mately the same extent. Compound **3a** was also found to be a potent irreversible inhibitor of transport ATPase in spite of the fact that **3b** (which has very weak cardiotonic activity[19]) did not appreciably inhibit the enzyme. This is in contrast to the finding of Hokin, *et al.*,[11a] that $\Delta^{5,14}$-dianhydrostrophanthidin 3-iodoacetate does not irreversibly inhibit transport ATPase whereas strophanthidin 3-iodoacetate does.

Experimental Section[20]

3β-Hydroxy-14,15α-epoxy-5β,14α-card-20(22)-enolide 3-Acetate (4).—To 418 mg (1.1 mmoles) of **3b**[13] in 8.6 ml of $CHCl_3$ was added a soln of 535 mg of *m*-$ClC_6H_4CO_3H$ (purity 68%) in 13 ml of C_6H_6. The reaction mixt was allowed to stand for 27 hr at room temp. $CHCl_3$ (42 ml) was added followed by 16 ml of 10% Na_2SO_3 soln. The org layer was sepd and washed with 5% Na_2CO_3 soln and H_2O and after drying (Na_2SO_4) yielded 385 mg of residue. Recrystn of the residue from Me_2CO–Et_2O gave 376 mg (84% yield) of **4** as needles: mp 186–188° (lit.[14] mp 220–226° from Me_2CO–petr ether; lit.[21] mp 187–198° from MeOH–Et_2O); nmr δ 0.83 (3 H, s, 18-CH_3; calcd[22] δ 0.82), 1.02 (3 H, s, 19-CH_3; calcd[22] δ 1.01), 2.11 (3 H, s, 3-CH_3CO_2), 3.60 (1 H, m, 15-CH), 4.77 (2 H, q, J = 1 cps, 21-CH_2), 5.17 (1 H, m, 3-CH), 5.90 (1 H, q, J = 1 cps, 22-CH); mass spectrum, parent ion at *m/e* 414, a (P − H_2O) peak at *m/e* 396, and a (P − HOAc) peak at *m/e* 354.

15α-Hydroxydigitoxigenin 3-Acetate (2e).—This compd was prepd from **4** by the procedure described by Okada and Hasunuma.[14] The product was obtained in 65% yield and after recrystn from MeOH–Et_2O had mp 260–262° (lit.[14] mp 245–253° from Me_2CO–Et_2O; lit.[21] mp 247–250° from MeOH–Et_2O).

15α-Hydroxydigitoxigenin 3-Acetate 15-Bromoacetate (2b).—A soln of 90 mg (0.2 mmole) of **2e** in 3.6 ml of dry dioxane[23] and 2 drops of pyridine was treated with 2 drops of $BrCH_2COBr$, whereupon a granular ppt formed. The suspension was stirred at 70° for 16 hr. The reaction mixt was dild with 30 ml of H_2O, and 5% Na_2CO_3 soln was added to pH 7. The mixt was then concd to dryness, and the residue was purified by preparative tlc on silica gel (plates developed in $CHCl_3$–MeOH 10:1, major product had R_f 0.4) to give, after 1 recrystn from MeOH, 54 mg (47% yield) of **2b**. An anal. sample had mp 230–232°; nmr δ 0.90 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 2.01 (3 H, s, 3-CH_3CO_2), and 3.80 (2 H, s, 15-$BrCH_2CO_2$). *Anal.* ($C_{27}H_{37}BrO_7$) C, H, Br.

Digitoxigenin 3-Bromoacetate (2a).—A soln of 50 mg of digitoxigenin (**5**) in 2.5 ml of dry dioxane was treated with 2 drops of pyridine followed by 2 drops of $BrCH_2COBr$. The white suspension was stirred at room temp for 1.5 hr. The reaction mixt was dild with 10 ml of H_2O, and the ppt was filtered off, washed with H_2O, and dried *in vacuo*. Prep tlc of this solid on silica gel (plates developed in $CHCl_3$–MeOH, 96:4) gave 2 major bands. The lower band (R_f 0.2) yielded 10 mg of starting material. The higher band (R_f 0.5) gave, after recrystn from MeOH, 38 mg (57% yield) of **2a**, mp 211–212°. *Anal.* ($C_{25}H_{35}BrO_5$) C, H.

