The water insoluble precipitate from the seven days standing was purified by solution in chloroform and precipitation by addition of alcohol. This was done three times to give a white solid melting at 200–235°.

Anal. Calcd. for $(C_{11}H_{10}O_3)_x$: C, 69.47; H, 5.26. Found: C, 68.83; H, 5.49; mol. wt., very high.

Decompostion of Other Aminochromanone Hydrochlorides.—Ten per cent. aqueous solutions of compounds 1, 5, 8 and 18 of Table II deposited insoluble oils after 20 hours of standing at room temperature.

INDIANAPOLIS, INDIANA RECEIVED MARCH 30, 1951

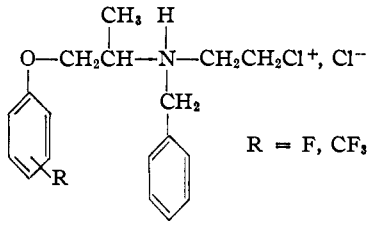
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Synthesis of Some Fluorine Substituted Adrenergic Blocking Agents

BY ALBERT F. LINDENSTRUTH[1] AND CALVIN A. VANDERWERF

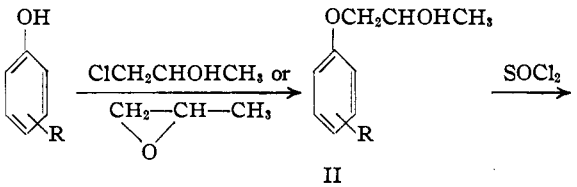
Synthesis and data on the adrenergic blocking activity of the hydrochlorides of N-benzyl-N-(2-chloroethyl)-1-(2-, 3- and 4-fluoro- and 2- and 3-trifluoromethyl-phenoxy)-isopropylamine are reported. The 4-fluorophenyl compound was the most active of the agents tested. Physical constants for these products and other new fluorine containing compounds prepared as intermediates are reported.

The discovery[2] that N-(2-chloroethyl)-dibenzylamine (Dibenamine)[3] hydrochloride blocks and reverses the excitatory effects of epinephrine has stimulated marked interest in N,N-disubstituted β-chloroethylamines as adrenergic blocking agents. An interesting series of compounds of this type which show noteworthy adrenergic blocking activity are the N-benzyl-N-(2-chloroethyl) hydrochlorides substituted in the phenoxy ring by alkyl groups, reported by Gump and Nikawitz.[4] As part of a study dealing with the effect of the substitution of fluorine into the molecule on the pharmacological behavior of medicinals, we have synthesized for pharmacological evaluation a series of closely related compounds, the N-benzyl-N-(2-chloroethyl)-1-(2-, 3- and 4-fluoro- and 2- and 3-trifluoromethyl-phenoxy)-isopropylamine hydrochlorides (I).

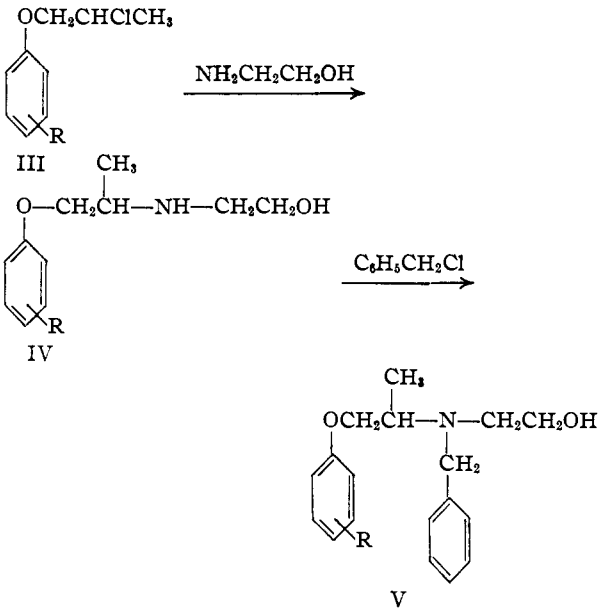


I

All of these compounds were prepared from the corresponding amino alcohols by treatment with thionyl chloride. The intermediate tertiary amino alcohols were synthesized from the appropriate fluoro- or trifluoromethyl-phenols according to the scheme



II



Because of the lability of *o*-trifluoromethylphenol in basic solution, its condensation with propylene chlorohydrin and with propylene oxide[5] to yield 1-(2-trifluoromethylphenoxy)-2-propanol presented experimental difficulties and the yield was poor.

