Esters of 4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol as Long-Acting Tranquilizing Agents. Synthesis of 4-{3-[2-(Trifluoromethyl)-phenothiazin-10-yl]propyl}-1-piperazineëthanol-ethyl-C^{14} and its Ester with Heptanoic Acid. III

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A number of esters of 4-{3-[2-(trifluoromethyl)-phenothiazin-10-yl]propyl}-1-piperazineëthanol have been prepared with triethylacetic, heptanoic, decanoic, undecylenic, stearic, 8-carbomethoxyoctanoic, azelaic, and 2,6-dimethyl-*p*-anisic acids. Several of these, administered in sesame oil solution, have shown long duration of tranquilizing activity. The heptanoate, for example, in a single dose of 8 to 32 mg./kg., has shown a duration of activity ranging from 12 to 15 days in the trained rat; the same compound has been tried in man and a single dose of 25 mg. has shown clinical effectiveness for 2 weeks.

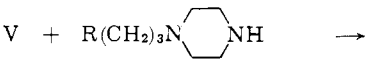
An objective of our program on central nervous system depressants[1] has been the synthesis of a long-acting tranquilizing agent. Earlier comparisons of the dihydrochlorides of 4-{3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol (I) and its ester with acetic acid (II), had demonstrated no significant pharmacological differences or duration of activity between the two compounds, due to the rapid

I R = HO
II R = CH_3CO_2
III R = $C_6H_{13}CO_2$
IV R = CH_3SO_3
V R = Cl

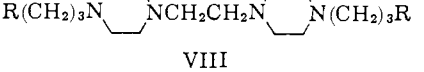
enzymatic hydrolysis of II.[2] A number of esters of I with higher molecular weight carboxylic acids have now been prepared, and the pharmacological evaluation of these has shown that several possess long duration of tranquilizing activity. For example, the ester with heptanoic acid (III), dissolved in seasame oil and injected subcutaneously into rats, in a single dose of 8–32 mg./kg., has shown a duration of activity ranging from 12 to 15 days[3]; the same compound has been tried in man and a single dose of 25 mg. has shown clinical effectiveness for 2 weeks.[4]

The general procedure for the synthesis of these compounds involved the reaction of I with the acyl chloride, in chloroform, under reflux. In this fashion, esters were prepared with triethylacetic, heptanoic, decanoic, undecylenic, stearic, 8-carbomethoxyoctanoic, and azelaic acids. While the ester with 2,6-dimethyl-*p*-anisic acid could not be prepared by this method, it was synthesized by the reaction of potassium 2,6-dimethyl-*p*-anisoate with 10-{-[4-(2-chloroethyl)-1-piperazinyl]propyl}-2-(trifluoromethyl)phenothiazine (V), in N,N-dimethylformamide. These esters were usually obtained as oils; the only exception was the stearate, which crystallized spontaneously. The esters form crystalline hydrochlorides or maleates. Their physical properties and analyses are summarized in Table I.

The reaction of I with methanesulfonyl chloride or methanesulfonic anhydride, under a variety of conditions, did not give the methanesulfonate (IV); nor, was IV obtained from the reaction of V with potassium methanesulfonate, or from the reaction between β-chloroethyl methanesulfonate (VI) and VII. The only identified product of the latter reaction was VIII, the structure of which was established by an independent synthesis from V and VII.



VII



VIII

R = 2-(trifluoromethyl)-10-phenothiazinyl

That this behavior of VI with secondary amines is somewhat general in nature was shown by its reaction (a) with N-methylpiperazine to give 1,1′-ethylenebis-(4-methylpiperazine) and (b) with N-methylaniline to give N,N′-dimethyl-N,N′-diphenylethylenediamine. In the latter reaction, N-(2-chloroethyl)-N-methylaniline was a by-product; its isolation sheds some light on a possible mechanism for these reactions, namely, nucleophilic attack of VI by the amine to form the more reactive N-(2-chloroethyl) derivative which can then condense with a second molecule of the amine.

An attempt to prepare the *p*-toluenesulfonate of I was also unsuccessful.

