[CONTRIBUTIONS FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF SYDNEY, AND THE COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

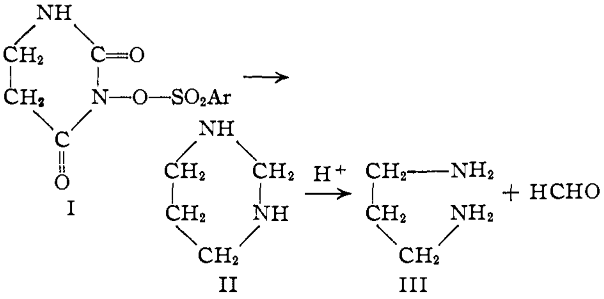
Reductive Lossen Rearrangement Induced by Lithium Aluminum Hydride

BY LUDWIG BAUER

RECEIVED NOVEMBER 23, 1955

Reduction of 3-benzenesulfonoxy-5,6-dihydrouracil (I) with lithium aluminum hydride afforded N,N′-dimethylethylenediamine. A mechanism for this novel rearrangement is advanced.

To prove the heterocyclic six-membered structure of 3-benzenesulfonoxy-5,6-dihydrouracil (I), previously synthesized,[1] reduction to the basic ring system was considered, and lithium aluminum hydride was chosen as the reagent. It was anticipated that the product of the reduction would either be hexahydropyrimidine (II) or its acid hydrolysis product, 1,3-propanediamine (III).



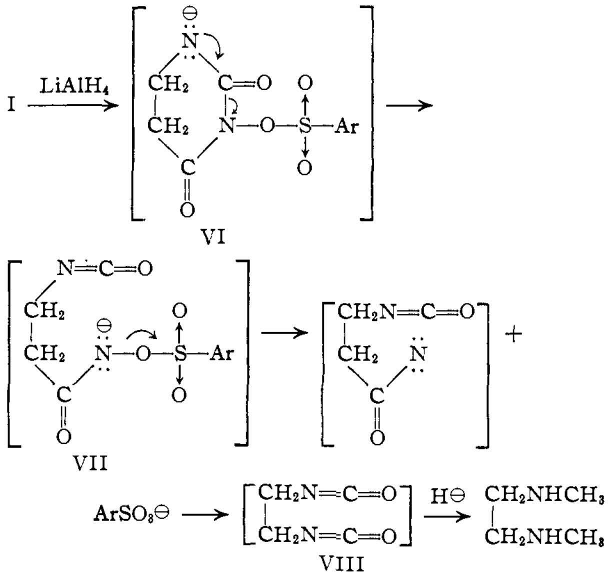
Each of these two bases has been characterized previously as solid crystalline benzamides. The dibenzoyl derivative of hexahydropyrimidine is reported to melt at 95°[2] and that of the 1,3-propanediamine at 147–148°[3] and 151°.[4]

The reduction of I with lithium aluminum hydride was carried out in refluxing tetrahydrofuran. The reaction mixture was decomposed with dilute hydrochloric acid, then made alkaline and an amine was steam distilled from the alkaline medium. Benzoylation of this base afforded a crystalline derivative, m.p. 177–178°. From its analysis, the parent base had the composition $C_4H_{12}N_2$, thus eliminating structures II and III from consideration.

On the assumption that in the original heterocyclic system, the atoms in the ring were linked in the sequence –N–C–C–C–N–C, the product expected was $NH_2CH_2CH_2CH_2NHCH_3$ (IV). This amine has been described in the literature,[5] although its benzoyl derivative has not been mentioned. Reduction of 3-methylaminopropiononitrile, $CH_3NHCH_2CH_2CN$, with lithium aluminum hydride readily yielded a sample of IV. A solid benzoyl derivative was not obtained. However, a crystalline benzenesulfonyl derivative, m.p. 95°, was easily prepared.

It was then decided to characterize the base from the reduction of I additionally as the benzenesulfonyl derivative. It melted at 129–131°. The literature revealed that the benzenesulfonyl derivative of the isomeric N,N′-dimethylethylenediamine, $CH_3NHCH_2CH_2NHCH_3$, (V), melts at 131°,[6] and indeed the melting point of the benzenesulfonyl derivative of the base obtained on reduction was not depressed on admixture with an authentic specimen. Furthermore, the benzoyl derivative of some authentic N,N′-dimethylethylenediamine did not depress the melting point of the similar derivative from the reduction of I.

