SYNTHESIS OF β-PHENYLETHYLAMINE DERIVATIVES X[1]* *N*-(HYDROXY- AND METHOXY-ARALKYL) DERIVATIVES

BY

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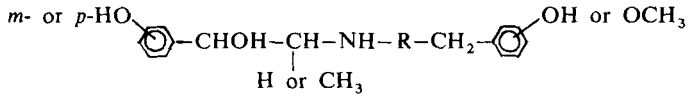
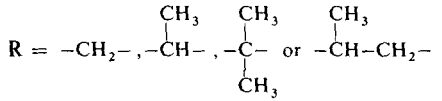
The synthesis and some pharmacological properties are described of compounds of the general structure:





The series contains strong and/or selective utero-relaxing agents. Stereoisomers of two interesting compounds were separated and characterized, and their configurations were established.

Introduction

In the past we have prepared several *N*-(aralkyl- or aryloxyalkyl-) derivatives of sympathomimetic alkanolamines[1-5]. Nearly all the

* Although compounds of this type are mainly secondary amines, they are in most cases indicated in the literature on medicinal chemistry as belonging to the group of phenethylamines, from which many members have a pronounced effect on the sympathic neuronal mechanism.

[1] Preceding publication: *J. van Dijk, V. G. Keizer, J. F. Peelen* and *H. D. Moed* Recl. Trav. Chim. Pays Bas **84**, 521–539 (1965).

[2] *H. D. Moed, J. van Dijk* and *H. Niewind* Recl. Trav. Chim. Pays Bas **74**, 919–936 (1955).

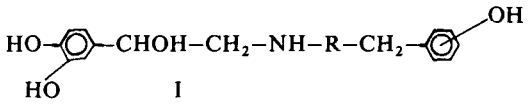
[3] *H. D. Moed* and *J. van Dijk* Recl. Trav. Chim. Pays Bas **75**, 1215–1220 (1956).

[4] *J. van Dijk* and *H. D. Moed* Recl. Trav. Chim. Pays Bas **78**, 22–42 (1959).

[5] *J. van Dijk* and *H. D. Moed* Recl. Trav. Chim. Pays Bas **80**, 573–587 (1961).

compounds of this type caused a pronounced effect on the various biological systems regulated by the sympathetic nervous system. By introducing structural variations we tried to obtain compounds, the effect of which on one organ was essentially stronger than on others, or to obtain compounds which had a favourable combination of effects.

Previously we found that the introduction of a phenolic $-OH$ group into an *N*-aralkyl substituent of catecholamines (structure I) could lead to a considerable reinforcement of their broncholytic effects[2,6].



I R as is indicated in Summary

This paper deals with the introduction of the phenolic $-OH$ group or of a methoxy group into the *N*-aralkyl part of sympathomimetics having a mono-phenolic structure of the "adrenaline like" part (structure depicted in summary). Of some promising compounds of this type, the racemates of diastereoisomeric forms were separated and their configurations established. The synthesis will be discussed and the utero-relaxing effects are compared in relation to their structures and configurations.

Synthesis

The choice of the syntheses used (**Schemes 1, 2 and 3**) was based on the availability of the starting materials and/or the need to make separation of stereoisomers feasible.

All compounds could be prepared in accordance with **Scheme 1**, and so these procedures were used for many of them.

The debenzylation and demethylation were performed in separate steps because a simultaneous dealkylation with 48% HBr was unfavourable in most cases. As the hydrogenation of the keto group is essentially slower than the hydrogenolytic debenzylation, the debenzylated hydroxymethoxyketones can be obtained in good yields. Starting with a phenolic amine (*e.g.* tyramine) a demethylation step could even be omitted, as proved in later experiments, and only hydrogenation of the

