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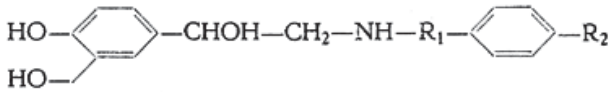
SYNTHESIS OF β-PHENYL-ETHYLAMINE DERIVATIVES III [1]) BRONCHODILATORS.

BY

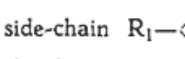
H. D. MOED, J. VAN DIJK, and H. NIEWIND

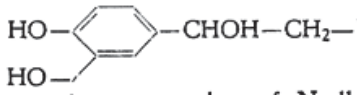
(Contribution from the Central Research Laboratory - N.V. Philips-Roxane, Weesp).

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

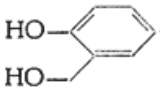


which were screened for their bronchodilator effect against acetylcholine-induced bronchoconstriction in the guinea pig, and for their cardiovascular action.

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 o bronchial asthma.

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

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

However, their activity after oral administration as a rule is poor, d their effect on the circulatory system is undoubtedly a dis-vantage.

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

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

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

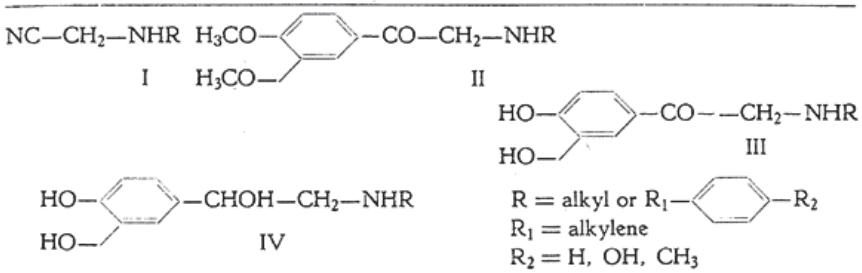
This derivative of epinephrine still has a pronounced effect on the culatory system.

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

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

On account of the publication by *Schneider c.s.* [6]) on the broncho-ator effect of adrenalone and its derivatives, a number of type III mpounds were included in our investigations. These relate to the emical synthesis, the determination of the U.V. absorption spectra, d the pharmacological properties of the above-mentioned compounds. he 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. gmund c.s.*, J. Pharmacol. Exptl. Therap. **97**, 14 (1949); *D. E. Marsh c.s.*, Pharmacol. Exptl. Therap. **92**, 108 (1948); *P. Siderius*, Acta Physiol. et Pharmacol. erl. **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. senmund*, Arch. exptl. Pathol. Pharmakol. **181**, 135 (1936); *F. Külz* and *M. hneider*, 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)-alkyl-arterenols 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≡N			II Hydrochlorides of RHN—CH_2—CO—(3,4-dimethoxyphenyl)			III Hydrochlorides of RHN—CH_2—CO—(3,4-dihydroxyphenyl)						
	M.P. °C[1]	Analysis % Cl found	Cl calc.	Yield %	M.P. °C[1]	Analysis % Cl found	Cl Calc	Yield %	M.P. °C[1]	Analysis % Cl found	Cl calc.	U.V. Abs. Spectrum λ_{max} mμ	ε	λ_{max} mμ	ε	λ_{max} mμ	ε	Broncho-dilator Activity[5]	
CH_2—				[2]								232	12100	279	8500	312	7300	1	1 2
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								3
$(CH_3)_2CH$—	*)94—97	26.24	26.36	*)62	193—194	12.98	12.96	[3]82	240—241	14.49	14.44							≲ 0.03	4
CH_3—CH_2—CH_2—				[2]				[3]				232	12900	279	8900	312	7800	≲ 0.05	5
$(CH_3)_2C$—				[2]				[3]											6
$(CH_3)_2C(CH_3)_2$—				[2]				[3]										< 0 05	7
$(CH_3)_2C(CH_3)_2$—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								8
$(CH_3)_2CH$—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	9
CH_3—O—C_6H_4—CH_2—CH_2—	*)158—159	15.70	15.65	*)82	209—211	10.63[4]	9.70												10
CH_3—C_6H_4—CH_2—CH_2—								*)43	202—204	10.95	10.96								11
$(CH_3)_2CH$—CH_2—	*)170—171	16.85	16.84	*)77	213—215	10.34	10.14	*)60	208—211	10.96	11.02							< 0.05	12
CH_3—O—C_6H_4—CH_2—$CH(CH_3)$—	*)174—175	15.17	14.74	*)70	203—205	9.28	9.34												13
CH_3—C_6H_4—CH_2—$CH(CH_3)$—								*)75	163—166	10.50	10.50							≲ 0.1	14
CH_3—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	15
CH_3—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		16
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												17
CH_3—C_6H_4—CH_2—CH_2—																			
—$CH(CH_3)$—								*)86	231—235	10.13	10.08	228	18700	281	10600	312	7900		18
CH_3—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							≲ 0.02	19
CH_3—$C(CH_3)_2$—	*)214—215,5	16.47[4]	15.79	*)68	238—240	9.85	9.75	*)79	227—230	10.54	10.56							≲ 0.05	20
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												21
CH_3—C_6H_4—CH_2—$C(CH_3)_2$—								*)78	252—253	10.18	10.08								22
CH_3—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								23
CH_3—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								24
CH_3—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								25
CH_3—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								26
$(CH_3)_2CH$—CH_2—	*)165—167	17.70	16.84	*)57	188—190	10.44	10.14	*)80	195—199	11.04	11.02								27

