Derivatives of 3,4-Dihydro-1(2*H*)-naphthalenone as β-Adrenergic Blocking Agents. 1. Bunolol and Related Analogs

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Received March 18, 1970

A new orally potent β-adrenergic blocking agent has been prepared which can be considered to be a classical antagonist since it had no β-sympathomimetic activity. Bunolol (**1**) (5-[3-(*t*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone) was 3 times more potent than propranolol (**30**) intravenously and 20–30 times more active orally. Bunolol possessed relatively weak activity against ouabain-induced ventricular arrhythmias. The synthesis of bunolol and its analogs was accomplished by treating the appropriate hydroxytetralone with epichlorohydrin followed by reaction of the epoxide intermediate so obtained with the desired amine. A systematic study of the positional isomers in the tetralone series possessing identical side chain structures showed that the 5 isomer (bunolol) had the greatest activity as a β-adrenergic blocking agent. The subsequent comparison of amino group substitutions was devoted mainly to the most active 5-isomeric series. It was shown that the classical structure requirements prevailed. Alteration in the side chain in other ways led to less active compounds. Resolution of bunolol revealed that the *l* isomer possessed the major activity. The keto group of bunolol was shown to be responsible for the greatly enhanced oral potency and for the relative lack of activity against ouabain-induced ventricular arrhythmias. Due to a favorable therapeutic index and greater oral activity, bunolol may have clinical advantage when compared to existing β-adrenergic blocking agents.

A new, orally-active, β-adrenergic blocking agent has been prepared having the structure 5-[3-*t*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone (**1**). When compared to propranolol (**30**), bunolol[1] (**1**) showed significant activity as a β-adrenergic blocking agent and higher oral potency. In addition, bunolol and related β-adrenergic blockers were shown to possess relatively weak antiarrhythmic action against ouabain-induced arrhythmias and no β-adrenergic stimulant activity in contrast to pronethalol and dichloroisoproterenol.[2,3]

β-Adrenergic blocking agents have been of interest for the treatment of angina pectoris and a variety of cardiac arrhythmias.[4]

A series of 30 compounds was studied including bunolol (**1**), a potent analog which was shown to be 3 times more potent than propranolol (**30**) iv and 20–30 times more potent orally. Bunolol (**1**) appears to be a classical type of β-adrenergic antagonist with no β-sympathomimetic action and little or no activity against ouabain-induced arrhythmias. Bunolol has shown enhanced oral absorption and good therapeutic ratio, indicating possible clinical advantage when compared to existing β-adrenergic blocking agents.

Chemistry.—Bunolol (**1**) and related compounds were prepared generally by the reaction of epichlorohydrin with the corresponding known hydroxytetralones[5a,b] in the presence of a base such as NaOH. The intermediate 5-(2,3-epoxypropoxy)-1-tetralone (**32**) obtained was further treated with the appropriate amine and gave the desired 3-substituted amino-2-hydroxypropoxytetralone usually isolated as a salt. The same product **1** was obtained through an alternate route involving the reaction of 5-hydroxy-1-tetralone (**31**) with *t*-butylamino-2,3-epoxypropane (**33**) in the presence of NaOH.

The oxazolidine (**14**) derivative of **1** was prepared by treatment of **1** with aq formaldehyde under reflux.[6] Analog **15** was prepared from **1** by reaction with phenyl chloroformate and NaOMe. A second route to **15** was established involving the addition of *t*-butylisocyanate to the epoxy intermediate **32** in the presence of LiBr as catalyst.[7]

Racemic bunolol (**1**) was resolved using *d*- and *l*-tartaric acids. The bitartrate monohydrate salts were obtained and recrystallized to constant rotation and analytical purity before conversion into the optically active bases. The enantiomorphs were further purified as their crystalline HCl salts to constant rotation samples possessing equal but opposite signs of rotation.

The preparation of the quaternary analogs **16** and **27** was accomplished by refluxing either **1** or 1-(3-diethylamino-2-hydroxypropoxy)naphthalene[6] in abs EtOH containing excess MeI.

