4-Phenyl-4-oxazolin-2-one (11), Structure Proof.§ A. The nmr spectrum ($CDCl_3$) showed singlet at δ 7.05 (1 H), complex multiplet centered at 7.36 (6 H), broad singlet at 10.94 (1 H, N-bond proton); Ir spectrum showed 3.15 μ (NH group), 5.73 (=C=O in 5-membered ring).

B. **$NaBH_4$ Reduction.** To a soln of 11 (500 mg) in 95% EtOH (10 ml), cooled at 0–5°, was added a soln of $NaBH_4$ (250 mg) in H_2O (2.0 ml). The mixt was allowed to stand 1 hr at room temp, then was dild with H_2O, made slightly acidic with 10% H_2SO_4, and extd with Et_2O. Evapn of the dried ($MgSO_4$) ext gave a residue which was crystd from PhH to afford **4-phenyloxazolidin-2-one** (VIII, 200 mg, 40%), identical with an authentic sample.[11]

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§ A literature reference[10] indicated for a compd, mp 175–177°, either structure 11 or the isomeric structure of 5-phenyl-4-oxazolin-2-one. The hypothesis was also advanced that the compd might be a constant-melting mixt of the two isomers. A sample of the product, kindly supplied by Professor Huisgen, gave on tlc a single spot and did not show in its ir spectrum some absorption bands peculiar to 11. On this evidence, the compd melting at 175–177°, for whose prepn we refer to Professor Huisgen's paper, should be assigned the structure of 5-phenyl-4-oxazolin-2-one.

Derivatives of 4,5-Dihydro-1,3,dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine with Antiinflammatory Activity

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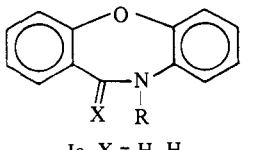
A new heterocyclic system, 4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine, was synthesized, and a number of derivatives were screened for antiinflammatory action. Two members of the series are compared to phenylbutazone in test models.

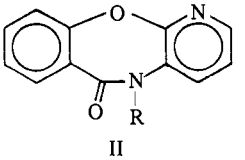
During the past several years, tricyclic systems containing the oxazepine ring have been reported to have antipyretic and antiphlogistic activity. Coyne and Cusic[1] ascribed these properties to a number of dialkylaminoalkylurea derivatives of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine (Ia). Derivatives of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (Ib), are the subject of a patent[2] with antiphlogistic claims. The 5,6-dihydropyrido[2,3-*b*][1,4]benzoxazepin-6(5*H*)-one ring system (II)[3] has also been reported to possess this type of pharmacological activity.

In an attempt to enhance this activity, we prepared the title compounds (III) incorporating the pyrazole nucleus, since the latter is present in many drugs used to treat arthritic conditions. Compd **30**, Table III, is of sufficient interest to warrant clinical evaluation. These compounds were easily prepared following analogous procedures once an adequate supply of 5-chloro-1,3-dimethyl-4-nitropyrazole was available.

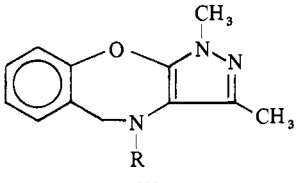
This chemical was first described by Musante,[4] but the method was impractical for the preparation of large quantities, and the product was thought to be contaminated with an isomer. A more convenient method was described by Geiszler[5] through low temperature nitration of 5-chloro-1,3-dimethylpyrazole.



