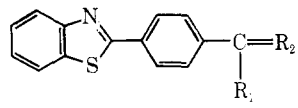
TABLE IV



No.	R_1	R_2	Mp, °C	Crystn	Formula[c]
32[a]	Me	O	179–181	EtOAc	$C_{15}H_{11}NOS$
33[b]	Et	O	159.5–161	EtOAc	$C_{16}H_{13}NOS$
34	Me	NOH	238.5–240	EtOH–H_2O (1:1)	$C_{15}H_{12}N_2OS$
35	Et	NOH	189–191	EtOH	$C_{16}H_{14}N_2OS$

[a] 2,4-DNP, mp 297.5–298.5 dec (DMF). *Anal.* ($C_{21}H_{15}N_5O_4S$) C, H, N. [b] 2,4-DNP, mp 246–248° dec (DMF). *Anal.* ($C_{22}H_{17}N_5O_4S$) C, H, N. [c] All compds were analyzed for C, H, N.

lar reduction of **35** gave the *N*-Ac deriv of **2**, mp 193–193.5° (C_6H_6) [*Anal.* ($C_{18}H_{18}N_2OS$) C, H, N], and the amine·HCl **2** (Table I).

Hydrogenation of 4-(2-benzothiazolyl)phenylacetonitrile.—Similar redns gave the *N*-Ac deriv of **6**, mp 172.5–174° (C_6H_6) [*Anal.* ($C_{17}H_{16}N_2OS$) C, H, N], and thence **6** (Table I).

4-(2-Benzothiazolyl)-α-hydroxymethylbenzylamine·HCl (12) was prepd by redn of **14** with LAH in Et_2O in the usual way (Table I).

3-[4-(2-Benzothiazolyl)phenyl]propionitrile was prepd from **27** by heating with NaCN (1.1 equiv) in DMSO at 95° for 2 hr. Diln with H_2O, gave a solid (100%), mp 110–113°. The pure nitrile had mp 113–114° (*i*-PrOH). *Anal.* ($C_{16}H_{12}N_2S$) C, H, N.

Ethyl 3-[4-(2-benzothiazolyl)phenyl]propionate was prepd by refluxing the above compd (3.35 g) in EtOH (75 ml) contg H_2SO_4 (concd, 18 ml), for 7 hr, pouring onto ice, extg with Et_2O, and evapg to give 3.85 g (98%), mp 46–47°. The pure compd had mp 48–49° (hexane). *Anal.* ($C_{18}H_{17}NO_2S$) C, H, N. Alk hydrolysis gave the acid, mp 184–187° [subl 170° (0.01 mm)]. *Anal.* ($C_{16}H_{13}NO_2S$) H, N; C: calcd, 67.8, found, 67.3.

4-(2-Benzothiazolyl)-β-methyl-β-nitrostyrene.—4-(2-Benzothiazolyl)benzaldehyde (5 g), $MeNO_2$ (50 ml), and *n*-$BuNH_2$ (10 drops) were refluxed 3 hr and cooled, and the solid (4.25 g, 69%), mp 187–189°, was collected. The pure styrene had mp 188–190.5° ($MeNO_2$). *Anal.* ($C_{16}H_{12}N_2O_2S$) C, H, N.

4-(2-Benzothiazolyl)-β-hydroxyamino-β-methylstyrene was prepd by redn of the above in EtOH contg 2 *N* HCl and 10% Pd/C at 14.06 kg/cm² for 4 hr. Filtration, evapn, neutralization, and extn with Et_2O gave the styrene, mp 182.5–183° (C_6H_6–EtOH). *Anal.* ($C_{16}H_{14}N_2OS$) C, H, N.

2-Amino-1-[4-(2-benzothiazolyl)phenyl]propane (16) prepd (63%) by redn of the above compd with LAH in Et_2O, had mp 120–120.5° (EtOAc–hexane), [*Anal.* ($C_{16}H_{16}N_2S$) C, H, N], HCl, mp 305.5–306° (MeOH–Et_2O). *Anal.* ($C_{16}H_{17}ClN_2S$) C, H, N.

