Monofluoromethanesulfonanilides. A New Series of Bronchodilators

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A new series of monofluoromethanesulfonanilides has been prepared. Compounds of this series are related to classical β-adrenergic catecholamines but are distinguished by a monofluoromethanesulfonamido group in place of the *m*-hydroxyl. Potent β-stimulant activity is observed with many of these monofluoromethanesulfonanilides in isolated muscle preparations, particularly if the *N*-alkyl substituent is cyclopentyl (**22** and **29**) or *p*-methoxyphenethyl (**23** and **35**).

The search for improved bronchodilator agents has generally centered on compounds possessing oral activity, selectivity of action, and long duration of effect. Although isoproterenol is an effective bronchodilator when given by inhalation, it lacks oral activity because of rapid deactivation due to ethereal sulfate formation in the gut.[1] However, even if isoproterenol were absorbed in biologically active form, the indiscriminate β-adrenergic effects of this agent would still result in strong chronotropic and inotropic effects on the heart at serum concentrations necessary for bronchodilatation. Partial selectivity is achieved *via* the inhalation route by rapid metabolic conversion in the lung to the inactive 3-O-methylated derivative.

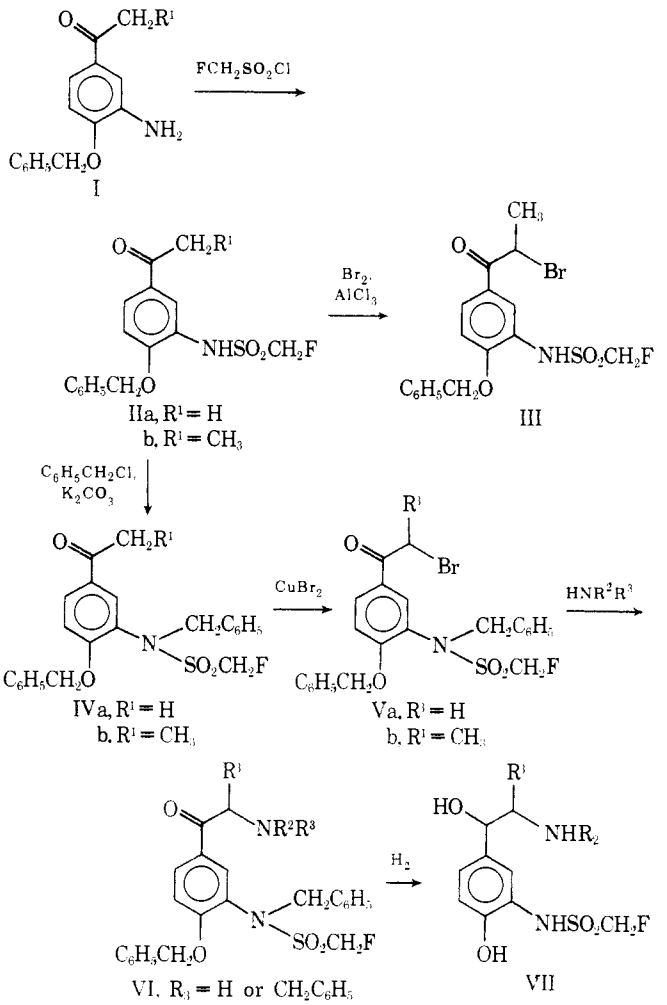
Of the many chemical manipulations of the catecholamine structure reported in the literature, the most rewarding, so far as the objectives for improved bronchodilator activity are concerned, has been replacement of the *m*-hydroxy group with a substituent that functions pharmacologically as a phenol, *e.g.*, salbutamol[2] and soterenol.[3] Replacement of the 3,4-dihydroxy function with a 3,5-dihydroxy orientation, *e.g.*, orciprenaline,[4] terbutaline,[5] and fenoterol,[6] has also been reported to be beneficial.

Approaches to the synthesis of new bronchodilators in our laboratory have included replacement of the *m*-hydroxy group with isosteric substituents. A number of meta functional groups have been explored, and we report here one of the more promising examples, the monofluoromethanesulfonamido group. Although the pK_a of this function is quite different from phenol, we have found it to confer desirable bronchodilator properties such as high selectivity, long duration, and oral activity on the catecholamine molecule.

