Reaction of 1-(Butylimino)-4-(dichloromethyl)-4-methyl-2,5-cyclohexadiene (IIIc) with Dibutylamine.—Dibutylamine hydrochloride is quantitatively insoluble in thea mine at room temperature; *i.e.*, a saturated solution does not give a test for chloride ion with silver nitrate. The reaction of dibutylamine with IIIc was followed by measuring the weight of the amine hydrochloride formed at intervals and by observation of the C=N band of the imine at 5.99 μ. A solution of 1.0 g (0.0046 mole) of IIIc in 10 ml of dibutylamine was thus found to contain 0.14 g (9.2% of theory) of dibutylamine hydrochloride after 1 hr at 150°. After another 5 hr at 150–155° an additional 0.28 g (18% of theory) of the amine hydrochloride had formed. During the heating period the solution became very dark and tarry, and the intensity of the C=N absorption band at 5.99 μ was noticeably diminished. A small quantity of butylamine which appeared was allowed to distil from the reaction flask as it formed.

After a total of 6 hr reaction time at 150–155°, the excess dibutylamine was evaporated under a current of nitrogen and the residue was dissolved in ether. Extraction of the ether solution with 10% HCl and salting the aqueous extract gave a small yield of N-butyl-*p*-toluidine hydrochloride, identified by comparing its infrared spectrum with that of an authentic sample.[20] No other identifiable products could be separated from the reaction mixture.

N-Butyl-*p*-formotoluidide.—A mixture of 13.5 g (0.10 mole) of *p*-formotoluidide[7] and 15.1 g (0.11 mole) of butyl bromide was warmed to 40° and a solution of 6.6 g of 85% potassium hydroxide (0.10 mole) in 30 ml of absolute ethanol was added with stirring over a period of 10 min. The mixture was then heated to reflux until it was no longer basic (90 min). Water was added to dissolve precipitated potassium bromide, the mixture was extracted with ether, and the ether solution was dried over potassium carbonate. Distillation of the ether and fractionation of the residue through a small Vigreux column gave 9.8 g (51% of theory) of N-butyl-*p*-formotoluidide, bp 80–86° (0.05 mm). The analytical sample distilled at 86° (0.05 mm): $n^{20}D$ 1.5298; $\lambda_{max}^{CHCl_3}$ 5.99 (C=O), 6.19 and 6.59 (aryl C=C), 7.32, and 12.13 μ (*p*-C_6H_4).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.23; H, 8.68; N, 7.29.

N-Butyl-N-(dichloromethyl)-*p*-toluidine (IVc) and Reaction with Dibutylamine.—A solution of 1.00 g (0.00524 mole) of N-butyl-*p*-formotoluidide in 25 ml of anhydrous ether was chilled in an ice bath and phosgene was bubbled in (45 min) until a large excess was present. The solution was stirred at ice-bath temperature for 2 hr then allowed to stand overnight at room temperature. Removal of the excess phosgene and ether under water pump vacuum left a yellowish oil which showed, in chloroform solution, a strong absorption band at 6.01 μ.[3] Addition of 15 ml of dibutylamine to the crude dichloromethylamine resulted in an immediate exothermic reaction. The mixture was stirred for 0.5 hr and filtered, and the precipitate was washed with ether and dried to constant weight to give 1.44 g (83% of theory) of dibutylamine hydrochloride. The organic reaction product was not isolated.

Methylation Studies on Arylidene-5-tetrazolylhydrazones[1a,b]

R. N. BUTLER[1c] AND F. L. SCOTT

Department of Chemistry, University College, Cork, Ireland

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Methylation of arylidene-5-tetrazolylhydrazones in basic medium occurs predominantly at the 1 position with much less, if any, occurring at the 2 and 6 positions. Dimethylation, *in situ* or independently, occurs at the 1 and 6 positions.

In a study of the alkylation of 5-aminotetrazole in a basic aqueous medium Henry and Finnegan[2] found the products to be a mixture of mono- and dialkylated isomers. Monoalkylation occurred at the 1 and 2 positions with the 1 isomer generally predominating. The dialkylated compounds isolated were the 1,3 and 1,4 isomers, and in less than 1% the 1- and 2-methyl-5-methylaminotetrazoles. Our work led to an investigation of the compounds formed when arylidene-5-tetrazolylhydrazones are treated with methylating agents under various conditions in basic aqueous and 50% aqueous ethanolic media. Table IV (Experimental Section) summarizes the results of this reaction with benzylidene-5-tetrazolylhydrazone (**1a**[3a]) as substrate and dimethyl sulfate and methyl iodide as methylating agents. The main products isolated were the 1-monomethylated isomer (**2a**) and the 1,6-dimethylated[3b] isomer (**3a**) along with a small quantity of the 6-methylated compound (**4a**).

Assuming adequate methylating agent, dimethylation depends on the quantity of sodium hydroxide present. With a large excess of base, the ratio of dimethylated to monomethylated materials produced is approximately 2:1. With 1 equiv of base this ratio becomes *ca.* 1:7. The extent to which mono- or dimethylation occurs depends on both the nucleophilicity and concentration of the anions of the unmethylated (**1**) and monomethylated (**2**)[4a] hydrazones. The population of the latter anion is low in the initial stages of the reaction. The effect of the methyl group on the system is to increase the nucleophilicity of this anion and to reduce its concentration by decreasing the acidity[4b] of the hydrazone (**2**) from which it is derived. These factors can offset one another and the results obtained (Table I) indicate that the anion of the monomethylated hydrazone (**2**) becomes a serious competitor for methylating agent during the course of the reaction. The dimethylated materials (**3**) which were isolated from the methylation reactions of the arylidene-5-

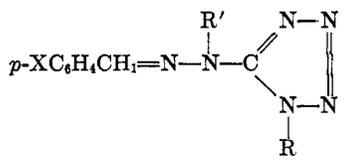
(1) (a) Dedicated to the memory of the late Professor E. Lieber, Fulbright Professor at Cork, 1964–1965. (b) Part of this work has appeared previously in communication form; see F. L. Scott, R. N. Butler, and D. C. Cronin, *Angew. Chem. Intern. Ed. Engl.*, **4**, 950 (1965). (c) This author is grateful for a State Maintenance Grant for Research.

