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SYNTHESIS OF ω-AMINOOXY ACIDS BY OXYGEN-ALKYL FISSION OF LACTONES

AN IMPROVED SYNTHESIS OF DL-CANALINE[1]

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Abstract—Lactones were found to react with benzophenone oxime salt to give ω-diphenylmethylidene-aminooxy acids which were hydrolyzed to the corresponding ω-aminooxy acids. The reaction was applied to an efficient synthesis of DL-canaline.

ω-AMINOOXY acids are of interest, i.e. owing to their structural relationship to canaline and cycloserine. We wish to report a method for introducing the aminooxy group into the ω-position of carboxylic acids, based on oxygen-alkyl fission of the lactones[3] corresponding to the acids by reaction of the latter with salts of oximes.

The lactones were: β-propiolactone, γ-butyrolactone, δ-valerolactone and ε-caprolactone. We tried the following oximes: acetoxime, benzophenone oxime, cyclohexanone oxime, fluorenone oxime and anthraquinone dioxime, all in the form of their sodium or potassium salt. Best results were obtained on using the sodium salt of benzophenone oxime; consequently, this oxime was used generally in the above reactions. The ω-diphenylmethylideneaminooxy acids (I) thus obtained were hydrolyzed to the corresponding ω-aminooxy acids (II), according to scheme I:

Scheme I

$$Ph_2C{=}NO^-Na^+ + \overbrace{O(CH_2)_nCO} \rightarrow \underset{\text{I}}{Ph_2C{=}NO(CH_2)_nCOOH} \rightarrow \underset{\text{II}}{H_2NO(CH_2)_nCOOH}$$

$n = 2,3,4,5$

Two competitive reactions can occur in the process of the oxygen-alkyl fission of the lactones to compounds of the type (I): (i) hydrolysis and (ii) polymerization. Their extent depends on the lactone used and affects the yields of compounds (I).

In the case of β-propiolactone, on trying to carry out the reaction in the conventional solvent, water,[4] hydrolysis of the lactone to β-hydroxypropionic acid sodium salt occurred, and the free oxime precipitated out. On the other hand, in aprotic solvents, polymerization became the predominant reaction. The maximal yield (20%) of β-diphenylmethylideneaminooxypropionic acid (I, $n = 2$) was obtained on using benzene as solvent.

In order to minimize the side reactions mentioned above, we tried successfully the

[1] Preliminary Communication: Y. Knobler, C. Gilon and M. Frankel, *Israel J. Chem.* **1**, 242 (1963).

[2] Part of a Ph.D. thesis to be submitted to the Hebrew University of Jerusalem.

[3] Previous examples of oxygen-alkyl fission of lactones by salts of weak acids were described by W. Reppe, *Liebigs. Ann.* **596**, 158 (1955) see also Ref. 4.

[4] H. E. Zaugg, *Organic Reactions*, Vol. 8; p. 305 (1954).

oxygen-alkyl fission of β-propiolactone, using the sodium salt of the stronger acidic N-hydroxysuccinimide in water. N-succinyl-β-aminooxypropionic acid was obtained in 50% yield.

