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Application of the Asymmetric Synthesis in the Determination of the Configuration of Amino Alcohols and Diamines with Two Adjacent Asymmetric Carbon Atoms*

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Received July 16, 1957

Optically active α-amino ketones of known configuration (D-) can be prepared by virtue of the Bowman ketone synthesis starting with optically active, natural α-amino acids as acylating components. By reduction of α-amino ketones and of their oximes with lithium aluminum hydride the hydroxy and the second amino group were induced asymmetrically yielding in both cases predominantly the *erythro* epimers of corresponding α-amino alcohols and α-diamines. This is in agreement with Cram's rule of the steric control of the asymmetric induction.

D(-)-2-Phthalimido-3-octadecanone (IV) was prepared from *N*-phthaloyl-L-alanyl chloride (II) and dibenzyl sodiotetradecylmalonate (I). The D-configuration was assigned to the ketone according to the proposal of Reihlen, Karrer et al. The hydrolysis of IV with hydrobromic acid gave D(-)-2-amino-3-octadecanone (V) which was reduced with lithium aluminum hydride to give D(+)-*erythro*-2-amino-3-hydroxyoctadecane. The oxime of V when reduced with lithium aluminum hydride gave D(+)-*erythro*-2,3-diaminoöctadecane.

The *erythro* configuration, i. e. trans conformation of the amino alcohol was confirmed by investigation of relative rates of $N \rightarrow O$ acyl migration of the *N*-benzoyl and *N*-acetyl derivatives.

This series of reactions enables the stereospacific synthesis of one of four possible isomers of aliphatic α-amino alcohols and α-diamines as well as the determination of absolute configuration of natural compounds such as dihydrosphingosine, necrosamine etc.

Much progress has been made in the past several years with respect to the elucidation of stereochemical questions of lipide bases containing two adjacent asymmetrically substituted carbon atoms. For example, one of the principal problems to be solved consisted in the determination of the absolute configuration of the amino alcohol sphingosine and of its dihydro derivative. For this purpose direct and indirect methods have been employed. However, the stereochemistry of natural aliphatic diamines such as necrosamine (4,5-diaminoeicosane or 3-methyl-4,5-diaminononadecane) and of the more complicated polyfunctional base phytosphingosine and similar compounds containing

* Presented at the XVI-th International Congress of Pure and Applied Chemistry, Paris, July 1957.

more than two adjacent asymmetric carbon atoms have been investigated in a very limited scope.

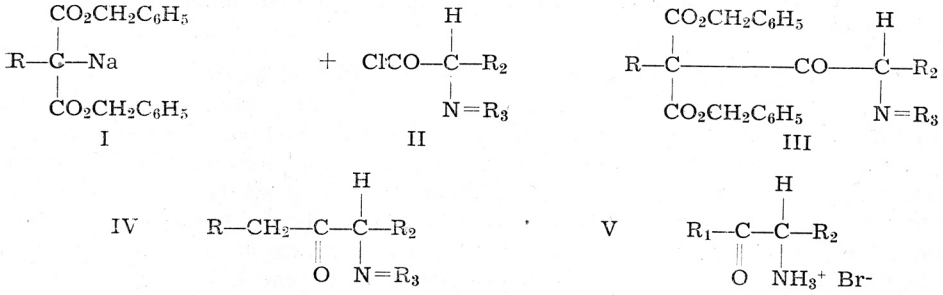
It is to be pointed out that a direct chemical proof for the configuration of C(2) atom in sphingosine was presented by its degradation into (+)-2-amino-öctadecane and, from the other side, by synthesis of the latter starting with natural L(+)-alanine — by chemical methods not involving the asymmetric carbon atom — and by applying the Bowman reaction. The same sign of the optical rotation of the amine obtained by both ways indicated that C(2) atom in sphingosine was of the D-configuration[1]. Thus, the Bowman ketone synthesis[2], the application of which to amino acids has been investigated in details in this laboratory[3], was employed for the first time for solving the configuration of one asymmetric center in the field of amino alcohols.

It seemed to us worth while to tackle the next question which remained to be elucidated, i. e. whether the Bowman reaction mighe be applicable for the stereochemical analysis of both adjacent asymmetric centers of amino alcohols and diamines.

