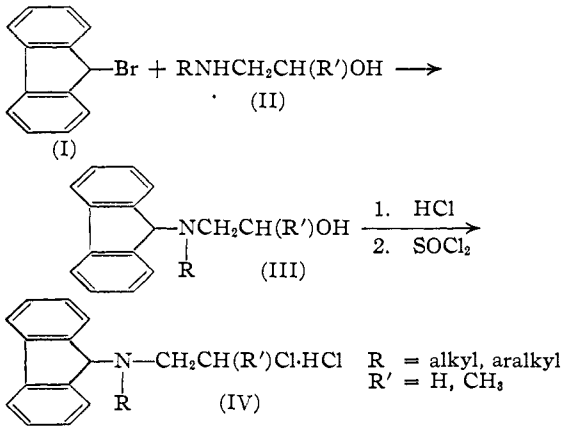
[CONTRIBUTION FROM THE SMITH, KLINE AND FRENCH LABORATORIES]

Adrenergic Blocking Agents. I. N-(9-Fluorenyl)-β-chloroethylamine Series[1]

BY JAMES F. KERWIN, THEODORE F. HERDEGEN, ROBERT Y. HEISLER AND GLENN E. ULLYOT

Recently there has been a marked interest in N,N-disubstituted β-chloroethylamines as adrenergic blocking agents, due largely to the discovery[2] that N,N-dibenzyl-β-chloroethylamine ("Dibenamine")[2a] blocks and reverses the excitatory effects of epinephrine. Only a few types of β-haloethylamines have been reported to have noteworthy adrenergic blocking activity, namely, the N-[α-naphthylmethyl]-N-ethyl, N-benzhydryl-N-ethyl, N-[β-(2-biphenyloxyethyl)]-N-ethyl[3,4,5,6,7,8] and N,N-dimethyl-β-phenyl[9] derivatives. The importance of compounds having this type of action as potential therapeutic agents prompted us to undertake the synthesis of additional compounds for pharmacological evaluation in the hope that information regarding the relationship between structure and activity might be obtained.

The fluorene compounds reported here were prepared readily according to the scheme



Reaction of 9-bromofluorene with an excess of N-substituted amino alcohols in refluxing benzene solution proceeded normally to give the intermediate amino alcohols (III) which were isolated as hydrochloride salts (Table I). These salts were then converted to the β-chloroethylamine hydrochlorides (IV) (Table II) with thionyl chloride in chloroform solution.

(1) Presented before the Division of Medicinal Chemistry at the A. C. S. meeting in San Francisco, California, on March 29, 1949.

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

(2a) Smith, Kline and French trademark for N,N-dibenzyl-β-chloroethylamine.

(3) Achenbach and Loew, *Federation Proc.*, **6**, 304 (1947).

(4) Rieveschl, Fleming and Coleman, "Abstracts 112th Meeting American Chemical Society," page 17K, 1947.

(5) Loew, Micetich and Achenbach, *Federation Proc.*, **6**, 351 (1947).

(6) Loew and Micetich, *ibid.*, **6**, 351 (1947).

(7) Loew and Micetich, *J. Pharm. Expt. Therap.*, **93**, 434 (1948).

(8) Loew and Micetich, *ibid.*, **94**, 339 (1948).

(9) Hunt, *Federation Proc.*, **7**, 229 (1948).

Pharmacological.—We are indebted to Dr. Edwin J. Fellows of our laboratories for the preliminary pharmacological results reported in Table II. A more detailed discussion of the pharmacology of these compounds will be reported elsewhere.

Adrenergic blocking activity was determined with anesthetized cats prepared for recording of carotid blood pressure. The compound to be tested was injected intravenously in propylene glycol solution and then, after approximately an hour, four successive test doses of increasing amounts of epinephrine were injected until a pressor response was obtained or until a final dose of 1.0 cc. of a 1:1000 solution of epinephrine per kilogram was attained without a rise in blood pressure.

The adrenergic blocking activities of the β-chloroethylamines are given in Table I, with "Dibenamine" included for comparison. Of the group, the N-ethyl derivative is the most active. In general, increasing the length of the alkyl chain decreases activity as does substitution of the β-carbon by a methyl group. In the case of the N-butyl compounds, branching increases activity, although the reverse is true of the N-propyl derivatives. The larger benzyl and β-phenylisopropyl groups render the compounds less active.

Experimental

9-Bromofluorene.—Technical fluorene was brominated with N-bromosuccinimide by the method of Wittig and Felletschin[10]; yield 70%, m. p. 102.5–103.5°.

N-Monosubstituted Amino Alcohols. A.—N-Methylethanolamine[11] and N-ethylethanolamine[12] were obtained from commercial sources and redistilled before use.