Chemistry. A general synthetic route to the fluoromethanesulfonanilides described in this paper is outlined in Scheme I. Aminobenzyloxyphenones I (R^1 = H, CH_3) were treated with fluoromethanesulfonyl chloride[7] in the presence of dimethylaniline with chloroform as a solvent. The products of this reaction, 2′-benzyloxy-5′-acylfluoromethanesulfonanilides (II), could be transformed into the phenacyl bromides III by bromination in ether with aluminum chloride catalysis. Treatment of III with primary amines appeared to be the most direct route leading to the desired final compounds. In certain cases, displacement of bromide by amine took place as expected and the desired 2-alkylamino ketones could be easily isolated. But with some amines the acidic fluoromethanesulfonamido group formed salts which complicated isolation and purification of the amphoteric 2-alkylamino ketone products. In our hands it was generally simpler and more expedient to block the acidic site prior to bromination and avoid possible salt formation during the subsequent amination step.

Since II already incorporated an *O*-benzyl blocking group, the most convenient choice for protecting the fluoromethanesulfonamido site was a second benzyl group. Thus, both sites could be subsequently deblocked simultaneously in a single reaction. Alkylation of II with benzyl chloride in a mixture of glyme and water containing potassium carbonate gave IV.

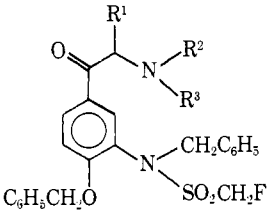
Scheme I



Although II was smoothly brominated α to the carbonyl with bromine–aluminum chloride, this reaction was less satisfactory for brominating the dibenzyl derivative IV and yielded a low-melting product which required extensive purification before use. A much cleaner route to phenacyl bromides V was bromination of IV with cupric bromide by the method of King and Ostrum.[8] Aminophenones VI were obtained by condensation of V with an appropriate amine. Bromine was cleanly displaced from the propiophenones Vb by primary amines to give the desired aminophenones VI (R^1 = CH_3; R^2 = H) shown in Table I. In the case of acetophenones Va, the use of primary amines resulted in complex mixtures, and products of acceptable purity could be obtained only with secondary amines, *i.e.*, *N*-benzylamines (Table I, compounds **1–3**).

†This paper is dedicated to my former professor and friend, Alfred Burger.

Table I. Aminoacylfluoromethanesulfonanilide Intermediates VI



Compd	R^1	R^3	R^2	Formula (analyses)	Mp, °C	Yield, %
1	H	$C_6H_5CH_2$	$(CH_3)_2CH$	*a*	*c*	77
2	H	$C_6H_5CH_2$	Cyclopentyl	*a*	*c*	47
3	H	$C_6H_5CH_2$	$4\text{-}CH_3OC_6H_4CH_2CH_2$	*a*	*c*	79
4	CH_3	H	$(CH_3)_2CH$	$C_{27}H_{31}FN_2O_4S\cdot HCl$ (C, H, N)[b]	199–201	36
5	CH_3	H	$CH_3CH_2CHCH_3$	$C_{28}H_{33}FN_2O_4S\cdot HCl$ (C, H, N)	185–187	43
6	CH_3	H	$(CH_3)_2CHCH_2$	*a*	186–192	41
7	CH_3	H	$(CH_3CH_2)_2CH$	*a*	176–183	35
8	CH_3	$C_6H_5CH_2$	Cyclobutyl	*a*	*c*	39
9	CH_3	H	Cyclopentyl	$C_{29}H_{33}FN_2O_4S\cdot HCl$ (C, H, N)	219–221	59
10	CH_3	H	1-Methylcyclopentyl	*a*	206–208	45
11	CH_3	H	2-Methylcyclopentyl	*a*	210–220	25
12	CH_3	H	Cyclohexyl	*a*	184–190	83
13	CH_3	H	$C_6H_5CH_2CH_2$	$C_{32}H_{33}FN_2O_4S\cdot HCl\cdot H_2O$ (C, H, N)	145–150	56
14	CH_3	H	$4\text{-}CH_3C_6H_4CH_2CH_2$	*a*	127–130 dec	61
15	CH_3	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	$C_{33}H_{35}FN_2O_5S\cdot HCl$ (C, H, N)	214–217	56
16	CH_3	H	$4\text{-}C_6H_5CH_2OC_6H_4CH_2CH_2$	*a*	*c*	77
17	CH_3	$C_6H_5CH_2$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	*a*	*c*	73
18	CH_3	H	$4\text{-}CH_3OC_6H_4CH_2CHCH_3$	$C_{34}H_{37}FN_2O_5S\cdot HCl$ (C, H, N)	181–183	55
19	CH_3	H	$3,4\text{-}(OCH_2O)C_6H_3CH_2CHCH_3$	*a*	*c*	79
20	CH_3	H	2-Indanyl	*a*	187–192	51

[a]Compound was not analyzed but hydrogenated without further purification. [b]Analysis for C, H, and N was within ±0.4% of theoretical values. [c]Amorphous glass.