The key intermediate in the synthetic course is the ketone of the general formula V which can readily be prepared starting with dibenzyl sodioalkylmalonates (I) and α-phthalimido acid chlorides (II) following the reactions shown in Sequence I.

At this stage of our considerations it is necessary to point out an important fact. In case when the natural amino acid of the L-configuration is used and when $R_1 \gtrless R_2$, the D-configuration should be assigned to the amino carbon atom. This statement is consistent with the proposals of Reihlen et al.[4], Barrow and Ferguson[5], and Karrer and Dinkel[6] and can be formulated as follows: Compounds derived from amino acids are sterically disposed in such a way as if the carboxyl group was replaced by the smaller alkyl rest.

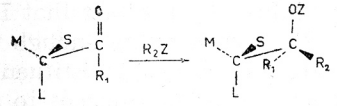
As a further step, the ketone V or its oxime can be reduced to yield the respective amino alcohol or diamine. The stereochemical analysis shows obviously that this reaction represents now a case of partial asymmetric synthesis, since the ketone V is optically active and the asymmetric carbon atom C_β exhibits the asymmetric induction with the formation of two enantiomorphs — with respect to C_α — in unequal proportion.



$R_1 = CH_3(CH_2)_{14}$, $R_2 = CH_3$
R_3 = Phthaloyl, $R = CH_3(CH_2)_{13}$

Sequence I.

On basis of a careful study of a number of reductions of α-ketones possessing one asymmetric carbon atom Cram and Abd Elhafez[7] have proposed the following rule of steric control of asymmetric induction: »In non-catalytic reaction of the type shown (Sequence II), that diastereoisomer will predominate which would be formed by the approach of the entering group (R_2) from the least hindered side of the double bond when the rotational conformation of the C—C bond is such that the double bond is flanked by the two least bulky groups (S and M) attached to the adjacent asymmetric center«.

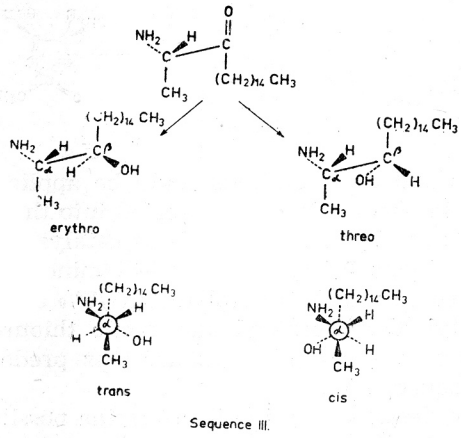


L=Large, M=medium, S=small
Sequence II.

By summarizing these considerations and concepts on the steric course of asymmetric syntheses expressed recently by different investigators — especially by Prelog[8], Cram[7], Doering[9] and Mosher[10] — it becomes obvious that the stereospecific synthesis of α-amino alcohols and α-diamines following the reactions outlined above should lead to the formation of predominantly one optically active stereoisomer. Moreover, the absolute configuration and the *erythro* or *threo* relation of this isomer can be fully predicted by Cram's and Reihlen's rules taken together.

In the present paper we describe a synthesis of D(+)-*erythro* and D(—)-*threo*-2-amino-3-hydroxyoctadecane. The *erythro* and *threo* relations predicted by means of the conformational analysis have been confirmed by investigation of the relative rates of $N \rightarrow O$ acyl migrations in *N*-benzoyl and *N*-acetyl derivatives of the amino alcohol. D(+)-*erythro*-2,3-Diaminoöctadecane which is structurally similar to necrosamine has been prepared as well.

The intermediate ketone — D(—)-2-amino-3-octadecanone hydrobromide (V), $[\alpha]_D - 3.5^0$ — was prepared in the usual manner starting with dibenzyl sodiotetradecylmalonate (I) and *N*-phthaloyl-L-alanyl chloride (II). The respec-

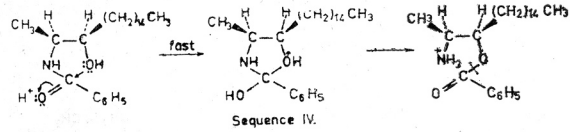


Sequence III.

