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Selective Ring Opening Reactions of 3,7-Diarylsulfonyl-1,3,5,7-tetrazabicyclo[3.3.1]nonanes (1)

H. Yoshida (2), C. Sen, and B. S. Thyagarajan

Chemistry Department, University of Idaho, Moscow, Idaho 83843

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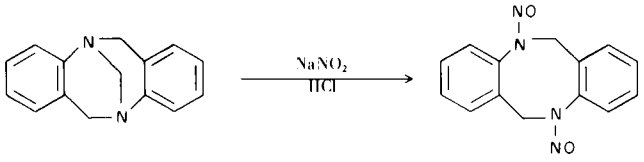
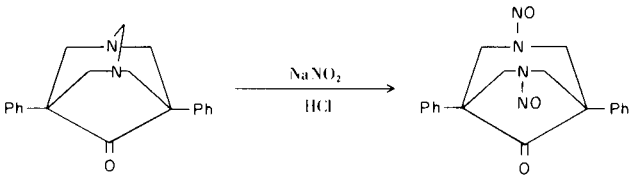
The selective formation of 1,3,5,7-tetrazacyclooctanes from the title compounds is described. Exclusive cleavage of the N-CH_2-N bonds at the bridge methylene is shown to be a facile process, thus providing a convenient route to tetrazacyclooctane derivatives.

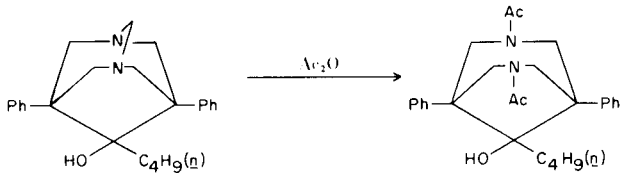
The methanediamine function is frequently encountered in a number of heterocyclic ring systems, such as endomethylenediazocines, endomethylenetriazocines, and endomethylenetetrazocine derivatives. Troeger's base (I) and its analogs (3,4,5) as well as derivatives of 1,5-diazaadamantanes (6,7,8) (III, V) represent functionalities which carry only a single N-CH_2-N linkage. In the above instance, a facile cleavage of the methanediamine bridge occurs on treatment with acid anhydrides or nitrous acid.



I II

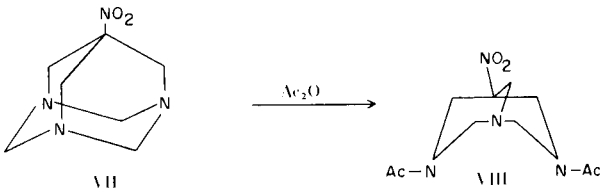


III IV

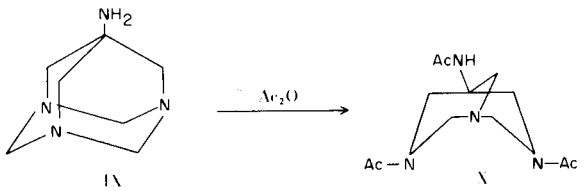


V VI

More recently the triazaadamantane derivatives VII and IX were subjected to cleavage by acetic anhydride (9) with the following results:



VII VIII



IX X

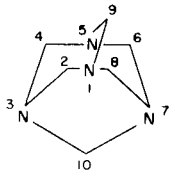
Similar cleavages of endomethylene bridges in tetrazabicyclononanes and 1,3,5,7-tetrazaadamantane have been extensively studied by a number of workers (10,11, 12).

In the examples cited above, only the triazaadamantane derivative and the 1,3,5,7-tetrazaadamantane derivatives carried more than one N-CH_2-N functionality and therefore, offered more than one site of attack for a ring cleavage. Frequently, as expected, such cleavage reactions led to mixtures of products containing the triazacyclohexane and the tetrazacyclooctane ring systems.

