administered orally as a suspension in 2% gum acacia, and blood sugar was determined at 1.5, 3, 5, 7, 9, and 24 hr by Somogyi's method[4] using Nelson's reagent.[5] The crossover tests were carried out with tolbutamide at 25 mg/kg dose level using 7 animals in each groups. One group was given the test drug while the other received tolbutamide. Following a rest period of 1 week, the drugs were crossed over and the test was repeated.

For alloxan-diabetic rats, healthy male albino rats weighing about 200 g were fasted overnight and injected with an aq solution of alloxan monohydrate at 200 mg/kg dose level and food given immediately. Only diabetic animals were used in the test.

**Chemical Method.**[6] **p-Ethylbenzhydrazide.**—Ethyl *p*-ethylbenzoate (44.5 g, 0.25 mol), $N_2H_4 \cdot H_2O$ (25 ml of 98%) and EtOH (100 ml) were mixed and heated under reflux for 2 hr. The residue after removal of EtOH was triturated with $Et_2O$, filtered, and washed ($Et_2O$). It was crystd ($H_2O$), yield 39.1 g (95%), mp 89–90°. *Anal.* ($C_9H_{12}N_2O$) C, H.

**1-*p*-Sulfamoylbenzoyl-4-ethylthiosemicarbazide.** *p*-Sulfamoylbenzhydrazide (21.5 g, 0.1 mol) was dissolved in dioxane (150 ml) and heated under reflux with ethyl isothiocyanate (9.5 ml, 0.11 mol) for 4 hr. The solid that sepd on cooling was collected by filtration, washed ($H_2O$), and crystd (EtOH).

All the thiosemicarbazides required for the present work were similarly prepared and crystd from EtOH. See Table IV for the new thiosemicarbazides.

**5-*p*-Sulfamoylphenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol.** 1-*p*-Sulfamoylbenzoyl-4-ethylthiosemicarbazide (6.0 g, 0.02 mol) was dissolved in 2 *N* NaOH (60 ml) and refluxed for 2 hr. The reaction mixture was cooled and acidified with HCl (pH 4). The white precipitate of the desired compound was filtered, washed ($H_2O$), and crystd (85% EtOH).

All the new triazoles which were prepared similarly and crystd from EtOH are listed in Table V with their melting points, analytical data, etc.

**Acknowledgments.**—The authors wish to thank Shri M. T. Jaokar and coworkers for the microanalyses and to Dr. N. K. Dutta, Director, Haffkine Institute, for his interest in the work.

(4) M. Somogyi, *J. Biol. Chem.*, **160**, 69 (1945).

(5) N. Nelson, *ibid.*, **153**, 375 (1944).

(6) The melting points were taken in capillary tubes with a partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within 0.4% of the theoretical values.

# Saligenin Analogs of Sympathomimetic Catecholamines[1a,b]

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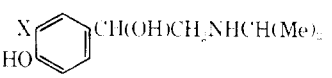
Analogs of isoproterenol have been prepared in which the catechol group has been replaced by salicylic acid (IX) or saligenin (VII) functions. Many of the latter are potent long-lasting β-adrenoreceptor stimulants that are effective orally and show a highly selective action on bronchial smooth muscle. Structure–activity relationships are discussed and related to current theories of molecular processes at β-adrenoreceptors.

Sympathomimetic amines that relax bronchial smooth muscle by stimulation of β-adrenoreceptors have been widely used as bronchodilators in reversible airways obstruction and extensive investigations of structure–activity relations have been made.[2] Maximum potency has always been associated with the presence of a catechol function as in isoproterenol (Ia). The catecholamines have only a short duration of parenteral action probably mainly owing to uptake into tissues[3,4] but also because of metabolism by catechol-*O*-methyl transferase (COMT) to a methyl ether, *e.g.*, Ib.[5] The latter is a β-adrenoreceptor blocker.[6] An additional metabolic barrier may underlie the ineffectiveness of the catecholamines when administered orally since it has been shown in the dog[3] and in man[4] that they are inactivated by conversion into an *O*-sulfate ester in the gut.

We hoped to circumvent these metabolic pathways and hence overcome some of the clinical deficiencies of isoproterenol by the preparation of compounds of formula I where X was a group which retained some of the attributes of the catechol but which would not be subject to attack by the enzymes that inactivate the latter.




Ia, X = HO  Ic, X = $MeSO_2NH$  Ie, X = $HOCH_2$
Ib, X = MeO  Id, X = HOOC

Previous replacement of one or both phenolic groups[7] by other substituents has drastically reduced sympathomimetic action except in the case of compounds such as Ie where the bioisosteric methanesulfonamide group produces a pseudocatechol.[8] The enhanced acidity of the *m*-phenolic group in the catecholamines, which is simulated by the methanesulfonamide group, is considered important for high biological activity.[8] An additional feature of possible importance is the ability of the catechol moiety to chelate with metals.[9] Both of these properties are displayed, with the minimum of steric disturbance, by the salicylic acid Id which was our first objective. A general synthetic route to Id, outlined in Scheme I, also leads to the saligenin derivative Ie which should still be capable of chelating

(1) (a) For preliminary communication of this work see D. Hartley, D. Jack, L. H. C. Lunts, and A. C. Ritchie, *Nature (London)*, **219**, 861 (1968). (b) Presented in part at the Fourth Rencontres Internationales de Chimie Thérapeutique, Clermont-Ferrand, 1968. (c) To whom inquiries should be addressed.

(2) For leading references see (a) P. Pratesi and E. Grana, *Advan. Drug Res.*, **2**, 127–142 (1965); (b) R. B. Barlow, "Introduction to Chemical Pharmacology," Methuen and Co., London, 1964, pp 282–343; (c) A. M. Lands and T. G. Brown in "Drugs Affecting the Peripheral Nervous System," Vol. 1, A. Burger, Ed., Dekker, New York, N. Y., 1967, p 390.

(3) W. D. Conway, H. Minagoya, A. M. Lands, and J. M. Sliekoski, *J. Pharm. Sci.*, **57**, 1135 (1968).

(4) D. C. Morgan, M. Sandler, D. S. Davies, M. Conolly, J. W. Paterson, and C. T. Dollery, *Biochem. J.*, **114**, 8P (1969).

(5) S. B. Ross, *Acta Pharmacol. Toxicol.*, **20**, 267 (1963).

