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

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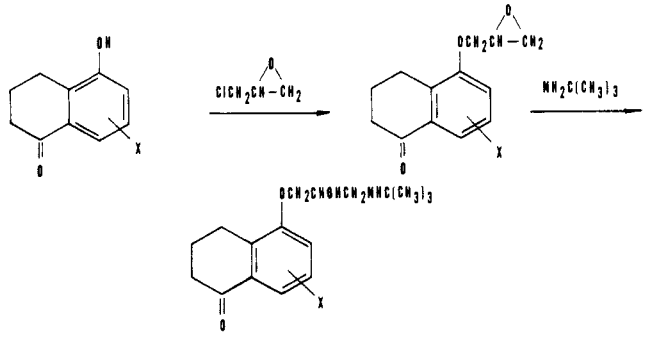
The effect of aromatic substitution on the β-adrenergic blocking activity of bunolol or 5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone was studied. A number of bunolol analogs were prepared possessing a variety of functional groups including acylamino, alkyl, allyl, chloro, hydroxy, nitro, and methoxy groups. The synthesis of these analogs involved the preparation of a number of new substituted 5-hydroxytetralones as intermediates. The acylamino analogs were prepared by reduction and acylation of the nitrotetralone after direct nitration of 1,5-dihydroxytetralin followed by oxidation. The 6-allyl-5-hydroxytetralone was prepared through a Claisen rearrangement of 5-allyloxytetralone. The structures of the 6-allyl- and 6-nitro-5-hydroxytetralones were inferred by the demonstration of intramolecular hydrogen bonding in the ir. None of the 18 analogs prepared were superior to bunolol in their β-adrenergic blocking activity.

Bunolol, or 5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone was the most potent, orally active, β-adrenergic blocking agent of the tetralone series.[1,2] A study of the side-chain amino substitution showed that optimum activity was obtained with the *tert*-butylamino group. In the present study, we determined the effect of aromatic substitution of the tetralone nucleus on β-adrenergic blocking activity.

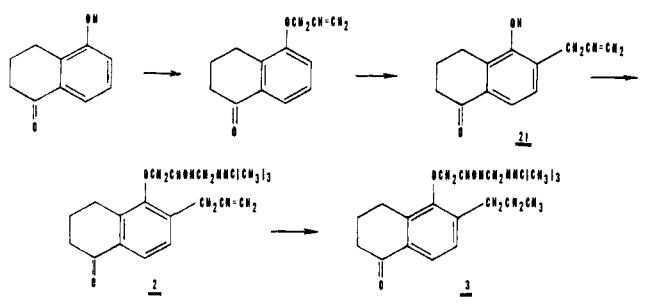
Chemistry. The synthesis of bunolol (**1**) and related analogs was described previously.[1] The substituted 5-hydroxytetralone was allowed to react with epichlorohydrin in the presence of base at room temperature for 16–66 hr. However, the nitro analogs **27** and **28** required refluxing for 16 and 48 hr, respectively. The substituted 5-(2,3-epoxypropoxy)tetralones obtained were allowed to react with *tert*-$BuNH_2$ to give the substituted analogs of **1** (Scheme I).

Scheme I



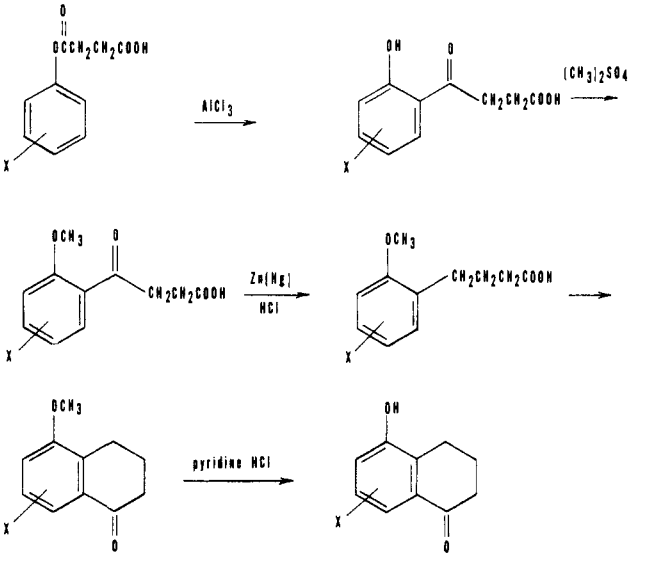
The 6-propyl analog **3** was prepared by catalytic reduction of the 6-allyl analog **2** (Scheme II).