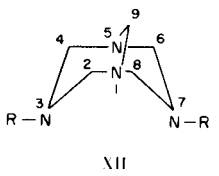
We have recently been concerned with selective cleavages of tetrazabicyclo[3.3.1]nonanes so as to produce

exclusively the tetrazacyclooctane derivatives. This stems from the belief that an easier access to the eight membered ring can be had through selective cleavages of tetrazabicyclo[3.3.1]nonanes rather than by a direct total synthesis. In the present study, we report some of the successes in this objective.

In the tetrazaadamantane system (XI) as well as the tetrazabicyclo[3.3.1]nonane system (XII) there are respectively six and five methylene carbons susceptibel to nucleophilic attack. In order to form an eight-membered ring selectively, attack should be directed exclusively at the carbon marked 9. Nucleophilic attack on carbon is



XI

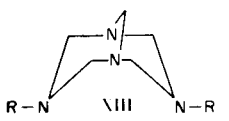


XII

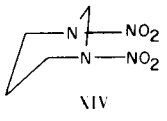
strongly promoted by an adjacent positive site. However, in the tetrazasystems under study, there is little discrimination among the four nitrogen atoms towards protonation under strongly acidic conditions. Any attempt to promote nucleophilic attack on carbon 9 exclusively must be preceded by marked reduction in the basicity of the 3 and 7 nitrogens leaving only the 1 and 5 nitrogens as the strongly basic centers. This could be readily achieved through conversion of the 3 and 7 nitrogens into amide functions. A few diarylsulfonyl derivatives of this kind have already been reported in the literature (13,14). Based on such methods, additional sulfonamide derivatives of the 1,3,5,7-tetrazabicyclo[3.3.1]nonane system were prepared by us (see Table I).

With the masking of the basicity of two of the nitrogens in the molecule, the other two nitrogens were free for electrophilic attack. In the present study, we limited our efforts to the use of species like NO^+ and NO_2^+ as electrophiles and generated these species under the following different conditions: 70% nitric acid and acetic anhydride; 99% nitric acid and concentrated sulfuric acid; liquid dinitrogen tetroxide; red fuming nitric acid; red fuming nitric acid and concentrated sulfuric acid and finally, dinitrogen tetroxide and concentrated sulfuric acid. The results of these reactions, with respect to each reagent, are described in the sequel.

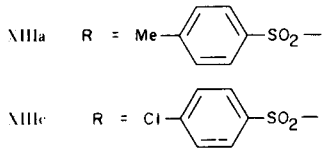
Treatment of compounds XIIIa and XIIIc with 70% nitric acid and acetic anhydride at -10° gave considerable amounts of resinous products. Small amounts of the six-membered ring compounds XIVa and XIVc were also isolated. The major product from the reaction was, however, the open chain derivative shown below:



XIII

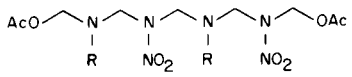


XIV



XIIIa R = Me

XIIIc R = Cl



XV

These nitrations left the aromatic rings unaffected. However, the others described on pages 281, 283, 284 and 285 introduced additional nitro groups on the benzene rings of compounds XVI and XVIII, (see Experimental). These compounds were identified by their elemental analysis, nmr spectra and mass spectra.

Reaction of XIIIa with 99% nitric acid (with or without sulfuric acid) gave no crystalline product characterizable in any manner.

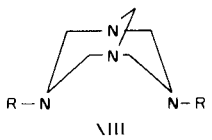
Reaction of the sulfonamido compounds XIIIa-e with liquid dinitrogen tetroxide afforded tetrazocine derivatives XVIa-e in yields ranging from 45% to 89% depending upon the substitution in the aromatic rings. The results are presented in Table I.

In the above reaction, even the crude products revealed no evidence for the formation of derivatives of the triazacyclohexane system. Thus, cleavage by liquid dinitrogen tetroxide provides a very clean and selective method for forming the tetrazocine system XVI from the tetrazabicyclo[3.3.1]nonanes (XIII).

