[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Bronchodilators, N-Substituted Derivatives of 1-(3′,4′-Dihydroxyphenyl)-2-aminoethanol (Arterenol)

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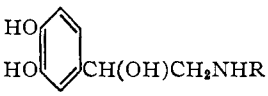
The 1-(3′,4′-dihydroxyphenyl)-2-aminoethanol skeleton, $(HO)_2C_6H_3CH(OH)CH(R')NHR''$, was chosen as the starting point for the synthesis of a wide variety of N-substituted derivatives where R′ was H or alkyl and R″ was *n*-alkyl, branched alkyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, aralkyl, substituted aralkyl and heterocyclic alkyl. The catechol aminoalcohols were obtained by the condensation of chloroacetylcatechol with a primary amine and subsequent catalytic reduction of the aminoketone to the alcohol. The compounds were screened for their broncholytic effect against histamine induced bronchoconstriction in the excised guinea pig lung. The more promising derivatives were further tested for their *in vivo* activity in guinea pigs by the histamine and mecholyl aerosol technique. Several of the N-substituted arterenol derivatives were equal or superior to both epinephrine and Isuprel as bronchodilators and exhibited the same potency when administered by either parenteral or oral route.

The basic structural requirement for potent bronchodilator activity appears to be a catecholethanolamine skeleton[1-3]



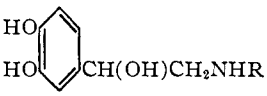
Until recently the N-methyl derivative, epinephrine, occupied the singular position of being the most effective therapeutic agent in the treatment of bronchial asthma. Konzett's[4] important discovery that higher N-alkyl homologs possessed important bronchodilator activity led to the development of another equally useful antiasthmatic agent, Isuprel (N-isopropylarterenol).

The chemical synthesis of several N-alkyl as well as N-cycloalkyl derivatives was described by Corrigan[5] and their pharmacological properties investigated by Siegmund, *et al.*[6] They reported N-isopropylarterenol to be the most active bronchodilator, higher alkyl substituents (butyl and amyl) yielding compounds of lesser potency.

Both epinephrine and Isuprel are limited in their clinical usefulness because of oral ineffectiveness, production of powerful cardiovascular side effects and evanescent action.

Although the work by the aforementioned investigators had shown that N-alkylation beyond the three-carbon chain offered little encouragement for the development of more generally useful bronchodilators, we nevertheless were interested in what effect the incorporation of a number of "pressor amines" into the 3,4-dihydroxyphenylethanol skeleton would have on the bronchodilator effect of the arterenol molecule. The term "pressor amines" is best illustrated by such compounds as 2-aminoheptane, 2-amino-4-methylhexane, β-cyclohexylisopropylamine, β-phenethylamine and β-phenylisopropylamine. We hoped that the introduction of such vasoconstrictor amines might potentiate the bronchodilator properties of arterenol and afford a clinically more satisfactory antiasthmatic agent. In order to see whether these structures yielded compounds of optimum activity we also prepared several of their isomers, isosteres and homologs.

This paper describes the chemistry and preliminary pharmacology of such compounds



where R is alkyl, branched alkyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, aralkyl, substituted aralkyl and heterocyclic-alkyl. The aminoalcohols were obtained by the condensation of chloroacetylcatechol with the appropriate primary amine and subsequent catalytic reduction of the aminoketone to the alcohol. The primary alkyl and cycloalkylamines were readily synthesized by the reduction of the corresponding aldoximes and ketoximes with Raney nickel in alcoholic ammonia at five atmospheres of hydrogen. The ketones, if commercially unavailable, were prepared by the condensation of dialkyl cadmium with acetyl chloride.[7] Catalytic reduction of the appropriate aralkylamines in glacial acetic acid[8] yielded the desired cycloalkylalkylamines.

The aralkyl, substituted aralkyl and heterocyclic-alkylamines were obtained in good yield by the condensation of the appropriate aldehyde with nitroethane,[9] hydrogenation of the nitroalkene to the oxime,[10] followed by the previously mentioned Raney nickel reduction to the primary amine.

Structure–Activity Relationship.—The compounds were screened under the supervision of Mr. P. A. Nuhfer of our Pharmacology Division for their broncholytic effect against histamine-induced bronchoconstriction in the excised perfused guinea pig lung. The data are summarized in Table II.

In the N-alkylarterenol series peak activity was obtained with the six and seven carbon atom chains and with the amino group attached to the second carbon atom of the N-alkyl substituent (no. VIII and XVI). A similar relationship exists in the aliphatic pressor amine series where the 2-hexylamines and 2-heptylamines afford optimum

(1) M. L. Tainter, J. R. Pedden and M. James, *J. Pharmacol. Exptl. Therap.*, **51**, 371 (1934).

