

## Alkaline Degradation of Tetraazahomoadamantane Derivatives (I)

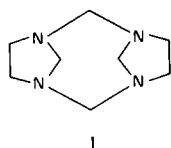
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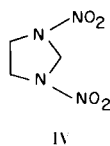
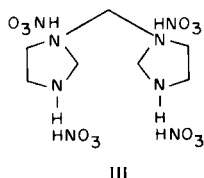
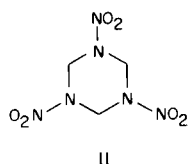
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Alkaline degradation of 1,3,6,8-tetraazatricyclo[4,4,1,1<sup>3,8</sup>]dodecane (V) and 11-Thia-1,3,5,7-tetraazatricyclo[3,3,1,1<sup>3,7</sup>]undecane-11,11-dioxide (VIII) are shown to generate readily formaldehyde and the respective amines, followed by resynthesis of imidazolidines in the presence of acylating or sulfonylating agents.

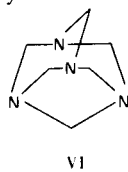
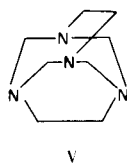
The condensation of formaldehyde with ethylenediamine was first described by Bischoff (2). The product of such a reaction was formulated as (I) 1,3,6,8-diendomethylene-1,3,6,8-tetraazacyclododecane.



Subsequently a number of chemical transformations of I were reported by Simkins and Wright (3). The following products II, III, and IV obtained by Simkins and Wright appeared to confirm the structural formulation I.



However, most recently Volpp (4) as well as Riddell and Murray-Rust (4a) questioned the validity of I and proposed an alternative formulation (V) by close analogy with the tetraazaadamantane structure VI prepared by the condensation of ammonia and formaldehyde.

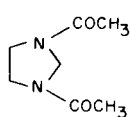


Such a revision of structure, based on symmetry considerations and nmr spectra evidence was readily accepted in a subsequent publication by Nelsen and Hintz (5) although no chemical evidence had been adduced to confirm the new formulation V. This would be deemed especially necessary in view of the prior report by Simkins and Wright (3) of the formation of 1,3-dinitroimidazolidine (IV) by the nitrolysis of the Bischoff compound. The formation of compound IV on the basis of the new structure would require extensive reorganization of the molecule. Whether such a transformation is possible is as yet undetermined. The present study was therefore undertaken to verify such a possibility.

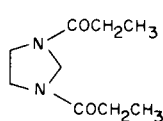
The methylenebisimidazolidine tetranitrate described by Simkins and Wright (3) was obtained in the manner described by them. The melting point of the product was in agreement with the earlier report. However, the NMR spectrum of this salt in deuterium oxide showed only two signals of equal intensity at 3.4 (8H) and 4.65 (8H), contrary to expectations for structure III. The observed percentage of nitric acid, (estimated by titration) in the salt, also corresponds correctly for the formulation C<sub>8</sub>H<sub>16</sub>N<sub>4</sub>·4HNO<sub>3</sub> rather than for the methylenebisimidazolidine (III). Thus, the methylenebisimidazolidine formulation is in error. Simkins and Wright additionally commented that "A solution of I in acetic acid is unstable and the dinitrate decomposes within an hour, whereas hexamethylenetetramine dinitrate is permanently stable." Our study, on the contrary shows that the tetranitrate salt retains the entire structure without loss of the methylene. This feature may draw support from the findings of Nelsen and Hintz (5) who report that 1,3,6,8-tetraazatricyclo(4,4,1,1<sup>3,8</sup>)dodecane (V) forms a stable cation radical, stable enough to show a re-reduction and "this implies that all four nitrogens share the positive charge."

