Menlo Park, Calif., for the CD determination. Dr. H. B. Wood of the Drug Evaluation and Development Section, Chemotherapy Branch, National Cancer Institute, kindly provided the antitumor screening results, and the Walter Reed Institute of Medical Research provided the results of the antimalarial tests.

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

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Bunolol or 5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone was the most potent β-adrenergic blocker of the tetralone series.[1] Side-chain modifications showed that the *tert*-C_4H_9NH group imparted optimum potency.[1] Aromatic substitution neither improved activity nor imparted any significant tissue-selective β blockade.[2] The present study determined what effect substitution or replacement of the cyclohexanone ring portion of bunolol had upon β-adrenergic blocking activity.

Chemistry. The compounds studied were prepared by reaction of the substituted phenols with epichlorohydrin in MeOH containing NaOH. The substituted 2,3-epoxypropoxy intermediates obtained were allowed to react with *tert*-$C_4H_9NH_2$ and gave the desired products. In the preparation of **18**, K_2CO_3 in acetone was used since NaOH led to the hydrolysis of the ester. Analog **20** was prepared in low yield from **19** by its reaction with dimethylsulfinyl anion, similar to a method described in the literature.[3] The benzylidene derivatives **3-5** were prepared from 5-hydroxytetralone utilizing either acid- or base-catalyzed condensation with the approximately substituted benzaldehyde. Catalytic reduction of **3** using 5% Pd/C in EtOH gave the 2-benzyl analog **2**.

Structure-Activity Relationships. The pharmacologic screening of the potential β-adrenergic blocking agents was conducted using methods previously described.[1,4] A series of 20 carbonyl-containing analogs was prepared and evaluated as β-adrenergic blockers. Since the 3-(*tert*-butylamino)-2-hydroxypropoxy side chain had been shown to be necessary for optimum β blockade, that portion of the β-blocker structure was maintained while structural modifications elsewhere were studied.

It was observed that substitution of the tetralone nucleus of bunolol with 2-benzyl (**2**) or 2-benzylidene (**3-5**) reduced activity. Replacement of tetralone by indanone (**6**) also was undesirable. Analogs possessing several fused rings in the aromatic nucleus (**7-9**) similarly possessed reduced potency.

Replacement of the tetralone nucleus by phenyl, substituted in the ortho position with benzoyl (**13**) or acetyl (**10**), resulted in β blockers of potency similar to bunolol (**1**). The corresponding meta and para isomers of **10** and **13** were less active. Other ortho-substituted keto analogs such as cyclohexyl (**16**) and propyl (**17**) were less potent than **13**. None of the analogs reported showed any cardioselective β blockade when their relative blockade of isoproterenol effects on heart rate, contractile force, and blood pressure were compared (Table I).

Preliminary studies showed that the most potent β blocker of this series, **13**, also reversed ouabain-induced cardiac arrhythmias using a screen previously reported.[1]

Experimental Section

The β-adrenergic blocking activity of this series of compounds was evaluated on barbiturate anesthetized mongrel dogs.[1,4] 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 effected. Isoproterenol challenges were interposed midway between doses of the drug in order to evaluate β-adrenergic blocking activity. Results obtained from one or a small number of dogs were reliable and served as a basis for further studies on selected analogs.

Melting points were taken in open capillary tubes on a Mel-Temp and are uncorrected. Each analytical sample had ir, uv, and nmr spectra compatible with its structure. Combustion analysis for C, H, N, and Br, Cl or S gave results within 0.4% of theory.

2-Benzylidene-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (22). A mixture of 19.4 g (120 mmol) of 5-hydroxytetralone,[5] 12.0 g (300 mmol) of NaOH, and 14.8 g (140 mmol) of benzaldehyde was heated at reflux for 2 hr in 100 ml of 50% MeOH. The mixture was allowed to stir at room temperature overnight. The reaction mixture was acidified with 30 ml of concentrated HCl and poured onto 500 ml of ice–H_2O giving the crude solid products as a precipitate, yield 26.1 g (87.3%). Recrystallization of the crude **22** from EtOAc-hexane gave