Purification of VI was often difficult because of poor crystallization properties but the structures of these intermediates were confirmed by infrared spectra which exhibited a strong carbonyl band at 5.9 μ and characteristic amine salt bands at 4.0–4.1 (sharp) and 3.6–3.8 μ (broad). Those aminophenones with $R^2 = CH_2C_6H_5$ were uniformly noncrystalline glasses and many of the others also were amorphous. All aminoacylfluoromethanesulfonanilide intermediates VI are collected in Table I.

Catalytic hydrogenation of VI (R^2 = H) resulted in rapid uptake of 2 mol of hydrogen corresponding to removal of the two benzyl groups. The intermediate deblocked ketones could be isolated at this point but normally were allowed to undergo further reduction without interruption to the 2′-hydroxy-5′-[1-hydroxy-2-(alkylamino)alkyl]fluoromethanesulfonanilides VII. In those special cases where $R^2 = CH_2C_6H_5$, longer hydrogenation periods under more vigorous conditions were sometimes required to remove the benzyl group on the basic nitrogen. The final fluoromethanesulfonanilides VII are listed in Table II.

All fluoromethanesulfonanilides VII reported in this paper contain at least one asymmetric center. Those compounds listed in Table II where $R^1 = CH_3$ have at least one additional asymmetric center giving rise to the possibility of erythro and threo racemic modifications. Several compounds (**25, 31, 38**, and **39**) have a third asymmetric carbon atom located in the amine moiety and in these cases four racemic modifications are possible. All fluoromethanesulfonanilides VII were isolated and studied as optically inactive racemic modifications. No attempt was made to obtain all possible racemates.

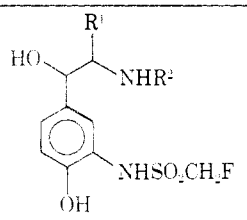
Earlier workers[9,10] have shown that catalytic reduction of aminophenones to phenethanolamines containing two adjacent asymmetric carbon atoms in the side chain yields predominantly the erythro isomer. The stereochemical assignments were made on the basis of a small coupling constant ($J_{H\alpha H\beta}$ = 3–4 Hz) for interaction of hydrogen atoms located on the adjacent asymmetric centers.[9,11,12] Nmr spectra of VII revealed coupling constants for the hydrogen–hydrogen interaction in the same range ($J_{H\alpha H\beta}$ = 3–4 Hz). Catalytic reduction of the carbonyl group in aminophenones VI therefore proceeded in the normal manner and all resultant fluoromethanesulfonanilides VII with adjacent asymmetric centers were obtained as the erythro racemic modifications.

Larsen, *et al.*,[11] report that methanesulfonamidophenethanolamines are stronger acids, by about 1.0–1.5 pK_a units, than the corresponding catecholamines. The electron-withdrawing effect of fluorine in the fluoromethanesulfonamido substituent further increases the acidity of this group. Comparative pK_a measurements on fluoromethanesulfonanilide **35** and its methanesulfonanilide counterpart[11] indicated that **35** is a stronger acid by about 0.9 pK_a units. Thus, **35** is a considerably stronger acid than the catecholamines. While the acidity of the functional group ortho to phenolic hydroxyl can be varied over a rather wide range, the presence of an acidic hydrogen on this group is essential. For example, compound **44**, prepared as outlined in Scheme II, differs from **35** only by substitution of methyl for hydrogen in the fluoromethanesulfonamido group but possesses no β-stimulant activity.