(2) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 923 (1954). See also, K. R. Wilson, R. M. Herbst, and W. J. Haak, *J. Org. Chem.*, **24**, 1046 (1959); D. F. Percival and R. M. Herbst, *ibid.*, **22**, 925 (1957).

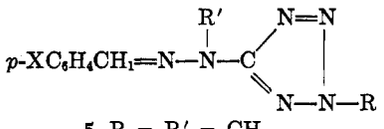
(3) (a) The letters a, b, c, d, and e are used to modify symbols throughout. These letters carry the following implications: where a is used X = H, for b, X = Cl, for c, X = Br, for d, X = CH_3, for e, X = $(CH_3)_2CH$. (b) For convenience throughout this paper we shall number substituents on the nitrogen atom of the exocyclic 5-amino (and 5-hydrazino) group as 6 substituents, *i.e.*, R′ in the formula as drawn.

(4) (a) While aromatic hydrazones are weakly acidic [L. E. Scoggins and C. K. Hancock, *J. Org. Chem.*, **26**, 3490 (1961)] with pK_a values of about 12 [N. V. Chugreeva, *Zh. Anal. Khim.*, **15**, 391 (1960)] they are much less so than aminotetrazoles (see part b). The acidity of arylidene-1-methyl-5-tetrazolylhydrazones is thus principally due to the stability conferred on the anion of these materials by delocalization of the ionic charge to the tetrazole nucleus. Disruption of the aromaticity in this monosubstituted tetrazole nucleus, a consequence of further alkylation at the 2 or 4 position, confers a predominance of reactivity at the 6 position of these ambident anions. (b) M. Charton, *J. Org. Chem.*, **30**, 3346 (1965); J. M. McManus and R. M. Herbst, *ibid.*, **24**, 1643 (1959); R. M. Herbst and W. L. Garbrecht, *ibid.*, **18**, 1286 (1953); E. Lieber, S. H. Patinkin and H. H. Tao, *J. Am. Chem. Soc.*, **73**, 1792 (1951).

tetrazolylhydrazones (1) were also obtained in high yield (75–90%) when the monomethylated hydrazones (2) were methylated separately.



1, R = R′ = H
2, R = CH_3; R′ = H
3, R = R′ = CH_3
4, R = H; R′ = CH_3



5, R = R′ = CH_3
6, R = CH_3; R′ = H

Table I summarizes the results obtained for the methylation reactions of a series of *para*-substituted tetrazolylhydrazones with methyl iodide. In each case the 1-substituted compound (2) is the major product along with lesser yields of the 1,6 derivative (3). A second monomethylated isomer was also obtained in low yield in the methylation of the compounds **1a**, **1c**, and **1d**. The 1,6 isomer (**3a**) was obtained by the further methylation of the second isomer obtained from compound **1a**; thus this material is the 6 isomer (**4a**), but, in the case of the compounds **1c** and **1d**, the second isomer on further methylation yielded a dimethylated product different from 1,6-substituted material.

TABLE I
METHYLATION OF ARYLIDENE-5-TETRAZOLYLHYDRAZONES[a]

		Products					
		2		3		4 or 6	
Substrate	Reflux period, min	Yield, %	Mp, °C	Yield, %	Mp, °C	Yield, %	Mp, °C
1a	45	54	209	12[b]	121–123	3	172
1b	20	42	219–221	18[c]	184–186	...	...
1c	15	60	249–250	...[d]	196–197	7	209
1d	30	75	230–232	<1[e]	134–136	4	164–165
1e	40	66	197	3	97	...	...

[a] In all of these reactions the ratio of base/methyl iodide/substrate used was 1:1.2:1. The solvent was 50% aqueous alcohol and the reactions were carried out at reflux temperature. [b] The quantity of compound **1a** recovered was 10%. [c] The quantity of **1b** recovered was 16.6%. [d] The quantity of **1c** recovered was 18%. [e] The quantity of **1d** recovered was 1.4%.

The orientation of the 1-monomethylated isomers (2) was effected by the synthesis of these materials in an unambiguous manner. This involved allowing the appropriate arylidene-4-methylthiosemicarbazone to react with litharge (PbO) and sodium azide in refluxing ethanol under nitrogen. The anion (7) formed as an intermediate, was reported by Stolle[5] to give only 1-arylideneamino-5-aminotetrazoles (8) (in his cases R was H and C_6H_5). We now report encountering cyclization of both types a and b (with R = CH_3 and X = H and Cl), the main product being again compounds of type **8**. To avoid ambiguity with the numbering system used for the tetrazoles above, closure a will be referred to as occurring toward the α-N atom and closure b toward the β-N atom in system **7**.

(5) R. Stolle and E. Gaertner, *J. Prakt. Chem.*, **132**, 209 (1931).

