vacuum distilled to obtain the products, which were all light yellow solids. These compounds were recrystallized from 95% alcohol.

Acknowledgment.—One of the authors (J. P. P.) wishes to acknowledge the help of a du Pont Fellowship in Chemistry for the year 1948–1949. The authors also wish to acknowledge the assistance of Mrs. B. Jarvis who performed the microanalyses.

Summary

Several new 8-quinolinols substituted in the pyridine ring have been prepared. Several new substituted 8-methoxyquinolines have also been prepared. The steric hindrance of substitution of 8-quinolinol in the 2-position on the reaction with aluminum ion is shown by the fact that shifting the substituent to the 3- or 4-position permits reaction.

BLOOMINGTON, IND. RECEIVED APRIL 26, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. II. Tertiary Aminoalkane Thiol Esters of Disubstituted Acetic Acids

BY H. G. KOLLOFF, JAMES H. HUNTER, E. H. WOODRUFF AND ROBERT BRUCE MOFFETT

Studies of synthetic spasmolytic agents of the type described in a recent report from this Laboratory[1] have been extended to the preparation of a series of analogous thiol esters for the purpose of comparative evaluation of their antispasmodic activity. This investigation appeared desirable since data on such thiol esters are relatively limited.[2,3]

In the synthesis of the thiol esters whose salts are listed in Table II, disubstituted acetic acid chlorides were condensed with 2-diethylaminoethanethiol[4] and various pyrrolidylalkanethiols. The latter were prepared from the corresponding alcohols,[5] via the intermediate pyrrolidylalkane chloride hydrochlorides and isothiouronium chloride hydrochlorides recorded in Table I, by the general procedure of Albertson and Clinton.[4] In order to suppress spontaneous oxidation of these thiols, the ethereal extract from the alkaline decomposition of the pyrrolidylalkane isothiouronium salts was dried and treated with the appropriate acid chloride immediately.

Preliminary pharmacological assays by Dr. Milton J. Vander Brook of our Department of Pharmacology indicate that these thiol esters have less activity against acetylcholine chloride induced spasms than the corresponding oxygen esters.

Experimental[6,7]

The examples below illustrate the procedures used for the preparation of the various intermediates and thiol ester salts.

2-(2-Methyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a cooled solution of 51.8 g. (0.4 mole) of 2-(2-methyl-1-pyrrolidyl)-ethanol[5] in 200 ml. of dry benzene until strongly acid. Then 36.3 ml. (0.5 mole) of thionyl chloride was added slowly with cooling in an ice–water-bath. When the addition was complete the solution was heated on a steam-bath for two hours during which time hydrogen chloride and sulfur dioxide were evolved. The chloride hydrochloride crystallized and, after cooling, was collected and washed first with benzene, then with absolute ether, and dried giving a quantitative yield of nearly white crystals, m. p. 183.5–185°. This was used without further purification for the preparation of the isothiouronium salt. An analytical specimen was prepared by recrystallization from isopropyl alcohol using decolorizing charcoal; m. p. 184–185.5°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-isothiouronium Chloride Hydrochloride.—A solution of 46.0 g. (0.25 mole) of the above chloride hydrochloride and 19.0 g. (0.25 mole) of thiourea in 50 ml. of 95% ethanol was refluxed on a steam-bath for twenty hours. The product which separated after cooling was collected, washed successively with ethanol and acetone, and recrystallized from about 250 ml. of 95% ethanol giving 43.3 g. of nearly white crystals, m. p. 216–218°. Dilution of the filtrate with acetone gave an additional 7.9 g., m. p. 215–217°.