Pharmacology.—β-Adrenergic blocking activity was evaluated using a small number of mongrel dogs of either sex (10.5–12.5 kg) which were anesthetized with barbital sodium (300 mg/kg, iv) and titrated to the level of surgical anesthesia with pentobarbital. Aortic blood pressure, heart rate, and contractile force were measured. The dogs were vagotomized bilaterally, thoracotomized, and maintained on artificial respiration. Control responses to isoproterenol (0.3 μg/kg, iv) were established, after which a saline solution of the compound was administered intravenously on a 0.5 log dose schedule (0.03–10.0 mg/kg) at 20-min intervals until total blockade could be affected. The isoproterenol challenges were interposed midway between doses of the drug in order to evaluate β-adrenergic blocking activity.

The relative oral (po) β-adrenergic blocking potencies were determined in barbiturate anesthetized, vagotomized mongrel dogs. The drug was administered to conscious dogs 1 hr prior to anesthesia. Potency estimates were based upon the inhibition of standard isoproterenol (0.3 μg/kg, iv) responses.

The antiarrhythmic screen procedure involved adult mongrel dogs of either sex (10–15 kg) which were

(1) Bunolol is the generic name for 5-[3-(*t*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride.

(2) E. J. Ariens, *Ann. N. Y. Acad. Sci.*, **139**, 606 (1967).

(3) R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968).

(4) A. C. Dornhorst, *Ann. N. Y. Acad. Sci.*, **139**, 968 (1967).

(5) (a) D. Papa, E. Schwenk, and H. Breiger, *J. Org. Chem.*, **14**, 366 (1949); (b) J. v. Braun, *Justus Liebigs Ann. Chem.*, **451**, 1 (1927).

(6) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968).

(7) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

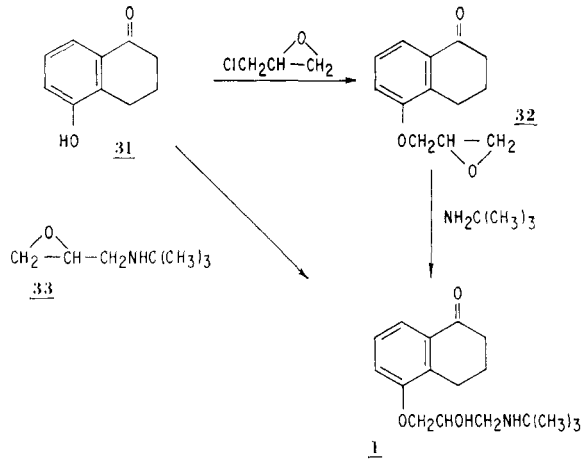
anesthetized to surgical levels with intravenous barbital sodium (300 mg/kg) and pentobarbital sodium. Parameters measured included arterial blood pressure, myocardial contractile force, heart rate, and lead II electrocardiogram. The animal was thoracotomized and maintained on artificial respiration. Ouabain was administered 40 μg/kg iv followed in 15 min by an additional iv dose of 20 μg/kg. Additional ouabain was then administered in increments of 10 μg/kg at 15-min intervals until a well-established venticular tachycardia (ouabain toxicity) was observed. After the arrhythmias had been established for 15 min, 5 mg/kg of the compound was administered at a rate of 1 mg/kg per min. Following drug administration, the animal was observed. A compound which did not elicit an effect on arrhythmias within 15 min was considered inactive.

Structure–Activity Relationships.—The initial study of β-blocking agents involved a systematic evaluation of the positional isomers in the tetralone or 3,4-dihydro-1(2*H*)-naphthalenone series. Results showed that when the side-chain substitution was maintained as 3-*t*-butylamino-2-hydroxypropoxy, the 5 isomer **1** exhibited the greatest potency as a β-adrenergic blocking agent, while the 6 and 7 isomers (**20** and **25**) were much less active. Therefore, most comparisons of the substitution effects on the amino function were made within the 5-isomeric series. Classical structure–activity requirements[2] for that portion of the β-blocker molecule prevailed. That is, for significant activity as a β-adrenergic blocker of the cardiovascular response to isoproterenol, a secondary OH and a secondary amino group possessing a branched alkyl substituent of 5 C atoms or less in size must be present. The observed potency order for the amino substituents was *t*-Bu > *i*-Pr > *sec*-Bu, cyclopentyl, and *i*-Bu for the 5-(3-substituted amino-2-hydroxypropoxy)-3,4-dihydro-1(2*H*)-naphthalenone series. Introduction of larger functional groups on N such as cyclohexyl or aralkyl or conversion into the tertiary amine led only to weakly active or inactive compounds.

