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The Reaction Between 5-Dimethylaminotetrazole and Sulfonyl Chlorides

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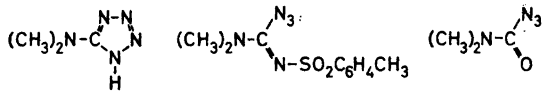
Sulfonyl chlorides react with 5-dimethylaminotetrazole in pyridine solution, and cause ring-opening, evolution of nitrogen and the formation of compounds which are considered to be 1-sulfonyl-4,4-dimethylcarbamohydrazonoylpyridinium chlorides (VII). These react with water, hydrogen sulfide, ammonia, and sodium azide to give 1-sulfonylsemicarbazides, 1-sulfonylthiosemicarbazides, 1-sulfonylaminoguanidines and 1-sulfonamidotetrazoles, respectively. 4,4-Dimethyl-1-*p*-toluenesulfonylsemicarbazide and -thiosemicarbazide and the isomers 1,1-dimethyl-4-*p*-toluenesulfonylsemicarbazide and -thiosemicarbazide were prepared in unambiguous ways for comparison.

At low temperature 5-dimethylaminotetrazole and *p*-toluenesulfonyl chloride react to give 2-*p*-toluenesulfonyl-5-dimethylaminotetrazole, a very unstable compound which splits off nitrogen even at room temperature. The isomer, *N*,*N*-dimethyl-*N'*-*p*-toluenesulfonylcarbamimidoyl azide which was prepared in an unambiguous manner, did not behave like an intermediate of the break down of 5-dimethylaminotetrazole.

During a study of the formation of guanyl azides by the reaction of 5-aminotetrazole with *p*-toluenesulfonyl chloride in pyridine [1] it was found that 1-methyl-5-aminotetrazole and 1-methyl-5-methylaminotetrazole were unaffected by the sulfonyl chloride,* which indicates that the point of attack is the NH group in the tetrazole ring. In accordance herewith 5-dimethylaminotetrazole (I) is attacked by *p*-toluenesulfonyl chloride but the expected sulfonylguanyl azide (II) was not isolated. After addition of water and removal of the pyridine, a solution in which qualitative reactions indicated the presence of a hydrazine, was obtained. It was initially thought that this was 1,1-dimethylhydrazine which had been formed by hydrolysis of the guanyl azide to dimethylcarbamoyl azide (III) and Curtius degradation of the latter.

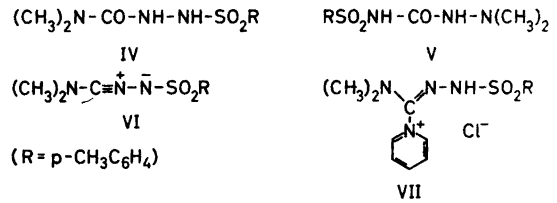
* Recently Shchipanov, Sheinker and Postovskii [2] have found that 1-methyl-5-aminotetrazole forms a toluenesulfonamide on prolonged reaction with *p*-toluenesulfonyl chloride, but no ring-opening takes place as in the case of 5-aminotetrazole.



I II III

However, it was found that authentic dimethylcarbamoyl azide did not form dimethylhydrazine under the conditions of the experiment and a closer examination has shown that the reaction takes place in the following way. Elimination of nitrogen takes place in the pyridine solution and a compound is formed which has the composition of the guanyl azide (II) minus nitrogen but plus pyridinium chloride. Excess pyridinium chloride could be removed by extraction with boiling chloroform, but one mole remained and evidently was an integral part of the compound formed. This compound could be obtained from the pyridine solution in a 85—95 % yield. It adds water, hydrogen sulfide, and ammonia to give a semicarbazide, a thiosemicarbazide, and an aminoguanidine, respectively.

The semicarbazide is identical with the semicarbazide (IV) formed from 4,4-dimethylsemicarbazide and *p*-toluenesulfonyl chloride rather than with its isomer (V) formed from *p*-toluenesulfonyl isocyanate and 1,1-dimethylhydrazine. Accordingly the compound formed from 5-dimethylaminotetrazole and *p*-toluenesulfonyl chloride could be considered as a compound (VII) of a nitrile imine (VI) with pyridinium chloride. An attempt was made to prepare the nitrile imine itself by performing the reaction in nitromethane or other inert solvents, but it was found that the reaction only took place in basic solvents.