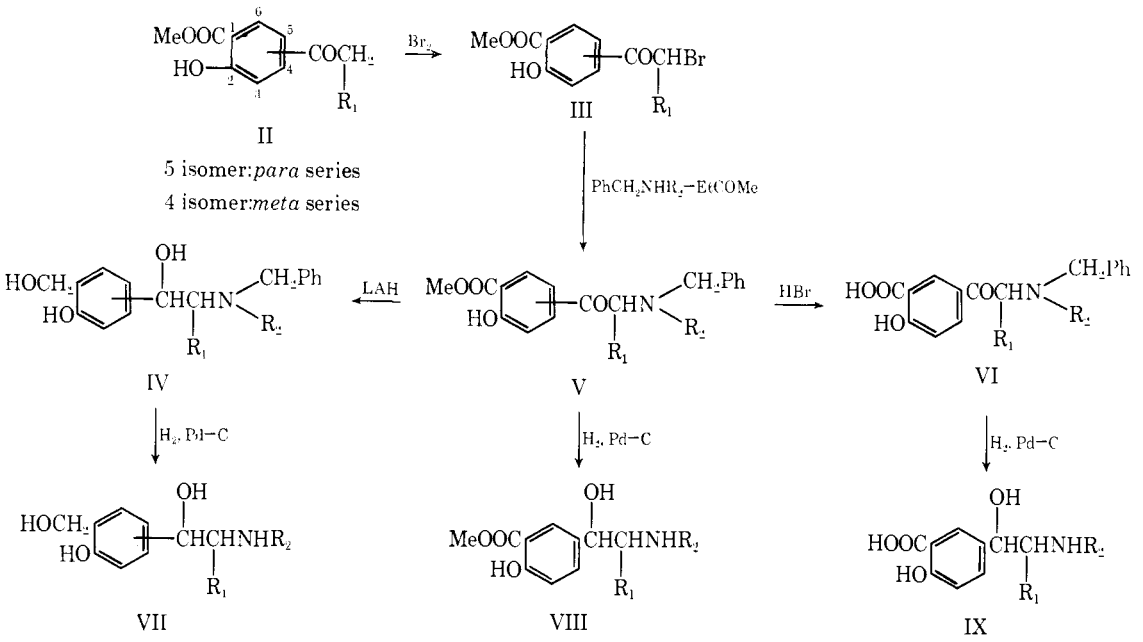
(6) J. W. Paterson, M. E. Conolly, D. S. Davies, and C. T. Dollery, *Lancet*, **2**, 126 (1968).

(7) For leading references see R. H. Uloth, G. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).

(8) A. A. Larsen, W. A. Gould, H. R. Roth, W. T. Comer, R. H. Uloth, K. W. Dungan, and P. M. Lish, *ibid.*, **10**, 462 (1967).

(9) B. Belleau in "Ciba Foundation Symposium on Adrenergic Mechanisms," J. R. Vane, G. E. Wolstenholme, and M. O'Connor, Ed., Churchill, London, 1960, p 233.

SCHEME I




with metals and of taking part in H bond formation although the $pK_a$ of the hydroxymethyl group will be much higher than those of the corresponding groups in Ia, Ic, or Id. A similar approach was also envisaged for the less accessible isomeric series in which the *p*-OH group of the catecholamine, Ia, is replaced by an acid or by a $CH_2OH$ group.

**Chemistry.**—A general synthesis of the desired phenethanolamines from the methyl esters of 4- and 5-acyl salicylic acids (II) is outlined in Scheme I.

The 5-acyl salicylic esters were obtained by Fries rearrangement[10] of the corresponding phenolic esters of salicylic acid followed by esterification. Methyl 4-acetyl salicylate was synthesized from methyl 4-amino salicylate by selective benzylation of the phenol, conversion of the amine into an acetyl group *via* diazotization and reaction with acetaldoxime,[11] and removal of the benzyl group by catalytic hydrogenation.[12] The acyl esters II and the phenacyl bromides III derived from them by bromination at room temperature in $CHCl_3$ are shown in Table I.

Methyl 5-bromoacetyl salicylate condensed readily with secondary benzylamines on heating in EtCOMe to give the amino ketones V. The use of primary amines was generally unsatisfactory as the product was often contaminated with a nonketonic base.[13] However, the more hindered methyl 5-bromobutyryl salicylate failed to react with bulky secondary amines such as isopropylbenzylamine but gave a fair yield of the required product (**24**) on refluxing with *i*-$PrNH_2$ in MeOH.

Methyl 4-bromoacetyl salicylate reacted with *i*-$PrNHCH_2Ph$ in EtCOMe, EtOH, or THF at room temperature but the resulting amino ketone was unstable and was best processed *in situ* through the next stage of the synthesis to IV. The greater stability of a *p*-hydroxyphenacylamine has been explained in terms of a resonance contribution which is not permitted for the *m*-OH isomer.[14] The arylamino ketones prepared are listed in Table II.

Hydrolysis of the 5-glycyl esters V with HBr followed by catalytic reduction of the ketone and concomitant removal of the benzyl group gave the salicyclic acid derivatives IX. Catalytic hydrogenation of V gave the corresponding esters VIII. Where $R_1$ is an alkyl group the products were predominantly the expected *erythro* isomers having nmr spin coupling constants of 4 Hz for the protons on adjacent asymmetric centers.[15]

Reduction of the amino ketones V with LAH in THF followed by catalytic hydrogenolysis of the protective benzyl group over Pd–C gave the corresponding saligenin derivatives VII. In this case, when $R_1$ was an alkyl group, IV and VII showed coupling constants of 8–9 Hz for protons on adjacent asymmetric C atoms in agreement with that expected for a *threo* configuration.[15] The catalytic reduction of the saligenins occasionally resulted in some degree of hydrogenolysis of the primary alcohol group to give an *o*-cresol, easily identified by the Me signal at *ca.* $\tau$ 7.8 in the nmr spectrum. This side reaction could be promoted by acid catalysis to give the Me compound (*e.g.*, XIV) in high yield or could be suppressed by addition of a base such as $Et_3N$.

In a modified process to the *p*-saligenin derivative, XIII, the intermediate aminoketone XI was first reduced with $NaBH_4$ prior to catalytic debenzylation, as shown in Scheme II.

The Me ether XII was also prepared from the amino ketone XI by refluxing with methanolic HCl and subsequent catalytic debenzylation.

The primary amines of the *para* series (VII and VIII, $R_2$ = H), obtained according to Scheme I from

(10) K. W. Rosenmund and W. Schnurr, *Justus Liebigs Ann. Chem.*, **460**, 56 (1928).

(11) See W. Beech, *J. Chem. Soc.*, 1297 (1954).

(12) 4-Acetyl salicylic acid has been previously prepared by a different route, see F. Mayer, O. Stark, and K. Schön, *Ber.*, **65B**, 1333 (1932).

(13) R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith [*J. Med. Chem.*, **11**, 1000 (1968)] have shown that aminopyrroles are formed by self condensation of similar aminoketones.

(14) A. Gero, *J. Org. Chem.*, **16**, 1222 (1951).

(15) See ref 7 for analogous correlations.

SCHEME II

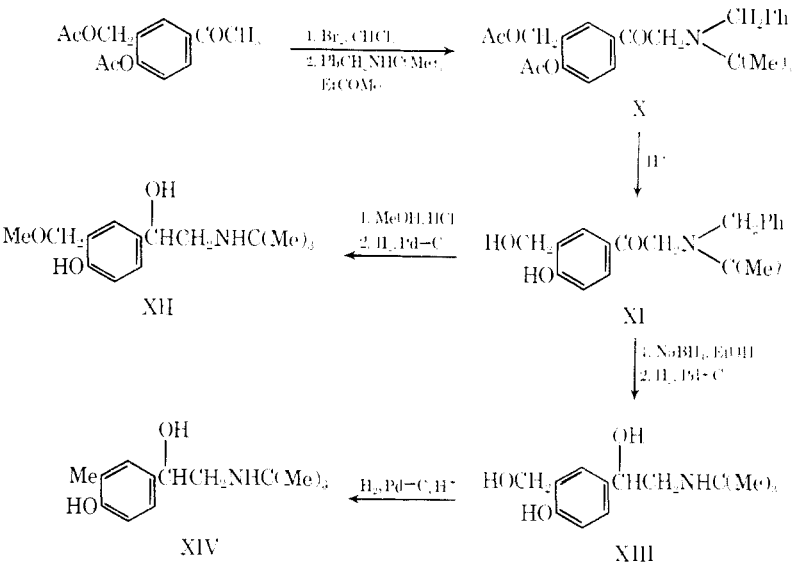
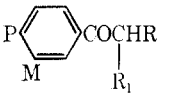



