloroacetylated compounds by reaction with chloroacetyl chloride in an acetate buffer after the

(3) N. Löfgren and T. Ekstrand, *Acta Chem. Scand.*, **6**, 1016 (1952).