Scheme II



Most of the requisite tetralones were prepared according to literature procedures.[3] These involved a Fries rearrangement of the appropriately substituted phenyl hydrogen succinate, methylation of the β-(substituted 2-hydroxybenzoyl)propionic acid by $(CH_3)_2SO_4$, and reduction with Zn (Hg) and HCl to give the α-(substituted 2-methoxyphenyl)butyric acid. Ring closure to the substituted 5-methoxytetralone was accomplished using polyphosphoric acid, $POCl_3$, or conversion to the acid chloride followed by $AlCl_3$-catalyzed cyclization. Demethylation to the phenol was accomplished by fusion with pyridine hydrochloride[4] or by refluxing with $AlCl_3$ in benzene solution (Scheme III).

Scheme III

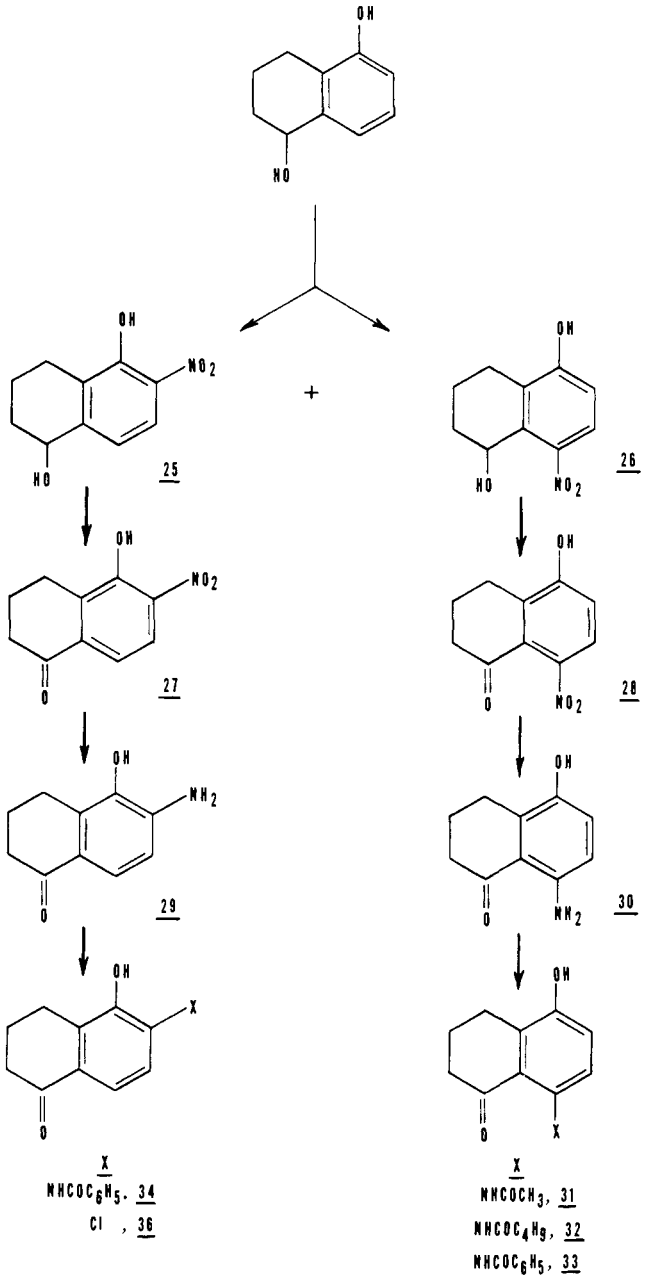


The 6-allyl-5-hydroxytetralone (**21**) was obtained by the Claisen rearrangement of 5-allyloxytetralone in refluxing diethylaniline. The ortho structure assignment was facilitated by the demonstration of intramolecular hydrogen bonding in the OH stretching region of the ir in CCl_4 solutions ranging from 0.5 to 2.5%.[5]

Nitration of 1,5-dihydroxy-1,2,3,4-tetrahydronaphthalene by 70% HNO_3 in AcOH gave a mixture of the 6- and 8-nitro derivatives which were separated by column chromatography on Al_2O_3. Oxidation by CrO_3 gave the corresponding tetralones **27** and **28**. The nmr signals for the aromatic region appeared as AB splitting patterns for both **25** and **26** and were consistent with the structural assignments. Intramolecular hydrogen bonding was observed for **27** in the OH stretching region of the ir by CCl_4 solutions from 0.5 to 2.5%, showing that the nitro group in **25** and **27** was ortho to the phenolic hydroxyl group.[5] Catalytic reduction with PtO_2

gave the aminotetralones **29** and **30**. The amide derivatives were obtained by acylation with the appropriate acyl chloride (Scheme IV).

Scheme IV



The direct nitration of 5-hydroxytetralone[6] gave only 6,8-dinitro-5-hydroxytetralone (**35**). This product subsequently failed to react with epichlorohydrin.