In the condensation reactions of propylene chlorohydrin with the sodium salts of the various phenols, it was observed that an almost quantitative amount of sodium chloride was precipitated rapidly, before appreciable quantities of the desired ether could be isolated from the mixture. Immediate working up of the material at this stage led to recovery of most of the starting phenol. Obviously, the condensation reaction of propylene chlorohydrin with sodium phenoxides proceeds, at least in part, *via* the epoxide. It was also found that the epoxide and the chlorohydrin could be used interchangeably in the reactions. These facts suggest that proof of structure of an alcohol formed in a base-catalyzed condensation with a halohydrin, based on the assumption that the attacking base directly replaces the halogen atom, is not reliable. Assignment of structure in the present work follows from the fact that the

(1) E. I. du Pont de Nemours & Co., Waynesboro, Virginia.

(2) M. Nickerson and L. S. Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exptl. Therap.*, **89**, 167 (1947); M. Nickerson and W. S. Gump, *ibid.*, **97**, 25 (1949).

(3) Trademark of Smith, Kline and French Laboratories, Philadelphia, Pa.

(4) W. S. Gump and E. J. Nikawitz, THIS JOURNAL, **72**, 3846 (1950).

(5) A. R. Sexton and E. C. Britton, *ibid.*, **70**, 3606 (1948).

TABLE I

SUBSTITUTED PHENYL ETHERS, R—O—CH_2—CH(CH_3)—R′

R	R′	Yield, %	B.p., °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
o-Fluorophenyl	OH	78	126–127	17	$C_9H_{11}O_2F$	63.5	63.7	6.5	6.7
m-Fluorophenyl	OH	71	124–125	17	$C_9H_{11}O_2F$	63.5	63.4	6.5	6.4
p-Fluorophenyl	OH	84	130–131	17	$C_9H_{11}O_2F$	63.5	63.7	6.5	6.4
o-Trifluoromethylphenyl	OH	8	116–117	15	$C_{10}H_{11}O_2F_3$	54.5	54.4	5.0	4.9
m-Trifluoromethylphenyl	OH	68	120–122	15	$C_{10}H_{11}O_2F_3$	54.5	54.4	5.0	5.0
o-Fluorophenyl	Cl	95	109–110	16	$C_9H_{10}OFCl$	57.3	57.5	5.3	5.4
m-Fluorophenyl	Cl	60	109–110	15	$C_9H_{10}OFCl$	57.3	56.9	5.3	5.6
p-Fluorophenyl	Cl	90	110–111	15	$C_9H_{10}OFCl$	57.3	57.7	5.3	5.5
o-Trifluoromethylphenyl	Cl	81	112–113	15	$C_{10}H_{10}OF_3Cl$	50.3	50.3	4.2	4.0
m-Trifluoromethylphenyl	Cl	65	110–111	15	$C_{10}H_{10}OF_3Cl$	50.3	50.2	4.2	4.3