Pharmacology. New compounds were initially tested *in vitro vs.* histamine-induced contraction of the isolated guinea pig trachea[3] in order to evaluate relative activity of all candidates compared to the reference bronchodilators isoproterenol and salbutamol. These data are shown in Table III. Compounds with sufficient potency were evaluated in a variety of additional systems. The Konzett–Rössler overflow method in the dog[13] gave an indication of potency, selectivity, and duration of activity. Oral activity was established in the aerosolized histamine-challenged guinea pig model.[14]

In general, this series of compounds exhibited a high

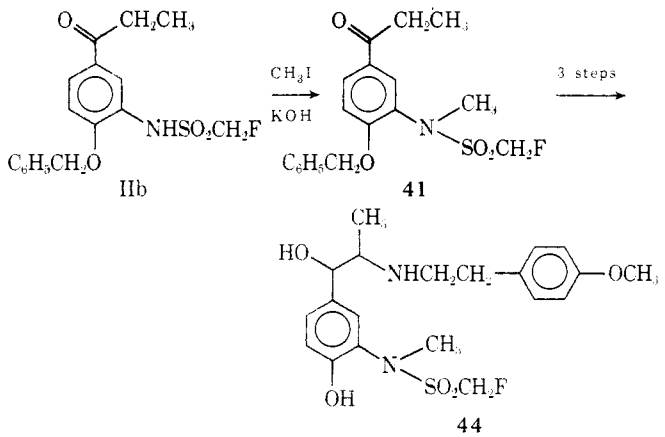
Table II. 2'-Hydroxy-5'-[1-hydroxy-2-(alkylamino)alkyl]fluoromethanesulfonanilides VII



Compd	R^1	R^2	Formula (analyses)[a]	Mp, °C	Crystn Solvent	Yield, %
21	H	$(CH_3)_2CH$	$C_{12}H_{19}FN_2O_4S \cdot HCl$	166–167	CH_3CN	27
22	H	Cyclopentyl	$C_{14}H_{21}FN_2O_4S \cdot HCl$	195 dec	CH_3CN	61
23	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	$C_{18}H_{23}FN_2O_5S \cdot HCl$	179–180	CH_3CN	18
24	CH_3	$(CH_3)_2CH$	$C_{13}H_{21}FN_2O_4S \cdot HCl$	157–158	CH_3CN	73
25	CH_3	$CH_3CH_2CHCH_3$	$C_{14}H_{23}FN_2O_4S \cdot HCl$	192–193	CH_3CN	60
26	CH_3	$(CH_3)_2CHCH_2$	$C_{14}H_{23}FN_2O_4S \cdot HCl$	208–210	CH_3CN–Et_2O	40
27	CH_3	$(CH_3CH_2)_2CH$	$C_{15}H_{25}FN_2O_4S \cdot HCl$	203–205	$EtOCH_2CH_2OH$–Et_2O	71
28	CH_3	Cyclobutyl	$C_{14}H_{21}FN_2O_4S \cdot HCl \cdot 0.5H_2O$	202–206	CH_3CN	64
29	CH_3	Cyclopentyl	$C_{15}H_{23}FN_2O_4S \cdot HCl$	238–239 dec	EtOH–Et_2O	68
30	CH_3	1-Methylcyclopentyl	$C_{16}H_{25}FN_2O_4S \cdot HCl$	179–184	CH_3OH–$(i\text{-}Pr)_2O$	45
31	CH_3	2-Methylcyclopentyl	$C_{16}H_{25}FN_2O_4S \cdot HCl$	229–231	CH_3CN	50
32	CH_3	Cyclohexyl	$C_{16}H_{25}FN_2O_4S \cdot HCl$	235–236	CH_3OH–$(i\text{-}Pr)_2O$	67
33	CH_3	$C_6H_5CH_2CH_2$	$C_{18}H_{23}FN_2O_4S \cdot HCl$	217–219	EtOH	41
34	CH_3	$4\text{-}CH_3C_6H_4CH_2CH_2$	$C_{19}H_{25}FN_2O_4S \cdot HCl$	197–199	CH_3CN	63
35	CH_3	$4\text{-}CH_3OC_6H_4CH_2CH_2$	$C_{19}H_{25}FN_2O_5S \cdot HCl$	184–185	CH_3CN	79
36	CH_3	$4\text{-}HOC_6H_4CH_2CH_2$	$C_{18}H_{23}FN_2O_5S \cdot HCl \cdot H_2O$	80 dec	EtOH–Et_2O	55
37	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	$C_{20}H_{27}FN_2O_6S \cdot HCl$	70 dec	CH_3CN–Et_2O	56
38	CH_3	$4\text{-}CH_3OC_6H_4CH_2CHCH_3$	$C_{20}H_{27}FN_2O_5S \cdot HCl$	135–145 dec	CH_3CN	34
39	CH_3	$3,4\text{-}(OCH_2O)C_6H_3CH_2CHCH_3$	$C_{20}H_{25}FN_2O_6S \cdot HCl$	201–204	*i*-PrOH	28
40	CH_3	2-Indanyl	$C_{19}H_{23}FN_2O_4S \cdot HCl$	217	CH_3CN	58

