several hours or until a homogeneous solution was obtained. After removal of the solvent and excess thionyl chloride, the acid chloride was distilled or recrystallized.

New intermediate acids and acid chlorides are described below.

4-Chlorocinnamoyl Chloride.—Treatment of 4-chlorocinnamic acid[15] with thionyl chloride as described above gave 98% of crude acid chloride melting at 79–81°. An analytical sample recrystallized twice from petroleum ether (40–60°) melted at 78–79°.

Anal. Calcd. for $C_9H_6OCl_2$: C, 53.76; H, 3.01; Cl, 35.27. Found: C, 53.64; H, 3.09; Cl, 34.87.

2,4-Dichlorocinnamoyl Chloride.—This compound was prepared by a similar procedure (87% crude yield). An analytical sample recrystallized from petroleum ether (70–90°) melted at 81–82°.

Anal. Calcd. for $C_9H_5OCl_3$: C, 45.90; H, 2.14; Cl, 45.17. Found: C, 46.17; H, 2.28; Cl, 45.02.

2,4-Dichlorohydrocinnamic Acid.—A mixture of 65 g. (0.3 mole) of 2,4-dichlorocinnamic acid,[16] 1 g. of platinum oxide and 600 cc. of purified anhydrous dioxane[17] was hydrogenated at room temperature under an initial pressure of 50 p.s.i. Hydrogen absorption was complete in two hours. After filtration and removal of the solvent under reduced pressure, the residue was washed with water and air-dried. Two recrystallizations from benzene–petroleum ether (70–90°) followed by two from aqueous ethanol gave 42.5 g. (65%) of pure product which melted at 95–97°.

Anal. Calcd. for $C_9H_8O_2Cl_2$: C, 49.36; H, 3.68; Cl, 32.39; neut. equiv., 219. Found: C, 49.00; H, 3.52; Cl, 32.35; neut. equiv., 220.

2,4-Dichlorohydrocinnamoyl chloride, obtained in 75% yield, boiled at 159–160° (18 mm.), $n^{25}D$ 1.5576.

Anal. Calcd. for $C_9H_7OCl_3$: C, 45.51; H, 2.97; Cl, 44.78. Found: C, 45.67; H, 3.15; Cl, 44.38.

Aminoester Hydrochlorides.—A solution of 0.21 mole of an acid chloride in 100 cc. of dry benzene was added fairly rapidly to a stirred solution of 0.20 mole of an aminoalcohol in 500 cc. of dry benzene. After the addition, the mixture was refluxed for six hours, then allowed to cool. In most cases, the aminoester hydrochloride precipitated on standing overnight and was separated by filtration, washed with benzene and ether and recrystallized. When the product did not precipitate on standing and seeding, the mixture was diluted with anhydrous ether until the hydrochloride precipitated.

N-2-Diethylaminoethyl 2,4-Dichlorobenzamide Hydrochloride.—A solution of 32.6 g. (0.156 mole) of 2,4-dichlorobenzoyl chloride in 100 cc. of dry benzene was added, during a 15 minute period, to a stirred solution of 20.0 g. (0.172 mole) of 2-diethylaminoethylamine in 400 cc. of dry benzene. The mixture was refluxed for six hours after the addition, then allowed to cool. Seeding the oily precipitate (seeds from butanone–ether) gave 42 g. of crude, solid product. Three recrystallizations from butanone and one from ethyl acetate yielded 18.8 g. (37%) of pure hydrochloride melting at 137–138°. Analyses are given in Table I.

2-Diethylaminoethyl 2,4-Dichlorobenzoate N-Oxide 2,4-Dichlorobenzoic Acid Salt.—A solution of 24 g. (0.073 mole) of 2-diethylaminoethyl 2,4-dichlorobenzoate hydrochloride in 300 cc. of water was covered with 300 cc. of ether and stirred during the rapid addition of 0.1 mole of aqueous sodium bicarbonate solution. The ether layer was separated immediately, dried over magnesium sulfate, filtered and evaporated. After addition of 79 g. (0.7 mole) of 30% hydrogen peroxide to the residual base, the mixture was allowed to stand at room temperature for six days with occasional shaking.

The precipitated white solid was separated by filtration, washed with a small amount of cold water and air-dried. Recrystallization from a 1:3 mixture of butanone and petroleum ether (70–90°), then from butanone alone gave 3.3 g. of pure product which melted at 114–115°.