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Synthesis and Norepinephrine-Depleting Activity of Some Esters of Metaraminol

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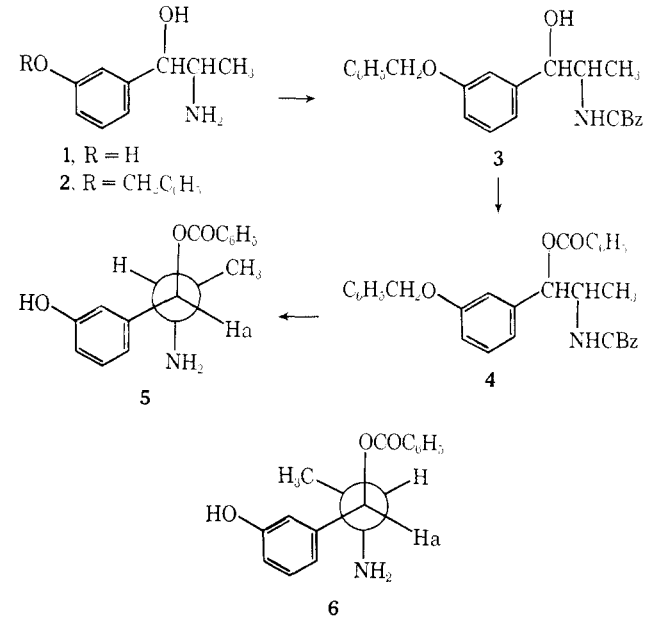
In a previous paper of this series,[2] it was reported that several ethers of the phenolic OH of metaraminol (**1**), (−)-erythro, were found to deplete the mouse heart of norepinephrine and to replace it with the substitute transmitter metaraminol.[3] Evidence was also presented showing that dealkylation of the ethers to metaraminol was necessary for norepinephrine depletion to occur. It was therefore of interest to consider other derivatives of metaraminol that would be susceptible to metabolic conversion to the phenethanolamine. In this report, we describe the synthesis and catecholamine-depleting activity of some esters of the side chain OH of metaraminol.

Chemistry.—Synthesis of the erythro benzoyl ester **5** uncontaminated by the threo isomer **6**[4] was accomplished by acylation of **3** in which the amino and phenolic OH functions of metaraminol were protected by the CBZ and benzyl ether blocking groups (Scheme I).

SCHEME I



Both protective groups were removed from **4** in one step by catalytic hydrogenation under acid conditions to give the (+)-erythro benzoyl ester **5**. The assignment of erythro stereochemistry to **5** was confirmed by nmr measurements which showed the expected erythro spin coupling constant of 4.0 Hz (at 6.20 ppm)[2,5] for the carbinol ester hydrogen H_a. Since this sequence of reactions would not be expected to affect the configuration at either of the 2 asymmetric centers in metaraminol, the (+)-erythro ester **5** has the same absolute configuration as metaraminol (α*R*, 1*S*).

The benzoyl ester **5** was also prepared by a method used for conversion of ephedrine to the corresponding benzoyl ester[8,9] (Scheme II). The (+)-threo halide[5]

(1) Deceased Oct 26, 1968.

(2) W. S. Saari, A. W. Raab, W. H. Staas, M. L. Torchiana, C. C. Porter, and C. A. Stone, *J. Med. Chem.*, **13**, 1057 (1970).

(3) For leading references to the substitute transmitter hypothesis, see: I. J. Kopin, *Annu. Rev. Pharmacol.*, **8**, 377 (1968); C. A. Stone and C. C. Porter, *Advan. Drug Res.*, **4**, 71 (1967); J. R. Crout, *Circ. Res.*, **18**, **19**, *Suppl.* **1**, 120 (1966).

(4) The threo isomers of **1** are considerably less active than metaraminol [(−)-erythro form of **1**] in depleting the mouse heart of norepinephrine.[5-7]

(5) W. S. Saari, A. W. Raab, and E. L. Engelhardt, *J. Med. Chem.*, **11**, 1115 (1968).

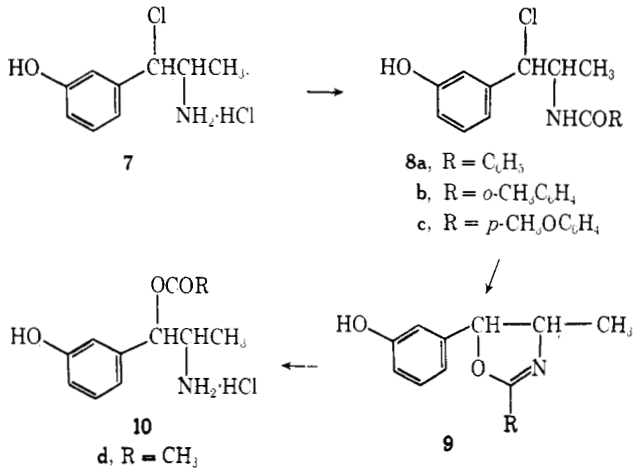
(6) M. L. Torchiana, C. C. Porter, and C. A. Stone, *Arch. Int. Pharmacodyn. Ther.*, **174**, 118 (1968).