Ia, X = H, H
b, X = O

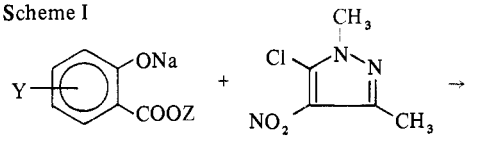


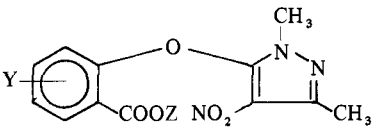
II



III

Scheme I





1. $Ni-H_2$
2. Δ, xylene

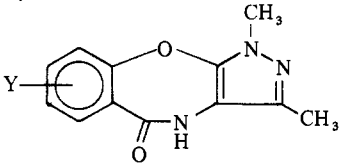
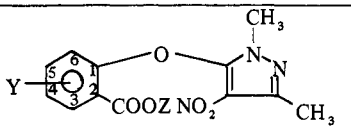
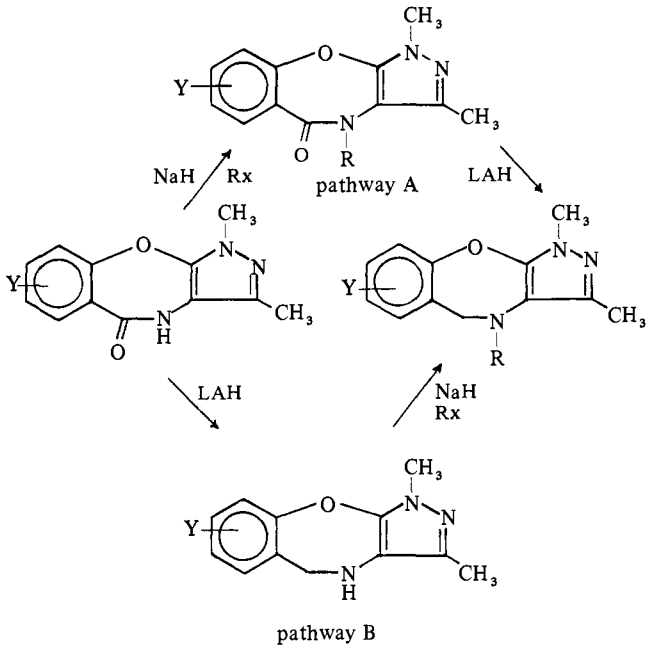


Table I. Nitro Esters and Acid

No.	Y	Z	Mp,[a] °C	Yield, %	Crystn solvent	Formula[b]
						
1	H	H	184–186	62	EtOH-H_2O	$C_{12}H_{11}N_3O_5$
2	4-Br	CH_3	124–125	57	MeOH	$C_{13}H_{12}BrN_3O_5$
3	4-Cl	CH_3	107–108	68	MeOH	$C_{13}H_{12}ClN_3O_5$
4	4-I	CH_3	136–137	69	MeOH	$C_{13}H_{12}IN_3O_5$
5	H	CH_3	92–93	71	MeOH	$C_{13}H_{13}N_3O_5$
6	H	C_2H_5	74–75	78	MeOH	$C_{14}H_{15}N_3O_5$
7	6-CH_3	CH_3	135–137	72	MeOH	$C_{14}H_{15}N_3O_5$
8	5-OC_2H_5	C_2H_5	111–112	65	EtOH	$C_{15}H_{19}N_3O_6$

[a] All melting points were uncorrected. [b] Anal. for C, H, N.

Scheme II



The synthetic scheme used is outlined in Schemes I and II. Condensation of 5-chloro-1,3-dimethyl-4-nitropyrazole with the Na salts of methyl or ethyl salicylates produced good yields of the corresponding ether derivatives (Table I).

The nitro ethers were then reduced in methyl Cellosolve with Ra Ni catalyst. As a general rule these amino ethers were not isolated, but converted directly to the cyclized product by refluxing in xylene, using catalytic amounts of *p*-TsOH. The physical properties of the lactams are given in Table II.

Two methods of preparing the alkylated oxazepines were investigated (Scheme II). Pathway A, wherein the lactam was alkylated prior to reduction with LAH proved unsatisfactory. LAH, in spite of a variety of reaction conditions, gave rise to several ring-opened products. Fortunately, the unalkylated lactam could be reduced with LAH without ring fission, and the resulting amine alkylated without difficulty. Therefore, pathway **B** was used to give the alkylated products shown in Table III.

The urea derivatives of amine (**30**) were prepared either from reactions with isocyanates or *via* the carbamoyl chloride (**31**).

Acylated products of (**30**) appearing in Table III were prepared by methods described in the Experimental Section.

Biological Activity. Preliminary biological tests for antiedema activity were run orally on groups of 6 male Sprague-Dawley rats, using a modification of the method described by Winter *et al.*[6] Antipyretic activity was assessed in rats made febrile with im injections of Brewer's yeast. Rectal temps were taken at hourly intervals for 3 hr after oral medication. Both analgetic activity and effects on vascular permeability were measured by a modification of the AcOH injection (ip) method of Whittle.[7] These findings were related to the mouse acute oral LD_{50} finding. Results of these studies are shown in Table IV.