*) 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.

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

	R	IV: RHN—CH_2—CHOH— (3,4-dihydroxyphenyl)												Oral activity at 200 γ
		Yield %	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	Broncho-dilator Act.	
1	H—											2	
2	CH_3—	[2]										50	
3	CH_3—CH_2—	[2]										30	
4	CH_3—CH_2—CH_2—	[3] [5]	171—172									5	
5	$(CH_3)_2CH$—	80	144—145,5	62.06	62.56	8.15	8.06	6.74	6.63	282	3200	100	—
6	CH_3—CH_2—CH_2—CH_2—	76										5	
7	CH_3—$C(CH_3)_2$—	[2] [3]										150	—
8	CH_3—$C(CH_3)_2$—CH_2—$C(CH_3)_2$—	[2] [6]											
9	C_6H_5—CH_2—CH_2—	79	139—139,5	67.57	68.33	9.50	9.62	4.99	4.98	282	3250	0,2	—
10	p.HO—C_6H_4—CH_2—CH_2—	[*]	172—173	69.55	70.34	7.00	6.97	5 14	5.13	282	3090	5	+
11	C_6H_5—CH_2—$CH(CH_3)$—	80	122—123	62.44	66.44	6.63	6.58	4.74	4.84	280	4700	50	
12	p.HO—C_6H_4—CH_2—$CH(CH_3)$—	[*]	154—155	70.42	71.09	7.37	7.32	4.75	4.88	282	3190	100	++
13	p.HO—C_6H_4—CH_2—$CH(CH_3)$—	56	167—167.5	66.81	67.34	6.99	6.94	4.51	4.62	280	4780	800	
14	p.H_3C—C_6H_4—CH_2—$CH(CH_3)$—	37	136—138	71.24	71.77	7.65	7.65	4.54	4.65	282	3190	50	
15	C_6H_5—CH_2—CH_2—$CH(CH_3)$—	47	163—164	70.65	71 77	7.65	7.65	4.75	4.65	282	3190	100	++
16	p.H_3C—C_6H_4—CH_2—CH_2—$CH(CH_3)$—	81	141—143	66.91	68.14	7.18	7.26	4.39	4.42	280	4820	400	
17	p.HO—C_6H_4—CH_2—CH_2—$CH(CH_3)$—	80	148—150	72.26	72.39	8.01	7.94	4.29	4.44	282	3180	25	+
18	C_6H_5—CH_2—CH_2—$C(CH_3)_2$—	35	161—162	70.93	71.77	7.57	7.65	4.52	4.65	282	3180	100	
19	p.HO—C_6H_4—CH_2—CH_2—$C(CH_3)_2$—	66	160—162	66.36	68.14	7.21	7.26	4.54	4.42	280	4590	800	
20	C_6H_5—CH_2—$C(CH_3)_2$—	50	168—169	71.82	72.39	8.08	7.94	4.39	4.44	282	3080	10	
21	p.HO—C_6H_4—CH_2—$C(CH_3)_2$—	77	142—143	71 80	72.39	7.99	7.94	4.44	4.44	282	3050	100	
22	p.H_3C—C_6H_4—CH_2—$C(CH_3)_2$—	71	162—163	72.21	72.39	7.90	7.94	4.38	4.44	282	3090	3	
23	C_6H_5—CH_2—CH_2—$C(CH_3)_2$—	74	151—152	72.84	72.95	8.28	8.21	4.17	4.25	282	3120	5	
24	C_6H_5—CH_2—$C(CH_3)(C_2H_5)$—	56	80—84	69.63	71.09	7.21	7.32	4.76	4.88	282	3000	1	
25	C_6H_5—CH_2—CH_2—$C(CH_3)_2$—	69											
26	C_6H_5—$CH(CH_3)$—CH_2—	43											

