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PROCESS FOR THE PREPARATION OF AMINO-ALCOHOLS

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6 Claims. (Cl. 260—570.6)

This application is a division of my application Ser. No. 219,917, filed July 18, 1938.

Various methods are already known according to which amino-alcohols may be prepared. The synthesis of compounds of this class is described in the works of Karrer et al. (Helv. 4, 76 (1921); 5, 469 (1922)) and is carried out by reduction of the corresponding esters of amino acids with sodium and alcohol according to the method of Bouveault and Blanc. In this way these authors succeeded in obtaining the amino-alcohols, alaninol, valinol, leucinol and phenyl-alaninol by the application of the above mentioned method of working. During the reduction process racemisation takes place. Therefore by starting from optically active natural amino acids, the above cited amino-alcohols are obtained in the optically inactive form. Only leucinol showed a weak rotation power and was also racemised to the greatest extent. The yields of amino-alcohols according to this process are very bad and amount in general to only a few percent of theory. Thus for example from 44 grams of the ester of valine only about 3 grams of valinol were obtained, which is a yield of about 10% of theory (Karrer, Helv. 5, 479 (1922)). Somewhat higher yields are obtained if the ester of the amino acid is first acetylated and the acetylated product then reduced. According to these methods one could obtain by the reduction of the ester of acetylated leucine a yield of leucinol amounting to about 20% of theory (Karrer, Helv. 4, 91 (1921)).

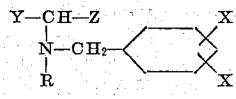
Barrow and Ferguson have recently found (Soc. 1935, 410) that the yields by this process can be somewhat improved if the reaction is carried out in n-butyl-alcohol completely dehydrated by means of magnesium butylate instead of in the usual "absolute alcohol." In this way, d,l-valinol-hydrochloride can be obtained in a yield of 45% of the theory from acetyl-valine ester. (By using ethyl-alcohol completely dehydrated by means of magnesium ethylate the yield of valinol-hydrochloride amounted to only 25% of theory).

As already stated, the amino-alcohols prepared by Karrer and others are obtained only in the racemic or strongly racemised form. Only recently through the work of Barrow and Ferguson (l. c.) a member of this series of compounds has been obtained for the first time in an optically pure form. Barrow and Ferguson were able to split d,l-valinol into its optical antipodes by means of tartaric acid.

The preparation of amino-alcohols became of utmost importance since one representative of these compounds has been found forming a part of a highly active natural product, for the synthesis of which a rational method for the preparation of amino-alcohols is needed. The example of Ergobasine (A. Stoll and A. Hofmann, Z. physiol. Chemie 251, 155 (1938)) shows also the necessity of preparing such amino-alcohols even in optically active form.

According to the present invention it has been found that the racemates, as also the pure optically active alcohols, can be obtained in good yield if aliphatic or araliphatic benzyl-amino fatty-acid esters are reduced, and in given cases, the racemates of the benzyl-amino-alcohols or the salts of these optically active acids are decomposed into the optically active components by fractional crystallization from a suitable solvent and the benzyl group split out from the same.

According to the present invention therefore it has been ascertained that the reduction of the easily accessible benzyl-amino fatty-acid esters which correspond to the general formula



wherein X represents hydrogen, alkyl and alkoxy, Y represents alkyl and aralkyl, Z represents a group carrying the carboxylic acid ester radical and R represents hydrogen, alkyl, aralkyl and acyl, gives appreciably better results, and that the hitherto unknown benzyl-amino-alcohols thereby obtained can be very easily isolated and obtained in a pure form on account of their good crystallizing power.

Furthermore the benzylamino-alcohols are especially suited to give well crystallized salts with optically active acids which are specially suited for splitting the racemates into optically active components. By splitting off the benzyl group, which can be done in the known manner by reduction, for example by hydrogen with palladium as catalyst, it has been possible for the first time to obtain without great difficulties the for the most part unknown pure optically active amino-alcohols.

The reduction of the benzylamino fatty-acid esters can be carried out in the known manner, for example according to the method of Bouveault and Blanc with sodium and alcohol, or by catalytic reduction, whereby as solvents organic solvents miscible with water or not miscible with water can be used, such as ethanol, butanol, toluene, tetrahydro- and decahydro-naphtha-

lene. The benzylamino-alcohols thus obtained can be readily isolated from the reaction mixture if they are converted for example into hydrochlorides and precipitated from aqueous solution by an addition of alkali. It is possible by vacuum distillation of the bases thus obtained to obtain without further treatment well crystallized compounds which are particularly suitable for example for separation into optically active components.

For the preparation of optically active benzylamino alcohols, the racemates are converted for example according to known methods into salts of optically active acids such as for instance tartaric acid, dibenzoyl-tartaric acid and mandelic acid, and the optically active components separated by fractional crystallization from a suitable solvent such as for example water, methanol, ethanol, acetic ester, etc., or from mixtures of these solvents. In order to obtain the unsubstituted optically active amino-alcohols, the optically active benzylamino-alcohols are advantageously subjected to catalytic reduction with hydrogen in the presence for example of palladium as a catalyst, preferably in the presence of an equal quantity of an organinc acid. The use of oxalic acid is especially advantageous as in such case the amino-alcohols are obtained as well crystallizing oxalates easy to be isolated.

