Acid Catalyzed Rearrangements of Thia and Aza Analogs of Adamantanes A New Derivative of Sulfamide, Formaldehyde and Ammonia

B. S. Thyagarajan and J. B. Kang*

Chemistry Department, University of Idaho,
Moscow, Idaho 83843

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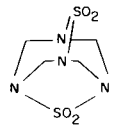
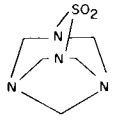
The conversion of 2-thia-1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane 2,2-dioxide under acid conditions into a hexaazatetracyclo derivative is described.

Derivatives of hexamethylenetetramine in which one or two methylene groups are replaced by a sulfone function have been known for some 30 years (1,2). These compounds I and II are thia and aza replacement analogs of adamantane. Whereas I is readily obtained by the condensation of sulfamide with formaldehyde, compound II is obtained by the reaction of ammonia, formaldehyde and sulfamide.

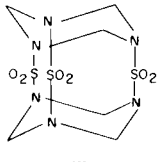


I

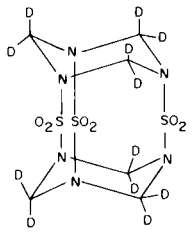


II

These structures are skeletally related to adamantane but they should possess nothing resembling adamantane-like stability towards acids in view of the N-C-N-C-N sequences. In keeping with this, treatment of I under mild conditions (ambient temperatures) with acids, readily transformed it into 4,10,13-trithia-1,3,5,7,9,11-hexaazatetracyclo-[5.5.1.1^{3,11}1.^{5,9}]pentadecane-4,10,13-tris(dioxide) (III). The structures of III and its completely deuterated isomer IV were established by us in our earlier study (3).



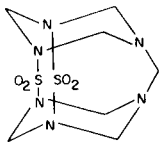
III



IV

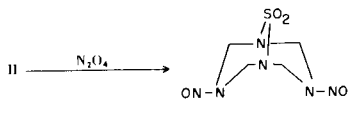
In this study, we wish to report the conversion of compound II under similar conditions into a derivative V, closely similar to III.

Treatment of II with strong aqueous mineral acids readily affords III. However, under slightly modified conditions, using different buffer systems (see experimental) within the *p*H range of 6.4 to 1.7, one obtains the compound V. The yields of this product, at best, varied between 5.16 and 24%. Elemental analyses and mass spectral data corroborated the molecular formula $C_7H_{14}N_6O_4S_2$. Infrared spectra clearly confirmed the presence of sulfamide bonds while the nmr spectrum showed signals at δ 4.1 ~ 5.6 for 14 protons. The presence of seven carbons and two SO_2 units suggested the possibility that compound V, by analogy with III may have the following structure:



V

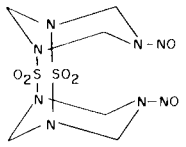
In compound II two of the nitrogens are of the amide type while the other two are more basic tertiary amines. Consequently, II reacts readily with liquid dinitrogen tetroxide at low temperatures resulting in the rupture of the N-CH_2-N linkage (4), to give VI in good yields.



VI

The sulfamide nitrogens are unaffected in this reaction. This is also additionally underscored by the fact that compound III are completely unaffected by dinitrogen tetroxide. If, therefore, the structure assigned for compound V is correct, then it should react with dinitrogen tetroxide affording a cleavage similar to II. In the event this proved to be true. Reaction of V with liquid dinitrogen

tetroxide readily afforded a dinitrosoderivative VII with loss of methylene group. Elsewhere (5) we have demonstrated the facility of such cleavage reactions in derivatives of 1,3,5,7-tetraazabicyclo[3.3.1]nonane.

