Rearrangement of *N*-Benzyl-2-cyano-2-(hydroxyimino)acetamide

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Abstract □ The reduction of *N*-benzyl-2-cyano-2-(hydroxyimino)-acetamide resulted in the formation of *N*-benzyl-1,2-ethanediamine and *N*-benzyl-*N'*-methyl-1,2-ethanediamine in approximately an equimolar ratio. The formation of the two unexpected products is explained by the migration of a cyano group in a Beckmann-type rearrangement.

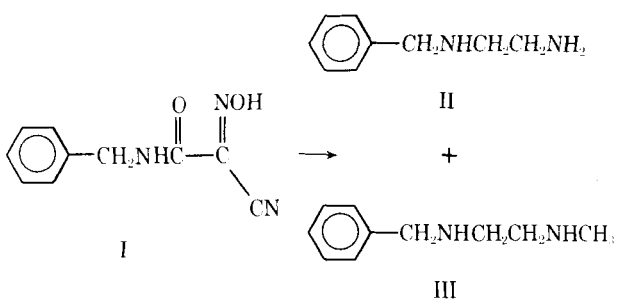
Keyphrases □ *N*-Benzyl -2- cyano-2-(hydroxyimino)acetamide—reduced, two diamines formed by Beckmann-type rearrangement □ Beckmann-type rearrangement—in reduction of *N*-benzyl-2-cyano-2-(hydroxyimino)acetamide, two diamines formed □ Diamines—formed by reduction of *N*-benzyl-2-cyano-2-(hydroxyimino)acetamide by Beckmann-type rearrangement

A Beckmann-type rearrangement of a compound (benzoyl cyanide oxime) containing a cyano group attached directly to the carbon atom of an oxime group was reported by Zimmermann (1). Hydrolysis of the product led to formation of *N*-phenyloxamide, indicating that the cyano group did not migrate. The authors were unable to find an example of a rearrangement in the literature in which a cyano group was the migrating group.

In a reduction of *N*-benzyl-2-cyano-2-(hydroxyimino)-acetamide (I) with sodium bis(2-methoxyethoxy)aluminum hydride[1], an equimolar ratio of *N*-benzyl-1,2-ethanediamine (II) and *N*-benzyl-*N'*-methyl-1,2-ethanediamine (III) was obtained (Scheme I) in less than 10% yield. The formation of the two unexpected products may be explained by the migration of a cyano group in a Beckmann-type arrangement.

EXPERIMENTAL[2]

Compound I—A mixture of *N*-benzyl-2-cyanoacetamide (2) (34.8 g, 0.20 mole) and sodium nitrite (20.7 g, 0.30 mole) in toluene (500 ml) was heated to reflux. Concentrated hydrochloric acid (26 ml, 0.26 mole) was added dropwise during 2 hr, and the resulting mixture was heated at reflux for 4 hr. The lower layer was separated and poured into a mixture of ice and water.



Scheme I

After filtering, the residue was washed with cold water and recrystallized from water, yielding 23.4 g (57.6%), mp 159.5–161°; IR (KBr): 3350 (oxime OH), 2230 (cyano), and 1645 (amide, C=O) cm^{-1}; NMR (acetone-d_6): δ 4.42 (m, 2H, CH_2), 7.27 (s, 5H, C_6H_5), 8.2 (broad, 1H, deuterium exchangeable), and 13.2 (broad, 1H, deuterium exchangeable) ppm.

Anal.—Calc. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.11; H, 4.46; N, 20.73.

Reduction of I to II and III Dihydrochlorides—A solution of I (20.3 g, 0.10 mole) in dry tetrahydrofuran (150 ml) was added dropwise to a solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (168 ml, 0.58 mole). The mixture was heated at reflux for 5 hr. Excess hydride was decomposed by successively adding absolute ethanol (25 ml), benzene (175 ml), and 10% sodium hydroxide solution (164 ml). The benzene layer was separated and washed with water (3 × 100 ml). The benzene solution was extracted with dilute hydrochloric acid (3 × 100 ml), and the combined acid extracts were neutralized with saturated sodium carbonate solution.