Diazotization of **29**, followed by Cu_2Cl_2 treatment of the intermediate diazonium salt, gave 6-chloro-5-hydroxytetralone (**36**). However, treatment of **30** in a similar manner was unsuccessful. Therefore, it was necessary to prepare 8-chloro-5-hydroxytetralone (**38**) from 8-chloro-5-methoxytetralone[7] according to Scheme III.

Structure-Activity Relationships. The initial study of a series of tetralones as β-adrenergic blocking agents established that the 3-(*tert*-butylamino)-2-hydroxypropoxy side chain yielded compounds which possessed optimum activity.[1] In addition, the 5 isomer within that series was more potent than the corresponding 6 or 7 isomeric analogs. Consequently, all subsequent substitution studies were done on bunolol (**1**) or 5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-tetralone. While some analogs retained potency, aromatic substitution did not yield any β-adrenergic blocker that was superior to bunolol. In addition, no significant cardioselectivity was found among the analogs tested. The analogs showed no apparent preference for blockade of vascular or heart β receptors when the relative blockade of isoproterenol effects on blood pressure, heart rate, and contractile force was compared.[2] Like bunolol, its analogs had no significant intrinsic β-sympathomimetic action and were ineffective against ouabain-induced cardiac arrhythmias.

Generally, the incorporation of smaller functional groups such as Cl, CH_3, or NO_2 was better at the 8 position than at the 6 position. The potency order for the three positions studied was 8 > 7 > 6. The introduction of bulkier groups such as acylamino, allyl, and propyl resulted in the loss of most β-adrenergic blocking activity.

The incorporation of an allyl group ortho to the side chain such as in **2** resulted in potency similar to alprenolol (**19**)[8] but less than **1**. The *p*-acylamino group necessary in the practolol (**20**) series did not impart any cardioselective activity to the tetralone analogs **15–17**. Factors such as hydrogen bonding and steric interactions between the functional groups, keto group and the immediate area of the β-receptor involved, may alter the contributions of certain functional groups to β-blocking activity.