Structure–Activity Relationships. In reviewing the pharmacological data generated by the 40 tricyclic compds described in Tables II and III, some general observations can be made. Y should be H. Other substituents placed in the 7, 8, and 9 positions completely eliminated activity. Keeping Y = H, compds possessing the largest therapeutic index were **11** and **30** where R = H. When substituents were made on the 4 position, R = propargyl seemed optimum. Compds **18** and **40** were of the same order of activity as **11** and **30**, but were slightly more toxic. Other compds of minimum activity were **19**, **28**, **33**, and **36**.

Experimental Section†

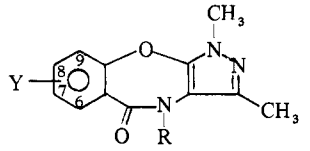
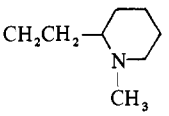
5-(2-Carbomethoxyphenoxy)-1,3-dimethyl-4-nitropyrazole (5). A soln of 45.6 g (0.30 mole) of methyl salicylate in 50 ml of dioxane was added dropwise to a stirred mixt of 400 ml of dioxane and 7.2 g (0.30 mole) of NaH. After the addn was complete, the mixt was stirred 3 hr at 80°. While maintg the temp at 80°, 52.5 g (0.30 mole) of 5-chloro-1,3-dimethyl-4-nitropyrazole in 150 ml of dioxane was added dropwise. The mixt was stirred for an addl 3 hr at this temp and filtered, and the solvent removed *in vacuo*. The residual oil solidified and the crude product crystd from MeOH to give 62 g (71%) of desired product. Compds **3** through **8** were prepd in a similar manner using the appropriate salicylate.

***o*-Carboxyphenoxy-1,3-dimethyl-4-nitropyrazole (1).** A mixt of 15 g (0.041 mole) of ester 5 and 300 ml of 10% HCl was stirred and heated on a steam bath for 6 hr. It was poured into 600 ml of H_2O, and the ppt was collected and washed with H_2O. Crystn (EtOH-H_2O) gave 7 g (62%).

4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepin-4(*H*)5-one (11). Compd 5 (29.1 g, 0.10 mole) and 6 g of Ra Ni catalyst were suspended in 250 ml of ethoxyethanol and hydrogenated at 2.8 kg/cm^2; 3 equiv of H_2 was absorbed. The catalyst was removed by filtration and washed with EtOH. The filtrate was concd *in vacuo* to give 4-amino-5-(2-carbomethoxyphenoxy)-1,3-dimethylpyrazole as a red viscous oil. The oil was dissolved in 500 ml

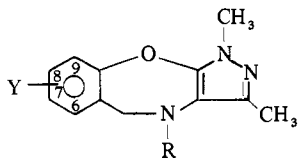
†Melting points were taken on a Fischer-Johns apparatus and are uncorrected. Analytical results for elements indicated were within ±0.4% of the theoretical values.

Table II. Derivatives of 4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepin-5(4*H*)-one

No.	Y	R	Mp[a] or bp (mm), °C	Yield, %	Crystn solvent	Formula[b]
						