It is possible according to the present process to obtain optically active amino-alcohols such as for example d- and l-alaninol, d- and l-α-aminobutanol, d- and l-leucinol and the like in good yields and in pure crystalline form.

For the characterization of the optically active forms I use the recently employed kind of designation, which indicates by the amino acids through the letters d- and l- the configuration and through the figures (+) and (—) the direction of the rotation. For the followingly cited amino acids it has been found that they are present in the nature as levo-forms and must, therefore, be designed as l-(+)-alanine, l-(+)-valine; l-(—)-leucine, l-(—)-phenylalanine.

The indication of the configuration of the amino-alcohols can therefore only then take place when their relation to the respective amino acids has been undoubtedly defined.

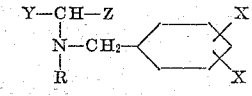
For the natural (+)-alaninol, that has been isolated as a basic splitting product from the ergot alcaloid ergo-basine (Jacobs and Craig, Science 82, 16 (1935)) the authors indicate that it derives from the natural alanine and must therefore be designed as l-(+)-alaninol. From natural l-(+)-valine, (weakly) dextro-rotary valinol (Barrow and Ferguson l. c.) can be obtained and from natural l-(—)-leucine a (weakly) levo-rotary leucinol (Karrer, Helv. 4, 91, 1921) can be obtained. The optically pure dextro-rotary valinol is therefore to be denoted as l-(+)-valinol and optically pure levo-rotary leucinol as l-(—)-leucinol.

As dextro-rotary N-benzylalaninol on hydrogenation gives (+) alaninol and levo-rotary N-benzylleucinol gives (—) leucinol, it follows that for these compounds the descriptions l-(+)-N-benzylalaninol and l-(—)-N-benzyl-leucinol and for the corresponding compounds of opposite rotation the descriptions d-(—)-N-benzylalaninol and d-(+)-N-benzylleucinol may be applied.

The two optically active α-benzylaminobutanols are denoted for the present as (+) and (—) according to their direction of rotation, as the genetic relations of the corresponding optical forms of the α-amino-butyric acids are not yet established.

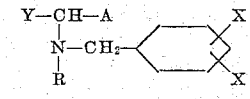
Recently l-(+)-aminobutyric acid has been found as forming part of the natural albumins (Abderhalden und Baln (H. 245, 246 (1937)).

One object of the present invention is a process for the manufacture of benzylamino-alcohols, comprising reducing benzylamino-fatty-acid esters of the general formula



wherein X stands for hydrogen, alkyl and alkoxy, Y stands for alkyl and aralkyl, Z stands for a group carrying a carboxylic acid ester group and R stands for hydrogen, alkyl, aralkyl and acyl.

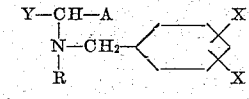
Another object of the present invention is the process of separation of the racemates of the benzylamino-alcohols into their optically active components, comprising the fractional crystallization of the salts of the benzylamino-alcohols of the general formula



wherein X stands for hydrogen, alkyl and alkoxy, Y stands for alkyl and aralkyl, A stands for hydroxyalkyl and R stands for hydrogen, alkyl and aralkyl with optically active acids.

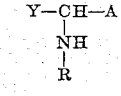
Still another object of the present invention is a process for the preparation of optically active amino-alcohols, comprising the treatment of the optically active forms or of the racemates of the above cited benzylamino-alcohols with hydrogen in presence of a catalyst.

Still other objects of the present invention are the racemates and the optically active benzylamino-alcohols of the general formula



wherein X stands for hydrogen, alkyl and alkoxy, Y stands for alkyl and aralkyl, A stands for hydroxyalkyl and R stands for hydrogen, alkyl and aralkyl.

Still other objects of the present invention are the optically active amino-alcohols of the general formula



wherein Y stands for alkyl and aralkyl, A stands for hydroxyalkyl and R stands for hydrogen, alkyl and aralkyl.

The optically active amino-alcohols, prepared by the process herein described are valuable compounds for the manufacture for example of alkaloids for instance according to the process described in U. S. Patent 2,900,430.

The following examples illustrate the invention, but the same is not limited to these examples.

EXAMPLE 1

100 g. of sodium cut up into large pieces are placed into a round flask and covered with 300 cc. of tetrahydronaphthalene. The whole is heated in an oil bath at 120° C. (inner temperature). The sodium melts and collects into globular lumps on the bottom of the vessel. A solution of 104

g. of α-benzylaminopropionic acid ethyl ester (0.5 mol.) in 300 cc. of absolute alcohol is allowed to flow in slowly so that the inner temperature is maintained as far as possible at 106–108° C. After the ester solution has run in, absolute alcohol is slowly added from a dropping funnel until the sodium is dissolved. The inner temperature thereby slowly sinks down to about 90° C.