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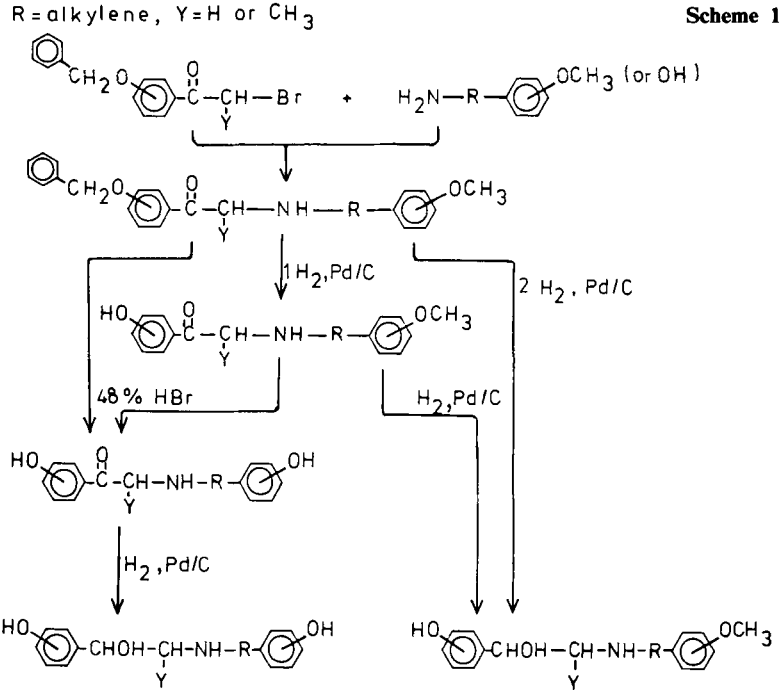
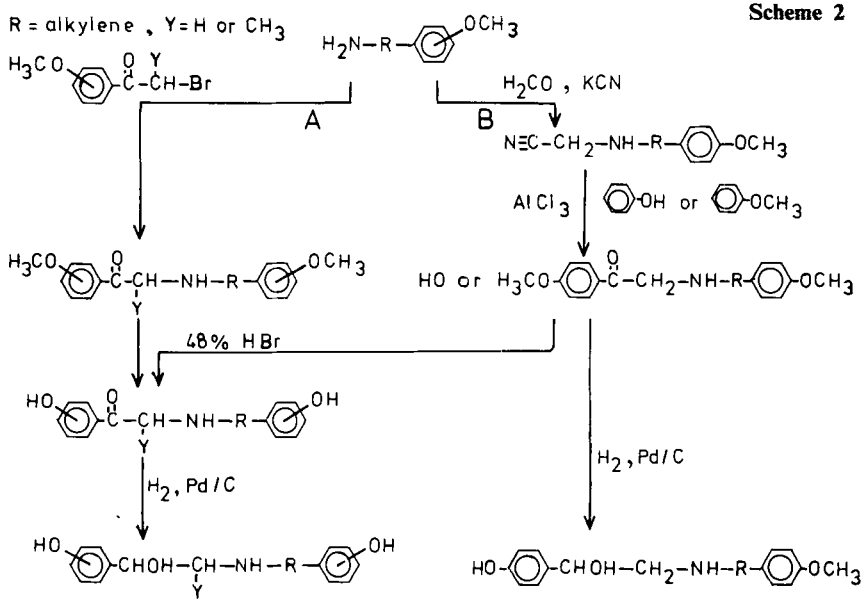
[6] *H. D. Moed, J. van Dijk* and *H. Niewind* Recl. Trav. Chim. Pays Bas **77**, 273–282 (1958).

Scheme 1



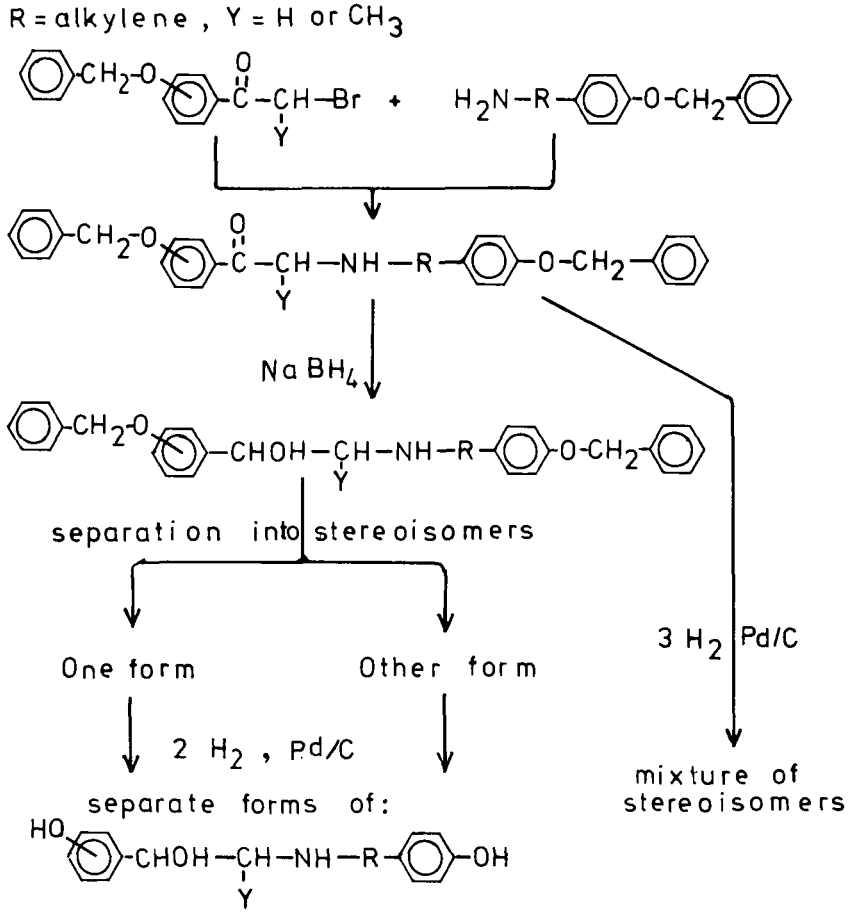
Scheme 2



benzyloxyaminoketone was required to produce a biphenolic end-product.