TABLE II

N-[2-(FLUORO- AND TRIFLUOROMETHYL-PHENOXY)-ISOPROPYL]-2-AMINOETHANOLS, R—O—CH_2CH(CH_3)—NH—CH_2CH_2—OH

R	Yield, %	B.p., °C.	Mm.	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
o-Fluorophenyl	76	148–149	4	54.2–55.0	$C_{11}H_{16}O_2NF$	6.6	6.8
m-Fluorophenyl	89	150–151	4	60.7–61.3	$C_{11}H_{16}O_2NF$	6.6	6.6
p-Fluorophenyl	68	152–153	4	71.8–72.4	$C_{11}H_{16}O_2NF$	6.6	6.5
o-Trifluoromethylphenyl	36	146–147	4	64.2–65.0	$C_{12}H_{16}O_2NF_3$	5.3	5.4
m-Trifluoromethylphenyl	73	149–150	4	88.8–89.2	$C_{12}H_{16}O_2NF_3$	5.3	5.3

base-catalyzed condensation of phenols with propylene oxide has been shown[5] to give secondary alcohol ethers.

Pharmacological[6].—Adrenergic blocking activity was determined in anesthetized cats prepared to record carotid blood pressure. One hour after intravenous injection of the blocking agent, four successively larger doses of epinephrine were given by vein. Complete blockade was assumed as that dose which would consistently reverse all the test doses of epinephrine. The *p*-fluorophenyl compound was the most active of the agents tested. It was also moderately active orally.

Experimental

Fluoro- and Trifluoromethyl-phenols.—The *o*- and *p*-fluorophenols were prepared from the corresponding phenetidines by the Schiemann reaction[7]; *m*-fluorophenol was obtained by direct diazotization of *m*-aminophenol in anhydrous hydrogen fluoride.[8]

o-Trifluoromethylphenol was prepared by the method of Jones.[9] The *m*-isomer was obtained by the decomposition of the diazonium salt of *m*-aminobenzotrifluoride with water.[10]

1-(Fluoro- and Trifluoromethyl-phenoxy)-2-propanols (II).—The following is a typical example: To a sodium ethoxide solution prepared by the addition of 6.9 g. (0.3 mole) of sodium to 250 ml. of absolute ethanol, 33.6 g. (0.3 mole) of *o*-fluorophenol was added with stirring. Propylene chlorohydrin (29.4 g., 0.31 mole) was added to the resulting clear solution and the mixture was refluxed for 12 hours. The sodium chloride was removed by filtration, the alcohol by distillation, and the resulting oil was fractionated to yield 40 g. (78.4%) of 1-(2-fluorophenoxy)-2-propanol, boiling at 126–127° (17 mm.). Data on this series of compounds are listed in Table I.

1-(Fluoro- and Trifluoromethyl-phenoxy)-2-chloropropanes (III).—An example is: Thionyl chloride (23 g., 0.17 mole) was added slowly to 25.8 g. (0.15 mole) of 1-(2-fluorophenoxy)-2-propanol. After the ensuing vigorous reaction had subsided, the mixture was shaken and allowed to stand until evolution of hydrogen chloride had ceased (about 1 hour). Several drops of pyridine were added, and the flask, fitted with a drying tube, was allowed to stand for 12 hours. The mixture was then refluxed on a steam-bath for 2 hours, excess thionyl chloride removed under vacuum and the resulting oil taken up in ether. The ethereal solution was washed with dilute hydrochloric acid, dried over Drierite, the ether removed by distillation and the residual oil distilled to yield 27 g. (95%) of 1-(2-fluorophenoxy)-2-chloropropane, boiling at 109–110° (16 mm.). Data on this series of compounds are summarized in Table I.

N-[2-(Fluoro- and Trifluoromethyl-phenoxy)-isopropyl]-2-aminoethanols (IV).—An example of the reaction method is: A mixture of 37.8 g. (0.2 mole) of 1-(2-fluorophenoxy)-2-chloropropane and 61 g. (1.0 mole) of redistilled ethanolamine was heated for 16 hours at 150° with vigorous agitation. The mixture was then cooled, 12 g. (0.21 mole) of potassium hydroxide dissolved in absolute ethanol was added and the precipitated salt removed by filtration. The alcohol solution was dried over Drierite, the alcohol removed by distillation and the residual oil distilled to yield 32.4 g. (76%) of N-[2-(2-fluorophenoxy)-isopropyl]-2-aminoethanol boiling at 148–149° (4 mm.). The distillate solidified upon cooling and was recrystallized from acetone to give colorless crystals melting at 54.2–55.0°. Data on the various members of this series are listed in Table II.