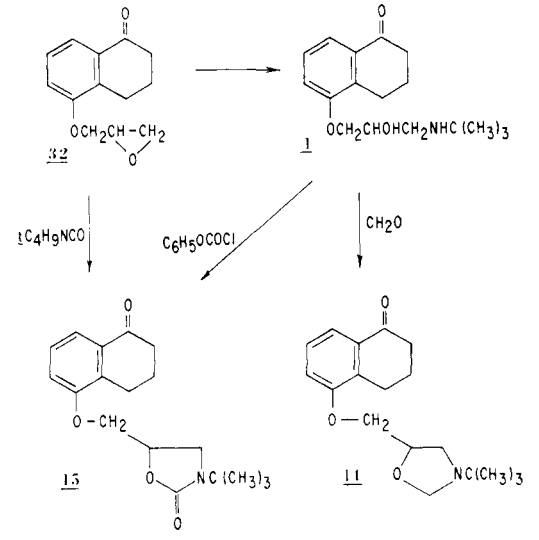
Alteration of the side chain structure such as by the formation of oxazolidine (**14**) or oxazolidone (**15**) derivatives resulted in a reduction of β-blocker potency. Recently, it has been shown that β-adrenergic blocking activity usually associated with oxazolidine analogs was most probably due to the rapid hydrolysis of the oxazolidine in aqueous solution which regenerated the active open-chained analog.[8] As has been found in other β-blocker series,[2,9] the *l*-antipode **17** of bunolol was most active and was approximately twice as active as **1**. The *d*-antipode **18** was weakly active and was about $^1/_{30}$ as active as **1**. The low order of activity possessed by **18** could also have resulted from contamination by small amounts of **17** which could not have been detected due to the limits of experimental error related to the resolution of **1**.

The tetralone nucleus was shown to contribute significantly to the activity of bunolol (**1**). The increased iv potency of **1** in comparison with propranolol (**30**) could be attributed to either the saturated ring or the *t*-Bu portions of the molecule. The contribution by the *t*-Bu group to activity was shown to be minimal

Scheme I



Scheme II

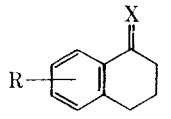


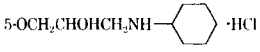
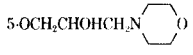
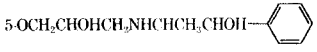
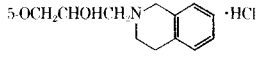
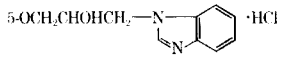
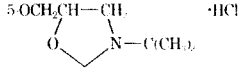
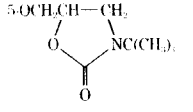
when the *t*-Bu analog **29** of propranolol **30** exhibited an activity approximately equal to that of **30**.[6] The increased potency of bunolol was shown to be due to the tetrahydro portion of the tetralone nucleus since analog **28** had approximately the same activity as **1**. Introduction of the keto group into **28** to give **1** enhanced the oral potency of **1** by 20–30 times when compared to **30** and by 7 times when compared with **28**. The oxime **13** of bunolol was less active as a β-adrenergic blocker.

Bunolol had little activity against ouabain-induced arrhythmias while **28**, **29**, and **30** all had significant ability to convert ouabain-induced ventricular tachycardia to normal sinus rhythm. Therefore, the keto group appeared to be responsible for the decreased antiarrhythmic action of **1**. The possibility existed that some useful antiarrhythmic activity could have been obtained in the tetralone series if the amino function was suitably altered. In the naphthyloxy series of propranolol (**30**), a quaternized analog[10] (**27**) was shown to separate β-blockade activity from antiarrhythmic action through elimination of β-blockade while retaining antiarrhythmic activity. A similar quaternary analog **16** of bunolol was shown to have lost its β-adrenergic blocking action without enhancing

(8) L. Almirante and W. Murmann, *Farmaco Ed. Sci.*, **24**, 744 (1969).
(9) R. Howe and B. S. Rao, *J. Med. Chem.*, **11**, 1118 (1968).
(10) B. R. Lucchesi and T. Iwami, *J. Pharm. Exp. Ther.*, **162**, 49 (1968).