The basic solution was then extracted with chloroform (9 × 100 ml), and the dried chloroform extract was concentrated *in vacuo*. The oily residue (18 g) was distilled, 1.6 g, bp 32–67°/0.025 mm. The distillate was converted to a hydrochloride salt with concentrated hydrochloric acid in acetone. Fractional recrystallization from methanol–activated charcoal gave III, 0.92 g (3.9%), mp 273–274°. Mixed melting-point determination with an authentic sample (3, 4) showed no depression.

Anal.—Calc. for $C_{10}H_{16}N_2 \cdot 2HCl$: C, 50.64; H, 7.65; N, 11.81. Found: C, 50.69; H, 7.44; N, 11.91.

The filtrates were combined and concentrated *in vacuo*. The residue was fractionally recrystallized from absolute ethanol to obtain II, 0.84 g (3.8%), mp 243–248°. Mixed melting-point determination with an authentic sample showed no depression.

Anal.—Calc. for $C_9H_{14}N_2 \cdot 2HCl$: C, 48.44; H, 7.23; N, 12.55. Found: C, 48.81; H, 7.39; N, 12.50.

Authentic Sample of III Dihydrochloride—Following a modification of the method of Crochet and Blanton (5), a mixture of II (7.5 g, 0.05 mole) and triethyl orthoformate (40 ml) was heated at reflux for 5 hr. After concentrating *in vacuo*, absolute ethanol (40 ml) was added and cooled to ice bath temperature. Sodium borohydride (3.7 g, 0.10 mole) was added with stirring, and the mixture was heated at reflux temperature for 16 hr. The mixture was concentrated *in vacuo*, the residue was dissolved in water, and the mixture was extracted with ether (3 × 50 ml). The dried ether extract (anhydrous magnesium sulfate) was concentrated *in vacuo*, and the residue was distilled, bp 89–98°/0.25 mm [lit. (3) bp 79–80.5°/0.02 mm]. The hydrochloride salt, prepared from acetone and concentrated hydrochloric acid, was recrystallized from ethanol (95%) and activated charcoal, 1.6 g (13.6%), mp 274–277°.

Anal.—Calc. for $C_{10}H_{16}N_2 \cdot 2HCl$: C, 50.64; H, 7.65; N, 11.81. Found: C, 50.21; H, 7.47; N, 11.99.

***N*-Benzyl-*N'*-cyanooxamide (IV)**—Using a modification of the method of Kretov and Momsenko (6), a mixture of ethyl oxalyl chloride (9.45 g, 0.069 mole) in benzene (100 ml) was cooled to 5° and triethylamine (13.96 g, 0.138 mole) was added dropwise with stirring. Cyanamide (2.91 g, 0.069 mole) was added in small portions, and the mixture was stirred at ambient temperatures for 20 hr. Petroleum ether (200 ml, bp 30–60°) was added, and the lower layer was diluted with dioxane (100 ml) after decanting. The mixture was filtered and the residue was washed with dioxane (50 ml).

The combined filtrate and washing were added to petroleum ether (200

[1] Red-Al, a 70% solution in benzene, Aldrich Chemical Co., Milwaukee, Wis.

[2] Elemental analyses were performed by Atlantic Microlab, Atlanta, GA 30366. IR spectra were obtained using a Beckman Acculab 6 spectrophotometer. NMR spectra were obtained using a Varian T60A spectrometer, and values are in parts per million (δ) from tetramethylsilane as the internal standard. Melting points were taken in open capillary tubes and are uncorrected. GLC analyses were performed using a Carle 9500 gas chromatograph with a 3% SE-30 column at 150°.

ml), and the mixture was decanted. The lower layer was cooled to −12°, and benzylamine (12.2 g, 0.11 mole) was then added dropwise with stirring. The mixture was stirred at ambient temperature for 16 hr and filtered. The residue was dissolved in methanol and treated with activated charcoal, and the product was precipitated with isopropyl ether, 2.8 g (12.5% crude yield), mp 151–153°; IR (KBr): 2190 (cyano) and 1660 (amide) cm^{-1}.