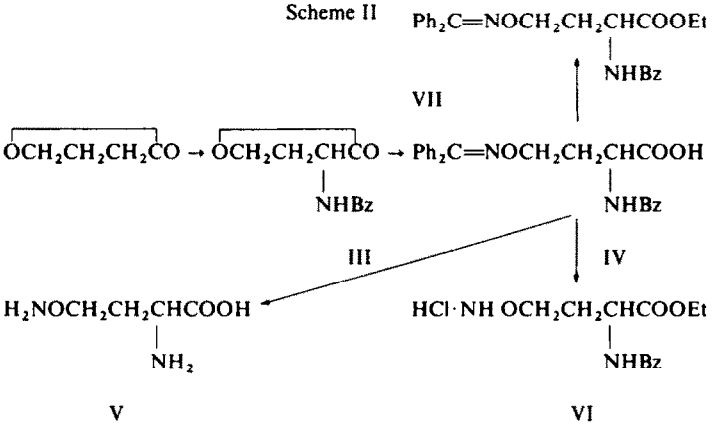
γ-Butyrolactone, δ-valerolactone and ε-caprolactone were found to react with benzophenone oxime sodium salt in dipolar aprotic solvents, such as diethylene glycol-dimethyl ether (diglyme), dimethylsulphoxide, dimethylformamide or N-methylpyrrolidone, at their respective b.ps. In the case of γ-butyrolactone the lactone itself, on using it in excess, can play the role of solvent. Best yields were obtained on using as solvent N-methylpyrrolidone which has the highest b.p. and the highest dipolar character. Yields were 70% for γ-diphenylmethylideneaminooxybutyric acid (I, $n = 3$) and 40% for δ-diphenylmethylidieneaminooxy valeric acid (I, $n = 4$) or ε-diphenylmethylideneaminooxy caproic acid (I, $n = 5$). The marked difference in yield is caused by the competitive polymerization of δ-valerolactone and ε-caprolactone, while γ-butyrolactone does not polymerize.[5]

Removal of the diphenylmethylidene or succinyl groups was effected by hydrolysis with dilute hydrochloric acid. ω-Aminooxy acid hydrochlorides were obtained, while on using ethanolic hydrogen chloride as hydrolysing agent ω-aminooxy acid ethyl ester hydrochlorides directly resulted. During acid hydrolysis some decomposition occurs, and therefore the crude product is sometimes contaminated with ammonium chloride. To overcome this, the diphenylmethylidene or succinyl groups were removed by refluxing the intermediate acid with Dowex 50 W in acetic acid–water. The free ω-aminooxy acids (II) were eluted from the resin by a solution of ammonia–diethylamine.

The method described above constitutes a convenient synthesis of DL-canaline. In the canaline synthesis reported previously from this laboratory,[7] α-benzamido-γ-butyrolactone was converted to γ-halogeno derivative prior to the introduction of the protected aminooxy group. The present synthesis eliminates this step.

Reaction of α-benzamido-γ-butyrolactone (III) with benzophenone oxime sodium salt in N-methylpyrrolidone gave N^{α}-benzoyl-N^{γ}-diphenylmethylidene canaline

Scheme II



[5] W. H. Carothers, G. L. Dorogh and F. J. Van Natta, *J. Am. Chem. Soc.* **54**, 761 (1932).

[6] Y. Knobler and M. Frankel, *J. Chem. Soc.* 1632 (1958).

[7] D. D. Nyberg and B. E. Christensen, *J. Am. Chem Soc.* **79**, 1222 (1957); K. Karpeiskii, R. Khomutov and A. Severin, *Zh. Obshei. Khim.* **32**, 1357 (1962).

(IV) (86% yield). Hydrolysis with aqueous hydrochloric acid yielded canaline dihydrochloride which was transformed to free canaline (V) on treatment with triethylamine. Canaline was also obtained by hydrolysis of IV with Dowex 50 W (yield 70%). Overall yield based on γ-butyrolactone was 30%. Removal of the γ-diphenylmethylidene group only, leading to N^{α}-benzoyl canaline ethyl ester hydrochloride (VI) was achieved by using as hydrolyzing medium an alcohol–water mixture (1:1). Use of ethanolic hydrogen chloride gave N^{α}-benzoyl-N^{γ}-diphenylmethylidene canaline ethyl ester (VII). Attempts to open α-phthalimido-γ-butyrolactone or N-benzyloxycarbonyl-α-amino-γ-butyrolactone by oxime salts failed at the high temperatures required, probably owing to decomposition.

The synthesis of canaline presented here constitutes a definite advantage over the canaline syntheses published up to now,[6,7] both as regards the number of steps involved and the overall yield.

