fined essentially by a method of preparation[7] rather than by a set of invariant chemical and physical properties which might be assigned to a single compound. Both the method of preparation and the close association of the Rh, A and B factors with elinin indicate that elinin is derived from the red cell wall. Evidently, then, we have degraded a tissue into relatively small particles by a series of chemical steps in such a way that the final product still has certain desired serological properties of the original tissue. The second consideration is the great heterogeneity in the particle size of elinin. This is really a consequence of the first. That elinin is very polydisperse even in solution is evident from the ultracentrifuge results and it is with these limitations in mind that we make some estimate of the size and shape of elinin particles.

We should remark that no physico-chemical differences have been observed among elinin samples prepared from the various blood types.

As noted before, the sedimentation studies, the light scattering studies and the electron micrographs in Fig. 7[11a] were all made on essentially identical preparations. The average particle weight from light scattering is in the region of forty million and the length about 3000 Å. The sedimentation data are in fair agreement with this picture. All of the data are certainly in qualitative accord in indicating the presence of very large asymmetric particles, all of which are, however, too small to be resolved in the light microscope.

Summary

Some of the physical characteristics of elinin, a lipoprotein preparation from red blood cells, have been studied, and an estimate made of its particle size and shape. It appears to consist of large asymmetric particles. The preparation of elinin is described elsewhere.[7] The chief practical interest of elinin resides in its content of Rh factor and A and B substances.

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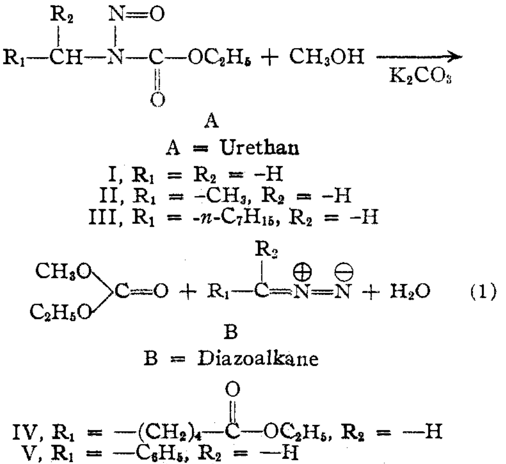
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Base-Catalyzed Decomposition of N-Nitroso-N-cyclohexylurethan[1,2]

BY FREDERICK W. BOLLINGER, F. N. HAYES AND SAMUEL SIEGEL

Meerwein's[3] process for the preparation of nascent diazomethane (IB) consists of the decomposition of N-nitroso-N-methylurethan (IA) in methanol containing a catalytic amount of finely-powdered potassium carbonate. The reaction is believed to take the course



$$\mathrm{R_1{-}CH(R_2){-}N(N{=}O){-}C({=}O){-}OC_2H_5 + CH_3OH \xrightarrow[K_2CO_3]{}}$$

A

A = Urethan

I, $R_1 = R_2 = -H$
II, $R_1 = -CH_3$, $R_2 = -H$
III, $R_1 = -n\text{-}C_7H_{15}$, $R_2 = -H$

$$\mathrm{(CH_3O)(C_2H_5O)C{=}O + R_1{-}C(R_2){=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H_2O} \qquad (1)$$

B

B = Diazoalkane

IV, $R_1 = -(CH_2)_4-C(=O)-OC_2H_5$, $R_2 = -H$
V, $R_1 = -C_6H_5$, $R_2 = -H$
VI, $R_1R_2 = -(CH_2)_5-$

If it is desired that diazomethane react with an aldehyde or ketone, neither carbonyl compound interferes with the above preparation and may, therefore, be present in the methanol solution.

Other bases such as sodium carbonate or magnesium ethoxide may be substituted for potassium carbonate.[3,4] Because these bases exhibit an exceedingly small solubility in methanol, a solid phase is present throughout the reaction.

The preparation and use of diazoalkanes other than diazomethane by the Meerwein process, which have been reported in the literature, include diazoethane[5] (IIB), 1-diazoöctane[5] (IIIB), 5-carbethoxy-1-diazopentane[5] (IVB) and phenyldiazomethane[6] (VB). No example in which an N-nitroso-N-alkylurethan (R_1 and R_2 = alkyl groups) was the reactant has been reported. Yields of diazoalkanes based on reaction products, range from practically quantitative downward to 10%. By-products of Meerwein's process for the preparation of diazoalkanes have not been reported.

This investigation reports the products of the base-catalyzed decomposition of N-nitroso-N-cyclohexylurethan (VIA). N-Cyclohexylurethan[7] prepared from cyclohexylamine and ethyl chloroformate, was treated with excess nitrous acid to

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[1] This paper was presented in part before the Organic Division of the American Chemical Society, Philadelphia Meeting, April, 1950.