Table I. $RCH_2CHOHCH_2NHC(CH_3)_3$

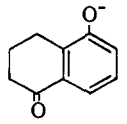
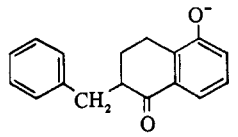
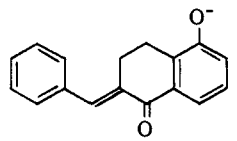
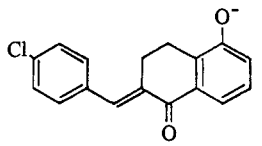
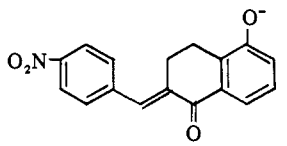
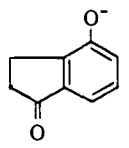
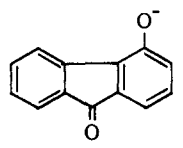
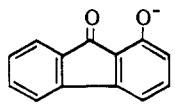
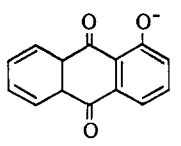
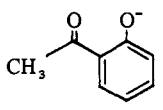
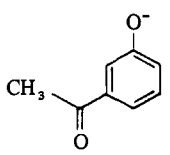
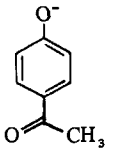
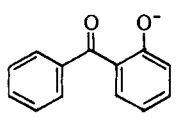
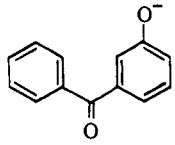
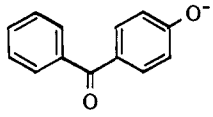
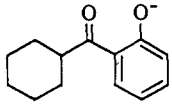
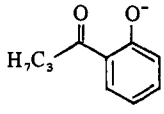
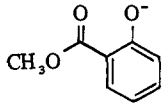
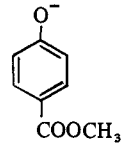
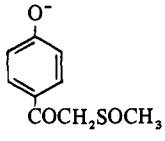
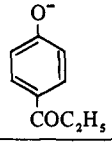
Compd	R	Mp, °C	Solvent	Formula	Analyses	Dose, mg/kg, iv, 100% β blockade[a]
1[b]						0.1
2		157–161	$C_6H_5CH_3$	$C_{24}H_{31}NO_3 \cdot C_7H_8O_3S$[c]	C, H, N, S	Weak
3		175–176	2-PrOH–Et_2O	$C_{24}H_{29}NO_3 \cdot HBr$	C, H, N, Br	Weak
4		239–241	1-PrOH	$C_{24}H_{28}ClNO_3 \cdot HCl$	C, H, N, Cl	Weak
5		260–262 dec	Absolute EtOH	$C_{24}H_{28}N_2O_5 \cdot HCl$	C, H, N, Cl	Weak
6[d]		206–210 dec	EtOH–Et_2O	$C_{16}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	3.0
7[e]		225–226	2-PrOH–Et_2O	$C_{20}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	1.0
8		240–241	1-PrOH	$C_{20}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	3.0
9		263–265	2-PrOH	$C_{21}H_{23}NO_4 \cdot HCl$	C, H, N, Cl	3.0
10[f]		155–157	2-PrOH–Et_2O	$C_{15}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	0.3
11		148–151 dec	2-PrOH (0.5% $C_2H_2O_4$)	$C_{15}H_{23}NO_3 \cdot C_2H_2O_4$[c]	C, H, N	3.0
12		90–92	C_6H_{12}	$C_{15}H_{23}NO_3$	C, H, N	Weak
13		120–121	C_6H_{12}	$C_{20}H_{25}NO_3$	C, H, N	0.1

Table I *(Continued)*

Compd	R	Mp, °C	Solvent	Formula	Analyses	Dose, mg/kg, iv 100% β blockade[a]
14		153–155	2-PrOH	$C_{20}H_{25}NO_3 \cdot HCl$	C, H, N, Cl	Weak
15		145–150	2-PrOH	$C_{20}H_{25}NO_3 \cdot C_2H_2O_4$	C, H, N	Weak
16[g]		219–220	1-PrOH	$C_{20}H_{31}NO_3 \cdot \frac{1}{2}C_2H_2O_4$	C, H, N	Weak
17		168–170 dec	2-PrOH	$C_{17}H_{27}NO_3 \cdot C_2H_2O_4$	C, H, N	0.3
18		144–145	MeOH–Et_2O	$C_{15}H_{23}NO_4 \cdot HCl$	C, H, N, Cl	3.0
19		196–198	MeOH–Et_2O	$C_{15}H_{23}NO_4 \cdot HCl$	C, H, N, Cl	Weak
20		115–120	EtOAc	$C_{16}H_{25}NO_4S$	C, H, S	Weak
21		200–202	1-PrOH	$C_{16}H_{25}NO_3 \cdot HCl$	C, H, N, Cl	Weak

