The Reduction of Some Phthalamic Acids with Lithium Aluminum Hydride

D. E. Sunko

Chemical Laboratory, Department of Physiology, Medical Faculty, University of Zagreb

and

Department of Biochemistry, Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

Received October 28, 1955

The phthalamic acids II and VII derived from 2-phthalimido-octadecane (I) and (-)-2-phthalimido-3-octadecanone (VI) were submitted to reduction with lithium aluminum hydride. The reduction of II afforded two products, i. e. 2-(o-hydroxymethylbenzamido)-octadecane (III) and 2-(o-hydroxymethylbenzylamino)-octadecane (IV). By reduction of VII only 2-(o-hydroxymethylbenzamido)-3-octadecanol (VIII) was obtained. When hydrolyzed III and VIII yielded, after subsequent acylation, 2-acetamidoöctadecane (V) and 2-benzamido-3-hydroxyoctadecane (IX), respectively. The hydrogenolysis of IV afforded V. These reactions may present an alternative method for the elimination of the phthaloyl group.

In connection with the investigation of long chain aliphatic amino alcohols, which is being carried out in our laboratories, α-phthalimidoketones have been used as intermediates[1, 2, 3]. In the course of this work a suitable method for the elimination of the phthaloyl group was required. Hydrazinolysis was unsatisfactory for this purpose mainly owing to undesirable side-reactions with the carbonyl group. The conditions normally applied in acid hydrolysis are more drastic and could not be effectively applied to long chain aliphatic compounds.

The objective of the experiments described in this paper was to investigate the reaction of lithium aluminum hydride with phthalamic acids which are readily obtainable from the corresponding phthaloyl derivatives by alkaline hydrolysis.

For model studies this reaction was first investigated with 2-phthalimido-octadecane (I). Alkaline hydrolysis of I afforded the corresponding phthalamic acid, i. e. 2-(o-carboxybenzamido)-octadecane (II). By reduction of II with lithium aluminum hydride in ether two compounds were obtained in approximatively equal amounts. The less soluble product proved to be 2-(o-hydroxymethylbenzamido)-octadecane (III). From mother liquors 2-(o-hydroxymethylbenzylamino)-octadecane (IV) could be isolated in the form of acid oxalate.

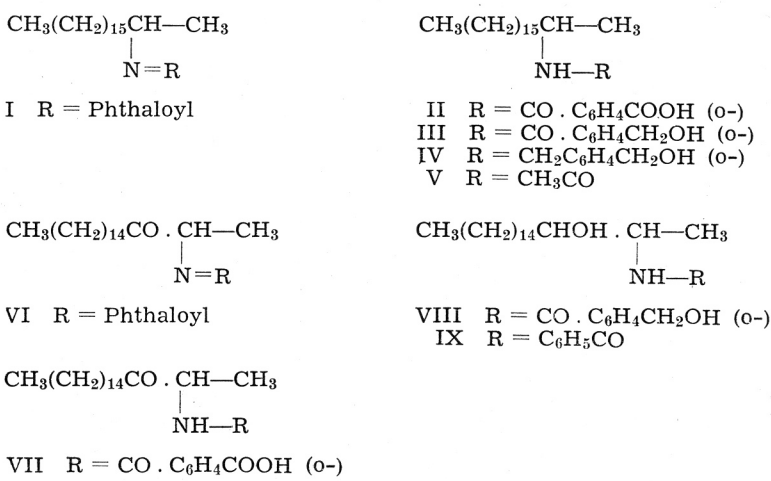
2-(o-Hydroxymethylbenzamido)-octadecane (III) was hydrolyzed with 10% methanolic suphuric acid[4]. The base was isolated and converted to the crystalline 2-acetamidoöctadecane (V), already described[5]. From the aqueous layer the well-known phthalide, m. p. 73° could be isolated. The structure of III was thus confirmed.

2-(o-Hydroxymethylbenzylamino)-octadecane (IV) was reduced catalytically with palladium-on-barium-sulphate catalyst and the product acetylated giving 2-acetamidoöctadecane (V) identical with the product obtained as described above.

In the following series of experiments the reaction was applied to (-)-2-phthalimido-3-octadecanone (VI). This ketone was prepared from L-alanine in the course of our work on determination of the configuration of the amino carbon atom in sphingosine[2]. The ketone VI was converted in the usual manner to (-)-2-(o-carboxybenzamido)-3-octadecanone (VII). Lithium aluminum hydride reduction of VII in tetrahydrofurane afforded as the sole product (+)-2-(o-hydroxymethylbenzamido)-3-hydroxyoctadecane (VIII). When hydrolyzed with methanolic sulphuric acid, VIII yielded, in addition to phthalide, crude 2-amino-3-hydroxyoctadecane (1-deoxy-dihydrosphingosine). Upon benzolyation (-)-2-benzamido-3-hydroxyoctadecane (IX) was obtained.

The course of the reduction of VII where only the carbonyl and the carboxyl group is reduced but not so the amido group may be explained by the fact that in competitive reductions of this type the reduction rates for the first two groups are greater than for the amido group. The dihydroxy compound probably forms an insoluble complex with the reducing agent and is in this way eliminated from the reaction.