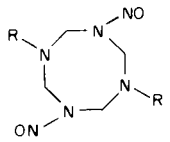
On the contrary, when the same compounds XIIIa-e were allowed to react with a mixture of liquid dinitrogen tetroxide and sulfuric acid, the yield of the tetrazocine derivatives dropped to between 36% and 53% while 11% to 21% yields of the triazacyclohexane derivatives XVII were formed concurrently. Thus addition of sulfuric acid to the medium destroyed any selectivity in the cleavage of the bicyclo[3.3.1]nonane system. Similar behavior was also observed when red fuming nitric acid alone or a mixture of red fuming nitric acid and sulfuric acid were employed as cation donors. These results are summarized in Table II.

TABLE I

Liquid Dinitrogen Tetroxide Cleavage of 1,3,5,7-tetrazabicyclo[3.3.1]nonanes



XIII



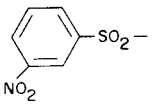
XVI

XIIIa R = Me—SO_2—

XIIIb R = H—SO_2—

XIIIc R = Cl—SO_2—

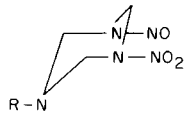
XIIId R = Br—SO_2—

XIIIe R = 

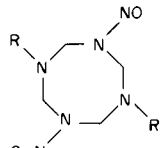
	Yield %
XVIa	54
XVIb	45
XVIc	89
XVId	58
XVIe	56

TABLE II

Formation of Triazacyclohexanes and Tetrazocine Derivatives



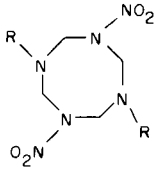
XVII



XVIII

Starting Compound	% Yields of Products: Red Fuming HNO_3 XVII	XVIII	Red Fuming HNO_3 + H_2SO_4 XVII	XVIII	Liquid N_2O_4 + H_2SO_4 XVII	XVIII
XIIIa	1	2	19	30	21	36
XIIIb		5		34		39
XIIIc	10	19	10	15	11	53
XIIId	11	18	17	15	12	38
XIIIe	trace	54	1	36	trace	38

The tetrazocine derivatives XVIIIa-e were easily transformed in excellent yields to the corresponding dinitro compounds XIXa-e by reaction with excess 99% nitric acid.

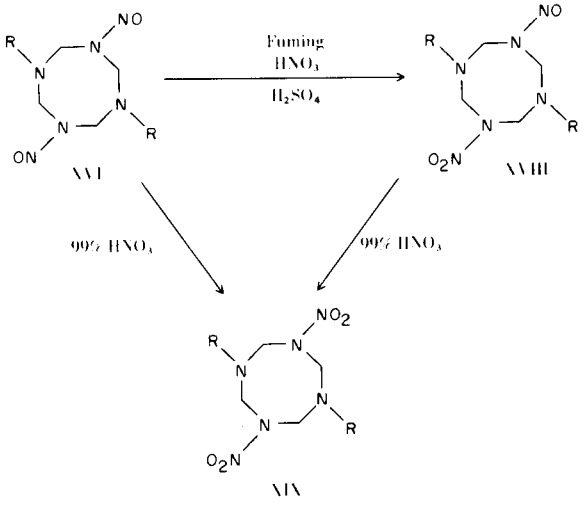


XIX

All the three reactions described above contain liquid dinitrogen tetroxide in some concentration as a reactant. Indeed, red fuming nitric acid is known to contain dissolved dinitrogen tetroxide and consequently affords results similar to the dinitrogen tetroxide-sulfuric acid system (see Table II).

However, when a mixture of 99% nitric acid and concentrated sulfuric acid is employed as reagent, there is no evidence of either the triazacyclohexanes or the tetrazacyclooctanes in the products. Only intractable resins result.