From the methods of Scheme 2, route B gave excellent yields of the hydrochlorides of the 2-aminoacetophenones[9], but this route was limited to *para*-substituted derivatives with Y = H. For the other derivatives route A may be used, depending on the availability of the starting materials.

When separation of stereoisomers was desirable Scheme 3 was preferred:



Scheme 3

[9] *M. Asscher* Recl. Trav. Chim. Pays Bas **68**, 960–968 (1949).

The dibenzyl ethers of stereoisomeric amino alcohols gave some well-crystallized and sharply melting salts, in contrast to the end-products. By fractional crystallization of suitable derivatives of these dibenzyl ethers from different solvents it was possible to obtain (racemic) stereoisomeric forms in a pure state (see characterization). The mild hydrogenolytic debenzylation of the individual dibenzyl ethers gave the separate stereoisomeric racemates of the end-products (*i.e.* **B2** and **C1** of Table III).

Characterization of stereoisomers

From the structures **B2** and **C1** (Table III), both of which have two asymmetric centres, the two individual racemates of both were separated and extensively purified.

The configuration of the stereoisomeric racemates of **B2** was established by comparing the NMR-spectra of their dibenzyl ethers with the NMR-spectra of the stereoisomers of structure **A14** (Table III). The configuration of these **A14** isomers was established by syntheses from compounds of known configuration[1]. Arbitrarily they were named "*normal*" and "*allo*"[1] for lack of a suitable nomenclature. In the NMR-spectra ($CDCl_3$ + 25% DMSO) the normal racemate of **A14** showed a triplet (J = 6 Hz) near δ 4,6 for the $-CH$*O*H proton, while the *allo* isomer showed a double doublet (J = 4 Hz and J = 8 Hz) for this proton. The isomers of **B2** showed comparable differences, so the configuration of the racemates could be arrived at by analogy. These configurations were supported by the biological activities: in the same

Table I

Comparison of melting points of individual racemates of structure B2

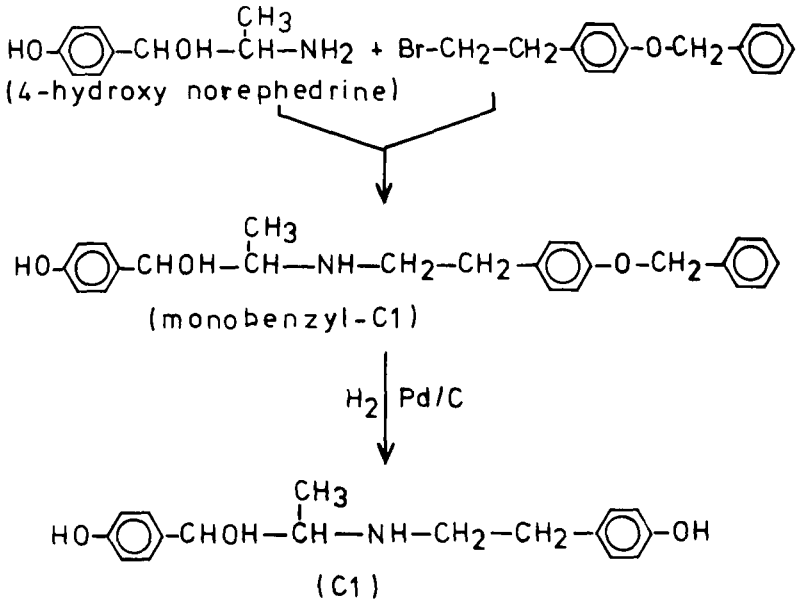
structure	derivative	melting points (uncorrected)		
		normal	*mixed*	*allo*
B2	base	not cryst.		162. –162.5
"	phenoxyacetate	160.5–161.2	140–144	146 –147
"	phenylacetate	157.5–158	131–133	141.7–142.8
"	3,5-dinitrobenzoate	193.5–194.2	192–196	209.5–210.5
dibenzyl-B2	base	94.5– 95.5	90– 92	113.3–114
"	*p*-toluenesulfonate	170 –170.5	148–152	149 –152
"	benzoate	107 –109 (aq)	106–109	122 –123.5
"	hydrochloride	122 –123 (aq)		170 –171.5
"	nitrate	146.5–147	123–140	125.5–126.5

tests (*e.g.* uterorelaxing properties) the related isomers of both compounds showed comparable differences in activity (Table III).

The steric purity of the racemates of **B2** could be checked quite well by the NMR-analysis also. Moreover, it was proved[5] by comparison of 5 derivatives of the dibenzyl ethers of **B2**, as well as of both the *normal-* and *allo-***B2** themselves. The derivatives were obtained in good yield, and the melting points are compared in Table I.

The configuration of the two racemates of **C1** was established by comparison of the NMR-spectra of both isomers with those of well-known ephedrine isomers. The (assumed) *erythro* isomer showed a doublet at δ 5,02 with J = 4,2 Hz for the $-CHOH$ proton (in D_2O), whereas in the other isomer this spin-coupling constant is 8 Hz. For *erythro-* and *threo-*ephedrine, values of J = 4.0 Hz and J = 8.4 Hz respectively were found[10].

