[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Analgesic Carbinols and Esters Related to Amidone (Methadon)[1]

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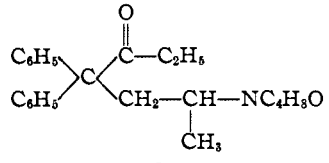
A number of ketones and imines related to the potent analgesic Amidone (Methadon) have been prepared[2,3,4,5,6,7,8] but no modifications of the Amidone structure involving other variations in the ketone moiety of the molecule have been reported. The present paper deals with the reduction of Amidone and a number of related ketones, esters and acids to carbinols. Since esterification of the carbinols potentiated the activity in a number of cases, a variety of carbinol derivatives was prepared.

The synthesis of the parent ketones in most cases was carried out using already established procedures.[2,6] When isomers were expected, hydrolysis of the Grignard reaction in the last step paralleled the original German procedure,[2] and isolation of the ketones and imines was accomplished through a combination of recrystallization and distillation methods. The morpholinyl analogs of Amidone and Isoamidone were assigned structures (I) and (II) through consideration of the



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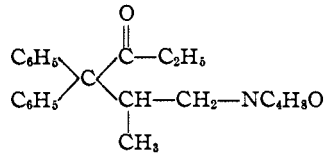

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similarities of the isolation procedures for these compounds to the isolation of the corresponding dimethylamino derivatives. The ketone II, isolated in part as the imine, was given the Isoamidone structure while ketone I, which separated as a highly insoluble hydrobromide salt, was assigned the Amidone structure. No degradative studies were carried out to definitely establish the position of the methyl group.[9]

Amidone was readily reduced catalytically by the use of Adams platinum oxide catalyst, but not with palladium. Isoamidone was resistant to all attempts at catalytic hydrogenation under a number of different conditions. The same resistance toward catalytic reduction conditions was shown by the morpholinyl analogs of Amidone I and Isoamidone II. The compound believed to have the structure represented by I was readily reduced by the same conditions employed for Amidone. Compound II was recovered unchanged from all catalytic reduction experiments. This behavior toward reduction of the "iso" forms of these members of the Amidone series is apparently related to steric factors. It was found that lithium aluminum hydride reduces Amidone, Isoamidone and the morpholinyl analogs in good yield.

Reduction of Amidone and the related branched chain compounds introduces a second asymmetric carbon atom in the molecule, making two diastereoisomeric pairs possible. One pure compound was isolated from the reduction of Amidone in sufficiently high yield (98%) to indicate that another isomer, if formed at all, is formed only in small amounts. The same compound was isolated from both the catalytic and lithium aluminum hydride reductions.

The primary alcohols and their esters in the Amidone series were prepared through the lithium aluminum hydride reductions of the appropriate ester or acid. 2,2-Diphenyl-4-(N-morpholinyl)-1-butanol was obtained in 85% yield from the corresponding ethyl γ-N-morpholinyl-α,α-diphenyl butyrate. Reduction of γ-dimethylamino-α,α-diphenylvaleric acid with lithium aluminum hydride proceeded in poor yield because of the low solubility of the acid in ether.

The general method for preparation of the esters involved refluxing of the carbinol in ethyl acetate with an excess of the acyl halide. It was found that some of the esters were hydrolyzed on attempted recrystallization from alcohols although a number of esters in the morpholinyl series, and esters of the higher molecular weight acids were stable in boiling alcohol.

Pharmacology.—In Table I physical constants on a number of ketones related to Amidone are given together with pharmacological data. Dr. Pfeiffer and co-workers have found the LD_{50} for

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(2) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of the Publication Board, Department of Commerce, Washington, D. C., pp. 91–98.

(3) Thorpe, Walton and Ofner, *Nature*, **159**, 679 (1947).

(4) Blicke and Zambito, paper presented before the Division of Medicinal Chemistry, American Chemical Society, Atlantic City, N. J., April 16, 1947.