[a] All compounds analyzed for C, H, and N within ±0.4% of theoretical values.

Scheme II



IIb 41 44

Table III. Spasmolytic Activity of Monofluoromethanesulfonanilides

Compd	Rel act.[a] Iso	Sal	Compd	Rel act.[a] Iso	Sal
21	0.04	0.2	**31**	0.003	0.02
22	0.04	0.2	**32**	0.001	0.005
23	0.02	0.1	**33**	0.02	0.1
24	<0.001	0.005	**34**	0.004	0.02
25	0.001	0.005	**35**	0.04	0.2
26	<0.001	<0.001	**36**	0.003	0.02
27	<0.001	<0.001	**37**	0.007	0.03
28	0.001	0.005	**38**	0.002	0.02
29	0.02	0.1	**39**	0.007	0.02
30	0.004	0.02	**40**	<0.001	0.002

[a] Based on the minimum effective dose required to give 100% relaxation of histamine-induced contraction of isolated guinea pig tracheal spiral. Doses of the standard drugs, isoproterenol and salbutamol, were 0.02 and 0.1 μg/ml, respectively. Each new test compound was assayed at least three times in the tracheal strip. Relative activity of isoproterenol (Iso) = 1 and salbutamol (Sal) = 1.

degree of selectivity *in vitro* (tracheal *vs.* atrial muscle strips), as well as in *in vivo* models. The duration of activity was 6–12 hr (po). The potency of the best compounds approached one-tenth isoproterenol when given intravenously. In several model systems used to establish oral activity, compound **35** compared favorably with salbutamol. The complete pharmacology of compound **35** will be the subject of a separate manuscript.

Discussion

The structure–activity relationships in this series of bronchodilators parallel that seen with known compounds. For instance, methyl groups adjacent to the basic nitrogen generally increased selectivity; compounds with branched alkyl chains on both sides of the basic nitrogen were considerably less potent as bronchodilators, *e.g.*, **25**, **27**, **31**, **32**, **38**, **39**, etc. Compounds **22** and **35** from this series were chosen for intensive pharmacological work-up. Both compounds were orally active and compared favorably in all respects with known bronchodilators. However, compound **35** caused irreversible eye changes in the dog when administered in extremely high doses during 90-day toxicity evaluation. Compound **22**, the most potent of the series, did not show any advantages over **35**.

Experimental Section

Boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

2'-Benzyloxy-5'-propionylfluoromethanesulfonanilide (IIb). Fluoromethanesulfonyl chloride (13.9 g, 0.105 mol) was added over 15 min to a stirred solution of 25.5 g (0.10 mol) of 3-amino-4-benzyloxypropiophenone,[11] 13.3 g (0.11 mol) of dimethylaniline, and 200 ml of $CHCl_3$. The solution was stirred at room temperature for 24 hr and heated under reflux 1 hr. After cooling, the solution was washed with 5% HCl and water and dried (Na_2SO_4). Solvent was evaporated *in vacuo*. Two recrystallizations of the residual solid from EtOH gave 26.3 g (75%) of 2'-benzyloxy-5'-

propionylfluoromethanesulfonanilide as pale yellow needles, mp 110–111°. *Anal.* ($C_{17}H_{18}FNO_4S$) C, H, N.

5′-Acetyl-2′-benzyloxyfluoromethanesulfonanilide (IIa). 3-Amino-4-benzyloxyacetophenone[11] was converted to 5′-acetyl-2′-benzyloxyfluoromethanesulfonanilide according to the same procedure described for IIb. The product was obtained as beige flakes after two recrystallizations from EtOH: mp 121–123°; yield 63.3%. *Anal.* ($C_{16}H_{16}FNO_4S$) C, H, N.

