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547.577-233.1

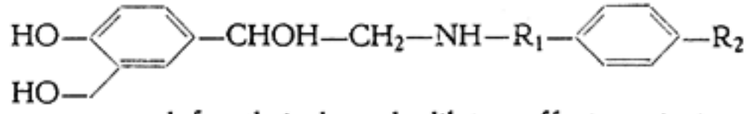
SYNTHESIS OF β-PHENYL-ETHYLAMINE DERIVATIVES. III [1]) BRONCHODILATORS.

BY

H. D. MOED, J. VAN DIJK, and H. NIEWIND

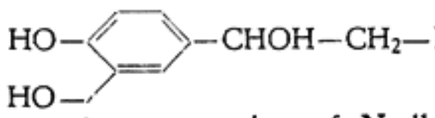
(Contribution from the Central Research Laboratory - N.V. Philips-Roxane, Weesp).

The synthesis is described of a number of β-(m,p-dihydroxyphenyl)-β-hydroxy-N-aralkyl-ethylamine derivatives,

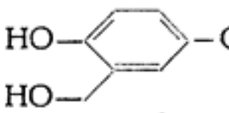


which were screened for their bronchodilator effect against acetylcholine-induced bronchoconstriction in the guinea pig, and for their cardiovascular action.

The influence of the side-chain  on the pharmacological activity of the basic structure,



was investigated. For comparison, a number of N-alkylarterenols were prepared and examined.

At the same time attention was paid to the bronchodilator activity of adrenalone,  and some N-alkyl and N-aralkyl derivatives of noradrenalone.

The U.V. absorption spectra of these sympathomimetics, aminoalcohols as well as aminoketones, were measured.

The results are discussed.

Introduction.

The sympathomimetics epinephrine (adrenalin) and N-isopropyl-arterenol are valuable compounds in the symptomatic treatment of bronchial asthma.

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[1]) II, *H. D. Moed c.s.*, Rec. trav. chim. **71**, 933 (1952).

Their therapeutic use covers a wide range of indications and their effect is obtained swiftly.

However, their activity after oral administration as a rule is poor, and their effect on the circulatory system is undoubtedly a disadvantage.

We therefore set out to find bronchodilators of the epinephrine type with relatively fewer side effects and greater oral activity.

In this investigation we did not consider it worth while to synthesize new N-alkyl- and N-cycloalkylarterenols, because so many of these compounds have already been prepared [2]) and examined [3]).

From the literature it appears that N-isopropylarterenol is the most active bronchodilator. In our opinion N-(phenyl-sec. butyl)arterenol, the strong bronchodilator effect of which has been published [4]), can be chosen as a starting point.

This derivative of epinephrine still has a pronounced effect on the circulatory system.

We investigated whether, and to what extent, the chemical structure of this substance could be changed into compounds in which the bronchodilator effect exceeds the effect on the cardiovascular system. At the same time attention was paid to the activity of such derivatives after oral administration.

We started with the synthesis of a number of N-aralkylarterenol derivatives. By varying the length and the branching of the alkylene group and by introducing substituents (OH, CH_3) into the benzene nucleus of the aralkyl group, the series of aralkylated sympathomimetics developed by *Külz* [5]) could be extended with a large number of new compounds. In order to have material available for comparison with regard to the pharmacological examination, a number of N-alkylarterenols were also prepared (IV).

On account of the publication by *Schneider c.s.* [6]) on the bronchodilator effect of adrenalone and its derivatives, a number of type III compounds were included in our investigations. These relate to the chemical synthesis, the determination of the U.V. absorption spectra, and the pharmacological properties of the above-mentioned compounds. The present paper describes the chemistry of the compounds

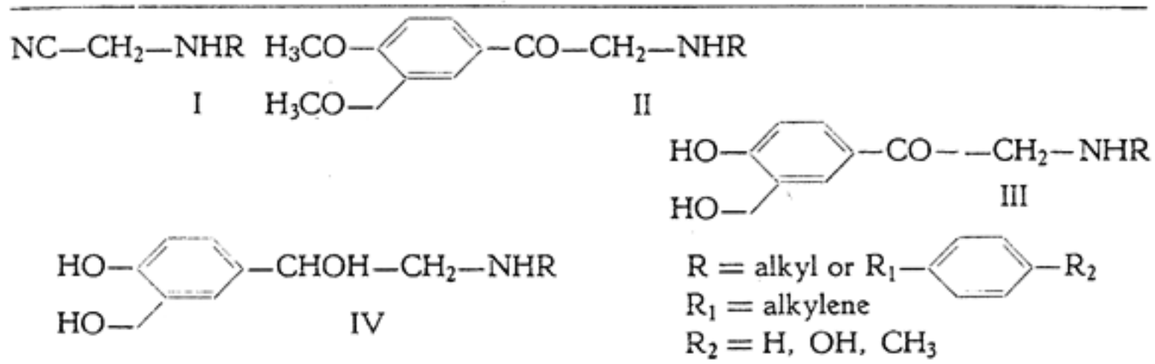
[2]) *J. R. Corrigan c.s.*, J. Am. Chem. Soc. **71**, 530-1 (1949).

[3]) *H. Konzett*, Arch. exptl. Pathol. Pharmakol. **197**, 41 (1940—'41); *O. H. Siegmund c.s.*, J. Pharmacol. Exptl. Therap. **97**, 14 (1949); *D. E. Marsh c.s.*, J. Pharmacol. Exptl. Therap. **92**, 108 (1948); *P. Siderius*, Acta Physiol. et Pharmacol. Neerl. **2**, 546 (1951).

[4]) *K. Wiemers*, Arch. exptl. Pathol. Pharmakol. **213**, 343 (1951).

[5]) *F. Külz*, Arch. exptl. Pathol. Pharmakol. **181**, 136 (1936); *F. Külz* and *K. W. Rosenmund*, Arch. exptl. Pathol. Pharmakol. **181**, 135 (1936); *F. Külz* and *M. Schneider*, Klin. Wochschr. **1950**, 535.

[6]) *M. Schneider c.s.*, Klin. Wochschr. **1950**, 709.



The amino-alcohols were obtained through catalytic reduction (Pd on C) of the hydrochlorides of the aminoketones, dissolved in water or in a mixture of alcohol and water. The bases were isolated by ammoniation of the hydrogenated solution, concentrated *in vacuo* under nitrogen. The arterenols, which became solid in a short time, were purified by extraction with hot water or by crystallization from methanol or dioxane.

