Vol. 76

Anal. Caled. for  $C_{19}H_{28}N_2O_4$ : C, 65.87; H, 7.57; N, 8.09. Found: C, 65.21; H, 7.66; N, 8.21.

The same product (m.p.  $228^{\circ}$ ) 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-Carbethoxy-2,3-dihydro-2-isopropyl-5,7-dimethyl-1Himidazo[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-carbethoxy-2,3-dihydro-5,7-dimethyl-1Himidazo[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  $92-94^\circ$ , 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-Carbethoxy-2-isopropylaminomethyl-3,5-dimethylpyrrole Hydrochloride.—Equimolar quantities of isopropylamine, formaldehyde and II in dioxane solution were heated at  $95^{\circ}$  in a closed system for one hour. The product was isolated as the hydrochloride, which melted at  $172^{\circ}$ , after recrystallization from methanol-ether; yield 39%.

Anal. Calcd. for  $C_{13}H_{23}CIN_2O_2$ : C1, 12.90. Found: C1, 12.23.

2-t-Butyl-4-carbethoxy-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-1Himidazo[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. Caled. for  $C_{15}H_{22}N_2O_2;\ C,\ 68.67;\ H.\ 8.45\cdot$  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<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O: C, 72.54; H, 9.74. Found: C, 72.35; H, 9.63.

Treatment of III with Potassium Hydroxide.—A solution of 6-carbethoxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1Himidazo[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. Caled. for C<sub>17</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 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.

SALT LAKE CITY, UTAH

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

# Some New 2,6-Disubstituted- $\omega$ -dialkylaminoacetanilides

By L. S. Fosdick and J. A. Carbon

RECEIVED OCTOBER 12, 1953

Twelve new 2,6-disubstituted- $\omega$ -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-Me<sub>2</sub>C<sub>6</sub>-H<sub>3</sub>NHCOCH<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, by Löfgren<sup>1</sup> in 1946, many compounds of the  $\omega$ -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 Löfgren<sup>2</sup> in 1948.

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

(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 alkoxyl or halogen substituents in the 2,6-positions had been synthesized until the recent work of Löfgren and Ekstrand,<sup>3</sup> 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).

Table I		
---------	--	--

## 2,6-Disubstituted- $\omega$ -dialkylaminoacetanilides

The hydrochlorides were recrystallized from methyl ethyl ketone-ether; compounds 9, 17, 21 and 23 from petroleum ether (60-70°); compound 19 from petroleum ether (30-50°)