tive phthalimido ketone (IV), $[\alpha]_D - 3.1^0$, was hydrolysed with 48% hydrobromic acid. The catalytic reduction of V in presence of Adams platinum catalyst yielded two diastereoisomeric amino alcohols: *erythro* (*trans* epimer) and *threo* (*cis* epimer) as represented by the perspective formulas (Sequence III). From the reaction mixture the *erythro* isomer could be isolated in 57% yield and the *threo* isomer in 9.2% yield. On the other hand, when the reduction of V was carried out under non-catalytic conditions by means of lithium aluminum hydride (LAH) the *erythro* isomer was obtained predominantly — as predicted by Cram's rule — and isolated in 78% yield. This stereospecificity may be explained by the fact that LAH in coördination with the carbonyl group makes the oxygen bulky enough to orient it preferentially to the side on which there are the smallest substituents S and M (Sequence II)[7].

In addition, the asymmetric centers adjacent to a carbonyl group are not affected when a group is reduced with lithium aluminum hydride as demonstrated by Noyce and Denney[11].

Accordingly, in the light of Reihlen's and Cram's rule the D-*erythro* (*trans* epimer), $[\alpha]_D + 2.2^0$, and the D-*threo* (*cis* epimer), $[\alpha]_D - 0.86^0$, configurations were allotted to the amino alcohol with highest degree of probability. In order to support this statement we have investigated the $N \rightarrow O$ acyl migrations in *N*-benzoyl and *N*-acetyl derivatives of both isomers. These studies are based on the previous work of Welsh[12] and Bruckner, Fodor et al.[13] When the *N*-benzoyl derivative of the *threo (cis)* compound, m. p. 95—96°, was treated with alcoholic hydrogen chloride the acyl migration combined with hydrolysis of the benzoyl group readily occurred (Sequence IV). It is to be noted that the $N \rightarrow O$ acyl shifts in *threo (cis)* amino alcohols usually proceed with retention of the configuration. On the other hand, the *erythro (trans)* isomer in form of *N*-benzoyl, m. p. 108—109°, $[\alpha]_D - 4.05^0$, and of *N*-acetyl derivative, m. p. 121—122°, — when treated under the same conditions — were recovered unchanged from the reaction mixture. However, under stronger conditions — at the boiling temperature — the acetyl shift produced D-2-amino-3-acetoxyoctadecane hydrochloride. The *trans* epimer might suffer Walden inversion at C(3) as shown by other authors in some cases.

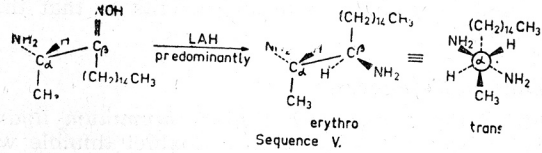


Sequence IV.

Similar reactions and considerations could be applied to the preparation of α-diamines. When the ketone V was converted into the oxime and the latter reduced under both catalytic (with Adams catalyst) and non-catalytic (with LAH) conditions D-(+)-*erythro*-2,3-diaminoöctadecane, $[\alpha]_D + 0.86^0$ (as a hydrochloride) could readily be isolated in 46% and 70% yield respectively. The *O,N*-diacetyl, *O,N*-dibenzoyl and cyclic thiourea derivatives were also prepared. Obviously, the *erythro* isomer was predominant in the non-catalytic reaction (Sequence V).

In conclusion, the described synthesis offers the possibility of unequivocal preparation of each of the four optical isomers of lipide bases — such as

dihydrosphingosine and necrosamine — which might be then compared with the isomers isolated from natural sources. The procedure might also be extended to bases containing three asymmetric centers such as phytosphingosine and similar compounds. Since the arbitrarily chosen configurations for (+)



and (—) glyceraldehyde have been found as true absolute configurations[14] and the configuration of α-amino acids has been correlated with that of glyceraldehyde[15], this general, purely chemical method enables the establishment of the absolute configuration of lipide bases containing two or more asymmetric carbon atoms.

EXPERIMENTAL

The melting points are uncorrected.