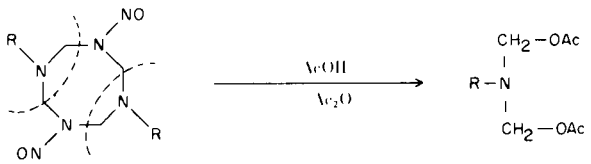
There appears to be a measure of instability associated with the ON-N-CH_2-N-NO function in contrast to those that carry the function O_2N-N-CH_2-N-NO_2. Such an inference is amply borne out by additional experiments we have carried out on the compounds XVI, XVIII, and XIX. In order to provide additional chemical evidence for the three tetrazocine derivatives XVI, XVIII, XIX, we subjected them to the following transformations:



XVI XVIII XIX

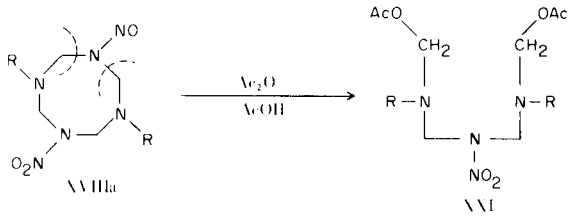
These transformations established the interrelationships among the three groups of products.

More interestingly, upon reaction with a mixture of acetic anhydride and acetic acid, XVIa gave a 65% yield of *N,N*-diacetoxymethyl-*p*-toluenesulfonamide (XX). The better than 50% yields of the product XX indicates the facile cleavage at the positions shown:



XVIa XX

Similar treatment of XVIIIa afforded the product XXI in 59% yield.



XVIIIa XXI

Once again cleavage occurs at carbons adjoining the N-NO function.

Contrary to the above two examples, compound XIX shows no reaction whatsoever with acetic anhydride-acetic acid mixture, thus confirming the great stability of the O_2N-N-CH_2-N-NO_2 function. It is thus clear that a methylene adjoining an *N*-nitroso group suffers nucleophilic attack by the acetate anion, while a methylene *alpha* to an *N*-nitro group is unaffected. This may also arise from the degree to which either function is capable of acting as a Lewis base. The stronger base is protonated to the ammonium cation thus favoring an easy nucleophilic attack at the *alpha* carbon.

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.

Synthesis of 3,7-Diarylsulfonyl-1,3,5,7-tetrazabicyclo[3.3.1]nonanes (XIII).

The following example is illustrative of the general preparative procedure adopted. To a solution of 20.7 g. of hexamine in 67.5 ml. of water was added with vigorous stirring 85.5 g. of *p*-toluenesulfonyl chloride and 10% sodium hydroxide solution simultaneously such that the *p*H of the solution was kept at 8-9 and the temperature between 70-75°. At the end of the addition, the reaction mixture was poured into 750 ml. of water containing 75 g. of sodium hydroxide and the mixture was stirred for an additional hour. The solid which formed was filtered, washed with water, and then with acetone to remove unreacted toluenesulfonyl chloride. The residual solid was recrystallized from hot DMSO to give 30.0 g. of white crystalline material melting at 237-239° (XIIIa), yield 46%, reported m.p. 236°. The properties of compounds XIIIb-e are listed in Table III.

Reaction of XIIIa and XIIIc with Nitric Acid in Acetic Anhydride.

To a suspension of 3.3 g. of XIIIa in 37.5 ml. of acetic anhydride was added dropwise 2.4 ml. of 70% nitric acid during a period of 5 minutes while keeping the temperature between -8° and -9°. After completion of addition, the mixture was stirred for an hour and a half longer. Most of the starting compound had completely gone into solution by this time and the mixture was poured into ice water and neutralized with potassium carbonate. A resinous mass separated. This was extracted with chloroform. Unreacted XIIIa remained insoluble in chloroform and amounted to 0.8 g. The 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 eluting with acetone as solvent. Fine needles of XIVa separated, yield 0.35 g. (18.5%) m.p. 181-183°; M^+ = 331; nmr (δ in DMSO-d_6): 2.43 (3H); 5.47 (4H); 6.05 (2H); 7.4-7.8 (4H).