(2) C. E. Arbesman, *N. Y. State J. Med.*, **51**, 2361 (1951).

(3) E. Bresnick, J. F. Beakey, L. Levinson and M. S. Segal, *J. Clin. Invest.*, **28**, 1182 (1949).

(4) H. Konzett, *Arch. exptl. Path. Pharmakol.*, **197**, 27 (1940).

(5) J. R. Corrigan, M. Langermann and M. L. Moore, THIS JOURNAL, **71**, 530 (1949).

(6) O. H. Siegmund, N. Beglin and A. M. Lands, *J. Pharmacol. Exptl. Therap.*, **97**, 14 (1949).

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(8) B. Zenitz, E. B. Macks and M. L. Moore, *ibid.*, **69**, 1117 (1947).

(9) H. B. Hass, A. G. Susie and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

(10) D. Nightingale and J. R. Janes, THIS JOURNAL, **66**, 352 (1944).

TABLE I

$3,4\text{-}(HO)_2C_6H_3COCH_2NH—R$

No.	R	Salts formula	M.p., °C.	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-Pentyl	$C_{13}H_{19}NO_3$[a]	150–151	...	...	5.90	5.60
2	*n*-Hexyl	$C_{14}H_{22}ClNO_3$	203–204	12.39	12.34	4.87	5.04
3	2-Hexyl	$C_{14}H_{22}ClNO_3$	195–196	12.39	12.75	4.87	4.92
4	4-Methyl-2-pentyl	$C_{14}H_{22}ClNO_3$	206–208	12.39	12.10	4.87	4.78
5	*n*-Heptyl	$C_{15}H_{24}ClNO_3$	213–215	11.80	11.62	4.64	4.85
6	2-Heptyl	$C_{15}H_{24}ClNO_3$[b]	201–203	...	...	4.64	4.43
7	3-Heptyl	$C_{15}H_{24}ClNO_3$	191–193	11.80	11.87	4.64	4.64
8	4-Methyl-2-hexyl	$C_{15}H_{24}ClNO_3$	204–206	11.80	11.83	4.64	4.71
9	5-Methyl-2-hexyl	$C_{15}H_{24}ClNO_3$	204–206	11.80	11.88	4.64	4.68
10	*n*-Nonyl	$C_{17}H_{28}ClNO_3$	230–233	10.80	10.82	4.24	4.30
11	2-Nonyl	$C_{17}H_{28}ClNO_3$	198–199	10.80	10.47	..	..
12	2-Hydroxyethyl	$C_{10}H_{14}ClNO_4$	195–196	14.33	14.30	5.66	5.59
13	2-Hydroxypropyl	$C_{11}H_{16}ClNO_4$	195–196	13.60	13.41	5.36	5.54
14	Cyclohexylmethyl	$C_{15}H_{22}ClNO_3$	184–185	12.35	12.47	4.87	4.93
15	2-Cyclohexylethyl	$C_{16}H_{24}ClNO_3$	226–228	11.30	11.08	..	..
16	2-Cyclohexylisopropyl	$C_{17}H_{26}ClNO_3$	216–218	10.82	10.78	4.28	4.25
17	1-Phenylethyl	$C_{16}H_{18}ClNO_3$	206–208	11.54	11.33	4.55	4.54
18	2-Phenylethyl	$C_{16}H_{18}ClNO_3$	220–221	11.54	11.36	4.55	4.51
19	3-Phenylpropyl	$C_{17}H_{20}ClNO_3$	218–220	11.03	10.88	4.36	4.33
20	2-Phenylpropyl	$C_{17}H_{20}ClNO_3$	219–220	11.03	11.02	4.36	4.34
21	2-Phenylisopropyl	$C_{17}H_{20}ClNO_3$	206–208	11.03	10.99	4.36	4.35
22	4-Phenyl-2-butyl	$C_{18}H_{22}ClNO_3$	223–225	10.59	10.54	4.17	4.20
23	2-(*p*-Methoxyphenyl)-isopropyl	$C_{18}H_{22}ClNO_4$	203–205	10.11	9.89	3.99	3.97
24	2-(*o*-Chlorophenyl)-isopropyl	$C_{17}H_{19}Cl_2NO_3$	201–203	19.92	20.00	3.93	4.02
25	2-(3′,4′-Methylenedioxyphenyl)-isopropyl	$C_{18}H_{20}ClNO_3$	232–234	9.70	9.59	3.84	3.84
26	2-(α-Furyl)-isopropyl	$C_{15}H_{18}ClNO_4$	181–182	11.41	11.33	4.49	4.55