Hydrolysis of a part of the ester apparently furnished sufficient free 2,4-dichlorobenzoic acid to form the salt. The possibility of the product being a 2,4-dichloroperbenzoic acid salt of the unoxidized ester was precluded by the failure of an aqueous solution of the product to give a peroxide test.

2-Diethylaminoethyl 2,6-Dichlorobenzoate Hydrochloride.—A solution of 20 g. (0.0956 mole) of 2,6-dichlorobenzoyl chloride in 50 cc. of dry benzene was added to a stirred solution of 10.7 g. (0.0910 mole) of 2-diethylaminoethanol in 250 cc. of dry benzene. After refluxing for six hours and standing for several days, the mixture was evaporated to dryness on the steam-bath, diluted with anhydrous ether and filtered to remove the solid material. The ether filtrate was evaporated and the procedure of dilution with dry ether, removal of solid and re-evaporation to dryness was repeated several times. The first two crops of solid were very hygroscopic and were discarded. Subsequent crops were combined and recrystallized from butanone to obtain 3 g. (10%); m.p. 178°. Analyses are given in Table I.

CINCINNATI, OHIO

(17) L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 369.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Antispasmodics. Basic Esters and Amides of Some Heterocyclic N-Carboxylic Acids

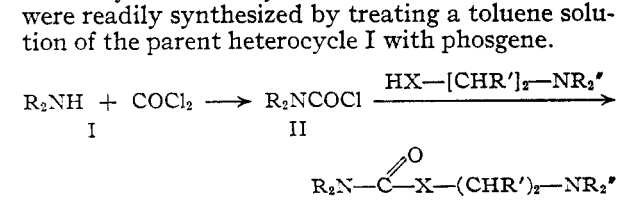
BY ARTHUR W. WESTON, ROBERT W. DENET AND R. J. MICHAELS, JR.

RECEIVED MARCH 18, 1953

A series of N,N-disubstituted aminoalkyl esters and amides of phenothiazine-10-, carbazole-9-, acridane-10- and 5,10-dihydro-5-methylphenazine-10-carboxylic acids is described. These products, prepared by condensing the N-carboxylic acid chlorides with an aminoalcohol or diamine, and some of their quaternary salts have been evaluated as antispasmodics.

In continuing our search for substances with antispasmodic properties,[1] the investigation of basic carbamates and ureas represented by Formula III was undertaken. In this paper are reported basic esters and amides of some heterocyclic N-carboxylic acids which may be considered basic carbamates and ureas in which one of the nitrogen atoms forms part of a heterocyclic ring. In addition, the quaternary salts of some of these compounds were prepared for comparative purposes.

The tertiary amines III were obtained by condensation of an N-carboxylic acid chloride II with two moles of the dialkylaminoalkanol or dialkylaminoalkylamine in dry benzene. The acid chlorides were readily synthesized by treating a toluene solution of the parent heterocycle I with phosgene.



R_2NH = phenothiazine, carbazole, acridan, 5,10-dihydro-5-methylphenazine
X = O, S, NH, NCH_3
R′ = H or CH_3
NR_2'' = dimethylamino, diethylamino, pyrrolidino, morpholino

(1) Previous paper, A. W. Weston and W. B. Brownell, THIS JOURNAL, 74, 653 (1952).