D(—)-2-*Phthalimido-3-octadecanone* (IV)

To a suspension of 1.93 g. (0.084 g. atom) of sodium powder in benzene (250 ml.) was added a solution of 40.4 g. (0.084 mole) of dibenzyl tetradecylmalonate (I) dissolved in benzene (250 ml.). The mixture was stirred for 1—2 hr. at room temperature until all sodium was dissolved and then a solution of *N*-phthaloyl-L-alanyl chloride (II) (20 g., 0.084 mole) in benzene (150 ml.) was added at room temperature with stirring. The thick, turbid reaction mixture was left to stand overnight and then poured into ice-water to which a few drops of concentrated sulphuric acid were added. The extraction with benzene and evaporation of the solvent in vacuo gave yellow oil which was dissolved in ethanol (400 ml.) and hydrogenated in the presence of two 3 g. portions of palladium on barium sulphate catalyst. After 12 hrs. 3550 ml. (86.6%) of hydrogen was absorbed at 20° and at 750 mm. The catalyst was removed by filtration and the filtrate refluxed for 2 hr. The solvent was evaporated, the residual oil dissolved in benzene (50 ml.) and left to stand overnight. The crystalline tetradecylmalonic acid (4.05 g.) was filtered off and the filtrate chromatographed over activated alumina (150 g., »Fluka«). The benzene eluates gave after crystallization from ethanol 12.2 g. (35.1%) of a substance melting at 69—71°. Two additional crystallizations from ethanol gave a product, m. p. 73—73.5°, which showed no depression in admixture with a sample of (—)-2-phthalimido-3-octadecanone prepared earlier.[1] $[\alpha]_{20}^{D}$ — 3.1° (c, 11, in chloroform).

D(—)-2-*Amino-3-octadecanone hydrobromide* (V)

The ketone IV (2.9 g., 7 m*M*) was refluxed with glacial acetic acid (30 ml.) and 66% hydrobromic acid (25 ml.) for 10 hrs. The reaction mixture was evaporated in vacuo to dryness and the residue was refluxed with chloroform (50 ml.). The undissolved phthalic acid (1.1 g., m. p. 196—198°) was removed by filtration and the mother liquid evaporated in vacuo to dryness. Crystallization from ethyl acetate gave 2.3 g. (92.3%) colourless crystals which sintered at 112—116° and at 170° decomposed. For analysis the substance was recrystallized five times from a mixture ethyl acetate-ethanol (10:1); sint. at 115—116°; $[\alpha]_{D}^{20}$ — 3.5 (c, 3.4, in pyridine).

Anal. 8.470 mg. subst.: 18.43 mg. CO_2, 7.90 mg. H_2O
$C_{18}H_{38}ONBr$ (364.40) calc'd: C 59.23; H 10.51%
found: C 59.38; H 10.56%

D-2-Amino-3-octadecane oxime

A sample of V (4 g., 10.9 m*M*) was refluxed for 3 hrs. with a solution of hydroxylamine acetate prepared from hydroxylamine hydrochloride (4 g.), sodium acetate (8 g.) and absolute ethanol (80 ml.). The residue after removal of the solvent was shaken with water (200 ml.) and the crystalline oxime filtered by suction. Two crystallizations from ethyl acetate gave 3 g. (92%) colourless crystals, m. p. 123—124°. The substance was slightly soluble in usual solvents so that the specific rotation could not be determined.

D(+)-erythro-2,3-Diaminoöctadecane

A. By reduction of the oxime with lithium aluminum hydride. A sample of the oxime (1.5 g., 5 m*M*) was extracted from a Soxhlet thimble with ether into the solution of lithium aluminum hydride (3 g.) in ether (500 ml.) in the course of 50 hrs. The excess of the reagent was decomposed with water (20 ml.), the ether layer dried with anhydrous sodium sulphate and then saturated with hydrogen chloride. After standing in the refrigerator overnight colourless crystals separated (1.25 g., 69.8%), m. p. 303—304°. The substance was purified for analysis by precipitating the ethanol solution with ether; m. p. 304—306° (sint. from 180°); $[\alpha]$ + 0.86° (c, 2.69, in absolute ethanol).