Studies on the absorption, distribution, and metabolism of III have also been initiated in rats. Due to the minute quantities of material involved and the resultant difficulties in obtaining quantitative data, 4-{3-[2-(trifluoromethyl)-phenothiazin-10-yl]propyl}-1-piperazineëthanol-*ethyl*-C^{14} (IX) and its ester with heptanoic acid (X) were prepared by the reaction of VII with

(1) For the preceding papers in this series, see (*a*) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957) (I); (b) H. L. Yale and F. Sowinski, *ibid.*, **82**, 2039 (1960) (II); see also, F. Sowinski and H. L. Yale, *J. Med. Pharm. Chem.*, **5**, 54 (1962).

(2) C. I. Smith and J. C. Burke, *Toxicol. Appl. Pharmacol.*, **2**, 553 (1960); J. P. High, G. L. Hassert, Jr., B. Rubin, J. J. Piala, J. C. Burke, and B. N. Craver, *ibid.*, **2**, 540 (1960).

(3) J. C. Burke, J. P. High, R. J. Laffan, and C. L. Ravaris, *Federation Proc.*, **21**, 339 (1962).

(4) J. Kinross-Wright, A. H. Vogt, and K. D. Characzanowski, *Am. J. Psychiatry*, **119**, 779 (1963).

TABLE I

ESTERS WITH 4-[3-[2-(TRIFLUOROMETHYL)PHENOTHIAZIN-10-YL]PROPYL]-1-PIPERAZINEËTHANOL

R	Salts			Salt analyses, %[a]						Base yield, %[b]	Base analyses, %[c]					
	Mol. formula	Yield, %	M.p., °C[d]	Calcd.			Found				Calcd.			Found		
				C	H	N	C	H	N		C	H	N	C	H	N
$CH_3(CH_2)_5$	$C_{29}H_{38}F_3N_3O_2S\cdot 2HCl\cdot 0.5H_2O^{e,f}$	44	184–185 dec.	55.15	6.51	6.66	54.82	6.59	6.73	98	63.37	6.98	7.64	63.09	7.10	7.91
$(C_2H_5)_3C$	$C_{30}H_{40}F_3N_3O_2S\cdot 2C_4H_6O_4^g$	42	167–168	57.34	6.08	5.28	57.28	6.33	5.27	90	63.91	7.15	7.45	64.12	7.47	7.79
4,2,6-(MeO)$Me_2C_6H_2$	$C_{32}H_{36}F_3N_3O_5S\cdot 2C_4H_4O_4\cdot H_2O^h$	75	160–161	56.53	5.46	4.94[d]	56.64	5.42	5.34	27	64.00	6.05	7.01	63.70	6.57	6.80
$CH_2{=}CH(CH_2)_8$	$C_{33}H_{44}F_3N_3O_2S\cdot 2HCl^{e,i}$	83	153–155			6.21			6.23	94	65.64	7.34	6.96[d]	65.73	7.26	7.32
$CH_3(CH_2)_8$	$C_{32}H_{44}F_3N_3O_2S\cdot 2HCl^h$	63	175–176	57.81	6.97	6.32	57.55	7.18	6.42	84	64.94	7.42	7.09	65.19	7.68	7.29
$CH_3OCO(CH_2)_7$	$C_{32}H_{42}F_3N_3O_4S\cdot 2C_4H_4O_4^j$	65	160–161 dec.	56.25	5.90	4.91	56.19	5.96	4.90	65	61.81	6.81	6.76	61.89	6.97	6.55
$CH_3(CH_2)_{16}$	$C_{30}H_{60}F_3N_3O_2S\cdot 2HCl^{f,k}$	59	80–81			5.41			5.48	58[k]	68.24	8.59	5.97	67.84	8.76	6.36
$-(CH_2)_4-^l$	$C_{36}H_{61}F_3N_6O_8S_2\cdot 4C_4H_4O_4^m$	82	190–191	55.56	5.40	5.63	55.41	5.69	5.42	95	61.96	6.28	8.18	62.09	6.50	7.87

[a] Calcd.: total volatiles, 1.4. Found: 1.6. [b] Recrystallized from butanone. [c] Recrystallized from acetonitrile. [d] Calcd.: CH_4O, 3.65. Found: CH_4O, 3.49. [e] Calcd.: Cl, 10.49. Found: Cl, 10.57. [f] Recrystallized from a mixture of acetone and anhydrous ether. [g] Calcd.: S, 5.31. Found: S, 5.53. [h] Recrystallized from acetone. [i] Recrystallized from methanol. [j] Calcd.: Cl, 9.13. Found: Cl, 9.77, 9.81. [k] M.p. 33–34°. [l] Diester with azelaic acid. [m] Recrystallized from 90% ethanol. [n] The nitrogen analyses were carried out by Messrs. J. F. Alicino, V. Abate, J. Hyden, C. Sabo, and Mrs. Grabowich. [o] Calcd. on recovery of base from purified salt.