In addition, the configuration of the stereoisomers of **C1**, obtained according to Scheme 3, was confirmed by synthesis starting from *erythro-* and from *threo-*4-hydroxynorephedrine[5], as shown in Scheme 4.



Scheme 4

[10] *J. B. Hyne* Can. J. Chem. **39**, 2536–2542 (1961).

The products obtained *via* Scheme 4 were compared with these obtained *via* Scheme 3 by means of their melting points (Table II) and their IR spectra.

Table II

Comparison of melting points of individual racemates of structures Cl

structure	method acc. scheme	derivative	melting points (uncorrected)[a]		
			erythro	*mixed*	*threo*
Cl	3	base	about 87-9		not cryst.
"	3,4	hydro-chloride	189-192	176-179	173.5-175.5
"	3	sulfate	223-224		
mono-benzyl-Cl	4	hydro-chloride	213-214.5	166-168	174.5-175.5
dibenzyl-Cl	3	base	99-100	69- 85	80.5- 81.5
"	3	hydro-chloride	221.5-222.5		

[a] The salts melted with decomposition.

Figure 1 summarizes the established configurations of **B2** and **C1**, represented by Fischer projection formulas with Cahn indications.

The configurations or composition of stereoisomers of the other compounds containing more than one asymmetric centre, indicated in Tables III and V, were established by comparison of the NMR spectra with those of the well-established analogues mentioned above.

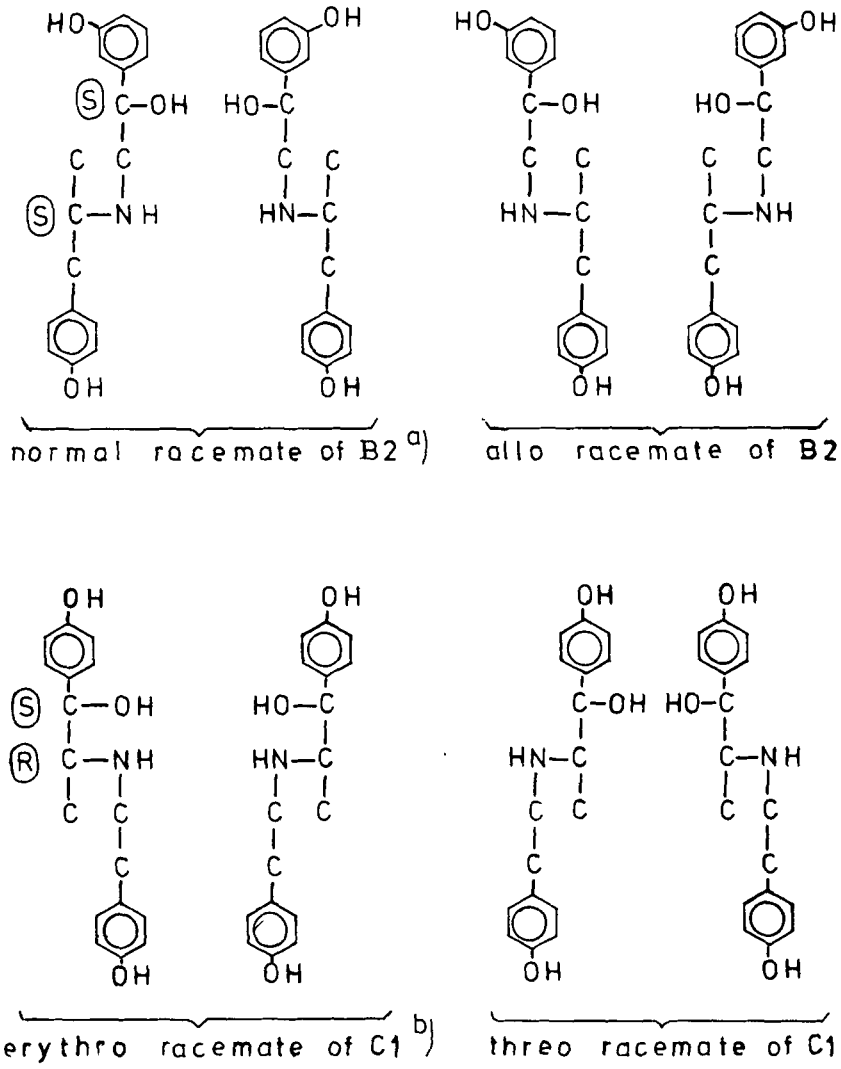


Fig. 1. Fischer projection formula of stereoisomers of structures B2 and C1

[a] The phenylacetic acid salt of this racemate was tested under code number DU 21600[7]

[b] The hydrochloride of this racemate was tested under code number DU 21220. International non-proprietary name: ritodrine.
Registered trade name: Prepar (Philips-Duphar B.V. the Netherlands).

Pharmacological effects

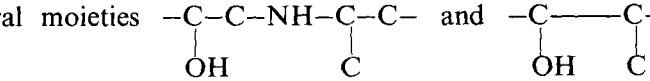
Most of the compounds were investigated both *in vitro* and *in vivo* in several tests. As the effect on the uterus is one of the interesting aspects of this series, and the *in vitro* test gives suitable values for the comparison of activities in the whole series, these are discussed in the following (Table III).