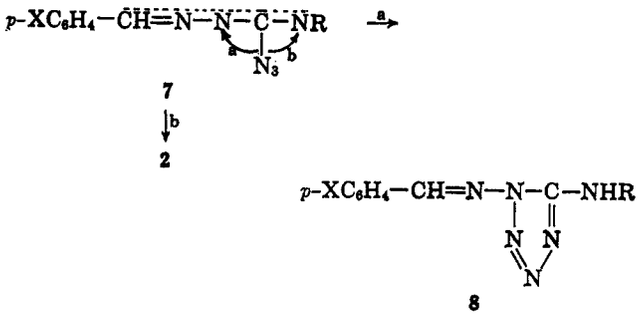


Table II summarizes the data for these reactions. Our results are consistent with the findings of Lieber and co-workers[6] that the closure of azidines[7] occurs to the adjacent nitrogen atom of highest electron density. The increased electron density of the β-N atom of the intermediate **7**, when R = CH_3, is sufficient to induce closure of type b to a small extent. This is further enhanced by the reduction in the electron density at the α-N atom caused by the insertion of an electron-withdrawing substituent on the aromatic nucleus. With an electron-donating substituent in the aromatic ring, closure of type b was not detected. Also of interest in these reactions was the isolation, in one case (X = H), of the imidic ether corresponding to the addition of ethanol to an intermediate carbodiimide, an indication of competition between solvent and azide ion for this intermediate.

TABLE II
REACTION OF ARYLIDENE-4-METHYLTHIOSEMICARBAZONES WITH LITHARGE AND SODIUM AZIDE

	Products			
	2	8		
Aryl group in substrate	Yield, %	Yield, %	Mp, °C
p-ClC_6H_4	1.9	42	197–199
C_6H_5	1.1	40	186–188
p-$CH_3C_6H_4$	0.0 (*i.e.*, <0.1)	35	203–205

The remaining members in the series of 1-N-methylated compounds were prepared unambiguously by coupling the appropriate aldehydes with 1-methyl-5-hydrazinotetrazole, itself prepared by steam distilling benzaldehyde off from compound **2a** in a solution of 8 *N* hydrochloric acid.

The location of one of the methyl groups in the main series of dimethylated compounds is established at the 1-N position by the synthesis of these materials from the monomethylated materials (2). The second methyl group may be located at any of the remaining four nitrogen atoms. For the phenyl compound (X = H) however the 4 position is eliminated by the isolation of the dimethylated hydrazone from the methylations of two different monomethylated materials. The dimethylated compounds encountered throughout this work were all stable crystalline solids under normal conditions displaying none of the properties characteristic of the *meso*-ionic 1,3-dialkylated tetrazoles,[8] thus ruling these out. That the second methyl group

(6) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(7) The use of the word azidine for an iminoazide was suggested by F. L. Scott, A. Kocsarski, and J. Reilly, *Nature*, **170**, 922 (1952).

(8) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

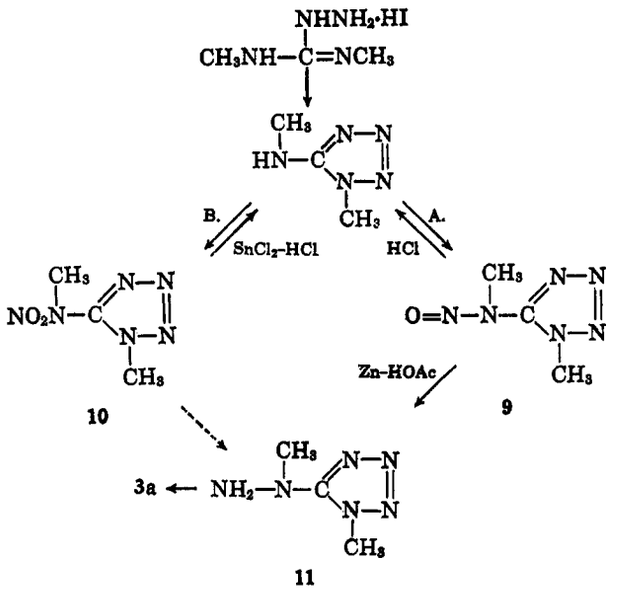


Figure 1.

is located at the 6 position was established by unambiguous synthesis of the 1,6-dimethylated hydrazones (**3**). This proved difficult but was finally achieved by method A in Figure 1. 1-Methyl-5-methylnitrosaminotetrazole (**9**), which was formed by cyclization of 1,2-dimethyl-3-azidoguanidine to 1-methyl-5-methylaminotetrazole[6] with subsequent nitrosation of this entity *in situ*, was reduced with zinc and acetic acid[9] to the hydrazine (**11**), this being isolated as its benzaldehyde derivative (**3a**).

The remaining members in the series of 1,6-dimethylated compounds were subsequently prepared by coupling the appropriate aldehydes with the hydrazine (**11**), itself prepared by the hydrolysis of compound **3a** in acidic solution.

The nitrosamine (**9**) proved inert to lithium aluminium hydride under the normal conditions[10] used for the reduction of such materials with this reagent. N–N bond rupture and loss of the nitroso group resulted from the reaction of concentrated hydrochloric acid with compound **9**. Synthesis of compound **3a** was also attempted by method B (Figure 1) in which 1-methyl-5-methylaminotetrazole was converted to nitramine **10**, using the method that Garrison and Herbest[11] used in the nitration of 1-methyl-5-aminotetrazole (and which we confirmed). When compound **10** was stirred with stannous chloride in hydrochloric acid solution at 25° N–N bond rupture occurred with the formation of 1-methyl-5-methylaminotetrazole. This result, coupled with the observation of Garrison and Herbst[11a] that a similar loss of the nitro group occurred on the reaction of 1-methyl-5-nitraminotetrazole with hydrogen on a palladium oxide catalyst, appears to indicate considerable ease of N–N bond rupture in nitraminotetrazoles.