Some N-alkylarterenols were isolated as salts. Hydrogenation in alcohol involved difficulties: ethoxylation of the CHOH-group in some of the arterenols took place, probably under the influence of the weak acid medium.

The N-aralkylarterenols with two asymmetrical C-atoms (IV 12, 14, 15, 16, 18, 19, 25, 27 in table II) may belong to two stereochemical series. As the compounds were prepared in a similar way and the melting points are close to each other, while there is little difference in the bronchodilator activity of the crude bases and those purified to a constant melting point, it is not unlikely that these amino-alcohols will belong to the same stereochemical series.

In order to be able to reduce the possible influence of this uncertain factor in the study and the comparison of the pharmacological activities, we prepared a number of N-aralkylarterenols without an asymmetrical C-atom in the side-chain (IV 20, 22, 23,, 24 and 26 in table II).

The yields, melting points, and analyses of the N-(ar)-alkylarterenols have been summarized in table II.

The aminoketones (III) were obtained by demethylation [1]) of the ω-amino-m, p-dimethoxy-acetophenones (II), prepared by condensation of veratrole with aminoacetonitriles (I) [1]).

Melting points and analyses of the hydrochlorides of I, II, and III, and the yields of the hydrochlorides of II and III have been listed in table I.

The U.V. absorption spectra of the amino-alcohols (IV) and the aminoketones (III) were measured *) under the supervision of Dr. *K. J. Keuning* and *Drs. F. J. Mulder* of our Analytical Department. The data (λ_{max}, ε_{max}) are summarized in tables II and I.

*) Ca.3 mg in 100 ml of ethanol.

Table I.

Yields, melting points, analysis, u.v. absorption spectra ($\lambda_{max.}$ and ε), bronchodilator activity

	R	I Hydrochlorides of $RHN-CH_2-C\equiv N$			II Hydrochlorides of $RHN-CH_2-CO-C_6H_3(OCH_3)_2$			III Hydrochlorides of $RHN-CH_2-CO-C_6H_3(OH)_2$							
		M.P. °C[1])	Analysis % Cl found	Analysis % Cl calc.	Yield %	M.P. °C[1])	Analysis % Cl found	Analysis % Cl Calc	Yield %	M.P. °C[1])	Analysis % Cl found	Analysis % Cl calc.	U.V. Abs. Spectrum λ_{max} mμ	ε	Bronchodilator Activity[5])
1	H				[2])										
2	CH_3-				[2])								232	12100	279 8500 312 7300 1
3	CH_3-CH_2-	141—142	29.46	29.42	*)67	190—192	13.18	13.66	[3])71	255—257	15.15	15.31			
4	$CH_3-CH_2-CH_2-$	*)94—97	26.24	26.36	*)62	193—194	12.98	12.96	[3])82	240—241	14.49	14.44			≲ 0.03
5	$(CH_3)_2CH-$				[2])				[3])				232	12900	279 8900 312 7800 ≲ 0.05
6	$CH_3-CH_2-CH_2-CH_2-$				[2])				[3])						
7	$CH_3-C(CH_3)_2-$				[2])				[3])						≲ 0 05
8	$CH_3-C(CH_3)_2-CH_2-C(CH_3)_2-$	*)198—201	17.40	17.33	*)52	208—211	10.23	10.32	*)44	199,5—201	11.40	11.23			
9	$C_6H_5-CH_2-CH_2-$	*)137—140	18.32	18.04	*)73	219—220	10.56	10.56	*)79	220—222	10.92	11.53[6])			≲ 0.05
10	$p.CH_3-O-C_6H_4-CH_2-CH_2-$	*)158—159	15.70	15.65	*)82	209—211	10.63[4])	9.70							
11	$p.HO-C_6H_4-CH_2-CH_2-$								*)43	202--204	10.95	10.96			
12	$C_6H_5-CH_2-CH(CH_3)-$	*)170—171	16.85	16.84	*)77	213—215	10.34	10.14	*)60	208—211	10.96	11.02			≲ 0.05
13	$p.CH_3-O-C_6H_4-CH_2-CH(CH_3)-$	*)174—175	15.17	14.74	*)70	203—205	9.28	9.34							
14	$p.HO-C_6H_4-CH_2-CH(CH_3)-$								*)75	163—166	10.50	10.50			≲ 0.1
15	$p.H_3C-C_6H_4-CH_2-CH(CH_3)-$	*)168—169	15.91	15.79	*)73	200—202	9.81	9.75	*)67	176—180	10.43	10.56			≲ 0.1
16	$C_6H_5-CH_2-CH_2-CH(CH_3)-$	[2])139—140	15.85	15.79	[2])69	216—218	9.68	9.75	*)88	225—227	10.54	10.56	232	13600	279 9200 312 8100
17	$p.CH_3-O-C_6H_4-CH_2-CH_2-CH(CH_3)-$	*)161—163	13.87	13.95	*)57	210—212	9.04	9.02							
18	$p.HO-C_6H_4-CH_2-CH_2-CH(CH_3)-$								*)86	231—235	10.13	10.08	228	18700	281 10600 312 7900
19	$p.H_3C-C_6H_4-CH_2-CH_2-CH(CH_3)-$	*)119—120	14.80	14.88	*)63	193—196	8.72[4])	9.41	*)85	196—200	10.17	10.17			
20	$C_6H_5-CH_2-C(CH_3)_2-$	*)214—215,5	16.47[4])	15.79	*)68	238—240	9.85	9.75	*)79	227—230	10.54	10.56			≲ 0.02 ≲ 0.05
21	$p.CH_3-O-C_6H_4-CH_2-C(CH_3)_2-$	*)208—209	14.60[4])	13.95	*)50	217—220	9.49	9.02							
22	$p.HO-C_6H_4-CH_2-C(CH_3)_2-$								*)78	252—253	10.18	10.08			
23	$p.H_3C-C_6H_4-CH_2-C(CH_3)_2-$	*)217—218	15.63[4])	14.86	*)37	223—224	9.13	9.39	*)47	234—235	10.24	10.14			
24	$C_6H_5-CH_2-CH_2-C(CH_3)_2-$	*)202—203	15.48[4])	14.86	*)48	223—225	9.02	9.39	*)79	227—230	10.07	10.14			
25	$C_6H_5-CH_2-C(CH_3)(C_2H_5)-$	*)198—199	15.62[4])	14.86	*)34	218—220	9.53	9.39	*)45	206—208	10.40	10.14			
26	$C_6H_5-CH_2-CH_2-CH_2-C(CH_3)_2-$	*)187—190	14.45	14.04	*)68	221—223	8.50[4])	9.05	*)49	237—240	9.80	9.75			
27	$C_6H_5-CH(CH_3)-CH_2-$	*)165—167	17.70	16.84	*)57	188—190	10.44	10.14	*)80	195—199	11.04	11.02			

*) New compound.