[2] Abstracted in part from a dissertation to be submitted by Frederick W. Bollinger to the Graduate School of Illinois Institute of Technology in partial fulfillment of the requirements for the degree Doctor of Philosophy.

[3] Meerwein, German Patent 579,309; *Chem. Zentr.*, **104**, II, 1758 (1933).

[4] Kohler, Tishler, Potter and Thompson, THIS JOURNAL, **61**, 1057 (1939).

[5] Adamson and Kenner, *J. Chem. Soc.*, 181 (1939).

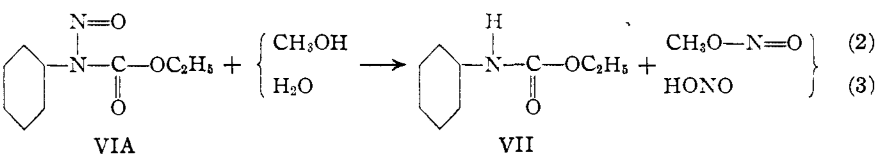
[6] Gutsche, THIS JOURNAL, **71**, 3513 (1949).

[7] Skita and Rolfes, *Ber.*, **53**, 1249 (1920).

yield N-nitroso-N-cyclohexylurethan (VIA). This product was allowed to decompose in methanol which was in contact with a catalytic amount of potassium carbonate.

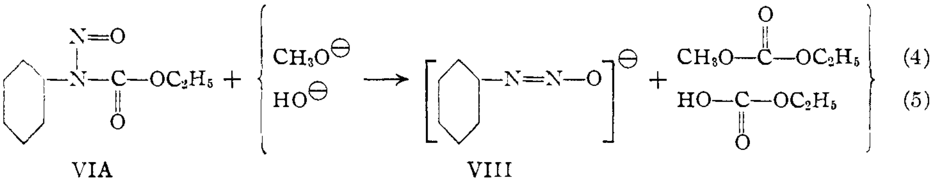
Nitrogen, carbon dioxide and methyl nitrite were evolved in the course of the reaction. Methanol, ethanol, methyl cyclohexyl ether, ethyl cyclohexyl carbonate and N-cyclohexylurethan were obtained by a careful fractional distillation. Also isolated were azeotropic mixtures of methanol–cyclohexene, water–methyl ethyl carbonate, and a mixture of cyclohexanol and ethyl cyclohexyl ether, which was separated by fractional crystallization.

The formation of these compounds from N-nitroso-N-cyclohexylurethan can be rationalized in terms of two divergent reaction paths: (a) the solvolysis by methanol or water (formed in the reaction) to yield methyl nitrite or nitrous acid as illustrated by equations (2) and (3) (the latter reacts rapidly with methanol to form methyl nitrite and water)[8]; and (b) a displacement of the cyclohexyldiazotate ion (VIII) by methoxide or hydroxide ion with the formation of methyl ethyl carbonate or ethyl bicarbonate as shown in equations (4) and (5). Ethyl bicarbonate decomposes to ethanol and carbon dioxide. Methyl nitrite escapes from the medium while N-cyclohexylurethan (VII) and methyl ethyl carbonate are *stable* toward solvolysis under the conditions of the experiment.


VIA VII

(2)

(3)

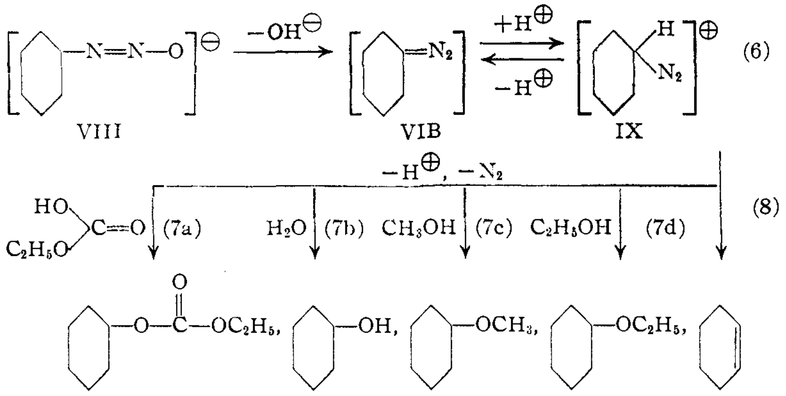

VIA VIII

(4)

(5)

The plausibility of these two paths of decomposition is supported by the quantitative hydrolysis of N-nitroso-N-cyclohexylurethan to N-cyclohexylurethan by water vapor. Further, an increase in the amount of potassium carbonate increases the yield of methyl ethyl carbonate.