9	7-Br	H	270–271	43	DMF–H_2O	$C_{12}H_{10}BrN_3O_2$
10	7-Cl	H	264–265	48	DMF–H_2O	$C_{12}H_{10}ClN_3O_2$
11	H	H	219–220	59	EtOH–H_2O	$C_{12}H_{11}N_3O_2$
12	H	CH_3	195 (1.7)	62		$C_{13}H_{13}N_3O_2$
13	9-OCH_3	H	223–224	68	EtOH	$C_{13}H_{13}N_3O_2$
14	H	CH_2COOH	264–265	47	DMF–H_2O	$C_{14}H_{13}N_3O_4$
15	H	CH_2CONH_2	256–258	39	DMF–H_2O	$C_{14}H_{14}N_4O_3$
16	8-OC_2H_5	H	207–208	41	EtOH–H_2O	$C_{14}H_{15}N_3O_3$
17	7-Cl	$CH_2C{\equiv}CH$	141–142	65	EtOH	$C_{15}H_{12}ClN_3O_2$
18	H	$CH_2C{\equiv}CH$	127–128	67	EtOH	$C_{15}H_{13}N_3O_2$
19	H	$CH_2CH{=}CH_2$	59–60	32	Et_2O–pentane	$C_{15}H_{15}N_3O_2$
20	H	$(CH_2)_3OH$	143–145	18	EtOAc–pentane	$C_{15}H_{17}N_3O_3$
21	9-CH_3	$CH_2C{\equiv}CH$	127–128	53	EtOH	$C_{16}H_{15}N_3O_2$
22	H	$CH_2C{\equiv}CCH_3$	92–93	80	C_6H_6–pentane	$C_{16}H_{15}N_3O_2$
23	H	$CH_2COOC_2H_5$	155–156	66	EtOH	$C_{16}H_{17}N_3O_4$
24	8-OC_2H_5	$CH_2C{\equiv}CH$	135–136	71	EtOH	$C_{17}H_{17}N_3O_3$
25	H	$(CH_2)_3N(CH_3)_2$	98–100[c]	51	Me_2CO	$C_{17}H_{22}N_2O_2 \cdot H_2O \cdot HCl$
26	H	$CH_2C_6H_5$	139–140	79	C_6H_6	$C_{19}H_{17}N_3O_2$
27	7-Cl		Oil	32		$C_{20}H_{25}ClN_4O_2$
28	H		120–122[c]	54	Me_2CO	$C_{20}H_{26}N_4O_2 \cdot HCl \cdot 2H_2O$
29	9-CH_3		Oil	42		$C_{21}H_{28}N_4O_2$

[a]All melting points were uncorrected. [b]Anal. for C, H, N. [c]Characterized as HCl salts which contained H_2O of hydration.

Table III. Derivatives of 4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine

No.	Y	R	Mp,[a] °C	Yield, %	Crystn solvent	Formula[b]
						
30	H	H	218–220[c]	78	EtOH	$C_{12}H_{13}N_3O \cdot HCl$
31	H	COCl	127–129	43	EtOAc	$C_{13}H_{12}ClN_3O_2$
32	H	CON_3	76–78	22	Skelly B	$C_{13}H_{12}N_6O_2$
33	H	CHO	108–109	60	EtOAc–Skelly B	$C_{13}H_{13}N_3O_2$
34	H	$CONH_2$	253–255	61	EtOH	$C_{13}H_{14}N_4O_2$
35	9-OCH_3	H	200–202[c]	63	EtOH	$C_{13}H_{15}N_3O \cdot HCl$
36	H	CH_3	70–71	67	Skelly B	$C_{13}H_{15}N_3O$
37	H	$COCH_2Cl$	121–122	32	C_6H_6–pentane	$C_{14}H_{14}ClN_3O_2$
38	H	$COCH_3$	128–129	70	EtOAc–Skelly B	$C_{14}H_{15}N_3O_2$
39	H	$CSNHCH_3$	228–229	55	EtOH	$C_{14}H_{16}N_4OS$
40	H	$CH_2C{\equiv}CH$	100–102	48	Skelly B	$C_{15}H_{15}N_3O$
41	H	$COOC_2H_5$	106–107	42	EtOAc–Skelly B	$C_{15}H_{17}N_3O_3$
42	H	$CONHC_2H_5$	156–157	88	EtOAc–Skelly B	$C_{15}H_{18}N_4O_2$
43	H	$CONHCH_2C{\equiv}CH$	170–171	56	EtOH	$C_{16}H_{16}N_4O_2$
44	H	CO–◁	112–113	52	EtOAc–Skelly B	$C_{16}H_{17}N_3O_2$
45	H	COC_6H_4Cl-*p*	178–179	78	EtOH	$C_{19}H_{16}ClN_3O_2$
46	H	COC_6H_5	150	77	EtOH	$C_{19}H_{17}N_3O_2$
47	H	$CSNHC_6H_5$	181–182	80	EtOH	$C_{19}H_{18}N_4OS$
48	H	$CONHC_6H_5$	206–207	62	EtOAc–Skelly B	$C_{19}H_{16}N_4O_2$

[a]All melting points were uncorrected. [b]Anal. for C, H, N. [c]Characterized as HCl salts.

of xylene which contd 1 g of *p*-TsOH and refluxed 6 hr. The solvent was removed *in vacuo* and the solid triturated with dil HCl and finally with H_2O. The solid was collected and crystd (EtOH–H_2O) to give 14 g (59%). Compds 9, 10, 13, and 16 were prepd by this procedure.