[1]) All the compounds melted with decomposition; m. points are uncorrected.

[2]) *H. D. Moed c.s.*, Rec. trav. chim. **71**, 939 (1952).

[3]) *J. R. Corrigan c.s.*, J. Am. Chem. Soc. **71**, 530-1 (1949).

[4]) Impure compound (see experimental).

[5]) N-isopropylarterenol = 100.

[6]) Product contains 1 aq.

Table II.

Yields, melting points, analysis, u.v. absorption spectra ($\lambda_{max.}$ and ε.), bronchodilator activity.

RHN—CH_2—CHOH—(3,4-dihydroxyphenyl)

R	IV Yield %	IV M.P.[1] °C	Analysis[4], % C found	C calc.	H found	H calc.	N found	N calc.	U.V. Abs. Spectrum λ_{max} mμ	U.V. Abs. Spectrum ε	Bronchodilator Act.	Oral activity at 200 γ
1 H— [2]											2	—
2 CH_3— [2]											50	—
3 CH_3—CH_2— [3] [5]	80	171—172	62.06	62.56	8.15	8.06	6.74	6.63	282	3200	30	—
4 CH_3—CH_2—CH_2—	76	144—145,5									5	—
5 $(CH_3)_2CH$— [2]											100	—
6 CH_3—CH_2—CH_2—CH_2— [3]											5	—
7 CH_3—$C(CH_3)_2$— [2] [6]											150	—
8 CH_3—$C(CH_3)_2$—CH_2—$C(CH_3)_2$— *)	79	139—139,5	67.57	68.33	9.50	9.62	4.59	4.98	282	3250	0,2	—
9 C_6H_5—CH_2—CH_2— *)	80	172—173	69.55	70.34	7.00	6.97	5 14	5.13	282	3090	5	+
10 p.HO—C_6H_4—CH_2—CH_2— *)	56	122—123	62.44	66.44	6.63	6.58	4.74	4.84	280	4700	50	+
11 C_6H_5—CH_2—$CH(CH_3)$— *)	37	154—155	70.42	71.09	7.37	7.32	4.75	4.88	282	3190	100	++
12 p.HO—C_6H_4—CH_2—$CH(CH_3)$— *)	47	167—167,5	66.81	67.34	6.99	6.94	4.51	4.62	280	4780	800	++
13 p.H_3C—C_6H_4—CH_2—$CH(CH_3)$— *)	81	136—138	71.24	71.77	7.65	7.65	4.54	4.65	282	3190	50	+
14 C_6H_5—CH_2—$CH(CH_3)$— *)	80	163—164	70.65	71.77	7.65	7.65	4.75	4.65	282	3190	100	++
15 p.HO—C_6H_4—CH_2—CH_2—$CH(CH_3)$— *)	35	141—143	66.91	68.14	7.18	7.26	4.39	4.42	280	4820	400	++
16 p.H_3C—C_6H_4—CH_2—CH_2—$CH(CH_3)$— *)	66	148—150	72.26	72.39	8.01	7.94	4.29	4.44	282	3180	25	+
17 p.HO—C_6H_4—CH_2—CH_2—$CH(CH_3)$— *)	50	161—162	70.93	71.77	7.57	7.65	4.52	4.65	282	3180	100	+
18 C_6H_5—CH_2—$C(CH_3)_2$— *)	77	160—162	66.36	68.14	7.21	7.26	4.54	4.42	280	4590	800	+
19 p.HO—C_6H_4—CH_2—$C(CH_3)_2$— *)	74	168—169	71.82	72.39	8.08	7.94	4.39	4.44	282	3080	10	+
20 p.H_3C—C_6H_4—CH_2—$C(CH_3)_2$— *)	74	142—143	71.80	72.39	7.99	7.94	4.44	4.44	282	3050	100	+
21 C_6H_5—CH_2—CH_2—$C(CH_3)_2$— *)	56	162—163	72.21	72.39	7.90	7.94	4.38	4.44	282	3090	3	+
22 C_6H_5—CH_2—$C(CH_3)(C_2H_5)$— *)	69	151—152	72.84	72.95	8.28	8.21	4.17	4.25	282	3120	5	+
23 C_6H_5—CH_2—CH_2—$C(CH_3)_2$— *)	43	80—84	69.63	71.09	7.21	7.32	4.76	4.88	282	3000	1	+
24 C_6H_5—$CH(CH_3)$—CH_2— *)												

*) New compound.

1) All the compounds melted with decomposition; m. points are uncorrected.

2) *H. D. Moed c.s.*, Rec. trav. chim. **71**, 943 (1952).

3) *J. R. Corrigan c.s.*, J. Am. Chem. Soc. **71**, 530-1 (1949).

4) The C, H, and N micro-analyses were carried out by Mr. *P. J. Hubers*, Micro-Anal. Dept., Laboratory for Org. Chem., Mun. Univ., Amsterdam.

5) *Isolated as HCl-salt.*

6) *As sulphate.*

The arterenols IV 11, 14, 18, 22 (IV′) possess a diphenol as well as a monophenol configuration.

We considered it worth while to compare the spectra of the four compounds with those of the isolated chromophore groups, phenol and pyrocatechol.

