The Rearrangement of N-Acyl Derivatives of Aminoxyacetic Acid

G. ZVILICHOVSKY AND C. GILON

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

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In this Note we present a novel rearrangement of N-acyl derivatives of aminoxyacetic acid to give ester derivatives of glycolic acid. Treatment of these N-acyl derivatives with $NaNO_2$ was found to cause the migration of the acyl group from nitrogen to oxygen with the elimination of the NH group. N-Acyl derivatives of aminoxyacetic acid were described earlier.[1,2] By using the appropriate derivatives, the present rearrangement reaction could lead to the formation of simple O-acyl derivatives as well as carbonates and depsipeptides derived from glycolic acid. Thus treatment of benzamidoxyacetic acid[1] with $NaNO_2$ gave O-benzoylglycolic acid (**1**)[3] in 90% yield. Upon treatment of

$$PhCONHOCH_2COOH \longrightarrow \underset{\mathbf{1}}{PhCOOCH_2COOH}$$

carbobenzoxyaminoxyacetic acid[2] with $NaNO_2$, O-carbobenzoxyglycolic acid (**2**) was obtained, as a result of

$$PhCH_2OCONHOCH_2COOH \longrightarrow \underset{\mathbf{2}}{PhCH_2OCOOCH_2COOH}$$

the migration of a carbobenzoxy group. Similarly carbobenzoxy-DL-alanylaminoxyacetic acid[2] gave O-carbobenzoxy-DL-alanylglycolic acid (**3**) in 70% yield. The mild conditions of the reaction enabled the rearrangement of the amidoxy group to occur without affecting the unprotected amino group of free amidoxy peptides.[2] Thus treatment of DL-alanylaminoxyacetic acid[2] followed by carbobenzoxylation also gave **3**.

$$ZNHCH(CH_3)CONHOCH_2COOH \longrightarrow \underset{\mathbf{3}}{ZNHCH(CH_3)COOCH_2COOH}$$

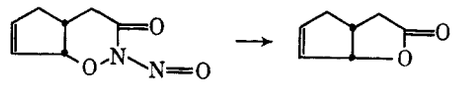
$$H_2NCH(CH_3)CONHOCH_2COOH \longrightarrow [H_2NCH(CH_3)COOCH_2COOH]$$

Glycylaminoxyacetic acid[4] gave under the same procedure the depsipeptide derivative O-carbobenzoxyglycylglycolic acid.[5]

This rearrangement, which takes place at room temperature and in aqueous solution, probably proceeds *via* the formation of the N-nitroso derivative **4**.

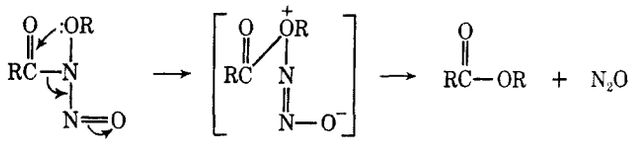
$$RCONHOCH_2 + NaNO_2 \longrightarrow \underset{\mathbf{4}}{RCON(NO)OCH_2COO^-Na^+}$$

Rearrangement of a cyclic N-nitroso derivative (**5**) to give the lactone **6** has been described.[6] The spon-



5 **6**

taneous decomposition of N-nitroso-N-acyl-O-alkylhydroxylamines was shown to yield nitrogen, carbon dioxide, nitrous oxide, and products resulting from either a homolytic or a heterolytic cleavage of the molecule.[7] A thermal rearrangement of N-acetyl-N-nitroso-O-butylhydroxylamine was reported[8,9] to yield esters and peresters, together with molecular nitrogen. However, in our case the gas which evolved after acidification was not molecular nitrogen but rather a nitrogen oxide, as it was absorbed completely in sodium hydroxide. The course of the reaction should be further investigated in order to propose a reaction mechanism; one possibility is formation of a hyponitrite derivative **7** which gives an ester on loss of N_2O. The intermediate **7** might



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explain the formation of O-acyl-O′-alkyl hyponitrite, which was suggested[7] as an intermediate in the decomposition of N-nitroso-N-acyl-O-alkylhydroxylamines, by migration of the alkyl group from the positively to the negatively charged oxygen.

Experimental Section

Melting points are uncorrected; elemental analyses for known compounds were in agreement with the calculated values.