2′-Benzyloxy-5′-(2-bromopropionyl)fluoromethanesulfonanilide (III). Bromine (4.0 g, 0.025 mol) was added dropwise over 20 min to a stirred solution of 8.8 g (0.025 mol) of IIb and 0.025 g of $AlCl_3$ in 50 ml of Et_2O. The solution was stirred 1 hr, diluted with 75 ml of Et_2O, and filtered. The filtrate was washed with H_2O, 5% $NaHCO_3$, and brine and dried (Na_2SO_4). Evaporation of solvent under vacuum gave a thick syrup which slowly solidified. Recrystallization from trichloroethylene gave III as beige flakes: mp 76–79°; yield 82%. An analytical sample, mp 77–79°, was obtained after two additional recrystallizations from the same solvent. *Anal.* ($C_{17}H_{17}BrFNO_4S$) C, H, N.

***N*-Benzyl-2′-benzyloxy-5′-propionylfluoromethanesulfonanilide (IVb).** To a stirred solution of 20.7 g (0.15 mol) of K_2CO_3 and 1.0 g of NaI in 100 ml of H_2O was added 35.1 g (0.10 mol) of IIb, 15.2 g (0.12 mol) of benzyl chloride, and 150 ml of glyme. The mixture was stirred vigorously under reflux 24 hr, cooled, and concentrated under reduced pressure to remove most of the glyme. The semisolid which separated was extracted with CH_2Cl_2 and the organic solution was washed with H_2O, 5% NaOH, and brine and dried (Na_2SO_4). Evaporation of the solvent gave an oil which slowly solidified. Recrystallization from EtOH provided *N*-benzyl-2′-benzyloxy-5′-propionylfluoromethanesulfonanilide as ivory needles: mp 90–91.5°; yield 59%. *Anal.* ($C_{24}H_{24}FNO_4S$) C, H, N.

***N*-Benzyl-2′-benzyloxy-5′-acetylfluoromethanesulfonanilide (IVa).** The benzylation procedure described above for the preparation of IVb gave *N*-benzyl-2′-benzyloxy-5′-acetylfluoromethanesulfonanilide as white plates: mp 90–92° (EtOH); yield 75%. *Anal.* ($C_{23}H_{22}FNO_4S$) C, H, N.

***N*-Benzyl-2′-benzyloxy-5′-(2-bromopropionyl)fluoromethanesulfonanilide (Vb).** A solution of 55.9 g (0.127 mol) of IVb in 200 ml of $CHCl_3$ was added dropwise over 30 min to a stirred, refluxing suspension of 54.1 g (0.242 mol) of $CuBr_2$ and 200 ml of CH_3CO_2Et. The mixture was then stirred vigorously for another 6 hr or until the color of the solution had completely changed from green to brown. The mixture was cooled and CuBr was removed by suction filtration. The filtrate was diluted with 400 ml of $CHCl_3$, washed with H_2O, 5% $NaHCO_3$, and brine, and dried (Na_2SO_4). Removal of solvent yielded a thick oil which crystallized from EtOH to give Vb as yellow needles: mp 106–108°; yield 66%. Recrystallization provided an analytical sample, mp 108–109°. *Anal.* ($C_{24}H_{23}BrFNO_4S$) C, H, N.

***N*-Benzyl-2′-benzyloxy-5′-(2-bromoacetyl)fluoromethanesulfonanilide (Va).** Bromination of IVa was performed in a similar manner to that used in the preparation of Vb. The product was isolated as ivory granules, mp 102–105°, after crystallization from MeOH: yield 35%. One recrystallization provided an analytical sample, mp 106–108°. *Anal.* ($C_{23}H_{21}BrFNO_4S$) C, H, N.