2-(2-Methyl-1-pyrrolidyl)-ethyl Phenyl-Δ^2-cyclopentenylthiolacetate Hydrochloride.—In an apparatus designed for continuous extraction[8] of an aqueous solution by ether was placed a solution of 16.9 g. (0.065 mole) of the above isothiouronium salt in 30 ml. of water and the air in the apparatus displaced with nitrogen. A solution of 5.3 g. of sodium hydroxide in 20 ml. of water was added and the mixture extracted continuously with peroxide-free ether for six hours. The ether extract was dried over Drierite, filtered and added to a solution of 13.3 g. (0.06 mole) of phenyl-Δ^2-cyclopentenylacetyl chloride[9] in 50 ml. of dry benzene. The mixture became warm and an oil separated. After refluxing for two hours, the mixture was shaken with ice-water containing a small amount of hydrochloric acid. The ether layer was extracted again with water and the combined aqueous solution washed with ether and made basic with sodium hydroxide. The oily ester which separated was taken up in ether, washed well with water and dried first over sodium sulfate and then over Drierite. The solution was filtered and hydrogen chloride gas introduced until strongly acidic. The hydrochloride separated as a viscous oil which crystallized partly on standing. After decanting the ether, the crude hydrochloride was dissolved in warm ethyl acetate. On cooling it crystallized and was collected, washed with ethyl acetate and dried. It was recrystallized from ethyl acetate giving 7.0 g. of white crystals, m. p. 111–115°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-Δ^2-cyclopentenyl-*n*-propylthiolacetate Acid Citrate.—The hydrochloride cor-

(1) Kolloff, Hunter, Woodruff and Moffett, THIS JOURNAL, **70**, 3862 (1948).

(2) Richardson, U. S. Patent 2,390,555.

(3) Clinton and Salvador, THIS JOURNAL, **68**, 2076 (1946).

(4) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(5) Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(6) Melting points and boiling points are uncorrected.

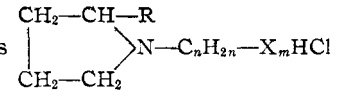
(7) Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratory.

(8) This apparatus is a modification of that described in "Organic Syntheses," **23**, 49 (1943).

(9) Horclois, *Chemie and industrie*, Special No. 357 (April, 1934).

TABLE I

PYRROLIDYLALKANE CHLORIDE AND ISOTHIOURONIUM CHLORIDE HYDROCHLORIDES

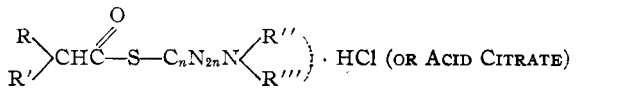


R	C_nN_{2n}	m	X	Yield, %	M. p., °C.[a]	Formula	Analyses, % Chlorine Calcd.	Chlorine Found[f]	Nitrogen Calcd.	Nitrogen Found[f]	Sulfur Calcd.	Sulfur Found[f]
H	$-CH_2CH_2-$	2	$-S-CN_2H_3$[a]	77.7	174–175	$C_7H_{17}Cl_2N_3S$	...	...	17.07	17.11	13.02	13.18
CH_3	$-CH_2CH_2-$	1	Cl	100	184–185.5	$C_7H_{15}Cl_2N$	38.52	38.72	...	...	...	...
CH_3	$-CH_2CH_2-$	2	$-SCN_2H_3$	78.7	216–218	$C_8H_{19}Cl_2N_3S$	...	...	16.15	16.07	12.32	12.47
H	$-CH(CH_3)CH_2-$	1	Cl	65.3[b]	150–163	$C_7H_{15}Cl_2N$	38.52	38.48	...	...	...	...
H	$-CH(CH_3)CH_2-$	2	$-SCN_2H_3$	50.0[c]	184.5–186	$C_8H_{19}Cl_2N_3S$	...	...	16.15	16.15	12.32	12.60
H	$-(CH_2)_4-$	1	Cl	66.3[d]	111–113	$C_8H_{17}Cl_2N$	35.79	35.68	...	...	...	...
H	$-(CH_2)_4-$	2	SCN_2H_3	86.2	168–169.5[e]	$C_9H_{21}Cl_2N_3S$	...	...	15.32	15.43	11.69	11.61
H	$-CH_2CH(CH_3)CH_2-$	1	Cl	100[f]	164.5–165.5	$C_8H_{17}Cl_2N$	35.79	35.13	...	...	...	...
H	$-CH_2CH(CH_3)CH_2-$	2	SCN_2H_3	71.7[g]	215–216.5	$C_9H_{21}Cl_2N_3S$	...	...	15.32	15.42	11.69	11.34