							Ion		
	acetanilide	м.р., °С.	в.р., °С.	$\frac{1}{8}$	Formula	Calcd.	found	Caled.	ie, % Found
1	ω-Dimethylamino-2-methoxy-6-								
	methyl-		188–189 (7 mm.)	88	C19H18N9O9				
2	Hydrochloride	a			$C_{12}H_{13}C_{1N_2}O_2$	10.83	10.71	13.70	13.66
3	ω-Diethylamino-2-methoxy-6-				- 1215				
	methyl-		195–196 (7 mm.)	64	C14H99N9O9				
4	Hydrochloride	a			C14H93ClN9O9	9.77	9.60	12.36	12.30
5	ω-Di-n-propylamino-2-methoxy-				- 1110				
	6-methyl		204–205 (6 mm.)	79	$C_{18}H_{26}N_2O_2$				
6	Hydrochloride	147-148			C16H27CIN2O2	8.90	8.81	11.26	11.23
7	ω-Di-n-butylamino-2-methoxy-6-								
	methyl-		227-229 (7 mm.)	58	$C_{18}H_{30}N_2O_2$				
8	Hydrochloride	120-122			$C_{18}H_{31}C1N_2O_2$	8.14	7.99	10.34	10.36
9	ω-Dimethylamino-2,6-dimethoxy	71 - 72	210-212 (10 mm.)	68	$C_{12}H_{18}N_2O_3$				
10	Hydrochloride	150–153 d.			$C_{12}H_{19}C1N_2O_3$	10.20	10.09	12.91	12.90
11	ω-Diethylamino-2,6-dimethoxy <sup>b</sup>		163–164 (1 mm.)	62	$C_{14}H_{22}N_2O_3$				
12	Hydrochloride	173 - 174			$C_{14}H_{23}C1N_2O_3$	9.25	9.11	11.71	11.79
13	ω-Di- <i>n</i> -propylamino-2,6-dimeth-								
	oxy-		175–176 (1 mm.)	68	$C_{16}H_{26}N_2O_3$				
14	Hydrochloride	158 - 159			$C_{16}H_{27}C1N_2O_3$	8.47	8.36	10.72	10.72
15	$\omega$ -Di- <i>n</i> -butylamino-2,6-dimeth-								
	oxy-		187–188 (1 mm.)	63	$C_{18}H_{30}N_2O_3$				
16	Hydrochloride	144 - 145			$C_{18}H_{31}C1N_2O_3$	7.81	7.59	9.88	10.02
17	$\omega$ -Dimethylamino-2,6-dichloro-	115 - 116	• • • • • • • • • • • • • • •	55	$C_{10}H_{12}Cl_2N_2O$				
18	Hydrochloride	250 d.			$C_{10}H_{13}Cl_{3}N_{2}O$	9,88	9.68	12.41	12.55
19	$\omega$ -Diethylamino-2,6-dichloro-	47-48		63	$C_{12}H_{16}Cl_2N_2O$				
20	Hydrochloride	174 - 175	•••••		$C_{12}H_{17}Cl_3N_2O$	8.99	8.75	11.38	11.36
21	ω-Di- <i>n</i> -propylamino-2,6-dichloro-	83-84	169–170 (1 mm.)	44	$C_{14}H_{20}Cl_2N_2O$		• • •		
22	Hydrochloride	172 - 173		••	$C_{14}H_{21}Cl_3\mathrm{N_2O}$	8.25	8.04	10.44	10.40
23	ω-Di-n-butylamino-2,6-dichloro-	20 - 21	• • • • • • • • • • • • • • •	••	$C_{1 \circ} H_{2 4} C l_2 N_2 O$				
<b>24</b>	Hydrochloride	158 - 160	•••••	60	$C_{1\delta}H_{25}Cl_3N_2O$	7.62	7.57	9.64	9.63

<sup>a</sup> Too hygroscopic to permit an accurate melting point determination. <sup>b</sup> Described by Löfgren and Ekstrand, reference 3, after our work was completed.

method of Jacobs and Heidelberger<sup>4</sup> as modified by Löfgren.<sup>2</sup> However, since this method was unsatisfactory with 2,6-dichloroaniline due to the insolubility of this compound in the acetate buffer, the chloroacetylation was run in glacial acetic acid according to the method used by Beilstein and Kurbatow<sup>5</sup> to produce 2,6-dichloroacetanilide.

The three compounds thus produced were then refluxed with the various dialkylamines in benzene solution to give the products desired. The hydrochlorides were made by passing dry hydrogen chloride gas through a solution of the free base in anhydrous ether and filtering off the resulting white precipitate. The compounds synthesized are listed in Table I with their corresponding physical constants. The reaction scheme used is



(4) W. Jacobs and M. Heidelberger, This Journal,  $\mathbf{39},\,1439,\,1477$  (1917).

$$\underbrace{\overset{\mathbf{R}'}{\underset{\mathbf{R}''}{\overset{0}{\overset{}}}}}_{\mathbf{R}''}^{\mathbf{N}} \overset{\mathbf{O}}{\underset{\mathbf{C}}{\overset{}}} \operatorname{CH}_{2}\mathrm{NR}_{2} + \mathrm{R}_{2}\mathrm{NH}\cdot\mathrm{HCl}}$$

In a preliminary screening of these compounds for anesthetic potency and irritation performed at the Abbott Laboratories, compounds 2, 4, 6, and 8 (Table I) exhibited very strong anesthetic action increasing in the order named, but were considered to be too irritating to warrant clinical testing. The four compounds of the 2,6-dimethoxy series possessed anesthetic potencies weaker than that of Xylocaine and were also slightly irritating. Chlorine substitution on the benzene nucleus had the effect of increasing the anesthetic action slightly; however, the irritating tendencies were also increased.

In each series as the dialkylamino group was varied from dimethyl to di-*n*-butyl the anesthetic potency and irritating properties increased with increase in the length of the chain. However,  $\omega$ -di*n*-propylamino-2,6-dichloroacetanilide hydrochloride possessed the strongest anesthetic action in the chlorinated series of compounds.