B. 1-Ethylamino-2-propanol, b. p. 155–157°, was prepared from propylene oxide and ethylamine by the method of Krasouskii.[13]

The other N-alkylethanolamines were produced by reductive amination of the appropriate aldehyde or ketone with ethanolamine according to the procedure of Cope and Hancock.[14]

C. N-Benzylethanolamine was prepared by reductive amination of benzaldehyde with ethanolamine by the method used in D.

D. N-(β-Phenylisopropyl)-ethanolamine was prepared from benzyl methyl ketone and ethanolamine by reductive amination. A solution of 122 g. (2.0 moles) of ethanolamine, 268 g. (2.0 moles) of redistilled benzyl methyl ketone and 300 ml. of alcohol No. 30 was shaken with hydrogen in the presence of 1.0 g. of platinum oxide catalyst at an initial pressure of 600 lb. After four hours, hydrogenation was substantially completed and the solution was filtered free of catalyst. On distillation, an 81% yield of amino alcohol, b. p. 118–122° (3 mm.), was obtained.

(10) Wittig and Felletschin, *Ann.*, **555**, 133 (1944).

(11) Carbide and Carbon Chemicals Corp.

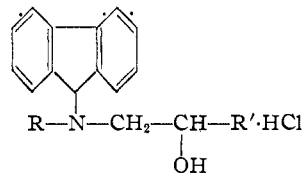
(12) Sharples Chemicals, Inc.

(13) Krasouskii, *J. Chim. Ukraine*, **1**, 398 (1925); *C. A.*, **20**, 2820 (1926).

(14) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

TABLE I

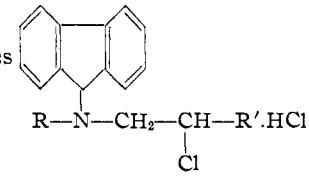
N-(9-FLUORENYL)-ETHANOLAMINE HYDROCHLORIDES



R	R'	Yield, %	Recryst. solvent	M. p., °C.	Empirical formula	Chlorine, % Calcd.	Found
Methyl	H	83	Alcohol	198–200	$C_{16}H_{18}ClNO$	12.86	12.71
Ethyl	H	76	Alcohol-ether	202–204	$C_{17}H_{20}ClNO$	12.29	12.17
n-Propyl	H	48	Alcohol	154–156	$C_{18}H_{22}ClNO$	11.67	11.70
Isopropyl	H	64	Alcohol	213.0–214.5	$C_{18}H_{22}ClNO$	11.67	11.57
n-Butyl	H	67	Alcohol-ether	160–161.5	$C_{19}H_{24}ClNO$	11.16	10.93
s-Butyl	H	50	Alcohol-ether	156–158	$C_{19}H_{24}ClNO$	11.16	11.20
Isobutyl	H	52	Alcohol-ether	146–147	$C_{19}H_{24}ClNO$	11.16	11.08
n-Amyl	H	70	Alcohol-ether	129–131	$C_{20}H_{26}ClNO$	10.69	10.44
Isoamyl	H	28	Alcohol-ether	126–128.5	$C_{20}H_{26}ClNO$	10.69	10.72
n-Heptyl	H	55	Alcohol-ether	94–95	$C_{22}H_{30}ClNO$	9.85	9.76
Benzyl	H	65	Alcohol-acetone	178.5–179.5	$C_{22}H_{22}ClNO$	10.08	9.94
β-Phenylisopropyl	H	41	Alcohol-ether	186–187	$C_{24}H_{26}ClNO$	9.33	9.38
Ethyl	CH_3	66	Alcohol-ether	187.5–188.5	$C_{18}H_{22}ClNO$	11.67	11.62