EXPERIMENTAL

N-β-Diphenylmethylideneaminooxypropionic acid (I, n = 2). Benzophenone oxime sodium salt (4·4 g, 0·02 mole) was dispersed in dry benzene (50 ml) under N_2 atm, the mixture was cooled to 5° and freshly distilled β-propiolactone (1·4 g, 0·02 mole) in benzene (5 ml) was added dropwise under vigorous stirring. Stirring was continued for 1 hr at 5° and 2 hr at room temp. Benzene was removed under reduced press and the residue was dissolved in water (250 ml). Undissolved polymer and benzophenone oxime were filtered off and the soln cooled and acidified with dil acetic acid. The ppt was collected and dissolved in acetone. After treatment with Norit, cold water was added carefully till turbidity appeared and the mixture was refrigerated overnight. More water was added and the ppt was collected and recrystallized from hot dil AcOH, to give N^{β}-diphenylmethylidenepropionic acid (1 g, 20%), m.p. 106°. (Found: C, 71·5; H, 5·7; N, 5·0. $C_{16}H_{15}NO_3$ requires: C, 71·4; H, 5·6; N, 5·2%.)

N-β-*Succinylaminooxypropionic acid*. N-Hydroxysuccinimide (23 g, 0·2 mole) was dissolved in 1N NaOH (200 ml), cooled to 5° and freshly distilled β-propiolactone (14·4 g, 0·2 mole) was added dropwise with stirring during 1 hr. Stirring was continued for 1 hr in the cold and 3 hr at room temp. The soln was then acidified with citric acid and extracted 3 times with AcOEt and twice with ether. The combined organic extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from EtOH–pet. ether to give β-N-succinyl aminooxypropionic acid (15·3 g, 49%), m.p. 111°. (Found: C, 44·6; H, 5·0; N, 7·5. $C_7H_9NO_5$ requires: C, 44·9; H, 4·85; N, 7·5%.)

N^{γ}-*Diphenylmethylideneaminooxybutyric acid* (I, n = 3). Benzophenone oxime (10 g, 0·05 mole) was dissolved in dry N-methylpyrollidone (20 ml) Na (1·16 g, 0·05 mole) was added and the mixture stirred at 60° until all the Na dissolved. The soln was cooled to room temp and freshly distilled γ-butyrolactone (4·3 g, 0·05 mole) was added. The mixture was refluxed with stirring for 4 hr, then concentrated *in vacuo* to half the volume and poured into water (500 ml). Undissolved material was removed and the soln was cooled and acidified with AcOH. After standing 1 hr at room temp the ppt was collected by filtration and dissolved in acetone. The soln was treated with Norit, cold water was added carefully till turbidity appeared and the mixture was refrigerated overnight. More water was added and γ-N-diphenylmethylideneaminooxybutyric acid was collected and recrystallized from hot dil AcOH.

N^{δ}-*Diphenylmethylideneaminooxyvaleric acid* (I, n = 4) *and* N^{ϵ}-*diphenylmethylideneaminooxycaproic acid* (I, n = 5) were prepared in the same manner. Properties and yields of the compounds prepared are listed in Table 1.

ω-*Aminooxy acid hydrochlorides*. N^{ω}-Diphenylmethylideneaminooxy acid (0·03 mole) was added to 18% HCl (100 ml). AcOH (20 ml) was added and the mixture was refluxed for ½ hr, cooled, washed with ether and evaporated *in vacuo*. The residue was dissolved in abs EtOH and treated with Norit. Dry ether was added until turbidity appeared and the mixture was kept overnight in a deep freezer. The ω-aminooxy acid hydrochlorides were collected and recrystallized from EtOH–ether. In some cases the product was hygroscopic and an additional recrystallization was required. The compounds prepared gave a positive Jaffe test[8] and are listed in Table 2.

[8] M. Kitagawa and A. Takani, *J. Agric. Chem. Soc. Japan* **11**, 1077 (1935).