TABLE II

PROTON MAGNETIC RESONANCE DATA

VII Side chain

I Side chain

Proton position	τ value	
	VII	I
(a)	6.06	6.05
(b)	8.11	8.09
(c)(d)(e)(d')(e')(i)	7.68	7.57
(f)(g)	7.23	...
(h)	8.42	...
(j)	...	6.41
(k)	...	6.93

C^{14}-labeled 2-bromoethanol (XI) followed by esterification with heptanoyl chloride.

During attempts, in cold runs, to determine optimum conditions for these reactions, it was observed that solutions of VII reacted rapidly with atmospheric carbon dioxide to give a bicarbonate (XII); the presence of XII made the reaction with 2-bromoethanol most erratic and led to low yields of I. The procedure which was eventually evolved and used with XI required that the weighings, transfers, and reactions be carried out in a nitrogen atmosphere, with benzene as the solvent and anhydrous barium hydroxide as the acid acceptor. In this manner, the yield of IX, as the recrystallized maleate salt, in a 0.005 *M* run, was 82%. Experimental conditions were then developed for the conversion of IX and X in essentially quantitative yields.[5]

The need for a rapid estimation of the conversion of VII to I directly on the reaction mixture, made it necessary to study several possible analytical procedures. Paper chromatographic separation of VII and I could not be achieved, since in all of the systems studied, these compounds had identical R_f values. It was found, however, after an analysis of the nuclear magnetic resonance spectra of the two compounds, that these could be used to estimate the conversion. The proton assignments of the peak signals seen in the spectra are summarized in Table II.

Since the triplet at τ 6.41 was present in the spectrum of I and not in that of VII, while the triplet at τ 6.05 was common to both compounds, the conversion of VII to I could be estimated by the formula

$$\frac{\text{Wt. of area under triplet } \tau\ 6.41}{\text{Wt. of area under triplet } \tau\ 6.05} \times 100 = \%\ \text{conversion to I}$$

In a cold run carried out subsequently under optimum

(5) A preliminary report on the metabolism of IX and X in rats was presented by S. M. Hess, H. L. Yale, and A. G. Ebert, International Congress on Phenothiazine Metabolism, Paris, France, September 8, 1962. For a more complete report, see A. G. Ebert, H. L. Yale, and S. M. Hess, *Federation Proc.*, **22**, 539 (1963).

conditions, the estimated conversion to I was 77%, while the actual conversion to I was 79%.

Pharmacology.—The dihydrochlorides of I and III given intraperitoneally as aqueous solutions, were equipotent in inhibiting the avoidance of an electric shock by rats conditioned to climb a pole after warning by a buzzer. The ED_{100} for each compound was 2 mg./kg.; duration of inhibition did not exceed 24 to 48 hr. Compound III, at 5% in sesame oil and injected subcutaneously as a depot, in doses 4 to 16 times above the ED_{100}, produced 50 to 100% inhibition for 12 to 15 days. The degree of sedation and motor depression at no time exceeded those produced by the ED_{100} of the aqueous solutions of the dihydrochlorides. Similarly, the other esters described in this manuscript, when injected subcutaneously as a 5% solution of the free base in sesame oil, in doses 4 to 16 times above their ED_{100}, produced 50 to 100% inhibition for a minimum of 12 to 15 days. The same concentration of III in oil, given subcutaneously to dogs, elevated their thresholds to the emetic action of apomorphine 32-fold for 4 weeks. The thresholds gradually returned to pre-dose levels over the following 3 weeks.