Anal. Calcd. for $C_{10}H_{13}N_5O_6S$: C, 36.25; H, 3.96; N, 21.14. Found: C, 36.16; H, 3.93; N, 21.04.

Similar treatment of XIIIc gave only a 2.1% yield of XIVc, melting at 211-213°; nmr (δ in acetone-d_6 and DMSO-d_6 2:1 v/v): 5.63 (4H); 6.17 (2H); 7.5-8.2 (4H); M^+ = 351.

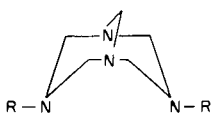
Anal. Calcd. for $C_9H_{10}ClN_5O_6S$: C, 30.74; H, 2.87; N, 19.91. Found: C, 31.50 (15); H, 2.83; N, 19.63.

Reaction of XIIIa and XIIIc in acetic anhydride solution with 99% acid at room temperature was also studied. However, the product was highly resinous and resisted crystallization from any solvents. The nmr spectra corresponded to structures XVa and XVc.

Reaction of the Sulfonamido derivatives XIIIa-e with Dinitrogen Tetroxide.

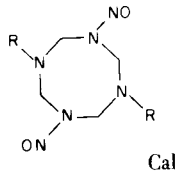
To 5.0 ml. of liquid dinitrogen tetroxide was added 2.0 g. of XIIIa and the suspension stirred efficiently at room temperature for 1.25 hours. At the end of this period, the solution became clear and was poured into ice water. Neutralization with potassium carbonate gave a solid precipitate which was recrystallized from a mixture of nitromethane and ether. Compound XVIa crystallized in the form of needles in 54% yield, m.p. 210-211°; nmr (δ in DMSO-d_6): 2.40 (6H); 4.9-5.2 (4H); 5.8-6.1 (4H); 7.2-7.9 (8H).

TABLE III



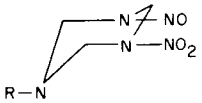
Compound	M.p., °C	Solvent for Recrystallization	% Yield	Molecular Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIIIb	221-224	DMSO	56	$C_{17}H_{20}N_4O_4S_2$	49.99	4.93	13.72	50.28	4.99	13.79
XIIIc	245-249	DMSO	38	$C_{17}H_{18}Cl_2N_4O_4S_2$	42.72	3.80	11.74	42.79	4.03	11.72
XIIId	251	DMSO	8	$C_{17}H_{18}Br_2N_4O_4S_2$	36.06	3.20	9.89	35.78	3.32	9.90
XIIIe	229-230	DMSO	11	$C_{17}H_{18}N_6O_8S_2$	40.96	3.64	16.86	40.42	3.63	17.00

TABLE IV



Compound	M.p., °C	Solvent for Recrystallization	% Yield	Molecular Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (DMSO-d_6): (in δ)
XVIb	149-150 dec.	nitromethane	45	$C_{16}H_{18}N_6O_6S_2$	42.28	3.99	18.48	42.25	3.79	18.40	5.1-5.3 (4H); 6.0-6.2 (4H); 8.5-9.1 (10H)
XVIc	206 dec.	nitromethane	89	$C_{16}H_{16}Cl_2N_6O_6S_2$	36.72	3.08	16.06	36.75	3.27	16.07	5.1-5.2 (4H); 5.9-6.1 (4H); 7.30 (8H)
XVId	203-205	nitromethane	58	$C_{16}H_{16}Br_2N_6O_6S_2$	31.39	2.63	13.73	31.51	2.77	13.52	5.1-5.2 (4H); 5.9-6.1 (4H); 7.7-7.9 (8H)
XVIe	182-183	nitromethane	56	$C_{16}H_{16}N_8O_{10}S_2$	35.50	2.96	20.58	35.25	2.93	20.59	5.2-5.3 (4H); 6.1-6.2 (4H); 7.7-8.5 (8H)