How then does one account for the formation of

imidazolidine derivatives from a compound with the structure V? We describe in the sequel results which reveal the propensity of such molecules as V to undergo facile degradation into ethylenediamine and formaldehyde followed by cyclization into imidazolidine derivatives. The striking feature of this transformation is, that it occurs at as low a temperature as  $-10^{\circ}$  in the presence of acylating agents and alkali. This change is not brought about by alkali alone. An aqueous solution of compound V when treated with NaOH at  $-10$  to  $-15^{\circ}$  underwent little alteration. Whereas when the same aqueous solution was treated with acetic or propionic anhydride and alkali at  $-10$  to  $-15^{\circ}$ , the imidazolidines VIIa and VIIb were formed in 84 and 55% yields, respectively.

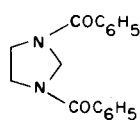


VIIa

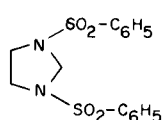


VIIb

When the reaction was carried out by bubbling a stream of nitrogen through the solution, formaldehyde was carried in the nitrogen stream and detected by an aqueous solution of the sensitive reagent: 3-methyl-2-benzothiazolinonehydrazone (MBTH) giving the characteristic intense blue dye (6). Appropriately, the yield of the diacylimidazolidines also diminished. The formation of formaldehyde in the reaction of V with alkali and acid anhydrides is thus demonstrated. If ethylenediamine is also formed, will it undergo condensation under those conditions to give the imidazolidines? The 1,3-diacyl-imidazolidines described in the literature (7) were prepared by the *acid-catalyzed* condensation of formaldehyde with the diamides of ethylenediamine. There is no information on the base-catalyzed, low temperature condensation of formaldehyde with ethylenediamine. In the event, it was observed by us, imidazolidines were obtainable in yields as high as 51.3%. It is clear, therefore, that the tetraazatricyclododecane (V) rapidly regenerates formaldehyde and ethylenediamine in the presence of acylating agents and alkali. Additional corroboration of this was obtained by the reaction of benzoic anhydride and benzene sulfonyl chloride separately with V to give VIIc and VIId, respectively.

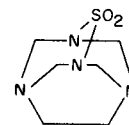


VIIc



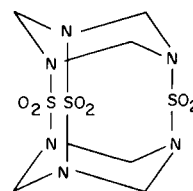
VIId

That this characteristic of alkaline degradation of V into its component amine and aldehyde is shared by another analogous derivative VIII has also been discovered by us in this study.



VIII

Compound VIII, prepared by the condensation of formaldehyde, ethylenediamine and sulfamide (8), has been shown by us (9) to undergo an acid-catalyzed transformation of a very different nature, leading to the synthesis of a more complex derivative (IX), from the components formaldehyde and sulfamide.

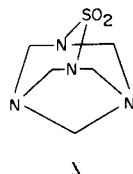


IX

In the light of the behavior of V under alkaline treatment, it was of interest to study the response of VIII under analogous conditions. Upon heating with 10% aqueous sodium hydroxide, compound VIII underwent slow conversion to a sulfur-free derivative melting at  $190-200^{\circ}$ . Over 48 hours, the yield of this compound rose to a maximum of 45%. Comparison with an authentic sample of V by nmr and mass spectra and by mixed melting point established the identity of the two. Thus alkaline treatment of compound VIII appears to break it down to its component reactants. This was additionally confirmed by the reaction of VIII with benzene sulfonyl chloride and aqueous alkali, when it readily gave close to 50% yield of 1,3-dibenzoylsulfonyl-imidazolidine (VIIId). Sweeping the reaction mixture with a stream of nitrogen, in both of these experiments, gave ample evidence for the generation of formaldehyde.

There is, nevertheless, a minor difference between the behavior of V and VIII under alkali treatment. The former undergoes little alteration on treatment with alkali alone; the imidazolidines from it are formed only in the added presence of acylating agents. However, the latter (VIII) breaks down to ethylenediamine and formaldehyde in the presence of alkali alone. The sulfamide moiety in VIII apparently takes the place of the acylated nitrogen function in V, in inviting attack by the hydroxide ion on the methylenes alpha to the nitrogen. The validity

of this surmise is corroborated in the behavior of an additional example (X). Compound X reported first by Paquin (8) results from the condensation of ammonia, formaldehyde and sulfamide.