TABLE I



Compd	R	X	Mp, °C	Solvent	Formula	Analysis	Dose 100%[a] blockade, mg/kg	Potency[b] ratio relative to propranolol
1	5-$OCH_2CHOHCH_2NHC(CH_3)_3 \cdot HCl$	O	224–226	MeOH–Et_2O	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	0.1	3
2	5-$OCH_2CHOHCH_2NHCH(CH_3)_2 \cdot HCl$	O	198–200	EtOH	$C_{16}H_{23}NO_3 \cdot HCl$	CHNCl	0.2	1.5
3	5-$OCH_2CHOHCH_2NHCH(CH_3)CH_2CH_3 \cdot HCl$	O	128–152 dec	MeOH–Et_2O	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	1.0	0.3
4	5-$OCH_2CHOHCH_2NHCH_2CH(CH_3)_2 \cdot HCl$	O	134–139	MeOH–Et_2O	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	Weak[c]	
5		O	158–161	2-PrOH	$C_{18}H_{25}NO_3 \cdot HCl$	CHNCl	1.0	0.3
6	5-$OCH_2CHOHCH_2NHC(CH_3)_2CH_2OH \cdot HCl$	O	180–183	EtOH–Et_2O	$C_{17}H_{25}NO_4 \cdot HCl$	CHNCl	0.3	1.0
7		O	222–223	MeOH	$C_{19}H_{27}NO_3 \cdot HCl$	CHNCl	3.0	0.1
8		O	145–147 dec	2-PrOH (1% oxalic acid)	$C_{18}H_{25}NO_3 \cdot C_2H_2O_4$[d]	CHN	2	0.15
9		O	68–70	EtOAc–hexane	$C_{17}H_{23}NO_4$	CHN	Weak	
10		O	198–206	MeOH–Et_2O	$C_{22}H_{27}NO_4 \cdot HCl$	CHNCl	Weak	
11		O	205–208	2-PrOH	$C_{22}H_{25}NO_3 \cdot HCl$	CHNCl	Weak	
12		O	220–223	MeOH–Et_2O	$C_{20}H_{20}N_2O_3 \cdot HCl$	CHNCl	Weak	
13	5-$OCH_2CHOHCH_2NHC(CH_3)_3$	NOH	171–174	EtOH	$C_{17}H_{26}N_2O_3$	CHN	0.3	1.0
14		O	139–144	MeOH–Et_2O	$C_{18}H_{25}NO_3 \cdot HCl$	CHNCl	0.3	1.0
15		O	132–135	CCl_4	$C_{18}H_{23}NO_4$	CHN	Weak	
16	5-$OCH_2CHOHCH_2N^+(CH_3)_2C(CH_3)_3 \cdot I^-$	O	177–180 dec	PrOH–Et_2O	$C_{18}H_{27}NO_3 \cdot CH_3I$	CHNI	Weak	
17	5-$OCH_2CHOHCH_2NHC(CH_3)_3$[e] $\cdot HCl$ levo isomer	O	209–211	MeOH–Et_2O	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	0.05	6
18	5-$OCH_2CHOHCH_2NHC(CH_3)_3$[f] $\cdot HCl$ dextro isomer	O	209–211	MeOH–Et_2O	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	3.0	0.1
19	6-$OCH_2CHOHCH_2NHCH(CH_3)_2 \cdot HCl$	O	168–169	EtOH	$C_{16}H_{23}NO_3 \cdot HCl$	CHNCl	Weak	
20	6-$OCH_2CHOHCH_2NHC(CH_3)_3 \cdot HCl$	O	219–221	2-PrOH	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	Weak	
21	6-$OCH_2CHOHCH_2NHCH_2CH(CH_3)_2 \cdot HCl$	O	185–187	CH_3CN	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	Weak	
22	6-$OCH_2CHOHCH_2NHCH(CH_3)_2$	$NNHC(S)NH_2$	183–184	EtOH	$C_{17}H_{26}N_3O_2S$	CHNS	Weak	

23	6-$OCH_2CHOHCH_2NHCH(CH_3)_2$	O	211–213	MeOH	$C_{19}H_{28}N_2O_4 \cdot 2HCl$	CHNCl	Weak	
24	7-$OCH_2CHOHCH_2NHCH(CH_3)_2 \cdot HCl$	O	172–173	EtOH	$C_{16}H_{23}NO_3 \cdot HCl$	CHNCl	Weak	
25	7-$OCH_2CHOHCH_2NHC(CH_3)_3 \cdot HCl$	O	211–213	EtOH	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	Weak	
26	7-$OCH_2CHOHCH_2NHCH_2CH(CH_3)_2 \cdot HCl$	O	203–205	CH_3CN	$C_{17}H_{25}NO_3 \cdot HCl$	CHNCl	Weak	
27[a]			119–123	MeOH–Et_2O	$C_{17}H_{23}NO_2 \cdot CH_3I$	CHNI	Weak	
28		H_2	147–149	2-PrOH	$C_{17}H_{27}NO_2 \cdot HCl$	CHNCl	0.1	3.0
29[b]			180–181	MeOH–Et_2O	$C_{17}H_{23}NO_2 \cdot HCl$	CHNCl	0.3	1.0
30							0.3	1.0