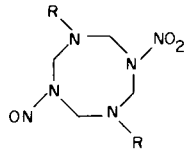
TABLE V



Compound	M.p., °C	Solvent for Recrystallization	M^+	Molecular Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (acetone-d_6): (in δ)
XVIIa (a)	157-159	Acetone	360	$C_{10}H_{12}N_6O_7S$	33.34	3.36	23.33	33.53	3.57	23.19	2.69 (3H); 5.45-6.45 (6H); 7.6-8.5 (6H)
XVIIb (b)											
XVIIc	151-153	Acetone	335	$C_9H_{10}ClN_5O_5S$	32.20	3.00	20.86	31.99	3.05	20.77	5.38-6.43 (6H); 7.5-8.0 (4H)
XVIId	166-168	Acetone	380	$C_9H_{10}BrN_5O_5S$	28.43	2.65	18.42	28.49	2.59	18.51	5.37-6.47 (6H); 7.8-9 (6H)
XVIIe (c)											

(a) Nitration also occurs in the aromatic ring in the *ortho* position relative to the methyl group. (b) Resinous material intractable for characteriztion. (c) XVIIe was obtained in an amount too small to be characterized.

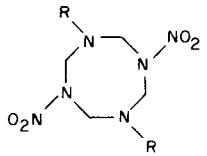
TABLE VI



Compound	M.p., °C	Solvent for Recrystallization	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N	Nmr (DMSO-d_6): (in δ)
XVIIIa (a)	224-225 dec.	nitromethane	$C_{18}H_{20}N_8O_{11}S_2$	36.73	3.43	19.04	36.92	3.48	18.96	2.61 (6H); 5.20, 5.54, 5.68, 6.06 (8H); 7.6-8.5 (6H)
XVIIIb	196 dec.	nitromethane	$C_{16}H_{18}N_6O_7S_2$	40.85	3.86	17.86	40.71	3.85	17.81	5.11, 5.41, 5.63, 5.98 (8H); 7.5-7.9 (10H)
XVIIIc	212 dec.	nitromethane	$C_{16}H_{16}Cl_2N_6O_7S_2$	35.63	2.99	15.58	35.30	2.94	15.74	5.17, 5.49, 5.66, 6.04 (8H); 7.5-8.0 (8H)
XVIIId	198 dec.	nitromethane	$C_{16}H_{16}Br_2N_6O_7S_2$	30.59	2.57	13.38	30.25	2.49	13.32	5.14, 5.44, 5.63, 6.00 (8H); 7.93 (8H)
XVIIIe	218-220 dec.	nitromethane	$C_{16}H_{16}N_8O_{11}S_2$	34.29	2.88	19.99	34.29	2.93	20.08	

(a) Nitration also occurs in the aromatic ring in the *ortho* position relative to the methyl group.

TABLE VII



Compound	M.p., °C	Solvent for Recrystallization	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N	Nmr (DMSO-d_6): (in δ)
XIXa	241 dec.	nitromethane	$C_{18}H_{20}N_8O_{12}S_2$	35.76	3.32	18.53	35.79	3.21	18.61	2.59 (6H); 5.55 (8H); 7.6-8.5 (6H)
XIXb (a)	244-245 dec.	nitromethane	$C_{16}H_{16}N_8O_{12}S_2$	33.34	2.80	19.44	33.38	2.89	19.30	showed the same pattern as XIXe (see below)
XIXe	247-248 dec.	nitromethane	$C_{16}H_{16}N_8O_{12}S_2$	33.34	2.80	19.44	33.55	2.97	19.33	5.63 (8H); 7.9-8.8 (8H)

(a) Nitration also occurs in the aromatic ring in the *meta* position relative to $-SO_2-$ group.

Anal. Calcd. for $C_{18}H_{22}N_6O_6S_2$: C, 44.80; H, 4.60; N, 17.42. Found: C, 44.57; H, 4.83; N, 17.61.