In order to be able to give a correct interpretation of the contributions of the chromophore systems, it was also necessary to determine the extinction curves of type V compounds **)

HO—(C6H4)—CHOH—CH_2—NH—R_1—(C6H5)

V

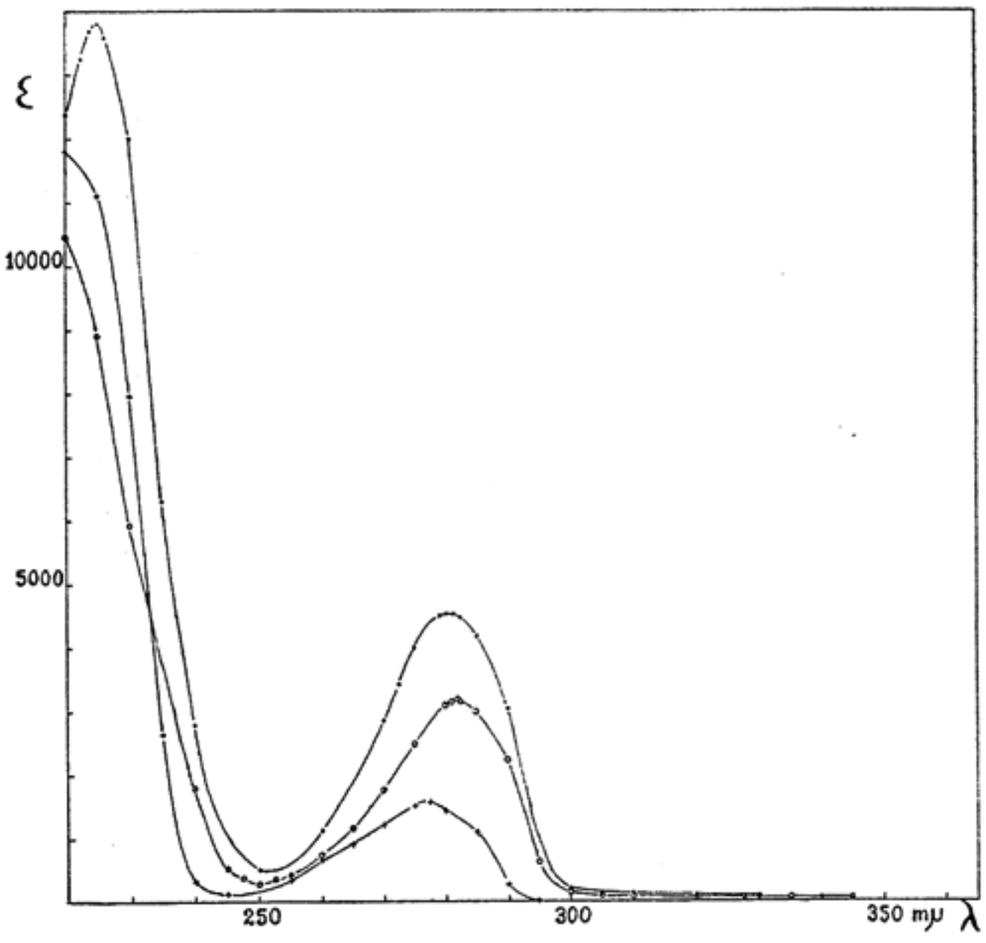


Fig. 1. Molecular extinction curves of three representatives of IV, IV′ and V.

–o–o– = m,p-$(HO)_2C_6H_3$—CHOH—CH_2—NH—R_1—C_6H_5 (IV)
–+–+– = p-HO—C_6H_4—CHOH—CH_2—NH—R_1—C_6H_5 (V)
–.–.– = m,p-$(HO)_2C_6H_3$—CHOH—CH_2—NH—R_1—C_6H_4—p.OH (IV′)

**) The synthesis of these substances will be published at a later date.

In the compounds IV and V, phenol and pyrocatechol form part of molecules with a similar structure.

In fig. I the molecular extinction curves of three representatives of IV, IV′ and V are given.

Figure 2 shows the extinction curves of two types of N-aralkylnoradrenalones (III and III′).