Metabolism and Distribution of the C^{14}-Labeled Compounds.—Radioactivity in rat brain, urine, and feces were measured after a single 30 mg./kg. subcutaneous dose of IX or X in sesame oil solution. Twenty-four hours after dosing, brains of rats receiving IX or X contained only IX in concentrations of 3.9 μg./g. and 0.4 μg./g., respectively. This represented 69% of the total brain radioactivity in animals given IX but only 31% of brain radioactivity in animals given X. During the 10 days following the administration of IX, 8% of the radioactivity administered appeared in urine and 36% in feces; animals treated with X excreted 4% of the administered radioactivity in urine and 13% in feces. Paper chromatograms of extracts of 24 hr. urine samples revealed the presence of IX and IX-sulfoxide in concentrations of 0.6 μg./ml. and 6.4 μg./ml. of urine, respectively. These metabolites represented 15–30% of total urine radioactivity.

Experimental

The melting points are corrected and were determined by the capillary technique using a well stirred liquid bath.

The preparation below is typical of the procedure used for the synthesis of esters via the reaction of I[1b] and an acyl chloride.

4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol, Stearate Ester.—To a stirred solution of 11.8 g. (0.025 mole) of I (purified by molecular distillation) in 100 ml. of dry chloroform was added, dropwise, a solution of 9.1 g. (0.03 mole) of stearoyl chloride in 100 ml. of dry chloroform. Subsequently, the mixture was stirred and heated under reflux for 6 hr., 50 ml. of the chloroform was distilled, and the residue dissolved in 250 ml. of ether. The ether solution was shaken with two 100 ml. portions of 5% aqueous hydrochloric acid, then with two 100 ml. portions of a saturated aqueous sodium bicarbonate solution, dried, filtered, and a slight excess of ethereal hydrogen chloride added to the filtrate with stirring and cooling. The hygroscopic solid was filtered rapidly, dried, and recrystallized from anhydrous acetone–ether to give 11.4 g. of the dihydrochloride, m.p. 80–81°. This salt was added to an ice-cooled, stirred mixture of 100 ml. of 5% aqueous sodium bicarbonate solution and 200 ml. of ether. When no solid remained, the ether solution was separated, dried and concentrated to give 10.1 g. of the base as an oil which crystallized spontaneously to a solid, m.p. 33–34°.

4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol, Azelaate Diester.—When the chloroform–ether solution obtained from the reaction of I and azelayl chloride was shaken as above with 5% aqueous hydrochloric acid, three layers formed. The lower chloroform and upper aqueous layers were discarded while the middle layer was shaken with 5% aqueous potassium carbonate and ether until two phases formed. The ether layer was separated, dried, and treated with a saturated solution of maleic acid in acetone to give the maleic acid derivative. The purified maleate was decomposed in the usual manner with aqueous sodium bicarbonate solution to give the base.

4-{3-(2-Trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol, 2,6-Dimethyl-*p*-anisate Ester.—To 5.1 g. (0.025 mole) of 2,6-dimethyl-*p*-anisic acid in 10 ml. of 95% ethanol was added 1.7 g. (0.026 mole) of 85% potassium hydroxide in 25 ml. of 95% ethanol. The solution was filtered, concentrated to 10 ml., and 50 ml. of anhydrous ether added. The precipitated solid was filtered, washed with ether, and dried to give 4.1 (67%) of the **potassium salt**, m.p. 279–280°.

Anal. Calcd. for $C_{10}H_{11}O_3K$: K, 17.91. Found: 17.43.

To 21.9 g. (0.05 mole) of I in 250 ml. of dry benzene was added 7.1 g. (0.06 mole) of thionyl chloride, the mixture kept overnight, heated for 3 hr. under reflux, cooled, and treated with an excess of ethereal hydrogen chloride. The solid was filtered and recrystallized from absolute ethanol–anhydrous ether to give 18.4 g. of product, m.p. 215–216° dec., suitable for further synthesis; pure **10-{3-[4-(2-chloroethyl)-1-piperazinyl]propyl}-2-(trifluoromethyl)phenothiazine (V) dihydrochloride,** m.p. 224–225° dec., was obtained by an additional recrystallization from absolute ethanol.[6]

Anal. Calcd. for $C_{22}H_{25}F_3ClN_3S \cdot 2HCl$: total Cl, 20.11; N, 7.94. Found: Cl, 20.27; N, 7.96.