In order to rationalize the formation of V a novel Lossen rearrangement of I is postulated. Attack by lithium aluminum hydride (acting as a base) on nitrogen could give the anion VI. Under the influence of the very strong electronegative benzenesulfonic ester grouping the ring would easily open to give VII, which is the anion required for a Lossen rearrangement. It has previously been shown that the arenesulfonic esters of non-cyclic hydroxamic acids rearrange spontaneously.[1,7] Thus VII would rearrange to VIII, which is indeed a plausible precursor for the reduction to N,N′-dimethylethylenediamine. Furthermore, the reduction of isocyanates to N-methylamines has been reported previously.[8,9]



Treatment of I with one equivalent of sodium hydroxide solution effects rearrangement to a water-soluble intermediate, postulated as N,N′-ethyleneurea. Further hydrolysis, either by means of

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(2) A. W. Titherley and G. E. K. Branch, *J. Chem. Soc.*, **103**, 330 (1913).

(3) H. Strache, *Ber.*, **21**, 2365 (1888).

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(7) M. A. Stolberg, R. C. Tweit, G. M. Steinberg and T. Wagner-Jauregg, THIS JOURNAL, **77**, 765 (1955).

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(9) W. Ried and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

hydrochloric acid or sodium hydroxide, yields ethylenediamine.[10] The mechanism of the rearrangement of I by sodium hydroxide could parallel that induced by lithium aluminum hydride. Attack by hydroxide ion on I could produce the anion VI which would rearrange to VIII. Reaction of VIII with water would then give N,N'-ethyleneurea.

The above sequence of reactions provide a facile three-step degradation of ethyl succinate to either N,N'-dimethylethylenediamine or ethylenediamine.

Experimental

3-Benzenesulfonoxy-5,6-dihydrouracil.—The improved preparation is described by a typical experiment: To a stirred solution of sodium succinohydroxamate (11.3 g.) in pyridine (65 ml.) at 25° was added dropwise benzenesulfonyl chloride (25 g.). The temperature of the mixture was kept between 25 and 30°. After the addition of the chloride, the solution was stirred for 45 minutes. The pyridine solution was poured into 300 ml. of water, then neutralized by 75 ml. of glacial acetic acid. The mixture was refrigerated overnight and the crystals filtered off next day. The yield of dry crude product was 11.3 g. (88% based on the salt), m.p. 170–173°. Further crystallization from 2-propanol afforded a pure sample, m.p. 175–176°. The m.p. reported previously was 158–160°. A new sample prepared by the older method now melted at 175–176°.

Reductive Lossen Rearrangement.—(a) To a suspension of lithium aluminum hydride (2.5 g.) in ice-cold tetrahydrofuran (50 ml.) was added 3-benzenesulfonoxy-5,6-dihydrouracil (2.5 g.) and the mixture refluxed for 5 hours. The mixture was poured onto ice and dilute hydrochloric acid and extracted with ether. The acid solution was warmed to expel dissolved ether, cooled, was made alkaline with solid sodium hydroxide pellets and distilled in part. The distillate (200 ml.) was made alkaline with solid sodium hydroxide pellets and treated with benzenesulfonyl chloride (7 ml.). After this mixture had stood at room temperature for several days, the derivative crystallized. The benzenesulfonyl derivative recrystallized from alcohol in fine needles, m.p. 123–124°. The yield was then 0.95 g. or 29% based on the starting material. Two further crystallizations from alcohol, and one from acetic acid raised the m.p. to 129–131°. Further recrystallization from ethyl acetate did not raise the m.p.

Anal. Calcd. for $C_{16}H_{20}N_2O_4S_2$: C, 52.15; H, 5.47; N, 7.61. Found: C, 51.90; H, 5.21; N, 7.62.

The mixed m.p. with an authentic specimen[11] of similar m.p. was undepressed.

(b) Similarly, 3-benzenesulfonoxy-5,6-dihydrouracil (1.1 g.) was reduced by lithium aluminum hydride (2.7 g.) in tetrahydrofuran (50 ml.), and worked up as above. The alkaline distillate (200 ml.) was again made alkaline and treated with benzoyl chloride to afford the crystalline derivative (0.5 g., 41%), m.p. 175°. Recrystallization from benzene raised the m.p. to 177–178°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.46. Found: C, 72.86; H, 6.85; N, 9.37.