Figure I



In summarizing these results it seems that the reduction of phthalamic acids with lithium aluminum hydride with subsequent hydrolysis or hydrogenolysis of the reduction products could present an alternative method for the removal of the phthaloyl group in cases where standard methods are unsuitable.

EXPERIMENTAL*

(with Miss J. Pastorčić)

2-(*o-Carboxybenzamido*)-*octadecane* (II)

A mixture of 1.0 g. of 2-phthalimidoöctadecane[5] (I), 10 ml. of 96% ethanol, and 4 ml. of 17% solution of potassium hydroxide in ethanol was left to stand at room temperature with occasional shaking. After 24 hours 2 *N* sulphuric acid (12 ml.) was added and the precipitated acid fitered off. After crystallization from ethanol 943 mg. (91%) of the acid, m. p. 109—110° were obtained. For analysis the product was recrystallized from ethanol; colorless crystals, m. p. 110—111°.

Anal. 8.750 mg. subst.: 23.91 mg. CO_2, 8.24 mg. H_2O
$C_{26}H_{43}O_3N$ (417.61) calc'd.: C 74.70; H 10.33%
found: C 74.57; H 10.54%

2-(*o-Hydroxymethylbenzamido*)-*octadecane* (III)

In the thimble of a micro-extractor 600 mg. of II was placed, and a suspension of lithium aluminum hydride (600 mg.) in ether (40 ml.) maintained at a moderate rate of boiling until all II was dissolved (10 hours). The excess of hydride was destroyed by succesive addition of wet ether (20 ml.) and water (3 ml.). The ether solution was decanted and the remaining hydroxide digested three times with boiling ether. From the combined extracts the solvent was evaporated leaving 487 mg. of a waxy solid. It was dissolved in warm ether and allowed to crystalize. Colorless crystals, m. p. 93—95° (254 mg., 43.8%) were obtained. The filtrate was left aside for the isolation of IV. After several recrystallizations from petroleum ether the product melted at 98—99°.

A sample was used for the determination of the neutralization equivalent which was equal to zero.

Anal. 8.945 mg. subst.: 25.28 mg. CO_2, 8.74 mg. H_2O
$C_{26}H_{45}O_2N$ (403.62) calc'd.: C 77.30; H 11.24%
found: C 77.12; H 10.94%

2-(*o-Hydroxymethylbenzylamino*)-*octadecane* (IV)

The ether filtrate recovered after isolating III was evaporated to dryness. Two hundred milligrams (35.8% based on II) of a light brown oil were obtained. The oil was dissolved in apsolute ethanol (1 ml.) and added to a warm solution of oxalic acid (100 mg.) in ethanol (1 ml.). The solution crystallized upon cooling. The crystals were filtered, washed with ether and dried. Thus, 180 mg. of crude oxalate, m. p. 141—145° were obtained. For analysis the product was several times recrystallized from absolute ethanol. Colorless prismatic needles, m. p. 154—155° (with some sintering at 150°).

Anal. 8.490 mg. subst.: 21.93 mg. CO_2, 7.77 mg. H_2O
$C_{26}H_{47}ON(COOH)_2$ (479.68) calc'd.: C 70.11; H 10.30%
found: C 70.49; H 10.24%

The free base was obtained from the oxalate with 2 *N* sodium carbonate; light yellow colored oil.

2-*Acetamidoöctadecane* (V)

A. By Acid Hydrolysis of III. — A solution of III (227 mg.) in 5 ml. of 10% methanolic sulphuric acid was refluxed for 24 hours. The solution was made alcaline with aquaeous potassium hydroxide and extracted with ether. After evaporation of the solvent there remained 139 mg. (91.6%) of crude 2-aminoöctadecane. It was acetylated in the usual manner[5]. After recrystallization from 96% ethanol the product melted at 80—81° undepressed in admixture with an authentic sample of 2-acetamidoöctadecane.

---

* The melting points are uncorrected

The alkaline aqueous solution which remained after the extraction with ether (see above) was acidified with 5 *N* suphuric acid and exhaustively extracted with ether. The solvent was removed giving 61 mg. of a solid, m. p. 67—69°. After recrystallization from aqueous ethanol, colorless leaflets of phthalide, m. p. 73°, were obtained.

B. By Hydrogenolysis of IV. — To a suspension of palladium-on-barium-sulphate catalyst[6] (1.0 g.) in 15 ml. of 96% ethanol a warm solution of the oxalate of IV (184 mg.) in ethanol (15 ml.) was added. The hydrogenation was carried out at room temperature and ordinary pressure until the hydrogen absorption ceased. The catalyst was removed, and the solvent evaporated *in vacuo*, giving 133 mg. (96.4%) of crude 2-aminoöctadecane oxalate. The salt was decomposed with sodium carbonate solution, the base isolated in the usual manner, and acetylated[5]. Pure 2-acetamidoöctadecane (V), m. p. 80—81.5° was obtained.