Comparison of the activities of these compounds, substituted in the *N*-aralkyl side chain with a phenolic OH or an OCH_3 group, with those of their unsubstituted counterparts demonstrates that generally such substitution enhances the activity, sometimes even to a considerable extent (activity ratios **A2/A13** = 14, **A7/A13** = 10, **C1/C12** = 600). Comparable introduction of the *meta*- or *para*-phenolic OH group in the catecholamine type of sympathomimetics (formula I), as has been stated previously[2,6], leads even to extremely high uterine activities (*e.g.*: IIa in[6] = 11,000).

Furthermore, the ethanolamines (types **A** and **B**) in general show a higher activity than the 1-methyl-ethanolamines (type **C**) in this *in vitro* test.

Striking differences in activities are found between corresponding –NH–C–C–Ø–OH(OC) and –NH–C–C–C–Ø–OH(OC) derivatives, indicating that the length of the alkylene group has a pronounced influence. This appears especially in the compounds **A** (the activity ratios **2/5** and **7/10** are respectively 50 and 1000) and, less pronounced, also in some **B** and **C** derivatives (**2/5**, 3 and 5 respectively). In this connection the structural resemblance of the –C–C–Ø–OH moiety with those of the natural "adrenergic" hormones is striking.

To sum up, it can be concluded that the structural moiety –C–C– –NH–C–C–, provided on both sides with a (*meta* or *para*) hydroxyphenyl group and possibly substituted with a methyl group, is a favourable combination for activity in this series. In this situation, the structural moieties



particularly, having the right configuration (RR′/SS′ and *erythro* respectively) give very high activities (nos. **A2**, **B2**, **C1** and **D1**).

An appropriate combination of all these structural elements might lead also to favourable, selective action.

In more extensive pharmacological investigations the compounds *erythro*-**C1** and *normal*-**B2** showed *in vivo* a favourable utero-relaxing activity with relatively few side effects (heart rate, blood pressure). Detailed pharmacological properties of *normal*-**B2**[7] and clinical properties of *erythro*-**C1**[8] have been published already and will continue to be given also in the future.

Table III Utero-relaxing activities[a]; Activity of Isoxsuprine[1] (*erythro*-C14) = 1[b]

Number:	A	B	C[d]	D[d]
1	24		*erythro* 80	280
			threo 3	
2	[c] 1000	*normal* 1300	10	
		allo 100	*e/ae* = 1/1	
3	[c] 170			
4		360	6	
5	[c] 20	[c] 220	2	
6	40		16	
7	[c] 700		1	
			e/ae = 2/1	
8	320		4	
			e/ae = 1/1	
9			4	
			e/ae = 2/1	
10	[c] 0,6			
11			2	
12		17	[e] 0.13	
13	[c] 70	[c] 430	[e] 3.2	
			e/ae = 1/1	
	normal 6		*erythro*[1] 1	
14	*allo* 0,10		*allo* er.[1] 0.08	

[a] On rat-uterus *in vitro* with pituitrin as spasmogen. [b] Isuprel = 2000. [c] Approx. 1/1 mixture of the *normal* and *allo* form. [d] All these compounds have *(normal) erythro* configuration, unless otherwise indicated. For the indications **e** *(erythro)* and **ae** *(allo erythro)* see also [4]. [e] USP 2, 661, 373 (C.A. **49** 1793 i).

Experimental part

The methods employed in Schemes 1 and 2 have been described in our previous publications, and only a more general discussion of the variations of experimental conditions used for the new compounds is given here. The methods of Schemes 3 and 4 are illustrated by a representative example. The melting points of the new intermediates are compiled in Table IV, and those of the end-products in Table V. Melting points are uncorrected and were determined in an apparatus developed by Dr. *Tottoli*, by placing the compounds in the bath at 10° below their m.p. and warming up at a rate of 3°/minute. The infrared absorption spectra were measured on a Perkin-Elmer 337, using the KBr disc technique. NMR spectra was measured on a Varian HA 100, with solutions in deuteriopyridine unless otherwise indicated. Tetramethylsilane was added as internal reference. The U.V. absorption spectra were determined on an ethanolic solution using a Beckman recording spectrophotometer (DK2). Satisfactory elementary analyses were obtained.

General discussion

For the synthesis of the aminoketones the "bromoketone" method[4,6] (Schemes 1, 2 and 3) gives a low yield in the case of aminoacetophenones, and requires an extra mole of reacting amine to bind HBr. For the aminopropiophenones the "bromoketone" method gives good yields[4], but a much longer reaction time is needed. In this case Et_3N can be used for acid binding, without lowering the yield.