After all the sodium is dissolved the contents of the flask are allowed to cool to 80° C. and 200 g. of crushed ice are carefully added. By placing in cold water it is cooled further to about 30° C. and then it is neutralized with diluted hydrochloric acid (2 vols. of conc. HCl+1 vol. H_2O) until distinctly acid to Congo. It is then allowed to stand for about 1 hour at 20° C. and the separated common salt filtered off on a suction filter and well washed with alcohol. The filtrate is then separated from separated tetrahydronaphthalene in a separating funnel and the alcoholic solution which still has a distinctly acid reaction to Congo is evaporated in a vacuum until crystallization of common salt takes place. The residue is taken up in absolute alcohol, filtered by suction from common salt which is well washed with absolute alcohol, and the filtrate again evaporated in a vacuum to a syrup. It is now taken up in a little water and thereupon treated with a considerable amount of a concentrated caustic soda solution. The benzyl-alaninol thereby separates out as a dark colored oil. It is taken up in ether and the solution dried over Glauber salt. After distilling off the ether it is fractionated in a vacuum B. $P_{.20}$=155–157° C. A colorless, thickly fluid, easily crystallizable oil is obtained. The yield after recrystallization from 120 cc. of cyclohexanol is of 53 g., i. e. 64% of the theory.

The d,l-N-benzylalaninol of the formula

$$CH_3-\underset{\displaystyle NH-CH_2.C_6H_5}{\overset{\displaystyle \bullet}{CH}}-CH_2OH$$

crystallizes from benzol in fine needles, from acetic ester and cyclohexanol in thin water-clear prisms M. P.=70–72° C. $B.P._{.20}$=155–157° C. It is fairly easily soluble in water with a strongly alkaline reaction It separates out from aqueous solutions on the addition of strong lyes as a colorless oil (method of isolation). It is very readily soluble in alcohol and ether.

3.120 mg. substance gave 0.227 cc. of N_2.(20° C., 746 mm.)

0.2199 g. substance used 13.31 cc. of *n*/10 HCl

$C_{10}H_{15}ON$ Calc. N=849% mol. weight=165.

Found N=8.31% mol. weight=165.2.

Hydrochloride: M. P.=111–113° C. Prisms from alcohol-ether. Easily soluble in water.

Picrate: M. P.=135–137° C. Yellow prisms or rhombs from alcohol. Difficultly soluble in water.

Acid oxalate: M. P.=176–178° C. (decomp.). Needles difficultly soluble in water.

Optical separation of the d,l-N-benzylalaninol

66 g. d,l-N-benzylalaninol (0.2 mol.) and
60 g. tartaric acid (0.2 mol.)

are dissolved hot in 100 cc. of alcohol and 100 cc. of acetic ester are slowly added while shaking to the somewhat cooled solution. On cooling, a separation of a colorless syrup ensues. The same is inoculated with a few crystals which have been obtained by a small previous experiment, and the whole is allowed to stand in a closed vessel for 2 days in the ice-cupboard. The greater part of the syrup is then crystallized. The crystal cake is well shaken up and filtered under suction. The contents of the suction filter are freed from adhering syrup by washing with alcohol-acetic ester (1:1), and after drying, are recrystallized for further purification twice from a mixture of 80 cc. of alcohol and 80 cc. of acetic ester.

The thin glass splittering crystals thus obtained consist of the pure bitartrate of the levorotary benzylalaninol. The yield amounts to 40–45 g., i. e. 63–71% of the theory.

The alcohol-acetic ester mother liquors of the crude (—)-N-benzylalaninolbitartrate are evaporated to a syrup in a vacuum, and this is taken up in water and the base completely separated by the addition of an excess of a strong caustic soda solution. It is taken up in ether and after drying over Glauber salt, the solvent is distilled off. The residual syrup is dissolved in 60 cc. of warm cyclohexanol. After cooling to 40° C. it is filtered by suction from the separated crystals which consist of nearly pure racemate and then washed with cyclohexanol warmed to 40° C. The filtrate is evaporated in a vacuum and the residual syrup (25 g.) dissolved in 90 cc. of water with 19 g. of oxalic acid (cryst.). On cooling the acid oxalate of the (+)-N-benzylalaninol crystallizes out in pure form. Yield: 32 g., i. e. 63% of the theory.

From the two salts of optically active free bases are isolated in the usual manner and purified by crystallization from cyclohexanol-petroleum-ether.

d(—)-N-benzylalaninol crystallizes out from cyclohexanol-petroleum-ether in form of fine light needles. M. P. 47–49°. It is more soluble in organic solvents than the racemic compound.

Polarisation: in alcohol (*c*=4.0).

$$[\alpha]_D^{22} = -44.25°$$

Hydrochloride: M. P.=136–138° C. Prisms from alcohol-ether.

$$[\alpha]_D^{21} = -14.75°$$

(Water: *c*=4.0.)

Picrate: M. P.=73–75° C. Yellow prisms from dilute alcohol.

Acid oxalate: M. P.=187–189° C. (decomp.), needles difficultly soluble in water.

d-bitartrate: M. P.=94–96° C. Prisms from alcohol or water.

l-(+)-N-benzylalaninol

Polarisation: In alcohol (*c*=4.0).

$$[\alpha]_D^{23} = +44.0°.$$

The remaining data are the same as in the case of the levo-form.