Δ^{14}-Anhydrodigitoxigenin 3-Bromoacetate (3a).—The reaction leading to this compd was carried out as described in the synthesis of **2a** except that the reaction time was 3 hr. Prep tlc of the crude product on silica gel (plates developed in $CHCl_3$–MeOH, 96:4) gave a major band at R_f 0.8 which, after recrystn from MeOH, gave 41 mg (65% yield) of **3a**, mp 193–195°; nmr δ 0.82 (3 H, s, 18-CH_3), 1.01 (3 H, s, 19-CH_3), 3.85 (2 H, s, 3-$BrCH_2CO_2$), and 5.27 (1 H, m, 15-CH). *Anal.* ($C_{25}H_{33}BrO_4$), C, H, Br.

Digoxigenin 3,12-Dibromoacetate (2c).—A soln of 78 mg of digoxigenin (**6**) in 3.6 ml of dry dioxane was treated with 2 drops of pyridine and 2 drops of $BrCH_2COBr$. The white suspension was stirred for 4 hr at 75°, dild with H_2O, and adjusted to pH 7 with 5% Na_2CO_3 soln. The solvents were removed under reduced pressure, and the residue was purified by prep tlc on silica gel (plates developed in $CHCl_3$–MeOH, 10:1). The major band at R_f 0.7 gave, after recrystn from MeOH–H_2O, 72 mg (56% yield) of **2c**, mp 215–218°. *Anal.* ($C_{27}H_{36}O_7Br_2$) C, H, Br.

Acknowledgments.—The authors are indebted to Dr. John Oliver's group for the nmr spectra and to Drs. Don DeJongh and David Brent for the mass spectral data. This work was made possible by a grant from the Michigan Heart Association.

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(20) Melting points are corrected and were detd on a Fisher-Johns melting point apparatus. Ir spectra were detd with a Beckman Model IR-8 spectrophotometer and were consistent with the assigned structures. Nmr spectra were recorded with a Varian A-60A spectrometer in $CDCl_3$(Me_4Si). In nmr descriptions s = singlet, q = quartet, m = multiplet. Mass spectra were taken on an A.E.I. MS-902 instrument using 70 eV with a direct source inlet system. Preparative tlc plates (0.75-mm thick), prepared using E. Merck silica gel G, were activated at 110° for 2 hr before use. Bands were located under uv light and were extd from the plates with MeOH–$CHCl_3$, 1:1. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The anal. samples gave combustion analyses within 0.3% of theory.

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β-Adrenergic Blocking Agents. 10. (3-Amino-2-hydroxypropoxy)anilides

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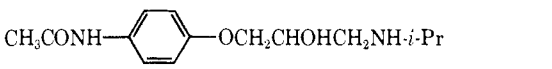
Several (3-amino-2-hydroxypropoxy)acylanilides have been synthesized. In experimental animals, they have potent β-adrenergic blocking actions on the myocardium but not at some other sites, for example, the peripheral blood vessels. Of the compounds tested 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (practolol) was selected for clinical trial on the basis of optimal potency and selectivity.

In extension of our work on 1-amino-3-aryloxy-2-propanols related to propranolol[1] we have prepared several analogs in which the aryl residue contains an acylamino substituent. In these preliminary studies, only relatively minor variations of the substituent (R_1) on the propanolamine side chain have been made. The acylamino substituents (R_2CONH) examined have included examples of alkanoyl, aroyl, and aralkanoyl groups. In general the compounds are potent β-adrenergic blocking agents. They differ, however, from previously known active compounds in that the inhibition of β-adrenergic responses is restricted to certain sites. Thus, the most studied compound of the new

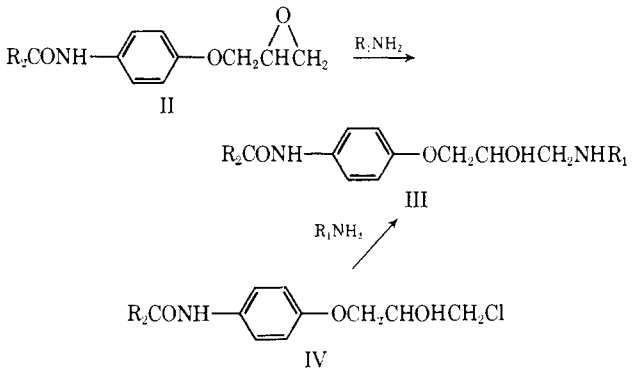
(1) Inderal.