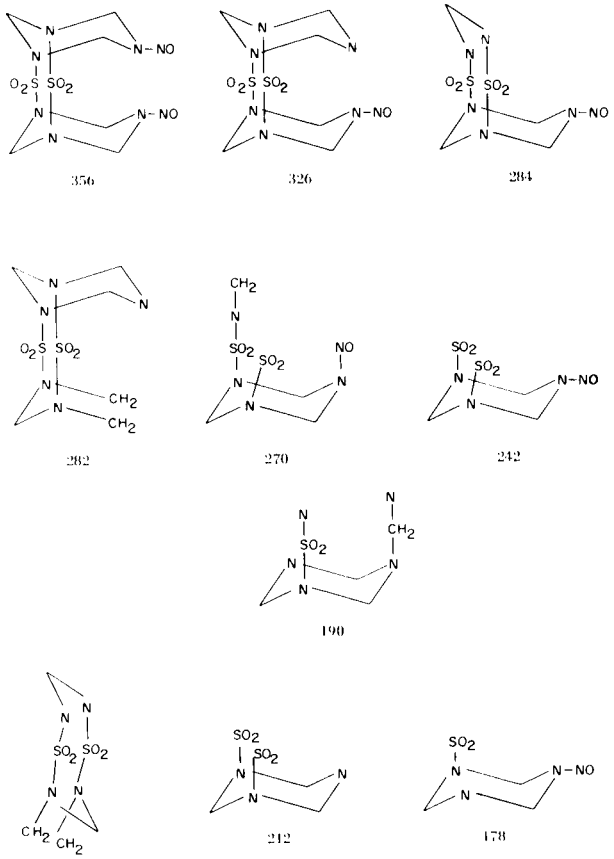


VII

Elemental analyses and mass spectral data completely confirm the molecular formula $C_6H_{12}N_8O_6S_2$. Infrared data confirm the presence of the *N*-nitroso function. A detailed analysis of the mass spectral fragmentation reveal the occurrence of the fragments detailed in Scheme I.

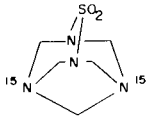
Additional chemical support for V is derived from two other interesting reactions. Treatment of V with aqueous alkali results in the formation of hexamethylenetetramine. Reaction of V with trifluoroacetic acid on the other hand leads to the formation of I. These same products are also obtainable from II under identical conditions. Scheme II summarizes these reactions.

SCHEME I

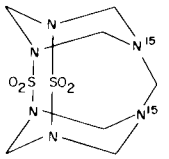


Further substantiation for V was sought by the following means. The fully deuterated isomer VIII of II was prepared by the condensation of ammonia, sulfamide and deuterated paraformaldehyde. The product VIII showed no signals in proton nmr. Mass spectral data confirmed the molecular formula $C_5D_{10}N_4O_2S$. Treatment of VIII under conditions identical to that required for converting II to V gave a product IX corresponding to the molecular formula $C_7D_{14}N_6O_4S_2$. This compound also showed no signals in proton nmr. A detailed analysis of the mass spectrum revealed fragments corresponding to the masses shown in Scheme III, thereby further substantiating the structure for V.

A further series of supportive evidence was secured by preparing compound II utilizing ammonia-^{15}N in place of ammonia. The derived compound provided mass spectral data revealing the incorporation of ^{15}N at the sites shown in the following formula:

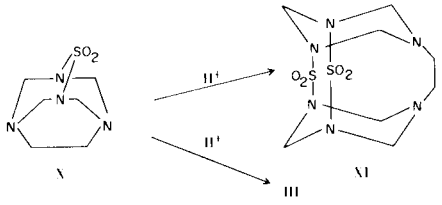


Conversion of this into the analog of IX was achieved by an identical treatment resulting in the structure shown below, fully substantiated by mass spectral data.