Experimental Section

The pharmacology screening methods have been reported previously.[1,2] The β-adrenergic blocking activity was evaluated using one or a small number of mongrel dogs which were anesthetized, reserpinized, vagotomized, thoracotomized, and maintained on artifical 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. Isoproterenol challenges were interposed midway between doses of the drug in order to evaluate β-adrenergic blocking activity.

The antiarrhythmic screen involved adult mongrel dogs 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 ventricular tachycardia had been observed. After the arrhythmia 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.

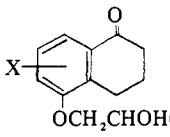
Melting points were taken in open capillary tubes on a Mel-Temp and are uncorrected. Each analytical sample was homogeneous by tlc and had ir, uv, and nmr spectra compatible with its structure. Combustion analysis for C, H, N, and Cl gave results within 0.4% of theory. The physical properties of 2–18 and 21–38 are given in Tables I and II.

The synthetic procedures reported in the Experimental Section may serve as general methods for the preparation of similar analogs.

The nmr spectra were recorded on a Varian A-60 spectrophotometer using tetramethylsilane as an internal standard. The ir spectral studies of hydrogen bonding were performed on a Perkin-Elmer 621 spectrophotometer. The hydroxyl-stretching frequencies were investigated in the fundamental region at 3600 cm^{-1}. The samples were run in CCl_4 at concentrations from 2.5 to 0.5% in 0.5- and 1.0-mm path length cells.

3,4-Dihydro-5-hydroxy-7-methyl-1(2*H*)-naphthalenone (23). The 3,4-dihydro-5-methoxy-7-methyl-1(2*H*)-naphthalenone[3] (17.1 g, 90.0 mmol) was dissolved in C_6H_6 (500 ml) and 36.0 g (270 mmol) of anhydrous $AlCl_3$ was added to the mixture before refluxing for 2 hr. The reaction mixture was poured onto 500 ml of ice-H_2O and HCl was added. The mixture was extracted with $CHCl_3$ (500 ml).

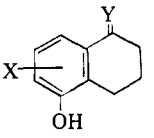
Table I



Compd	X	Recrystn solvent	Mp, °C	Formula	Analyses	Dose,[a] mg/kg iv for 100% β blockade
1	H					0.1[b]
2	6-$CH_2CH{=}CH_2$	EtOAc-C_6H_{14}	165-167	$C_{20}H_{29}NO_3 \cdot HCl$	CHNCl	Weak[c]
3	6-C_3H_7	EtOAc-C_6H_{14}	166-170	$C_{20}H_{31}NO_3 \cdot HCl$	CHNCl	Weak
4	6-Cl	2-PrOH-Et_2O	211-213	$C_{17}H_{24}ClNO_3 \cdot HCl$	CHNCl	3.0
5	6-NO_2	2-PrOH-Et_2O	205-207	$C_{17}H_{24}N_2O_5 \cdot HCl$	CHNCl	Weak
6	6-CH_3	2-PrOH-Et_2O	183-184	$C_{18}H_{27}NO_3 \cdot C_2H_2O_4$	CHN	Weak[d]
7	6-$NHCOC_6H_5$	1-PrOH	267-269	$C_{24}H_{30}N_2O_4 \cdot HCl$	CHNCl	Weak
8	7-Cl	2-PrOH	238-240	$C_{17}H_{24}ClNO_3 \cdot HCl$	CHNCl	1[d]
9	7-CH_3	2-PrOH-Et_2O	195-197	$C_{18}H_{27}NO_3 \cdot HCl$	CHNCl	3[d]
10	8-Cl	2-PrOH	190-192	$C_{17}H_{24}ClNO_3 \cdot HCl$	CHNCl	0.3[d]
11	8-CH_3	2-PrOH-Et_2O	156-158	$C_{18}H_{27}NO_3 \cdot HCl$	CHNCl	0.3
12	8-NO_2	MeOH	263-264	$C_{17}H_{24}N_2O_5 \cdot HCl$	CHNCl	0.3
13	8-OH[e]	MeOH-Et_2O	208-211 dec	$C_{17}H_{25}NO_4 \cdot HCl$	CHNCl	3.0
14	8-OCH_3[e]	MeOH-Et_2O	187-189	$C_{18}H_{27}NO_4 \cdot HCl$	CHNCl	1.0
15	8-$NHCOCH_3$	2-PrOH	232-234	$C_{19}H_{28}N_2O_4 \cdot HCl$	CHNCl	Weak
16	8-$NHCOC_4H_9$	2-PrOH-Et_2O	153-155	$C_{22}H_{34}N_2O_4 \cdot HCl$	CHNCl	Weak
17	8-$NHCOC_6H_5$	PhMe	128-130	$C_{24}H_{30}N_2O_4 \cdot HCl$	CHNCl	Weak
18	7,8-$(CH_3)_2$[f]	2-PrOH	207-209	$C_{19}H_{29}NO_3 \cdot HCl$	CHNCl	3.0
19[g]	*o*-$CH_2CH{=}CH_2 \cdot C_6H_4OCH_2CHOHCH_2NHCH(CH_3)_2$					1.0
20[h]	*p*-$CH_3CONHC_6H_4OCH_2CHOHCH_2NHCH(CH_3)_2$					3.0