To 2.7 g. of the above potassium salt in 25 ml. of N,N-dimethylformamide, under nitrogen, was added the V obtained from 5.3 g. (0.01 mole) of the dihydrochloride. The mixture was stirred and heated for 5 hr. on the steam bath, cooled, diluted with cold water, 10% aqueous sodium hydroxide added to pH 10, and the product extracted with ether. The ether extracts were dried, and filtered and the filtrate was concentrated to give 3.5 g. (58% yield) of the crude ester, as a viscous yellow oil. To the crude ester, in 50 ml. of anhydrous ether, was added 1.5 g. (0.013 mole) of maleic acid in 10 ml. of acetone. The precipitated solid was filtered and recrystallized from ethyl methyl ketone to give 3.6 g. (75%) of the maleate, m.p. 160–161°. The maleate was added to 50 ml. of cold, saturated aqueous sodium bicarbonate solution and 50 ml. of ether and the whole stirred until no solid remained. The ether layer was separated, dried, and concentrated to give 1.6 g. of the pure ester as a viscous oil.

Attempted Preparation of IV.—The following summarizes the unsuccessful experiments carried out: I and methanesulfonyl chloride in acetone, in the presence of anhydrous potassium carbonate; reaction of I with sodium hydride in xylene to give the sodium salt, followed by treatment with methanesulfonyl chloride; I and methanesulfonyl chloride in pyridine; and, I and methanesulfonic anhydride–pyridine complex.

10,10′-Ethylenebis(1,4-piperazinediyl)bispropylenebis[2-(trifluoromethyl)phenothiazine]. (A).—A mixture of 3.93 g. (0.01 mole) of VII,[1b] 3.64 g. (0.008 mole) of V, 1.5 g. of anhydrous, potassium carbonate, 100 mg. of copper powder, and 25 ml. of toluene was stirred and heated under reflux for 16 hr., filtered, and the filtrate concentrated to dryness *in vacuo*. The residue crystallized when treated with acetone and cooled. Recrystallization from ethyl methyl ketone gave 0.9 g. (14%) of product, m.p. 146–147°, and this m.p. was not depressed by the product obtained in (B) below.

Anal. Calcd. for $C_{42}H_{46}F_6N_6S_2$: C, 42.04; H, 5.70; N, 10.34; S, 7.89. Found: C, 42.64; H, 6.18; N, 10.48; S, 7.87.

(B).—From the reaction between 3.93 g. (0.01 mole) of VII, 1.9 g. (0.012 mole) of VI, 1.4 g. of anhydrous potassium carbonate, 100 mg. of copper bronze, and 25 ml. of toluene, after 16 hr. of heating under reflux, there was obtained 350 mg. (8% yield) of product, m.p. 146–147°, after recrystallization from ethyl methyl ketone.

Reaction between N-Methylaniline and VI.—A mixture of 21.4 g. (0.2 mole) of N-methylaniline, 15.8 g. (0.1 mole) of VI, 13.8

(6) E. L. Anderson, G. B. Bellinzona, P. N. Craig, G. E. Jaffe, K. P. Janeway, C. Kaiser, B. M. Lester, E. J. Nikawitz, A. M. Pavloff, H. E. Reiff, and C. L. Zirkle, *Arzneimittel-Forsch.*, **12**, 937 (1962), report a m.p. of 209–211° for the recrystallized compound obtained by a somewhat different procedure.

g. of anhydrous potassium carbonate, 0.1 g. of copper powder, and 50 ml. of dry toluene was stirred and heated under reflux for 24 hr., filtered, and the insoluble material extracted with hot benzene. The combined filtrate and extracts were concentrated to dryness and the residue distilled to give 4.8 g. of unreacted N-methylaniline, b.p. 42–46° (0.5 mm.), 2.8 g. of N-β-chloroethyl-N-methylaniline, b.p. 75–78° (0.5 mm.), characterized as the hydrochloride, m.p. 126–127° dec.,[7] after recrystallization from anhydrous acetone–ether.

Anal. Calcd. for $C_9H_{12}ClN \cdot HCl$: C, 52.44; H, 6.35; N, 6.79. Found: C, 52.39; H, 6.27; N, 6.59.

Further distillation gave 5.1 g. of N,N'-dimethyl-N,N'-diphenylethylenediamine,[8] b.p. 149–151° (0.5 mm.).