series, 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (I) (practolol),[2] has been found to be effective in the blockade of isoproterenol-induced tachycardia in the anesthetized cat, but this compound had little effect on the vasodepressor action of isoproterenol or on the relaxation of isolated tracheal chains exposed to adrenalin or isoproterenol solutions.[3] Practolol is at present undergoing extensive clinical trials.[4]

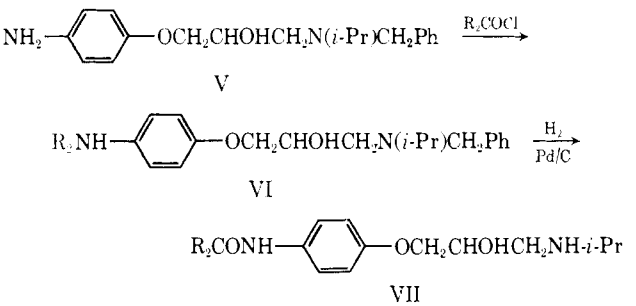


I

Chemistry.—The compounds were prepared[5] in a manner analogous to that for the 1-amino-3-naphthoxy-2-propanols[6] (methods A and B) by treating the 4-(2,3-epoxypropoxy)acylanilide (II) or the 4-(3-chloro-2-hydroxypropoxy)acylanilide (IV) with the appropriate amine.

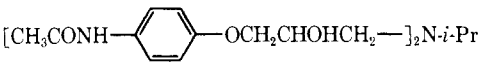


The following route (method C) was used to provide ready variation of the acylamino moiety.



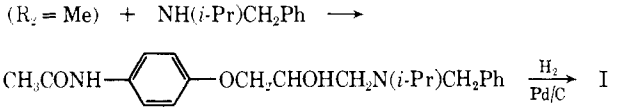
The intermediates VI could be used without further purification.

Routes A and B, when used for the preparation of practolol, initially gave rise to the tertiary amine VIII, present to the extent of 3–5% in the product. Thus in the preparation of 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide by method A, the secondary amine III (R_1 = *i*-Pr; R_2 = Me) appeared to react further with the epoxide II (R_2 = Me) to give the tertiary amine VIII even when a large excess of *i*-$PrNH_2$ was used.



VIII

Pure practolol free from VIII was obtained chromatographically from the crude product and by hydrogenolysis of IX (method D).



IX

Structure–Activity Relationships.—Throughout the *p*-acylamino series the compounds markedly inhibited isoproterenol-induced tachycardia but had only small effects on the isoproterenol depressor response. This is in marked contrast with the effects of previously described β-adrenergic blocking agents, for example, propranolol, which inhibit the responses to isoproterenol, to a large degree, independently of the site of action. Results with compounds **1–5** showed that good blockade of the tachycardia response was associated with *N*-*i*-Pr and *N*-*tert*-Bu in parallel with the results of our previous work.[6,7] With variation of the acylamino moiety (**6–10**) there was retention of high blocking activity of the tachycardia response and little or no inhibition on the depressor response except in the case of **6**.

Movement of the acylamino group to the 3 or 2 position (**11**, **12**) caused a loss of the selectivity shown by most of the other compounds. Results of biological tests are given in Table I. The total dose, infused over a period of 30 min, that caused a 50% inhibition of the tachycardia in anesthetized cats produced by 0.2 μg/kg (iv) of isoproterenol is given; the degree (%) of blockade of the vasodepressor response at that dose level is also given. A low per cent block of the depressor response is an indication of cardiac selectivity.[8,9]

Experimental Section[10,11]

4-(2,3-Epoxypropoxy)acetanilide.—To a stirred soln of 4.5 g of 4-acetoamidophenol and 1.5 g of NaOH in 50 ml of H_2O was added 3.5 ml of epichlorohydrin at ambient temp. The mixt was stirred for 16 hr and filtered. The solid product was washed (H_2O) and air-dried at ambient temp, mp 110°. This material was used without further purification for the prep of 1.