[a]Dose, mg/kg, iv necessary for total β-adrenergic blockade of heart effects produced by isoproterenol (0.3 μg/kg iv) in a reserpinized dog. Each drug was screened using one or a small number of dogs. [b]Cited in ref 1. [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. [d]A modified procedure was used with an unreserpinized dog. The methodology and results were the same as the procedures outlined in ref 1 and 2 using reserpinized dogs. [e]The precursers, 5,8-dihydroxy- and 5-hydroxy-8-methoxytetralone, were prepared as previously described: W. F. Newhall, S. A. Harris, F. W. Holly, E. L. Johnston, J. W. Richter, E. Walton, A. N. Wilson, and K. Folkers, *J. Amer. Chem. Soc.*, 77, 5646 (1955). [f]The precurser 7,8-dimethyl-5-hydroxytetralone was prepared as outlined in W. Cocker, B. E. Cross, A. K. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson, and D. R. A. Whyte, *J. Chem. Soc.*, 1781 (1950). [g]Cited in ref 8. [h]Cited in ref 7.

Table II



Compd	X	Y	Mp, °C	Formula	Analyses	Recrystn solvent
21	6-$CH_2CH{=}CH_2$	O	80-83	$C_{13}H_{14}O_2$	CH	PhMe-C_6H_{14}
22[a]	6-CH_3	O	131-133	$C_{11}H_{12}O_2$	CH	PhH-C_6H_{14}
23[b]	7-CH_3	O	177-179	$C_{11}H_{12}O_2$	CH	PhMe-C_6H_{14}
24[c]	8-CH_3	O	188-190	$C_{11}H_{12}O_2$	CH	PhMe
25	6-NO_2	H, OH	98-100	$C_{10}H_{11}NO_4$	CHN	EtOAc-C_6H_{14}
26	8-NO_2	H, OH	183-185	$C_{10}H_{11}NO_4$	CHN	MeOH-H_2O
27	6-NO_2	O	130-131	$C_{10}H_9NO_4$	CHN	EtOAc-C_6H_{14}
28	8-NO_2	O	254 dec	$C_{10}H_9NO_4$	CHN	EtOAc-C_6H_{14}
29	6-$NH_2 \cdot HCl$	O	226-230 dec	$C_{10}H_{11}NO_2 \cdot HCl$	CHNCl	2-PrOH-MeOH
30	8-$NH_2 \cdot HCl$	O	211-213 dec	$C_{10}H_{11}NO_2 \cdot HCl$	CHNCl	2-PrOH
31	8-$NHCOCH_3$	O	224-226	$C_{12}H_{13}NO_3$	CHN	MeOH
32	8-$NHCOC_4H_9$	O	150-151	$C_{15}H_{19}NO_3$	CHN	PhMe
33	8-$NHCOC_6H_5$	O	223-225	$C_{17}H_{15}NO_3$	CHN	PhMe
34	6-$NHCOC_6H_5$	O	229-231	$C_{17}H_{15}NO_3$	CHN	PhMe
35	6,8-$(NO_2)_2$	O	238-239	$C_{10}H_8N_2O_6$	CHN	EtOAc
36	6-Cl	O	133-135	$C_{10}H_9ClO_2$	CHCl	C_6H_{14}
37[d]	7-Cl	O	200-203	$C_{10}H_9ClO_2$	CHCl	PhMe
38[e]	8-Cl	O	229-231	$C_{10}H_9ClO_2$	CHCl	PhMe