IV V

VI

(R = p-$CH_3C_6H_4$)

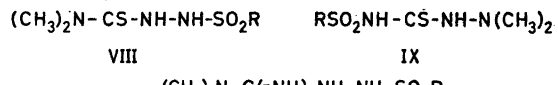
VII

In accordance with the proposed structure the compound VII has a pronounced polar character. It is insoluble in most organic solvents, except alcohols and amines; it may well react with some of these solvents in a similar way as with water or ammonia, but can be recrystallized without change from ethanol.

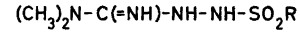
Other sulfonyl chlorides give compounds of the same type and with similar properties. Thus, the compound formed from 5-dimethylaminotetrazole and methanesulfonyl chloride (VIIb) reacted with water to give a semicarbazide (IVb) identical with that prepared from 4,4-dimethylsemicarbazide and methanesulfonyl chloride.

Similarly, the thiosemicarbazide formed from VII and hydrogen sulfide was found to be identical with the thiosemicarbazide formed from 4,4-dimethylthiosemicarbazide and *p*-toluenesulfonyl chloride (VIII) rather than with the thiosemicarbazide formed from *p*-toluenesulfonyl isothiocyanate and 1,1-

dimethylhydrazine (IX). Analogously, the aminoguanidine derivative formed from VII and ammonia must have the structure X.



VIII IX

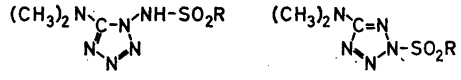


X

The thiosemicarbazide (VIII) undergoes a base catalyzed McFadyen-Stevens reaction (*cf.* Jensen and Holm [3]) in aqueous solution even at room temperature:

The same reaction takes place slowly in an inert solvent. By manometric measurement of the nitrogen evolved the reaction in molten benzophenone as a solvent has been found to follow first order kinetics.

Compound VII was also found to react with other nucleophiles, such as CN^-, SCN^-, and N_3^-. With sodium azide a crystalline compound having the composition of 1-*p*-toluenesulfonamido-5-dimethylaminotetrazole (XI) is formed (its infrared spectrum shows no azide bands, so that ring-closure of the isomeric azide has taken place spontaneously). The nature of the compound(s) formed from VII and potassium thiocyanate is under investigation.

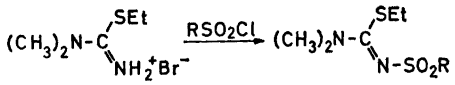


XI XIV

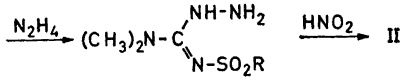
It is remarkable that the compound formed from 5-dimethylaminotetrazole and *p*-toluenesulfonyl chloride should have the constitution VII, since this seems to indicate that 5-dimethylaminotetrazole, in contrast to 5-aminotetrazole, is attacked by the sulfonyl chloride in the 2-position. Similarly, Huisgen *et al.*[4], in their investigations of reactions of 5-alkyltetrazoles or 5-aryltetrazoles with electrophilic agents, have assumed that the latter attack the tetrazole ring in the 2-position. No unambiguous proof of this reaction mechanism has been given, and it seemed quite possible that the reagent actually attacks in the 1-position with ring-opening and formation of an azide, which subsequently splits off a nitrogen molecule and rearranges. For example, compound VI could have been formed from the azide II by such a reaction.

To test this possibility the azide II was prepared from *N*,*N*-dimethyl-*S*-ethylthiouronium bromide by the sequence of reactions shown on p. 2798.