(5) Easton, Gardner and Stevens, THIS JOURNAL, **69**, 976, 2941 (1947).

(6) Easton, Gardner, Evanick and Stevens, *ibid.*, **70**, 76 (1948).

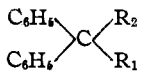
(7) Schultz, Robb and Sprague, *ibid.*, **69**, 2454 (1947).

(8) Cheney, Smith and Binkley, *ibid.*, **71**, 53 (1949).

(9) Since this work was completed P. B. L-70056 (Frames 1229–1232B) reported pharmacological data on compound I although no physical constants or proof of structure were given. The Germans claim I to be a potent analgesic in animals and predict II would have much lower activity through analogy with other series. These data support our structural assignments in view of the pharmacological data for I and II in Table I.

TABLE I[a]

KETONES AND OTHER INTERMEDIATES



R_1	R_2	M. p., °C. uncor.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	LD_{50}	Analgesic dose	Activity index
$CH_3CH_2NC_4H_8O$	C_2H_5CO	229–230	$C_{28}H_{37}NO_3 \cdot HCl$	70.75	70.60	7.55	7.48	114 ± 10	15	7+
$CH_3CH_2NC_4H_8O$	C_6H_5CO	114–115	$C_{29}H_{37}NO_2$	78.30	78.20	8.08	7.96			
$CH_3CH(CH_3)NC_4H_8O$	C_2H_5CO	222–223	$C_{29}H_{39}NO_3 \cdot HCl$	71.18	71.50	7.78	7.64	131 ± 7	12.5	10.5
$CH_3CH(CH_3)NC_4H_8O$	C_2H_5CO	230–231	$C_{29}H_{39}NO_3 \cdot HBr$	63.83	63.70	6.99	6.84			
$CH(CH_3)_2CH_2NC_4H_8O$	C_2H_5CO	229–230	$C_{30}H_{41}NO_3 \cdot H_2O \cdot HCl$	68.03	67.80	7.95	7.24	194 ± 18	50	4
$CH(CH_3)_2CH_2NC_4H_8O$	C_2H_5CO	139–140	$C_{30}H_{41}NO_3$	78.58	78.80	8.35	8.48			
$CH_3CH_2NC_4H_{10}$	C_2H_5CO	142–143	$C_{28}H_{39}NO \cdot HNO_3$	69.30	69.10	7.58	7.45	79 ± 4	15	5.3
$CH_2CH_2NC_4H_8O$	$COOC_2H_5$	168–169	$C_{32}H_{47}NO_3 \cdot HCl$	67.90	67.80	7.25	7.38	257 ± 6	12.5	20
$CH_3CH_2NC_4H_8O$	$COOC_2H_5$	68–70	$C_{32}H_{47}NO_3$	74.80	74.80	7.71	7.56			
$CH_3CH(CH_3)N(CH_3)_2$	CH_3CO	164–165	$C_{20}H_{33}NO \cdot HBr$	64.00	64.10	6.93	7.10	57 ± 1	20	3
$CH_3CH(CH_3)N(CH_3)_2$	$COOC_2H_5$	178–179	$C_{21}H_{37}NO_2 \cdot HCl$	69.80	69.70	7.80	7.87	49.3	20	2.5
$CH_3CH(CH_3)N(CH_3)_2$	COOH	200–201	$C_{19}H_{33}NO_2$	76.80	76.90	7.79	8.13			

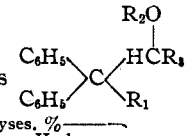
[a] See footnotes to Table II for data on methods of pharmacological evaluation and comparison data with Amidone and Isoamidone.

Amidone intraperitoneally in the mouse to be 28.6 ± 2 mg./kg. while the minimal analgesic dose subcutaneously in the guinea pig is 12.5 mg./kg. It is thus apparent that several of the morpholinyl ketones and esters are nearly as potent as Amidone on a weight basis and much less toxic.