TABLE I

BASIC ESTERS AND AMIDES, $R_2NC(=O)—X$

X	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Phenothiazine-10-carboxylic Acid								
$OCH_2CH_2N(CH_3)_2$	215–216[a]	$C_{17}H_{18}N_2O_2S\cdot HCl$	58.19	58.45	5.45	5.53	7.98	8.17
$OCH_2CH_2N(C_2H_5)_2$[b]	165–166	$C_{19}H_{22}N_2O_2S\cdot HCl$	60.22	59.98	6.11	6.25	7.39	7.40
$OCH_2CH(CH_3)N(C_2H_5)_2$[c]	187–188[a]	$C_{20}H_{24}N_2O_2S\cdot HBr$	54.92	55.09	5.76	5.76	6.41	6.31
$OCH(CH_3)CH_2N(C_2H_5)_2$	180–182	$C_{20}H_{24}N_2O_2S\cdot HBr$	54.92	55.21	5.76	5.89	6.41	6.35
$OCH_2CH_2NC_4H_8$	215–216	$C_{19}H_{20}N_2O_2S\cdot HCl$	60.56	60.63	5.61	5.65	7.43	7.42
$OCH_2CH_2NC_4H_8O$	213–214	$C_{19}H_{20}N_2O_3S\cdot HCl$	58.08	57.97	5.39	5.61	7.13	6.92
$SCH_2CH_2N(C_2H_5)_2$	197–198	$C_{19}H_{22}N_2OS_2\cdot HCl$	57.77	57.53	5.87	5.83	7.09	6.86
$NHCH_2CH_2N(CH_3)_2$	202–203	$C_{17}H_{19}N_3OS\cdot HCl\cdot{}^1/_2H_2O$	56.89	56.63	5.89	5.77	11.71	11.85
$NHCH_2CH_2N(C_2H_5)_2$	185–186	$C_{19}H_{23}N_3OS\cdot HCl\cdot{}^1/_2H_2O$[d]	58.99	58.87	6.51	6.51	10.86	10.73
$N(CH_3)CH_2CH_2N(C_2H_5)_2$	160–161	$C_{20}H_{25}N_3OS\cdot HBr$	55.04	55.32	6.00	6.00	9.63	9.80
Carbazole-9-carboxylic Acid								
$OCH_2CH_2N(CH_3)_2$[e]	192–193	$C_{17}H_{18}N_2O\cdot HCl$	64.04	64.26	6.01	5.89	8.78	8.93
$OCH_2CH_2N(C_2H_5)_2$[f]	182–183	$C_{19}H_{22}N_2O_2\cdot HCl$	65.78	65.99	6.68	6.76	8.08	7.97
$NHCH_2CH_2N(CH_3)_2$	197–198	$C_{17}H_{19}N_3O\cdot HCl$	64.24	64.20	6.34	6.26	13.22	13.08
$NHCH_2CH_2N(C_2H_5)_2$	152–153	$C_{19}H_{23}N_3O\cdot HCl$	65.98	65.99	6.99	6.98	12.15	12.06
5,10-Dihydro-5-methylphenazine-10-carboxylic Acid								
$OCH_2CH_2N(C_2H_5)_2$	164–165	$C_{20}H_{25}N_3O_2\cdot C_2H_2O_4$[g]	61.52	61.02	6.33	6.48	9.78	9.35
Acridane-10-carboxylic Acid								
$OCH_2CH_2N(C_2H_5)_2$	147–148	$C_{20}H_{24}N_2O_2\cdot C_2H_2O_4$[g]	63.75	63.98	6.32	6.12	6.76	6.66
$NHCH_2CH_2N(C_2H_5)_2$	148–149	$C_{20}H_{25}N_3O\cdot C_2H_2O_4$[g]	63.90	63.61	6.58	6.74	10.16	10.07

[a] With decomposition. [b] Free base melts at 54–55°. Calcd. for $C_{19}H_{22}N_2O_2S$: N, 8.18. Found: N, 8.33. [c] Free base melts at 75–77°. Calcd. for $C_{20}H_{24}N_2O_2S$: N, 7.86. Found: N, 7.84. [d] Calcd. for hemihydrate: H_2O, 2.33. Found: H_2O, 2.44. [e] Ref. 2 reports m.p. 192.5°. [f] Ref. 2 gives m.p. 182.5°. [g] Oxalic acid salt.

The free bases III which crystallized were isolated in this form. The others were converted directly to a suitable salt since it was not found possible to purify them by distillation. The yields of pure material varied from 50–90%. Information regarding these esters and amides is recorded in Table I.

The melting points of the hydrochlorides of the two esters derived from carbazole-9-carboxylic acid have been disclosed previously.[2] However, no experimental details or analyses were included in this paper which dealt with the local anesthetic effect of these substances.

Pharmacological studies[3] conducted in these laboratories indicate that the greatest antispasmodic effectiveness is associated with the phenothiazine derivatives,[4] although the dihydrophenazine ester also has appreciable activity. On the other hand, the carbazole and acridan derivatives are weak antispasmodic agents. The most active tertiary amine, β-diethylaminoethyl phenothiazine-10-thiocarboxylate, possesses about $^1/_3$ the activity of atropine against acetylcholine spasms and is equipotent to papaverine against barium chloride spasms of the isolated rabbit intestine. Quaternization of this and other esters and amides greatly enhances their potency as acetylcholine antagonists. For instance, the methobromide quaternary salts of β-diethylaminoethyl phenothiazine-10-carboxylate and 10-thiocarboxylate compare favorably with atropine as inhibitors of acetylcholine spasms of the isolated muscle. With the exception of the quaternary salts, which are somewhat more toxic, the intraperitoneal LD_{50} of these compounds in mice lies in the 100–200 mg./kg. range.

(2) P. K. Knoefel, *J. Pharmacol. Exptl. Therap.*, **47**, 69 (1933).