(7) N. F. Albertson, F. C. McKay, A. E. Lape, J. O. Hoppe, W. H. Selberis, and A. Arnold, *J. Med. Chem.*, **13**, 132 (1970).

(8) L. H. Welsh, *J. Org. Chem.*, **32**, 119 (1967).

(9) H. Pfanz and H. Wieduwilt, *Arch. Pharm.*, **288**, 563 (1955).

SCHEME II



7 was converted to the benzamide **8a** and cyclized with inversion at the benzyl carbon atom to give the *cis*-oxazoline **9a**. This intermediate was not isolated in this instance but was hydrolyzed directly to the (+)-erythro benzoyl ester **10a**.[10] This product proved to be identical with that prepared by the method in Scheme I which did not involve inversion at any asymmetric center. Additional confirmation of erythro stereochemistry for this benzoyl ester was obtained by an O → N acyl migration which afforded the benzamide of metaraminol.[11]

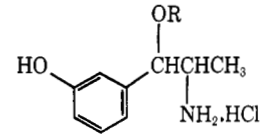
Two substituted benzoyl esters, **10b** and **10c**, were also prepared by the method in Scheme II. Although no threo isomer was detected in the *o*-methylbenzoyl ester **10b**, the *p*-methoxybenzoyl ester **10c** was found by nmr measurements to be a mixture of approximately 60% erythro and 40% threo isomers.[14] However hydrolysis of the purified intermediate *cis*-oxazoline **9c**, prepared from metaraminol and *p*-methoxybenzimidate,[15] under the same conditions used to effect rearrangement of **8c** gave only the erythro ester **10c** uncontaminated by the threo isomer. It would therefore appear that formation of the threo ester **10** from **8c** probably results from partial isomerization of the threo chloroamide prior to oxazoline formation and hydrolysis.

We have also studied the acid-induced N → O acyl migration of the benzoyl group of *N*-benzoylmetaraminol. The results parallel those reported for *N*-benzoylephedrine[8,12,13] in that both retention of configuration and inversion at the benzyl C occur to give a mixture of the erythro and threo isomers of **10a** as the HCl salts. However the pure erythro isomer can be isolated from the mixture of hydrochlorides simply by neutralization, which converts the threo ester to the threo amide by an O → N acyl transfer, and acidification to trap the remaining erythro ester **10a** as the HCl salt. This type of acyl migration, O → N, is known to be faster in the pseudoephedrine (threo) series than in the ephedrine (erythro) series.[12,13,16]

The erythro acetate **10d** was obtained by treatment of *N*-acetylmetaraminol with HCl.

Biological Results.—All of the metaraminol esters tested proved to be less potent than metaraminol in depleting the mouse heart of norepinephrine.[17] The results, summarized in Table I, also show that the structure of the acyl portion of the ester has a marked influence on catecholamine depletion. The relative importance of catecholamine depletion due to release by metaraminol formed through metabolism of the esters and that resulting from release by the esters *per se* cannot be determined from the available data.

TABLE I
NOREPINEPHRINE-DEPLETION ACTIVITY OF METARAMINOL ESTERS



No.	R	Norepinephrine depletion,[17] mouse heart, po ED_{50}, mg/kg
1	H	0.1
10d	CH_3CO	0.4
5	C_6H_5CO	1.0
10c	p-$CH_3OC_6H_4CO$	1.6
10b	o-$CH_3C_6H_4CO$	17

Iv administration of the Ac ester **10d** in doses of 0.05, 0.25, and 1.25 mg/kg to the anesthetized dog resulted in a rapid dose-dependent rise in arterial pressure.[17] At the highest dose, marked inotropic and chronotropic effects were also evident. The pattern of response was similar to that observed with metaraminol, at approximately 0.1 the dose. Under the same conditions, the aryl esters **5**, **10b**, and **10c** showed no significant pressor responses.