TABLE I

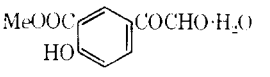
ARYL KETONES




| Compd | P | M | $R_2$ | R | Yield, % | Crystn[a] solvent | Mp, °C | Formula | Analysis |
|---|---|---|---|---|---|---|---|---|---|
| 1 | HO | MeOOC | H | H | 86 | Et | 55[b] | $C_{10}H_{10}O_4$ | |
| 2 | HO | MeOOC | Me | H | 30 | Pe | 59–60[c] | $C_{11}H_{12}O_4$ | |
| 3 | HO | MeOOC | Et | H | 79 | Pe | 70–71[d] | $C_{12}H_{14}O_4$ | |
| 4 | HO | EtOOC | H | H | 64 | Et | 62–63[e] | $C_{11}H_{12}O_4$ | |
| 5 | MeO | MeOOC | H | H | 77 | W | 93–94[f] | $C_{11}H_{12}O_4$ | |
| 6 | H | MeOOC | H | H | 93[g] | Et | 45–46 | $C_{16}H_{16}O_3$ | C, H |
| 7 | $PhCH_2O$ | MeOOC | H | H | 51[h] | B–Pe | 71–72 | $C_{17}H_{16}O_4$ | H, O; C[i] |
| 8 | MeOOC | $PhCH_2O$ | H | H | 10[j] | C | 71–72 | $C_{17}H_{16}O_4$ | C, O; H[k] |
| 9 | MeOOC | HO | H | H | 75[l] | C | 120–121.5 | $C_{10}H_{10}O_4$ | C, H |
| 10 | AcO | $AcOCH_2$ | H | H | 80[m] | | 50[n] | $C_{13}H_{14}O_6$ | H; C, O[m] |
| 11 | MeO | MeOOC | H | Br | 90 | Me | 153–154 | $C_{11}H_{11}BrO_4$ | C, H, Br |
| 12 | HO | MeOOC | H | Br | 72 | Pe | 90–92[o] | $C_{10}H_9BrO_4$ | |
| 13 | $PhCH_2O$ | MeOOC | H | Br | 71 | B–C | 127–128.5 | $C_{17}H_{15}BrO_4$ | C, H |
| 14 | MeOOC | HO | H | Br | 88 | Ip | 88–90 | $C_{10}H_9BrO_4$ | C, H, Br |
| 15 | HO | MeOOC | Me | Br | 62 | Me | 105–108 | $C_{11}H_{10}BrO_4$ | C, H |
| 16 | HO | MeOOC | Et | Br | 96 | Al | 83 | $C_{12}H_{13}BrO_4$ | C, H, Br |
| 17 | HO | EtOOC | H | Br | 95 | Me | 99–102 | $C_{11}H_{11}BrO_4$ | C, H, Br, O |
| 18 | H | MeOOC | H | Br | 70 | Me | 68–70 | $C_{16}H_{13}BrO_3$ | C, H |
| 19 | AcO | $AcOCH_2$ | H | Br | o | | | $C_{13}H_{13}BrO_6$ | |

[a] Al, EtOH; B, PhH; C, cyclohexane; Et, $Et_2O$; Ip, *i*-PrOH; Me, MeOH; Pe, petroleum ether (bp 60–80°); W, $H_2O$. [b] J. H. Amin and H. D. Desai [*J. Sci. Ind. Res.*, **13B**, 178 (1954)] reported mp 55°. [c] E. H. Cox [*J. Amer. Chem. Soc.*, **52**, 356 (1930)] reported mp 64–65°. [d] Lit.[c] mp 73°. [e] L. Crombie, D. E. Games, and M. H. Knight [*J. Chem. Soc.*, C, 763 (1967)] reported mp 61–2°. [f] H. von Kraemichfeldt [*Ber.*, **47**, 159 (1914)] reported mp 96°. [g] Prepared by esterification of 5-acetyl benzoic acid [see H. Rupe and K. von Majewski, *Ber.*, **33**, 3408 (1900)] with $CH_2N_2$ in $Et_2O$. [h] Prepared by benzylation of methyl 5-acetyl salicylate with $PhCH_2Cl$ and $K_2CO_3$ in refluxing EtCOMe. [i] C: calcd, 71.82; found, **72.31**. [j] See Experimental Section. [k] H: calcd, 5.67; found, 6.1. [l] Purified by distillation, bp 145° (0.5 mm). [m] C: calcd, 62.41; found, 61.76. O: calcd, 32.01; found, 32.73. [n] A. Bazas [U. S. Patent 3,113,962] reported mp 95–96°. [o] Bromination was carried out in $C_6H_6$ and the crude product was used directly in the next stage.

the dibenzyl intermediates (IV and V, $R_2$ = $PhCH_2$), could be alkylated reductively with carbonyl compounds to provide another route to N-substituted phenethanolamines. Alternatively, the esters VIII were obtained by reductive alkylation of an amine with the glyoxal, XV. The latter was prepared as a crystalline hydrate (gem diol) by oxidation of methyl 5-bromoacetyl salicylate with DMSO. The esters VIII could then be reduced to the *p*-saligenins, VII, with LAH.

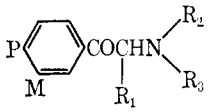



XV

Examples of compounds with tertiary alcohol groups *ortho* to the phenol were prepared from the ester VIII with PhMgBr and from the dibenzyl ester **40** with MeMgBr followed by catalytic debenzylation.