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.94; H, 8.39; N, 11.65. Found: C, 80.08; H, 8.50; N, 11.96.

This compound formed a dihydrochloride, m.p. 184–185° dec., after recrystallization from absolute ethanol–anhydrous ether.

Anal. Calcd. for $C_{16}H_{20}N_2 \cdot 2HCl$: Cl, 22.63; N, 8.94. Found: Cl, 22.93; N, 8.73.

Reaction between N-Methylpiperazine and VI.—A stirred mixture of 20.1 g. (0.2 mole) of N-methylpiperazine, 15.8 g. (0.1 mole) of VI, 13.8 g. of anhydrous potassium carbonate, 100 mg. of copper powder, and 50 ml. of anhydrous toluene was heated under reflux for 24 hr. The toluene solution was decanted, concentrated, and the residue distilled to give 5.2 g. of N-methylpiperazine, b.p. 68° (30 mm.), and 6.9 g. (27%) of 1,1'-ethylene-bis (4-methylpiperazine),[9] b.p. 163–166° (10 mm.), $n^{25}D$ 1.4833. The distillate crystallized spontaneously to a solid, m.p. 58–59°; recrystallization from ligroin raised the m.p. to 59–61°.

Anal. Calcd. for $C_{12}H_{26}N_4$: N, 24.75. Found: N, 24.86.

The base was further characterized as the tetrahydrochloride, m.p. 290–292° dec. after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{26}N_4 \cdot 4HCl$: Cl, 38.09; N, 15.05. Found: Cl, 38.04; N, 15.04.

4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol-ethyl-C^{14}, Heptanoate Ester. (Cold Run).—A mixture of 1.97 g. (0.005 mole) of carefully purified VII, 1.71 g. (0.01 mole) of anhydrous barium hydroxide, 25 mg. of copper powder, 50 mg. of pulverized potassium iodide, 0.625 g. (0.005 mole) of 2-bromoethanol, and 20 ml. of anhydrous benzene (all weighings and transfers, as well as the reaction itself, were carried out in a nitrogen-purged drybox) was stirred and heated gradually so that reflux was reached after 2 hr. The mixture was heated under reflux for 19 additional hr., cooled, the mixture centrifuged, the benzene solution decanted, the solid resuspended in 10 ml. of anhydrous benzene, centrifuged, and the benzene washings were combined with the original benzene solution. A 0.3 ml. quantity of this solution was evaporated to dryness, reconstituted in deuteriochloroform, and the n.m.r. spectrum[10] determined. The excised τ 6.41 area weighed 0.0890 g. and the τ 6.05 area 0.1160 g., indicating a 77% conversion to I.

To the combined benzene solution at room temperature, was added dropwise and with stirring 1.20 g. (0.0104 mole) of maleic acid in 10 ml. of boiling anhydrous 2-propanol, 5 ml. of anhydrous benzene added, the whole cooled and centrifuged. The solid was dried *in vacuo* and recrystallized from 50 ml. of anhydrous 2-propanol to give 2.64 g. (79% yield) of pistol-dried pure maleate, m.p. 158–160°; a mixture m.p. with authentic maleate was 158–160°.[11]

Anal. Calcd. for $C_{22}H_{26}F_3N_3S \cdot 2C_4H_4O_4$: C, 53.81; H, 5.12; N, 6.28. Found: C, 53.91; H, 5.03; N, 6.32.

The above purified maleate was transferred to a separatory funnel by means of 15 ml. of water, 100 ml. of ether was added, the mixture was treated slowly with 5 g. of solid sodium bicarbonate and 3 g. of sodium chloride and carefully shaken until no solid remained. The water layer was separated and the ether layer was dried and concentrated to give 1.64 g. (95% recovery) of I. This material was shown to be homogeneous, with an R_f 0.70 (identical with that of authentic I), when chromatographed on paper with the biphasic system, benzene–acetic acid–water (2:2:1).[12] This base (1.60 g., 0.0037 mole), 1.18 g. (0.008 mole) of heptanoyl chloride, and 10 ml. of dry chloroform were stirred and heated under reflux for 22 hr. The cooled mixture was transferred to a separatory funnel by means of 50 ml. of ether, 10 ml. of water was added, the mixture was treated slowly with 4 g. of solid sodium bicarbonate and carefully shaken. The water layer was separated, the ether layer dried and concentrated to give 2.00 g. (100% yield) of III. This material was shown by chromatography on paper to contain as the only impurity, 0.8% (w./w.) of I; in the same system used above, the ester had R_f 0.92 (identical with that of III prepared from authentic I and heptanoyl chloride).