By comparison with the behavior of VIII, compound X could also be expected to fragment to formaldehyde and ammonia, which could resynthesize the tetraazaadamantane VI. In the event, X readily gave rise to VI in good yields.

In summary, alkaline degradation into component reactants, appears to be a common feature of systems incorporating formaldehyde, ammonia or ethylenediamine.

#### EXPERIMENTAL

Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer. Mass spectra were determined on a Hitachi-Perkin-Elmer RMU-6E spectrometer.

1,3,6,8-tetraazaadamanthane(V) was prepared according to Bischoff (2).

##### 1,3-Diacetylimidazolidine (VIIa).

To a stirred solution of 1.68 g. (0.01 mole) of V in 10 ml. of water kept at  $-10^{\circ}$ , a solution of 4 g. (0.1 mole) sodium hydroxide in 15 ml. of water was added over 2 minutes. To this mixture was added 10.2 g. (0.1 mole) of acetic anhydride with stirring over a period of 15 minutes while maintaining the temperature between  $-15$  and  $-10^{\circ}$ . After subsequent stirring for one more hour at  $-15$  to  $-10^{\circ}$ , the reaction mixture was extracted several times with cold chloroform after saturation of the aqueous solution with sodium chloride. The chloroform extract was dried (anhydrous sodium sulfate) and distilled at  $30$  to  $33^{\circ}$  under a vacuum, whereby a viscous liquid was obtained. This was chromatographed over basic alumina eluting with acetone as solvent. White crystals of VIIa separated out, m.p.  $93-94^{\circ}$  (reported  $90-92^{\circ}$  (7)), yield, 2.6 g. (83.3%);  $M^{\dagger} = 156$ ; nmr ( $\delta$  in deuteriochloroform): sharp singlet at 4.93 (2H); broad singlet at 3.80(4H); sharp singlet at 2.08(6H).

*Anal.* Calcd. for  $C_7H_{12}N_2O_2$ : C, 53.86; H, 7.69; N, 17.95. Found: C, 53.67; H, 7.84; N, 17.95.

The above reaction was repeated under the same conditions while bubbling a stream of nitrogen through the solution during the whole reaction period. Part of the formaldehyde generated and carried over by the nitrogen stream was absorbed in an aqueous solution of MBTH. This aqueous solution, when treated with a very dilute solution of ferric chloride, gave intense blue color indicative of formaldehyde (6). The yield of VIIa in this run was consequently decreased to 2.19 g. (70.1%).

##### 1,3-Dipropionylimidazolidine (VIIb).

This compound was prepared similarly, m.p.  $86-87^{\circ}$ , yield, 2 g. (54.4%);  $M^{\dagger} = 184$ ; nmr ( $\delta$  in deuteriochloroform): singlet at 4.91 (2H); broad singlet at 3.76 (4H); quartet at 2.51-2.15

(4H); triplet (centered at 1.15) at 1.28-1.03 (6H).

*Anal.* Calcd. for  $C_9H_{16}N_2O_2$ : C, 58.69; H, 8.69; N, 15.22. Found: C, 58.54; H, 8.77; N, 15.21.

##### Synthesis of VIIa from Ethylenediamine, Formaldehyde and Acetic Anhydride under Alkaline Condition.

To a stirred solution of 1.2 g. (0.02 mole) ethylenediamine in 10 ml. of water, kept at  $-10^{\circ}$ , a solution of 4 g. (0.1 mole) of sodium hydroxide in 15 ml. of water was added over 2 minutes. To this stirred solution kept between  $-15$  and  $-10^{\circ}$  were added over 15 minutes 3.5 ml. of 37% aqueous formaldehyde and 10.2 g. (0.1 mole) of acetic anhydride such that the rate of addition of acetic anhydride was faster than that of formaldehyde.