Rearrangement of Benzamidoxyacetic Acid.—Benzamidoxyacetic acid[1] (mp 145–146°)[10] (0.195 g, 0.001 mol) was dissolved in water (3 ml) by the addition of solid $NaNO_2$ (0.069 g, 0.001 mol) portionwise during 5 min. The solution was kept at room temperature for 3 hr and then cooled and acidified with hydrochloric acid. O-Benzoylglycolic acid (**1**) precipitated (0.165 g, 90% yield), mp 112° (lit.[3] 112°).

Rearrangement of Carbobenzoxyaminoxyacetic Acid.—Carbobenzoxyaminoxyacetic acid[2] (mp 79°) (0.225 g, 0.001 mol) in water (6 ml) was dissolved by the addition of solid $NaNO_2$ (0.105 g, 0.0015 mol). The solution was kept at room temperature for 30 min, filtered, cooled, and acidified with hydrochloric acid to pH 1. After the filtrate was kept for 24 hr at 0°, an oil precipitated which crystallized to give O-carbobenzoxyglycolic acid (**2**) (0.94 g, 45% yield), mp 79°. After recrystallization from ethanol–water the melting point did not change: ν^{Nujol} (cm^{-1}) 1770 (C=O), 1710 (C=O).

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.13; H, 4.73.

Rearrangement of Carbobenzoxy-DL-alanylaminoxyacetic acid.[2] This compound (mp 104°) (0.296 g, 0.001 mol) was dissolved in water (3 ml) by addition of $NaNO_2$ (0.069 g, 0.001 mol) and stirred for 30 min at room temperature. The solution was cooled and acidified to pH 1 by HCl. The solution was extracted with ethyl acetate, the organic layer was dried ($MgSO_4$) and concentrated

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(4) Y. Knobler, S. Bittner, and M. Frankel, *J. Chem. Soc.*, 3941 (1964).
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(10) It is essential to note the melting points of these compounds because of the variation of the melting points recorded in the literature, as a result of polymorphism (see ref 1).

under vacuum to a small volume, and then petroleum ether (bp 40–60°) was added. O-Carbobenzoxyalanylglycolic acid (**3**) precipitated (0.2 g, 70% yield), mp 85°.

Anal. Calcd for $C_{13}H_{15}O_6N$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.66; H, 5.68; N, 5.18.

Rearrangement of DL-Alanylaminoxyacetic Acid.—DL-Alanylaminoxyacetic acid[2] (mp 197°) (0.162 g, 0.001 mol) was dissolved in water (1 ml) and cooled to 10° $NaNO_2$ (0.069 g, 0.001 mol) was added portionwise during 10 min. The solution was stirred at room temperature for 30 min until the effervescence of gas stopped, was acidified to pH 3, and was cooled overnight. A solution of 5% $NaHCO_3$ (5 ml) was added together with carbobenzoxychloride (0.38 g, 0.0015 mol) and stirred overnight at 10°. After washing with ether the solution was acidified to congo red. The precipitated O-carbobenzoxy-DL-alanylglycolic acid (**3**) was collected and recrystallized from ethyl acetate–petroleum ether (0.1 g, 35%), mp 86°. A mixture melting point and ir spectrum showed this product to be identical with that which is described in the preceding preparation.

Rearrangement of Glycylaminoxyacetic Acid.—Glycylaminoxyacetic acid[4] (mp 150°) (0.148 g, 0.001 mol) was treated as the alanyl derivative above, yielding O-carbobenzoxyglycylglycolic acid (0.07 g, 30% yield), mp 110° (lit. 105–106°).[5]

Registry No.—**2**, 21347-35-3; **3**, 21343-30-6.