Experimental Section

All mp were obtained on a calibrated Thomas-Hoover Uni-Melt capillary mp app. Where analyses are indicated only by symbols of the elements, anal. results obtd for those elements were within ±0.4% of the theoretical values. Ir spectra were detd with a Perkin-Elmer Model 21 spectrophotometer, nmr spectra with a Varian A60-A spectrophotometer (Me_4Si). Spectra recorded in D_2O used the DOH band at 4.65 ppm as an internal std. Optical rotations were detd with a Zeiss photoelectric precision polarimeter. Tlc's were performed on fluorescent silica gel G plates, spots detected by uv or exposure to I_2 vapor.

(αR,1S)-m-Benzyloxy-α-[1-*N*-carbobenzyloxyaminoethyl]-benzyl Alcohol (3).—A 10% NaOH soln was added dropwise to a cold, stirred mixt of 30.0 g (0.0803 mole) of the hydrogen maleate salt of (αR,1S)-α-(1-aminoethyl)-*m*-benzyloxybenzyl alcohol,[2] 300 ml of H_2O, and 300 ml of Me_2CO until the pH of the soln remained at 8.5 or higher. Carbobenzyloxy chloride, 15.3 g (0.090 mole), was added dropwise over 40 min to the slightly basic soln of the amino alcohol cooled to ice bath temp accompanied by a simultaneous addn of 10% NaOH to maintain a pH of 8.0–8.5. After addn was complete, the reaction mixt was stirred at ice bath temp 2.5 hr before 6 *N* HCl was added to adjust

(10) Synthesis of the erythro benzoyl ester **5** by hydrolysis of the *cis*-oxazoline has been reported by the Sterling–Winthrop group.[7]

(11) This type of O → N acyl migration has been shown to proceed with retention of configuration.[12,13]

(12) D. J. Cram in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 293–294.

(13) L. H. Welsh, *J. Amer. Chem. Soc.*, **69**, 128 (1947).

(14) Estimated by relative nmr integration values for the erythro carbinol H_a proton doublet (see formula **5**) centered at 6.19 ppm and threo H_a proton doublet (see formula **6**) centered at 6.00 ppm.

(15) Synthesis of 2-oxazolines from amino alcohols by this method is known to proceed with retention of configuration: W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, **72**, 2187 (1950).

(16) This difference in the rates of acyl migration has been attributed to differences in steric repulsions between the Me and Ph groups of the erythro and threo isomers in the transition states.[12,13]

(17) Testing procedures are described in an earlier report.[2]

the pH to 2.0. The product was filtered and recrystd from EtOAc–petr ether (bp 30–60°) to give 15.2 g (48.4%) of product, mp 114–116°. Recrystn from C_6H_6–petr ether gave an analytical sample, mp 116–117°. *Anal.* ($C_{24}H_{25}NO_4$) H, N. Calcd C, 73.63; found C, 74.05.

(αR,1*S*)- or (+)-*erythro*-α-(1-Benzamidoethyl)-*m*-hydroxybenzyl Alcohol.—To a stirred soln of 37.5 g (0.118 mole) of (αR,1*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (+)-hydrogen tartrate (metaraminol bitartrate) in 375 ml of H_2O, cooled to 5°, were added 97.5 g of $NaHCO_3$ and 56.4 g (0.25 mole) of Bz_2O. The reaction mixt was stirred at 20–25° for 20 hr and then extd with two 200-ml portions of EtOAc. After concg the org ext under reduced pressure, the residue was dissolved in a mixt of 200 ml of CH_3OH and 100 ml of 10% NaOH and stirred at room temp for 20 hr. The soln was acidified with 6 *N* HCl, and the product was extd quickly into two 200-ml portions of EtOAc which were then washed ($NaHCO_3$, H_2O), dried (Na_2SO_4), filtered, and concd. The residue was recrystd from EtOH–C_6H_6 to give 20.7 g (64.7%) of the benzamide: mp 123–126°; homogeneous on tlc, 5% MeOH–$CHCl_3$. An anal. sample, mp 126.6–128.6°, $[\alpha]^{25}D$ + 42.8° (*c* 2, MeOH), was obtd by recrystn from EtOAc–hexane. *Anal.* ($C_{16}H_{17}NO_3$) C, H, N.