The pharmacological data summarized in Table II establish several generalizations for these series. In all cases the alcohols are less toxic than the corresponding ketones; however, the analgesic activity of the carbinols is unpredictable, being undetectable in some cases. The acetate esters are uniformly more analgesic and more toxic than the parent ketones. The increase in analgesic potency of the acetate esters over the ketones is in all cases sufficient to produce a marked increase in the activity index in spite of the increased toxicity.

TABLE II

CARBINOLS RELATED TO AMIDONE AND THEIR ESTERS



R_1	R_2	M. p., °C. uncor.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	LD_{50}[a]	Analgesic[b] dose	Activity[c] index
			$R_3 = C_6H_5$							
$CH_3CH(CH_3)N(CH_3)_2$	H	206–207	$C_{21}H_{29}NO \cdot HCl$	72.47	72.20	8.68	8.56	76 ± 1.5	12.5	6
$CH_3CH(CH_3)N(CH_3)_2$	H	101–102	$C_{21}H_{29}NO$	80.95	80.80	9.37	9.34			
$CH_3CH(CH_3)N(CH_3)_2$	CH_3CO	213–214	$C_{23}H_{31}NO_2 \cdot HCl$	70.70	70.30	8.28	8.38	13.8 ± 2.50	1.0	14
$CH_3CH(CH_3)N(CH_3)_2$	CH_3CH_2CO	185–186	$C_{24}H_{33}NO_2 \cdot HCl$	71.34	71.10	8.48	8.55	35 ± 6	7.6	5
$CH_3CH(CH_3)N(CH_3)_2$	CH_3CH_2OCO	167–169	$C_{24}H_{33}NO_2 \cdot HCl$	68.70	68.70	8.17	8.15	39.6 ± 4.1	10.0	4
$CH_3CH(CH_3)N(CH_3)_2$	$C_6H_5CH_2CO$	172–173	$C_{29}H_{35}NO_2 \cdot HCl$	74.71	74.40	7.79	7.92	76.0 ± 11	20.0	3.8
$CH_3CH(CH_3)N(CH_3)_2$	C_6H_5CO	135–136	$C_{28}H_{33}NO_2 \cdot H_2O \cdot HCl$	71.50	71.30	7.70	7.42	206 ± 16	50.0	4.0
$CH_3CH(CH_3)N(CH_3)_2$	C_6H_5NHCO	150–151	$C_{28}H_{34}N_2O_2 \cdot H_2O \cdot HCl$	69.32	69.30	7.69	7.57	134 ± 16	100.0	1.3
$CH(CH_3)CH_2N(CH_3)_2$	H	204–205	$C_{21}H_{29}NO \cdot HCl$	72.47	71.80	8.68	8.69	Inact. 50 mg./kg.		
$CH(CH_3)CH_2N(CH_3)_2$	H	109–110	$C_{21}H_{29}NO$	80.95	80.80	9.37	9.59			
$CH(CH_3)CH_2N(CH_3)_2$	CH_3CO	228–229	$C_{23}H_{31}NO_2 \cdot HCl$	70.70	70.80	8.28	8.40	44.5 ± 2.5	4.0	11.0
$CH_2CH_2NC_4H_8O$	H	185–186	$C_{22}H_{29}NO_3 \cdot HNO_3$	65.70	65.50	7.48	7.31	182 ± 7	15	12
$CH_2CH_2NC_4H_8O$	H	130–131	$C_{22}H_{29}NO_2$	77.80	77.70	8.63	8.89			
$CH_2CH_2NC_4H_8O$	CH_3CO	242–243	$C_{24}H_{31}NO_3 \cdot HCl$	68.90	69.00	7.72	7.94	106 ± 9	4	26
$CH_2CH(CH_3)NC_4H_8O$	H	225–226	$C_{23}H_{31}NO_2 \cdot HCl$	70.80	70.80	8.33	8.23	.....	..[d]	
$CH_3CH(CH_3)NC_4H_8O$	H	118–119	$C_{23}H_{31}NO_2$	78.30	78.10	8.85	8.83			
$CH_2CH(CH_3)NC_4H_8O$	CH_3CO	221–222	$C_{25}H_{33}NO_3 \cdot HCl$	69.46	69.50	7.94	8.22	79.8 ± 12	2	40
$CH_2CH_2CH_2N(CH_3)_2$	H	172–173	$C_{21}H_{29}NO \cdot HCl$	72.46	72.60	8.68	8.72	185	75	2.5
$CH_3CH_2CH_2N(CH_3)_2$	CH_3CO	183–184	$C_{23}H_{31}NO_3 \cdot HCl$	70.70	70.70	8.28	7.92	110.2 ± 3.7	25	4.5
$CH_2CH_2N(CH_3)_2$	H	156–157	$C_{20}H_{27}NO \cdot HNO_3$	66.70	66.50	7.84	7.22	Inactive 30 mg./kg.		
$CH_2CH(CH_3)N(CH_3)_2$	H[e]	[f]	$C_{21}H_{35}NO$	79.50	79.80	11.11	11.10	103 ± 8	15	7
			$R_3 = H$							
$CH_3CH_2NC_4H_8O$	H	244–245	$C_{20}H_{25}NO_2 \cdot HCl$	69.00	68.90	7.54	7.66	Inactive 75 mg./kg.		
$CH_3CH_2NC_4H_8O$	H	155–156	$C_{20}H_{25}NO_2$	77.12	76.70	8.10	8.28	296	..[g]	..
$CH_3CH_2NC_4H_8O$	CH_3CO	159–160	$C_{22}H_{27}NO_3 \cdot HCl$	67.74	67.20	7.24	7.02	175	60	3
$CH_2CH(CH_3)N(CH_3)_2$	H	210–211	$C_{19}H_{25}NO \cdot HCl$	71.30	71.30	8.19	8.47	120	50	2