The decomposition postulated for cyclohexyldiazotate ion (VIII) has been rationalized as proceeding through diazocyclohexane (VIB). Since the solution becomes acidic as the decomposition proceeds (carbon dioxide is evolved) and since the decomposition of diazoalkanes is catalyzed by acids[9] it seems reasonable to suggest an intermediate cyclohexane diazonium ion (IX), equation (6), which reacts with any nucleophilic species present in the solution as shown in equation (7a, b, c, d).


VIII VIB IX

(6)

(7a) (7b) (7c) (7d)

(8)

Methyl cyclohexyl ether did not result from a reaction between methanol and cyclohexene under the conditions of the experiment. Cyclohexanediazonium ion (IX) may also lose nitrogen and a proton to yield cyclohexene, equation (8).

The possibility that either cyclohexyldiazotate ion (VIII) or diazocyclohexane (VIB) decomposes into free radicals cannot be excluded but rationalization of the major products of the reaction would be awkward.

Of the N-nitroso-N-cyclohexylurethan (VIA) 95% of the cyclohexyl fragment and 97% of the ethyl fragment were accounted for in the combined yield of crude products.

Experimental[10]

N-Cyclohexylurethan.—Following the method of "Organic Syntheses,"[11] for alkylurethans this compound was obtained in 96% yield, m. p. 56.0–56.5° (lit.[8] m. p. 57°), b. p. 134° (18 mm.).

Anal.[12] Calcd. for $C_9H_{17}O_2N$: C, 63.12; H, 10.01. Found: C, 63.40; H, 9.82.

N-Nitroso-N-cyclohexylurethan (VIA).—The directions specified in "Organic Syntheses"[13] for N-nitroso-N-alkylurethans were modified by the use of petroleum ether (b. p. 32–38°) instead of ethyl ether, the use of external cooling instead of the addition of ice to the reaction mix-

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(8) Fischer, *Z. physik. Chem.*, **65**, 61 (1908) has pointed out the rapid esterification of primary alcohols by nitrous acid.

(9) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 288.

(10) Melting and boiling points are uncorrected.

(11) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 278.

(12) Carbon, hydrogen and nitrogen analyses were performed by Micto-Tech Laboratories, Skokie, Illinois.

(13) Ref. 12, p. 464.

ture, the removal of solvent *in vacuo* without distillation of the product and the omission of shaking the ethereal solution with anhydrous potassium carbonate. Oxides of nitrogen are less soluble in petroleum ether than in wet ethyl ether and, therefore, the process of washing out excess gases is shortened. Because water is less soluble in petroleum ether than in ethyl ether, hydrolysis of N-nitroso-N-cyclohexylurethan is suppressed. The shaking of anhydrous potassium carbonate with an ethereal solution of N-nitroso-N-cyclohexylurethan causes slight decomposition; this is not surprising since complete decomposition would take place if the solvent were methanol. Unlike N-nitroso-N-methyl urethan, N-nitroso-N-cyclohexylurethan is not a skin irritant.

In the reaction 85.6 g. (0.5 mole) of N-cyclohexylurethan gave N-nitroso-N-cyclohexylurethan, an orange liquid, n^{20}_{D} 1.4702, d^{20}_{4} 1.0846 in 99% of the theoretical amount.

Anal. Calcd. for $C_9H_{16}O_3N_2$: N, 14.00. Found: N, 13.85.

By hydrolysis 0.2648 g. of N-nitroso-N-cyclohexylurethan gave 0.2268 g. (calcd. 0.2264 g.) of N-cyclohexylurethan, m. p. 55.5–56.5° and mixed m. p. with an authentic sample 56.0–56.5°.

Decomposition of N-Nitroso-N-cyclohexylurethan.—To a mixture of 55 ml. of methanol and 1 g. of finely-powdered potassium carbonate was added, dropwise over a period of 2 hours, 100 g. (0.5 mole) of N-nitroso-N-cyclohexylurethan. The reaction was maintained at room temperature for one week. At the end of this time the evolution of gases had practically ceased and complete decomposition was insured by refluxing for one hour on a steam-bath. The gases were passed through a trap immersed in a Dry Ice–acetone-bath and then through lime water. The colorless trap liquid (b. p. below 0°) was identified as methyl nitrite (lit.[14] b. p. −12°) from the fact that it gave a positive nitrite test after dilute acid hydrolysis. Carbon dioxide was identified by a white precipitate from lime water which was soluble in dilute acetic acid. A solid was filtered off and identified as potassium bicarbonate; nitrite and carbonate ions were absent.