[a] Dose mg/kg, iv necessary for total β-adrenergic blockade of heart rate effects produced by isoproterenol (0.3 μg/kg, iv). [b] Ratio of potency in comparison to known β-adrenergic blocker propranolol expressed as 100% blockade dose of propranolol/100% blockade dose of other compound. [c] All analogs tested which exhibit incomplete or no blockade at doses greater than 3 mg/kg, iv were considered only weakly active as β-adrenergic blocking agents. Potency ratio = 0.1 or less. [d] Oxalic acid was inactive as a β-adrenergic blocking agent. [e] Resolved *l* isomer, $[\alpha]_{589}^{24}$ −19.6 ± 0.7° (*c* 2.85, MeOH). [f] Resolved *d* isomer, $[\alpha]_{589}^{24}$ +19.7 ± 0.7° (*c* 2.80, MeOH). [g] Cited in ref 10. [h] Cited in ref 6.

or unmasking any possible antiarrhythmic activity to any significant degree. Therefore, quaternization of β-blockers which already possess antiarrhythmic action simply removes β-blocking activity from that structure and does not enhance or create antiarrhythmic activity.

When analogs containing a variety of other amino groups were evaluated, it was found that **9** and **11** possessed antiarrhythmic activity but of a lower potency than **30** against ouabain-induced arrhythmias.

A more detailed report on the pharmacology of bunolol will be published elsewhere.

Thus, in the tetralone series, bunolol (**1**) appears to be a classical β-blocking agent. When compared to existing β-adrenergic blocking agents, bunolol may have clinical advantage due to its increased oral potency and favorable therapeutic index.

Experimental Section

Melting points were taken in open capillary tubes on a Mel-Temp and are corrected. Each analytical sample had ir, uv, and nmr spectra compatible with its structure. Combustion analysis for C, H, N, and Cl, I, or S gave results within 0.4% of theory. Optical rotations were taken on a Perkin-Elmer 141 polarimeter. The physical properties of **1–29** are given in Table I.

The 5- and 6-hydroxy-1-tetralones[5a] were prepared from commercially available 5- and 6-methoxy-1-tetralone by refluxing in HBr–AcOH. The 7-hydroxy-1-tetralone was prepared according to the published procedure.[5b]

The experimental procedures (A and B) for the synthesis of **1** and **32** may also serve as a general route for the preparation of similar analogs.

A. 5-(2,3-Epoxypropoxy)-3,4-dihydro-1(2*H*)-naphthalenone (32).—A solution containing 8.30 g (208 mmol) of NaOH in 36.5 ml of H_2O was diluted with 292 ml of EtOH and 28.5 g (17.6 mmol) of **31** and 98.0 g (1.06 mol) of epichlorohydrin were added. The mixture was stirred at room temperature for 16 hr and then evaporated *in vacuo* to a residue which was partitioned between 180 ml of H_2O and 250 ml of $CHCl_3$. The separated aqueous phase was extracted with $CHCl_3$ (1 × 100 ml), and the combined organic extracts were washed with H_2O (2 × 100 ml) and dried ($MgSO_4$). Evaporation of the volatile components gave 34.0 g (88.8%) of a crude syrup which was purified by distillation; yield 26.1 g (68.1%), bp 136–144° (0.08 mm). The distillate **32** was not further purified.

B. 5-[3-(*t*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (1).—A reaction mixture containing 20.1 g (91.8 mmol) of **31**, 33.0 g (452 mmol) of *t*-$BuNH_2$, and 90 ml of EtOH was refluxed for 40 min. The reaction mixture was evaporated *in vacuo* and gave **1** as a crude solid; yield 25.8 g (96.7%), mp 84–86°. The crude **1** was converted into a white crystalline HCl salt; yield 28.0 g (93.2%), mp 223–225°. The analytical sample of **1** was obtained by recrystallization from EtOH, mp 224–226°.