The compound thus prepared had the expected composition and its infrared spectrum showed a strong absorption band at 2160 cm^{-1} in accordance with the azide structure (II). On dissolution in pyridine it did not evolve nitrogen (except on boiling) and was not transformed into compound VII; thus, the possibility that the azide II is an intermediate in the formation of VII may definitely be excluded. Further, when the reaction between 5-dimethylamino-



XII



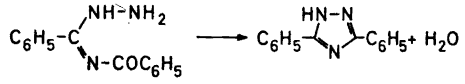
XIII

tetrazole and *p*-toluenesulfonyl was carried out at about 10°C only a little nitrogen was evolved, and a compound could be isolated which had the same composition as the azide (II) but which did not exhibit azide absorption in its infrared spectrum. Nitrogen was evolved readily at room temperature both in the solid state and in solution, and with hot water it was converted into the same semicarbazide (IV) as was compound VII. Accordingly, this compound, which must have the structure of 2-*p*-toluenesulfonyl-5-dimethylaminotetrazole (XIV), is the true intermediate in the formation of compound VII.

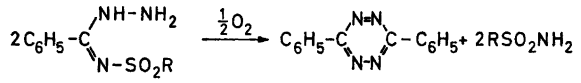
Whereas 5-aminotetrazole and *p*-toluenesulfonylchloride in pyridine react to form *p*-toluenesulfonylguanyl azide when the temperature of the solution does not exceed 70°C, a violent reaction with spontaneous nitrogen and heat evolution, takes place when the temperature is raised above 90°C. The structure of the compound thus formed, as well as the structures of the compounds formed by elimination of nitrogen from the tetrazole XIV and the azide II, respectively, are being investigated.

During this work attempts were made to prepare two other azides, analogous to the azide II, from the corresponding hydrazides XV and XVII, but these hydrazides could not be obtained. A compound supposed to be benzhydrazide benzoylimide (XV), and still listed in Beilstein's Handbuch as such, was prepared by Beckmann [5] from *N*-benzoylbenzimide chloride and hydrazine. Reaction of *N*-benzoyl *S*-ethyl thiobenzimidate and hydrazine would be expected to be equivalent to the method used by Beckmann, but the compound obtained was found to be 3,5-diphenyl-1,2,4-triazole (XVI), a well known compound, which has been prepared by numerous other methods. Perusal of the properties listed for Beckmann's compound leaves no doubt that his compound was, in fact, 3,5-diphenyl-1,2,4-triazole. It crystallizes from aqueous ethanol with one molecule of water, but the infrared spectrum of the hydrate shows no C=O band, so that the hydrate is not the hydrazide XV.

The *p*-toluenesulfonyl derivative of *S*-ethyl thiobenzimidate reacted with hydrazine to give a good yield of 3,6-diphenyltetrazine (XVIII) and here again the intermediate hydrazide could not be isolated.



XV XVI



XVII XVIII

Table 1. Characteristic infrared bands of some of the compounds discussed in the text (Perkin-Elmer model 21 spectrophotometer or model 337 grating spectrophotometer).

Compound No.	Formula	Medium	Absorption bands (cm^{-1})	Assignment
III	$(CH_3)_2N-\underset{\displaystyle N_3}{\overset{\displaystyle |}{C}}=O$	CCl_4, CS_2	2190s, 2140s, 1230vs, 725s, 643s 1690vs	N_3 C=O
	$(CH_3)_2N-\underset{\displaystyle N_3}{\overset{\displaystyle |}{C}}=NH_2^+\ Cl^-$	KBr	2200m, 2160s, 1283s, 730w, 655m 1665vs 1625s	N_3 NH_2 C=N
II	$(CH_3)_2N-\underset{\displaystyle N_3}{\overset{\displaystyle |}{C}}=NSO_2C_6H_4CH_3(p\text{-})$	CCl_4, KBr	2160s, 1280s, 775m 1590vs 1300s, 1140s	N_3 C=N SO_2
VIIb	$(CH_3)_2N-\underset{\displaystyle C_5H_5N^+\ Cl^-}{\overset{\displaystyle |}{C}}=N-NHSO_2CH_3$	KBr	2760−2820w,br 1630vs 1570w, 1200m, 1112m, 715m, 677s 1327vs, 1158	NH C=N pyridine SO_2
VII	$(CH_3)_2N-\underset{\displaystyle C_5H_5N^+\ Cl^-}{\overset{\displaystyle |}{C}}=N-NHSO_2C_6H_4CH_3(p\text{-})$	KBr, nujol	2660m 1630vs 1593m, 1290w, 1090m, 750s 1565w, 1200m, 1112w, 705w, 677w 1325s, 1160vs	NH C=N phenyl pyridine SO_2
IVb	$(CH_3)_2N-CO-NH-NHSO_2CH_3$	KBr	3360s, 3140s 1660vs 1515vs 1325vs, 1160vs 867m	NH C=O amide II SO_2
IV	$(CH_3)_2N-CO-NH-NHSO_2C_6H_4CH_3(p\text{-})$	KBr	3320s, 3140s 1663vs 1515s 1332s, 1160vs 865m	NH C=O amide II SO_2
VIII	$(CH_3)_2N-CS-NH-NHSO_2C_6H_4CH_3(p\text{-})$	KBr	3293s, 3088m 1532s 1332s, 1162vs	NH thioamide B SO_2