The nmr spectra[12] of some of these compounds were investigated (Table III). Of interest are the different

TABLE III

NMR DATA ON METHYLATED TETRAZOLYLHYDRAZONES

Compound	Chemical shift, τ: 1-N-CH3	6-N-CH3	H1	Δτ for H1
2a[a]	5.75	...	1.86	...
3a	5.75	6.30	2.32	0.46
2b[b]	5.76	...	1.91	...
3b	5.77	6.32	2.36	0.45
2d[c]	5.70	...	1.92	...
3d[c,e]	5.78	6.33	2.36	0.44
2e[d]	5.72	...	1.86	...
3e[d,e]	5.76	6.32	2.35	0.49
3c[e]	5.74	6.28	...	...

[a] In the spectrum of this compound the N–H proton appeared as a weak band at τ − 1.61. [b] N–H appeared at τ − 1.39. [c] The *p*-CH_3 protons appeared at τ 7.62. [d] The methyl protons of the *p*-isopropyl group appeared as a doublet at τ 8.71 (J = 6–7 cps). The C–H proton of this group appeared as a quadruplet, midpoint τ 7.04 (J = 7 cps). [e] The spectra of these materials were measured on a Varian A-60 instrument.

chemical shifts of both N-methyl groups, the shift of the arylidene proton (H_1) to higher fields caused by the insertion of the second methyl group, and the relatively low chemical shift of the N–H proton. Very recently Markgraf, Bachmann, and Hollis[13a] have reported τ 5.70 for the N-methyl protons at the 2-tetrazole position in 2,5-dimethyltetrazole, a value which is considerably lower than τ 6.31 ± 0.01 for the 6-methyl group in the dimethylated tetrazolylhydrazones but very similar to τ 5.75 ± 0.02 which we have observed for the methyl group at the 1-tetrazole position. Thus, while the nmr signal may be used to differentiate between methyl groups in a tetrazole nucleus and another part of a molecule, it does not afford a method for the exact location of the methyl group within the tetrazole nucleus.[13b] Low N–H chemical shifts which were encountered in the work of Markgraf and his associates were found to be due to dimerization of the methyltetrazoles through hydrogen bonds.

The ultraviolet absorption of these compounds was also investigated. The three series of compounds **1**, **2**, and **3** display almost identical ultraviolet spectra containing an absorption band in the region 221–226 mμ (log ε 4.08–4.18) and another band between 297–310 mμ (log ε 4.30–4.42). The former band is attributed to the aminotetrazole absorption and its location is consistent with the results of previous studies[14] on the ultraviolet absorption of aminotetrazoles. Insertion of successive methyl groups into the tetrazolylhydrazones does not produce the bathochromic shift in this band which was observed in the case of the aminotetrazoles,[13] but a slight bathochromic shift (4–7 mμ) is produced in the band at *ca.* 300 mμ on insertion of the second methyl group. 1-Methyl-5-hydrazinotetrazole hydrochloride shows a single absorption at 231 mμ (log ε 3.42) in its ultraviolet spectrum. 1-Methyl-6-methylhydrazinotetrazole hydrochloride which was isolated from the hydrolysis of compound **3a** shows a single absorption

(9) R. Stolle, *J. Prakt. Chem.*, **134**, 282 (1932).

(10) (a) F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **73**, 4996 (1951); F. W. Schueler and C. Hanna, *ibid.*, **74**, 3693 (1952); (b) R. A. La Forge, C. E. Cosgrave, and A. D'Adamo, *J. Org. Chem.*, **21**, 988 (1956).

(11) (a) J. A. Garrison and R. M. Herbst, *ibid.*, **22**, 278 (1957); (b) for an alternative synthesis of nitraminotetrazoles, see F. L. Scott, F. C. Britten, and J. Reilly, *ibid.*, **21**, 1519 (1956).

(12) For sources of assignments in the nmr data, see J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall Co., Inc., Englewood Cliffs, N. J., 1965; L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectoscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959.

(13) (a) J. H. Markgraf, W. T. Backmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965); (b) see also D. W. Moore and A. G. Whittaker, *J. Am. Chem. Soc.*, **82**, 5007 (1960).

(14) E. Lieber, C. R. Rao, and C. N. Pillai, *Current Sci.* (India), **26**, 167 (1957).

band at 230 mμ which compares with the λ_{max} of 232 mμ reported[8] for 1-methyl-5-methylaminotetrazole. The ultraviolet data are significant in eliminating the *meso*-ionic, 1,3-dialkylated isomers as possible structures for the main series of dimethylated compounds since neither these hydrazones nor the hydrazine from which they are derived display the absorption at 254–258 mμ, which is characteristic of these materials.[8]

As previously stated a second monomethylated material was isolated in low yield from the methylation of the compounds **1c** and **1d** (Table I). The location of the methyl group in these materials cannot be definitely made at this time although the 2-N position (as in compound **6**) is considered to be the most likely.[14a] When these materials are subjected to further methylation, dimethylated compounds which are different from the 1,6 isomers discussed above are obtained. On the basis of arguments similar to those previously outlined, and since to date neither the isolation nor the unequivocal preparation of a 1,2-disubstituted 5-aminotetrazole has been accomplished,[8] these materials are assigned the 2,6-dimethylated structure **5**. Were the monomethylated materials the 6 isomers the dimethylated compounds (**3**) would be the expected products from further methylation.