Anal. 8.915 mg. subst.: 19.81 mg. CO_2, 9.38 mg. H_2O
6.750 mg. subst.: 0.451 ml. N_2 (22°, 750 mm)
$C_{18}H_{42}N_2Cl_2$ (357.44) calc'd: C 60.48; H 11.84; N 7.83%
found: C 60.64; H 11.78; N 7.63%

B. By catalytic reduction in presence of Adams catalyst. A solution of the oxime (0.4 g., 1.3 m*M*) in absolute ethanol (100 ml.), to which 1 ml. conc. hydrochloric acid was added, was hydrogenated in presence of Adams platinum catalyst. After 24 hrs. 81 ml. of hydrogen was taken up at 20° and at 740 mm. The catalyst was filtered off, the solvent removed by distillation and the residue shaken with 2 *N* sodium hydroxide (10 ml.) and ether. Dry ether extracts were saturated with anhydrous hydrogen chloride and allowed to stand in the refrigerator overnight. An amount of 220 mg. (45.9%) colourless crystals, m. p. 304—306°, was obtained which did not show the melting point depression in admixture with a sample prepared by the procedure *A*.

Cyclic Thiourea of D(+)-erythro-2,3-Diaminoöctadecane

A sample of the diamine dihydrochloride (100 mg.) was added to 2 *N* sodium hydroxide (5 ml.), the mixture extracted with ether, the solvent evaporated to dryness, the residue dissolved in ethanol (10 ml.) and carbon disulfide added to this solution. The dithiocarbamate salt was precipitated on standing, m. p. 125—127°. A solution of the salt in ethanol (10 ml.) was refluxed for 2 hr. until the odour of hydrogen sulfide was no longer present. The solvent was then removed by distillation and the residue recrystallized from petroleum ether (50—70°) to give colourless crystals, m. p. 85—86°. For analysis the substance was recrystallized three times from the same solvent; m. p. 88—89°, $[\alpha]_D^{20}$ — 3.5° (c, 2.6, in absolute ethanol).

Anal. 9.110 mg. subst.: 23.40 mg. CO_2, 9.70 mg. H_2O
7.235 mg. subst.: 0.547 ml. N_2 (22°, 750 mm)
$C_{19}H_{38}N_2S$ (326.57) calc'd: C 69.88; H 11.73; N 8.58%
found: C 70.10; H 11.91; N 8.63%

D-erythro-2,3-Dibenzoylaminoöctadecane

A sample of the diamine dihydrochloride (200 mg.) was suspended in water (10 ml.) and shaken with 2 *N* sodium hydroxide (10 ml.). Benzoyl chloride (1 ml.) and 2 *N* sodium hydroxide (20 ml.) was then added and stirred for 1 hr. The reaction mixture was extracted with ether (400 ml.), the ethereal extract evaporated to

dryness and the residue crystallized from ethanol. Three crystallizations yielded a product which melted at 158—162°.

Anal. 8.925 mg. subst.: 25.54 mg. CO_2, 7.86 mg. H_2O
6.375 mg. subst.: 0.314 ml. N_2 (23.5°, 754 mm)
$C_{32}H_{48}O_2N_2$ (492.70) calc'd: C 78.00; H 9.81; N 5.68%
found: C 78.09; H 9.86; N 5.63%

D-erythro-*2,3-Diacetylaminoöctadecane*

A mixture of the diamine dihydrochloride (400 mg.), acetic anhydride (8 ml.) and pyridine (1 ml.) was heated at 100° for 2 hr. The reaction mixture was poured into 2 *N* sulphuric acid (120 ml.), extracted with ether, the ethereal extract washed with water and evaporated to dryness. Crystallization of the oily residue from acetonitrile yielded 100 mg. colourless crystals, m. p. 126—127°.

Anal. 8.600 mg. subst.: 22.76 mg. CO_2, 9.06 mg. H_2O
3.955 mg. subst.: 0.275 ml. N_2 (22°, 743 mm)
$C_{22}H_{44}O_2N_2$ (368.58) calc'd: C 71.68; H 12.03; N 7.60%
found: C 72.22; H 11.79; N 7.87%

D(+)-erythro *and* D(—)-threo-*2-Amino-3-hydroxyoctadecane*

A. By reduction of V with lithium aluminum hydride. — A sample of V (1.5 g., 4.1 m*M*) was dissolved in a mixture of ether (500 ml.) and tetrahydrofurane (50 ml.) and refluxed with lithium aluminum hydride (1.5 g.) for 12 hrs. The excess of the reagent was decomposed with water (20 ml.), the ether — tetrahydrofurane layer filtered, dried with sodium sulphate and evaporated to dryness. The residue was dissolved in absolute ether and the solution saturated with dry hydrogen chloride. Thereby 1.02 g. (77.8%) of colourless crystals of the *erythro* isomer, m. p. 177—179° (sint. from 113—115°), were obtained. The melting point was unchanged after crystallization from a mixture of acetonitrile — absolute ethanol (2:1); $[\alpha]_D^{20}$ + 2.2° (c 2.78, in absolute ethanol).