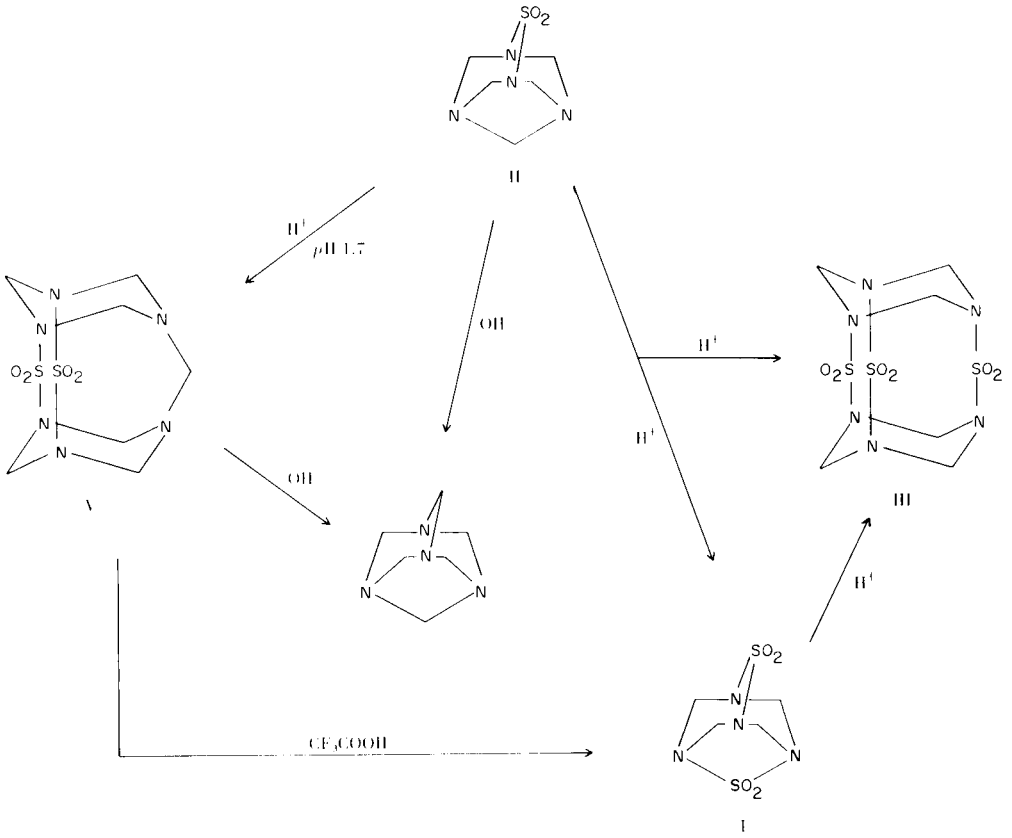


Scheme IV summarizes some of the significant fragments in the mass spectrum of the ^{15}N labeled derivative.

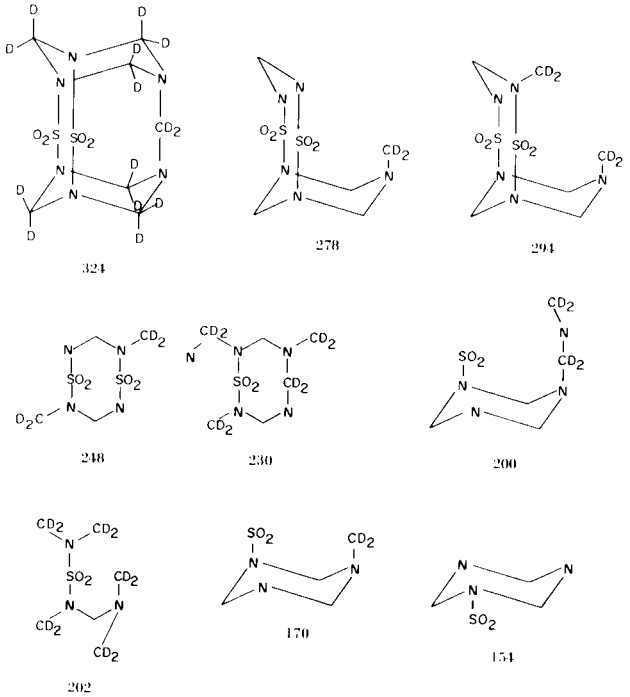
The acid catalyzed transformations of I and II into the higher molecular weight systems III and V point out the facile degradation and resynthesis of the N-CH_2-N function into larger more complex heterocyclic systems. It is of interest to explore the constraints and limitations to ring modifications of this kind. As part of the present study, we also investigated the behavior of 11-thia-1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]undecane 11,11-dioxide (X) under conditions that gave III and V. Degradation and resynthesis did occur, only to give III and not XI.



SCHEME II



SCHEME III



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. Elemental analyses were performed by Dr. Dave Harsch.

Reaction of II with Buffer Solution (*p*H 1.7).

A suspension of 1.9 g. of II in 30 ml. of the buffer solution (*p*H 1.7) was stirred at 95° for 24 hours. During this period the entire solid went into solution and the product separated as a precipitate. This was filtered, washed thoroughly with water and dried. Recrystallization of this solid from acetonitrile gave 0.37 g. of crystals of V (23.87%), m.p. 255-260°; nmr (δ DMSO-d_6): 5.6-4.1 δ (14 H).

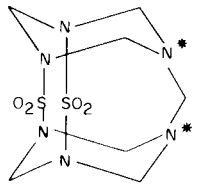
Anal. Calcd. for $C_7H_{14}N_6O_4S_2$: C, 27.05; H, 4.5; N, 27.05; S, 20.3. Found: C, 27.16; H, 4.62; N, 27.02; S, 20.7.

Results of treatment of II with different buffer solutions are summarized in Table I.

Reaction of II with Dinitrogen Tetroxide.

To 15 ml. of liquid dinitrogen tetroxide was added in portions 1.0 g. of II during 5 minutes while maintaining the temperature around -10°. The suspension was further stirred efficiently at -5° to -10°. At the end of this period, the solution became clear and was poured into ice-water and neutralized with potassium carbonate when some solid material precipitated. The solid material (0.79 g.)