(3) We are indebted to Dr. R. K. Richards and Dr. K. Hwang of the Pharmacological Department for permission to report some of their preliminary data here.

(4) A recent pharmacological report, R. Dahlbom, T. Edlund, T. Ekstrand and A. Katz, *Arch. intern. pharmacodynamie*, **90**, 241 (1952), on some of the phenothiazine esters described in this paper substantiates these findings.

Experimental

Phenothiazine-10-[5] and carbazole-9-carboxylic[6] acid chlorides were obtained by the procedures described in the literature. Modifications of Ruigh's method[6] were employed to prepare the other acid chlorides.[7]

Acridan-10-carboxylic Acid Chloride.—A slurry of 84.3 g. (0.465 mole) of acridan and 39.5 g. (0.5 mole) of pyridine in 150 cc. of dry toluene was gradually added with stirring to 63.5 g. (0.64 mole) of phosgene dissolved in 340 cc. of dry toluene. The reaction mixture was allowed to stand at room temperature for 60 hours. The precipitate which had formed during this period was removed by filtration. After the filtrate was washed with water, it was dried and concentrated whereby 5.8 g. of product m.p. 183–185° was obtained. The major portion of the product was recovered by boiling the original precipitate with benzene, separating the insoluble oil and cooling the yellow benzene solution. The crystalline material which separated weighed 69.3 g., m.p. 182–185°; total yield 75.1 g. (64%). A sample crystallized from dioxane for analytical purposes melted at 184–185°.

Anal. Calcd. for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14. Found: C, 69.38; H, 3.92.

5,10-Dihydro-5-methylphenazine-10-carboxylic Acid Chloride.—A solution of 1.7 g. (0.0088 mole) of 5,10-dihydro-5-methylphenazine and 1.2 g. (0.015 mole) of pyridine in 65 cc. of dry toluene was added dropwise with stirring to 6 g. (0.061 mole) of phosgene in 24 g. of toluene. The green reaction mixture was then heated on the steam-bath for one hour. It was cooled and treated with an additional

(5) S. Paschkowesky, *Ber.*, **24**, 2905 (1891).

(6) W. L. Ruigh, U. S. Patent 2,089,985 (Aug. 17, 1937).

(7) We are grateful to Dr. A. H. Sommers and Mr. J. D. Barnes for preparing these intermediates.

2 g. of phosgene in 20 cc. of toluene and 1 g. of pyridine. The mixture was heated at 90° for one hour, cooled and filtered. The filtrate was washed successively with dilute acid and water. By concentration of the toluene solution, there was obtained 1 g. (45%) of a brownish solid, m.p. 183–186°. Crystallization from Skelly B gave material of m.p. 188–190°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O$: N, 10.83. Found: N, 10.76.

N-(β-Diethylaminoethyl)-N-methylphenothiazine-10-carboxamide.—A solution of 5.6 g. (0.021 mole) of phenothiazine-10-carboxylic acid chloride and 5.6 g. (0.042 mole) of N-(β-diethylaminoethyl)-methylamine in 50 cc. of dry benzene was refluxed overnight. The reaction mixture was washed with water and the benzene layer separated and extracted with dilute hydrochloric acid. Addition of alkali to the acid extracts liberated the free base which was taken up in ether. Concentration of the ether solution yielded a thick oil which solidified on standing. The weight of material melting at 69–71° was 5.7 g. (77%). Crystallization from Skelly B gave 4.5 g. of product, m.p. 70–71°.

Anal. Calcd. for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.08; N, 11.82. Found: C, 67.75; H, 6.84; N, 11.55.

The base dissolved in dry ether was treated with hydrogen bromide gas. The hydrobromide salt which separated melted at 160–161°, after crystallization from isopropyl alcohol.

β-Dimethylaminoethyl Phenothiazine-10-carboxylate.—A solution of 12.3 g. (0.05 mole) of phenothiazine-10-carboxylic acid chloride and 8.9 g. (0.10 mole) of β-dimethylaminoethanol in 100 cc. of dry benzene was refluxed overnight. After the reaction mixture was washed with water, the benzene was separated and the solvent removed. The residue was dissolved in ether and the solution treated with hydrogen chloride gas. The salt, collected by filtration, weighed 13.3 g. (76%), m.p. 211–213° (dec.). Purification from absolute alcohol gave material, m.p. 215–216° (dec.).