#### Experimental

2-Methoxy-6-methylaniline.<sup>6</sup>—This compound has been previously obtained through the reduction of 2-nitro-m-

<sup>(5)</sup> F. Beilstein and Kurbatow, Ann., 196, 220 (1898).

<sup>(6)</sup> R. D. Haworth and A. Lapworth, J. Chem. Soc., 123, 2982 (1923).

tolvl methyl ether<sup>6</sup> with stannous chloride and hydrochloric acid. However, since this procedure is likely to give extensive chlorine substitution on the benzene nucleus, the compound was obtained by catalytic reduction using a platinum catalyst.

2-Nitro-m-tolyl methyl ether (0.31 mole, 53 g.) was placed in the hydrogenation flask with 250 ml. of ethanol and 0.6 g. of Adams catalyst and hydrogenated at a pressure of 50 lb./sq. in. at room temperature. At the end of three hours the catalyst was filtered off and the alcohol removed in vacuo. The oil which remained (40 g., 0.29 mole) was subjected to the next step after purification by vacuum distillation.

ω-Chloro-2-methoxy-6-methylacetanilide.-The amine from above was dissolved in 255 ml. of glacial acetic acid and cooled in an ice-bath to 10°. Chloroacetyl chloride (37.2 g., 0.33 mole) was added with constant stirring followed by a solution of 99 g. of NaOAc  $3H_2O$  in 414 ml. of water. After shaking mechanically for one-half hour the heavy white precipitate was filtered off with suction and dried in the air. Upon recrystallization from dilute ethanol the product appeared as a felted mass of white needles, m.p. 128–129°, with a yield of 37 g. (59%). Anal. Calcd. for  $C_{10}H_{12}CINO_2$ : N, 6.56. Found: N,

6.38.

ω-Chloro-2,6-dimethoxyacetanilide.<sup>3</sup>—2-Aminoresorcinol dimethyl ether<sup>7</sup> (50 g., 0.33 mole) was treated as above with chloroacetyl chloride (41.3 g., 0.37 mole) to yield 52 g. (69%) of fine colorless needles, m.p.  $165-166^\circ$ . This compound was recrystallized from benzene.

Anal. Calcd. for C10H12CINO3: N, 6.10. Found: N, 6.02.

 $\omega$ -Chloro-2,6-dichloroacetanilide.—2,6-Dichloroaniline (27.3 g., 0.17 mole), synthesized as directed by Seikel,8 was

(7) H. Kaufmann and W. Franck, Ber., 40, 3999 (1907).

(8) M. K. Seikel, Organic Syntheses, 24, 47 (1944).

dissolved in 55 ml. of glacial acetic acid, and 20.3 g. (0.18 mole) of chloroacetyl chloride was added. The reaction mixture, containing a heavy white precipitate, was warmed on the steam-bath until no further evolution of HCl gas was apparent (about 15 minutes), and then 250 ml. of cold water was added. The resulting thick sludge was filtered with suction, washed with a little water, and dried in the air. Upon recrystallization from 50% acetic acid, 29.3 g. (72%) of long, colorless needles was obtained, m.p. 176–177° with sublimation.

Anal. Caled. for C<sub>8</sub>H<sub>6</sub>Cl<sub>3</sub>NO: N, 5.87. Found: N, 5.70.

The  $\omega$ -Dialkylaminoacetanilides (Table I).—The appropriate  $\omega$ -chloro-2,6-disubstituted acetanilide (0.044 mole) was refluxed for five hours with 0.122 mole of the dialkylamine in 100 ml. of dry benzene. After cooling, the colorless precipitate of the dialkylamine hydrochloride was filtered off with suction and washed with a little dry ben-The combined filtrates were then evaporated to a zene. thick sirup in vacuo, the residue taken up in sufficient 3 N HCl, shaken out with a little ether, and finally made strongly basic with 20% NaOH solution. The oil or solid which separated was isolated by ether extraction or suction filtration and distilled under diminished pressure.

To produce compounds 1, 9 and 17, dry dimethylamine gas was bubbled through a hot solution of the starting material in benzene for five hours and subsequently worked up as described above.