C. 5-[3-*t*-Butylamino-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (1).—To a MeOH solution (25 ml) containing 2.51 g (15.5 mmol) of **31** and 618 mg (15.5 mmol) of NaOH was added 1.00 g (7.76 mmol) of **33**,[9] and the resulting mixture was heated at reflux for 1 hr. Evaporation of the reaction mixture *in vacuo* gave an oily residue which was dissolved in 250 ml of $CHCl_3$ and washed with 5% NaOH (2 × 250 ml) and H_2O (1 × 250 ml) before drying ($MgSO_4$). Evaporation of the $CHCl_3$ phase gave 1.33 g (59.0%) of the oily base **1**, which was converted into its crystalline HCl salt; yield 537 mg (21.1%), mp 218–223°. Recrystallization of crude **1** from MeOH–Et_2O gave the pure sample of **1**; yield 425 mg (16.7%), mp 224–227°. By tlc, mp, and ir comparisons both synthetic routes gave the same product, **1**.

D. 5-[(3-*t*-Butyl-5-oxazolidinyl)methoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (14).—An EtOH solution (3.2 ml) of 460 mg (1.58 mmol) of **1** and 0.2 ml of 40% formalin was heated at reflux for 3.5 hr. An additional 0.2 ml of the 40% formalin was added to the reaction mixture and refluxing was continued for a total of 21 hr. After evaporating the reaction mixture *in vacuo* to a residual oil, the crystalline hydrochloride was prepared by trituration with Et_2O (HCl). The crude **14** was recrystallized from

MeOH–Et_2O to give the analytically pure sample; yield 291 mg (54.2%), mp 139–144° dec.

E. 5-[(3-*t*-Butyl-2-oxo-5-oxazolidinyl)methoxy]-3,4-dihydro-1(2*H*)-naphthalenone (15).—To a solution of 9.17 g (31.6 mmol) of **1** in 50 ml of dry THF was added, at 0°, 4.05 g (40.0 mmol) of Et_3N and 5.50 g (35.0 mmol) of phenyl chloroformate, and the resulting mixture was stirred at room temperature for 19.5 hr. The resulting intermediate was obtained by evaporation of the volatile components of the mixture and dissolving the remaining residue in C_6H_5–CH_3 (100 ml) and extracting with 5% HCl before drying ($MgSO_4$). The solution containing the intermediate was heated at reflux for 22 hr with 2.05 g (38.0 mmol) of NaOMe. After the reaction mixture had been extracted with 5% NaOH (2 × 50 ml), the organic phase was dried ($MgSO_4$), evaporated *in vacuo* and gave **15** as a solid residue. White crystalline **15** was obtained in analytical purity by recrystallizing from CCl_4: yield 6.65 g (66.5%) mp 132–135°.

F. 5-[(3-*t*-Butyl-2-oxo-5-oxazolidinyl)methoxy]-3,4-dihydro-1(2*H*)-naphthalenone (15).—To a refluxing mixture of 1.09 g (5.00 mmol) of **32**, 100 mg of LiBr, and 5 ml of DMF was added 0.71 ml (594 mg, 6.00 mmol) of *t*-BuNCO [in 3 portions every 20 min]. The resulting mixture was refluxed for a total of 4 hr. The reaction mixture was allowed to cool to room temperature and was added to 50 ml of H_2O. The aq mixture was extracted with $CHCl_3$ (2 × 50 ml) and the combined $CHCl_3$ extracts were washed with H_2O (2 × 50 ml) and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave a quantitative yield of crude solid **15**. Two recrystallizations from CCl_4 gave the white crystalline **15**; yield 927 mg (58.7%), mp 130–134°. The product was shown by tlc and melting point to be homogeneous and identical with **15** obtained from **1** and phenyl chloroformate.

G. Optical Resolution of DL-5-[3-(*t*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (1).—Racemic **1** (140 g, 0.427 mol) was converted into its free base form by suspending the salt in $CHCl_3$–1 *N* NaOH. A quantitative yield of the base was obtained from the $CHCl_3$ phase after drying with $MgSO_4$ and evaporating.