SCHEME IV



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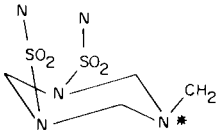

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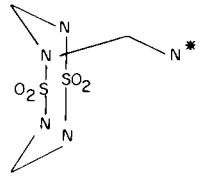

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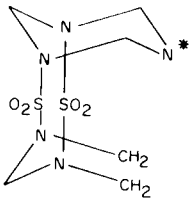

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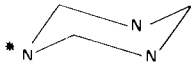

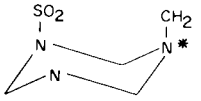

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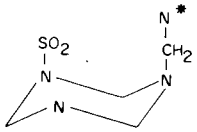

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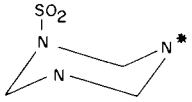

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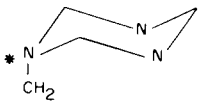

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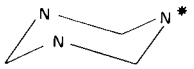

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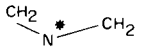

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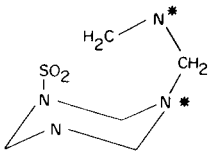

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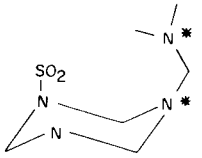

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TABLE I

Exp. No.	Amount of II used (g)	Reaction time (hours)	Reaction temp.	Buffer system used	*p*H of Buffer solution	Amount of buffer solution used (ml.)	Compound obtained	Yield %
I	1.9	24	95°	$\underline{Na_3PO_4}$ Na_2HPO_4	10.8	30	/	0
II	1.9	24	95°	$\underline{Na_2CO_3}$ $NaHCO_3$	9.4	30	/	0
III	1.9	24	95°	$\underline{Na_2HPO_4}$ NaH_2PO_4	6.4	30	V	5.16
IV	1.9	24	95°	$\underline{NaOAc}$ HOAc	4.9	30	V	5.16
V	1.9	24	95°	$\underline{NaH_2PO_4}$ H_3PO_4	1.95	30	V	19.35

was chromatographed over basic alumina using chloroform-methanol (1:1) as eluent to give 0.68 g. of VI (54.8%), m.p. 170°; nmr (δ DMSO-d_6): 6.57-4.5 (8 H) M^+ = 236.

Anal. Calcd. for $C_4H_8N_6O_4S$: C, 20.34; H, 3.39; N, 35.5. Found: C, 20.36; H, 3.399; N, 35.45.

Reaction of V with Dinitrogen Tetroxide.

To 50 ml. of liquid dinitrogen tetroxide was added, in portions, 0.05 g. of V during 2 minutes at room temperature. The solution was further stirred for 3 hours at -3° and then quenched by pouring into ice-water and neutralized with potassium carbonate to give a semi-solid mass. Recrystallization of this material from dimethylformamide gave 0.027 g. of faint yellow solid VII (47%) m.p. 179°-180°; nmr (δ DMSO-d_6): 6.2-3.9 (12H).

Anal. Calcd. for $C_6H_{12}N_8O_6S_2$: C, 20.22; H, 3.37; N, 31.46. Found: C, 20.17; H, 3.29; N, 31.63.

Reaction of II with 10% Aqueous Sodium Hydroxide Solution.

A suspension of 1.9 g. of V 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 combined 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 hexamine from its nmr, ir and mass spectral data.

Reaction of V with 10% Aqueous Sodium Hydroxide Solution.

Treatment of 0.44 g. of V with 10 ml. of 10% aqueous sodium hydroxide solution at 85-90° for 24 hours gave 13.7% of hexamine.

Reaction of II with Concentrated Sulfuric Acid.

To 20 ml. of concentrated sulfuric acid was added in poritons, 1.9 g. of II during 10 minutes while maintaining the temperature around 10°. The solution was further stirred for 50 minutes at 10°, then quenched by pouring into ice-water and neutralized with potassium carbonate to give a slurry mass. This was filtered, washed thoroughly with water and dried. On stirring this material with 50 ml. of acetone at room temperature, a white solid separated out which was filtered and dried; m.p. ≫ 360°, yield 0.64 g. (34.6%). This compound was identified as III by comparison of nmr and mass spectral data of authentic sample. The first aqueous filtrate on keeping in the refrigerator overnight yielded another solid material (50 mg.), m.p. 260-265°. Mixed m.p. with authentic sample of I was undepressed, yield, 4.15%. This compound was further identified as I from its nmr, ir and mass spectral data.

Reaction of X with Concentrated Sulfuric Acid.

Treatment of 2 g. of X with 20 ml. of concentrated sulfuric acid under the same conditions gave 0.2 g. of III in 17% yield.

Reaction of V with Trifluoroacetic Acid.