16.5 g. l-(+)-benzyl-alaninol are dissolved in 200 cc. of dilute alcohol, 6.3 g. of cryst. oxalic acid in 100 cc. water are added and shaken with a slight excess pressure with 1.5 g. of palladium sponge and hydrogen. After about 24 hours the absorption of hydrogen is achieved. It is filtered from catalyst and the solution evaporated in a vacuum to a syrup. On distillation with 150 cc. of absolute alcohol, the l-(+)-alaninol-oxalate crystallizes out in snow-white glittering crystal leaflets. Yield of pure compound 11.3 g. corresponding to 95% of the theory. By concentration of the mother liquor a further 0.5 g. can be obtained.

l-(+)-alaninol-oxalate melts at 171° C. (corr.)

$$[\alpha]_D^{20} = +18.8°$$

(c=2 in water). Composition: $(C_4H_{10}O_3N)_2$. The compound is easily soluble in water, very difficultly soluble in alcohol.

The reaction takes place in the case of d-(−)-alaninol in exactly the same way as with the dextro-rotary antipode.

d-(−)-alaninol-oxalate has a specific rotation

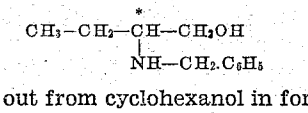
$$[\alpha]_D^{20} = -18.8°$$

In its other properties it naturally corresponds with those of l-(+)-alaninol-oxalate.

EXAMPLE 2

100 g. of sodium cut into coarse pieces are added during short intervals to a boiling solution of 110.5 g. of α-benzylamino-butyric-acid-ethyl-ester (0.5 mol.) in 1 liter of absolute alcohol. It is heated until all the sodium is dissolved, if necessary with the addition of a further quantity of absolute alcohol. It is allowed to cool to about 80° C. and 200 g. of ice are added and it is carefully neutralized after cooling with diluted hydrochloric acid (2:1). After the separation of common salt is finished this is filtered off by suction and the alcohol distilled off in vacuum. The syrup thus obtained is treated with an excess of strong soda or caustic potash solution and the separated oil taken up in ether. After drying over Glauber salt the solvent is distilled off and the residue fractionated in a vacuum. B. P.$_{14}$= 155–157° C.

The d,l-2-benzylaminobutanol-1 thus obtained having the formula



crystallizes out from cyclohexanol in form of thin prisms. M. P. 58–60° C. B. P.$_{14}$=155–157° C. It is soluble in water, easily soluble in alcohol and ether.

4.040 mg. substance gave 0.276 cc. of N_2 (21° C., 750 mm.).

0.2048 g. substance used 11.63 cc. of $n/10$ HCl.

$C_{11}H_{17}ON$ Calc. N=7.82% mol. weight=179.
Found N=7.83% mol. weight=179.2.

Hydrochloride: M. P.=127–129° C. Leaflets or needles from alcohol-acetic-ester. Easily soluble in water.

Picrate: M. P.=144–146° C. Yellow thin prisms.

35.8 g. of d,l-2-benzylaminobutanol-1 (0.2 mol.) and 30.4 g. of (−)-mandelic acid (0.2 mol.) are dissolved in 50 cc. of warm acetic ester. On allowing the solution to stand, spontaneous crystallization takes place. After this is complete, it is filtered under suction and washed with acetic ester. The product is recrystallized twice from 120 cc. of acetic ester+5 cc. of absolute alcohol until the melting point is constant. White felted needles of melting point 111–117° C. are obtained. Yield: 23 g., i. e. 69% of the theory. The product is the pure (−)-mandelic acid salt of (−)-2-benzylaminobutanol-1.

For the preparation of the dextro-rotary compounds the first two mother liquors of the (−)-mandelic acid levo-rotary compound are evaporated in a vacuum and the base is regenerated (21 g.). It is dissolved with 18 g. of (+)-mandelic acid in 50 cc. of acetic ester. The crystals which separate out on standing are again recrystallized twice from 120 cc. of acetic ester+5 cc. of absolute alcohol. 26 g., i. e., 79% of pure (+)-mandelate of (+)-2-benzylamino-butanol-1 are thus obtained. M. P. likewise 111–113° C.

Isolation of the free optically active base takes place in the usual manner. Purification is obtained by recrystallization from cyclohexane.

(−)-2-benzylamino-butanol-1 crystallizes out from cyclohexanol in form of fine needles of M. P=76–78° C.

Polarisation in alcohol (c=4.0).

$$[\alpha]_D^{21} = -25.0°$$

Hydrochloride: M. P.=141–143° C., needles from alcohol-ether, easily soluble in water.

Picrate: M. P.=111–113° C., yellow prisms from alcohol of 50%.

(+)-2-benzylamino-butanol-1

Polarisation: In alcohol (c=4.0).

$$[\alpha]_D^{23} = +25.5°.$$

17.9 g. (+)-N-2-benzylamino-butanol-1 are dissolved in 200 cc. of absolute alcohol, 6.3 g. of crystallized oxalic acid in 100 cc. of water are added and the whole is shaken with hydrogen with the use of 1.5 g. of palladium sponge as catalyst. After about 24 hours, the absorption of hydrogen is terminated.