N-Benzyl-N-[2-(fluoro- and Trifluoromethyl-phenoxy)-isopropyl]-2-aminoethanols (V).—The following procedure is general: A mixture containing 100 ml. of absolute ethanol, 17 g. (0.08 mole) of N-[2-(2-fluorophenoxy)-isopropyl]-2-aminoethanol, 10.1 g. (0.08 mole) of benzyl chloride and 6.9 g. (0.05 mole) of potassium carbonate was refluxed for 24 hours with efficient stirring. Solid material was removed by filtration and the alcohol by distillation, and the residual crude oil was dissolved in 200 ml. of 10% hydrochloric acid. The acid solution was cooled to 5°, and 6.9 g. (0.1 mole) of solid sodium nitrite was added slowly with vigorous stirring. After one-half hour the cold solution was extracted with two 100-ml. portions of ether, made basic with a 30% solution of sodium hydroxide and the basic solution extracted with three 100-ml. portions of ether. These combined ether extracts were dried over Drierite, the ether removed by distillation and the resulting oil fractionated to yield 20.4 g. (84%) of N-benzyl-N-[2-(2-fluoro-

(6) We are indebted to Dr. Edwin J. Fellows of the Smith, Kline and French Laboratories for the pharmacological testing.

(7) G. Schiemann and T. Miau, *Ber.*, **66**, 1179 (1933); G. Schiemann, *Z. physik. Chem.*, **156A**, 416 (1931).

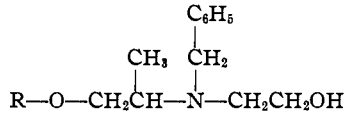
(8) R. L. Ferm and C. A. VanderWerf, THIS JOURNAL, **72**, 4809 (1950).

(9) R. G. Jones, *ibid.*, **69**, 2346 (1947).

(10) F. Swarts, *Bull. acad. roy. Belg.*, 241 (1913).

TABLE III

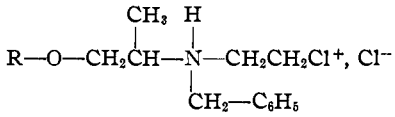
N-BENZYL-N-[2-(FLUORO- AND TRIFLUOROMETHYL-PHENOXY)-ISOPROPYL]-2-AMINOETHANOLS



R	Yield, %	B.p., °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
o-Fluorophenyl	84	178–179	0.5	$C_{18}H_{22}O_2NF$	71.3	71.3	7.2	7.1	4.6	4.8
m-Fluorophenyl	79	174–175	.4	$C_{18}H_{22}O_2NF$	71.3	71.4	7.2	7.5	4.6	4.9
p-Fluorophenyl	79	180–181	.4	$C_{18}H_{22}O_2NF$	71.3	71.7	7.2	7.0	4.6	4.7
o-Trifluoromethylphenyl	45	168–169	.4	$C_{19}H_{22}O_2NF_3$	64.6	65.1	6.3	6.3	4.0	4.0
m-Trifluoromethylphenyl	82	173–174	.5	$C_{19}H_{22}O_2NF_3$	64.6	64.7	6.3	6.0	4.0	4.2