[a] This compound was prepared by Dr. William Bradley Reid, Jr., in this Laboratory. [b] Yield after recrystallization from methyl ethyl ketone. [c] This yield represents the first crop of pure crystals. An additional yield of 32% of material melting at 170–175° was obtained from the filtrate. [d] Yield after recrystallization from a mixture of methyl ethyl ketone and ethyl acetate. [e] Crystallized from ethanol with the aid of decolorizing charcoal. [f] The yield reported was obtained by diluting the reaction mixture with absolute ether. It was nicely crystalline material melting at 156–161° and was used without further purification. A small sample for melting point and analysis was recrystallized from a mixture of methyl ethyl ketone and a little ethyl acetate. [g] Yield of material, m. p. 214–217°, obtained directly from the reaction mixture. A small sample was recrystallized from ethanol for melting point and analysis.

TABLE II

TERTIARY AMINOALKANE THIOL ESTER SALTS



R	Acid used R′	Amino thiol	Yield, %[a]	Crystn. solvent	M. p., °C.[b]	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found[j]	Sulfur Calcd.	Sulfur Found[j]	Chlorine Calcd.	Chlorine Found[j]
C_6H_5-	C_6H_5	$(CH_2)_4-N-(CH_2)_2-$	...	MeEtCO	140–141[b]	$C_{20}H_{24}ClNOS$	3.87	4.09	8.86	9.02[c]	9.80	9.63
$(CH_2)_4CH-$	$CH_3(CH_2)_2-$[c]	$(CH_2)_4-N-(CH_2)_2-$	[d]	EtOAc	146–148	$C_{16}H_{30}ClNOS$	..	..	10.02	9.89	11.08	11.09
C_6H_5	A[p,q]	$(CH_2)_3CH(CH_3)-N-(CH_2)_2-$	50[l]	EtOAc	111–115	$C_{20}H_{28}ClNOS$	3.83	3.61	8.76	8.83	9.69	9.64
A[p]	$CH_3(CH_2)_2-$[g]	$(CH_2)_3CH(CH_3)-N-(CH_2)_2-$	45[m]	EtOAc–MeEtCO	100–102	$C_{23}H_{37}NO_3S$	2.87	2.90	6.58	6.79	...	...
C_6H_5	$(CH_3)_2CHCH_2-$	$(CH_2)_4-N-CH(CH_3)CH_2-$	66[e]	H_2O	158–158.5	$C_{26}H_{37}NO_3S$	2.74	2.91	6.27	6.31	...	...
C_6H_5	B[q,r]	$(CH_2)_4-N-(CH_2)_4-$	31[n]	MeEtCO	133–134	$C_{22}H_{32}ClNOS$	3.56	3.69	8.14	8.14	9.00	9.13
C_6H_5	$(CH_2)_4CH-$[r]	$(CH_2)_4-N-CH_2CH(CH_3)CH_2-$	52[f]	EtOAc	121–124	$C_{21}H_{32}ClNOS$	3.67	3.77	8.39	8.36	9.28	9.46
C_6H_5	$(CH_2)_4CH-$[r]	$(CH_3CH_2)_2N-(CH_2)_2-$[s]	30[g,h]	PhH–Et_2O	106–108	$C_{19}H_{30}ClNOS$	3.94	3.79	9.00	8.79	9.96	10.21
C_6H_5	A[p,q]	$(CH_3CH_2)_2N-(CH_2)_2-$[s]	20[h,i]	PhH–Et_2O	102–105	$C_{19}H_{28}ClNOS$	..	..	...	..	10.00	9.93
C_6H_5	C_6H_5-O-i	$(CH_3CH_2)_2N-(CH_2)_2-$[s]	30[h,k]	EtOAc	97–98[l]	$C_{20}H_{25}ClNO_2S$	..	..	8.44	8.83	9.33	9.39