***N*-Benzyl-2′-benzyloxy-5′-(2-alkylaminoacyl)fluoromethanesulfonanilide Hydrochloride (VI, Table I). General Procedure.** A solution of the desired phenacyl bromide (Va or Vb, 0.01 mol) in 20 ml of CH_3CN was added dropwise at 25° to a stirred solution of the desired amine (0.02 mol) in 20 ml of CH_3CN. In some cases the hydrobromide salt of the starting amine precipitated from solution during the addition. The mixture was stirred 2 hr at 25° and then poured into 300 ml of Et_2O to complete precipitation of the hydrobromide salt. Filtration of the solution gave 75–90% of the theoretical amount of hydrobromide. The filtrate was concentrated under vacuum and the residual thick syrup was taken up in CH_2Cl_2. The solution was washed three times with H_2O, dried (Na_2SO_4), concentrated to a volume of 30–40 ml, and slowly added with stirring to 200 ml of Et_2O saturated with dry HCl. The flocculent HCl salt which separated was isolated by filtration and dried at 50° *in vacuo*. Compounds listed in Table I with acceptable analyses were purified by recrystallization from CH_3CN. Many of the remaining compounds crystallized poorly and no attempt was made to achieve analytical purity. Those compounds with $R^2 = CH_2C_6H_5$ were uniformly noncrystalline glasses. However, all of these compounds were used in the subsequent step without rigorous purification and gave satisfactory results.

2′-Hydroxy-5′-[1-hydroxy-2-(alkylamino)alkyl]fluoromethanesulfonanilide Hydrochloride (VII, Table II). General Procedure. *N*-Benzyl-2′-benzyloxy-5′-(2-alkylaminoacyl)fluoromethanesulfonanilide hydrochloride (VI, 0.05 mol) was dissolved in 150 ml of warm 90% EtOH. After the solution had cooled to 25° it was added to a paste of 0.75 g of 10% Pd/C in water and hydrogenated for 16 hr on a Parr apparatus. The mixture was filtered to remove catalyst and the filtrate was refiltered with added Super Cel. Evaporation of the solvent under vacuum left a glassy foam. The crude product was then either recrystallized from CH_3CN directly or triturated with hot CH_3CN and recrystallized from the solvent indicated in Table II. The trituration step effectively converted the foamy crude product to a granular crystalline material.

***N*-Benzyl-*p*-methoxyphenethylamine.** *N*-Benzyl-*p*-methoxyphenethylamine, bp 148–150° (0.15 mm) [lit. bp 148° (0.01 mm)[15]; 210° (13 mm)[16]], was prepared in 75% yield using the method described by Corrigan, *et al.*,[17] for the synthesis of *N*-benzylcyclopentylamine. *Anal.* ($C_{16}H_{19}NO$) C, H, N.

2′-Benzyloxy-*N*-methyl-5′-propionylfluoromethanesulfonanilide (41). 2′-Benzyloxy-5′-propionylfluoromethanesulfonanilide, IIb (15 g, 0.0427 mol), was added to a solution of 2.4 g (0.0427 mol) of KOH in 75 ml of EtOH. The solution was stirred briefly and concentrated to dryness. To the dry potassium salt of IIb was added 150 ml of acetone and 17 g (0.12 mol) of CH_3I. The solution was stirred overnight at 25°, heated under reflux 4 hr, and concentrated to dryness. Water and ether were added. The organic phase was washed with 10% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to a viscous oil which solidified. One recrystallization (EtOH) provided 13.6 g (87.2%) of **41** as ivory crystals, mp 81.5–84°.

2′-Benzyloxy-*N*-methyl-5′-(2-bromopropionyl)fluoromethanesulfonanilide (42). Bromination of **41** with $CuBr_2$ following the procedure described for Vb gave **42**. Crude product was chromatographed on silica gel and eluted with C_6H_6 and, after removal of solvent, recrystallized from C_6H_6: mp 110–114°; yield 63.4%. The position of the bromine atom was confirmed by nmr.

2′-Benzyloxy-*N*-methyl-5′-[2-(*p*-methoxyphenethylamino)-propionyl]fluoromethanesulfonanilide Hydrochloride (43). A solution of 9.55 g (0.0215 mol) of **42** in 40 ml of CH_3CN was added dropwise at 25° to a stirred solution of 6.5 g (0.043 mol) of *p*-methoxyphenethylamine in 40 ml of CH_3CN. After the solution had stirred 2 hr, solvent was evaporated under vacuum and the residue was triturated with 300 ml of CH_3CO_2Et. Insoluble *p*-methoxyphenethylamine hydrobromide was removed by suction filtration. The filtrate was acidified by addition of 2-propanolic HCl and stirred 2 hr. The solid which separated was collected by filtration and recrystallized from CH_3OH to give the hydrochloride salt of **43**: mp 159–165°; yield 6.0 g (51.7%). This sample was used without further purification in the subsequent step.