*) 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.

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

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

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

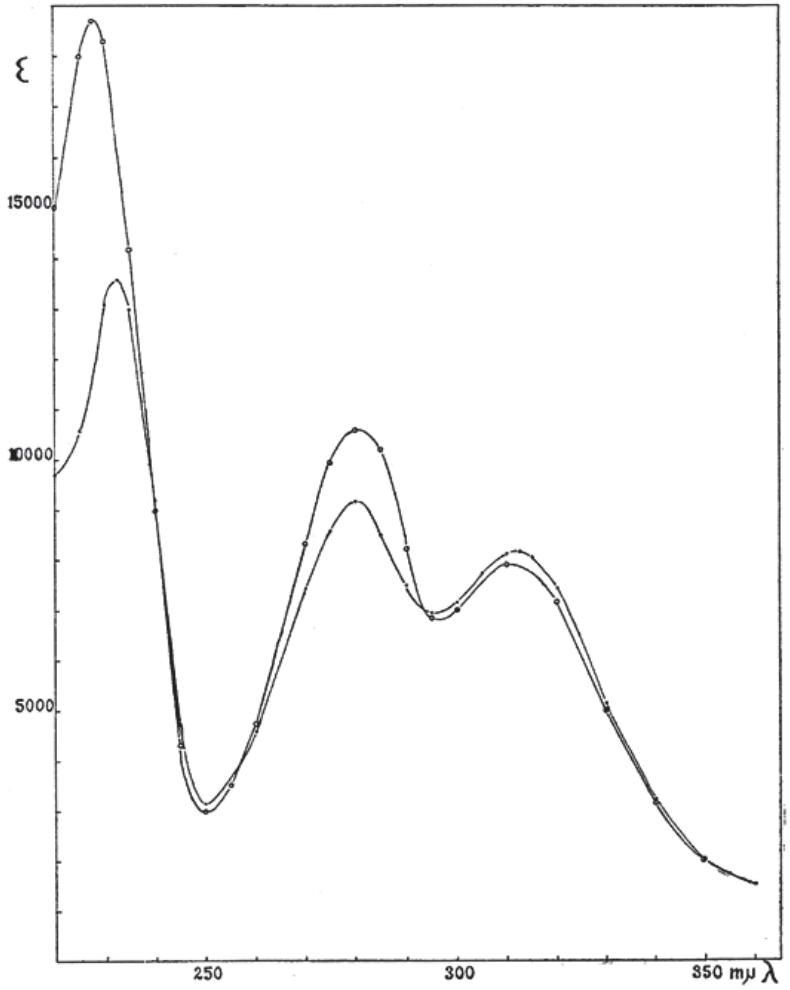


Fig. 2. Molecular extinction curves of the two types of N-aralkylnoradrenalones.

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

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