C^{14}-Labeled Runs.—The labeled experiment employed as the only variation in the above run the use of 0.625 g. (0.005 mole, 3200 μc.) of C^{14}-labeled-2-bromoethanol.[13] The yield of the recrystallized maleate of IX was 2.72 g. (82%), with an activity of about 0.91 μc./mg. Nine hundred mg. of the maleate gave 570 mg. (97% recovery) of IX, with an activity of about 1.39 μc./mg. The maleate salt (1800 mg.) was converted to IX and the latter reacted with 0.83 g. of heptanoyl chloride in 10 ml. of dry chloroform. This gave 1.550 g. of X, with an activity of about 1.0 μc./mg. Both IX and X were shown to be homogeneous by paper chromatography in the system described above; the homogeneity was confirmed by radioactive profiles of the paper chromatograms.

Formation of Bicarbonate of VII.—Since VII is a viscous gum and difficult to transfer for weighing, it seemed desirable for practical purposes to prepare a stock solution. The compound, therefore, was weighed into a tared beaker and rinsed into a volumetric flask with boiling toluene, the solution was allowed to cool and additional solvent added to bring to the full volume. This solution, after about 2 hr., began to deposit a fine crystalline precipitate, and the quantity increased with time. After 24 hr., this solid was separated by centrifugation; the clear supernatant continued to deposit additional solid. The dried solid, m.p. 166°, was recrystallized from toluene to give material, m.p. 182–184°, which was unchanged after an additional recrystallization from the same solvent. In the infrared, the compound showed strong absorption in the 4.03–4.08 and 6.30 μ regions. This absorption is not seen with VII. These two bands are seen characteristically in the spectra of inorganic bicarbonates, *e.g.*, NH_4HCO_3, $NaHCO_3$, etc., but not in inorganic carbonates.[14] Analyses indicated that the compound was a sesquibicarbonate of VII.

Anal. Calcd. for $C_{23}H_{22}F_3N_3S \cdot 1.5H_2CO_3$: C, 55.07; H, 5.18; N, 8.65; neut. equiv., 243. Found: C, 52.18; H, 5.89; N, 9.12; neut. equiv. ($+HCl$), 231.

When a toluene solution of VII was treated with solid carbon dioxide, a solid separated directly, and this was shown to be identical with the above solid by means of melting point and mixture melting point.

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(7) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Am. Chem. Soc.*, **79**, 2221 (1957), who prepared this compound reported m.p. 100–105° for the crude material.

(8) G. R. Clemo and W. H. Perkin, Jr., *J. Chem. Soc.*, **121**, 642 (1922), treated N-methylaniline with β-chloroethyl-*p*-toluenesulfonate and obtained N-β-chloroethyl-N-methylaniline, b.p. 124° (10 mm.), and N,N'-dimethyl-N,N'-diphenylethylenediamine, m.p. 47°. The b.p. of the latter compound, 220–223° (15 mm.), was reported by J. V. Braun and Z. Arkuszewski, *Ber.*, **49**, 2611 (1916).

(9) F. G. Mann and F. C. Baker, *J. Chem. Soc.*, 1881 (1957), who prepared this compound by a different procedure reported a b.p. of 100–103° (0.1 mm.) and a melting point of 286–288° for the tetrahydrochloride.

(10) The n.m.r. spectra were obtained on a Varian A-60 spectrometer; tetramethylsilane was the internal standard.

(11) V. Fishman and H. Goldenberg, *Proc. Soc. Exptl. Biol. Med.*, **104**, 99 (1960).

(12) The C^{14}-labeled-2-bromoethanol, as obtained from the New England Nuclear Corp., consisted of a mixture of double labeled and completely unlabeled species; it follows, then, that IX and X represent a similar mixture of labeled and unlabeled species.

(13) F. A. Miller and C. H. Wilkins, *Anal. Chem.*, **24**, 1253 (1952).