(-)-2-(o-Carboxybenzamido)-3-octadecanone (VII)

(-)-2-Phthalimido-3-octadecanone (VI), m. p. 78—79°, $[\alpha]_D^{18}$ —3.2°, (1.0 g.) was hydrolyzed in the same manner as described for I (see above). The crude product (907 mg., 87%) was recrystallized from petroleum ether. Colorless crystals, m. p. 117—118.5°, $[\alpha]_D^{19}$ —2.32° (c, 2.33 in chloroform).

Anal. 8.285 mg. subst.: 21.95 mg. CO_2, 7.16 mg. H_2O
$C_{26}H_{41}O_4N$ (431.59) calc'd: C 72.35; H 9.57%
found: C 72.30; H 9.65%

(+)-2-(o-Hydroxymethylbenzamido)-3-hydroxyoctadecane (VIII)

A solution of VII (957 mg.) in tetrahydrofurane (15 ml.) was slowly added to a stirred suspension of lithium aluminum hydride (1.0 g.) in tetrahydrofurane (10 ml.). The resulting mixture was refluxed for two hours and after cooling decomposed with wet ether (75 ml.) and water (2 ml.). After centrifugation and washing with ether, the combined extracts were evaporated to dryness *in vacuo*. There remained 752 mg. (77.4%) of crude product, m. p. 89—91°.

For analysis the product was recrystallized from petroleum ether. Colorless prismatic needles, m. p. 96—97°, $[\alpha]_D^{20}$ + 1.7° (c, 2.04 in chloroform).

Anal. 8.435 mg. subst.: 23.04 mg. CO_2, 8.46 mg. H_2O
$C_{26}H_{45}O_3N$ (419.63) calc'd.: C 74.41; H 10.81%
found: C: 74.54; H 11.23%

(-)-2-Benzamido-3-hydroxyoctadecane (IX)

A solution of VIII (148 mg.) in 10% methanolic sulphuric acid (5 ml.) was refluxed for 24 hours, and worked up in the same manner as described above (see V *A.*). The crude product (103 mg.) was suspended in ether (2 ml.) and shaked with benzoyl chloride (0.08 ml.), and 2 *N* sodium hydroxide (1 ml.) during 20 minutes at room temperature. The reaction mixture was diluted with ether, some water was added, and the aqueous layer discarded. After adding few drops of methanol the ether solution was washed neutral with water. The solvent was evaporated, and 134 mg. (95%) of a crude product, m. p. 74—77° were obtained. For analysis the product was several times recrystallized from petroleum ether, and finally from acetonitrile. M. p. 95—97° with transition in crystalline from at 84—87°, $[\alpha]_D^{20}$ —3.3° (c, 0.78 in chloroform).

Anal. 6.20 mg. subst.: 17.47 mg. CO_2, 6.10 mg. H_2O
6.31 mg. subst.: 0.216 ml. N_2 (22°, 750 mm.)
$C_{25}H_{43}O_2N$ (389.6) calc'd.: C 77.07; H 11.12; N 3.60%
found: C 76.89; H 11.01; N 3.87%

From the alkaline aqueous solution which remained after the hydrolisis of VIII, phthalide, m. p. 72—73° could be isolated in the same manner as described above (see V *A.*).

Acknowledgment. Thanks are due to Professor M. Proštenik for his interest, and to Mrs. M. Munk-Weinert for the microanalyses.

REFERENCES

1. D. E. Sunko and M. Proštenik, *Arhiv kem.* **26** (1954) 7.
2. M. Proštenik, M. Munk-Weinert and D. E. Sunko, *J. Org. Chem.* (in press) *(Abstracts of papers,* XIVth International Congress of Pure and Applied Chemistry, Zürich, July 1955, p. 198).
3. N. Ž. Stanaćev and M. Proštenik, *Arhiv kem.* **27** (1955) 203.
   M. Proštenik and N. Ž. Stanaćev, *Arhiv kem.* **27** (1955) 197.
4. M. Munk-Weinert, D. E. Sunko and M. Proštenik, *J. Org. Chem.* **19** (1954) 378.
5. M. Munk-Weinert and M. Proštenik, *Arhiv kem.* **26** (1954) 89.
6. C. Paal, D. R. P. 236488 and 265500; cit. from C. Weygand, *Organisch-chemische Experimentierkunst,* Leipzig 1938., p. 154.

IZVOD

O redukciji nekih ftalamidnih kiselina s litium aluminium hidridom

D. Sunko

Opisana je redukcija ftalamidnih kiselina, pripremljenih iz 2-ftalimido-oktadekana i (-)-2-ftalimido-oktadekanona-3, s litium aluminium hidridom. Dobiveni produkti podvrgnuti su hidrolizi, odnosno hidrogenolizi, i na taj su način pripremljeni 2-amino-oktadekan i 2-amino-3-hidroksi-oktadekan, koji su identificirani kao N-acetil, odnosno N-benzoil derivati.

MEDICINSKI FAKULTET
ZAVOD ZA FIZIOLOGIJU
I
INSTITUT »RUĐER BOŠKOVIĆ«
BIOKEMIJSKI ODJEL
ZAGREB

Primljeno 28. oktobra 1955.