[a]The known β-(2-hydroxy-3-toluoyl)propionic acid [J. D. Raval, K. V. Bokil, and K. S. Nargund, *J. Univ. Bombay*, 7 (3), 184 (1938)] was converted to 22 by the general route outlined in Scheme III. [b]The known precurser 5-methoxy-7-methyltetralone was prepared as reported in ref 3. [c]Prepared from 5-methoxy-8-methyltetralone [W. Cocker, C. Lipman, and D. R. A. Whyte, *Chem. Ind. (London)*, 237 (1950)] utilizing a pyridine hydrochloride fusion reported in ref 4. Compound 24 was also recently reported [M. A. Tobias, *J. Org. Chem.*, 35, 267 (1970)] utilizing an alternate route of synthesis. [d]Prepared according to Scheme III from the known precurser β-(4-chloro-2-methoxybenzoyl)-propionic acid: F. G. Boddar and I. Enayat, *J. Chem. Soc.*, 343 (1967). [e]The precurser 8-chloro-5-methoxytetralone was prepared as outlined in J. W. Huffman, *J. Org. Chem.*, 24, 1759 (1959).

The extract was washed with 5% $NaHCO_3$ (1 × 100 ml) and H_2O (2 × 100 ml), dried with $MgSO_4$, and evaporated *in vacuo* to solid 23: yield 2.62 g (16.6%); mp 158-165°. Recrystallization of the solid from $PhCH_3$-hexane gave the analytical sample, mp 177-179°.

6-Chloro-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (36). A solution of 8.28 g (120 mmol) of $NaNO_2$ in 100 ml of cold H_2O was added dropwise over 30 min to a cooled suspension of 21.3 g (100 mmol) of 29 in 100 ml of 6 *N* HCl. The reaction mixture was stirred

at 0° for 15 min and a solution of 11.9 g (60.0 mmol) of Cu_2Cl_2 in 100 ml of 6 *N* HCl was added dropwise. After the evolution of N_2 gas had ceased, the reaction mixture was heated to boiling for 30 min. Cooling gave a solid which was collected by filtration to give 16.7 g (84.8%), mp 95–110°, of crude **36**. The crude 36 was sublimed at 120° (2 mm) and 7.40 g (37.6%), mp 128–133°, of the purified product was collected. The analytical sample was obtained by recrystallization from hexane, mp 133–135°.

6-Allyl-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (21). Allyl bromide (17.0 g, 140 mmol), anhydrous K_2CO_3 (19.3 g, 140 mmol), and 5-hydroxy-1-tetralone[6] (20.0 g, 124 mmol) were refluxed for 21 hr in dry Me_2CO. The reaction mixture was evaporated *in vacuo* and gave a residue which was dissolved in EtOAc (400 ml). After washing the EtOAc solution with 5% NaOH (2 × 400 ml) and H_2O (1 × 400 ml), the EtOAc was dried with $MgSO_4$ before being evaporated to give 24.6 g (97.5%) of the crude 5-allyloxytetralone.