Compound No.	Formula	Medium	Absorption bands (cm^{-1})	Assignment
V	p-$CH_3C_6H_4SO_2NH-CO-NH-N(CH_3)_2$	KBr	3300s 1717vs 1435vs 1338s, 1168s, 1155s 982m	NH C=O amide II SO_2
	p-$CH_3C_6H_4SO_2NH-CO-NH-N<^{CH_3}_{C_2H_5}$	KBr	3230s 1700vs 1445vs 1350s, 1167s 965m	NH C=O amide II SO_2
	p-$CH_3C_6H_4SO_2NH-CO-NH-N(C_2H_5)_2$	KBr	3220s 1705vs 1440vs 1355s, 1167s 972m	NH C=O amide II SO_2
	p-$CH_3C_6H_4SO_2NH-CO-NH-N<^{CH_3}_{C_6H_5}$	KBr	3270 1700vs 1445vs 1355s, 1165vs 965m	NH C=O amide II SO_2
X	p-$CH_3C_6H_4SO_2NH-CS-NH-N(CH_3)_2$	KBr	3280s 1450s 1340s, 1170s, 1145s	NH thioamide B SO_2
XIX	p-$CH_3C_6H_4SO_2N=C(-SC_2H_5)-C_6H_5$	KBr	1550vs 1320s, 1162vs	C=N SO_2
	$(CH_3)_2N-C(=NH_2^+Br^-)-SC_2H_5$	KBr	1640vs 1600s	NH_2 C=N
XII	$(CH_3)_2N-C(=NSO_2C_6H_4CH_3(p\text{-}))-SC_2H_5$	KBr	1545vs 1275s, 1140vs	C=N SO_2

Infrared spectra. Although the infrared spectra of the compounds prepared were mainly recorded for identification purposes they allow some conclusions of more general interest:

The infrared spectra of 1-sulfonyl-4,4-methylsemicarbazides (IV) and 4-sulfonyl-1,1-dialkylsemicarbazides (V, and higher homologues, see Table 2)

Table 2. 4-Tosylsemicarbazides, p-$CH_3C_6H_4SO_2NH-CO-NR^1NR^2R^3$.

R^1	R^2	R^3	Formula	Yield, %	M.p., °C	Analyses (C, H, N)
H	CH_3	CH_3	$C_{10}H_{15}N_3O_3S$	40[a]	178–179	Found: 46.84; 5.71; 16.66 Calc.: 46.69; 5.88; 16.34
H	CH_3	C_2H_5	$C_{11}H_{17}N_3O_3S$	40[b]	136–138	Found: 48.75; 6.32; 15.56 Calc.: 48.70; 6.32; 15.49
H	C_2H_5	C_2H_5	$C_{12}H_{19}N_3O_3S$	35[a]	150–152	Found: 50.30; 6.40; 14.96 Calc.: 50.52; 6.71; 14.73
H	CH_3	C_6H_5	$C_{15}H_{17}N_3O_3S$	67[a]	187–189	Found: 56.20; 5.49; 13.39 Calc.: 56.42; 5.57; 13.16
CH_3	CH_3	H	$C_{10}H_{15}N_3O_3S$	30[c]	150–152	Found: 46.35; 5.72; 15.90 Calc.: 46.69; 5.88; 16.34
CH_3	CH_3	CH_3	$C_{11}H_{17}N_3O_3S$	70[a]	149–151	Found: 48.60; 6.28; 15.36 Calc.: 48.70; 6.32; 15.49
H	H	C_6H_5	$C_{14}H_{15}N_3O_3S$	60[a]	222–224	Found: 54.78; 5.14; 14.24 Calc.: 55.08; 4.95; 13.80