(αR,1*S*)- or (+)-*erythro*-α-(1-Aminoethyl-*m*-hydroxybenzyl Benzoate Hydrochloride (5). Method A. From (αR,1*S*)-*m*-Benzyloxy-α-[1-*N*-carbobenzyloxyaminoethyl]benzyl Alcohol (3).—BzCl (1.9 g, 0.0135 mole) in 50 ml of anhyd pyridine was added slowly to a stirred soln of 5.0 g (0.0128 mole) of the *N*-CBZ deriv of the (−)-erythro benzyl ether of metaraminol in 100 ml of pyridine at 100°. After addn was complete, the reaction mixt was stirred at 100° for an addnl hr and then allowed to cool to room temp over 18 hr. Pyridine was removed under reduced pressure, and the residual oil was dissolved in 200 ml of EtOAc. The soln was washed with 200 ml of H_2O contg 1 ml of 6 *N* HCl, and the aq layer was reextd with EtOAc. The combined EtOAc ext were dried (Na_2SO_4) and concd under reduced pressure to give the crude Bz ester with the benzyl and CBZ-protecting groups intact. Both protecting groups were removed by hydrogenation with 0.8 g of catalyst (10% Pd/C) in 200 ml of EtOH containing 12 ml of 6 *N* HCl at room temp and atm pressure. After absorption of H_2 was complete, the catalyst was filtered and the filtrate concd under reduced pressure to give a solid. Recrystn from EtOH–Et_2O gave 1.8 g (45.7%) of the (+)-erythro benzoyl ester·HCl: mp 241.3–242.3° dec; $[\alpha]^{25}D$ + 81.7° (*c* 2, MeOH);[18] tlc (10% EtOH–PhH) homogeneous; ir (KBr) 1720 cm^{-1} (ester CO); nmr (D_2O) δ1.42 (3, d, CH_3, *J* = 7 Hz), 3.7–4.2 (1, m, CHN), 6.20 (1, d, CHO, *J* = 4 Hz), 6.8–7.6 (7, m, arom CH), 8.0–8.2 (2, m, *o*-H in C_6H_5CO). *Anal.* ($C_{16}H_{17}NO_3$·HCl) C, H, N.

Method B. From (+)-*threo*-3-(2-Amino-1-chloropropyl)-phenol·HCl·H_2O (7).—A soln of 6.3 g of anhyd $NaHCO_3$ in 25 ml of H_2O was added slowly to a well-stirred mixt of 3.36 g (0.0140 mole) of (+)-*threo*-3-(2-amino-1-chloropropyl)phenol·HCl·H_2O[5] and 2.12 g (0.0151 mole) of BzCl in 25 ml of EtOAc. After addn was complete, the mixt was stirred at room temp for 10 min. The EtOAc soln was then sepd, and the aq layer was extd with EtOAc (2 × 50 ml). The combined org ext were dried (Na_2SO_4), filtered, and concd at 60° under reduced pressure to give 4.3 g of the intermediate benzamide as an oil, homogeneous upon tlc (10% MeOH–$CHCl_3$). A soln of the oil in 50 ml of 7 *N* HCl in anhyd EtOH was stirred at reflux for 6 hr and then overnight at room temp. The ppt was removed and dried to give 1.65 g (38.3%) of the (+)-erythro benzoate·HCl, mp 238.3–241.3° dec, $[\alpha]^{25}D$ + 80.9° (*c* 2, MeOH). This product was identical with that obtd in method A as detd by mmp, ir, and nmr.

Method C. From (αR,1*S*)-α-(1-Benzamidoethyl)-*m*-hydroxybenzyl Alcohol.—A mixt of 3.25 g (0.012 mole) of the (+)-erythro benzamide of metaraminol and 2.0 ml of concd HCl in 50 ml of EtOH was refluxed for 4 hr. After concg under reduced pressure, the residual solid was twice dissolved in 25 ml of MeOH and 10 ml of PhH and concd. Recrystn first from *i*-PrOH then from MeOH–Me_2CO–Et_2O gave 2.65 g (72%) of a mixt of erythro and threo ester hydrochlorides, mp 210.5–212.5° dec. Further recrystn from MeOH–Me_2CO–Et_2O gave an anal. sample, mp unchanged, which contd approx 35% of the threo benzoate. The ratio of erythro and threo esters was detd by the relative intensities in the nmr (D_2O) of the erythro carbinol proton signal at 6.19 ppm (*J* = 4 Hz) and the threo carbinol proton signal at 6.0 ppm (*J* = 8 Hz). *Anal.* ($C_{16}H_{17}NO_3$·HCl) C, H, N, Cl.

(18) Reported[7] mp 244–245° dec, $[\alpha]^{25}D$ + 83.5° (*c* 1, MeOH).