The crude 5-allyloxytetralone (12.6 g, 61.8 mmol) was heated at reflux in diethylaniline (50 ml) for 28 hr. The reaction mixture was poured into 20% NaOH (1 l.) and extracted with Et_2O (3 × 1 l.). The alkaline phase was acidified with HCl and extracted with $CHCl_3$ (3 × 1.5 l.). The $CHCl_3$ extracts were combined, dried with $MgSO_4$, and evaporated to give 7.20 g (57.2%) of crude **21** which crystallized upon standing. The analytical sample was obtained by recrystallization from $PhCH_3$–hexane, mp 80–83°.

1,5-Dihydroxy-6-nitro-1,2,3,4-tetrahydronaphthalene (25) and 1,5-Dihydroxy-8-nitro-1,2,3,4-tetrahydronaphthalene (26). To a solution of 76.5 g (467 mmol) of 1,5-dihydroxy-1,2,3,4-tetrahydronaphthalene in 750 ml of AcOH, H_2O (150 ml) was added and the solution was cooled to 0° before 70% HNO_3 (59.0 ml) was added. The HNO_3 was added slowly maintaining a reaction temperature below 15°. After 30 min, the reaction mixture was poured onto 5 l. of ice–H_2O and extracted with $CHCl_3$ (2 × 1 l.) and CH_2Cl_2 (1 × 1 l.). An insoluble solid was collected by filtration and 10.4 g (10.7%), mp 179–184°, of homogeneous **26** was obtained. The combined organic extracts were dried with $MgSO_4$ and evaporated *in vacuo* and gave 74.2 g (76.1%) of a brown, oily residue. This crude mixture of products was placed on an acid-washed Al_2O_3 column (1 kg) and eluted with $CHCl_3$–MeOH fractions of 500 ml. Homogeneous **25** was obtained from 1% MeOH–$CHCl_3$ eluate, yield 26.4 g (27.0%). Analytically pure **25** was obtained by recrystallization from EtOAc–hexane: mp 98–100°; λ max, mμ (ε × 10^{-3}) 25% EtOH–0.1 *N* NaOH 237 (13.5), 298 (5.25), 435 (6.25); 25% EtOH–H_2O 215 (13.6), 295 (8.41), 358 (3.56); nmr (DMSO-d_6), aromatic region, δ 7.92 (1 H, d, J = 9.0 cps, C_7H) and 7.20 (1 H, d, J = 9.0 cps, C_8H).

The 8-isomeric product **26** was obtained from the MeOH eluate and gave a total yield of 12.3 g (13.0%), mp 179–184°, when combined with solid recovered from the extraction. The analytical sample btained by recrystallization from MeOH–H_2O: mp 183–185°; ς, mμ (ε × 10^{-3}) 25% EtOH–0.1 *N* NaOH 233 (6.07), 268 (4.77), 19.2); 25% EtOH–H_2O 240 (5.61), 315 (4.87); nmr (DMSO-d_6), aromatic region, δ 7.67 (1 H, d, J = 9.0 cps, C_7H) and 6.87 (1 H, d, J = 9.0 cps, C_6H).

3,4-Dihydro-5-hydroxy-6-nitro-1(2*H*)-naphthalenone (27). To an acetone solution (250 ml) containing 28.5 g (136 mmol) of **25**, a mixture of 15.0 g (150 mmol) of CrO_3 in H_2O (50 ml) and H_2SO_4 (16.5 ml) was added in a dropwise manner below 10°. The reaction was allowed to stir at 0° for 30 min and poured onto ice–H_2O (2 l.). The solid, **27**, which formed was collected by filtration: yield 26.3 g (93.6%); mp 127–128°. The analytical sample was obtained by recrystallization from EtOAc–hexane, mp 130–131°.