β-Diethylaminoethyl Phenothiazine-10-carboxylate Methiodide and Methobromide.—The addition of excess methyl iodide to a dry ether solution of β-diethylaminoethyl phenothiazine-10-carboxylate resulted in the separation of the quaternary salt, m.p. 200–205° (dec.). After two crystallizations from absolute alcohol, the product melted at 210–211° (dec.).

Anal. Calcd. for $C_{20}H_{25}IN_2O_2S$: C, 49.59; H, 5.20; N, 5.78. Found: C, 49.87; H, 5.31; N, 5.79.

The methobromide obtained by addition of methyl bromide to an ether solution of the free base melted at 207–208° (dec.) after crystallization from absolute alcohol.

Anal. Calcd. for $C_{20}H_{25}BrN_2O_2S$: C, 54.91; H, 5.76. Found: C, 54.59; H, 5.82.

β-Diethylaminoethyl Phenothiazine-10-thiocarboxylate Methiodide and Methobromide.—The methiodide prepared in the foregoing manner melted at 230–231° (dec.) after crystallization from absolute alcohol.

Anal. Calcd. for $C_{20}H_{25}IN_2OS_2$: C, 48.00; H, 5.03; N, 5.59. Found: C, 47.93; H, 4.94; N, 5.70.

The methobromide, similarly prepared, crystallized from absolute alcohol, m.p. 228° (dec.).

Anal. Calcd. for $C_{20}H_{25}BrN_2OS_2$: C, 52.96; H, 5.56; N, 6.18. Found: C, 53.17; H, 5.75; N, 5.96.

N-(β-Diethylaminoethyl)-phenothiazine-10-carboxamide Methobromide.—This quaternary salt, after crystallization from absolute alcohol, melted at 225–226° (dec.).

Anal. Calcd. for $C_{20}H_{26}BrN_3OS \cdot {}^1/_2H_2O$: C, 53.93; H, 6.11; N, 9.43. Found: C, 54.04; H, 5.95; N, 9.57.

Acknowledgment.—The authors are indebted to Mr. E. F. Shelberg and staff of the Department of Microchemical Analyses for the analyses reported in this paper.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

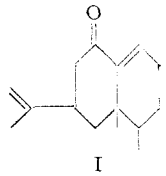
On the Structure of Eremophilone

BY T. A. GEISSMAN

RECEIVED MARCH 30, 1953

A re-examination of the oxidation of hydroxyeremophilone has disclosed that the product of the oxidation formerly regarded as having the composition $C_{12}H_{18}O_3$ is really a compound $C_{15}H_{22}O_4$. The structure advanced for this substance is in full accord with and constitutes additional evidence in support of the "unnatural" (non-isoprenoid) skeleton for hydroxyeremophilone.

The structures advanced for eremophilone (I) and hydroxyeremophilone (II) by Simonsen and his co-workers[1a-e] are of particular interest because their carbon skeletons cannot be constructed of isoprene units. While many of the experimental observations adduced in support of the structures



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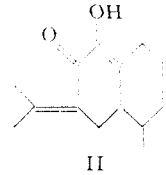

II

I and II were satisfactorily interpreted[1] in terms of these formulas, there remain in the articles cited a number of findings and provisional conclusions which remained unexplained or unaltered when the final structure assignments were made and a summing up of the evidence was presented. Because the direct evidence of the unusual structure of hydroxyeremophilone, so far as the arrangement of the carbon skeleton is concerned, rests chiefly upon the degradation of the hydroxy ketone to 1,2-dimethylcyclohexane-2-acetic acid, it was of particular interest that an oxidation product isolated in the course of these same degradative experiments could not be satisfactorily accounted for on the basis of the structure II. This compound, described as a "phenol," $C_{12}H_{18}O_3$, was formed[1b] when hydroxyeremophilone, its benzoate and its methyl ether were oxidized, ozone and chromic acid being used in the several experiments performed.[2] The "phenol," which was soluble in alkali but not in sodium bicarbonate solution, formed an acetate and a methyl ether, both of which

(1) (a) A. E. Bradfield, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 1744 (1932); (b) A. E. Bradfield, N. Hellström, A. R. Penfold and J. L. Simonsen, *ibid.*, 767 (1938); (c) A. R. Penfold and J. L. Simonsen, *ibid.*, 87 (1939); (d) F. C. Copp and J. L. Simonsen, *ibid.*, 415 (1940); (e) A. E. Gillam, J. I. Lynas-Gray, A. R. Penfold and J. L. Simonsen, *ibid.*, 60 (1941).

(2) The term "phenol" was (and is here) used simply with reference to its solubility in alkali and insolubility in sodium bicarbonate solution.