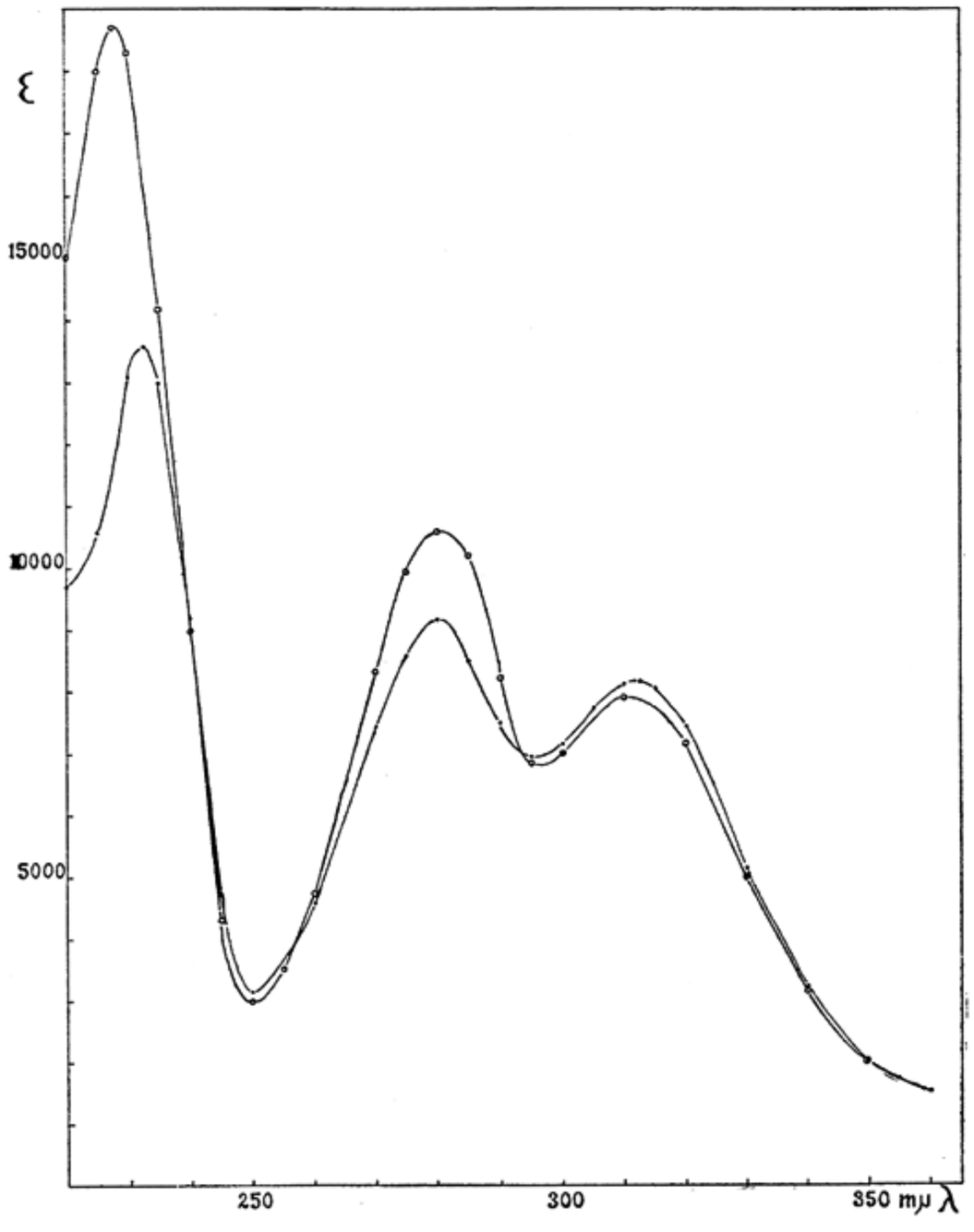


Fig. 2. Molecular extinction curves of the two types of N-aralkylnoradrenalones.

–.–.– = m,p-$(HO)_2C_6H_3$—CO—CH_2—NH—R_1—C_6H_5 (III)
–o–o– = m,p-$(HO)_2C_6H_3$—CO—CH_2—NH—R_1—C_6H_4—p.OH (III′)

The pharmacological research, which will be published elsewhere, was carried out by Prof. Dr. *F. Brücke c.s.* [7]), Prof. Dr. *J. H. Gaarenstroom c.s.* [8]), and Drs. *Th. W. J. Hendriksen* [9]), who kindly permitted us to mention already in this publication the preliminary pharmacology of our compounds.

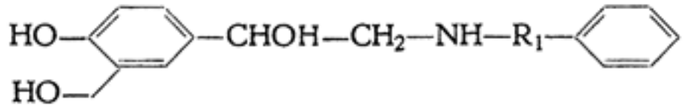
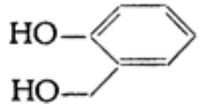
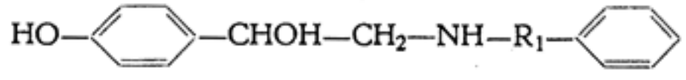
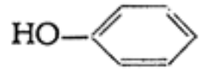
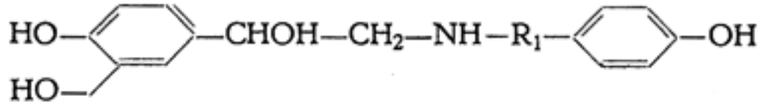
The arterenols and some derivatives of noradrenalone were screened for their bronchodilator effect against acetylcholine-induced bronchoconstriction in the guinea pig [10]). The data are also summarized respectively in tables II and I. Several amino-alcohols were tested for their in *vivo* effect on the circulatory system in dog (heart rate) and cat (blood pressure).

The therapeutic usefulness of some arterenols has been investigated by clinical tests.

Discussion.

U.V. Absorption spectra.

Table III.

	λ_{max} mμ	ε_{max} (average)
IV 	282	3100
	278	2700
V 	277	1600
	273	1800
IV′ 	280	4700

[7]) Pharmacological Laboratory of the University of Vienna.
[8]) Pharmacological Laboratory of the University of Groningen. (Dr. *P. Siderius,* Dr. *B. Louwerens,* Dr. *D. de Wied).*
[9]) Pharmacological Laboratory of N.V. Philips-Roxane.
[10]) Method: *P. Siderius,* Acta Physiol. et Pharmacol. Neerl. **2,** 546 (1951).

The characteristic points in table III refer to the low-intensity B bands of the benzenoid systems. It appears that the effect of the side-chains, in which the absorption of the benzene nucleus is negligible, on the U.V. absorption of phenol and pyrocatechol is slight, but obvious. As a result of the interaction of the π-electrons of the benzenoid system with the σ-electrons of the adjacent bond, the λ_{max} of IV and V have increased by 4 mμ.

The changes in the ε_{max}, however, are different. In spite of the fact that phenol and pyrocatechol have been substituted by the same side-chains, the molecular extinction coefficient has increased for IV and decreased for V. Apparently, the increase of the chromophore area in V has been compensated by a decrease of the transition probability.

The arterenols IV′ have two isolated chromophore systems, in which, just as in IV and V, the π-electrons interact with the σ-electrons of both adjacent bonds in the joint aliphatic side-chain.

One would expect that for every wavelength the following equation holds:

$$\varepsilon_{IV'} = \varepsilon_{IV} + \varepsilon_{V}$$

From figure 1 it can be deduced that this is true indeed.

The molecular extinction curves of the aminoketones have a maximum not only at 280 mμ, but also at 312 mμ. As the amino-alcohols do not absorb at this wavelength, this difference in absorption has been used to demonstrate the possible presence of aminoketones in the amino-alcohols. The N-(p-hydroxyaralkyl)-noradrenalone derivatives (III′) give a greater absorption at 280 mμ as a result of the contribution of the monophenol group in the side-chain (fig. 2, table I).

Structure - Activity Relationship (tables I and II).

It appears from table II, that the side-chain R_1—⬡—R_2 has a great and variable influence upon the bronchodilator activity of the basic structure (arterenol). The N-aralkylarterenols form a group of active bronchodilators, the activity of which is dependent on the structure (length and branching) of the alkylene group and on the substituents in the benzene nucleus of the aralkyl chain.

The influence of the alkylene group can be found by comparing the activities of the arterenols of nos. 9, 12, 16, 20, 24, 25, 26, and 27, summarized in table II. These amino-alcohols have no substituents in the benzene nucleus. *An activity equal to that of N-isopropylarterenol is present in arterenols having the side-chain:*

$$R = \text{—C(H, CH}_3\text{)—(CH}_2\text{)}_n\text{—⬡} \quad CH_3 \qquad n = 1, 2 \text{ (nos 12, 16,20, and 24)}$$

These side-chains are characterized by the presence of one or two methyl groups at the C atom beside the N atom and an alkylene group with from three to six C atoms. In the side-chain of no. 26 the branched alkylene group has been lengthened to four C atoms:

$$R = \text{—C(CH}_3\text{)}_2\text{—(CH}_2\text{)}_3\text{—⬡}$$

This has led to a considerable decrease in activity. The same effect is obtained when the methyl group at the α-C atom is replaced by an ethyl group:

$$R = \text{—C(CH}_3\text{)(C}_2\text{H}_5\text{)—CH}_2\text{—⬡} \qquad \text{(no 25 in table II)}$$

It is worth mentioning that the isomeric aralkyl chains of nos 24 and 25 have a mutually different influence on the bronchodilator activity of the basic structure. The same is true for the side-chains of nos 12 and 27.