3,4-Dihydro-5-hydroxy-8-nitro-1(2*H*)-naphthalenone (28). Using **26** and the procedure outlined above for the preparation of **27**, a crude yield of the 8-nitro analog **28** was obtained in 77.4% yield, mp 250–251° dec. The sample of analytical purity was obtained by recrystallization from EtOAc–hexane, mp 254° dec.

6-Amino-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone Hydrochloride (29). A suspension of 2.07 g (10.0 mmol) of **27** in MeOH (150 ml) was hydrogenated over 100 mg of PtO_2 until the theoretical uptake of hydrogen was observed. The catalyst was removed by filtration after 10 ml of 6 *N* HCl had been added to the reaction mixture The MeOH filtrate was evaporated and a solid product was obtained. The solid residue was recrystallized from 2-PrOH–MeOH and gave the analytically pure **29**: yield 1.15 g (54.0%); mp 226–230° dec.

8-Amino-3,4-dihydro-1(2*H*)-naphthalenone Hydrochloride (30). Compound **28** was catalytically reduced to **30** using the procedure outlined above for the preparation of **29**. An 88% yield of crude solid **30** was obtained, mp 204–212° dec. Recrystallization of the material from 2-PrOH gave the analytical yellow HCl salt, mp 211–213° dec.

8-Benzamido-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (33). To a cold suspension of 4.27 g (19.9 mmol) of **30** in 100 ml of CH_2Cl_2 and Et_3N (20 ml) was added 11.6 ml (100 mmol) of PhCOCl slowly over a period of 30 min. The mixture was refluxed for 2 hr and extracted with 6 *N* HCl (1 × 100 ml), 10% NaOH (1 × 100 ml), and H_2O (2 × 100 ml). The CH_2Cl_2 solution was dried with $MgSO_4$ and evaporated *in vacuo* to give the crude dibenzoyl intermediate.

The benzoyl dreivative was refluxed for 1 hr in a mixture of MeOH–20% NaOH (200 ml, 1:1). The reaction mixture was added to H_2O (250 ml), acidified, and extracted with CH_2Cl_2 (3 × 500 ml). The CH_2Cl_2 extracts were combined, washed with 10% Na_2CO_3 (200 ml) and H_2O (200 ml), and dried with $MgSO_4$. Evaporation of the solvent gave the crude **33**: yield 4.10 g (72.9%); mp 220–222°. One recrystallization from $PhCH_3$ gave the analytical sample: yield 2.65 g (47.2%); mp 223–225°.

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References

(1) C. F. Schwender, S. Farber, C. Blaum, and J. Shavel, Jr., *J. Med. Chem.*, 13, 684 (1970).
(2) R. D. Robson and H. R. Kaplan, *J. Pharmacol. Exp. Ther.*, 175, 157 (1970).
(3) A. M. El-Abbady, F. G. Baddar, and A. Labib, *J. Chem. Soc.*, 3420 (1960).
(4) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, 11, 1009 (1968).
(5) A. W. Baker and A. T. Shulgin, *J. Amer. Chem. Soc.*, 80, 5358 (1958).
(6) D. Papa, E. Schwenk, and H. Breiger, *J. Org. Chem.*, 14, 366 (1949).
(7) A. F. Crowther, R. Howe, and L. H. Smith, *J. Med. Chem.*, 14, 511 (1971).
(8) A. Brandstrom, H. Corrodi, U. Junggren, and T.-E. Jonssen, *Acta Pharm. Suecica*, 3, 303 (1966).

Preparation of Some 7-Oxaandrostane Derivatives

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The conversion of a 5α-7-keto steroid, *via* a *B*-homo lactone, into its 7-oxa analog is outlined. The preparation and endocrinological properties of several 7-oxa derivatives are described.

In recent years, as a result of the investigations on structural modifications of naturally occurring hormones, numerous publications (for leading references, see ref 1) have described the synthesis of novel nucleo-hetero steroids, some of which have exhibited interesting biological activities.[2-4] In spite of the abundance of the various oxa and aza steroids