TABLE II

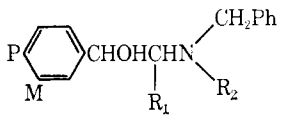
ARYLAMINO KETONES



| Compd | P | M | $R_1$ | $R_2$ | $R_3$ | Yield, % | Crystn[a] solvent | Mp, °C | Formula | Analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | HO | EtOOC | H | Me | $PhCH_2$ | 52 | Al–Et | 169–171 | $C_{19}H_{21}NO_4 \cdot HCl$ | C, H, Cl, N, O |
| 21 | MeO | MeOOC | H | $Me_2CH$ | $PhCH_2$ | 45 | Me–Ea[b] | 193–194 | $C_{21}H_{25}NO_4 \cdot HCl$ | C, H, Cl, N |
| 22 | HO | MeOOC | H | $Me_2CH$ | $PhCH_2$ | 34 | Me–Ea | 168–170 | $C_{20}H_{23}NO_4 \cdot HCl$ | C, H, Cl, N |
| 23 | HO | HOOC | H | $Me_2CH$ | $PhCH_2$ | 80[c] | W | 188–189 | $C_{19}H_{21}NO_4 \cdot HBr$ | C, H, Br, N |
| 24 | HO | MeOOC | Et | $Me_2CH$ | H | 43 | Me–Et | 250 | $C_{15}H_{21}NO_4 \cdot HCl$ | C, H, N |
| 25 | $PhCH_2O$ | MeOOC | H | $Me_2CH$ | $PhCH_2$ | 70 | Et–Ac[d] | 160–162 | $C_{27}H_{29}NO_4 \cdot HCl$ | Cl, N |
| 26 | MeO | MeOOC | H | $Me_3C$ | $PhCH_2$ | 98 | Ea | 181–183 | $C_{22}H_{27}NO_4 \cdot HCl$ | C, H, Cl, N |
| 27 | HO | MeOOC | H | $Me_3C$ | $PhCH_2$ | 77 | Me–Ea | 182.5–183 | $C_{21}H_{25}NO_4 \cdot HCl$ | C, H, Cl, N, O |
| 28 | AcO | $AcOCH_2$ | H | $Me_3C$ | $PhCH_2$ | 45 | Et–Al | 173–175 | $C_{24}H_{29}NO_5 \cdot HCl$ | C, H, N |
| 29 | HO | $HOCH_2$ | H | $Me_3C$ | $PhCH_2$ | 90[e] | W | 173 | $C_{20}H_{25}NO_3 \cdot HCl$ | C, H, Cl, N |
| 30 | HO | $MeOCH_2$ | H | $Me_3C$ | $PhCH_2$ | 62[f] | Me–Et | 202–205 | $C_{21}H_{27}NO_3 \cdot HCl$ | C, H, N |
| 31 | H | MeOOC | H | $Me_3C$ | $PhCH_2$ | 83 | Me–Ea | 184–186 | $C_{21}H_{25}NO_3 \cdot HCl$ | C, H, N |
| 32 | MeO | MeOOC | H | $PhCH_2$ | $PhCH_2$ | 51 | Me–Ea | 166–168 | $C_{25}H_{25}NO_4 \cdot HCl$ | C, H, Cl, N |
| 33 | HO | MeOOC | H | $PhCH_2$ | $PhCH_2$ | 87 | Me–Ea | 167–169 | $C_{24}H_{23}NO_4 \cdot HCl \cdot 0.5\ H_2O$ | C, H, Cl, N |
| 34 | HO | HOOC | H | $PhCH_2$ | $PhCH_2$ | 99[c] | Al | 163–164 | $C_{23}H_{21}NO_4 \cdot HBr \cdot H_2O$ | C, H, Br, N |
| 35 | HO | MeOOC | H | 4-$HOC_6H_4CH_2CHMe$ | $PhCH_2$ | 71 | Ip | 177–181 | $C_{26}H_{27}NO_5 \cdot HCl$ | H, N; C[g] |
| 36 | HO | MeOOC | Me | 4-$MeOC_6H_4CH_2CH_2$ | $PhCH_2$ | 64 | Ea–Et | 161–163 | $C_{27}H_{29}NO_5 \cdot HCl$ | H; C, N[h] |

[a] See footnote *a*, Table I. [b] Ea, EtOAc. [c] Prepared by hydrolysis of the preceding salicylic or anisic esters with refluxing aq 48% HBr for 3 hr. [d] Ac, AcMe. [e] Prepared by hydrolysis of the preceding diacetate **28** with 5 *N* HCl for 70 hr at room temperature. [f] See Experimental Section. [g] C: calcd, 66.4; found, 66.9. [h] C: calcd, 67.0; found, 67.5. N: calcd, 2.89; found, 3.39.

TABLE III



| Compd | P | M | $R_1$ | $R_2$ | Method | Yield, % | Crystn[a] solvent | Mp, °C | Formula | Analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| 37 | HO | $HOCH_2$ | H | Me | A | 49 | Et | 132–134 | $C_{17}H_{21}NO_3$ | C, H, N, O |
| 38 | HO | $HOCH_2$ | H | $Me_2CH$ | A | 63 | Et–Pe | 115–116 | $C_{19}H_{25}NO_3$ | C, H, N, O |
| 39 | $HOCH_2$ | HO | H | $Me_2CH$ | A[b] | 59 | Et | 103–108 | $C_{19}H_{25}NO_3$ | *c* |
| 40 | $PhCH_2O$ | MeOOC | H | $Me_2CH$ | B | 93 | Ea | 134–136 | $C_{27}H_{31}NO_4 \cdot HCl \cdot 0.5\ H_2O$ | C, H, N |
| 41 | $PhCH_2O$ | $HOC(Me)_2$ | H | $Me_2CH$ | C | 80 | Ea–Tf[d] | 174.5–175 | $C_{28}H_{35}NO_3 \cdot HCl$ | H, N: C[e] |
| 42 | MeO | $HOCH_2$ | H | $Me_3C$ | A | 70 | Me–Ea | 196–197 | $C_{21}H_{29}NO_3 \cdot HCl$ | C, H, N, O |
| 43 | HO | $HOCH_2$ | H | $Me_3C$ | B | 87 | Et–Pe | 109–111 | $C_{20}H_{27}NO_3$ | C, H, N |
| 44 | H | $HOCH_2$ | H | $Me_3C$ | A | 96[f] | Al–Ea | 173–174 | $C_{20}H_{27}NO_2 \cdot HCl$ | C, H, N |
| 45 | HO | $HOCH_2$ | H | $PhCH_2$ | A | 80 | Ea–C | 110–111 | $C_{23}H_{25}NO_3$ | C, H, N |
| 46 | HO | $HOCH_2$ | H | 4-$HOC_6H_4CH_2CHMe$ | A[g] | 50[h] | | Oil | $C_{25}H_{29}NO_4$ | *c* |
| 47 | HO | $HOCH_2$ | Me | 4-$MeOC_6H_4CH_2CH_2$ | A[i] | 63[h] | | Oil | $C_{26}H_{31}NO_4$ | *c* |

[a] See footnote *a*, Table I. [b] The intermediate arylamino ketone was formed in THF and reduced *in situ* with LAH. [c] Not analyzed. [d] Tf, THF. [e] C: calcd, 71.5; found, 70.8; [f] Yield of free base isolated as an oil. [g] *p*-[2-(Benzylamino)propyl]phenol prepared by reductive alkylation of *p*-hydroxyamphetamine with PhCHO (see Method F), 69%, mp 101–103°. *Anal.* ($C_{16}H_{19}NO$)C, H, N. [h] Crude yield; product is a mixture of diastereoisomers. [i] *N*-Benzyl-*p*-methoxyphenethylamine, bp 142° (0.01 mm); K. Kindler, K. Schrader, and B. Middelhoff [*Arch. Pharm.*, **283**, 184 (1950)] reported bp 210° (13 mm).

The phenethanolamines prepared by the above procedures are listed in Tables III, IV, and V.

## Experimental Section

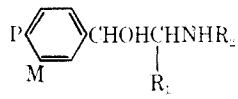
Melting points were determined in open capillary tubes on a Townson–Mercer apparatus and have not been corrected. Compounds gave satisfactory uv, ir, and nmr spectral data obtained, respectively, on a Perkin-Elmer Model 137 uv spectrophotometer, Unicam SP 100, and Varian Associates A-60A spectrometers. Microanalyses were determined on a F and M 185 C, H, and N analyser and by Dr. A. Bernhardt, 5251 Elbach über Engelskirchen, West Germany. Where analyses are indicated only by the symbols of the elements, analytical values obtained were within ±0.4% of the calculated values.

Each general method discussed in the theoretical part of this paper is described here by only one representative example. Hydrogenations were carried out at room temperature and atmospheric pressure.

**Methyl 4-Amino-2-benzyloxybenzoate.**—Methyl 4-aminosalicylate (20.88 g, 0.125 mol) in 5% NaOH (100 ml) and DMSO (250 ml)[16] was heated to 80° and $PhCH_2Br$ (21.38 g, 0.17 mol) slowly added with stirring. After a further 0.5 hr the mixture was poured onto ice and the product isolated by extraction with $CHCl_3$. Two recrystallizations (PhH–cyclohexane) gave colorless needles 8.9 g (28%) mp 124–127°; $\lambda_{max}$ at 236 mμ (ε 13,100), 282 (ε 13,950), and 304 (15,000). *Anal.* ($C_{15}H_{15}NO_3$) C, H, N.