[a] Free base. [b] *Anal.* Calcd. for $C_{15}H_{24}ClNO_3$: C, 59.40; H, 7.93. Found: C, 59.45; H, 7.91.

pressor activity.[11] Their introduction into the catechol–ethanol skeleton apparently enhanced the bronchodilator properties of the arterenol molecule which is generally described to produce only one-eighth the bronchodilator effect of epinephrine.[12] Placing the amino group in any other position or branching of the alkyl chain generally reduced activity with the exception of compound XVI, where branching occurred at too great a distance from the amino group to exert any influence on the bronchodilator potency of this compound. Replacement of a terminal methyl group by an isosteric hydroxyl group (no. XVIII) did not alter the broncholytic effect of *n*-propylarterenol (no. I).

The cyclopentyl derivative (no. XX) was somewhat more potent than 2-pentylarterenol (no. VII), whereas the cyclohexyl compound (no. XXI) was considerably weaker than any of the straight or branched N-hexylarterenols investigated by us. In the cyclohexylalkyl series the compounds having the amino group in β-position to the ring (no. XXIII, XXIV) afforded better protection against histamine-induced asthma than the cyclohexyl methyl derivative (no. XXII).

Activity in the aralkylarterenol series was closely associated with the position of the amino group in regard to the phenyl ring. Of the two possible phenethyl isomers the β-phenylethyl isomer (no. XXV) was twice as potent as the α-phenylethyl isomer (no. XXVI), while in the phenylpropyl series N-3-phenylpropylarterenol (no. XXVIII) was the most active bronchodilator. It was equal to Isuprel and epinephrine in potency. Lengthening the N-aralkyl chain to phenylbutyl (no. XXX) did not alter the activity.

p-Methoxy substitution in the aralkyl moiety (no. XXXI) of phenylisopropylarterenol (no. XXIX) resulted in a fourfold increase in bronchodilator activity. This compound was twice as potent as either epinephrine or Isuprel and the most effective broncholytic agent of all the compounds described in this paper. Substitution of 4-methoxy by 3,4-methylenedioxy (no. XXXII) decreased activity. Isosteric replacement of the phenyl ring in compound (XXIX) by a furan ring (no. XXXIII) yielded a derivative of comparable potency.

These agents were screened also for their antihistaminic and antiacetylcholine activity in the excised guinea pig ileum. The most potent histamine antagonists were N-2-hexylarterenol (no. VIII) and N-cyclopentylarterenol (no. XX) with approximately 4% of the activity of Tripelennamine (N,N-dimethyl-N′-benzyl-N′-(α-pyridyl)-ethylenediamine). The other compounds were considerably weaker. Several of the derivatives (no. IX, III, IV, VI, VII and XXX) exhibited an antiacetylcholine effect in the same dilution range as Adiphenine (2-diethylaminoethyl diphenylacetate). There was little correlation between the histaminolytic and cholinolytic activity of these compounds in the gut and their ability to prevent histamine or mecholyl-induced bronchoconstriction in the guinea pig lung. Indeed it would appear that they owe their antiasthmatic activity less to an

(11) E. E. Swanson and K. K. Chen, *J. Pharmacol. Exptl. Therap.*, **88**, 10 (1946).

(12) A. M. Lands, F. P. Luduena, E. Ananenko and J. I. Grant, *Arch. intern. pharmacodynamie*, **83**, 602 (1950).