Anal. 9.040 mg. subst.: 22.39 mg. CO_2, 10.01 mg. H_2O
7.720 mg. subst.: 0.284 ml. N_2 (19.5°, 752 mm)
$C_{18}H_{40}ONCl$ (321.96) calc'd: C 67.14; H 12.51; N 4.35%
found: C 67.59; H 12.39; N 4.25%

B. By catalytic reduction in presence of Adams catalyst. — A solution of V (1.5 g., 4.1 m*M*) in ethanol (200 ml.) was hydrogenated in presence of Adams platinum catalyst (200 mg.) at room temperature and at atmospheric pressure. After 2 hr. 130 ml. of hydrogen was absorbed, the catalyst was filtered off and the ethanol solution evaporated to dryness. The crystalline residue (1.5 g.) was shaken with 2 *N* sodium hydroxide (250 ml.) and ether (200 ml.). The ether layer was washed with water, dried with sodium sulphate and saturated with dry hydrogen chloride. An amount of 740 mg. (56.5%) colourless crystals of the *erythro* isomer, m. p. 177—179° (sint. from 113—115°) was obtained. No melting point depression was observed in admixture with a product prepared according to the procedure *A*. The ethereal mother liquid was evaporated to dryness and the the yellow, oily residue crystallized from ethyl acetate to yield 120 mg. (9.16%) colourless crystals of the *threo* isomer, m. p. 175—176° (sint. from 56°). For analysis the substance was recrystallized four times from ethyl acetate; m. p. 176—177° (sint. from 60—70°); $[\alpha]_D^{20}$ — 0.86° (c, 2.77, in absolute ethanol).

Anal. 9.110 mg. subst.: 22.05 mg CO_2, 9.98 mg. H_2O
6.045 mg. subst.: 0.235 ml. N_2 (20°, 755 mm)
$C_{18}H_{40}ONCl$ (321.96) calc'd: C 67.14; H 12.51; N 4.35%
found: C 66.05; H 12.26; N 4.50%

D(—)-erythro-*2-Benzamido-3-hydroxyoctadecane*

To a mixture of D(+)-*erythro*-2-amino-3-hydroxoctadecane (300 mg.), 2 *N* sodium hydroxyde (40 ml.) and ether (20 ml.) benzoyl chloride (0.5 ml.) was added and

shaken for 20 minutes. The precipitate was extracted with ether (300 ml.), the ether extract washed with water, dried with sodium sulphate and the solvent evaporated to dryness. Crystallization from acetonitrile yielded colourless substance (300 mg.), m. p. 108—109°. For analysis it was recrystallized from the same solvent; m. p. 108—109°; $[\alpha]_D^{20}$ —4.05° (c 2.47, in chloroform).

Anal. 8.445 mg. subst.: 23.93 mg. CO_2, 8.55 mg. H_2O
7.970 mg. subst.: 0.240 ml. N_2 (20°, 751 mm).
$C_{25}H_{43}O_2N$ (389.6) calc'd: C 77.07; H 11.12; N 3.60%
found: C 77.33; H 11.33; N 3.47%

D(—)-threo-*2-Benzamido-3-hydroxyoctadecane*

D(—)-*threo*-2-Amino-3-hydroxyoctadecane (90 mg.) was benzoylated in the usual manner and the product crystallized from petroleum ether. Colourless crystals, m. p. 86—88° (110 mg.). Three more crystallizations from acetonitrile yielded a substance melting at 95—96° (sint. from 85°).