TABLE 1. ω-DIPHENYLMETHYLIDENEAMINOOXY ACIDS $Ph_2 \cdot C{=}N \cdot O \cdot (CH_2)_n \cdot COOH$

n =	Yield (%)	°C m.p.	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
3	78	85	71·6	5·9	5·1	$C_{17}H_{17}NO_3$	72·1	6·1	4·9
4	60	80	72·6	6·5	4·5	$C_{18}H_{19}NO_3$	72·7	6·4	4·7
5	30	92	73·2	6·9	4·3	$C_{19}H_{21}NO_3$	73·3	6·8	4·5

TABLE 3. ω-AMINOOXY ACIDS $NH_2O(CH_2)_nCOOH$

n =	Yield (%)	°C m.p.	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
2	69	74	34·1	6·8	13·5	$C_3H_7NO_3$	34·3	6·7	13·3
3	72	115	40·2	7·7	11·0	$C_4H_9NO_3$	40·3	7·6	11·7
4	65	98	45·3	8·2	10·2	$C_5H_{11}NO_3$	45·1	8·3	10·5
5	59	82	49·5	9·0	9·3	$C_6H_{13}NO_3$	48·9	8·9	9·5

TABLE 2. ω-AMINOOXY ACIDS HYDROCHLORIDE $HCl \cdot NH_2O(CH_2)_nCOOH$

n =	Yield (%)	°C m.p.	Found (%)				Formula	Required (%)			
			C	H	N	Cl		C	H	N	Cl
2	73	145	25·4	5·5	9·7	25·5	$C_3H_8NO_3Cl$	25·5	5·7	9·9	25·5
3	61	138	31·2	6·4	8·8	22·6	$C_4H_{10}NO_3Cl$	30·9	6·5	9·0	22·8
4	56	121	34·9	7·2	8·2	20·1	$C_5H_{12}NO_3Cl$	35·2	7·1	8·3	20·9

ω-Aminooxy acids (II). Compound I (0·075 mole) and Dowex 50W × 12, 200/400 mesh (H^+ form, 5 g) were added to 50% AcOH (60 ml). The mixture was refluxed for 8 hr with stirring, filtered and the resin was washed with EtOH, ether, EtOH and water. The washed resin was added to a soln of concentrated ammonia (30 ml) and Et_2NH (20 ml) and the mixture was stirred at room temp for 1 hr. The resin was removed by filtration and washed with water and the filtrate was evaporated. The residue was dissolved in abs MeOH and treated with Norit. The ω-aminooxy acids precipitated after addition of ether and keeping overnight in a deep freezer and were recrystallized from isopropanol–AcOEt. Jaffe test[8] was positive. The compounds obtained are listed in Table 3.

Methyl γ-aminooxybutyrate hydrochloride. γ-Diphenylmethylideneaminoxybutyric acid (9·34 g, 0·33 mole) was dissolved in MeOH (80 ml) and 18% HCl (80 ml) was added. The mixture was refluxed for 6 hr. MeOH was removed and the soln was cooled, washed with ether and evaporated. The residue was crystallized from MeOH–ether to give methyl-γ-aminooxybutyrate hydrochloride (3·1 g, 54%), m.p. 155°. (Found: C, 35·5; H, 7·3; N, 8·3; Cl, 20·9. $C_5H_{12}NO_3Cl$ requires: C, 35·4; H, 7·1; N, 8·3; Cl, 20·9%.)

*N^{α}-Benzoyl-N^{γ}-diphenylmethylidene-*DL*-canaline* (IV). Benzophenone oxime (20 g, 0·1 mole) was dissolved in dry N-methylpyrrolidone (40 ml). Na (2·3 g, 0·1 mole) was added and the mixture stirred at 60° until all the Na dissolved. To the cooled soln III[9] (20·8 g, 0·1 mole) was added and the mixture was refluxed for 4 hr, then concentrated *in vacuo* and poured into water (1 l.). Unreacted oxime was removed and the soln cooled and acidified with AcOH. After standing 1 hr at room temp the ppt was collected by filtration and dissolved in acetone, treated with Norit, and cold water was added carefully till turbidity appeared. The mixture was refrigerated overnight, more water was added and the ppt was collected and recrystallized from hot dil AcOH to give N^{α}-benzoyl-N^{γ}-diphenylmethylidene-DL-canaline (35 g, 86%) m.p. 127°. (Found: C, 71·5; H, 5·4; N, 7·0. $C_{24}H_{22}N_2O_4$ requires: C, 71·6; H, 5·5; N, 7·0%.)