The *O*-demethylation in the *N*-aralkyl group with boiling 48% HBr was completed within 10 minutes. The hydroxy-methoxy compounds, formed after the hydrogenolytic debenzylation, were often demethylated without isolation or purification. In many cases the hydrobromide of the dihydroxyaminoketone crystallized from the reaction mixture on cooling. It was purified by crystallization from water (or ethanol) with activated carbon and the addition of a little concentrated hydrochloric acid to the filtered solution, which simultaneously converted it into the hydrochloride. If the aminoketones contain two asymmetric centres, this crystallization may afford a separation of the diastereoisomers as was the case with compound **H5**.

The catalytic hydrogenation of the hydrochlorides to the aminoalcohols[4] is quantitative. However, often it was difficult to obtain good, crystalline products in this end-stage, especially in the case of the *meta*-substituted derivatives. For this reason the base was sometimes precipitated by adding ammonia to an aqueous solution of the hydrochloride. The resulting resinous mass was used for testing. In four other cases of unsuccessful crystallization the aqueous solution of the hydrogenated hydrochloride was analysed by UV[3,1], and then used for the tests. One reason for the delayed crystallization may be the formation of mixtures of diastereoisomers. For such compounds the methods of Scheme 3 proved the best choice for their initial preparation.

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[7] *P. Gans* and *J. N. van Proosdij* Arch. Int. Pharmacodyn. Ther. **175**, 251–256 (1968).

[8a] *A. Wesselius-de Casparis, M. Thiery, A. Yo le Sian, K. Baumgarten, I. Brosens, O. Gamisans, J. G. Stolk* and *W. Vivier* Brit. Med. J. **1971**, **3**, 144–147.

[b] *K. Baumgarten, H. Fröhlich, A. Seidl, K. Sokol, F. Lim-Rachmat* and *R. Hager* Europ. J. Obstet. Gynec. **2**, 69–83 (1971).

[c] *Tom P. Barden* Am. J. Obstet. Gynec. **112**, 645–652 (1972).

Examples

Synthesis and separation of stereoisomers of B2 (Scheme 3)

a. Aminoketone formation

The starting materials were prepared as for analogous compounds[6].

To a solution of 25.5 g (0.106 mole) of β-(4-benzyloxyphenyl)isopropylamine in 100 ml of benzene was added, with stirring and without cooling, 13.8 g (0.045 mole) 3'-benzyloxy-1-bromoacetophenone (m.p. 45–51°). The bromo compound dissolved and the resulting hydrobromide of the primary amine started to crystallize. After two hours the crystals were separated by suction and washed with benzene. The filtrate was mixed with 50 ml of 2.7 *N* alcoholic HCl. After standing overnight in the refrigerator, the crystallized hydrochloride was separated and washed with ethanol. By concentration of the mother liquor a second crop was obtained. Both crops were combined and recrystallized from ethanol, giving 6.5 g (0.013 mole = 29%) hydrochloride of *3'-benzyloxy-2-[1-(4-benzyloxybenzyl)-ethylamino]acetophenone.*

b. $NaBH_4$ reduction of the dibenzyloxyaminoketone

To a suspension of 12.1 g (0.024 mole) of the above mentioned hydrochloride in 250 ml methanol was added with stirring 6 ml 4.4 *N* NaOH solution, immediately followed by 2.00 g (0.053 mole), of sodium tetrahydridoborate. The temperature rose to 35°, after which the mixture was cooled to 15°. The mixture was stirred at room temperature for about one hour and an additional amount of 0.4 g of sodium tetra-hydridoborate was added. After standing overnight the resulting precipitate was separated by suction, washed with ethanol and water, and dried *in vacuo*. Yield 4.87 g (0.0104 mole) of *1-(3-benzyloxyphenyl)-2-[1-(4-benzyloxybenzyl)ethylamino]ethanol*, the "*dibenzyl ether of B2*" (first crop). By concentration of the filtrate and washings *in vacuo* until about 150 g of residue remained, the remaining amount of reduction product separated as an oil*. It was extracted with ether, the ethereal extract washed with water and dried briefly over anhydrous sodium sulphate. After being concentrated the residue (7.5 g) crystallized from 30 ml of ether to give a second crop of 3.6 g (0.0076 mole). The filtrate gave a third crop of 2.4 g (0.0051 mole). Total yield 0.0231 mole = 96%.

c. Separation of stereoisomers

The first crop (4.87 g) of preparation b. contained mainly the *allo*-isomer of the dibenzyl ether of **B2**. One crystallization from methanol was sufficient to obtain 3.97 g (0.0085 mole = 35%) of the pure *allo*-form, m.p. 113.3–114°. The second crop (3.6 g), mainly the *normal* isomer, was dissolved in 60 ml of methanol and this solution was mixed with 4.25 ml 1.80 *N* HNO_3. Seeding with the pure nitrate of the *normal* form (obtained in previous experiments) induced crystallization of 3.0 g (0.0056 mole = 23%) of the nitrate of the pure *normal* form of *dibenzyl-B2*. The third crop (2.4 g) was added to the mother liquor of the second crop (3.0 g); 2.65 ml 1.80 *N* HNO_3 were added and the solution seeded again and cooled. This gave 2.5 g, which after one recrystallization from 25 ml methanol gave 2.0 g (0.0038 mole = 16%) pure *normal* isomer. An equivalent amount of ammonia was added to a warm methanolic solution of the nitrate (3 g/40 ml), followed by 6 ml of water. On seeding at about 20° the base crystallized. It was separated by suction, washed with water and dried *in vacuo*. Yield 2.5 g (94%), m.p. 94.5–95.5°.