[a] The yield is reported for recrystallized material and is based on the isothiouronium chloride hydrochloride. [b] Some sintering at 132–134°. [c] Moffett, Hart and Hoehn, THIS JOURNAL, 69, 1849 (1947). [d] The free base was distilled, b. p. 107° (0.025 mm.) but did not seem to be pure. [e] This is the yield of acid citrate crystallized from the reaction mixture, m. p. 154–156°. A sample for analysis was recrystallized from ethanol and then from water. [f] The free base was distilled, b. p. 160–170° (0.05 mm.), but did not seem to be pure. [g] The free base was distilled, b. p. 133° (0.042 mm.). [h] The yield reported for recrystallized hydrochloride is based on the acid used. [i] The free base was distilled, b. p. 145° (0.09 mm.). [j] Meyer and Boner, *Ann.*, **220**, 51 (1883). [k] The free base was distilled, b. p. 180° (0.14 mm.). [l] Started to sinter at 94.5°. [m] Acid citrate salt. [n] With methyl ethyl ketone. [p] A = $(CH_2)_2CH{=}CH-CH-$. [q] B = $(CH_2)_3-CH{=}CH-CH-$. [r] Moffett, Hart and Hoehn, THIS JOURNAL, 69, 1849 (1947). [s] The free base was distilled, b. p. 160–170° (0.05 mm.), but did not seem to be pure.

responding to this compound, prepared by a method similar to that described above, was an intractable oil. It was reconverted to the free base, and a solution of 10.7 g. (0.036 mole) of this basic ester in 50 ml. of ethyl acetate was treated with 7.66 g. (0.04 mole) of citric acid in 10 ml. of absolute ethanol. The product which separated was recrystallized from a mixture of methyl ethyl ketone and ethyl acetate giving 14.2 g. of white crystalline powder with the properties listed in Table II.

Phenylisobutylacetyl Chloride.—Crude phenylisobutylacetic acid[10] was prepared by alkylation of diethyl phenylmalonate with isobutyl bromide, followed by hydrolysis and decarboxylation. Although the crude product was contaminated with phenylacetic acid, it was converted to

(10) This acid has been prepared by Bodroux and Taboury [*Bull. soc. chim.*, **7**, 668 (1910)] by the alkylation of benzyl cyanide, followed by hydrolysis.

the acid chloride with thionyl chloride, and the resulting mixture of acid chlorides separated by distillation through a 12-in. column packed with 1/8-in. glass helices. After removing the phenylacetyl chloride, a sharp cut of the desired acid chloride was obtained; b. p. 115° (14 mm.), $n^{25}D$ 1.5071.

Anal. Calcd. for $C_{12}H_{15}ClO$: Cl, 16.83. Found: Cl, 16.50.

Phenyl-Δ²-cyclohexenylacetyl Chloride.—A solution of 125.7 g. (0.615 mole) of phenyl-Δ²-cyclohexenylacetic acid[1] in 100 ml. of dry benzene and 73 ml. of thionyl chloride was heated on a steam-bath for one hour. After removal of the solvent the product was distilled through a short column giving 111 g. (77%) of yellow product, b. p. 97° (0.04 mm.), $n^{25}D$ 1.5478.

Anal. Calcd. for $C_{14}H_{15}ClO$: Cl, 15.11. Found: Cl, 15.24.

Summary

Ten new pyrrolidylalkyl and diethylaminoethyl thiol esters of disubstituted acetic acids have been prepared.

Several new intermediate pyrrolidylalkyl chloride hydrochlorides and isothiouronium salts are reported.