TABLE II

9-FLUORENYL-β-CHLOROETHYLAMINE HYDROCHLORIDES



R	R'	Yield, %	Recryst. solvent	M. p., °C.	Empirical formula	Analyses, % Calcd. C	H	Cl⁻	Found C	H	Cl⁻	Adrenergic blocking dose[b] in mg./kg.
Methyl	H	80	Alc.-ether	182.5–184	$C_{16}H_{17}Cl_2N$	65.30	5.82	12.05	65.23	5.97	11.81	5–10
Ethyl	H	89	Alc.-ether	195–196.5	$C_{17}H_{19}Cl_2N$	66.23	6.21	11.51	66.54	6.21	11.38	1
Ethyl	CH_3	55	Alc.-ether	156.5–157.5	$C_{18}H_{21}Cl_2N$	67.08	6.57	11.00	66.77	6.49	11.19	5–10
n-Propyl	H	71	Alc.-ether	194–195.5	$C_{18}H_{21}Cl_2N$	67.08	6.57	11.00	67.15	6.75	11.04	5–10
Isopropyl	H	70	Alc.	204–205	$C_{18}H_{21}Cl_2N$	67.08	6.57	11.00	66.86	6.55	11.23	10
n-Butyl	H	74	Alc.-ether	180.5–182.5	$C_{19}H_{23}Cl_2N$	67.85	6.89	10.54	67.88	7.07	10.50	>10
s-Butyl	H	80	Alc.-ether	192.5–194	$C_{19}H_{23}Cl_2N$	67.85	6.89	10.54	67.73	7.16	10.86	5–10
Isobutyl	H	51	Alc.-ether	163–165	$C_{19}H_{23}Cl_2N$	67.85	6.89	10.54	67.53	7.02	10.72	>10, too toxic to test at 15
n-Amyl	H	74	Alc.-ether	180–182.5	$C_{20}H_{25}Cl_2N$	68.56	7.19	10.12	68.41	7.48	10.08	Inactive at 10
Isoamyl	H	76	Alc.-ether	176.5–178.5	$C_{20}H_{25}Cl_2N$	68.56	7.19	10.12	68.71	7.51	10.43	Inactive at 20
n-Heptyl	H	84	Benz.-pet. ether	107.5–109.5	$C_{22}H_{29}Cl_2N$	69.82	7.72	9.37	69.74	7.99	9.36	Inactive at 10
Benzyl	H	91	Chloroform-ether	184–186	$C_{22}H_{21}Cl_2N$	71.35	5.69	9.58	71.15	5.89	9.53	Inactive at 20
β-Phenylisopropyl "Dibenamine"	H	62	Alcohol	187.5–188.5	$C_{24}H_{25}Cl_2N$	72.35	6.32	17.80[a]	72.43	6.39	18.03[a]	Inactive at 10 10

[a] Total chlorine. [b] Dose in mg./kg. of compound which blocks or reverses pressor response to four test doses of epinephrine in cats; test dose IV = 1 mg./kg. of epinephrine.

The hydrochloride, recrystallized from alcohol and ether, melted at 110–111°.

Anal. Calcd. for $C_{11}H_{17}ClNO$: Cl, 16.45. Found: Cl, 16.36.

N-Substituted-N-(9-fluorenyl)-ethanolamine Hydrochlorides (See Table I).—Details of the preparation of N-(9-fluorenyl)-N-(*n*-butyl)-ethanolamine illustrates the method used for preparing the 9-fluorenyl compounds. A solution of 49 g. (0.2 mole) of 9-bromofluorene, 46.8 g. (0.4 mole) of N-(*n*-butyl)-ethanolamine and 150 ml. of dry benzene was refluxed for one and one-quarter hours. The cooled reaction mixture was diluted with 100 ml. of ether and N-(*n*-butyl)-ethanolamine hydrobromide (34 g.) removed by filtration. Dry hydrogen chloride was passed into the filtrate with cooling and the salt was recrystallized twice from alcohol and ether to give 43 g. of product.

N-(9-Fluorenyl)-β-chloroethylamine Hydrochlorides (See Table II).—A typical preparation will serve to illustrate the method. A solution of 19 g. (0.16 mole) of thionyl chloride in 50 ml. of chloroform was added in portions to 38 g. (0.138 mole) of N-(9-fluorenyl)-N-methylethanolamine hydrochloride suspended in 50 ml. of chloroform. The mixture was warmed on a water-bath until the hydrochloride dissolved and then the solution was heated at 50–55° for an hour. The solvent was removed under reduced pressure and the oily residue was triturated with ether until it solidified. The solid was collected and recrystallized twice from alcohol and ether.

Summary

The synthesis of a series of N-(9-fluorenyl)-N-

alkyl(or aralkyl)-β-chloroethylamines has been described. These compounds possess adrenergic blocking activity; N-(9-fluorenyl)-N-ethyl-β-chloroethylamine hydrochloride being outstanding in this regard.

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[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Synthesis of Enantiomeric α-Lecithins[1]

BY ERICH BAER AND MORRIS KATES[2]

A critical survey of the pertinent literature reveals the surprising fact that it was not until 1941 that the first individual lecithin, (dipalmitoyl) lecithin[3] (DPL), was isolated from a natural source (*Cysticercus fasciolaris*).[4] The same compound was later isolated also from brain, lung and spleen.[5]

The great difficulties encountered in obtaining individual lecithins from natural sources have prompted numerous attempts to obtain these compounds by synthesis. The properties of these racemic "synthetic lecithins" were in some respects similar to those of natural lecithins, but they differed widely in others. On examining critically the earlier work in the field of "synthetic lecithins"[6-8] it becomes evident that the reported compounds were not, as claimed, pure individual lecithins but most likely mixtures of α- and β-lecithins and/or the choline salts of α- and β-phosphatidic acids.