* In other experiments the oil crystallized. It was then filtered off, washed with water, and converted into the nitrate.

d. Hydrogenolytic debenzylation

A suspension of a palladium-on-carbon catalyst was freshly prepared by hydrogenating 25 ml of an aqueous 1% palladium chloride solution mixed with 25 ml ethanol and 2.5 g of activated carbon (Norite^R). To this suspension 9.5 g (0.020 mole) of the *normal* form of *dibenzyl-B2* and 200 ml ethanol were added. After the addition of 11 ml 2*N*-HCl the mixture was hydrogenated at room temperature and a pressure of about 1.1 atmospheres until no more hydrogen was absorbed. The catalyst was removed by suction filtration and washed 4 times with 50 ml of water. The combined filtrate and washings were mixed with an aqueous solution of an equivalent amount of sodium phenylacetate, and the mixture concentrated *in vacuo* until 120 g residue. On seeding, "scratching", and cooling, 3.9 g (0.0092 mole = 46%) of the phenylacetate of *the normal racemate of 1-(3-hydroxyphenyl)-2-[1-(4'-hydroxybenzyl)ethylamino]ethanol* crystallized. After standing overnight in the refrigerator, it was collected by suction filtration, washed with cold water and dried *in vacuo*. By concentrating the filtrate an additional 0.84 g (0.0020 mole = 10%) was obtained.

As a matter of course the *allo-isomer of B2* can be obtained in the same way. In this case the end-product was isolated as a crystalline base.

The details of the methods of Scheme 4 are illustrated by the preparation of the *threo-isomer of C1*:

a. Starting materials

(4-benzyloxyphenyl)acetic acid was reduced by $LiAlH_4$ in ether, giving an 81% yield of 2-(4-benzyloxyphenyl)ethanol, m.p. 81–84°. This was converted with PBr_3 in benzene at 60° into 2-(4-benzyloxyphenyl)ethyl bromide, which was purified by distillation (b.p. about 155°/0,2 mm) and crystallization from ethanol. M.p. 63.5–64.5°.

b. Alkylation of the primary amine

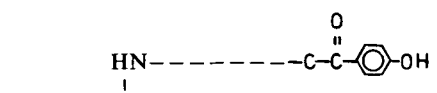
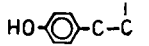
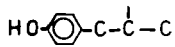
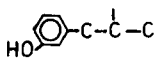
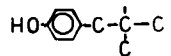
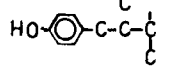
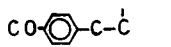
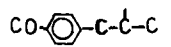
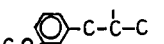
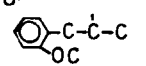
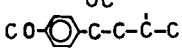
A solution of 0.93 g (0.0050 mole) *threo*-2-amino-1-(4-hydroxyphenyl)propanol[4] and 0.73 g (0.0025 mole) 2-(4-benzyloxyphenyl)ethyl bromide in 7 ml dimethylformamide was heated on a steam bath for 1¼ hour. The reaction mixture was concentrated *in vacuo* until 2.5 g of residue remained. This residue was mixed with ether and 5 ml water, and the layers were separated. The ethereal solution was washed twice with water, and mixed with 2 ml 2*N*-HCl, whereupon an oil separated which crystallized on scratching. It was separated by suction, washed with ether and water, and dried *in vacuo*. Yield 0.78 g (0.0019 mole = 76%). Two recrystallizations from about 10 ml water gave 0.45 g of the pure hydrochloride of *threo-1-(4-hydroxyphenyl)-2-[2-(4-benzyloxyphenyl)ethylamino]propanol*, m.p. 175.5–176.5°.

c. Hydrogenolytic debenzylation

A solution of 0.35 g (0.00085 mole) of the above hydrochloride in 18 ml of 50% ethanol was mixed with 1.5 ml of a 1% palladium chloride solution and 0.14 g Norite^R, and hydrogenated as before. After removal of the catalyst, the solution was concentrated *in vacuo* until a residue of 0.5 g remained. After some hours the hydrochloride of the *threo-racemate* of *1-(4-hydroxyphenyl)-2-[2-(4-hydroxyphenyl)ethylamino]propanol* crystallized. It was mixed with 1.5 ml isopropanol and gradually with 10 ml ether. The precipitate was filtered by suction and washed with isopropanol/ether 1 : 10. The 0.20 g obtained (0.00062 mole = 73%) was recrystallized by dissolution in 3 ml of isopropanol and mixing this solution with 9 ml of dry ether.