(16) DMSO added to suppress N-benzylation. See S. L. Solar and R. R. Schumaker, *J. Org. Chem.*, **31**, 1996 (1966).

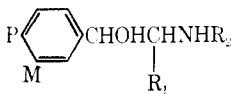
TABLE IV

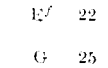


| Compd | P | M | $R_1$ | $R_2$ | Method | Yield, % | Crystn solvent | Mp, °C | Formula | Analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| 48 | HO | MeOOC | H | H | D | 76 | Me-Et | 187–188 | $C_{10}H_{13}NO_4 \cdot HCl$ | C, H, Cl, N |
| 49 | HO | MeOOC | H | H | D | 81 | Me-Et | 222–224 | $C_{11}H_{15}NO_4 \cdot HCl$ | C, H, N |
| 50 | HO | MeOOC | H | $Me_2CH$ | D | 88 | Me-Et | 153–155 | $C_{13}H_{19}NO_4 \cdot HCl$ | C, H, Cl, N |
| 51 | HO | HOOC | H | $Me_2CH$ | D | 86 | Me-Et | 165–166 | $C_{12}H_{17}NO_4 \cdot HBr$ | C, H, Br, N |
| 52 | HO | MeOOC | H | $Me_3C$ | D | 90 | Al | 147 | $C_{13}H_{19}NO_4$ | C, H, N |
| 53 | HO | MeOOC | H | $PhCH_2CHMe$ | E | 48[b] | | | $C_{19}H_{23}NO_4$ | |
| 54 | HO | MeOOC | H | $PhOCH_2CHMe$ | E | 45[c] | C | 94–104 | $C_{19}H_{23}NO_5$ | C, H, N |
| 55 | HO | MeOOC | H | $4\text{-}MeOC_6H_4CH_2CHMe$ | E | 39[c] | Et-Ac | 169–171 | $C_{20}H_{25}NO_5 \cdot HCl$ | C, H, Cl, N |
| 56 | HO | MeOOC | H | $4\text{-}MeOC_6H_4CH_2CMe_2$ | F[d] | 42 | C-Pe | 119–121 | $C_{21}H_{27}NO_5$ | C, H, N |
| 57 | HO | MeOOC | H | Adamantyl | F | 39 | Me-Ea | 220–221 | $C_{20}H_{27}NO_4 \cdot HCl$ | C, H, N |
| 58 | HO | MeOOC | Me | $4\text{-}MeOC_6H_4CH_2CH_2$ | D[e] | 74 | Me-Ea | 191.5–193.5 | $C_{20}H_{25}NO_5 \cdot HCl$ | H, N; C[f] |

[a] See footnote *a*, Table I. [b] Crude yield; product is a noncrystalline mixture of diastereoisomers. [c] Product is an unknown mixture of diastereoisomers. [d] α,α-Dimethyl-*p*-methoxyphenethylamine, bp 166–168° (0.8 mm); C. Mentzer, Buü-Hoï, and P. Cagniant [*Bull. Soc. Chim. Fr.*, 813 (1942)] reported bp 225–226° (16 mm). [e] *erythro*. [f] C: calcd 67.0; found, 67.5.

TABLE V



| Compd | P | M | $R_1$ | $R_2$ | Method | Yield, % | Crystn solvent | Mp, °C | Formula | Analysis | β-Stimulant Activity: tracheal muscle[b] | β-Stimulant Activity: cardiac muscle[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 59 | HO | $HOCH_2$ | H | $4\text{-}HOC_6H_4CH_2CHMe$ | G | 62 | Me-Et | 60–110[d] | $C_{18}H_{23}NO_4 \cdot C_9H_8O_3 \cdot H_2O$[e] | C, H, N | 300 | 0.05 |
| 60 | HO | $HOCH_2$ | H | $4\text{-}MeOC_6H_4CH_2CHMe$ | G | 37 | B | 81–83[d] | $C_{19}H_{23}NO_4$ | C, H, N | 150 | 0.075 |
| 61 | HO | $HOCH_2$ | H | $Me_3C$ | G | 88 | Ea-C | 157–158 | $C_{13}H_{21}NO_3$ | C, H, N, O | 100 | 0.05 |
| 62 | HO | $HOCH_2$ | H |  | E[f] | 22 | Ea | 148–151[d] | $C_{16}H_{26}N_2O_4$ | C, H, N | 50 | 0.025 |
| 63 | HO | $HOCH_2$ | H | $PhCH_2CHMe$ | G | 25 | Ea | 113–115[d] | $C_{18}H_{23}NO_3$ | H, N, C; O[g] | 50 | 0.05 |
| 64 | HO | $HOCH_2$ | H | $Me_2CH$ | G | 86 | Tf-Et | 143–145 | $C_{12}H_{19}NO_3$ | C, H, N, O | 40 | 0.1 |
| 65 | HO | $HOCH_2$ | H | $4\text{-}MeOC_6H_4CH_2CMe_2$ | A | 54 | Ea | 156–157.5 | $C_{20}H_{27}NO_4$ | C, H, N | 25 | 0.005 |
| 66 | HO | $HOCH_2$ | H | $3,4,5\text{-}MeO_3C_6H_2CH_2CHMe$ | E[h] | 48 | Et | 90–98[d] | $C_{21}H_{29}NO_6$ | C, H, N | 20 | 0.1 |
| 67 | HO | $HOCH_2$ | H | $4\text{-}MeOC_6H_4CH_2CH_2CHMe$ | E | 63 | Et-Pe | 99–107[d] | $C_{20}H_{27}NO_4$ | C, H, N | 20 | [i] |
| 68 | HO | $HOCH_2$ | H | $4\text{-}EtOC_6H_4CH_2CHMe$ | E[j] | 10 | Ea-C | 98–107[d] | $C_{20}H_{27}NO_4$ | C, H, N | 20 | 0.01 |
| 69 | HO | $HOCH_2$ | Me | $4\text{-}MeOC_6H_4CH_2CH_2$ | A | 50 | Ea-Et | 111–113[k] | $C_{19}H_{25}NO_4 \cdot 0.5H_2O$ | C, H, N | 20 | 0 |
| 70 | HO | $HOCH_2$ | H | $PhOCH_2CHMe$ | A | 36 | Ea-C | 128–130 | $C_{18}H_{23}NO_4$ | C, H, N, O | 10 | 0.1 |
| 71 | HO | $HOCH_2$ | H | $3,4\text{-}MeO_2C_6H_3CH_2CHMe$ | E | 47 | B | 73–113[d] | $C_{20}H_{27}NO_5$ | C, H, N | 5 | 0.05 |
| 72 | HO | $HOCH_2$ | H | Cyclopentyl | E | 43 | Ea-C | 120–131 | $C_{14}H_{23}NO_3$ | C, H, N | 4 | 0.05 |
| 73[k] | HO | $HOCH_2$ | Et | $Me_2CH$ | A | 55 | Al | 199[l] | $C_{14}H_{23}NO_3 \cdot HCl$ | C, H, N | 2 | 0.005 |
| 74 | HO | $HOCH_2$ | Me | $4\text{-}MeOC_6H_4CH_2CH_2$ | G | 35 | Me-Ea | 79–81[m] | $C_{19}H_{23}NO_4 \cdot C_2H_4O_2$[n] | H, N; C[o] | 1 | 0 |
| 75 | HO | $HOCH_2$ | H | Adamantyl | A | 58 | Ea | 147–148 | $C_{19}H_{27}NO_3$ | C, H, N | 0 | 0 |
| 76 | MeO | $HOCH_2$ | H | $Me_3C$ | G | 75 | B-Pe | 115–116 | $C_{14}H_{23}NO_3$ | C, H, N | 0[p] | 1 |
| 77 | HO | $MeOCH_2$ | H | $Me_3C$ | [q] | 52 | Me-Et | 210 | $C_{14}H_{23}NO_3 \cdot HCl$ | C, H, N | 0[p] | [r] |
| 78 | H | $HOCH_2$ | H | $Me_3C$ | G | 85 | Al-Ea | 128–130 | $C_{13}H_{21}NO_2 \cdot C_2H_4O_2$[n] | H, N; C[s] | 0[p] | [r] |
| 79 | HO | Me | H | $Me_3C$ | [q] | 80 | Ea | 168–171 | $C_{13}H_{21}NO_2$ | H, N; C[s] | 0[p] | 0.005 |
| 80 | HO | $HOC(Ph)_2$ | H | $Me_3C$ | C | 78 | Tf-Ea | 186–187 | $C_{25}H_{29}NO_3 \cdot HCl \cdot 0.5H_2O$ | C, H, N | 0[t] | [i] |
| 81 | HO | $HOC(Me)_2$ | H | $Me_2CH$ | G | 81 | Tf-Et | 162–164 | $C_{14}H_{23}NO_3 \cdot C_{14}H_{10}O_3$[u] | C, H, N | 0[p] | [i] |
| 82 | $HOCH_2$ | HO | H | $Me_2CH$ | G | 70 | Tf-Pe | 103–105 | $C_{12}H_{19}NO_3$ | C, H, N | 0 | |
| 83 | HO | $HOCH_2$ | H | H | G[v] | 94 | Me-Ea | 149–151 | $C_9H_{13}NO_3$ | H, N, O; C[w] | 0[m] | |
| 84 | HO | $HOCH_2$ | H | Me | G | 52 | Ea | 109–111 | $C_{16}H_{21}NO_7 \cdot C_4H_4O_4$[x] | H, N; C[y] | 0[z] | |