In summary, methylation of arylidene-5-tetrazolylhydrazones in basic medium occurs predominantly at the 1 position with much less, if any, occurring at the 2 and 6 positions. Dimethylation, *in situ* or independently, occurs at the 1 and 6 positions.

Experimental Section

Melting points are corrected and were measured on a electrothermal apparatus. Microanalytical determinations were carried out by Pascher Microanalytical Laboratories, Bonn, Germany. Ultraviolet spectra were measured on a Perkin-Elmer Model 137 ultraviolet spectrophotometer with 95% alcohol as solvent. Nmr spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as internal reference and deuteriochloroform as solvent except where otherwise stated.

A. Tetrazolylhydrazones and Thiosemicarbazones.—*para*-Substituted arylidene-5-tetrazolylhydrazones were prepared as described in the literature.[15] The melting points were in excellent agreement with those reported. Benzylidene-4-methylthiosemicarbazone was also prepared as described,[16] mp 158° (lit.[16] mp 160°). The *p*-chloro compound, mp 207–209°, and the *p*-tolyl compound, mp 196–198°, were prepared similarly.

Anal. Calcd for $C_9H_{10}ClN_3S$: C, 47.47; H, 4.39; Cl, 15.62; N, 18.46; S, 14.04. Found: C, 47.26; H, 4.21; Cl, 16.26; N, 18.34; S, 14.04.

Anal. Calcd for $C_{10}H_{13}N_3S$: C, 57.97; H, 6.28; N, 20.29; S, 15.41. Found: C, 58.42; H, 6.07; N, 20.29; S, 15.27.

B. Methylation of Benzylidene-5-tetrazolylhydrazone. i.—To a solution of the hydrazone (6 g) in 11.6 ml of 10% sodium hydroxide solution was added 25 ml of absolute alcohol, 13.4 ml of water (to make the whole 50% aqueous ethanol), and then 2.5 ml of methyl iodide (in 10 ml of acetone). The solution was refluxed gently for 45 min. At the end of this period a white solid had separated. The mixture was stirred and cooled in an ice bath for 30 min. The solid was filtered off (filtrate A) and washed thoroughly with water. When dry it weighed 3.87 g, mp 185–195°. Recrystallization from chloroform gave white crystals of compound **2a**, mp 209°, 3.3 g, 54%.

Anal. Calcd for $C_9H_{10}N_6$: C, 53.46: H, 4.95; N, 41.58. Found: C, 53.31; H, 5.03; N, 41.19.

The chloroform filtrate was evaporated to one-third of its volume. Addition of petroleum ether (bp 40–60°) brought down a white solid, 200 mg, mp 160–174°. Two recrystallizations of this material from aqueous alcohol gave compound **4a**, mp 172°, 190 mg, 3%.

Anal. Calcd for $C_9H_{10}N_6$ as above. Found: C, 53.46; H, 4.86; N, 41.48.

On addition of water to the hot filtrate (A), followed by cooling in ice, a white solid separated (750 mg), mp 112°, which when recrystallized from aqueous alcohol gave white needles of compound **3a**, mp 121–123°, 700 mg, 10%.

Anal. Calcd for $C_{10}H_{12}N_6$: C, 55.65; H, 5.53; N, 38.79. Found: C, 55.29; H, 5.61; N, 38.69.

Further work-up of the reaction solution gave 600 mg of starting material. The above was the general procedure followed in the reactions outlined in Table I.

ii.—To a solution of hydrazone (8 g) in 50 ml of 10% sodium hydroxide solution, dimethyl sulfate (4 ml) was added dropwise with stirring over a period of 1.5 hr. At the end of this time a solid had separated; so the mixture was cooled in ice for 30 min. The insoluble material (2.7 g), mp 95–120°, was filtered off (filtrate B) and washed thoroughly with water. Two recrystallizations from chloroform–pentane gave pure compound **3a**, mp 121–123°, 1.35 g, 15%. The yellow filtrate (B) was cooled by addition of crushed ice and then acidified by dropwise addition, with stirring, of a few milliliters of glacial acetic acid. The white solid (6 g), mp 185–200°, which separated was collected and washed thoroughly with distilled water. This material was extracted with boiling chloroform (four 50-ml portions). The insoluble portion, (2.1 g), mp 232°, was identified as unreacted starting material by a mixture melting point.

The combined chloroform extracts on evaporation to 50 ml and cooling in ice yielded a crop of white crystals, 1.1 g, mp 207–209° (a). Further evaporation yielded a second crop, 960 mg, mp 170–200° (filtrate C). Upon leaching this crop with boiling ether the insoluble portion weighed 400 mg, mp 204–206° (b). Crops a and b when combined and recrystallized from chloroform proved to be compound **2a**, mp 209°. Addition of petroleum ether (bp 40–60°) to the original chloroform mother liquor (filtrate C) yielded 600 mg of an off-white solid, mp 160–170°. Recrystallization from benzene–chloroform solution (50%, v/v) and leaching with boiling ether raised the melting point to 165–171°. Further recrystallizations from aqueous alcohol raised the melting point to 172°. This substance was compound **4a**, 280 mg, 3.2%.

The results of a study of these methylations are summarized in Table IV. In general, the methylation reactions were carried out by stirring the reactants at room temperature except where otherwise stated.