4,5-Dihydro-1,3-dimethyl-4-propargyl-1*H*-pyrazolo[3,4-*b*][1,4]-benzoxazepin-5-one (18). A soln of 9.16 g (0.04 mole) of 11 in 300 ml of dioxane was added to a stirring mixt of 1.92 g (0.04 mole) of NaH in 100 ml of dioxane. The mixt was stirred 2 hr at 80° and cooled to room temp, and 4.8 g (0.04 mole) of propargyl bromide was added dropwise. The temp was raised to 60°, and after stirring for 5 hr, the mixt was filtered and the filtrate concd *in vacuo*. The gummy residue was triturated with pentane and solid crystd from EtOH to give 7.2 g (67%). Compds **12**, **14**, 15, 17, **19** through **29** and **34** through **38** were prepd by this method using the appropriate halo intermediates. Compds 25 and 28 were characterized as HCl salts.

4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepin Hydrochloride (30). A soln of 9.16 g (0.04 mole) of **11** in 200 ml of THF was added dropwise to a stirring mixt of 3.04 g (0.08

Table IV

Tests	Oral ED_{50} responses in mg/kg: Compd 30	Compd 40	Phenylbutazone
Antiedema[a]	40	40	17.9
Antipyresis	20.5	18	17.5
Analgetic (AcOH)	130	130	172
Vascular permeability (AcOH and Evans Blue)	160	170	160
Acute oral LD_{50} (mice)	1420	980	760

[a] ED_{50} values.

mole) of LAH in 200 ml of THF. The mixt was refluxed 12 hr and cooled, and the complex was carefully decompd by sequential dropwise addns of 2.9 ml of H_2O, 2.9 ml of 15% NaOH soln, and 8.7 ml of H_2O. After stirring for 3 hr the mixt was filtered, and the filter cake washed with Et_2O. The combined filtrates were dried ($MgSO_4$), filtered, and gassed with dry HCl. The crude HCl salt was crystd from EtOH to give 7.8 g (78%).

4-*p*-Chlorobenzoyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (45). A soln of 5.25 g (0.03 mole) of *p*-chlorobenzoyl chloride in 50 ml of Et_2O was added slowly to a stirred soln of 6.45 g (0.03 mole) of base prepd from **30**, and 2.4 g (0.03 mole) of pyridine in 300 ml of Et_2O. The mixt was stirred 6 hr at room temp and successively washed with H_2O, 5% HCl, H_2O, 5% $NaHCO_3$, and finally with H_2O. The dried Et_2O soln ($MgSO_4$) was concd *in vacuo*. One recrystn from EtOH gave 8.3 g (78%). Other compds prepd by this method were **37**, **38**, **41**, **44**, and **46**.

4-Chloroformyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (31). A satd soln of $COCl_2$ in EtOAc was made by bubbling a slow stream of the gas into 800 ml of EtOAc, chilled in ice, for 30 min. To this was added rapidly a soln of 47 g (0.22 mole) of base prepd from **30**, in a min of EtOAc. The mixt was refluxed for 3 hr and then gassed again with $COCl_2$ for 0.5 hr. The hot mixt was filtered, and the filtrate was washed with H_2O, and dried ($MgSO_4$). The dry filtrate was concd to an oil which crystd. One recrystn from EtOAc gave 21 g (43%).

4,5-Dihydro-1,3-dimethyl-4(2-propynylcarbamoyl)-1*H*-pyrazolo-[3,4-*b*][1,4]benzoxazepine (43). A soln of 2.2 g (0.04 mole) of propargylamine and 4.56 g (0.02 mole) of **31** in 100 ml of EtOAc was stirred 12 hr at room temp. The soln was washed with H_2O, dried ($MgSO_4$), and concd to a solid. Crude product was crystd from EtOAc to give 3.2 g (56%).