In another experiment, the crude product obtd from a similar acid treatment of 2.7 g (9.96 mmoles) of the (+)-erythro benzamide was shaken with excess Na_2CO_3 soln and 50 ml of EtOAc. After a second extrn of the aq layer with 50 ml of fresh EtOAc, the org ext were combined, dried (Na_2SO_4), filtered, and allowed to stand at room temp for 20 hr. A small amt of insol solid was removed by filtration and excess EtOH–anhyd HCl soln was added to the filtrate to ppt 0.50 g (16.3%) of the (+)-erythro benzoyl ester·HCl, mp 231.5–235.5° dec. This sample was identical with the product of method A as judged by ir (KBr) and nmr (D_2O). Presence of the threo isomer could not be detected by nmr. Recrystn from EtOH–Et_2O gave product (80% recovery) with a constant mp of 239.5–241.5° dec.

(αR,1*S*)- or (+)-*erythro*-α-(1-Aminoethyl)-*m*-hydroxybenzyl *o*-Methylbenzoate Hydrochloride (10b).—The intermediate *o*-methylbenzamide, 5.8 g, was prepd from 7.94 g of $NaHCO_3$, 3.5 g (0.0146 mole) of (+)-*threo*-3-(2-amino-1-chloropropyl)phenol·HCl·H_2O, and 4.9 g (0.0317 mole) of *o*-methylbenzoyl chloride following method B for the prepn of the unsubstituted Bz ester. This benzamide, without further purification, was dissolved in 60 ml of abs EtOH, 7 *N* in anhyd HCl, containing 10 drops of H_2O and heated at reflux for 30 hr. Solvent was removed at 75° under reduced pressure and the solid residue recrystd from MeOH–EtOAc to give 0.58 g (12.3%) of the (+)-erythro ester·HCl, mp 221–224° dec. Further recrystn gave an anal. sample: mp 226.8–228.8° dec; $[\alpha]^{25}D$ +45.0° (*c* 2, MeOH); nmr (DMSO-d_6) 6.16 ppm (1, d, CHO, *J* = 2.5 Hz). *Anal.* ($C_{17}H_{19}NO_3$·HCl) C, H, N.

(4*S*,5*R*)- or (−)-*cis*-*m*-(2-(4-Methoxyphenyl)-4-methyl-2-oxazolin-5-yl)phenol (9c).—A mixt of 650 mg (3.63 mmoles) of ethyl *p*-methoxybenzimidate[19] and 600 mg (3.61 mmoles) of metaraminol base was heated on a steam bath under 50–100 mm vacuum for 5 hr. The residue was crystd from EtOAc–hexane to give 0.5 g (49.0%) of the oxazoline, mp 138.5–142.5°. Further recrystn from EtOAc–hexane gave an anal. sample: mp 141.0–143.0°; $[\alpha]^{25}D$ − 304.4° (*c* 2, MeOH). *Anal.* ($C_{17}H_{17}NO_3$) C, H, N.

(1*S*,2*S*)- or (+)-*threo*-3-(2-(4-Methoxybenzamido)-1-chloropropyl)phenol (8c).—A soln of $NaHCO_3$ (6.35 g) in 50 ml of H_2O was added dropwise to a well-stirred mixt of 2.8 g (11.7 mmoles) of (+)-*threo*-3-(2-amino-1-chloropropyl)phenol·HCl·H_2O[5] and 4.4 g (26 mmoles) of *p*-methoxybenzoyl chloride in 50 ml of EtOAc. After addn was complete, the reaction mixt was stirred at room temp for an addnl 30 min. The EtOAc layer was sepd and treated with hexane to ppt the product. Recrystn from EtOAc–hexane gave 3.3 g (88.2%) of the amide, mp 149.0–152.0°. Further recrystn gave an anal. sample: mp 151.4–153.9°, $[\alpha]^{25}D$ + 102.4° (*c* 2, Me_2CO). *Anal.* ($C_{17}H_{18}ClNO_3$) C, H, N.

(αR,1*S*)- or (+)-*erythro*-α-(1-Aminoethyl)-*m*-hydroxybenzyl *p*-Methoxybenzoate Hydrochloride (10c). Method A. From (−)-*cis*-*m*-(2-(4-Methoxyphenyl)-4-methyl-2-oxazolin-5-yl)-phenol (9c).—A mixt of 250 mg (0.882 mmole) of the oxazoline and 7 ml of 2 *N* HCl was heated under reflux for 20 min. The clear soln was cooled to ppt 150 mg (50.3%) of the erythro *p*-methoxybenzoyl ester·HCl, mp 222–227.0° dec, uncontaminated by the threo isomer (nmr). Recrystn from EtOH–EtOAc gave an anal. sample: mp 232.4–236.4° dec; $[\alpha]^{25}D$ + 115.9° (*c* 2 MeOH); nmr (D_2O) δ 6.03 (1, d, CHO, *J* = 4.0 Hz), 1.33 (3, d, CH_3, *J* = 6.0 Hz); ir (KBr) 1715 cm^{-1} (ester C=O). *Anal.* ($C_{17}H_{19}NO_4$·HCl) C, H, N.