TABLE IV

METHYLATION OF BENZYLIDENE-5-TETRAZOLYLHYDRAZONE

1a/NaOH, molar ratio	1a/methylating agent, molar ratio	Stirring time, hr	Products, % 2a	3a	4a	1a[f]
1:3	1:1[b]	1.5	21.6	17.1	3.4	40
1:3	2:1[b]	1.5[d]	11.5	26	3	41[g]
1:50	2:1[b]	12.0	16.0	27	...	40[g]
1:1	2:1[b]	1.0	28	4	3	47
1:1	1:1.2[c]	6.0	15	15	5.4	45
1:1[a]	1:1.2[c]	0.75[e]	54	11	3	10

[a] Solvent was 50% aqueous ethanol for this reaction; for all others the solvent was water. [b] Methylating agent was dimethyl sulfate in these reactions. [c] Methylating agent was methyl iodide. [d] This reaction mixture was heated at 90°. [e] This reaction was conducted under gentle reflux conditions. The reactants were not stirred. [f] Recovered unreacted. [g] See ref 17.

C.—1,6-Dimethyl-5-tetrazolylhydrazones (Compounds 3).—These materials were prepared by refluxing the 1-methylated componds (**2**) in 50% aqueous alcohol containing an excess of sodium hydroxide (10% solution) and methyl iodide. On addition of water and cooling in ice the dimethylated materials separated. The yields were in all cases greater than 75%. In the case of compound **3a**[17] there was evidence of a second material formed in low yield, but numerous attempts to isolate a pure sample of this compound were unsuccessful.

(14a) NOTE ADDED IN PROOF.—We have now confirmed by unambiguous synthesis that these compounds are the 2-substituted materials.

(15) F. L. Scott, W. N. Morrish, and J. Reilly, *J. Org. Chem.*, **22**, 692 (1957).

(16) G. Pulvermarker, *Ber.*, **27**, 613 (1894).

(17) We are indebted to Dr. D. A. Cronin who carried out these reactions with compound **3a**.

The methylation of the second monomethylated isomers from the compounds **1a**, **1c**, and **1d** was carried out in a similar manner. The products (formed in yields greater than 85%) were compounds **3a**, **5c**, and **5d**, respectively, no other materials being encountered.

D.—Unambiguous Synthesis of Arylidene-1-N-methyl-5-tetrazolylhydrazones.—A suspension of benzylidene-4-methylthiosemicarbazone (7.7 g), sodium azide (5.2 g), and litharge (55 g) was refluxed and stirred for 11 hr in 300 ml of absolute alcohol under an atmosphere of nitrogen. The lead sulfide which had formed was filtered off and water was added to the filtrate. The solid (a), mp 170–300° (3.5 g), which separated was collected (filtrate D) and was washed thoroughly with alcohol. This solid was extracted with boiling absolute alcohol (four 50-ml portions). The insoluble portion, inorganic material, was removed (400 mg). The combined alcoholic extracts were evaporated to 50 ml and cooled in ice. A crop of white crystals (2 g) separated, mp 178–182°. Recrystallization from absolute alcohol gave 1-benzylideneamino-5-methylaminotetrazole (**8**, X = H), mp 186–188°. Repeated evaporations of the alcoholic filtrate gave successive crops of this material, 3.2 g, 40%.

Anal. Calcd for $C_9H_{10}N_6$: C, 53.46; H, 4.95; N, 41.58. Found: C, 53.16; H, 5.06; N, 42.00.

The filtrate (D) was concentrated at 80°. Further solid which separated was treated as above to remove inorganic material. The filtrate from this (110 ml) was distributed between ether and water. The layers were separated and the aqueous layer was reextracted with ether (three 100-ml portions). The solutions were then treated as follows.

i.—The aqueous solution was evaporated to 20 ml at 80°, and cooled by addition of crushed ice (*ca.* 5 g). Dilute hydrochloric acid was carefully added until the pH of the solution was 6. The white solid which separated was collected (100 mg), mp 200–310°, and boiled in absolute alcohol (20 ml). The insoluble portion was removed and the alcoholic filtrate was evaporated to 10 ml and cooled in an ice bath. A crop of white crystals (30 mg), mp 209°, separated. A mixture melting point between this material and benzylidene-1-N-methyl-5-tetrazolylhydrazone prepared as described above showed no depression and the infrared spectra of both compounds were identical.

Anal. Found: C, 53.07; H, 5.15.

ii.—The ethereal solution was washed thoroughly with water, dried, and evaporated. The residue was extracted with boiling pentane. The pentane solution was decanted from the insoluble material which was then stirred in 20 ml of cold ether. The insoluble material (90 mg) was collected, mp 140–160°. Three recrystallizations from aqueous alcohol gave 64 mg of compound **2a**, mp 207°, 94 mg, 1.1%.

The combined pentane and ether solutions on evaporation to dryness deposited 1.2 g of a yellow solid, mp 45–70°. This residue was separated into a yellow oil and a white solid material (490 mg, 6%), mp 70–72°, by fractional evaporation from pentane. The white material is the adduct of ethanol and the carbodiimide intermediate.

Anal. Calcd for $C_{11}H_{16}N_8O$: C, 64.40; H, 7.31; N, 20.46; O, 7.80. Found: C, 65.00; H, 7.43; N, 20.08; O, 7.38.

The yellow oil was not investigated further. The analogous reactions for the *p*-chloro- and *p*-tolylidene-4-methylthiosemicarbazones were carried out in a similar fashion.