The melting point of this benzoyl derivative was undepressed on admixture with an authentic specimen.[12]

N-Methyl-1,3-propanediamine.—A solution of 3-methylaminopropiononitrile (4.2 g.) in ether (10 ml.) was added dropwise to lithium aluminum hydride (1.9 g.) in ether (100 ml.). The mixture was refluxed 0.5 hour, and decomposed by 20% NaOH (1.5 ml.) and then water (7 ml.). The ether solution was decanted from the granular inorganic precipitate and distilled. The amine distilled at 140–143°, $n^{13}D$ 1.4453. Tarbell[5] lists the boiling point of this amine as 138–141° and $n^{20}D$ 1.4479.

Benzoylation of the amine in pyridine afforded a gum which could not be induced to crystallize. Treatment of the amine (0.4 g.) with benzenesulfonyl chloride (0.3 ml.) in 10% potassium hydroxide solution caused the separation of an oil. The alkaline solution was decanted from the alkali-insoluble material and acidified. The gum which precipitated crystallized on trituration with alcohol and was recrystallized from the same solvent. It formed colorless needles, m.p. 95°.

Anal. Calcd. for $C_{16}H_{20}N_2O_4S_2$: C, 52.15; H, 5.47; N, 7.61. Found: C, 52.07; H, 5.93; N, 7.34.

Acknowledgment.—Professor A. J. Birch is kindly thanked for providing facilities in his laboratory at the University of Sydney.

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[10] C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955).

[11] This sample, kindly donated by Dr. F. Lions, was prepared by the methylation of N,N'-ethylenedibenzenesulfonamide.

[12] This specimen was synthesized from N,N'-dimethyl-N,N'-ethylenedibenzeneamide by hydrolysis with hydrobromic acid in phenol, and benzoylation of the resulting amine (Found: N, 9.42).

CHICAGO 12, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICS AND CHEMISTRY, GAKUSHUIN UNIVERSITY]

On the Thermal Dissociation of Organic Compounds. X. The Effects of the Solvents (Amines and Fatty Acids) on the Thermal Dissociation of Urethans

BY TERUAKI MUKAIYAMA AND YOICHI HOSHINO

RECEIVED SEPTEMBER 7, 1955

The rate constants of the thermal dissociation of urethans in amine and fatty acid solvents have been measured. The dissociation of urethan proceeds through the double transfer of a proton under the influence of both a basic and an acidic medium. The mechanisms of dissociation of urea and urethan are similar to those of carbonyl addition compounds, *i.e.*, the carbonyl-forming elimination reaction. It can be shown that these amphoteric compounds dissociate in the presence of either basic or acidic catalysts.

Introduction

Previous papers in this series[1-9] have shown that, on heating, ureas and urethans dissociate as

$$\mathrm{RHNCONHR} \rightleftharpoons \mathrm{RNCO} + \mathrm{H_2NR} \qquad (1)$$

$$\mathrm{RHNCOOR} \rightleftharpoons \mathrm{RNCO} + \mathrm{HOR} \qquad (2)$$

In the dissociation of urethan, for example, the nitrogen atom of urethan donates a proton to form an isocyanate and the oxygen atom accepts a proton to form an alcohol. Therefore, it can be assumed

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[1] T. Hoshino, T. Mukaiyama and H. Hoshino, THIS JOURNAL, **74**, 3097 (1952).

[2] T. Hoshino, T. Mukaiyama and H. Hoshino, *Bull. Chem. Soc. Japan*, **25**, 392 (1952).

[3] T. Hoshino, T. Mukaiyama and H. Hoshino, *ibid.*, **25**, 396 (1952).

[4] T. Mukaiyama, S. Motogi and Y. Hamada, *ibid.*, **26**, 49 (1953).

[5] T. Mukaiyama and T. Matsunaga, THIS JOURNAL, **75**, 6209 (1953).

[6] T. Mukaiyama, S. Ozaki and T. Hoshino, *Bull. Chem. Soc. Japan*, **27**, 578 (1954).

[7] T. Mukaiyama, *ibid.*, **28**, 253 (1955).

[8] T. Mukaiyama, S. Ozaki and Y. Kobayashi, *ibid.*, **29**, 57 (1956).

[9] T. Mukaiyama and Y. Fujita, *ibid.*, **29**, 54 (1956).