The *p*-methoxybenzoyl ester could also be obtd by hydrolysis of the *cis*-oxazoline under the condns of method B. In this case, examination of the total reaction product by nmr revealed that no detectable amount of the threo isomer was present.

Method B. From (+)-*threo*-3-[2-(4-Methoxybenzamido)-1-chloropropyl]phenol (8c).—A soln of 1.0 g (3.13 mmoles) of the chloroamide in 50 ml of abs EtOH, 7.6 *N* in anhyd HCl, and 10 drops of H_2O was stirred at reflux for 6 hr and then at room temp overnight. After concg under reduced pressure, the residue was recrystd from EtOH–EtOAc to give 0.40 g (37.7%) of product: mp 220–224° dec, as an approx 60% erythro–40% threo mixt of isomers; nmr (D_2O) δ 6.19 (d, erythro CHO, *J* = 4 Hz), 6.00 (d, threo CHO, *J* = 8 Hz), 1.35 (t, overlapping erythro and *threo* CH_3C, *J* = 5–6 Hz). *Anal.* ($C_{17}H_{19}NO_4$·HCl) C, H, N.

A mixt of erythro and threo isomers was also obtd when the rearrangement was carried out in 2 *N* HCl at reflux for 45 min.

Rearrangement of (αR,1*S*)-α-(1-Aminoethyl)-*m*-hydroxybenzyl Benzoate Hydrochloride (5) to (αR,1*S*)-α-(1-Benzamido-

(19) R. H. DeWolfe and F. B. Augustine, *J. Org. Chem.*, **30**, 699 (1965).

ethyl)-*m*-hydroxybenzyl Alcohol.—A soln of 0.50 g (1.62 mmoles) of the (+)-erythro benzoate·HCl in 50 ml of 10% NaOH soln was stirred at room temp for 1 hr, cooled in an ice–NaCl bath, and acidified with concd HCl. The ppt was filtered and dried to give 0.20 g (45.5%) of the benzamide of metaraminol: mp 125.5–127.0°, softens at 123.0°; identical with an authentic sample prepd from metaraminol by mmp, tlc (10% EtOH–PhH), ir, and nmr.

(αR,1*S*)- or (−)-*erythro*-α-(1-Aminoethyl-*m*-hydroxybenzyl Acetate (10d).—A soln of 5.3 g (0.025 mole) of (αR,1*S*)-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol in 3.8 ml of concd HCl and 150 ml of EtOH was heated at reflux for 1 hr. After concg reduced pressure, the residue was mixed with 100 ml of 50% C_6H_6–EtOH and reconcd. This process was repeated 4 times before the residue was dissolved in THF, filtered through a charcoal pad, and dild with Et_2O to give an oil. Since the oil failed to cryst from various solvents, it was dried under high vacuum to give the (−)-erythro acetate as a glass: mp 102° dec, sinters at 90°, $[\alpha]^{25}D$ − 34.5° (*c* 2, MeOH); nmr (D_2O), δ 1.28 (3, d, CH_3, J = 7 Hz), 2.27 (3, s, CH_3CO) 3.5–4.1 (1, m, CHN), 5.87 (1, d, CHO, J = 4 Hz), 6.8–7.5 (4, m, aromatic CH), weak absorption at δ 1.20 (d), 2.23 (s), 4.95 (d). *Anal.* ($C_{11}H_{15}NO_3$·HCl·0.25H_2O) C, H, N.