TABLE II

3,4-$(HO)_2C_6H_3CH(OH)CH_2NH$—R

No.	R	Salts[a] formula	M.p. °C.	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Bronchodilator activity
Epinephrine	Methyl	.....	.....	...	...	..	..	100
I	*n*-Propyl[b]	.....	159–160	...	...	..	..	10
II	*n*-Butyl[b]	.....	141–142	...	...	..	..	8
III	*n*-Hexyl	$C_{14}H_{24}ClNO_3$	166–167	12.20	12.15	4.83	4.98	12
IV	*n*-Heptyl	$C_{15}H_{26}ClNO_3$	106–108	11.70	11.70	4.62	4.83	10
V	*n*-Nonyl	$C_{17}H_{28}ClNO_3$	128–129	10.82	11.14	4.24	4.46	7
Isuprel	2-Propyl[b]	$C_{11}H_{18}ClNO_3$	176–177	14.40	14.34	5.66	5.65	100
VI	2-Butyl[b]	.....	168–169	...	...	..	..	33
VII	2-Pentyl	$C_{15}H_{25}NO_5$[c,d]	123–124	...	...	4.69	4.68	33
VIII	2-Hexyl	$C_{16}H_{27}NO_5$[c,e]	135–136	...	...	4.32	4.14	100
IX	2-Heptyl	$C_{17}H_{29}NO_5$[c,f]	126–127	...	...	4.28	4.20	50
XI	2-Nonyl	$C_{17}H_{28}ClNO_3$	81– 83	10.72	10.42	..	..	17
XII	3-Heptyl	$C_{17}H_{29}NO_5$[c,g]	106–108	...	...	4.28	4.02	10
XIII	3-Methyl-2-butyl[b]	$C_{13}H_{22}ClNO_3$	162–163	12.88	12.62	5.08	5.31	15
XIV	4-Methyl-2-pentyl	$C_{14}H_{24}ClNO_3$	123–125	12.20	12.05	4.83	4.76	25
XV	4-Methyl-2-hexyl	$C_{17}H_{29}NO_5$[c,h]	136–137	...	...	4.28	4.32	25
XVI	5-Methyl-2-hexyl	$C_{17}H_{29}NO_5$[c,i]	126–127	...	...	4.28	4.31	100
XVII	3-Pentyl[b]	$C_{13}H_{22}ClNO_3$	138–139	12.91	12.55	5.08	5.24	10
XVIII	2-Hydroxyethyl	$C_{10}H_{16}ClNO_4$	116–117	14.25	14.29	5.62	5.50	10
XIX	2-Hydroxypropyl	$C_{11}H_{18}ClNO_4$	136–138	13.44	13.32	5.32	5.40	8
XX	Cyclopentyl[b]	.....	183–184	...	...	..	..	50
XXI	Cyclohexyl[b]	$C_{14}H_{22}ClNO_3$	187–188	12.35	12.47	4.87	4.93	4
XXII	Cyclohexylmethyl	$C_{15}H_{24}ClNO_3$	152–153	11.78	11.77	4.65	4.74	2
XXIII	2-Cyclohexylethyl	$C_{16}H_{26}ClNO_3$	162–163	11.24	11.53	4.42	4.50	4
XXIV	2-Cyclohexylisopropyl	$C_{17}H_{28}ClNO_3$	140–141	10.79	10.78	4.25	4.34	17
XXV	2-Phenylethyl	$C_{16}H_{20}ClNO_3$	141–142	11.45	11.60	4.52	4.57	17
XXVI	1-Phenylethyl	$C_{18}H_{23}NO_5$[c,j]	153–154	...	...	4.20	4.24	8
XXVII	2-Phenylpropyl	$C_{17}H_{22}ClNO_3$	65– 70	10.99	10.68	4.33	4.20	2
XXVIII	3-Phenylpropyl	$C_{17}H_{22}ClNO_3$	131–132	10.99	10.82	4.33	4.47	100
XXIX	2-Phenylisopropyl	$C_{17}H_{22}ClNO_3$	139–140	10.99	11.00	4.33	4.31	50
XXX	4-Phenyl-2-butyl	$C_{20}H_{25}NO_5$[c]	70 dec.	...	...	3.88	3.92	100
XXXI	2-(*p*-Methoxyphenyl)-isopropyl	$C_{18}H_{24}ClNO_4$	122–123	10.05	9.86	3.97	3.97	200
XXXII	2-(3′,4′-Methylenedioxyphenyl)-isopropyl	$C_{18}H_{22}ClNO_5$	126–127	9.68	9.60	3.81	3.76	100
XXXIII	2-(α-Furyl)-isopropyl	$C_{15}H_{20}ClNO_4$	70 dec.	11.32	11.20	4.47	4.42	50

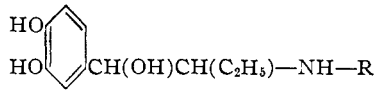
[a] Hydrochlorides unless otherwise indicated. [b] J. R. Corrigan, M. Langerman and M. L. Moore, THIS JOURNAL, **71**, 530 (1949). [c] Acetate salt. [d] *Anal.* Calcd.: C, 60.05; H, 8.34. Found: C, 59.82; H, 8.14. [e] *Anal.* Calcd.: C, 61.30; H, 8.63. Found: C, 61.26; H, 8.69. [f] *Anal.* Calcd.; C, 62.40; H, 8.87. Found: C, 62.42; H, 8.87. [g] *Anal.* Calcd.: C, 62.40; H, 8.87. Found: C, 62.24; H, 8.77. [h] *Anal.* Calcd.: C, 62.40; H, 8.87. Found: C, 62.08; H, 8.75. [i] *Anal.* Calcd.: C, 62.40; H, 8.87. Found: C, 62.49; H, 9.13. [j] *Anal.* Calcd.: C, 64.83; H, 6.92. Found: C, 64.55; H, 6.83.

antagonism toward histamine or acetylcholine but rather to a definite bronchodilator effect of their own which is displayed even in the absence of any constrictor substance.