4-(2-Hydroxy-3-isopropylaminopropoxy)acetanilide (1). Method A.—A mixt of 2.0 g of 4-(2,3-epoxypropoxy)acetanilide and 10 ml of *i*-$PrNH_2$ was stirred at room temp for 16 hr. The mixt was evapd to dryness, and the residue was crystd from BuOAc; yield 0.7 g (26%), mp 134–136°. *Anal.* ($C_{14}H_{22}N_2O_3$) C, H, N.

A soln of 10 g of crude 1 in a mixt of 594 ml of MeOH and 6 ml of NH_4OH (*d* 0.88) was passed through a column of silica gel (Kieselgel HF 254, Merck). The fraction corresponding to material of R_f 0.3 was collected and evapd. The residue was pure 1 by nmr, mp 141–142°.

(1) **Method D.**—A mixt of 109 g of 4-(2,3-epoxypropoxy)-acetanilide, 76 g of benzylisopropylamine, and 500 ml of MeOH was heated under reflux for 2 hr. The mixt was then evapd under

(2) Eraldin.

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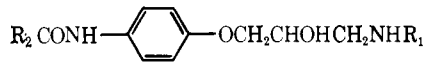
(10) All melting points were taken using open capillaries and are uncorrected.

(11) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table I

(3-Amino-2-hydroxypropoxy)acylanilides



No.	R_1	R_2	Mp, °C	Crystn solvent	Empirical formula	Analyses	Method of prepn	Dose, μg/kg, giving 50% inhibition of tachycardia	Inhibition, %, of depressor response
1	*i*-C_3H_7	CH_3	142–143	MeCOEt	$C_{14}H_{22}N_2O_3$	C, H, N	A, D	167	8
2	*tert*-C_4H_9	CH_3	126	EtOAc	$C_{15}H_{24}N_2O_3$	C, H, N	A	134	7
3		CH_3	122–124	EtOAc	$C_{16}H_{24}N_2O_3$	C, H, N	A	744	4
4	$CH(CH_3)(CH_2)_2C_6H_5$	CH_3	125	*n*-BuOAc	$C_{21}H_{28}N_2O_3$	C, H, N	A	372	30[c]
5	$CH(CH_3)CH_2C_6H_4OCH_3$-*p*	CH_3	117–118	*n*-BuOAc	$C_{21}H_{28}N_2O_4$	C, H, N	A	349	26
6	*i*-C_3H_7	$(CH_2)_4CH_3$	136–138	EtOAc	$C_{18}H_{30}N_2O_3 \cdot 0.5H_2O$	C, H, N	C	99	28[c]
7	*i*-C_3H_7	C_6H_5	172–174	*n*-PrOH–*n*-BuOAc	$C_{19}H_{24}N_2O_3 \cdot HCl$	C, H, N	A	161	0
8	*i*-C_3H_7	4-Cl-C_6H_5	178–180	*i*-PrOH	$C_{19}H_{23}ClN_2O_3$	C, H, N	C	117	0
9	*i*-C_3H_7	$C_6H_5CH_2$	138–140	EtOAc	$C_{20}H_{26}N_2O_3$	C, H, N	C	65	1
10	*i*-C_3H_7	C_2H_5O	112–113	EtOAc	$C_{15}H_{24}N_2O_4$	C, H, N	C	742	17
11[a]	*i*-C_3H_7	CH_3	99–101	*n*-BuOAc–petr ether (60–80°)	$C_{14}H_{22}N_2O_3$	C, H, N	B	804	42
12[b]	*i*-C_3H_7	CH_3	98–100	MeCOEt	$C_{14}H_{22}N_2O_3$	C, H, N	C	457	41
13	Propranolol							62	85

[a] 3-Acetylamino isomer of 1. [b] 2-Acetylamino isomer of 1. [c] With compounds **4** and **6** there was a significant fall in diastolic blood pressure which obscured any cardiospecificity.

reduced pressure to leave 4-(3-benzylisopropylamino-2-hydroxypropoxy)acetanilide (IX) as a pale yellow syrup of satisfactory purity for hydrogenolysis; tlc on silica gel (Merck, Kieselgel HF 254) in *n*-BuOH–AcOH–H_2O (8:2:1) gave R_f 0.15 and with NH_4OH (SG 0.89)–MeOH (1:99) R_f 0.7.