During the past twelve years methods have been developed in this Laboratory which permit the synthesis of the pure enantiomeric forms of asymmetrically substituted glycerol derivatives of predetermined constitution and configuration.[9]

It was thought that these methods might be applicable to the preparation of individual lecithins. In a previous communication it was shown that α-glycerylphosphorylcholine[9m] (α-GPC) obtained from natural lecithins belongs to the L-series. The introduction of two acyl groups into L-α-GPC therefore should yield α-lecithins with the configuration of the natural products. Various attempts to esterify the synthetic L-α-GPC by means of stearoyl chloride and pyridine did not, however, produce the desired α-lecithin but instead yielded products which consisted mainly of mono stearoyl-GPC (lyso-lecithin), as indicated by the analytical values and a strong hemolytic activity. When further efforts to improve the acylating procedure remained unproductive the method was abandoned.

In the second approach to the synthesis the order of introducing the various substituents into the glycerol molecule was reversed, *i. e.*, the fatty acids were introduced first. After overcoming several technical difficulties this procedure proved to be successful. The sequence of reactions and the steric relationships of the various intermediary compounds are illustrated in the accompanying reaction scheme.

The synthesis is as follows. The D-α,β-diglyceride (I)[10] is phosphorylated with monophenylphosphoryl dichloride in the presence of *one mole* of pyridine[11] giving rise to the formation of diacyl L-α-glycerylphenylphosphoryl chloride (II) and bis-(diacylglyceryl)-phenylphosphate (IIa). Without isolating the intermediate compound (II) the reaction mixture is immediately treated with choline chloride in the presence of a large excess of pyridine. The ether- and water-insoluble part of the reaction product consists almost entirely of a mixture of diacyl α-glycerylphenylphosphorylcholine chloride (III) and bis-(diacylglyceryl)-phosphoric acid phenyl ester (IIa).[12] The choline ester (III) is isolated and

(1) A preliminary report of the subject matter of this paper has appeared in *Science*, **109**, 31 (1949). Patents applied for.

(2) This paper forms part of a thesis submitted by M. Kates to the Department of Chemistry, University of Toronto, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, November, 1948. Present address: National Research Council, Ottawa, Canada.

(3) Since the name *lecithin* has been used for generations to describe the whole molecule, prefixes such as distearoyl—cannot be applied correctly in the chemical sense since this suggests substitution; it is therefore proposed to place these purely descriptive prefixes within parentheses.

(4) Lesuk and Anderson, *J. Biol. Chem.*, **139**, 457 (1941).

(5) Thannhauser, Benotti and Boncoddo, *ibid.*, **166**, 669 (1946); Thannhauser and Boncoddo, *ibid.*, **172**, 135 (1948).

(6) Grün and Limpächer, *Ber.*, **59**, 1345, 1350 (1926); *ibid.*, **60**, 147 (1927).

(7) Kabashima and Suzuki, *Proc. Imp. Acad. (Tokyo)*, **8**, 492 (1932); *C. A.*, **27**, 1634 (1933); Kabashima, *Ber.*, **71B**, 76 (1938).

(8) Obata, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **22**, 115 (1943); *C. A.*, **42**, 522 (1948).

(9) Baer and Fischer, (a) *J. Biol. Chem.*, **128**, 463 (1939); (b) **128**, 475 (1939); (c) **128**, 491 (1939); (d) **135**, 321 (1940); (e) **140**, 397 (1941); (f) **145**, 61 (1942); (g) Baer, Cushing and Fischer, *Can. J. Res.*, **21B**, 119 (1943); (h) Baer, Rubin and Fischer, *J. Biol. Chem.*, **155**, 447 (1944); (i) **170**, 337 (1947); (j) Baer and Fischer, THIS JOURNAL, **61**, 761 (1939); (k) **67**, 944 (1945); (l) **67**, 2031 (1945); (m) Baer and Kates, *ibid.*, **70**, 1394 (1948).

(10) Prepared according to the method of Sowden and Fischer, *ibid.*, **63**, 3244 (1941).

(11) In contrast to the phosphorylation of D-acetone-glycerol with monophenylphosphoryl dichloride[9m] it was found that the phosphorylation of the diglyceride had to be carried out in the presence of the more strongly basic pyridine rather than quinoline and at temperatures ranging from +10 to +35°.

(12) These compounds are being converted to the corresponding bis-(diacylglyceryl)-phosphoric acids which may have some relationship to the complex phosphatidic acid, cardiolipin, of M. C. Pangborn (*J. Biol. Chem.*, **168**, 351, 1947). On separating the phosphorylation mixtures derived from distearin, dipalmitin and dimyristin, it was found that they contain compounds (IIa) and (III) in the approximate molar ratios of (1:8), (1:4) and (1:3), respectively. Apparently the formation of bis-(diacylglyceryl) phosphoric acid phenyl esters increases with decreasing length of the fatty acid.