Several of the more potent derivatives were tested for *in vivo* bronchodilator activity in the guinea pig by the histamine and mecholyl aerosol technique, the drugs being administered both intravenously and orally. Of the N-alkylarterenols the 2-hexyl compound (no. VIII) was the most active agent with the same order of potency as Isuprel. Among the aralkyl compounds 2-phenylisopropylarterenol (no. XXIX) was the best bronchodilator. *p*-Methoxyphenylisopropylarterenol (no. XXXI) proved to be twice as effective as Isuprel in preventing bronchoconstriction.

At equal dosage levels oral administration of these compounds afforded the same protection against histamine or mecholyl-induced asthma as did intravenous administration, which shows that the agents are readily absorbed from the gastrointestinal tract of the guinea pig. No orally effective dose for Isuprel could be established due to the toxic symptoms this compound elicited at a dosage where it might have been active. The acute toxicities following intravenous administration in the guinea pig for compounds XXIX, XXXI and XXXII ranged from 70–140 mg./kg.

In addition to the N-substituted catecholethanolamines several derivatives of 1-(3′,4′-dihydroxyphenyl)-2-aminobutanol were also prepared



(R = 2-phenylethyl, 3-phenylpropyl and 2-*p*-methoxyphenylisopropyl)

The introduction of a β-ethyl group into compounds XXV, XXXI, XXVIII reduced bronchodilator activity by one half to one third. A similar finding was reported by Lands and his co-workers[13] for the corresponding N-isopropyl derivatives.

Conclusion.—The introduction of certain alkyl, aralkyl and substituted aralkylamines into a 1-

(13) A. M. Lands, O. H. Siegmund and E. Ananenko, *Federation Proc.*, **8**, 312 (1949).

(3',4'-dihydroxyphenyl)-ethanol skeleton produced compounds of potent bronchodilator activity and relatively low toxicity. Only clinical trial, however, can establish the therapeutic usefulness of these agents in human asthma which may be quite unrelated to the artificially induced bronchospasms in guinea pigs.

Acknowledgment.—We wish to thank Dr. Harvey L. Daiell for his continued interest throughout the course of this project and Messrs. Harold C. Krahnke and Elmer F. Kluchesky for supplying the analytical data. The microanalytical assays for carbon and hydrogen were performed by Clark Microanalytical Laboratory.

Experimental

Due to the number of steps involved in the preparation of many of the compounds procedures were developed that afforded optimum yields of the desired intermediates. The examples described below are illustrations of the preparative methods employed.

Ketones, 2-Hexanone.—The general directions of Cason[7] were followed. Dibutylcadmium reacted with acetyl chloride in benzene to yield methyl butyl ketone in 50–60% yield, b.p. 123–124°.[14]

Oximes. Procedure A. Methyl *n*-Amyl Ketoxime.—A mixture of 68 g. (0.60 mole) of methyl amyl ketone (Carbide and Carbon Chemicals Co.), 62 g. (0.75 mole) of sodium acetate and 42 g. (0.60 mole) of hydroxylamine hydrochloride in 400 cc. of 50% aqueous ethanol was stirred and refluxed for 7 hours. The water layer was separated and the organic phase washed several times with a saturated sodium bicarbonate solution to remove any acetic acid. The washings were added to the aqueous phase which in turn was extracted repeatedly with ether. The ether extracts were combined with the organic layer, the combined solutions dried with potassium carbonate, filtered and fractionated. The product was collected at 85–87° (7 mm.),[15] yield 70 g. (91%).

Procedure B. *p*-Methoxybenzyl Methyl Ketoxime.—To a mixture of 147 g. (0.73 mole) of 1-(*p*-methoxyphenyl)-2-nitro-1-propene,[9] 184 g. (2.82 moles) of zinc and 730 cc. of isopropyl ether stirred vigorously with a Hershberg stirrer was added 405 cc. of 25% aqueous acetic acid at such a rate as to maintain a vigorous reflux. Stirring and refluxing were continued for 12 hours. The reaction mixture was then filtered with the aid of Celite and washed by suspension with one liter of isopropyl ether. The water layer was separated from the filtrate. The ether layer was washed with 500 cc. of 10% bicarbonate solution, dried with anhyd. potassium carbonate, filtered and distilled. The product was collected at 117–122° (0.05 mm.),[16] yield 96 g. (73%).