Rearrangement of a 4,4-Disubstituted Homophthalimide to the Benzo[*b*]phenanthridine System

WALTER J. GENSLER, MARY VINOVSKIS, AND NANCY WANG

Department of Chemistry, Boston University, Boston, Massachusetts 02215

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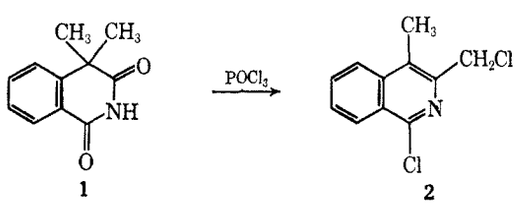
Heating 4,4-dimethylhomophthalimide (**1**) with phosphorus oxychloride produces dichloride $C_{11}H_9Cl_2N$,[1] which has been shown to be 1-chloro-3-chloromethyl-4-methylisoquinoline (**2**).[2–4] We have now succeeded in



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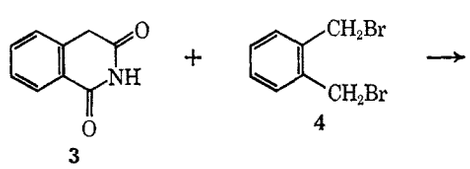
utilizing a skeletal rearrangement analogous to the **1** to **2** process for the generation of the benzo[*b*]phenanthridine system. Homophthalimide (**3**),[5] on alkylation with 1,2-bis(bromomethyl)benzene (**4**), gives spiro compound **5**.[6] When the spiro compound is heated at



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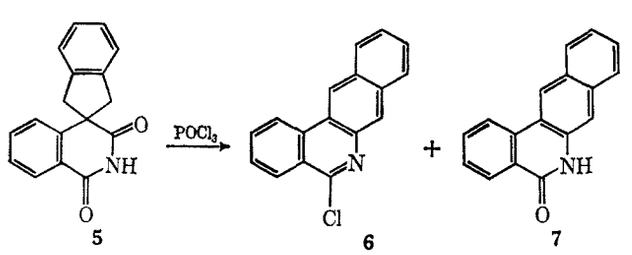

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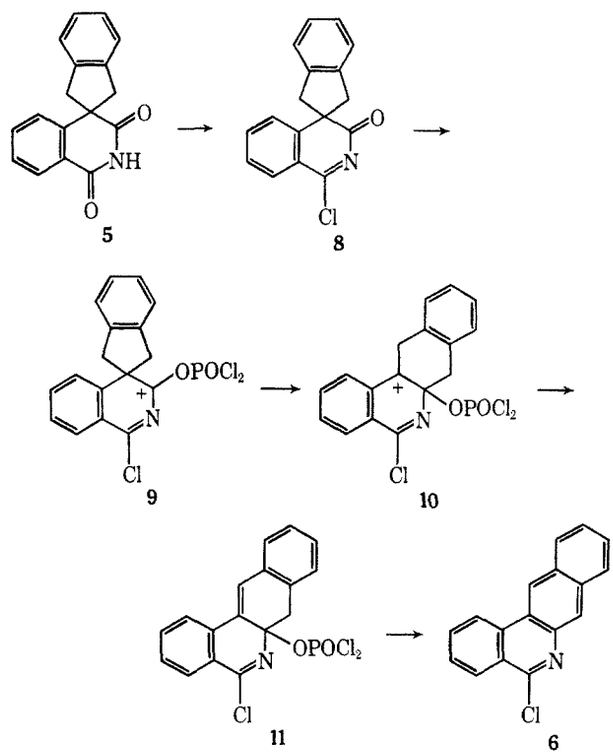
130° with phosphorus oxychloride, products **6** and **7** as well as unchanged starting material **5** were isolated. Direct comparison of the 6H-benzo[*b*]phenanthridin-5-one (**7**) with the same substance prepared in a different way established its structure as shown.[7]

We suggest a reaction sequence in which the spiro compound **5** is first converted with phosphorus oxychloride into chloro compound **8**. Further reaction with phosphorus oxychloride gives carbonium ion **9**, skeletal rearrangement of which forms **10**. Loss of a



proton would give the stilbene-like intermediate **11**, and subsequent loss of the oxyphosphoryl grouping and a second proton would lead to the fully aromatic product **6**. Since oxo compound **7** can be derived readily from chloro compound **6** by acid-catalyzed hydrolysis, possibly, though not necessarily, the oxo compound originates from **6** during the processing of the reaction mixture.[4]

We intend to exploit this kind of rearrangement for the preparation of other polycyclic nitrogen compounds and, in this connection, have prepared spiro compound **13** by alkylating homophthalimide with 2,3-bis(dibromomethyl)naphthalene (**12**). Also, during the course of this work we have developed conditions for the original rearrangement of 4,4-dimethylhomo-

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