Anal. 8.605 mg. subst.: 24.29 mg. CO_2, 8.17 mg. H_2O
$C_{25}H_{43}O_2N$ (389.6) calc'd: C 77.07; H 11.12%
found: C 77.03; H 11.63%

N → O *Acyl Migration in* D(+)erythro-*2-Benzamido-3-hydroxy-octadecane*

A. A solution of the *erythro* compound (100 mg., 0.2 m*M*), m. p. 108—109°, in absolute ethanol (10 ml.) was added to a 26.8% solution of hydrogen chloride in absolute ethanol (5 ml., 29.1 m*M*). The reaction mixture was allowed to stand at room temperature for 15 hrs., the solvent was evaporated *in vacuo* to dryness and the residue crystallized from acetonitrile. An amount of 90 mg. (90%) of unreacted substance, m. p. 106—107°, was obtained.

B. A solution of the *erythro* compound (100 mg., 0.2 m*M*), m. p. 108—109°, in absolute ethanol was added to a 26.8% solution of hydrogen chloride in absolute ethanol (0.4 ml., 2.9 m*M*). The reaction mixture was allowed to stand at room temperature for 120 hrs. An amount of 70 mg. (70%) of unreacted substance, m. p. 104—105°, was obtained.

C. A solution of the *erythro* compound (90 mg., 0.23 m*M*), in absolute ethanol (10 ml.) and 10% hydrochloric acid (2 ml.) was refluxed for 3 hrs. The reaction mixture was evaporated *in vacuo* to dryness and the residue crystallized from acetonitrile. Unreacted product (62 mg., m. p. 104—105°) was obtained. One more crystallization from the same solvent yielded 60 mg. (66.6%) crystals melting at 106—107°, identical with the starting *erythro* compound.

N → O *Acyl Migration in* D-threo-*2-Benzamido-3-hydroxyoctadecane*

To a solution of the *threo* compound (60 mg., 0.15 m*M*), m. p. 85—87°, in absolute ethanol (5 ml.) was added 28% solution of hydrogen chloride in ethanol and the reaction mixture was allowed to stand at room temperature for 120 hrs. The solvent was evaporated *in vacuo* to dryness and the residue crystallized from a mixture acetonitrile-ethanol. Colourless crystals (58 mg.), m. p. 176—179°, of D-*threo*-2-amino-3-hydroxyoctadecane hydrochloride were obtained.

Anal. 8.115 mg. subst.: 19.79 mg. CO_2, 8.80 mg. H_2O
$C_{18}H_{40}ONCl$ (321.96) calc'd: C 67.14; H 12.51%
found: C 66.55; H 12.14%

D-erythro-*2-Acetamido-3-acetoxyoctadecane*

D(+)-2-Amino-3-hydroxyoctadecane hydrochloride (300 mg., 0.93 m*M*), acetic anhydride (5 ml.) and pyridine (10 ml.) were heated at 100° for 2 hr. The reaction mixture was poured into 2 *N* sulphuric acid, extracted with ether and the ethereal extracts evaporated to dryness. The residual oil was crystallized from acetonitrile to

yield 150 mg. (43·5%) colourless substance, m. p. 69—70°. Two more crystallizations from the same solvent yielded a product melting at 70—70.5°.

Anal. 8.835 mg. subst.: 23.20 mg. CO_2, 9.08 mg. H_2O
4.500 mg. subst.: 0.174 ml. N_2 (20.5°, 756 mm)
$C_{22}H_{43}O_3N$ (369.57) calc'd: C 71.49; H 11.73; N 3·79%
found: C 71.66; H 11.50; N 4.38%

D-erythro-2-*Acetamido-3-hydroxyoctadecane*

The diacetyl compound (100 mg., 0.27 m*M*) was heated with ethanolic *N* sodium hydroxide (10 ml.) at 40—50° for 1 hr. The reaction mixture was then poured into water, the colourless precipitate extracted with ether, the ethereal extracts washed with water and evaporated to dryness. Crystallization from acetonitrile yielded 65 mg. (75.5%) of a substance melting at 121—122°.