By a careful fractional distillation, methanol, ethanol, methyl cyclohexyl ether, ethyl cyclohexyl carbonate and N-cyclohexylurethan were obtained. Ethanol (crude yield 56%), b. p. 78–79°, n^{20}_{D} 1.3720 (lit,[15] b. p. 78.5°, n^{20}_{D} 1.3610) gave an α-naphthylurethan derivative, m. p. 78° (lit.[16] m. p. 78°). Methyl cyclohexyl ether (crude yield 14%, purified yield 10%), b. p. 133–134°, n^{20}_{D} 1.4346 (lit.[17] b. p. 131.5 (713 mm.), n^{20}_{D} 1.4344) gave negative tests for carbonyl and active hydrogen.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.84; H, 12.50.

Ethyl cyclohexyl carbonate (crude yield 17%, purified yield 13%) b. p. 101–102° (18 mm.), n^{20}_{D} 1.4413 (lit.[18] b. p. 99° (18 mm.), n^{20}_{D} 1.4393) was identical with the compound made by independent synthesis and reported below. N-Cyclohexylurethan (crude yield 15%, purified yield 12%) was identified (m. p. 55–56° and mixed m. p. with an authentic sample 56–57°).

Also isolated by fractional distillation were azeotropic mixtures of methanol–cyclohexene and water–methyl ethyl carbonate, and a mixture of cyclohexanol and ethyl cyclohexyl ether. The azeotrope of methanol and cyclohexene (b. p. 56°) was extracted with water, leaving 17 g. of crude hydrocarbon. From a middle cut of the hydrocarbon b. p. 82–84°, n^{20}_{D} 1.4406, 3.2 g. was oxidized with neutral permanganate solution. A yield of 3.0 g. (53% of the theoretical amount) of adipic acid was obtained and identified (m. p. and mixed m. p. with authentic adipic acid 148–151°). The hydrocarbon was thus identified as cyclohexene (crude yield 42%) (lit.[19] b. p. 83°, n^{20}_{D} 1.4464). The azeotrope of water and methyl ethyl carbonate (b. p. 85°) separated into two layers. The upper layer, b. p. 98–99°, n^{20}_{D} 1.3432 was identified as water (lit.[20] b. p. 100°, n^{20}_{D} 1.3330) (crude yield 5.6%). The lower layer, b. p. 105–106°, n^{20}_{D} 1.3767, was identified as methyl ethyl carbonate (lit.[21] b. p. 107.2–107.8° (765 mm.), n^{20}_{D} 1.3779) (crude yield 4.4%). The mixture of cyclohexanol and ethyl cyclohexyl ether was separated by fractional crystallization from petroleum ether (b. p. 32–38°). The less soluble fraction, cyclohexanol (crude yield 3.6%), n^{20}_{D} 1.4622 (lit.[17] n^{20}_{D} 1.4657), gave an α-naphthylurethan derivative, m. p. and mixed m. p. with an authentic derivative 127–128° (lit.[16] m. p. 128–129°). The more soluble fraction was tentatively identified as ethyl cyclohexyl ether (crude yield 4.0%), n^{20}_{D} 1.4530 (lit.[17] n^{20}_{D} 1.4401), by analogy to methyl cyclohexyl ether above.

When the amount of potassium carbonate was increased from a catalytic quantity to an amount equimolar with the N-nitroso-N-cyclohexylurethan (VIA) used, all other conditions unchanged, the crude yield of methyl ethyl carbonate increased from 4.4 to 67% of the theoretical amount.

Ethyl Cyclohexyl Carbonate.—A mixture of 12.24 g. (0.122 mole) of cyclohexanol, 13.23 g. (0.122 mole) of ethyl chloroformate and 8.0 g. of powdered calcium carbonate was heated on a steam-bath for 24 hours. The mixture was then filtered, the solid washed with ether and the washings united with the filtrate. The fraction that distilled at 97–102° (17 mm.) was ethyl cyclohexyl carbonate and amounted to 9.26 g. (44% yield); 6.01 g. (49%) of the cyclohexanol was recovered. Redistillation provided a center cut, b. p. 100–101° (17 mm.), n^{20}_{D} 1.4399, d^{20}_{4} 1.0151 (lit.[18] b. p. 99° (18 mm.), n^{20}_{D} 1.4393, d^{20}_{4} 1.015).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.86; H, 9.27.

Summary

1. The base-catalyzed decomposition of N-nitroso-N-cyclohexylurethan in methanol yields nitrogen, carbon dioxide, methyl nitrite, cyclohexene, ethanol, methyl ethyl carbonate, water, methyl cyclohexyl ether, ethyl cyclohexyl ether, ethyl cyclohexyl carbonate and N-cyclohexylurethan.

2. To account for all the observed products, reactions and intermediates are postulated.

CHICAGO 16, ILL. RECEIVED JANUARY 27, 1950

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