[a]Dose, mg/kg, iv necessary for total β-adrenergic blockade of heart effect produced by isoproterenol (0.3 μg/kg, iv) in dogs. Each drug was screened using one or a small number of dogs. All analogs tested which exhibited incomplete or no blockade at doses greater than 3 mg/kg iv were considered only weakly active as β-adrenergic blocking agents. [b]Cited in ref 1. [c]Oxalic acid and *p*-toluenesulfonic acid were inactive as β blockers. [d]4-Hydroxyindanone was prepared as previously described: J. D. London and R. K. Razdan, *J. Chem. Soc.*, 4299 (1954). [e]Belgium Patent 724,929 (April 12, 1968). [f]W. Kunz, H. Jacobi, and K. Koch, German Patent 1,236,523 (Feb 15, 1962) [*Chem. Abstr.*, 67, 64045j (1967)]. [g]2-Hydroxycyclohexylphenone was prepared according to S. S. Bhargava, *Indian J. Chem.*, 5, 543 (1967).

a tan analytical sample: yield 12.0 g (40.0%); mp 168–171° dec. *Anal.* ($C_{17}H_{14}O_2$) C, H.

2-(4-Chlorobenzylidene)-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (23). Using the procedure outlined for the synthesis of **22**, a crude yield of 31.6 g (92.2%), mp 217–220°, of **23** was obtained from 19.4 g (120 mmol) of 5-hydroxytetralone[5] and 140 mmol of 4-chlorobenzaldehyde. One recrystallization from MeOH–Et_2O gave the analytical sample, mp 229–231°. Anal. ($C_{17}H_{13}ClO_2$) C, H, Cl.

5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-2-(4-nitrobenzylidene)-1(2*H*)-naphthalenone Hydrochloride (5). A reaction mixture containing 6.51 g (40.2 mmol) of 5-hydroxytetralone,[5] 7.56 g (50.0 mmol) of 4-nitrobenzaldehyde, 10 ml of concentrated H_2SO_4, and 50 ml of HOAc was allowed to stir at room temperature for 72 hr. The mixture was poured onto 500 ml of ice–H_2O and 11.9 g (100%), mp 230–240°, of crude solid 2-(4-nitrobenzylidene)-5-hydroxytetralone (**24**) was obtained by filtration.

A methanolic solution (25 ml) of 40.2 mmol of crude **24**, 2.00 g (50.0 mmol) of NaOH, and 25 ml of epichlorohydrin was stirred at room temperature for 66 hr. Evaporation of the mixture gave a solid residue which was dissolved in a mixture of CH_2Cl_2 (300 ml) and 20% NaOH (100 ml). The CH_2Cl_2 phase was separated, washed with H_2O (2 x 100 ml), and dried with $MgSO_4$ before being evaporated to give the crude 5-(2,3-epoxypropoxy)-2-(4-nitrobenzylidene)-1-tetralone (**25**) in a quantitative yield.

The crude epoxide **25** was refluxed with *tert*-$C_4H_9NH_2$ (50 ml) in 100 ml of MeOH for 2 hr. An oily product was obtained upon evaporation of the reaction mixture. A crystalline HCl salt was purified by recrystallization from absolute EtOH yielding 5.72 g (29.5%) of a tan analytical **5**, mp 260–262° dec.

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Book Reviews

Pesticide Chemistry. Edited by A. S. Tahori. Gordon and Breach, New York, N. Y. 1971. Vol. II, Insecticide Resistance, Synergism, Enzyme Induction, with 20 contributors. viii + 302 pp. 16 × 23.5 cm. $12.50. Vol. III, Chemical Releasers in Insects, with 24 contributors. viii + 227 pp. 16 × 23.5 cm. $12.50.

The Second International Congress of Pesticide Chemistry, sponsored by IUPAC and by the Israel National Council for Research and Development, was held in Israel Feb 22–26, 1971. The proceedings of the 18 invited symposia and 14 workshop sessions on various aspects of the chemistry of insecticides, herbicides, and fungicides will be published as a six-volume set entitled "Pesticide Chemistry." The first three volumes relate to insect chemistry. Volumes II and III were published initially and Volume I concerned with insecticides has recently appeared.

The individual presentations vary in length and breadth but all are scholarly and thought provoking. The chapters in Volume II by Fumio Matsumura on the Biochemistry of Resistance to Insecticides, C. F. Wilkinson on the Mode of Action of Synergists, and by I. Ishaaya and W. Chefurka on RNA and Protein-biosynthesis Induction in Housefly Microsomes represent the high-caliber work reported in this volume.

Volume III covers insect hormones, pheromones, and defense substances. The discussion by Peter Karlson on the mode of action of ecdysone and juvenile hormone is an excellent summary of over a decade or work in his laboratory. Equally fine reviews are offered by Beroza, Silverstein, and Roelofs and Comeau on pheromones.