The effects of the substituents methyl and hydroxyl in the benzene nucleus of the aralkyl group are by no means the same. The methyl group diminishes (nos 12 and 15, 16 and 19, 20 and 23) and the hydroxyl group (nos 9 and 11, 12 and 14, 16 and 18, 20 and 22) increases the bronchodilator activity. A number of N-(p-hydroxyaralkyl)arterenols have greater activity than N-isopropylarterenol. It may be assumed to be highly probable that *arterenols with the following side-chains are the most active bronchodilators ever examined:*

$$R = \text{—C(H, CH}_3\text{)—(CH}_2\text{)}_n\text{—⬡—OH} \quad CH_3 \qquad n = 1, 2. \text{ (nos 14, 18, 22 in table II)}$$

Comparing the effect of the side-chains R_1—⬡—R_2 and R_1H, we see little difference after intravenous administration (nos 5 and 12, 7 and 20, 3 and 9 in Table II). An exception is formed by nos 4 and 27, where the N-aralkyl derivative is less active.

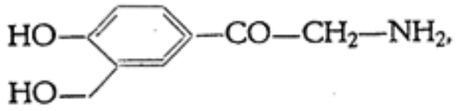
With regard to some N-aralkylarterenols we have established the fact that, after oral administration, they give protection against

histamine-induced asthma in the guinea pig at lower dosage levels than do the N-alkylarterenols (Table II, last column). This shows that the first-mentioned agents are readily absorbed from the gastro-intestinal tract of the guinea pig. Apparently, the phenyl group is responsible for the greater oral effectiveness of these N-aralkyl-arterenols.

It is interesting to compare our results with those of *Ludwigs* and *Schneider* [11]). These investigators studied the effect of various aralkyl side-chains upon the bronchodilator activity of a number of basic structures (β-phenyl-ethylamine derivatives). One of these basic structures was arterenol. *Ludwigs* and *Schneider* arranged the side-chains in the order of their bronchodilator activity (activity series). Apparently, their starting point was the unproved premise that the influence of the side-chains would be similar for all basic structures. We believe this assumption to be erroneous.

In our opinion, it may be assumed that each type of epinephrine derivative has its own rules concerning the influence of the side-chain structure upon the pharmacological activity of the compound. *Ludwigs* and *Schneider* included only a relatively small number of N-aralkyl-arterenols in their investigations. On the other hand, we have been able to prepare and to test a more complete series of N-aralkylated arterenols. The difference between their activity series and that which can be deduced from the bronchodilator activities of our arterenols (Table II) must be ascribed to this fact.

Of our aminoketones, derivatives of arterenone (noradrenalone),



adrenalone is the most active bronchodilator. In this series there is no evidence of any connection between the bronchodilator activity and the side-chain structure.

Ludwigs and *Schneider* also included some derivatives of noradrenalone in their research. From Table I it can be deduced that our results do not agree with the mentioned activity series either.

The N-aralkylarterenols described in the present paper lower the blood pressure of the cat and accelerate the heart rate of the dog in different degrees after intravenous administration. It has been shown that in the compounds mentioned as a rule the tachycardia in the dog and the bronchodilator effect in the guinea pig are parallel. Clinical tests have shown that the bronchodilator activity of N-(p-hydroxy-phenylisopropyl) arterenol is much greater than that of epinephrine and isopropylarterenol.

11) *N. Ludwigs* and *M. Schneider*, Arch. exptl. Pathol. Pharmakol. **218**, 432 (1953).

Note. After the completion of this investigation we read the publication by *John H. Biel c.s.* about bronchodilators, N-substituted derivatives of arterenol [12]). The pharmacological activity of some of these compounds has been published by *Seibert* and *Handley* [12a]).

During our investigation we became acquainted with *John H. Biel*'s preliminary communication (Abstr. of Papers, 121st meeting Am. Chem. Soc., 1952) about the same subject.

Experimental. [13])

A. **Amines (H_2N—R)** (table I).

These data refer to new compounds and to those amines for which we deviated from the directions given in the literature.

a) The amines **H_2N—R 10, 13, and 15** were prepared by reduction with $LiAlH_4$ of the corresponding arylnitroalkenes [14]), obtained from the aromatic aldehyde and a nitroalkene (Table IV).

Table IV.

Arylnitroalkenes	Yield %	B.p./mm	Amines	Yield %	B.p./mm
CH_3—C_6H_4—CH=C(CH_3)NO_2 *)	55	135-139/10	H_2N—R_{15}	67	103—105/10
CH_3O—C_6H_4—CH=C(CH_3)NO_2	54	174/3	H_2N—R_{13}	60	129—132/8
CH_3O—C_6H_4—CH=CH—NO_2 [15])	82		H_2N—R_{10}	69	132—136/12

1-p-Tolyl-isopropylamine-2 (H_2N—R_{15}).

A mixture of 50 ml (0.65 mol.) of concentrated ammonia, 60.2 grams (0.375 mol.) of nitroethane, 4 ml of n-butylamine, and 35 ml of absolute ethanol is refluxed for 6 hours, after which the solvent is distilled and the residue fractionated *in vacuo*. Yield: 19.4 grams of *1-(p-tolyl)-2-nitropropene*.

A solution of this nitro-compound in 200 ml of absolute ether is slowly added with continuous stirring to a solution of 20 grams of $LiAlH_4$ in 500 ml of absolute ether, so that the reaction mixture is just boiling. By cautiously adding wet ether

12) *John H. Biel c.s.*, J. Am. Chem. Soc. **76**, 3149 (1954).

12a) *R. A. Seibert* and *C. A. Handley*, J. Pharmacol. Exptl. Therap. **110**, 304 (1954).

13) In collaboration with *D. Trap* and *W. van Wageningen*. The micro-analyses were carried out by *P. J. Hubers*. The melting and boiling points have not been corrected. Compounds marked *) are new.

14) *F. A. Ramirez* and *A. Burger*, J. Am. Chem. Soc. **72**, 2781 (1950).