After filtering off from the catalyst the solution is evaporated to a syrup and diluted with 150 cc. of absolute alcohol. (+)-2-amino-butanol-1-oxalate crystallizes out in form of snow-white needles. Yield 12–13 g., which amounts almost to the theory. M. P. 190-192° C. (corr.).

$$[\alpha]_D^{20} = +11.3°$$

(c=3 in water). Composition: $(C_5H_{12}O_3N)_2$.

(−)-2-amino-butanol-1-oxalate can be prepared in the same manner from its N-benzyl derivative. Except in its specific rotation

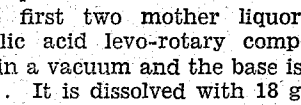
$$[\alpha]_D^{20} = -11.3°$$

this compound corresponds in its properties to the dextro-rotary antipode.

EXAMPLE 3

124.5 g. of the ethyl ester of benzylaminoisocapronic acid are dissolved in 1 liter of butyl-alcohol which has been dehydrated with Mg-butylate and the solution is heated to boiling. 100 g. of cut-up sodium are introduced as quickly as possible into the boiling solution. Thereupon it is heated with the addition of a further quantity of dehydrated butyl-alcohol until all the metal is dissolved. It is allowed to cool, treated with 200 g. of ice and neutralized with dilute hydrochloric acid (2:1) with good external cooling. It is filtered from the separated salt and the alcohol is completely distilled off in a vacuum. The residue thus obtained is treated with an excess of a caustic soda solution and the crude d,l-N-benzyl-leucinol which has separated in the form of an oil is taken up with ether. The solution is dried with Glauber salt. The ether having been distilled off, there remains a colorless syrup which is fractionated in a vacuum.

The pure d,l-N-benzyl-leucinol having the formula



distills off at 170–172° C. at 16 mm. Hg as a colorless oil which soon completely solidifies in crystalline form. After recrystallization from cyclohexane, fine needles are obtained of M. P. 61–63° C.

The d,l-N-benzyl-leucinol is difficultly soluble in water, easily soluble in alcohol, ether and benzene.

4.418 mg. substance gave 0.263 cc. of N_2 (21°, 750 mm.)
0.2163 g. substance used 10.58 cc. of n/10 HCl
$C_{13}H_{21}ON$ calc. N=6.76% mol. weight 207
Found N=6.82% mol. weight 204.4.
Hydrochloride: M.P.=151–153° C. Prisms from water, rather difficulty soluble in water.
Picrate: M.P.=152–154° C. Yellow prisms from alcohol, difficulty soluble in water.

The racemic base was first converted by means of d-dibenzoyl-tartaric acid (Butler and Cretscher, Am. 55, 2605, 1933) in aqueous alcoholic solution into the acid salt. On allowing the solution to stand crystallization results of a salt which can be purified to a constant melting point by recrystallization from alcohol-water. In this way the d-(+)-N-benzyl-leucinol-d-dibenzoyl-tartrate is obtained in pure form.

20.7 g. d,l-N-benzyl-leucinol (0.1 mol.) and 37.6 g. d-dibenzoyltartaric acid (0.1 mol.) are dissolved warm in 150 cc. of alcohol of 60%. After cooling to room temperature, it is inoculated and allowed to stand over night. The separated crystals are filtered off by suction, washed with alcohol of 60% and recrystallized three times from 100 cc. of alcohol of 60% until constant melting point. The pure d-(+)-N-benzyl-leucinol-d-dibenzoyl-tartrate forms good well-developed colorless prisms of M.P. 169–171° (the M.P. is somewhat dependent on the manner of heating). They are easily soluble in warm alcohol, very difficultly soluble in water. Yield 50% of the theory.

The crude l-base (11 g.) regenerated from the first two mother-liquors of the dibenzoyltartrate is dissolved warm in 50 cc. of alcohol of 50% with the equivalent quantity of (+)-o-nitromandelic acid (10.5 g.). On cooling the solution, the 1-(−)-N-benzyl-leucinol-(+)-o-nitromandelate crystallizes out and becomes completely pure after a further recrystallization from a little alcohol of 50%. Pale yellowish green prisms of M.P. 128–130° C. are thus obtained.

From the two salts the free bases are isolated in the usual way and purified by crystallization from cyclohexane.

d(+)-N-benzyl-leucinol crystallizes from cyclohexane in form of fine, felted needles of M. P.=77–79° C.

Polarisation: in alcohol (c=4.0)

$$[\alpha]_D^{20} = +30.75°$$

Hydrochloride: M. P. 160–162° C. Prisms from alcohol-ether or water, which are fairly difficultly soluble in water.
Picrate: M. P.=121–123° C. Yellow prisms from 50% - alcohol.

$$[\alpha]_D^{20} = -30.25°$$

20.7 g of d-(+)-N-benzyl-leucinol are dissolved in 600 cc. of absolute alcohol, 6.3 g. of crystalline oxalic acid in 200 c. of water added thereto and the whole is shaken with 2.5 g. of palladium sponge and hydrogen. After about 12 hours the reduction cleavage is achieved.

The solution freed from crystals is concentrated in a vacuum to y syrup and this is diluted with 100 cc. of alcohol. d-(+)-leucinol-oxalate crystallizes out in form of glittering leaflets. In order to complete the separation it is diluted with another 200 cc. of ether. Yield 14–15 g. corresponding to about 90% of the theory. Melting point 216° C. (corr.). Polarisation

$$[\alpha]_D^{20} = +7.2°$$

(c=3 in water). Composition: $(C_7H_{16}O_3N)_2$.