After subsequent stirring for one more hour at  $-15$  to  $-10^{\circ}$ , the reaction was saturated with sodium chloride and extracted repeatedly with cold chloroform. Extract was dried (anhydrous sodium sulfate) and stripped of solvent at  $30-35^{\circ}$  to give a viscous oil. After chromatography over basic alumina eluting with acetone, two compounds, VIIa and *N,N'*-ethylenebisacetamide separated out, yield of VIIa, 1.6 g. (51.3%), m.p.  $88-92^{\circ}$ , a mixed m.p. with authentic VIIa was undepressed, yield of *N,N'*-ethylenebisacetamide 0.2 g. (6.9%) m.p.  $174-175^{\circ}$ .

*Anal.* Calcd. for  $C_6H_{12}N_2O_2$ : C, 50.00; H, 8.33; N, 19.45. Found: C, 49.94; H, 8.14; N, 19.36.

##### 1,3-Dibzenesulfonylimidazolidine (VIIId).

To a stirred solution of 1.68 g. (0.01 mole) of V in 20 ml. of water kept between  $58$  and  $68^{\circ}$ , 11.02 g. (0.062 mole) of benzenesulfonylchloride was added over 10 minutes, keeping the pH of the reaction mixture between 8 and 10 by adding 10% aqueous caustic soda solution. After stirring for one more hour at  $58$  to  $68^{\circ}$  at a pH of 8-10 by occasional addition of alkali, the reaction mixture was poured into 75 ml. of 10% aqueous alkali and stirred for a half hour at room temperature.

The resulting gummy mass was filtered, washed thoroughly with water and dried. On stirring this material with two 50 ml. portion of methanol at room temperature, a white solid crystallized out which was filtered and air dried, m.p.  $153-154^{\circ}$  (methanol), yield, 5.4 g. (76.6%); nmr ( $\delta$  in deuteriochloroform): complex multiplet at 7.88-7.5 (10H); singlet at 4.6 (2H); singlet at 3.25 (4H).

*Anal.* Calcd. for  $C_{15}H_{16}N_2O_4S_2$ : C, 51.14; H, 4.54; N, 7.95. Found: C, 51.08; H, 4.58; N, 7.94.

##### 1,3-Dibenzoylimidazolidine (VIIc) and *N,N'*-Ethylenebisbenzamide.

To a stirred solution of 5.04 g. (0.03 mole) of V in 60 ml. of water kept between  $55$  and  $65^{\circ}$  40.7 g. (0.18 mole) benzoic anhydride was added over 10 minutes keeping the pH between 8 and 10 by the addition of 10% aqueous caustic soda solution. After stirring for 65 minutes longer at  $55$  to  $60^{\circ}$  with occasional addition of 10% aqueous alkali to maintain the pH between 8 and 10, the reaction mixture was poured into 20 ml. of 10% aqueous alkali and stirred for 30 minutes at room temperature. The white solid which separated was filtered, washed thoroughly with water and dried in air. By fractional crystallization from boiling acetone, two compounds were separated.

(a) *N,N'*-ethylenebisbenzamide (less soluble fraction) yield, 0.85 g. (5.3%) m.p.  $249-250^{\circ}$ ;  $M^{\dagger} = 268$ .

*Anal.* Calcd. for  $C_{16}H_{16}N_2O_2$ : C, 71.63; H, 5.97; N, 10.45. Found: C, 71.54; H, 6.02; N, 10.42.

Mixed m.p. with an authentic sample was undepressed. (b) 1,3-dibenzoylimidazolidine (VIIc) (more soluble fraction) yield, 7.6 g. (54.2%), m.p.  $140-141^{\circ}$ ,  $M^{\dagger} = 280$ .

*Anal.* Calcd. for  $C_{17}H_{16}N_2O_2$ : C, 72.85; H, 5.71; N, 10.00. Found: C, 72.90; H, 5.75; N, 9.96.

The Tetranitrate Salt of V.