*N^{α}-Benzoyl-*DL*-canaline ethyl ester hydrochloride* (VI). Compound IV (7·3 g, 0·018 mole) was dissolved in EtOH (50 ml) and 20% HCl (50 ml) was added. The soln was refluxed for 3 hr, EtOH was removed by evaporation and the soln was washed with ether and then evaporated to dryness. The residue was dissolved in a little abs EtOH and treated with Norit. Precipitation with dry ether and recrystallization from MeOH–ether gave VI (3·9 g, 72%), m.p. 163°. (Found: C, 51·3; H, 6·4; N, 9·2; Cl, 12·0; OEt, 15·0. $C_{13}H_{19}N_2O_4Cl$ requires: C, 51·6; H, 6·3; N, 9·3; Cl, 11·7; OEt, 14·9%.)

N^{α}-Benzoyl-N^{γ}-diphenylmethylidene-canaline ethyl ester (VII). Compound IV (6·5 g, 0·016 mole) was dissolved in 10% ethanolic HCl (100 ml) and the mixture was refluxed for 4 hr. After concentration *in vacuo* VII crystallized out upon cooling (6·8 g, 97%), m.p. 95–97°. (Found: C, 72·5; H, 5·9; N, 6·5; OEt, 9·9. $C_{26}H_{26}N_2O_4$ requires: C, 72·5; H, 6·1; N, 6·5; OEt, 10·5%.)

DL-*Canaline* (V)

(a) Compound IV (6·5 g, 0·016 mole) was added to a mixture of 18% HCl (40 ml) and AcOH (13 ml) and was refluxed for 3 hr, cooled and the ppt formed was removed. The filtrate was washed with ether and evaporated to yield canaline dihydrochloride as an oil which did not crystallize. The oil was dissolved in abs EtOH (30 ml). Et_3N was added dropwise until basic (pH = 8). The ppt was collected, dispersed in EtOH and water was added until a clear soln was obtained. The soln was treated with Norit cooled and abs EtOH was added dropwise until tubidity appeared. The mixture was kept overnight in a refrigerator and the ppt was recrystallized from acetone: water–EtOH to give DL-V (1·5 g, 70%), m.p. 192° dec. (Found: N, 20·6. Calc. for $C_4H_{10}N_2O_3$ N, 20·9%.)

(b) Compound IV (4 g, 0·01 mole) and Dowex 50 W × 12 (200/400 mesh, 20 g) were added to 50% AcOH (200 ml). The mixture was refluxed for 9 hr with stirring, filtered and the resin was washed repeatedly with EtOH, ether, EtOH and water. To the washed resin concentrated ammonia (100 ml) and Et_2NH (80 ml) were added and the mixture stirred at room temp for 1 hr. The resin was removed by filtration and washed with water. The filtrate was evaporated and the residue was dispersed in hot EtOH, water was added until a clear soln was obtained. After treatment with Norit the soln was cooled and abs EtOH was added dropwise until turbidity appeared, and the mixture cooled overnight. The ppt was recrystallized from acetone: water EtOH to give DL-canaline (1 g, 67%) m.p. 195° dec. (Found: N, 20·5. Calc. for $C_4H_{10}N_2O_3$: N, 20·9%.)

DL-*Canaline methyl ester dihydrochloride.* Crude DL-canalinedihydrochloride described above was dissolved in abs MeOH (100 ml). Dry HCl gas was bubbled in the cold for 3 hr, the soln was concentrated *in vacuo*, MeOH (50 ml) was added and dry HCl was again passed through in the cold for 3 more hr. This

[9] Y. Knobler and M. Frankel, *J. Chem. Soc.* 1629 (1958).

procedure was repeated again and the MeOH was evaporated. The oily residue solidified upon standing for 2 days in a deep freezer. A little propanol was added and DL-canaline methyl ester dihydrochloride was collected, washed with a little propanol and dried over P_2O_5 (2·25 g, 66·6%), m.p. 165° dec. (Found: N, 12·8. Calc. for $C_5H_{12}N_2O_3Cl_2$: N, 12·8%.)

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