[a] Intraperitoneal LD/50 in the mouse in mg./kg. The pharmacological data were obtained by Dr. Carl C. Pfeiffer and coworkers of the University of Illinois Medical School. These data were presented in part at the Federation Meetings, Atlantic City, March 15–19, 1948. See *Federation Proceedings*, 7, 255 (1948). [b] Subcutaneous analgesic dose in the guinea pig in mg./kg. [c] For comparison the activity index for Amidone by the same pharmacological methods is 2.3, for Isoamidone 3.1 (Pfeiffer and co-workers). [d] No analgesia or toxicity found. [e] In this compound one phenyl ring has been reduced to cyclohexyl. [f] The product was obtained as an oil. b. p. 150–153° (1 mm.). [g] Inactive at 75 mg./kg

Acknowledgments.—We wish to express our appreciation to Mr. R. M. Downing for the microanalyses recorded herein. We also wish to thank Dr. Carl Pfeiffer of the University of Illinois Medical School for permission to present the pharmacological data.

Experimental

Preparation of Substituted Acetonitriles.—Diphenylacetonitrile was purchased commercially[10] while the intermediate dialkylaminoalkyl halides were prepared according to literature methods or minor modifications thereof.[2] Published procedures for the preparation of the dialkylaminoalkylacetonitriles[2] were used with the substitution in all cases of lithium amide[11] for sodium amide.

2,2-Diphenyl-4-(N-morpholinyl)-valeronitrile and 2,2-Diphenyl-3-methyl-4-(N-morpholinyl)-butyronitrile.—The mixed nitriles were obtained in 90% yield through the condensation of 1-(N-morpholinyl)-2-chloropropane[12] with diphenylacetonitrile. On standing the heavy oil partially crystallized. A portion of these crystals melted at 100–102° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{21}H_{24}N_2O$: C, 78.75; H, 7.55. Found: C, 78.60; H, 7.03.