Anal. 8.765 mg. subst.: 23.51mg. CO_2, 9·68 mg. H_2O
5.910 mg. subst.: 0.216 ml. N_2 (21°, 755 mm)
$C_{20}H_{41}O_2N$ (327.53) calc'd: C 73.34; H 12.62; N 4.27%
found: C 73.20; H 12.36; N 4.22%

N → O *Acyl Migration in* D-erythro-2-*Acetamido-3-hydroxyoctadecane*

A. To a solution of the *erythro* compound (58 mg., 0.17 m*M*) in absolute ethanol (10 ml·) 30% solution of hydrogen chloride in ethanol (1 ml., 0.3 g., 8 m*M*) was added and left to stand at room temperature for 4 hrs. The reaction mixture was evaporated *in vacuo* to dryness and the residue crystallized from acetonitrile. An amount of 50 mg. (86%) of unreacted substance, m. p. 107—114°, was obtained. Crystallization from ethyl acetate yielded 38 mg. (65.5%) of crystals, m. p. 119—120°, identical with the starting material.

B. To a solution of the *erythro* compound (100 mg., 0.305 m*M*) in absolute ethanol (10 ml.) 30% solution of hydrogen chloride in ethanol (1 ml., 0.3 g., 8 m*M*) was added and left to stand at room temperature for 64 hrs. Crystallization of the dry residue from acetonitrile yielded 90 mg. substance, m· p. 98—99°. Two more crystallizations gave 40 mg. of unreacted *erythro* compound, m. p. 119—120°.

C. A mixture of the *erythro* compound (48 mg., 0.14 m*M*), ethanol (10 ml.) and 10% hydrochloric acid (2 ml.) was refluxed for 2 hr. The reaction mixture was evaporated in vacuo to dryness and the residue crystallized from acetonitrile. An amount of 32 mg. colourless crystals of D-2-amino-3-acetoxyoctadecane hydrochloride, m. p. 94—95° (sint. from 90°) was obtained. A sample for analysis was recrystallized once more from acetonitrile; m. p. 94—95°.

Anal. 9.025 mg. subst.: 21.96 mg. CO_2, 9.70 mg. H_2O
$C_{20}H_{42}O_2NCl$ (364.0) calc'd: C 65.99; H 11.63%
found: S 66.40; H 12.03%

Acknowledgment. We are indebted to Mrs. M. Munk-Weinert from our microanalytical laboratory for the microanalyses.

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IZVOD

Primjena asimetričke sinteze pri određivanju konfiguracije amino-alkohola i diamina sa dva susjedna asimetrička atoma

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Optički aktivni α-amino-ketoni poznate konfiguracije (D-, u skladu s Reihlenovim pravilom) mogu se pripraviti s pomoću Bowmanove ketonske sinteze iz optički aktivnih, prirodnih α-amino-kiselina (L-konfiguracije). Nekatalitičkom redukcijom bilo samih α-amino-ketona, bilo njihovih oksima s litijevim aluminijevim hidridom (LAH) asimetrički se uvodi u molekulu hidroksilna, odnosno druga amino-skupina. U oba slučaja nastaju pretežno *eritro* epimeri (*trans* konformacije) pripadnih α-amino-alkohola i α-diamina, kako to predviđa Cramovo pravilo o steričkoj kontroli asimetričke indukcije.

D(-)-2-Ftalimido-3-oktadekanon (IV) pripravljen je iz *N*-ftaloil-L-alanil-klorida (II) i dibenzil-natrium-tetradecilmalonata (I). Ketonu IV pripisuje se D-konfiguracija — u skladu s Reihlenovim pravilom. Hidrolizom ketona IV bromovodičnom kiselinom dobiva se D(-)-2-amino-3-oktadekanon-hidrobromid (V), koji reduciran s LAH daje u pretežnoj količini D-(+)-*eritro*-2-amino-3-hidroksi-oktadekan. Nadalje je pripravljen — redukcijom oksima ketona V s LAH — D(+)*eritro*-2,3-diamino-oktadekan.

Eritro konfiguracija (*trans* konformacija) amino-alkohola dokazana je konformacijskom analizom, t. j. određivanjem relativnih brzina $N \rightarrow O$ acil-migracija *N*-benzoil i *N*-acetilderivata.

Opisani niz reakcija omogućuje stereospecifičku sintezu jednog od četiri moguća izomera alifatskih α-amino-alkohola i α-diamina, kao i određivanje apsolutne konfiguracije prirodnih spojeva, kao što su dihidro-sfingozin, nekrozamin i drugi.

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Primljeno 16. srpnja 1957.