KALAMAZOO, MICHIGAN RECEIVED MARCH 28, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS COLLEGE OF PHARMACY]

Methoxysubstituted Benzamidines as Local Anesthetics[1]

BY N. J. SINTOV,[2a] J. S. RODIA, J. A. TURSICH,[2b] H. L. DAVIS AND G. L. WEBSTER

The hydrochlorides of certain amidines, derived from both aliphatic and aromatic acids, have been shown to exhibit local anesthetic activity.

Most, if not all, of the fatty acid amidines fall into three categories: (1) homologs of Holocaine, $CH_3 \cdot C(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5)$, (2) Holocaine or its homologs in which different substituents appear on the N-substituted phenyl groups, and (3) compounds of the type of Holocaine or its homologs in which one or both of the substituents on the nitrogen atoms are varied.

Taube[3] prepared a number of amidines of the Holocaine type in which the two phenyl groups were substituted with methoxy or ethoxy groups, ortho (or para) in one phenyl group and para (or ortho) in the other.

Goldschmidt[4] prepared a series of similarly substituted formamidines which showed local anesthetic activity. He also prepared formamidines in which the two N-substituted phenyl groups were substituted in the para-position with either carbethoxy or carbomethoxy groups.

Hill and Rabinowitz[5] attempted to overcome the undesirable characteristics of Holocaine by substituting for the methyl group the ethyl, propyl, butyl, isobutyl and benzyl radicals. In the amidines containing the two latter radicals one of the phenetidyl groups was replaced by an amino group and one phenetidyl radical in Holocaine was replaced by a diethylamino group. Hill and Cox[6] modified the lower homologs of Holocaine by substituting for one or both of the phenetidyl groups the *p*-carbethoxyphenyl group.

The substituted and unsubstituted benzamidines have not generally exhibited local anesthetic activity. Easson and Pyman[7] prepared and tested meta and para aminobenzamidine and 3,4-dimethoxybenzamidine, none of which showed local anesthetic properties, but they found slight anesthetic activity in both *p*-carbethoxybenzamidine and *p*-carbethoxyphenylguanidine. These authors, reasoning from the structure and properties of Holocaine, prepared and tested N-veratrylbenzamidine and found that it "had well-marked" local anesthetic character.

With the results of this previous work in mind, the purpose of these experiments was to prepare and test pharmacologically N,N′-diphenylbenzamidines in which one or more of the three phenyl groups were substituted with one or more methoxy groups.

These amidines, listed in Table I, were prepared by a modification of the method of Hill and Cox[6] in yields ranging from 32 to 62%.

In the preparation of these compounds it made no difference in the yield or purity of the product if the imidyl chloride was formed first and then it reacted with the appropriate amine or if the anilide and amine were at once added to the benzene solution of phosphorus pentachloride and the reaction completed in one operation.

The hydrochlorides of amidines numbered 1, 2, 5, 6, 8, 9 and 10 in Table I precipitated as a cream-colored powder during refluxing and no yield of hydrochloride was obtained from the benzene filtrates.

Since the disubstituted amidines are tautomeric[8] those having two different substituents on

(1) From theses presented by the first three authors in partial fulfillment of the requirements for the M.S. degree. This work was supported in part by a grant from the Lederle Laboratories, Pearl River, N. Y.

(2) Present addresses: (a) Searn Laboratories, Inc., Franklin Park, Ill.; (b) Riley Tar and Chemical Corporation, Indianapolis, Ind.

(3) "Chemische Technologie" (Wagner) **41**, 620, 621 (1895).

(4) Goldschmidt, *J. Chem. Soc.*, 785 (1902).

(5) Hill and Rabinowitz, THIS JOURNAL, **48**, 732 (1926).

(6) Hill and Cox, THIS JOURNAL, **48**, 3215 (1926).

(7) Easson and Pyman, *J. Chem. Soc.*, 2991 (1931).

(8) Burtles and Pyman, *J. Chem. Soc.*, 361 (1923).