The hydrochlorides were obtained by passing dry hydrogen chloride gas through a solution of the free base in anhydrous ether. After recrystallization from methyl ethyl ketone-ether mixture the product usually appeared as a white microcrystalline powder.

CHICAGO 11, ILLINOIS

#### [CONTRIBUTION FROM THE NOVES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Synthesis of $DL-\alpha$ -Amino- $\beta$ -(6-methyl-3-indazolyl)-propionic Acid

### By H. R. SNYDER AND JOHN K. WILLIAMS<sup>1</sup>

**Received September 21, 1953** 

The indazole analog of 6-methyltryptophan,  $\alpha$ -amino- $\beta$ -(6-methyl-3-indazolyl)-propionic acid, has been synthesized via the sequence: nitro-p-xylene, the sodium enolate of ethyl 2-nitro-4-methylphenylpyruvate, the oxime of sodium 2-nitro-4-methylphenylpyruvate, 2-nitro-4-methylphenylacetonitrile, 2-amino-4-methylphenylacetonitrile, 6-methyl-3-cyanoinda-zole, 6-methylindazole-3-carboxylic acid, methyl 6-methylindazole-3-carboxylate, the dimethylamide of 6-methylindazole-3-carboxylic acid, 6-methyl-3-dimethylaminomethylindazole, 6-methyl-3-dimethylaminomethylindazole methiodide, ethyl  $\alpha \text{-acetamido-} \alpha \text{-carbethoxy-} \beta \text{-} (6\text{-methyl-}3\text{-indazolyl}) \text{-} \text{propionate}, \quad \alpha \text{-acetamido-} \alpha \text{-carboxy-} \beta \text{-} (6\text{-methyl-}3\text{-indazolyl}) \text{-} \text{propionic} (\beta \text{-} \beta \text{-} \beta$ acid,  $\alpha$ -acetamido- $\beta$ -(6-methyl-3-indazolyl)-propionic acid, and  $\alpha$ -amino- $\beta$ -(6-methyl-3-indazolyl)-propionic acid.

In connection with studies of the antimetabolic activity of substances related to tryptophan the indazole analog of 6-methyltryptophan has been prepared. The steps employed in the synthesis are shown in the accompanying equations.

The nitro-p-xylene (I) was prepared as reported previously.<sup>2</sup> The sodium enolate of ethyl 2-nitro-4-methylphenylpyruvate (II) separated as a dark purple solid when I was allowed to react with diethyl oxalate and sodium ethoxide in absolute ether. When II was dissolved in warm water, it presumably decomposed to give the ester and sodium hydroxide, which then interacted to give sodium 2-nitro-4-methylphenylpyruvate in solution. When aqueous hydroxylamine was added to this solution, the sodium salt of the oxime III separated. The decarboxylation and dehydration of III were accomplished in one step by adding III to a mixture of acetic anhydride and glacial acetic

acid heated to 70-100°. If acetic anhydride was used alone, as has been reported<sup>3</sup> for the conversion of the oxime of 2-nitrophenylpyruvic acid to 2nitrophenylacetonitrile, the sodium salt III decomposed violently and was converted to a black intractable mass. When 2-nitro-4-methylphenylacetonitrile (IV) was shaken with hydrogen over palladium on carbon at room temperature, it was converted smoothly to 2-amino-4-methylphenylacetonitrile (V). Diazotization of V resulted in cyclization to 3-cyano-6-methylindazole (VI).

Hydrolysis of VI produced 6-methylindazole-3carboxylic acid (VII) in high yield. Conversion of VII to 3-carbomethoxy-6-methylindazole (VIII) was accomplished by heating the acid with absolute methanol in the presence of sulfuric acid. When VIII was heated at 100° in a pressure bottle with 70% methanolic dimethylamine, the dimethylamide (IX) was obtained. The amide IX was converted to 3-dimethylaminomethyl-6-methyl-(3) V. Rousseau and H. Lindwall, ibid., 72, 3047 (1950).

<sup>(1)</sup> Allied Chemical and Dye Corporation Fellow, 1952-1953.

<sup>(2)</sup> H. R. Snyder and F. J. Pilgrim, THIS JOURNAL, 70, 3787 (1948).