Table IV

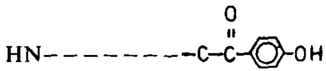
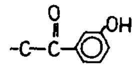
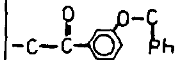
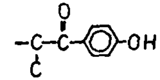
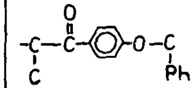
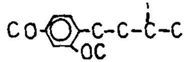
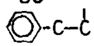
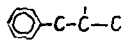
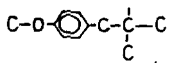
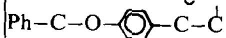
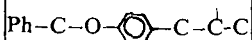
Melting points[a] of new intermediates[b]

	Number:	E	F	G	H	J
	1	242–3			129–136 (aq)	223–227 base: 137–9
	2	249–251	210–212		233–235*	
	3	120–170 (aq)				
	4		242–245		145–150 (aq)	
	5	243–246	217–223		219–221 allo: 209 (aq)	
	6	164–167 (aq)			not cryst.	209–211
	7	221–223			194–198*	195–198*
	8	235–238				193–6*
	9	184–191				196–8*
	10	238–240			160–187*	225–227*

— continued on next page —

Table IV *(cont.)*

Melting points[a] of new intermediates[b]

	Number:	E	F 	G 	H 	J 
	11					209–213*
	12					243–246
	13	224–226		173–5		195–198*
	17		193–197	162–166	251–253	192–197
	18					215–217
	19			196–197		182–210*

* Mixtures of stereoisomers are indicated with an asterisk.

[a] Melting points are uncorrected and are often "decomposition points". Unless otherwise indicated, the melting points are those of the hydrochlorides. Purity was checked by, at least, Cl′-determinations.

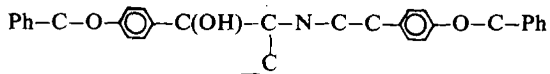
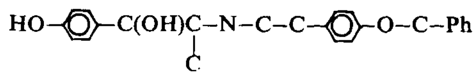
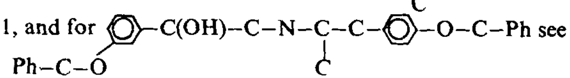
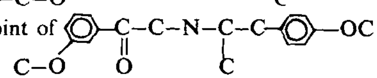
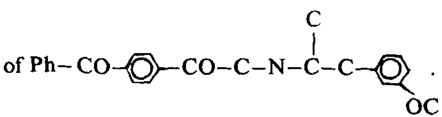
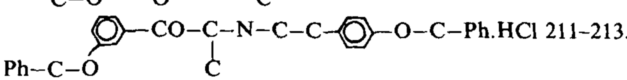
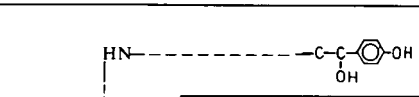
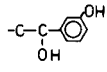
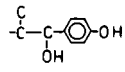
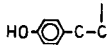
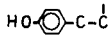
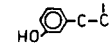
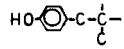
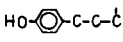
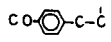
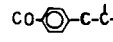
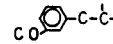
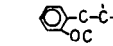
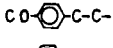
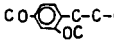
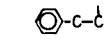
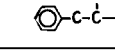
[b] For the intermediates  and  see Table 1, and for  see Table 2.
Melting point of  hydrochloride 178.5–180, of  . HCl 185–189.
and of  .HCl 211–213.

Table V

Melting points[a] and composition of stereoisomers of new compounds[c]

	Number:	A	 B	 C[d]
	1	base: 78–84		see table 2
	2	[c] base: 166–8	see Table I	base: 166–9 benzoate: 189–90
	3	not crystalline[b]		
	4		[b] 3.5-d.n.b.: 232–5	cryst. with 1 aq; anhydr. 162–3
	5	104–7	not crystalline[b]	216–7
	6	base: 154–6		160–2
	7	[c] 155–8		215–7 *e/ae* = 2/1
	8	[c] 173–5		182–4 *e/ae* = 1/1
	9	[c] 191–3		191–3 *e/ae* = 2/1
	10	[c] 154–7		
	11			187–90 *e/ae* = 1/1
	12		145–7	C.A. **49** 1793 i
	13	[c] base: 149–50	not crystalline[b]	C.A. **49** 1793 i

[a] Melting points as indicated in footnote [a] Table IV. Purity was checked by at least C, H, Cl/N determinations.

[b] Tested as solution of the hydrochloride of a mixture of almost equal parts of the 2 racemates.

[c] From NMR measurements the presence of almost equal parts of both racemates must be assumed in this mixture.

[d] See footnote [d] Table III.

[e] Compound D 1 (Table III) cryst. with 1 aq. Melting point anhydrous 181.5–4.5.

Acknowledgement

We gratefully acknowledge the collaboration in our laboratories with Messrs. *V. G. Keizer, D. Trap* and *W. van Wageningen* in the syntheses, with Messrs. *R. Mooyman* and *G. Breman* for the I.R. and NMR-analyses of many stereoisomers, and with Mr. *J. M. A. Zwagemakers* and co-workers who supplied the pharmacological data and kindly gave permission for their publication. Most of the C, H and N micro-analyses were carried out by Mr. *W. M. Hazenberg* and his staff, Lab. for Org. Chemistry, State University, Groningen.

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