To 11 ml. of trifluoroacetic acid was added in portions 0.3 g. of V during 1 minute at room temperature. The suspension was further stirred for 24 hours at 65° and then quenched by pouring into ice water. Most of the unreacted starting material was removed by filtration. The filtrate was neutralized with potassium carbonate and repeatedly extracted with chloroform. The combined chloroform extract was washed with water, dried over anhydrous sodium sulfate and stripped of the solvent. The resinous mass left behind was chromatographed over basic alumina using acetone as eluent when 0.11 g. of I was isolated in 4.75% yield, m.p. 260-265°; nmr (δ DMSO-d_6): 5.56 (8H); M^+ = 240. Mixed m.p. with an authentic sample was undepressed.

Reaction of II with Trifluoroacetic Acid.

Treatment of 1.90 g. of II with 11.4 ml. of trifluoroacetic acid gave after the usual work-up 7.5% of I, m.p. 260-265°. Mixed m.p. with an authentic sample was undepressed.

Reaction of X with Trifluoroacetic Acid.

Treatment of 2 g. of X with 20 ml. of trifluoroacetic acid in same fashion as the reaction of II with trifluoroacetic acid gave 12.0% yield of I, m.p. 260-265°.

Decadeuterio-II (VIII).

Deuterated formaldehyde gas [generated by heating 3.02 g. of deuterated paraformaldehyde on an oil bath at 150° for 2 hours] was directly introduced into a solution of 0.6 g. of sulfamide in 5 ml. of deuterium oxide. The unreacted deuterated formaldehyde that escaped was absorbed in a trap containing 2 ml. of deuterium oxide. This unreacted deuterated formaldehyde in deuterium oxide was also added to the solution of sulfamide in deuterium oxide. The combined solution was stirred and 35 ml. of 30% ammonium hydroxide was added in portions during 15 minutes, maintaining temperature at 60-65°. The solution was filtered, washed thoroughly with water and dried. Recrystallization of this solid from ethanol gave 0.35 g. of VIII in 28% yield, m.p. 242°. M^+ = 200.

Anal. Calcd. $C_5D_{10}O_2S$: C, 30.00; D, 10.0; N, 28.00. Found: C, 29.72; D, 9.70 (H, 4.85); N, 27.76.

Reaction of VIII with Buffer Solution (*p*H 1.7).

A suspension of 0.21 g. of VIII with 2.5 ml. of buffer solution (*p*H 1.7) was stirred at 95° for 24 hours. During this period, the entire solid went into solution and the product separated as a precipitate. This was filtered, washed thoroughly with water and dried. Recrystallization of this solid from acetonitrile gave 0.034 g. of IX in 20.2% yield, m.p. 277°. M^+ = 324; nmr (δ DMSO-d_6): No absorption.

Anal. Calcd. for $C_7D_{14}N_6O_4S_2$: C, 25.93; D, 8.44; N, 25.93. Found: C, 25.64; D, 8.44 (H, 4.22); N, 25.64.

Preparation of N^{15} Labelled II.

To a stirred solution of 0.95 g. of sulfamide in 12 ml. of formaldehyde, 3 ml. of $N^{15}H_4OH$ (1500 ml. of $N^{15}H_3$ condensed by a liquid nitrogen bath was absorbed in 3 ml. of water) was added in poritons during one minute while maintaining temperature at 65-70°.

This solution was stirred for 2 hours at 50-55°. During this period, a white solid precipitated, which was filtered, washed well with water and dried. Recrystallization from ethanol gave 0.41 g. of labelled N^{15}-II, yield, 22.8%, m.p. 222-223°; M^+ = 192.

Anal. Calcd. for $C_5H_{10}N_2N_2{}^{15}O_2S$: C, 31.25; H, 5.21; N, 29.17 (as N^{14}). Found: C, 31.39; H, 5.05; N, 28.95 (as N^{14}).

Preparation of N^{15} Labelled V.

A suspension of 0.21 g. of N^{15} labelled V in 2 ml. of buffer solution (*p*H 1.7) was stirred at 95° for 24 hours. During this period the entire solid went into solution and the product separated as a precipitate. This was filtered, washed thoroughly with water and dried. Recrystallization of this solid from acetonitrile gave 90 mg. of labelled N^{15} V, yield, 55%, m.p. 265-266°; M^+ = 312.

Anal. Calcd. for $C_7H_{14}N_4N_2{}^{15}O_4S_2$: C, 26.92; H, 4.49; N, 26.92 (as N^{14}). Found: C, 26.73; H, 4.35; N, 26.72 (as N^{14}).

Acknowledgements.

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