[a] See footnote *a*, Table I, footnote *b*, Table II, footnote *d*, Table III. [b] Relative potency (isoproterenol = 100) from Kenzett Rossler preparation. [c] Relative potency (isoproterenol = 100) from isolated guinea pig atria preparation. [d] Product is a mixture of diastereoisomers. [e] Hydrated *p*-anisate salt. [f] 1-Morpholino-2-propanone bp 72–76° (0.5 mm). H. J. Roth and H. Muehrle [*Arch. Pharm.*, **297**, 58 (1964)] reported bp 98° (14 mm). [g] C: calcd, 71.73; found, 72.48. O: calcd, 15.93; found, 15.45. [h] 1-(3,4,5-Trimethoxyphenyl)-2-propanone, mp 62–65°. J. M. Pepper and M. Saha [*Can. J. Chem.*, **42**, 113 (1964)] reported mp 66–67°. [i] Not tested. [j] (*p*-Ethoxyphenoxy)-2-propanone prepared by refluxing *p*-ethoxyphenol with $ClCH_2COCH_2$–$K_2CO_3$ in EtCOMe for 24 hr, 41%, bp 127–130° (1.3 mm), mp 37–39° [from petroleum ether (bp 40–60°)]. *Anal.* ($C_{11}H_{14}O_3$) C,H. [k] We thank Mr. S. Buchanan for preparing this compound. [l] *erythro*. [m] *threo*. [n] Acetate salt. [o] C: calcd, 64.43; found, 63.8. [p] Weak β-adrenergic antagonist. [q] See Experimental Section. [r] C: calcd, 63.58; found 64.0; [s] C: calcd, 69.9; found, 70.6. [t] *o*-Benzoylbenzoate salt. [u] Debenzylation of **45** took 6 hr. [v] C: calcd, 59.0; found, 58.5; [w] α-Adrenoreceptor stimulant, 0.1 times the activity of norepinephrine. [x] Maleate salt. [y] C: calcd., 53.67; found, 53.1. [z] α-Adrenoreceptor stimulant 0.1 times the activity of epinephrine.

**Methyl 4-Acetyl-2-benzyloxybenzoate (8).**—$NaNO_2$ (2.58 g, 0.0374 mol) in $H_2O$ (3.5 ml) was added to a stirred suspension of the preceding ester (9.5 g, 0.0338 mol) in $H_2O$ (20 ml) and concentrated HCl (8.5 ml) at 0–5° followed by NaOAc (3.25 g) in $H_2O$ (10 ml). The mixture was gradually added below the surface of a stirred solution of hydrated $CuSO_4$ (1.85 g), $Na_2SO_3$ (0.15 g), hydrated NaOAc (24.1 g), and acetaldoxime (3.5 g, 0.0593 mol) in $H_2O$ (200 ml) at 10–15°. After 1 hr the liquid was decanted from a red-brown gum and the latter was stirred under reflux for 2 hr with ferric ammonium sulfate (44.2 g) in $H_2O$ (350 ml). The mixture was filtered and the filtrate extracted with $CHCl_3$. The extracts gave a residual dark oil which was dis-

solved in MeOH (285 ml) and heated to reflux with Girard "P" reagent (10 g) in HOAc (15 ml) for 1 hr. The solution was cooled, added to NaOH (9.5 g) in $H_2O$ (1 l.), and extracted with $Et_2O$. The aq phase was then acidified with concentrated HCl (50 ml), left at room temperature for 1 hr, and again extracted with $Et_2O$. The extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to give a colorless solid 1.05 g (10%). mp 68–70°. Recrystallization from cyclohexane gave pure product.

**Methyl 4-Acetylsalicylate (9).**—The preceding ester (2.6 g, 0.009 mol) in 90% EtOH (250 ml) was hydrogenated over 10% Pd–C (0.3 g). The rate of hydrogenation markedly decreased when 270 ml of $H_2$ had been absorbed. The catalyst was removed, the filtrate evaporated to dryness, and the residue crystallized from cyclohexane to give **9** as needles 1.2 g (75%), mp 120–121.5°.

**4′-Hydroxy-3′-hydroxymethylacetophenone Diacetate (10).**—3′-Chloromethyl-4′-hydroxyacetophenone[17] (110 g, 0.6 mol), NaOAc (49 g, 0.6 mol), $Ac_2O$ (110 ml), and HOAc (200 ml) were heated at 100° for 2 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in PhH, washed with 10% $Na_2CO_3$ solution and $H_2O$, and dried ($Na_2SO_4$). The PhH was evaporated and the residue distilled *in vacuo* to give **10** as a colorless liquid which solidified on cooling.

**Preparation of Phenacyl Bromides. Methyl 5-Bromoacetylsalicylate (12).**—$Br_2$ (6.3 g, 0.039 mol) in $CHCl_3$ (75 ml) was added dropwise with stirring to methyl 5-acetylsalicylate (7.5 g, 0.039 mol) in $CHCl_3$ (25 ml) at room temperature. Evaporation to dryness and crystallization from petroleum ether (bp 60–80°) gave **12**.