1-N-Methyl-5-hydrazinotetrazole Hydrochloride.—Compound **2a** (10 g) was heated in 150 ml of 8 *N* hydrochloric acid. Steam was passed through the slurry and the regenerated benzaldehyde distilled over. When the distillate ceased to contain oil the distillation was stopped and the solution was filtered and cooled in ice. Unreacted starting material which separated was removed and the solution was evaporated to 200 ml at 80° (solution A). Four 20-ml portions of this were withdrawn and brought to pH 4 by stirring with sodium hydroxide and then to pH 8 with sodium acetate. Addition of these aliquots, with stirring, to alcoholic solutions of the appropriate aldehydes gave the compounds **2a**, **2c**, **2d**, and **2e**. The remaining solution (a) was evaporated to dryness on a steam bath. The residue was stirred in 5 ml of 95% alcohol, and the insoluble material (2 g), mp 191–194°, was collected. Addition of ether to the filtrate of this compound brought down an additional 1.7 g, mp 191°. Recrystallization from 95% ethanol gave pure 1-N-methyl-5-hydrazinotetrazole hydrochloride, mp 193–195°.

Anal. Calcd for $C_2H_6N_6HCl$: C, 16.00; H, 4.66; Cl, 23.66. Found: C, 16.15; H, 4.73; Cl, 23.49.

This compound was characterized by the formation of its benzaldehyde derivative (**2a**).

The analogous syntheses of the dimethylated compounds (**3**) were carried out in a similar fashion. 1-Methyl-6-methylhydrazinotetrazole hydrochloride was isolated as a colorless, crystalline solid, mp 54–56°.

Anal. Calcd for $C_3H_8N_6 \cdot HCl$: C, 21.90; H, 5.47; Cl, 21.60. Found: C, 21.56; H, 6.15; Cl, 21.00.

It was characterized by the formation of its benzaldehyde derivative (**3a**).

E. Unambiguous Synthesis of Benzylidene-1,6-dimethyl-5-tetrazolylhydrazone (3a). i. 1-Methyl-5-methylnitrosaminotetrazole (9).—To a solution of 4,4′-dimethylaminoguanidine hydriodide[6] (10 g) in water (150 ml) at 50° was added 0.4 ml of concentrated nitric acid, and then dropwise with stirring, silver nitrate (7.2 g) in 200 ml of water. Hydrochloric acid (1 ml) was added to the mixture, after its being stirred for 30 min at ambient temperature, to remove excess silver ion. The silver salts were removed and washed with two 50-ml aliquots of cold water. After another 0.5 ml of hydrochloric acid was added to the combined filtrates which were cooled to 5°, 3.25 g of sodium nitrite in 100 ml of water was introduced. The resulting solution, after its being stirred for 30 min at 5°, was neutralized to pH 8 with solid sodium carbonate (4.9 g), heated at 50° for a few minutes, and stirred at ambient temperature for 2 hr. The solution which was then reacidified with hydrochloric acid was evaporated to 80 ml under reduced pressure. After 4 ml of hydrochloric acid was added, the solution was cooled to 5° and sodium nitrite (3.25 g) in 20 ml of water was introduced. After its being stirred at 5–10° for 30 min, the resulting solution was neutralized to pH 8 with solid sodium carbonate, stirred at ambient temperature for 90 min and 50° for 3 min, acidified with hydrochloric acid, and cooled in ice. A crop (1.0 g) of white flakes separated, mp 46–47° (from absolute alcohol). This material was compound **9**.

Anal. Calcd for $C_3H_6N_6O$: C, 25.36; H, 4.22; N, 59.15; O, 11.26. Found: C, 25.05; H, 4.35; N, 59.33; O, 11.63.

Evaporation of the filtrate under reduced pressure yielded successive crops of this material, 3.06 g, 50%.

ii. Reduction of 1-Methyl-5-methylnitrosaminotetrazole with Zinc and Acetic Acid.—1-Methyl-5-methylnitrosaminotetrazole (1 g) was stirred for 7 hr at 25° with zinc dust (3.8 g) in 50 ml of 10% acetic acid (v/v) solution. At the end of this time a small quantity of inorganic material was removed and the solution was added to 1 ml of benzaldehyde in 95% ethanol (15 ml). The resulting solution was heated to boiling, then it was stirred for 20 min at ambient temperatures and cooled in ice. The white crystals which separated were washed with water and when dry weighed 403 mg, mp 121–123° (from aqueous alcohol). A mixture melting point between this material and compound **3a**, prepared as described above, showed no depression, and the infrared spectra of both compounds were identical.

Anal. Found: C, 55.55; H, 5.21.

A second crop of this material (170 mg) was obtained after the filtrate had stood overnight. Further work-up of the solution yielded another 105 mg of compound **3a** (total yield 678 mg 45%) and some benzoic acid resulting from the excess of benzaldehyde.

Reduction of 1-Methyl-5-methylnitrosaminotetrazole with Lithium Aluminum Hydride.—Compound **9** (1.2 g) dissolved in dry ether (100 ml) was added, dropwise with stirring, to lithium aluminium hydride (0.4 g) in dry ether (100 ml) and the mixture was stirred for 1 hr at ambient temperature. Wet ether (30 ml) followed by a few drops of water was then carefully added. The mixture was stirred for 10 min and 50 ml of 30% sodium hydroxide solution was introduced. After the layers had been separated, the sodium hydroxide solution was washed with ether (two 50-ml portions) and the combined ethereal solution was evaporated at 20° under reduced pressure. The residue, a yellow oil, was dissolved in a solution of 3 ml of hydrochloric acid in 10 ml of water, and on cooling in ice compound **9** (120 mg) separated. The filtrate was evaporated at 50° under reduced pressure and the residue, a white, crystalline solid, was dried *in vacuo* and then washed with ether. It weighed 710 mg, mp 213–215° (decomposition, with previous shrinking at 200°). This material was the hydrochloride of 1-methyl-5-methylaminotetrazole. A mixture melting point between it and a sample of this hydrochloride, prepared by dissolving 1-methyl-5-methylaminotetrazole in a solution of 3 ml of hydrochloric acid in 10 ml of water followed by evaporation of the solution, showed no depression.