Preparation of Ketones.—The ketones were prepared through Grignard reactions on the nitriles or through hydrolysis of imines isolated from the Grignard reactions.[4,8]

4,4-Diphenyl-6-(N-morpholinyl)-3-heptanone and 4,4-Diphenyl-5-methyl-6-(N-morpholinyl)-3-iminohexane.—A solution of 320 g. (1.0 mole) of the isomeric nitriles, from the previous reaction, in 400 ml. of dry xylene was added to a solution of ethylmagnesium bromide prepared from 49 g. (2 g. atoms) of magnesium and 218 g. (2 moles) of ethyl bromide in 500 ml. of anhydrous ether. All operations were carried out under nitrogen in a three-necked flask using a mercury-seal stirrer. After the addition of the nitriles the mixture was refluxed for six hours. The green reaction mixture was then poured as rapidly as possible into a 4-liter beaker containing 1 liter of water and 500 ml. of concentrated hydrochloric acid. The hydrolysis was exceedingly vigorous and the ether and xylene were vaporized. When the mixture had cooled somewhat, 500 ml. of benzene was added whereupon three layers separated. In a few hours the heavy, red middle layer sank to the bottom and began to crystallize. After forty-eight hours the brown solid was filtered, and washed with ether; yield 300 g. (calcd. yield of one isomer 216 g.). After recrystallization from 1500 ml. of water, the product weighed 235 g. and after recrystallization from 2500 ml. of isopropanol 171 g.; m. p. 230–231°, yield of ketone I, 79.3%. Analysis established that the compound was the hydrobromide salt of the ketone.

The acid layer from the hydrolysis of the Grignard reaction was made basic and extracted with benzene. The extracts were dried over potassium carbonate and concentrated. The heavy oil which separated was dissolved in hot Skellysolve C; the cooled solution deposited crystals, m. p. 104–105°. From the nitrogen analysis and the rapid reaction of the material with acetyl chloride the compound was considered to be 6-morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane, the imine of II.

Anal. Calcd. for $C_{23}H_{30}N_2O$: N, 7.99. Found: N, 8.03.

Acetylation of 6-Morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane.—Five grams of the imine was dissolved in 50 ml. of benzene and 5 ml. of acetyl chloride added. After a few minutes the mixture began to deposit crystals. The crystals were filtered after three hours and recrystallized from ethyl acetate. The yield of 6-morpholinyl-5-methyl-4,4-diphenyl-3-acetyliminohexane hydrochloride was 4 g.; m. p. 223–224°.

Anal. Calcd. for $C_{25}H_{32}N_2O_2 \cdot HCl$: C, 69.95; H, 7.76. Found: C, 69.50; H, 7.90.

Hydrolysis of 6-Morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane.—Two grams of the imine was refluxed for sixteen hours in 50 ml. of constant-boiling hydrochloric acid. The acid was distilled under reduced pressure and the residue made basic. The oil was extracted with ether and the ether solution dried and concentrated. The oily residue was dissolved in hot ethanol. The 6-morpholinyl-5-methyl-4,4-diphenyl-3-hexanone which separated from the cold solution melted at 139–140°.

Anal. Calcd. for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.34. Found: C, 78.80; H, 7.90.

Investigation of Mother Liquors from Ketone I Recrystallization.—To obtain the ketone II present, the filtrates from the water recrystallization of I were made basic, and the heavy oil which separated dissolved in hot ethanol. The cooled solution deposited crystals which were recrystallized from Skellysolve C, m. p. 139–140°, undepressed with previously obtained ketone II. Additional amounts of ketone II were isolated from isopropyl alcohol recrystallization mother liquors of I. The mother liquors were concentrated, and the oily mixture of ketone and imine hydrolyzed with concentrated hydrochloric acid. The oil liberated through addition of alkali was extracted and distilled, after removal of solvent; b. p. 187–190° (1.6 mm.), m. p. 138–140°. The total yield of ketone II was 75 g. or 42%.