Amines. 2-Aminoheptane.—To 70 g. (0.54 mole) of methyl pentyl ketoxime in 300 cc. of 12% alcoholic ammonia was added 6 g. (two level teaspoons of wet catalyst) of Raney nickel catalyst,[17] and the mixture reduced at 60 lb. of hydrogen during a period of 12–15 hours. The catalyst was separated by centrifugation and the alcohol solution fractionated through a 17" Stedman column, b.p. 139°,[18] yield 55 g. (89%).

N-(4-Methyl-2-pentyl)-aminomethyl 3',4'-Dihydroxyphenyl Ketone Hydrochloride.[4]—To 57.0 g. (0.48 mole) of 4-methyl-2-aminopentane in 125 cc. of 60% aqueous ethyl alcohol was added with stirring at reflux temperature 30.0 g. (0.16 mole) of chloroacetylcatechol dissolved in 150 cc. of ethyl alcohol over a period of 2 hours. An inert atmosphere was maintained in the reaction flask by bubbling nitrogen through the solution. The reaction mixture was stirred and refluxed for an additional 4 hours, cooled and acidified with hydrogen chloride gas to *p*H 2. On standing a crystalline precipitate formed which was filtered in a carbon dioxide atmosphere and washed repeatedly with acetone, yield 23 g. (50%), m.p. 206–208° dec.

(14) L. Clarke, THIS JOURNAL, **34**, 681 (1912).
(15) I. Simon, *Bull. soc. chim. Belg.*, **38**, 47 (1929).
(16) O. Wallach and F. Müller, *Ann.*, **332**, 314 (1904).
(17) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).
(18) T. Clarke, *ibid.*, **21**, 1027 (1899).

1-(3',4'-Dihydroxyphenyl)-2-N-(4-methyl-2-pentyl)-aminoethanol Hydrochloride (XIV).—An absolute alcoholic solution of 6.2 g. (0.02 mole) of the aminoketone was reduced with 1.0 g. of a 10% palladium-on-charcoal catalyst at a pressure of 60 lb. of hydrogen. The reaction mixture was clarified by filtration in an atmosphere of carbon dioxide and concentrated to dryness *in vacuo*. The residual oil crystallized when suspended in anhyd. ethyl ether. The crude solid was filtered and purified by suspending it in 10 cc. of ice-cold acetone. The product was collected by filtration, yield 3.1 g. (50%), m.p. 123–125° dec.

1-(3',4'-Dihydroxyphenyl)-2-N-(4-methyl-2-hexyl)-aminoethanol Acetate (XV).—A solution of 8.0 g. (0.025 mole) of the aminoketone in absolute ethyl alcohol was reduced with 0.1 g. of platinum oxide catalyst at a pressure of 60 lb. of hydrogen. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The oily residue was dissolved in water, the aqueous solution neutralized with sodium bicarbonate and the gummy precipitate immediately extracted with *n*-butyl alcohol. The butyl alcohol extract was acidified with glacial acetic acid and again concentrated *in vacuo*. The oily residue was crystallized from 60 cc. of acetone, yield 6.0 g. (75%), m.p. 136–137° dec.

N-(2-*p*-Methoxyphenylisopropyl)-aminomethyl 3',4'-Dihydroxyphenyl Ketone Hydrochloride.[23]—A solution containing 50.0 g. (0.30 mole) of *p*-methoxyphenylisopropylamine, 18.5 g. (0.10 mole) of chloroacetylcatechol in 80 cc. of 60% aqueous ethyl alcohol was stirred and heated at 60° for 6 hours in an atmosphere of nitrogen. The reaction mixture was acidified to *p*H 2 with aqueous hydrochloric acid solution and concentrated to a viscous consistency *in vacuo*. The gummy residue was dissolved in 200 cc. of hot isopropyl alcohol, the solution allowed to cool to room temperature and the crystalline aminoketone collected by filtration. After repeated washings with isopropyl alcohol a light tan colored product was obtained which was purified by suspension in 80 cc. of absolute ethyl alcohol, yield 14 g. (39%), m.p. 203–205° dec.

1-(3',4'-Dihydroxyphenyl)-2-N-(2-*p*-methoxyphenylisopropyl)-aminoethanol Hydrochloride (XXXI).—An alcoholic suspension of 35.5 g. (0.10 mole) of the aminoketone was reduced with platinum oxide at a pressure of 60 lb. of hydrogen, the catalyst removed by filtration and the filtrate concentrated *in vacuo*. The oily residue was washed repeatedly with anhyd. ether, dissolved in hot acetone, seeded and crystallization allowed to proceed at room temperature. A white crystalline product was collected by filtration and washed with acetone, yield 26 g. (73%), m.p. 122–123° dec.