1-(−)-N-benzyl-leucinol corresponds in its properties with the dextro-rotary antipode fully to the extent of the equal and opposite rotation value.

Example 4

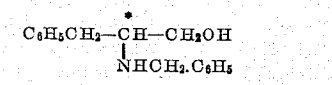
By the application of the method of working described in Examples 1 to 3, the d,l-N-benzylvalinol can be obtained in a good yield by the reduction of α-benzylamino-isovalerianic acid ethyl ester. The d,l-N-benzyvalinol distills in a vacuum at 146–148° C. at 8 mm. Hg. It is difficultly soluble in water, easily soluble in alcohol-ether and benzene. Hydrochloride: M. P. 152–154° C. Prismatic needles from alcohol-acetic ester, which are moderately difficultly soluble in water.

4.992 mg. substance gave 0.255 cc. of N_2 (22°, 749 mm.)
0.2224 g. substance used 9.65 cc. of n/10 $AgNO_3$ (according to Volhard)
$C_{12}H_{20}ONCl$ Calc. N=6.10% Cl=15.47%.
Found N=5.83% Cl=15.39%.
Picrate: M. P.=131–133° C. Yellow prisms from alcohol, difficultly soluble in water.

Example 5

In a similar manner to that described above 2 - N - benzylamino-3-phenyl-propane-ol-1 (N-benzyl-phenyl-alaninol) can be obtained by the reduction of α-benzylamino-β-phenyl-propionic acid ethyl ester.

The new compound having the formula

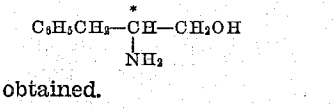


crystallizes out from cyclohexanol in form of thin needles of M. P.=69–71° C. and B. P.$_5$=198–200 C., difficultly soluble in water, easily soluble in alcohol, ether and benzene.

3.901 mg. substance gave 0.205 cc. of N_2 (21°, 740 mm.).
0.2182 g. substance used 9.02 cc. of n/10 HCl.
$C_{16}H_{19}ON$ Calc. N=5.81% mol. weight=241.
Found N=5.94% mol. weight=241.9.
Hydrochloride: M. P.=147–149° C. Small prisms or tablets from alcohol-ether.
Picrate: M. P.=166-168° C. Yellow rhombs from alcohol, difficultly soluble in water and alcohol.

The d,l-2-benzylamino - 3 - phenylpropaneol-1 may be separated into its optically active constituents by fractional crystallization of its salts and the optically active components hydrogenated in presence of palladium sponge in the manner herein above described

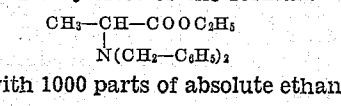
The optically active amino-alcohols of the formula



will thus be obtained.

Example 6

148.5 parts (0.5 mol.) of N-dibenzyl-α-amino-propionic acid ethylester of the formula



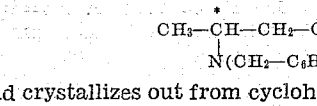
are mixed with 1000 parts of absolute ethanol and

the solution is heated under reflux up to the boiling point. Then 100 parts of sodium cut in small pieces are introduced as rapidly as possible into the solution, which is kept boiling until the metal has been completely dissolved. The solution is then allowed to cool down to about 70° C., 200 parts of broken ice are introduced thereinto and there is carefully neutralized under further cooling down to about 30° C. with diluted hydrochloric acid (2:1).

After the precipitation of sodium chloride has taken place, the solution is filtered, the precipitate washed with ethanol and the filtrate freed from ethanol by distillation in vacuo. The remaining, dark-brown colored syrup is dissolved in water and the solution made strongly alkaline by addition of a sodium or potassium hydroxide solution. The oily precipitated base is then extracted with ether. After drying of the ethereal solution with anhydrous sodium sulphate, the solvent is distilled off and the residue fractionated in vacuo.

The principal fraction boils at 210°–212° C. (14 mm.) and is obtained in form of a weakly colored syrup.

Further purification is carried out by using the well crystallized hydrochloride: the syrup is dissolved in 100 parts of ethyl acetate and neutralized with a hydrochloric acid solution in absolute ethanol. After short standing in the cold the hydrochloride crystallizes out in nearly theoretical yield, it is filtered and washed with ethyl acetate. After one recrystallization from a double quantity of ethanol under addition of ether, the salt will be obtained in pure form. M. P.=181–183° C. The base isolated therefrom in the usual manner is dissolved in ether, dried over sodium sulphate and will be obtained after evaporation of the solvent in form of a colorless syrup, which on cooling becomes crystalline. The d,l-N-dibenzylalaninol obtained in this manner has the formula



and crystallizes out from cyclohexane-petrolether in form of compact, glass glimmering plates, M. P.=56–58° C., easily soluble in ethanol, ether and benzene, nearly insoluble in water.

7,895 mg. of the substance gave 0.376 cc. of N_2 (20° C., 748 mm. Hg).

0,3411 g. substance used 13,12 cc. of $n/10$ HCl= 0.04784 g. HCl.