γ-Dimethylamino-α,α-diphenylvaleric Acid.—A mixture of 49.5 g. (0.178 mole) of 4-dimethylamino-2,2-diphenylvaleronitrile and 150 ml. of 70% sulfuric acid was heated at 150° for five hours, cooled and poured into water. The precipitated acid was filtered, dissolved in dilute alkali, and the filtered solution made slightly acidic. The precipitated acid was recrystallized from methyl isobutyl ketone and then from water; m. p. 200–201°.

Carbinols.—The following preparation illustrates the general method used for the catalytic reduction of the ketones.

Ten grams (0.03 mole) of Amidone hydrochloride was dissolved in 100 ml. of distilled water and 0.5 g. of Adams platinum oxide catalyst[13] added. The compound was then hydrogenated at room temperature under an initial hydrogen pressure of 55 pounds. After two hours the calculated amount of hydrogen was absorbed. The catalyst was filtered, the filtrate made basic and the oil was taken up into ether. The dried ether solution was saturated with dry hydrogen chloride and the oil which first separated soon crystallized. The precipitated material melted at 206–207°. Recrystallization from isopropyl alcohol or methyl isobutyl ketone gave well formed plates or prisms which melted at 195–196°. Prolonged drying at 100° under reduced pressure did not raise this value. The compound is evidently dimorphic.

Anal. Calcd. for $C_{21}H_{29}NO \cdot HCl$: N, 4.03. Found: N, 3.99.

6-Dimethylamino-5-methyl-4,4-diphenyl-3-hexanol.—This reaction illustrates the general method used for lithium aluminum hydride[14] reductions.[15] A solution of 18.5 g. (0.06 mole) of Isoamidone base in 300 ml. of ether was shaken for three hours with potassium hydroxide pellets to remove last traces of moisture. The dry solution was then added to a solution of 2.5 g. (0.067 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether. The reaction was mildly exothermic, and the mixture refluxed gently. The mixture was refluxed for twelve hours, cooled in an ice-bath, and 200 ml. of 10% aqueous sodium hydroxide added dropwise. The ether layer was decanted and the aqueous layer extracted with ether. The combined ether solutions were washed with water and dried over potassium carbonate. After removal of the ether the oily residue crystal-

(10) Dow Chemical Company, Midland, Michigan.

(11) Metalloy, Inc., Minneapolis, Minnesota.

(12) Prepared from the corresponding alcohol with thionyl chloride.[2] The hydrochloride melted at 172–173°. The alcohol, prepared from morpholine and propylene chlorohydrin, boiled at 85–87° (7 mm.).

(13) American Platinum Company, Newark, New Jersey.

(14) Metal Hydrides, Inc., Beverly, Massachusetts.

(15) Nystrom and Brown, THIS JOURNAL, 69, 1197 (1947).

lized. The crude yield was quantitative. The solid was recrystallized from Skellysolve C and melted at 108–110°.

6-Dimethylamino-4-cyclohexyl-4-phenyl-3-hexanol.—Ten grams (0.03 mole) of Amidone was dissolved in 60 ml. of glacial acetic acid and 1 g. of platinum oxide catalyst added. This mixture was shaken at 50–60° with an initial hydrogen pressure of 55 lb. During a seventy-two-hour period, the amount of hydrogen absorbed was somewhat more than that calculated for the complete hydrogenation of one benzene ring and reduction of the ketone to the carbinol. At this stage addition of fresh catalyst caused no additional absorption of hydrogen. The catalyst was filtered, and the filtrate concentrated under reduced pressure. The residue was made basic and extracted into ether. The solvent was removed from the dried extract and the residue distilled; b. p. 150–153° (1 mm.). Although a crystalline phosphate was obtained, all other salts prepared were oils.

6-Dimethylamino-4,4-diphenyl-3-acetoxyheptane Hydrochloride.—A mixture of 19 g. (0.061 mole) of Amidone carbinol, 250 ml. of anhydrous ethyl acetate and 7.8 g. (0.100 mole) of acetyl chloride was refluxed for two hours, and then cooled in an ice-bath. The precipitated crystals were recrystallized from ethyl acetate; yield 21.5 g. (90%), m. p. 213–214°.