**Preparation of Arylamino Ketones. Methyl 5-(*N*-Benzyl-*N*-*t*-butylglycyl)salicylate·HCl (27).**—The preceding phenacyl bromide (10 g, 0.0366 mol) in EtCOMe (250 ml) was added to *N*-*t*-butylbenzylamine (10.75 g, 0.066 mol) and gently heated at reflux for 3 hr. The mixture was cooled and filtered and the filtrate was evaporated under reduced pressure. The hydrochloride of the residue was formed in $Et_2O$ and recrystallized from MeOH–EtOAc; $\lambda_{max}$ 230 mμ (ε 21,300) and 280 (13,160).

**2-(Benzyl-*t*-butylamino)-4′-hydroxy-3′-methoxymethylacetophenone·HCl (30).**—2-(Benzyl-*t*-butylamino)-4′-hydroxy-3′-hydroxymethylacetophenone·HCl (**29**) (50 g, 0.138 mol) in MeOH (500 ml) containing 1% HCl was refluxed for 48 hr and then evaporated. The residue was crystallized from MeOH–$Et_2O$ to give **30**.

**Methyl 5-Dihydroxyacetylsalicylate (XV).**—Methyl 5-bromoacetylsalicylate (**12**) (44.7 g, 0.164 mol) in DMSO (150 ml) was left at room temperature for 1 week and then poured into $H_2O$ (2 l.). The precipitate was extracted continuously (Soxhlet) with $H_2O$ (3 l.). The glyoxal hydrate XV, separated on cooling as white crystals: 23.6 g; 64%; mp 110–113°; $\lambda_{max}$ 273 mμ (ε 13,570) and 306 (sh) (3,680). *Anal.* ($C_{10}H_{10}O_8$) C, H.

**Preparation of Phenethanolamines (See Tables III, IV, and V). Method A. α¹-Benzylisopropylaminomethyl-4-hydroxy-*m*-xylene-α¹,α³-diol (38).**—Methyl 5-(*N*-benzyl-*N*-isopropylglycyl)-salicylate·HCl (**22**) (11 g, 0.029 mol) was converted into the free base, dissolved in dry THF (150 ml), and added with stirring to LAH (3.8 g, 0.1 mol) in dry THF (300 ml). After heating under reflux for 2 hr the excess hydride was decomposed by the cautious addition of $H_2O$ and the solvent removed under reduced pressure. The residue was dissolved in dilute HCl, basified with $NaHCO_3$ solution, and extracted continuously ($Et_2O$). Evaporation of the ether and crystallization of the residue from $Et_2O$–petroleum ether (bp 60–80°) gave **38**.

**Method B. α¹-(Benzyl-*t*-butylaminomethyl)-4-hydroxy-*m*-xylene-α¹,α³-diol (43).**—$NaBH_4$ (1.51 g, 0.04 mol) in 1 *N* NaOH (20 ml) was added slowly to a solution of **29**·HCl (7.27 g, 0.02 mol) in EtOH (40 ml) below 15°. After 48 hr at room temperature the mixture was acidified with 5 *N* $H_2SO_4$ and the EtOH removed under reduced pressure. The aq phase was adjusted to pH 8 with 10% $Na_2CO_3$ solution and extracted with EtOAc. The extracts were concentrated to 20 ml and petroleum ether (60–80°) (30 ml) was added to give white crystals of **43**.

**Method C. α¹-Benzylisopropylaminomethyl-4-benzyloxy-α¹,α³-dimethyl-*m*-xylene-α¹,α³-diol·HCl (41).**—A solution of **40** (1.5 g, 0.0035 mol) in THF (50 ml) was treated with MeMgBr (0.05 mol) in $Et_2O$ (50 ml) and stirred at room temperature overnight. The mixture was decomposed with saturated $NH_4Cl$ and the organic layer separated, dried ($MgSO_4$), and evaporated. Trituration of the crude product with dilute HCl gave **41** as an insoluble hydrochloride which was recrystallized from THF–EtOAc.

**Method D. 5-(1-Hydroxy-2-isopropylaminoethyl)salicylic Acid·HBr (51).**—A solution of **23**·HBr (2.9 g, 0.0071 mol) in EtOH (50 ml) was hydrogenated in the presence of 10% Pd–C (0.5 g) until uptake of $H_2$ ceased (23 hr). Removal of the catalyst and solvent left an amber syrup which gave the crystalline hydrobromide **51** on trituration with EtOAc.

**Method E. Methyl 5-{[2-(1-Methyl-2-phenoxyethyl)amino-1-hydroxy]ethyl}salicylate (54).**—The amine·HCl **48** (6.6 g, 0.0267 mol) in MeOH (250 ml) was neutralized with NaOMe [from Na (0.614 g) in MeOH (50 ml)], phenoxyacetone (4 g, 0.0267 mol) was added and the mixture was gently refluxed for 2 hr. The cooled solution was then hydrogenated in the presence of 10% Pd–C (1 g) until uptake of $H_2$ ceased (18 hr). The catalyst and solvent were removed and the oil partitioned between $Et_2O$ and dilute HCl. The aq extracts were neutralized with $NaHCO_3$ solution and extracted exhaustively ($Et_2O$). The ether extracts were dried ($MgSO_4$) and evaporated, and the yellow oil crystallized after trituration with petroleum ether (40–60°). Recrystallization from cyclohexane gave **54**.

**Method F. Methyl 5-{[2-(1-Adamantylamino)-1-hydroxy]-ethyl}salicylate·HCl (57).**—1-Adamantylamino (3.3 g, 0.022 mol) and the glyoxal (XV) (5.65 g, 1.25 mol) were gently refluxed in MeOH (200 ml) for 1 hr. The cooled solution was then hydrogenated in the presence of 10% Pd–C (1 g) until the theoretical uptake of $H_2$ was achieved (30 hr). Because of catalyst poisoning by traces of S compounds in **XV** it was sometimes necessary to add further Pd–C. Catalyst and solvent were removed and the residue was crystallized by trituration with 2 *N* HCl and $Et_2O$. Recrystallization from MeOH–EtOAc gave the hydrochloride **57**.

**Method G. α¹-(*t*-Butylaminomethyl)-4-hydroxy-*m*-xylene-α¹,α³-diol (61).**—The phenethanolamine **43** (0.8 g, 0.0024 mol) in EtOH (20 ml) was hydrogenated in the presence of 10% Pd–C (0.5 g) until uptake of $H_2$ ceased (within 10 min). The product crystallized after removal of the catalyst and solvent and trituration of the residue with $Et_2O$–cyclohexane. Recrystallization from EtOAc–cyclohexane gave **61**.

**α-(*t*-Butylaminomethyl)-4-hydroxy-3-methylbenzyl Alcohol (79).**—The phenethanolamine **43** (16.5 g, 0.05 mol) in 1 *N* $H_2SO_4$ (45 ml) was hydrogenated in the presence of 10% Pd–C (2 g) until 0.1 mol of $H_2$ had been absorbed. The catalyst was removed, the solution basified to pH 8 and the product extracted with EtOAc. Crystallization from EtOAc gave **79**.

**Biological Test Procedures.**[18]—All the phenethanolamines were tested by iv administration for their effect against temporarily increased airway resistance caused by iv injections of acetylcholine, histamine, 5-hydroxytryptamine, and bradykinin in anesthetized guinea pigs. An effective β-adrenoreceptor stimulant antagonized the responses of all the spasmogens whereas a β-adrenoreceptor antagonist potentiated them. The action on cardiac muscle was ascertained *in vitro* by measuring the increase in isometric tension in the electrically driven left atrium of the guinea pig. The α-stimulant activity was estimated in the pithed rat preparation from the vasopressor responses to graded iv doses of the compound.