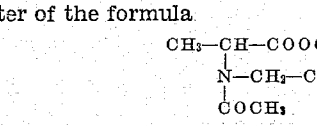
$C_{17}H_{21}ON$ Calc. N=5.49% mol. weight=255.
Found N=5.46% mol. weight=260.0.

Hydrochloride: Needles from ethanol-ether or ethanol-ethylacetate. M. P. 181–183° C.

Picrate: Yellow needles from a 50% aqueous ethanol solution. M. P.=149–151° C.

EXAMPLE 7

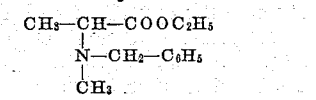
To a boiling solution of 124.5 parts (0.5 mol.) of N-acetyl-benzyl-α-aminopropionic acid ethylester of the formula



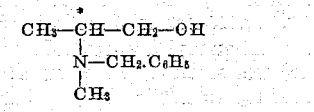
in 1000 parts of absolute ethanol are added 100 parts of sodium cut in small pieces and the solution is boiled until all sodium has been dissolved. After cooling down to about 70° C., 200 parts of ice are added thereto and the solution is neutralized with dilute hydrochloric acid under further cooling to about 30° C. The precipitated sodium chloride is filtered off, washed with ethanol and the filtrate evaporated in vacuo in order to produce a further precipitation of sodium chloride. After dilution with absolute ethanol, new filtration from sodium chloride and working up as described in Example 1, the d,l-N-benzyl-alaninol described in Example 1 will be obtained.

EXAMPLE 8

110.5 parts (0.5 mol.) of N-methyl-benzyl-α-aminopropionic acid ethylester of the formula



are reduced in the manner described in Examples 1–3, whereby after working up the reduced material the -d,l-N-methylbenzylalaninol of the formula



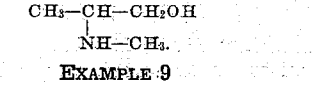
will be obtained in form of a colorless oil of boiling point 138–140° C. (14 mm.), easily soluble in ethanol, ether and benzene, very difficultly soluble in water.

5.263 mg. of substance gave 0.355 cc. of N_2 (19° C., 749 mm. Hg)

0.2893 g. of substance used 15.76 cc. of $n/10$ HCl (=0.0574 g. HCl)

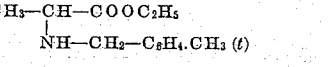
$C_{11}H_{17}ON$ Calc. N=7.82% mol. weight=179;
Found N=7.77% mol. weight=183.6.

10 parts of d,l-N-methylbenzylalaninol are dissolved in 100 parts of ethanol, a solution of 3.5 parts of crystallized oxalic acid (1 equivalent) in 50 parts of water and 3 parts of palladium sponge are added thereto and the solution shaken with hydrogen under a weak pressure. After 8 hours the absorption of hydrogen is achieved. The solution is then filtered from the catalyst and evaporated in vacuo to a syrup. By dissolving in ethanol the neutral oxalate of the d,l-N-methyl-alaninol crystallizes out with a yield of 6.6 parts=88% of the theory, in form of fine needles of M. P. 174° C. (corr.). On recrystallization from water and dilution with ethanol the melting point is no more altered. The base contained in the oxalate has the composition $C_4H_{11}ON$ and the formula

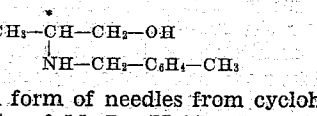


EXAMPLE 9

110.5 parts (0.5 mol.) of N-(p-methylbenzyl)-α-aminopropionic acid ethylester



are reduced in the manner described in Examples 1 to 3, whereby the d,l-N-(p-methylbenzyl)-alaninol of the formula



is obtained in form of needles from cyclohexane or ethylacetate of M. P.=75–77° C., which are easily soluble in ethanol and chloroform, difficultly soluble in water.

4.886 mg. of substance gave 0.323 cc. of N_2 (19° C., 749 mm. Hg)
0.2347 g. of substance used 13.11 cc. of $n/10$ HCl (=0.0478 g. HCl).
$C_{11}H_{17}ON$ Calc. N=7.82% mol. weight=179;
Found N=7.62% mol. weight=179.0.
Picrate: Yellow needles from ethanol M. P.= 145–147° C.

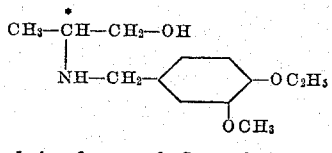
15.5 parts of d,l-N-(p-methylbenzyl)-alaninol are dissolved in 150 parts of ethanol, 5.45 parts of crystallized oxalic acid in 75 parts of water are added thereto and hydrogenated in the manner described in the preceding example. After the calculated quantity of hydrogen (1 mol. of hydrogen for 1 mol of base) has taken up, the hydrogenation ceases. After filtration from the catalyst and evaporation of the solvent, the residual syrup begins to crystallize on treatment with ethanol.

Yield: 10.0 parts of d,l-alaninoloxalate=97% of the theory. After one recrystallization from some water in presence of ethanol the compound shows the right melting point 182° C. (corr.).