TABLE V
ANALYTICAL DATA

Compd	Calcd, % C	H	N	Others	Found, % C	H	N	Others
2b	45.66	3.80	35.51	15.03 (Cl)	45.62	3.88	35.73	15.10 (Cl)
2c	38.43	3.20	29.89	28.48 (Br)	38.54	3.31	29.50	28.45 (Br)
2d	55.65	5.60	38.75	...	55.53	5.48	38.66	...
2e	59.02	6.56	34.43	...	59.62	6.25	34.32	...
3b	47.89	4.38	33.46	14.34 (Cl)	47.46	4.51	33.83	14.22 (Cl)
3c	40.67	3.69	28.47	27.11 (Br)	41.07	3.88	28.34	26.63 (Br)
3d	57.39	6.08	36.52	...	57.56	6.08	36.53	...
3e	60.46	6.97	32.56	...	60.48	7.16	32.60	...
6c	As for **2c**				38.82	3.09	29.54	28.84 (Br)
6d	As for **2d**				55.62	5.56	38.92	...
5c[a]	As for **3c**				41.15	3.64	28.49	26.93 (Br)
5d[b]	As for **3d**				57.30	6.28	36.82	...
8, R = CH_3; X = CH_3	As for **2d**				56.22	5.20	38.58	...
8, R = CH_3; X = Cl	As for **2b**				45.72	3.97	35.62	14.86 (Cl)

[a] Melting point 156–158°. [b] Melting point 115°.

Anal. Calcd for $C_3H_3N_5Cl$: C, 24.08; H, 5.35; Cl, 23.74. Found: C, 23.80; H, 5.17; Cl, 24.23.

When compound **9** was dissolved in a similar acid solution followed by evaporation, the product was again 1-methyl-5-methylaminotetrazole hydrochloride. The total recovery of both this material and **9** in the above experiment corresponds to 67%.

F. Nitraminotetrazoles.—1-Methyl-5-nitraminotetrazole was prepared as described in the literature,[11a] 57%, mp 128° (lit.[11a] 31%, mp 129–130°). 1-Methyl-5-aminotetrazole nitrate had mp 161° (lit.[11a] mp 158–160°).

1-Methyl-5-methylaminotetrazole Nitrate.—1-Methyl-5-methylaminotetrazole[6] (720 mg) was made into a paste with 0.5 ml of concentrated nitric acid. Gentle heating of the paste gave a clear solution which solidified on cooling in ice. Ether (10 ml) was added; the solid (1.06 g, 95%, mp 135–137°) was collected. This material was 1-methyl-5-methylaminotetrazole nitrate.

Anal. Calcd for $C_3H_5N_5O_3$: C, 20.45; H, 4.54; N, 47.72; O, 27.27. Found: C, 20.57; H, 4.56; N, 47.5; O, 27.36.

1-Methyl-5-methylnitraminotetrazole (10).—1-Methyl-5-methylaminotetrazole nitrate (3 g) was stirred with concentrated sulfuric acid (4 ml) for 10 min at 0°. The paste was then heated to 25° and poured onto 30 g of ice. When all the ice had melted, the white, crystalline solid (1.7 g, mp 54–56°) was collected and washed with water (filtrate A.) Recrystallization of this material (compound **10**) from benzene–pentane (bp 40–60°) raised the melting point to 58° (lit.[18] mp 57.5–58.5°).

Anal. Calcd for $C_3H_6N_6O_2$: C, 22.78; H, 3.79; N, 53.06; O, 20.25. Found: C, 23.16; H, 3.99; N, 53.16; O, 20.01.

Filtrate A was extracted with ether (four 80-ml portions). Evaporation of the dried ethereal solution yielded 360 mg of compound **10**, mp 50–52° (total yield 2.06 g, 77%).

(18) W. P. Norris and R. A. Henry, *J. Org. Chem.*, **29**, 650 (1964).

Reduction of 1-Methyl-5-methylnitraminotetrazole with Stannous Chloride.—Stannous chloride dihydrate (1.8 g) in 0.5 ml of hydrochloric acid and 10 ml of water was added to 1-methyl-5-methylnitraminotetrazole (600 mg) suspended in 3 ml of hydrochloric acid and 20 ml of water and the mixture was stirred for 11 hr at 25°. During this period the solution frothed up with gas evolution. Extraction of this solution with ether and subsequent evaporation of the ether gave a small quantity of a gum which on further work-up yielded no crystalline products. The solution was then evaporated to dryness, the white, solid residue dissolved in water (20 ml), and a few milliliters of 10% sodium hydroxide solution was added to break down stannate salts. Ethereal extraction of the basic solution with subsequent evaporation of the dried ethereal solution yielded 1-methyl-5-methylaminotetrazole, 36 mg, mp 172–174° (lit.[6] mp 173°). A mixture melting point between this material and a sample prepared as described in the literature showed no depression, and the infrared graphs of both samples were identical.

Evaporation of the basic solution to about 3 ml under reduced pressure and cooling in ice gave an additional crop (93 mg, mp 172°) of 1-methyl-5-methylaminotetrazole (total yield 129 mg, 30%).

Addition of benzaldehyde at various stages in the above reaction and in the reaction of compound **9** with lithium aluminium hydride failed to detect the presence of hydrazine **11**. The benzaldehyde was removed in ether before continuing the work-up (see Table V for analytical data).

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