3,4'-Dibenzyloxyphenyl 1-N-(2'-Phenylethyl)-aminopropyl Ketone Hydrochloride.—A mixture of 35.1 g. (0.08 mole) of 1-bromo-3',4'-dibenzyloxybutyrophenone,[19] 19.4 g. (0.16 mole) 2-phenylethylamine and 150 cc. of absolute ethyl alcohol was refluxed for 5 hours. The alcohol was removed by distillation *in vacuo* and the sirupy residue poured into 400 cc. of dry ether. The precipitate of phenylethylamino hydrobromide was removed by filtration and washed repeatedly with dry ether. The ether filtrate and washings were combined and 0.08 mole of ethereal hydrochloric acid added. A gummy mass precipitated which crystallized on standing. The solid was collected by filtration, washed with dry ether and recrystallized from isopropyl alcohol, yield 26 g. (63%), m.p. 174–176°.

Anal. Calcd. for $C_{32}H_{34}ClNO_3$: Cl, 6.89; N, 2.71. Found: Cl, 6.92; N, 2.86.

1-(3',4'-Dihydroxyphenyl)-2-N-(2'-phenylethyl)-aminobutanol Hydrochloride.—A solution of 25 g. (0.049 mole) of the dibenzyloxyphenyl phenethylaminopropyl ketone in 250 cc. of absolute alcohol was subjected to hydrogenation at 60 lb. pressure of hydrogen in the presence of 4 g. of 10% palladium-on-charcoal catalyst. When no more hydrogen was absorbed the catalyst was removed by filtration in an atmosphere of carbon dioxide and 0.3 g. of platinum oxide catalyst added to the filtrate. Hydrogenation was resumed until the theoretical amount of hydrogen had been taken up. The catalyst was again removed by filtration in an atmosphere of carbon dioxide, the filtrate concentrated by distillation *in vacuo* and the sirupy residue dissolved in 200 cc. of hot acetone. On standing for several hours at room temperature a white, crystalline solid separated which was collected by filtration, yield 15.5 g. (94%), m.p. 209–210°.

(19) C. M. Suter and A. W. Ruddy, U. S. Patent Re. 23,100 (1949).

Anal. Calcd. for $C_{18}H_{24}ClNO_3$: Cl, 10.52; N, 4.15. Found: Cl, 10.22; N, 4.13.

1-(3′,4′-Dihydroxyphenyl)-2-N-(2′-*p*-methoxyphenylisopropyl)-aminobutanol Acetate.—An alcoholic suspension of 40 g. (0.072 mole) of crude dibenzylated catechol aminoketone prepared from 1-bromo-(3′,4′-dibenzyloxy)-butyrophenone and 2-*p*-methoxyphenylisopropylamine was reduced successively with palladium-on-charcoal and platinum oxide catalysts as described in the preparation of the phenylethyl derivative. After removal of catalyst and solvent a sticky residue remained which was dissolved in 80 cc. of water and converted to the free base by the addition of 17.7 g. (0.21 mole) of sodium bicarbonate. The gummy precipitate was extracted with three 50-cc. portions of *n*-butyl alcohol and the butanol extracts neutralized with 4.3 g. (0.07 mole) of glacial acetic acid. The butanol was removed by distillation *in vacuo* in atmosphere of nitrogen. The residue was washed with dry ether and then crystallized from a mixture of acetone and ether (crystallization may take as long as two to three weeks). The solid was collected by filtration and washed with acetone–ether, yield 6.5 g. (23%), m.p. 127–129° dec.

Anal. Calcd. for $C_{22}H_{31}NO_6$: N, 3.46. Found: N, 3.28.

1-(3′,4′-Dihydroxyphenyl)-2-N-(3′-phenylpropyl)-aminobutanol Hydrochloride.—This aminoalcohol was prepared by the same procedure as the corresponding phenylethyl compound, yield[20] 28.5%, m.p. 179–180°.

Anal. Calcd. for $C_{19}H_{26}ClNO_3$: Cl, 10.10; N, 3.90. Found: Cl, 9.84; N, 3.65.

(20) Based on crude 3′,4′-dibenzyloxyphenyl 1-N-(3-phenylpropyl)-aminopropyl ketone hydrochloride which could not be purified further.