Other dinitroso tetrazocine derivatives prepared similarly are presented in Table IV.

Reaction of XIIIa-e with Fuming Nitric Acid, Fuming Nitric Acid in Sulfuric Acid and Dinitrogen Tetroxide in Sulfuric Acid.

Reaction with the three different sets of reagents was essentially the same and a common procedure is outlined below.

To a mixture of 50 ml. fuming nitric acid and 25 ml. concentrated sulfuric acid was added in portions, 5.0 g. of XIIIa during 5 minutes while maintaining the temperature around -10°. The compound reacted readily yielding a clear solution which was poured into ice water, and neutralized with potassium carbonate to give a faint yellow precipitate. The dried solid was separated into acetone soluble and insoluble parts. The acetone soluble material was chromatographed over basic alumina using acetone as eluent when 0.8 g. of XVIIa and 0.4 g. of XVIIIa were isolated. The acetone insoluble part, upon recrystallization from nitromethane, afforded an additional 1.6 g. of XVIIIa. All the compounds of the type XVII and XVIII are presented in Tables V and VI respectively.

Reaction of XVIa, b, e, XVIIIa, b, and e with 99% Nitric Acid.

Treatment of 0.33 g. of XVIIIa with 5 ml. of ice cold 99% nitric acid during 10 minutes gave after the usual work-up a 99% yield of the dinitro-derivative XIXa.

All the other compounds were also converted similarly into the corresponding dinitro compounds in excellent yields. Their physical and analytical data are given in Table VII (16).

Reaction of XVIa, XVIIIa, and XIXa with Acetic Anhydride-Acetic Acid Mixture.

A mixture of 0.90 g. of XVIa, 6 ml. acetic acid and 6 ml. acetic anhydride was refluxed for 10 minutes. The clear solution obtained was poured into ice water and neutralized with potassium carbonate to give a semisolid mass. Recrystallization of the solid from cyclohexane gave 0.76 g. of needles corresponding to XX in 65% yields, m.p. 86-87°; nmr (δ, acetone-d_6) 1.83 (6H); 2.4 (3H); 5.51 (4H); 7.3-8.0 (4H).

Anal. Calcd. for $C_{13}H_{17}NO_6S$: C, 49.52; H, 5.43; N, 4.43. Found: C, 49.67; H, 5.29; N, 4.41.

Compound XVIIIa on similar reaction gave XXI in 59% yield, m.p. 151° (from acetone-petroleum ether); nmr (δ in deuteriochloroform) 1.91 (6H); 2.72 (6H); 5.55, 5.63 (8H); 7.3-8.7 (6H).

Anal. Calcd. for $C_{22}H_{26}N_6O_{14}S_2$: C, 39.88; H, 3.96; N, 12.68. Found: C, 39.97; H, 3.91; N, 12.51.

Conversion of XVIa to XVIIIa.

To a mixture of 10 ml. of fuming nitric acid and 10 ml. of sulfuric acid was added in portions 0.47 g. of XVIa during 1 minute while keeping the temperature between 15° and 20°. The solution was then poured into ice water neutralized with potassium carbonate when 0.40 g. of solid was precipitated. The solid material was chromatographed over basic alumina using acetone as eluent to give 0.32 g. of XVIIIa melting at 220-223°.

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(16) Reaction of the *p*-methylbenzenesulfonamido compound XIIIa with fuming nitric acid-sulfuric acid mixture introduces new nitro group *ortho* to the methyl function. The unsubstituted benzenesulfonamido compound (XIIIb) is not nitrated in the benzene ring under these conditions. However, upon conversion to XVIIIb with fuming nitric acid-sulfuric acid, followed by further treatment with 99% nitric acid, a nitro group is introduced *meta* to the sulfonamido function, giving XIXb as product. This is easily verified by the identity of this product with the compound XIXe obtained directly from the *m*-nitrobenzene-sulfonamido derivative XVIIIe.