All of the papers are well documented and have sufficient introductory material to allow the nonexpert to grasp the significance of the presentations. Each chapter is preceded by an abstract and, in a few instances, followed by questions, answers, and comments. The composition is not uniform since the books were reproduced directly from original manuscripts. In a few cases structures and tables are minimal for perception by the naked eye, due to photoreduction of the originals. The variety of type and lack of a common format with regard to spacing of lines, citations, paragraph indentation, figure headings, etc., distracts from the volumes; however, these are minor drawbacks when judged against the wealth of current material offered by recognized experts in the field of insect chemistry.

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Methods in Cyclic Nucleotide Research. Edited by Mark Chasin with 11 other contributors. Marcel Dekker, New York, N. Y. 1972. x + 315 pp. 16 × 23.5 cm. $15.75.

This book is not meant to be a comprehensive review but is a collection of methods important in cyclic nucleotide research. The volume is comprised of three main divisions—Assays of Cyclic Nucleotides, Enzymology of Cyclic Nucleotides, and Uses of Whole Cell Systems. The individual chapters of these divisions were written so that each could be used as a laboratory manual, and most of the authors seem to have been successful in doing this.

Part I concerning assays of cyclic nucleotides has a section which is interesting from a historical point of view describing the phosphorylase activation method for quantitation of cyclic AMP. This method was used by Sutherland and his coworkers in much of their work with cyclic AMP and is still used to some extent. Two of the assay procedures given for measurement of cyclic AMP (high-pressure chromatographic purification and ultraviolet monitoring of cyclic AMP and the luciferase-luminescence assay) are relatively time consuming and require fairly specialized equipment although these procedures can also be used for the quantitation of other nucleotides. Details of the immunoassay and the protein kinase binding assay for cyclic AMP are given including not only the actual execution of the assay but also the purification of protein kinase and the preparation of the antibody and [^{125}I] labeled cyclic AMP antigen. The high specificity for cyclic AMP, convenience, and rapidity with which these two assays can be carried out is well known.

The middle section of the book entitled "Enzymology of Cyclic Nucleotides" includes methods of working with cyclic GMP as well as with cyclic AMP. The preparation of membranes and fat cell ghosts for adenyl cylcase assay, as well as preparation and purification of material for assay of guanylate cyclase activity, is described along with the details of several ways of performing the two assays. The isolation and assay for activity of phosphodiesterase are also given. Isolation of cyclic AMP and cyclic GMP specific protein kinases is well described; however, the method given for determination of the activity of protein kinase involving precipitation, centrifugation, dissolution, and reprecipitation of the labeled protein seems rather laborious.

The third section of the book deals with the measurement of cyclic AMP in preparations of whole cells. Procedures are described for the isolation of fat cells and adrenal cortical cells responsive to agents which affect cyclic AMP levels. And finally, the problems of detecting cyclic AMP by producing radioactive pools of ATP in whole cells and tissues are examined. This chapter covers findings from a large number of tissues and might be useful as a short review of the literature on this subject.

Although many of the procedures described in this volume can be found in some form in the literature, the authors give more details here and quite often give warnings and hints which should save time and tempers. This, as well as the wide scope of the work, should make it quite useful as a reference volume.

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Drug Metabolism in Man. Edited by Elliot S. Vessell with 63 contributors. New York Academy of Sciences, New York, N. Y. 1972. 773 pp. 14.9 × 22.7 cm. $35.00.

This volume represents the proceedings of a conference held in mid 1970 in which a reasonably successful attempt has been made to bring together a majority of the individuals who have and are making significant contributions to the study of drug metabolism in man. As might be expected from such a large number of contributors, the presentations run the gamut from broad outlines of the basic problems in the area to detailed studies of the metabolism of specific drugs and finally to a few presentations which would appear to be gratuitous as they have little to do with drug metabolism in man or animals.

Many of the general studies represent the collective efforts of numberous collaborators in the authors' laboratories and are valuable reviews of many basic problems both in the study of the basic mechanisms of drug metabolism at the cellular level and the overall metabolism of drugs in intact humans. Yet most of these reviews have been compiled to give a better understanding of current problems in the various investigators' laboratories rather than from a didactic point of view. Because of this, little attention has been paid to giving an overview of such important areas as the principles and pitfalls of pharmacodynamics or the role of conjugation in drug metabolism. For this reason this volume is definitely not a primer in drug metabolism. On the other hand, it is an invaluable collection of a number of well-rounded studies in drug metabolism in man which will often be cited in the years to come. It is, therefore, a volume which should be of great value to anyone who has an active interest in this area but it cannot be recommended as a general text.

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