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Synthesis, Transformation, and General Pharmacologic Activity in 1,4-Benzodiazepine-3,5-diones[1]

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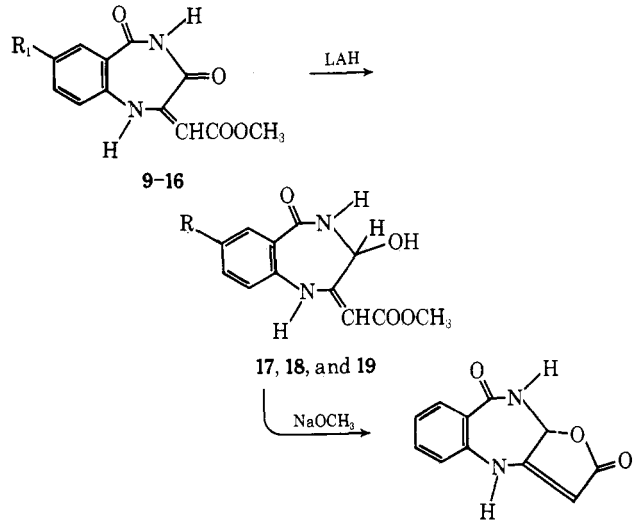
Although impressive potency was observed in 1,4-benzodiazepines possessing a lactam linkage[2] no syntheses or pharmacology have been reported for imide analogs. The original multistep synthesis of such 1,4-benzodiazepin-3,5-diones by Gartner[3] preceded any medicinal interest in the family and its complexity precludes its utility as a routine synthesis of this class. We have recently reported a facile direct cyclization of anthranilamide adducts of dimethyl acetylenedicarboxylate as a route to 2-carbomethoxymethylene-2*H*-1,4-benzodiazepin-3,5(1*H*,4*H*)-diones.[4] Herein we report an extension of this synthesis (**9**–**16**), some related transformations of the ring functions, and our results on the biological evaluation of this new class.

Hydride reduction, by inverse addition, reduced 3 of the benzodiazepinediones, (**9**, **11**, **12**) to their corresponding 3-OH analogs. Structural characterization of this hydroxybenzodiazepinone system has been reported elsewhere.[4] Treatment of the OH compound **17** with alcoholic alkoxide resulted in lactonization.



Biological Results.—The benzodiazepinediones (**10**–**16**) were tested in nonfasted albino rats (180–210 g), and the results were analyzed according to the methods of Malone and Carrano.[5] In general, all compds were nontoxic with no deaths observed up to 1000 mg/kg ip, except with **16** where death was observed at 1000 mg/kg at 48 hr postinjection. Compd **12** was tested only as high as 562 mg/kg and at this dosage showed some CNS depression which included decreased motor activity and body tone. Compd **14** was tested only at a maximum dose of 316 mg/kg.

Evaluation of **10**, **11**, **13**, **14**, **15**, and **16** in a CNS profile[6] resulted in no outstanding effects on pentylenetetrazole, strychnine, or maximal electroshock-induced convulsions. There was measurable, but not outstanding, antioxotremorine effects with all these compds at 200 mg/kg ip. Compd **10** did show a slight increase in hexobarbital sleep time and a slight protection of ACh writhing. In an anesthetized cat, **10** caused a fall in arterial blood pressure at 1–5 mg/kg iv, and potentiated the blood pressure response of norepinephrine and dimethylphenylpiperazinium (DMPP) at 1 and 25 mg/kg iv. Compd **11**, administered at 50 mg/kg ip, displayed no significant effects in the anesthetized cat. Compds **11**, **13**, **14**, and **16** showed a depression of weight gain which could indicate anorexigenic activity since the effect was delayed (*i.e.*, 24–48 hr postinjection) and no diarrhea or excessive urination was noted.

Compds **11** and **16** were tested in the isolated guinea pig ileum and had no outstanding effects at 10^{-4} *M* on the responses to ACh, histamine, serotonin, nicotine, or $BaCl_2$. Compds **11**, **14**, and **15** were tested in a combined antiinflammatory and analgetic test according

(1) Taken in part from the Ph.D. Thesis of T. F. L. (1968) and W. P. F. (1971) and the B.S. Honors thesis of H. W. S. (1970).

(2) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, "Drugs Affecting the Central Nervous System," A. Burger, Ed., M. Dekker, New York, N. Y., 1968, p 237.

(3) S. Gartner, *Justus Liebigs Ann. Chem.*, **332**, 226 (1904).

(4) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

(5) M. H. Malone and R. A. Carrano, "Hippocratic and Pharmacodynamic Screening," American Pharmaceutical Association Academy of Pharmaceutical Sciences, Symposium on Advances in Screening Methodology, Washington, D. C., November 1968.

(6) N. D. Heindel, W. P. Fives, T. F. Lemke, and R. A. Carrano, *J. Pharm. Sci.*, **60**, 703 (1971).