Example 10

100 parts of sodium cut in large pieces are placed in a round flask possessing a reflux condenser and a thermometer and covered with 300 parts of dry tetrahydronaphthalene. The whole is heated on an oil bath at 120° C. and a solution of 140.5 parts (0.5 mol.) of N-(3-methoxy-4-ethoxybenzyl)-α-aminopropionic acid ethyl ester in 400 parts of absolute ethanol is allowed to run in in such a manner that the inner temperature remains at 106–108° C. After the whole solution has been introduced into the flask, about 700 parts of absolute ethanol are slowly added to the solution, which is then heated to boil until the metal is completely dissolved. After cooling down to about 80° C., 200 parts of ice are added, the solution is cooled down to about 30° C. and neutralized with dilute hydrochloric acid. The precipitated sodium chloride is filtered and washed with ethanol. The tetrahydronaphthalene layer is then separated from the alcoholic solution which is then evaporated in vacuo until precipitation of sodium chloride takes place. The residue is diluted with absolute ethanol, filtered and evaporated. The dark brown syrup is then dissolved in some water and mixed with an excess of a concentrated sodium hydroxide solution. The new compound separates out in form of a dark oil, which is then taken up with ether. The separated ethereal solution is mixed with half its volume of chloroform, and dried over sodium sulphate. The solvents are then evaporated in vacuo and the still warm residue is dissolved in 100 parts of ether. On cooling with cold water, crystallization takes place immediately, especially after inoculation. The crystals are then filtered and washed with ether. For complete purification they may be twice recrystallized from ethylacetate in presence of some charcoal.

The d,l-N-(3-methoxy-4-ethoxybenzyl) alaninol of the formula



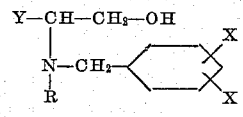
is obtained in form of fine, felted needles of M. P.=94–96° C., which are easily soluble in ethanol and chloroform, difficultly soluble in ether, difficultly soluble in cold, but better in hot water.

4.747 mg. of substance gave 0.248 cc. N_2 (21° C., 750 mm. Hg)
0.3424 g. of substance used 1422 cc. of $n/10$ HCl (=0.05185 g. HCl)
$C_{13}H_{21}O_3N$ Calc. N=5.85% mol. weight 239
Pound N=5.99% mol. weight 240.8.
Hydrochloride: Plates from ethanolether of M. P.=132–134° C., easily soluble in water.

The reductive splitting of the d,l-N-(3-methoxy-4-ethoxy-benzyl) alaninol takes place slower than this is the case with the derivatives of the above examples. 12.2 parts of the base are dissolved in 150 parts of ethanol, 3.2 parts of oxalic acid in 75 parts of water are added thereto and shaken with hydrogen in presence of 8 parts of palladium sponge. After a day about ⅔ of the calculated hydrogen quantity had been taken up and the hydrogenation did not more progress. After filtration from the catalyst 8 parts of fresh catalyst have been added to the solution, whereby the hydrogenation was terminated after 13 hours. The obtained reaction mixture is then worked up in the usual manner, whereby 5 parts of the neutral alaninol oxalate = 82% of the theory are obtained. After one recrystallisation the salt had the correct melting point 182° (corr.).

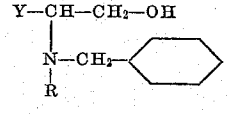
What I claim is:

1. A process for the manufacture of amino-alcohols, comprising the step of treating with hydrogen in the presence of palladium catalyst benzylamino-alcohols of the general formula



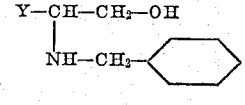
wherein X stands for a member of the group consisting of hydrogen, lower alkyl and lower alkoxy, Y stands for a member of the group consisting of lower alkyl and phenyl-lower alkyl and R stands for a member of the group consisting of hydrogen, lower alkyl and phenyl-lower alkyl.

2. A process for the manufacture of amino-alcohols, comprising the step of treating with hydrogen in presence of palladium catalyst benzyl-amino-alcohols of the general formula



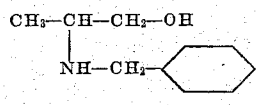
wherein Y stands for a member of the group consisting of lower alkyl and phenyl-lower alkyl and R stands for a member of the group consisting of hydrogen, lower alkyl and phenyl-lower alkyl.

3. A process for the manufacture of amino-alcohols, comprising the step of treating with hydrogen in presence of palladium catalyst benzyl-amino-alcohols of the general formula

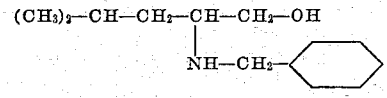


wherein Y stands for a member of the group consisting of lower alkyl and phenyl-lower alkyl.

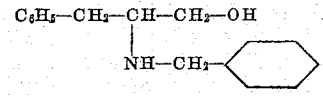
4. A process for the manufacture of an amino-alcohol, comprising the treatment with hydrogen in presence of palladium catalyst of the alcohol of the formula



5. A process for the manufacture of an amino-alcohol, comprising the treatment with hydrogen in presence of palladium catalyst of the alcohol of the formula



6. A process for the manufacture of an amino-alcohol, comprising the treatment with hydrogen in presence of palladium catalyst of the alcohol of the formula



JULIUS PEYER.