MILWAUKEE, WISCONSIN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XIV. Basic 1,3-Dioxanes

BY F. F. BLICKE AND E. L. SCHUMANN[1,2]

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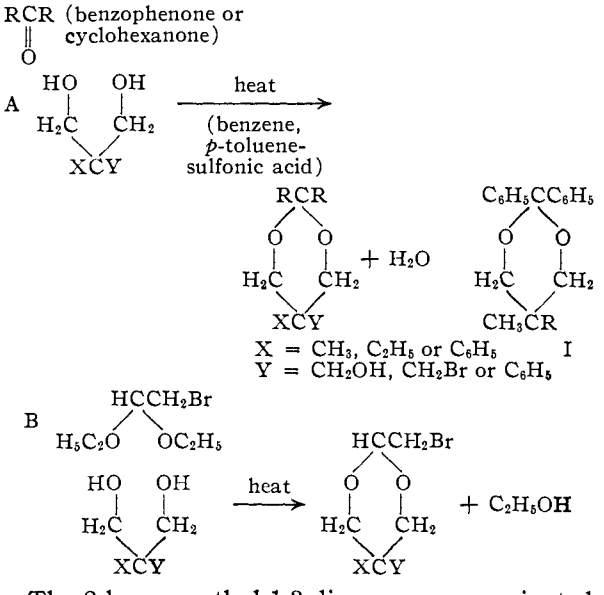
A series of substituted 1,3-dioxanes was prepared and the pharmacological activity of the basic derivatives is reported. The latter are characterized by the presence of a basic-alkyl group in the 2- or 5-position.

This paper describes a further study[3] of basic 1,3-dioxanes.

The bromo and iodo derivatives, listed in Table I, were used as intermediates for the preparation of the basic dioxanes (Table II). These intermediates (Table I) were obtained by the use of the azeotropic distillation method (A)[3] or by the alkoxy replacement process (B).



The 2-bromomethyl-1,3-dioxanes were aminated in the presence of sodium iodide or they were converted into the corresponding 2-iodomethyl derivatives and then aminated.

2,2-Diphenyl-5-methyl-5-iodomethyl-1,3-dioxane (I, R = CH_2I) was converted into the corresponding 5-cyanomethyl derivative which was hydrolyzed to the 5-carboxymethyl compound; esterification of the acid with β-diethylaminoethyl chloride[4] yielded the β-diethylaminoethyl ester (I, R = $CH_2COOCH_2CH_2N(C_2H_5)_2$). Reduction of the 5-cyanomethyl compound produced the 5-(β-aminoethyl) derivative (I, R = $CH_2CH_2NH_2$).

2,2-Diphenyl-5-methyl-5-hydroxymethyl-1,3-dioxane, in the form of its sodium derivative, reacted with β-dimethylaminoethyl chloride to yield the 5-(β-dimethylaminoethoxymethyl) derivative (I, R = $CH_2OCH_2CH_2N(CH_3)$); interaction with β-diethylaminoethyl chloride produced the corresponding diethylamino compound.

2,2-Diphenyl-5-methyl-5-nitro-1,3-dioxane was reduced to the corresponding 5-amino derivative which was methylated to form the 5-dimethylamino compound (I, R = $N(CH_3)_2$).

When 2,2-diphenyl-5-bromo-5-nitro-1,3-dioxane was hydrogenated, in the presence of platinum oxide catalyst, 2,2-diphenyl-5-amino-1,3-dioxane was obtained in very low yield.

The pharmacological data (Table II) were supplied by the research laboratories of the Wm. S. Merrell Company.

Experimental

The following compounds (Table I) were obtained by the azeotropic distillation method (A)[3] in the manner indicated: 2,2-pentamethylene-5-nitro-5-hydroxymethyl-1,3-dioxane (9) from cyclohexanone and trimethylolnitromethane; compounds 10, 11, 12 and 16 by interaction of benzophenone with 2-bromo-2-nitro-,13-propanediol,[5] 2-methyl-2-nitro-1,3-propanediol, 1,1,1-trimethylolethane and 2-ethyl-2-bromomethyl-1,3-propanediol, respectively.

The preparation of compounds listed in Table I, for which method B was used, is illustrated by the following example.

(1) This paper represents part of a dissertation submitted by E. L. Schumann in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) The Wm. S. Merrell Company Fellow.

(3) F. F. Blicke and E. L. Schumann, THIS JOURNAL, **76**, 1226 (1954).

(4) The Horenstein and Pählicke procedure (*Ber.*, **71**, 1644 (1938)) was used.

(5) E. Schmidt and R. Wilkendorf, *ibid.*, **52**, 389 (1919).