TABLE IV

N-BENZYL-N-(2-CHLOROETHYL)-1-(FLUORO- AND TRIFLUOROMETHYL-PHENOXY)-ISOPROPYLAMINE HYDROCHLORIDES,



R	Yield, %	M.p.,[a] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Adenergic blocking action intravenous dose in mg./kg.
o-Fluorophenyl	69	158–159	$C_{16}H_{22}ONFCl_2$	60.3	60.3	6.2	5.9	3.9	4.0	5
m-Fluorophenyl	62	140–141	$C_{18}H_{22}ONFCl_2$	60.3	60.2	6.2	6.0	3.9	3.8	5
p-Fluorophenyl	69	136–137	$C_{16}H_{22}ONFCl_2$	60.3	60.1	6.2	6.3	3.9	4.1	1.0–2.5
o-Trifluoromethylphenyl[b]	52	141–142	$C_{19}H_{22}ONF_3Cl_2$	55.9	56.0	5.4	5.2	3.4	3.7	5
m-Trifluoromethylphenyl	74	146–147	$C_{19}H_{22}ONF_3Cl_2$	55.9	56.1	5.4	5.5	3.4	3.6	10

[a] Repeated recrystallization from absolute ethanol–ether required to give products showing melting points indicated. [b] Reaction carried out in chloroform solution.

phenoxy)-isopropyl]-2-aminoethanol boiling at 178–179° (0.5 mm.). Table III contains data on this series of compounds.

N-Benzyl-N-(2-chloroethyl)-1-(fluoro- and trifluoromethyl-phenoxy)-isopropylamine Hydrochlorides (I).—A typical procedure was: N-benzyl-N-[2-(2-fluorophenoxy)-isopropyl]-2-aminoethanol (9.2 g., 0.0304 mole) was added gradually to 25 ml. of redistilled thionyl chloride. After the initial vigorous reaction had subsided, the mixture was refluxed for 1 hour and the excess thionyl chloride was removed under reduced pressure. Several recrystallizations of the residue from absolute ethanol–ether gave 7.5 g. (69%) of N-benzyl-N-(2-chloroethyl)-1-(2-fluorophenoxy)-isopropylamine melting at 158–159°. Data on all of the final products are listed in Table IV.

Acknowledgment.—These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Kansas.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

The Isolation and General Properties of Terramycin and Terramycin Salts

BY PETER P. REGNA, I. A. SOLOMONS, KOTARO MURAI, ALBERT E. TIMRECK, KARL J. BRUNINGS AND W. A. LAZIER

Methods for the isolation and purification of the broad spectrum antibiotic, terramycin, have been described. The high purity of the natural product obtained by these methods has been demonstrated by solubility measurements. The hydrated amphoteric base and the hydrohalides of terramycin have been prepared in a pure crystalline state and characterized with respect to molecular weight, composition, crystalline form, optical properties and solubility. The formation of water-insoluble mixed salts of terramycin has been described. The dissociation constants of the acid and base functions of terramycin have been determined by potentiometric titration. It has been observed that certain metal salts, such as calcium chloride, increase the acid strength of terramycin and the titration curves of these systems permit an interpretation as to the composition of the complexes formed.

Terramycin, a new broad spectrum antibiotic elaborated by *Streptomyces rimosus*, has been described by Finlay, *et al.*[1,2] Preliminary information on isolation and data on some of the chemical and physical properties of this new natural product have been given by Regna and Solomons.[3] In the present paper, other methods of isolation and purification are described and more detailed information is given concerning the general properties of terramycin and some of its salts.

Terramycin is a pale yellow compound having a composition best represented by the formula $C_{22}H_{24-26}N_2O_9$. It crystallizes readily from water as the dihydrate which loses its water of crystallization on heating *in vacuo* at 100°. The anhydrous compound melts at 184.5–185.5° with decomposition. Anhydrous terramycin is a relatively stable antibiotic, losing only about 20% of its activity on

(1) A. C. Finlay, G. L. Hobby, S. Y. P'an, P. P. Regna, J. B. Routien, D. B. Seeley, G. M. Shull, B. A. Sobin, I. A. Solomons, J. W. Vinson and J. H. Kane, *Science*, **111**, 85 (1950).

(2) B. A. Sobin, A. C. Finlay and J. H. Kane, U. S. Patent 2,516,080 (July 18, 1950).

(3) P. P. Regna and I. A. Solomons, *Ann. N. Y. Acad. Sci.*, **53**, 229 (1950).