Several attempts to isolate the product led to decomposition, as evidenced by the disappearance of IR absorption of the cyano group. Therefore, the product was used in the next step without further purification.

Reduction of IV—Crude IV (1.3 g, 0.005 mole) was suspended in anhydrous tetrahydrofuran (200 ml) and added dropwise to a solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (10 ml, 0.034 mole). The mixture was heated at reflux temperature for 3.5 hr. After stirring at ambient temperature for 13 hr, excess hydride was decomposed by successively adding ethanol (95%, 4 ml) and water (6 ml). The supernate was separated and concentrated *in vacuo*.

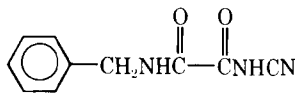
The oily residue was dissolved in chloroform (20 ml) and washed with water (3 × 10 ml). The dried chloroform solution (anhydrous magnesium sulfate) was evaporated *in vacuo*, and the residue was converted to a hydrochloride salt with acetone and concentrated hydrochloric acid. The product was recrystallized from absolute ethanol, 0.1 g (0.6% overall), mp 272–276°. Mixed melting-point determination with an authentic sample of III dihydrochloride showed no depression.

RESULTS AND DISCUSSION

In several repeat experiments, different workup procedures did not improve the yields of II and III. The components of the black tar, which make up the bulk of the crude yield, were not resolved.

Products II and III were identified as hydrochloride salts by microanalyses and mixed melting-point determinations with authentic samples. GLC analyses of the free bases provided confirming evidence.

Migration of a cyano group in a Beckmann-type rearrangement of I would be expected to yield IV as an intermediate. However, only starting



IV

material was recovered (90%) when I was treated under conditions known to cause a Beckmann rearrangement (7). When IV was treated under the same reducing conditions as I, only one product, III, was isolated. GLC analysis of the filtrate from the recrystallization of this reduction product failed to detect the presence of II.

Additional studies will be required to elucidate the rearrangement mechanism. However, sufficient evidence is presented to propose the migration of a cyano group.

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Interaction of Tricyclic Antipsychotic and Antidepressant Drugs with 1-Anilino-8-naphthalenesulfonic Acid

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Abstract □ The binding of 1-anilino-8-naphthalenesulfonic acid to selected tricyclic antipsychotic and antidepressant drugs was studied by fluorescence spectroscopy. The acid exhibited an increase in fluorescence intensity accompanied by a hypsochromic shift of the emission λ_{max} in the presence of these drugs. These fluorescence characteristics, in addition to those of acid–drug complexes after addition of potassium chloride or urea, suggested that binding was hydrophobic. The spectra also provided evidence regarding the importance of certain structural features of drugs in determining the nature of binding.

Keyphrases □ 1-Anilino-8-naphthalenesulfonic acid—binding to various antipsychotic and antidepressant drugs, fluorometric study □ Antipsychotics, various—binding to 1-anilino-8-naphthalenesulfonic acid, fluorometric study □ Antidepressants, various—binding to 1-anilino-8-naphthalenesulfonic acid, fluorometric study □ Binding—1-anilino-8-naphthalenesulfonic acid to various antipsychotics and antidepressants, fluorometric study □ Fluorometry—study of binding of 1-anilino-8-naphthalenesulfonic acid to various antipsychotics and antidepressants

Studies of molecular interactions in aqueous solution are important for elucidating the nature and mechanism of drug–protein binding in the body. Information pertaining to such interactions between small molecules can permit possible prediction of this drug–biomolecule binding. One technique commonly used is to measure spectral changes of drugs on binding to other molecules. Several reports (1, 2) concerned the use of absorption spectra for drug binding studies. Fluorescence spectroscopy (3) also was used to study molecular interactions.

Fluorescent probes, recently applied in drug–protein binding studies, are minimally fluorescent in their free form in aqueous solution. When these compounds are bound to other molecules, their spectral properties such as intensity and maximal emission wavelength change, reflecting their molecular environment. These spectral