Into a solution of 84.0 g (0.560 mol) of *l*-tartaric acid in 400 ml of EtOH was dissolved 0.427 mol of the free base form of **1**. The solution was allowed to cool slowly to room temperature. A crystalline precipitate formed which was obtained in maximum yield by cooling to 0° before collection by filtration; yield 93.6 g (47.8%), mp 125–135°, $[\alpha]^{25}_{589}$ −0.16° (*c* 5.60, MeOH). The crystalline *l*-tartrate salt was recrystallized several times from EtOH containing 1% *l*-tartaric acid and gave a white crystalline salt possessing constant melting and rotation values; yield 63.3 g (32.3%), mp 125–135°, $[\alpha]^{24}_{589}$ +1.92 ± 0.1, $[\alpha]^{24}_{436}$ +6.40 ± 0.1° (*c* 5.81, MeOH).

Anal. Calcd for $C_{17}H_{25}NO_3 \cdot C_4H_6O_6 \cdot H_2O$: C, H, N.

(+)5-[3-(*t*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (18).—A suspension of 60.0 g (130 mol) of the *l*-tartrate (+) salt in 1 l. of $CHCl_3$ and 0.5 l. of 5% NaOH was stirred at room temperature for 2 hr. The $CHCl_3$ phase, upon drying with $MgSO_4$, gave the free base form as an oil. This material was converted into its HCl salt; yield, 39.5 g (92.5%), mp 208–210°. The product was recrystallized twice from MeOH–Et_2O; white crystalline material of constant melting and rotating values; yield 23.4 g (54.8%), mp 209–211°, $[\alpha]^{24}_{589}$ + 19.7° ±0.7; $[\alpha]^{24}_{436}$ +38.9 ± 1.4° (*c* 2.80, MeOH). An overall yield of 16.7% of **18** was obtained from racemic **1**.

(−)5-[3-(*t*-Butylamino)-2-hydroxypropoxy]-2,3-dihydro-1(2*H*)-naphthalenone *d*-Tartrate.—The mother liquor containing the remaining 52.2% of *l*-tartrate salt was evaporated *in vacuo* and the residual solid obtained was partitioned between 1 l. of $CHCl_3$ and 0.5 l. of 5% NaOH. The $CHCl_3$ phase gave a quantitative yield of the free base after drying ($MgSO_4$) and evaporating *in vacuo* to the residual free base form.

An EtOH solution (500 ml) containing 84.0 g (0.560 mol) of *d*-tartaric acid and 0.223 mol of free base enriched in (−) isomer was allowed to cool slowly to room temperature and then to 0° for maximum precipitation. The crystalline *d*-tartrate salt was collected by filtration and 79.4 g (40.3%, mp 120–135°) of the solid was obtained. After several recrystallizations of the salt from EtOH containing 1% of *d*-tartaric acid, constant rotating and melting point material was obtained as a white crystalline solid; yield 66.1 g (33.8%), mp 125–135°, $[\alpha]^{24}_{589}$ −1.93 ± 0.1°, $[\alpha]^{24}_{436}$ −6.32 ± 0.1° (*c* 6.10, MeOH).

Anal. Calcd for $C_{17}H_{25}NO_3 \cdot C_4H_6O_6 \cdot H_2O$: C, H, N.

(−)5-[3-(*t*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone·HCl (17).—A mixture of 63.0 g (137 mmol) of *d*-tartrate (−) salt in 1 l. of $CHCl_3$ and 0.5 l. of 5% NaOH was stirred at room temperature for 2 hr. The free base of **17** was obtained in a quantitative yield by drying and evaporating the $CHCl_3$ phase to a residual oily material. The oil was converted into the solid HCl salt; yield 41.8 g (92.9%), mp 208–210°. Recrystallization from MeOH–Et_2O gave white crystalline material of constant melting point and rotation values; yield 25.1 g (55.8%), mp 209–211°, $[\alpha]^{24}_{589}$ −19.6 ± 0.7, $[\alpha]^{24}_{436}$ −38.8 ± 1.4° (*c* 2.85, MeOH). The overall yield of **17** was 18.2% from racemic **1**.

Acknowledgments.—The authors are indebted to the Chemical Development Department under the supervision of Dr. A. W. Ruddy and the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular, we wish to thank Mr. G. Conrad and Mr. J. Genzer for large-scale preparation of intermediates and Mrs. U. Zeek for microanalyses. We also wish to thank Dr. H. Kaplan, Dr. R. Robson, and Dr. J. Yelnosky[11] of the Pharmacology Department for testing the compounds reported.

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