2′-Hydroxy-5′-[1-hydroxy-2-(*p*-methoxyphenethylamino)propyl]fluoromethanesulfonanilide Hydrochloride (44). A solution of 6.0 g (0.011 mol) of **43** in 100 ml of EtOH was added to 1.0 g of 10% Pd/C and hydrogenated overnight on a Parr apparatus. The mixture was warmed, filtered hot, treated with decolorizing charcoal, filtered again, and allowed to cool slowly. Crystalline **44** was collected as a white solid: mp 220–222°; yield 2.3 g (45%). *Anal.* ($C_{20}H_{28}ClFN_2O_5S$) C, H, N.

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Synthesis of Monoaryl- and Diarylphosphorus Analogs of Methadone

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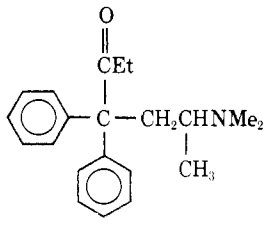
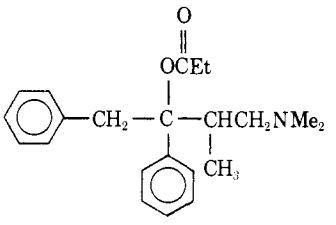
Fourteen monoarylphosphorus analogs of methadone belonging to three structural types (**4**, **5**, and **6**) were synthesized by reacting various chloroalkylamines with the appropriate phosphorus compounds. The phosphorus compounds were selected to vary the steric, electronic, and solubility properties of the final products. Ten diarylphosphorus analogs of methadone of two structural types (**7** and **8**) were synthesized in a similar manner. The success of the alkylation reaction for both series was markedly affected by the solvent system utilized. Pharmacological screening by the hot-plate and acetic acid writhing methods revealed moderate analgetic activity in some of the compounds apparently related to the lipophilicity of the molecule.

The research of Bockmuhl, Erhart, and Schaumann which produced methadone (**1**) has stimulated other researchers[1] to explore the relationship of chemical structure to pharmacological activity of various arylpropylamines. The introduction of propoxyphene (**2**) as an analgetic with low addiction liability was the result of such a systematic exploration of arylpropylamines. Recently the use of methadone (**1**) as a morphine substitute in the treatment of narcotic addiction has stimulated further interest in the exploration of arylpropylamines as analgetics.



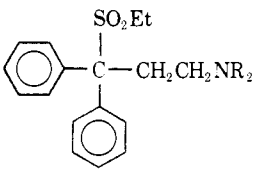
1



2

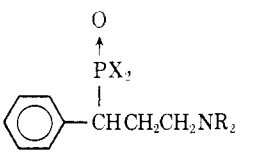
The general feature of the analgetic receptor proposed by Beckett and Casy,[2] an aromatic group with the proper orientation and distance from a basic nitrogen, encompasses the structure of most active analgetics. Methadone and meperidine both contain a polar side chain emanating from the carbon attached to the aromatic group. The function of the polar side chain remains a matter of conjecture although changes in this group can markedly affect the activity of the compound. The existance of an optimum in the chain length of the alkyl group attached to the polar side chain[3] implies a parabolic relationship between analgetic activity and solubility of the type proposed by Hansch[4] for many other types of medicinal agents. Others have explored the relationship between lipophilicity and analgetic activity.[5]

Other groups may be substituted for polar groups containing carbon. Previously, Slenk, Suter, and Archer[6] had synthesized a series of sulfones **3** related to methadone and found reasonable analgetic activity. Consequently,

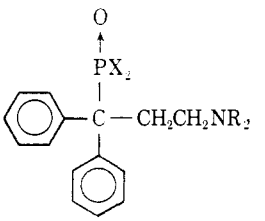


3

the authors synthesized and evaluated some phosphorus analogs of methadone of the types shown by **4**, **5**, and **6** (monarylphosphorus analogs of methadone) and **7** and **8** (diarylphosphorus analogs of methadone), each series utilizing a different phosphorus-containing group in place of



4, X = C_6H_5; NR_2 = dialkylamino
5, X = OEt; NR_2 = dialkylamino
6, X = Et; NR_2 = dialkylamino



7, X = C_6H_5; NR_2 = dialkylamino
8, X = OEt; NR_2 = dialkylamino

† This paper is dedicated to my former major professor, Dr. Alfred Burger, to whom medicinal chemistry owes much.

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