15) *K. W. Rosenmund*, Ber. **42**, 4780 (1909).

and water, the reaction mixture is decomposed. The hydroxides are filtered with suction, and the filtrate is shaken with 2N hydrochloric acid (150 ml); then an excess of 50 % caustic soda solution is added and the oil layer is dissolved in ether. After drying over NaOH, the ether is distilled and the residue fractionated *in vacuo* (11.0 grams).

Analysis:

$C_{10}H_{15}N$. Calc.: Equivalent weight 149.
Found: „ „ 149.

b) The amines **H_2N—R 20, 21, 24, 25 and 26** were prepared by hydrolysis of the formamides R—NH—CH=O, which were obtained from the carbinols R—OH and HCN [16]) (Table V).

Table V.

Formamides:	Yield %	B.p./mm	Amines:	Yield %	B.p./mm
R_{20}—NH—CH=O	65	186/20	R_{20}—NH_2	87	86—8/13
R_{21}—NH—CH=O [18])	19	ca. 200/1 [17])	R_{21}—NH_2	52	133—5/8
R_{24}—NH—CH=O *)	65	165—7/2	R_{24}—NH_2	75	114—8/20
R_{25}—NH—CH=O	58	160—180/5 [17])	R_{25}—NH_2	95	117—120/14
R_{26}—NH—CH=O *)	27	188/2	R_{26}—NH_2	91	126—130/16

Instead of with caustic soda solution [16]), the intermediates were hydrolyzed with 6N hydrochloric acid:

The formamide (200 grams) is refluxed for half an hour with 450 ml of 6N hydrochloric acid and, after cooling, the reaction mixture is extracted with ether. Then an excess of 50 % caustic soda solution is added, the amine is dissolved in ether, the solution is dried over Na_2SO_4, the ether is distilled, and the residue is fractionated *in vacuo*.

The amine **H_2N—R_{23}** *) was obtained in a different way [19]):

p-Tolyl—t.butylamine (H_2N—R_{23})

A solution of 187 grams (2.10 mol.) of 2-nitropropane, 210 grams (1.75 mol.) of p-tolylaldehyde, and 9.2 grams of sodium in 700 ml of absolute methanol, after standing for 24 hours is acidified with acetic acid and the methanol is distilled. The residue is dissolved in ether, extracted successively with a sodium bisulphite solution and water, dried over Na_2SO_4, and then the ether is distilled.

To a solution of the residue in a mixture of 370 ml of ethanol, 380 ml of glacial acetic acid, and 490 ml of water are added, with continuous stirring, 195 grams of zinc dust, and the reaction mixture is heated to 70° for six hours. It is then diluted with 875 ml of water and, after filtration, an excess of 50 % caustic soda solution

[16]) *J. J. Ritter* and *J. Kalish*, J. Am. Chem. Soc. **70**, 4048 (1948).
[17]) The product contains carbinol.
[18]) From p-CH_3O—C_6H_4—CH=$C(CH_3)_2$ and HCN; U.S.P. 2.597.446.
[19]) *B. L. Zenitz, E. B. Macks,* and *M. L. Moore*, J. Am. Chem. Soc. **70**, 955 (1948).

is added. The mixture is extracted with ether, dried over Na_2SO_4, and acidified with 5N alcoholic hydrochloric acid.

The hydrochloride of *1-(p-tolyl)-2-amino-2-methylpropanol-1* *) is filtered and dried (40 grams). Melting point 262—263° C (decomposition).

Analysis:

$C_{11}H_{17}ON$. HCl Calc. : C 61.27; H 8.36; Cl 16.45;
Found: „ 61.26; „ 8.24; „ 16.25.

A mixture of 42.5 grams (0.197 mol.) of the hydrochloride, 8 grams of red phosphorus, and 70 ml of 57 % HI-solution is refluxed for 25 hours and then poured into 270 ml of water. The reaction mixture is filtered, and an excess of 50 % caustic soda solution is added; the mixture is extracted with ether, dried over Na_2SO_4, and fractionated *in vacuo*, after distilling the ether. Yield: 24.5 grams (0.150 mol.) of *p-tolyt-t.butylamine* *) or 76 %.

Boiling point: 100–102° C/10 mm.

Analysis:

$C_{11}H_{17}N$ Calc. : Equivalent weight 163.
Found: „ „ 164.

c) The amines **H_2N—R 16, 17, and 19** were obtained by reductive amination of the corresponding benzal acetones [20]).

p-Tolyl-sec. butylamine (H_2N—R_{19}).

A mixture of 50 ml (0.65 mol.) of concentrated ammonia, 60.2 grams (0.375 mol.) of p-methylbenzalacetone, 200 ml of ethanol, and 20 grams of Raney nickel catalyst is hydrogenated at room temperature and atmospheric pressure. The reaction mixture is filtered, acidified with hydrochloric acid, and the alcohol distilled *in vacuo;* the residue is dissolved in water and the non-basic compounds are extracted with ether.

Then an excess of 50 % caustic soda solution is added, the amine is dissolved in ether and dried over sodium hydroxide; the ether is distilled and the residue is fractionated (29.0 grams = 47 %). Boiling point: 115—117° C/10 mm.

Analysis:

$C_{11}H_{17}N$. Calc.: Equivalent weight 163.
Found: „ „ 163.

B. **Amino-aceto-nitriles** (table I, I).

The preparation took place according to *Biltz* and *Slotta* [21]) (I, 1,2) and according to *Knoevenagel* and *Mercklin* [22]). The impure hydrochlorides may be contaminated with some R—NH_2 . HCl.

C. **ω-Amino-m,p-dimethoxyacetophenones** (table I, II).

These were prepared according to the directions given in a former publication [23]). Instead of with alcohol-acetone, the N-aralkyl derivatives were washed con-

[20]) *L. Haskelberg,* J. Am. Chem. Soc. **70**, 2811 (1948); *R. A. Davies* and *R. D. Howard,* J. Chem. Soc. **1947**, 191.
[21]) *H. Biltz* and *K. Slotta,* J. pract. Chem. 2 **113**, 252 (1926).
[22]) *E. Knoevenagel* and *H. Mercklin,* Ber. **37**, 4089 (1904); Org. Synth. **27**, 20 (1947).
[23]) *H. D. Moed c.s.,* Rec. trav. chim. **71**, 940 e.v. (1952).

secutively with ether and with water, in which these hydrochlorides, which are soluble in ethanol, are practically insoluble. The impure hydrochlorides, which were contaminated with $AlCl_3 . 6 H_2O$ and (or) nitrobenzene, were demethylated without further purification.