**Structure–Activity Relationships.**—Although the salicylic acid **51**, our primary objective, was inactive as a β-adrenoreceptor stimulant, the saligenin **64** was about 0.4 times as potent as isoproterenol and our interest in structure–activity relationships centered, therefore, around this compound (Table V).

An understanding of the molecular nature of processes occurring at β-adrenoreceptors has received great impetus from the speculation of Bloom and Goldman[19] and Belleau[20] which rationalize earlier observations on structure–activity relationships of the catecholamines. Both hypotheses invoke interactions of the phenethanolamine side chain with adenylcyclase-bound ATP which result in pyrophosphate fission and activation of β-adrenergic pathways *via* cyclic AMP. The analogous structural requirements of the ethanolamine side chain of our saligenins allow a similar interpretation. Thus the enhancement of β-sympathomimetic action by specific branched alkyl and arylalkyl substituents, *e.g.*, **59**, **60**, **61**, and **63**, is in good agreement

(17) R. Travo, *Gazz. Chim. Ital.*, **81**, 773 (1951).

(18) See V. A. Cullum, J. B. Farmer, D. Jack, and G. P. Levy, [*Brit. J. Pharmacol.*, **35**, 141 (1969)] for detailed procedures.

(19) B. M. Bloom and I. M. Goldman, *Advan. Drug Res.*, **3**, 121–169 (1966).

(20) B. Belleau, *Ann. N. Y. Acad. Sci.*, **139**, 580 (1967).

with the corresponding catecholamines.[21] The most potent compound was the *p*-hydroxyphenylisopropyl derivative **59**, the catecholamine analog of which is about 8 times as active as isoproterenol. This increase in efficacy has been attributed to high binding efficiency of the phenyl group to a flat portion of the receptor surface.[21a] In our compounds introduction of a phenyl group does not consistently enhance β-stimulant action, *e.g.*, **65**. **66**, **67**, **68**, **70**, and **71** are less active than **64**, while the morpholino derivative, **62**, although nonplanar, is a potent β-stimulant. The poor activity of the cyclopentyl compound **72** has no precedent in the catechol series where the analogous compound is twice as active as isoproterenol on guinea pig bronchial tissue.[22] The adamantyl derivative, **75**, is inactive, but the corresponding catechol has not been described. As in the catecholamines, introduction of an alkyl group at the α-C, e.g., **69**, **73**, and **74**, markedly reduces β-stimulant potency and increases selectivity for bronchial over heart muscle.

Modification of the saligenin moiety is limited by the synthetic routes used. However, it is clear that the labile protons on the phenol and hydroxymethyl groups are key factors since etherification, as in **76** and **77**, or replacement of either OH function by H, as in **78** and **79** abolishes stimulant action on bronchial muscle. The cresol, **79**, shows a slight but selective cardiac stimulant activity whereas **76**, **77**, and **78** are weak β-adrenoreceptor blockers.

In the tertiary alcohols, **80** and **81**, it appears that an unfavorable steric factor abolishes stimulant activity and the compounds are β-adrenoreceptor blockers.

The ability of the saligenin moiety to subserve also as a catechol function in α-adrenoreceptor stimulants is shown in **83** and **84** although the potency ratios relative to those of norepinephrine and epinephrine are less than that observed for the β-mimetic process when **64** is compared with isoproterenol. Compound **84** differs from epinephrine but resembles the corresponding methanesulfonamide analog[8] in having no β-adrenoreceptor stimulant action.

A remarkable feature of the saligenins is the loss of activity when the position of the phenol and hydroxymethyl groups are reversed as in **82**. A similar observation was reported by Larsen, *et al.*,[8] in the "pseudocatechol" series where only the compound with the *m*-methanesulfonamide substituent (soterenol) is active. They suggested that the active conformation of soterenol and isoproterenol at the receptor site is determined by primary binding of the most acidic group, which is the *meta* substituent in each case. When the *para* isomer is more acidic as in the reversed isomer of soterenol an unfavorable fit on the receptor is induced. In the same way, in the monophenolic analogs of isoproterenol the compound having the acidic group in the *meta* position is some 10 times more active than the *para* isomer at metabolic β-receptors.[23] However, our results clearly cannot be interpreted in these terms. Instead they emphasize the critical nature of the *para* phenolic group. In view of the relatively poor chelating properties of the saligenin group compared with those of catechol and salicylic acid, and also taking into account the inactivity of the reversed isomer **82**, it seems unlikely that metal chelation as proposed by Belleau[9] and adopted by Bloom and Goldman[19] is a major factor in the potency enhancement of β-responses. On the other hand, the postulate that the saligenin group may initiate formation of an ordered water crust that interacts with adenylcyclase to induce a highly favorable and specific conformational perturbation, is in accord with Belleau's later hypothesis.[20] Some refinement of this model, however, will be necessary to explain our observed structure–activity relationships which emphasize equally the importance of the *para* phenolic group and of a *meta* substituent containing a labile proton. A recent hypothesis[23] has sought to explain both these features and indeed has used them to propose a new general mechanism of adrenoreceptor responses involving a quinone methide intermediate, that is not possible with *meta* phenols.

An outstanding feature of the active saligenins is the degree of selectivity for bronchial over cardiac muscle. Such a separation of effects has been established in principle with catecholamines and has led Lands, *et al.*,[24] to propose the existence of two distinct β-receptors—$\beta_1$ in cardiac tissue and $\beta_2$ in bronchiolar and vascular smooth muscle. The magnitude of the observed selectivities in the catecholamines is small compared with that seen in the saligenin series. Thus at equiactive bronchodilator doses **61** is 2000 times less active than isoproterenol on cardiac muscle (Table V) compared with a figure of 30 times for the *t*-butyl catecholamine analog.[24a] Although our results are compatible with the subdivision of receptors into $\beta_1$ and $\beta_2$ types a detailed pharmacological examination of **61** may also suggest a degree of selectivity between $\beta_2$ receptors.[18] Thus the action of **61** on blood flow in the femoral artery of the anesthetized dog is 0.1 times that of isoproterenol for equivalent bronchodilator doses. A selectivity of action between the $\beta_1$ receptors that govern the force and those that control the rate of contraction of cardiac muscle has been observed in catecholamines with α-alkyl groups in the phenethanolamine side chain[25] and also in a resorcinol analog.[26]

These selective actions of unnatural β-agonists clearly show that there are variations between β-receptors in different tissues of the same animal. From our structure–activity studies we think it possible that these variations may result from the occurrence of isoenzymic forms of adenylcyclase. Thus there would be only one β-receptor for the natural catecholamines but the isoenzymes could generate a series of isoreceptors[27] with differing specificities for unnatural β-agonists.

In accord with our original hypothesis, the saligenins are not metabolized by COMT. Martin, *et al.*,[28] have shown that in contrast to isoproterenol the metabolic pathway of **61** (salbutamol)[29] does not depend on the route of administration. After oral or parenteral dosage to dogs, cats, rabbits, or guinea pigs the compound is recovered unchanged or as the phenolic glucuronide, the extent of each depending on the species used. The compound is thus well-absorbed orally and is an effective bronchodilator. The duration of bronchodilator action of salbutamol administered by aerosol inhalation is several times greater than an equipotent dose of isoproterenol by the same route. Clinical studies showing the efficacy of salbutamol in the treatment of asthma have been published.[30]

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