A mixt of 103 g of IX, 5 g of 5% Pd/C, and 300 ml of EtOH was hydrogenated at 133.6–123 kg/cm² in a Bergius converter at 27–35° for 16 hr. The mixt was then filtered through Kieselguhr, and the filtrate was evapd under reduced pressure. The residue was stirred with 300 ml of EtCOMe for 10 min and then filtered. The solid residue was dissolved in 150 ml of 1 *N* HCl and stirred with DY3 carbon for 30 min. The mixt was filtered, and the filtrate was basified with 75 ml of 10 *N* NaOH at 0–10°. The pptd product was filtered, and the solid residue was washed with H_2O, dried, and crystd from 350 ml of EtCOMe to give I; yield 16.7 g (27%), mp 142.2–142.8°. *Anal.* ($C_{14}H_{22}N_2O_3$) C, H, N.

3-(3-Chloro-2-hydroxypropoxy)acetanilide.—A mixt of 4.5 g of 3-acetamidophenol, 4.5 ml of epichlorohydrin, and 0.03 ml of piperidine was heated at 90° for 6 hr. It was then evapd to dryness and used without purification in the prepn of 11.

3-(2-Hydroxy-3-isopropylaminopropoxy)acetanilide (11). Method B.—A mixt of 7.2 g of 3-(3-chloro-2-hydroxypropoxy)-acetanilide and 20 ml of *i*-$PrNH_2$ was heated in a sealed tube for 10 hr at 100°. It was evapd to dryness, and the residue was dissolved in 50 ml of 2 *N* HCl. The soln so formed was C treated and filtered. The filtrate was basified with 2 *N* NaOH and extd with 50 ml of EtOAc. The dried ext ($MgSO_4$) was evapd to dryness, and the residue was crystd from EtOAc; yield 0.8 g (10%), mp 99–101°. *Anal.* ($C_{14}H_{22}N_2O_3$) C, H, N.

1-(Benzylisopropylamino)-3-(4-nitrophenoxy)-2-propanol·HCl.—A mixt of 21 g of 1-(4-nitrophenoxy)-2,3-epoxypropane[12] and 14.9 g of benzylisopropylamine was heated at 100° for 2 hr. The mixt was dissolved in 100 ml of EtOAc and acidified with ethereal HCl. It was filtered, and the solid residue was washed with EtOAc; yield 23.8 g (63%), mp 147–148°. *Anal.* ($C_{19}H_{24}N_2O_4 \cdot HCl \cdot 0.25H_2O$) C, H, N.

1-(4-Aminophenoxy)-3-benzylisopropylamino-2-propanol (V).—A mixt of 30.0 g of Fe powder, 120 ml of EtOH, and 0.5 ml of 11 *N* HCl was stirred rapidly under reflux. There was then added, portionwise, 11.4 g of 1-(benzylisopropylamino)-3-(4-nitrophenoxy)-2-propanol·HCl. The mixt was stirred and heated under reflux for 4 hr, 0.5 ml of 11 *N* HCl being added after the first hr. After 4 hr, 4 ml of 11 *N* NaOH was added, and the hot mixt was filtered. The filtrate was evapd to dryness, and the residue was distd; yield, 5.25 g (58%), bp 198–200° (0.15 mm). *Anal.* ($C_{19}H_{26}N_2O_2$) C, H, N.

1-(4-Ethoxycarbonylaminophenoxy)-3-isopropylamino-2-propanol (10). Method C.—To a stirred soln of 3.1 g of V in 50 ml of dry Et_2O there was added, at ambient temp, a mixt of 1 ml of ethyl chloroformate in 25 ml of dry Et_2O. The mixt was stirred for 1 hr at 20°, and the ethereal layer was decanted. The residue was dissolved in 50 ml of EtOH and hydrogenated in the presence of 0.4 g of 5% Pd/C, at atmospheric pressure and ambient temp. The mixt was filtered, and the filtrate was evapd to dryness. The residual solid was stirred with 1 *N* NaOH and EtOAc. The EtOAc ext was dried and evapd, and the residue was crystd from EtOAc; yield 0.35 g (12%), mp 112–113°. *Anal.* ($C_{15}H_{24}N_2O_4$) C, H, N.

Acknowledgment.—We are indebted to Professor A. M. Barrett, Mr. D. Dunlop, and Dr. R. G. Shanks for providing the biological data.

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