D. **ω-Amino-m,p-dihydroxy-acetophenones** (table I, III).

The directions for the demethylation were taken from a former publication [23]). In many cases more 48 % HBr-solution was used, because a number of ω-aminoketones are difficultly soluble. The hydrobromides of the N-aralkylnoradrenalones were washed with water instead of with acetone.

E. **β-(m,p-Dihydroxyphenyl)-β-hydroxy-N-(ar)alkylethylamine derivatives** (table II, IV).

The N-alkylaminoketones were hydrogenated in water at room temperature and atmospheric pressure.

N-t.Octyl-arterenol (IV, 8).

A mixture of 4.5 grams (0.0143 mol.) of the hydrochloride of ω-(1,1,3,3-tetramethyl)-butylamino-m,p-dihydroxy-acetophenone (III, 8), 15 ml of 1 % palladium chloride solution, 1.5 grams of norite, and 120 ml of water is hydrogenated. The catalyst is filtered, the solution is concentrated to a small volume, and 5 ml of ammonia (3N) are added. After standing for an hour, the solid material is separated by suction and dried *in vacuo* over P_2O_5.

Yield: 2.5 grams of *N-t-octylarterenol* or 63%.

The N-aralkylaminoketones were hydrogenated in water or in a mixture of ethanol and water at room temperature.

N-(Phenyl-t.butyl)-arterenol (IV, 20).

A mixture of 10.0 grams (0.030 mol.) of the hydrochloride of ω-(phenyl-t.butyl)-amino-m,p-dihydroxy-acetophenone, 2 grams of norite, a solution of 330 mg of $PdCl_2$, and 500 ml of water is hydrogenated. The catalyst is separated; the filtrate is evaporated *in vacuo* under N_2 and ammoniated. As soon as the tough mass has become crystalline, it is filtered and dried *in vacuo* over P_2O_5. The crude N-(phenyl-t.butyl)arterenol (83 %) melts at 147–149° C, and is purified by crystallization (twice) from methanol or dioxane (50 %). Melting point: 161–162° C (dec.).

N-(p-Hydroxyphenyl-isopropyl)arterenol (IV, 14).

19.0 grams (0.056 mol.) of ω-(p-hydroxyphenyl)amino-m,p-dihydroxyacetophenone hydrochloride are dissolved in 1000 ml of water and 60 ml of 1 % $PdCl_2$ solution, and 4 grams of norite are added. The mixture is hydrogenated and filtered, and the filtrate is concentrated *in vacuo* under N_2 to a small volume. Ammonia (3N) is added and the base is separated.

The viscous red product weighs 15.0 grams (88 %). The substance is purified by heating with water. The base becomes crystalline, and after cooling it is filtered and dried.

Yield: 8.0 grams (47 %) of *N-(p-hydroxyphenyl-isopropyl)arterenol.*

Melting point: 167–167.5° C (dec.).

N-[(α-Methyl-α-ethyl-β-phenyl)ethyl]arterenol (IV, 25).

A mixture of 15.0 grams (0.043 mol.) of the hydrochloride of ω-(α-methyl-α-ethyl-β-phenyl)ethylamino-m,p-dihydroxyacetophenone, 100 ml of ethanol, 50 ml of 1 % $PdCl_2$ solution, 50 ml of water, and 3 grams of norite is hydrogenated. The catalyst is filtered, the ethanol is evaporated *in vacuo* under N_2, and ammonia is added.

Yield: 10 grams (74 %). Melting point 80–90° C (dec.). The crude base is purified by crystallization from methanol.

Yield: 7.5 grams (56 %) of N-[(α-methyl-α-ethyl-β-phenyl)ethyl]arterenol.

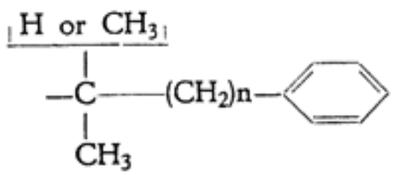
Melting point 162–163° C (dec.).

Summary.

1) A number of β-(m,p-dihydroxyphenyl)-β-hydroxy-N-aralkyl-ethylamine derivatives were prepared in order to obtain bronchodilators (table II).

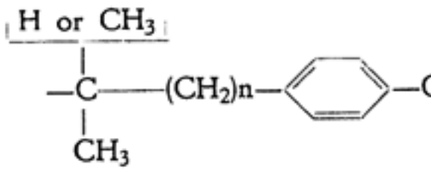
2) These sympathomimetics, derivatives of β-(m,p-dihydroxyphenyl)-β-hydroxyethylamine (arterenol), were obtained by catalytic reduction of the ω-aminoketones, which had been prepared by demethylation of the ω-aralkylamino-m,p-dimethoxyacetophenones synthesized according to *Houben Hoesch* (table I).

3) The bronchodilator activity of arterenols with the side-chains

R =  (n = 1, 2; table II)

is of the same order as the activity of N-isopropylarterenol.

4) The arterenols with side-chains

R =  (n = 1, 2; table II)

are more active than N-isopropylarterenol (4 à 8 ×).

5) As compared with the N-alkyl-, some N-aralkylarterenols show a greater oral activity.

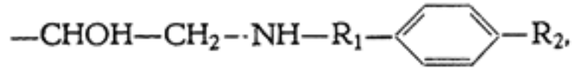
6) Of the aminoketones, adrenalone is the most active bronchodilator (table I).

7) There is no agreement with the activity series of *Ludwigs* and *Schneider* with regard to the effect of the side-chains on the bronchodilator activity of the basic structure (arterenol).

8) The tachycardia and the bronchodilator activity of these N-aralkylarterenols are parallel.

9) Clinical tests have shown that N-(p-hydroxyphenylisopropyl)-arterenol is a more active bronchodilator than epinephrine and N-isopropylarterenol.

10) The changes in the U.V. absorption spectra of pyrocatechol and phenol through substituion of the side-chains,



are obvious and different.

11) At 312 mμ the aminoketones (fig. 2) are strongly absorbent, the amino-alcohols, however, (fig. 1) are not; this difference makes it possible to determine the presence of ketone in the alcohol.

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