To a vigorously stirred solution of 2.1 g. (0.0125 mole) of V in 50 ml. of absolute ethanol kept between 0 and 10°, 4.5 ml. of 70% nitric acid was added over 5 minutes. A yellow slurry formed. This was stirred 15 minutes more allowing the temperature of the reaction mixture to rise to 17°. Stirring at this temperature for another 15 minutes caused the yellow slurry to change to a white precipitate. The solid was filtered in the cold, washed with cold absolute ethanol, cold acetone and finally with cold ether. The sample was dried in vacuum for 15 minutes below 10°, m.p. 142-143° (reported 143.8° (3)), yield, 4.5 g. (85.7%); nmr ( $\delta$  in deuterium oxide sodium 2,2-dimethyl, 2-silapentane-5-sulfonate was used as standard): 3.4 (8H) and 4.65 (8H).

Percentage of nitric acid calculated for the tetranitrate salt of V is 60.01, whereas Wright's reported value is 60.7% (3).

Study of the Action of Aqueous Solution of Caustic Soda on V.

To a solution of 1.68 g. (0.01 mole) of V in 10 ml. of water kept between -15° and -10°, a solution of 4 g. of caustic soda in 15 ml. of water was added with stirring over 2 minutes. After stirring for 1 hour and 15 minutes, the reaction mixture was extracted several times with cold chloroform after saturation of the aqueous solution with sodium chloride. The chloroform extract was dried (anhydrous sodium sulfate) and distilled at 30° and 35° under a vacuum, whereby a white solid was obtained, weight 1.45 g. (86.3% recovery) nmr, tlc and mass spectrum of this product were identical to those of V. There was no evidence for ethylenediamine.

The Reaction of 11-Thia-1,3,5,7-tetraazatricyclo[3,3,1,1<sup>3,7</sup>]undecane-11,11-dioxide (VIII) with 10% Aqueous Sodium Hydroxide.

A suspension of 2.04 g. (0.01 mole) of VIII in 20 ml. of 10% aqueous sodium hydroxide solution was stirred at 42 to 43° for 48 hours. During this period the whole solid went into solution. The solution was cooled, extracted repeatedly with chloroform, and the extract distilled to give a white solid, m.p. 190-200°, yield, 0.38 g. (45.2%).

This compound was identified as V by mixed melting point with an authentic sample and comparison of nmr and mass spectral data.

From the aqueous layer by neutralization with 37% hydrochloric acid, 0.11 g. of starting material (VIII) was recovered.

The Reaction of 2-Thia-1,3,5,7-tetraazatricyclo[3,3,1,1<sup>3,7</sup>]decane (X) with 10% Aqueous Sodium Hydroxide Solution.

A suspension of 1.90 g. (0.01 mole) of X in 20 ml. of 10% aqueous sodium hydroxide solution was stirred at 60° for 12 hours. During this period, the entire solid went into solution.

The solution was cooled to room temperature, extracted repeatedly with chloroform, the chloroform extract was dried (anhydrous sodium sulfate) and distilled, to give a white solid, yield, 0.41 g. (58.6%).

This compound was identified as VI from its nmr, ir and mass spectral data.

Reaction of VIII with Benzenesulfonylchloride in the Presence of Aqueous Alkali.

To a stirred suspension of 2.04 g. (0.01 mole) of VIII in 25 ml. of water kept at 65°, 5.3 g. (0.03 mole) benzenesulfonylchloride was added over a period of 5 minutes, while maintaining the pH of the reaction mixture 8 to 10 by adding 10% aqueous sodium hydroxide.

After stirring for two and a half hours more at 65° and keeping the pH between 8 and 10, the whole reaction mixture was poured into 20 ml. of 10% aqueous alkali and stirred for 15 minutes at room temperature. The solid which separated out was filtered, washed thoroughly with water and dried, m.p. 150°, yield, 1.75 g. (49.7%), a mixed m.p. with an authentic sample of VIII was undepressed.

The formaldehyde formed in this reaction was detected in the same fashion as discussed in an earlier experiment.

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