4-Azidoformyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (32). A soln of 4.56 g (0.02 mole) of **31** and 2.6 g (0.04 mole) of NaN_3 in 100 ml of 90% Me_2CO–H_2O was stirred for 12 hr. The soln was concd, and the residue was taken up in Et_2O and filtered, and the filtrate was dried ($MgSO_4$). The solid obtd upon concn was crystd from Skelly B to give 1.2 g (22%).

4-Carbamoyl and Thiocarbamoyl Derivatives of 4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine. A soln (0.037 mole) of RNCO or RNCS and 8 g (0.037 mole) of base prepd from **30** in 250 ml of Et_2O was stirred for 12 hr. The soln was concd, and the resulting solids were crystd to give yields ranging from 55 to 88%. Compds **39**, **42**, **47**, and **48** were prepd in this manner.

4,5-Dihydro-1,3-dimethyl-4-formyl-1*H*-pyrazolo[3,4-*b*][1,4]-benzoxazepine (33). Compd **30** (6.4 g, 0.03 mole) was refluxed for 2 hr in 75 ml of ethyl formate. The soln was concd and the oil chilled to effect crystn. Recrystn from Skelly B gave 4.3 g (60%).

5-Carbamoyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (34). An aq soln of KNCO (3.3 g, 0.04 mole) was added to 10 g (0.04 mole) of **31** in 70 ml of H_2O. After 1 hr the solid was collected and washed with H_2O. Crystn from EtOH gave 6.3 g (61%).

4,5-Dihydro-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (36). A soln of 21.5 g (0.10 mole) of base prepd from **30** in 50 ml of dioxane was added to a stirred mixt of 4.8 g (0.10 mole) of NaH in 150 ml of dioxane. The mixt was heated to 70° for 2 hr and then cooled to 20° while a soln of 14.2 g (0.10 mole) of MeI in an equal vol of dioxane was added dropwise. The temp was then raised to 40° for 3 hr. After removal of solvent, the residue was taken up in 5% HCl and washed with Et_2O. The acid soln was basified, extd with Et_2O, dried, and filtered, and the filtrate was evapd to yield a solid. The solid crystd from Skelly B to give 15.6 g (67%). Compd **40** was also prepd by this method.

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Studies on Cardiovascular Drugs. 5.[1] 1-Amino-3-phenoxy-2-propanol Derivatives as β-Adrenergic Blocking Agents

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Several 1-amino-3-(substituted phenoxy)-2-propanols have been synthesized and examined for adrenergic β-receptor blocking activity. Of the compds synthesized and tested, 1-*tert*-butylamino-3-[*o*-(furfuryloxy)-phenoxy]-2-propanol (**24**), 1-[*o*-(allyloxymethoxy)phenoxy]-3-*tert*-butylamino-2-propanol (**21**), 1-*tert*-butylamino-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]-2-propanol (**26a**, **26b**), and 1-*tert*-butylamino-3-[*o*-(methoxymethoxy)phenoxy]-2-propanol (**2**) showed potent activity.

A series of 1-amino-3-naphthoxy-2-propanols was synthesized by Crowther, *et al.*,[2] and proved to possess potent adrenergic β-receptor blocking properties. Among these compounds, 1-isopropylamino-3-(1-naphthoxy)-2-propanol (propranolol) was selected and has been used in the treatment of various cardiac arrhythmias and angina pectoris. Many synthetic and pharmacological investigations[3] on 1-amino-3-bicyclic aromaticoxy-2-propanols have been pursued by a number of workers.

The syntheses and adrenergic β-receptor blocking activities of 1-amino-3-(substituted phenoxy)-2-propanols were reported by Crowther, *et al.*[4] They showed that compds bearing substituents on the benzene nucleus, such as alkyl, alkoxy, aryloxy, arylthio, OH, Cl, and NO_2, were highly active. These findings prompted us to synthesize some further 1-amino-3-phenoxy-2-propanol derivatives bearing substituents on the benzene nucleus and to evaluate their pharmacological properties in comparison with propranolol.

Chemistry. The dihydroxybenzenes I were allowed to react with the halides III to give the substituted phenols IV, and these (II[5] and IV) with epichlorohydrin to afford the corresponding epoxides V and VI. Finally, the epoxides (V, VI) were treated with amine VII to give the desired compds