6-Dimethylamino-4,4-diphenyl-3-(N-phenylcarbamyloxy)-heptane Hydrochloride—Ten g. (0.033 mole) of Amidone carbinol was dissolved in ether and 6.7 g. (0.06 mole) of phenyl isocyanate added. After four hours a small quantity of diphenylurea had separated from the reaction mixture. The ether solution was decanted, and the diphenylurea recrystallized from ethanol; mixed m. p. 238–239°. The ether solution was extracted with 300 ml. of 4 *N* hydrochloric acid. After some time the crystalline hydrochloride separated from the extract, m. p. 150–151° after recrystallization from equal parts of methanol and hydrochloric acid.

Summary

1. Data on a number of ketones related to Amidone are presented.

2. The reduction of the ketones with lithium aluminum hydride and by catalytic hydrogenation is described.

3. Esters, carbonates and carbamates prepared from the carbinols are presented.

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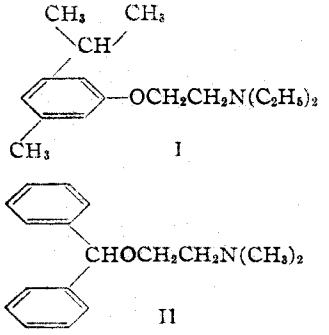
Alkylaminoalkyl Ethers of the Benzylphenols

BY L. C. CHENEY, RICHARD R. SMITH AND S. B. BINKLEY

In 1937 Bovet and Staub reported that a series of phenol ethers synthesized by E. Fourneau exerted a protective action against histamine intoxication[1] and anaphylactic shock[2] in guinea pigs. This discovery initiated the ensuing numerous pharmacological investigations of synthetic compounds which have been admirably reviewed by Loew.[3] The more extensive work of Staub[4] suggested that in general the ortho-substituted phenol ethers manifested higher antihistaminic activity than their para and meta isomers. Although the thymol derivative 929F (I) was selected as the most promising compound of this class, toxicity and untoward side-effects militated against its clinical usefulness.



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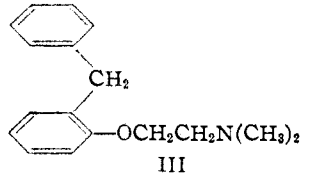
(1) Bovet and Staub, *Compt. rend. soc. biol.*, **124**, 547 (1937).
(2) Staub and Bovet, *ibid.*, **125**, 818 (1937).
(3) Loew, *Physiol. Revs.*, **27**, 542 (1947).
(4) Staub, *Ann. inst. Pasteur*, **63**, 400 (1939).



III

In 1945 Loew and his colleagues[5] announced their discovery of the potent antihistaminic action of benzohydryl β-dimethylaminoethyl ether (Benadryl) (II) synthesized by Rieveschl and Huber.[6]

Inasmuch as none of the Fourneau phenoxyethylamines investigated,[1,2,4] were substituted by a benzyl group, it was considered of interest to prepare 2-benzylphenyl β-dimethylaminoethyl ether (III) for pharmacological evaluation, especially since III is an isomer and vinylog of Benadryl (II). The present paper describes the preparation of II, its 4-isomer, certain homologs and salts thereof.

Pharmacological assays which will be reported elsewhere indicate that III (C-5581H) is to date more promising medicinally than any of the tabulated homologs. Its water-soluble hydrochloride is relatively non-toxic and it elicits a high order of antihistaminic and local anesthetic activity in animals. Clinical tests are in progress.

With the exception of the two hydrogenated derivatives (489-1 and 489-2), all of the com-

(5) Loew, Kaiser and Moore, *J. Pharmacol.*, **83**, 120 (1945).
(6) Wilson Frederick Huber, Doctoral Dissertation, University of Cincinnati, 1943. Rieveschl, U. S. Patent 2,421,714 (1947).