Solvents used for crystallization: [a] ethanol; [b] ethanol-water; [c] water.

differ in a characteristic way. The 1-sulfonylsemicarbazides exhibit CO absorption near 1660 cm^{-1} and an amide II band near 1515 cm^{-1}, whereas the 4-sulfonylsemicarbazides have the corresponding bands near 1700 cm^{-1} and 1440 cm^{-1}, respectively. This supports the assumption that introduction of a sulfonyl group in the amide grouping will make the resonance structure $^+N=C-O^-$ less important and thus shift the CO band towards higher frequencies and the amide II band (due, in part, to C=N stretching) towards lower frequencies. A similar difference is found in the infrared spectra of 1-sulfonyl- and 4-sulfonylthiosemicarbazides, which have the thioamide B-band [10] at 1533 cm^{-1} and 1440 cm^{-1}, respectively. A further difference between the infrared spectra of the 1-sulfonyl and 4-sulfonyl derivatives is that the spectra of the 1-sulfonyl derivatives show two strong and sharp NH-stretching bands, whilst the 4-sulfonyl derivatives show only one. Finally, a medium strong band near 860 cm^{-1} appears only in the spectra of the 1-sulfonyl derivatives, and a medium strong band near 965 cm^{-1} only in the spectra of the 4-sulfonyl derivatives. The origin of these bands is probably an NH deformation mode.

A characteristic band of all the azides investigated is a strong band near 2200 cm^{-1}, often appearing as a doublet. Dimethylcarbamoyl azide (III) has three strong bands, at 1230, 725, and 643 cm^{-1}, which undoubtedly are due to the azide group, since similar bands appear also in the infrared spectra of dimethylcarbamimidoyl azide and hydrazoic acid.

The presence of the SO_2 group in these compounds is apparent from two strong bands within the usual range (near 1160 cm^{-1} and 1300 cm^{-1}). For compound XIV, which has the sulfonyl group directly bonded to a tetrazole ring, the second band seems to appear at a higher frequency than normal (1390—1400 cm^{-1} in $CHCl_3$). However, this compound decomposed with nitrogen evolution during the recording of the spectrum, so that no exact data can be given.

The C=N band of these compounds is a strong band, usually near 1600 cm^{-1}. For the compounds having an SC_2H_5 group adjacent to a $C{=}NSO_2R$ grouping (XII and XIX) the band appears at somewhat lower frequencies, indicating participation of a resonance structure $C(=^{+}SEt){-}NSO_2R$, which will diminish the double-bond character of the C=N bond.

The compounds VII and VII b both show a broad band in the 2600 cm^{-1} range. This is assigned to hydrogen-bonded NH. Similarly, 5-dimethylaminotetrazole has a series of bands between 2500 and 2800 cm^{-1}.

All the tetrazoles (I, XI, and XIV) have a very strong band between 1600 and 1650 cm^{-1} which is assigned to ring vibrations (C=N and N=N stretching).

By comparison of the spectra of the compounds VII and VII b the bands due to the pyridine ring and the phenyl group, respectively, could be identified.

Antidiabetic activity. The sulfonylsemicarbazides and sulfonylthiosemicarbazides prepared during this investigation were tested for antidiabetic activity, and since the semicarbazides IV and V showed pronounced activity a number of homologues of IV were prepared (Table 2). The most active compound was found to be 1,1,2-trimethyl-4-*p*-toluenesulfonylsemicarbazide, which possessed approximately the same activity as *N*-*p*-toluenesulfonyl-*N'*-butylurea (tolbutamide). It was, however, found to be more toxic and the hypoglycemic effect was of shorter duration; therefore this type of compound was not investigated further. Two of these compounds were prepared simultaneously (but in a different manner) by another group [6] for the same purpose.

In connection with these investigations, some *p*-toluenesulfonyl derivatives of alkoxycarbonyl- and alkoxythiocarbonylhydrazines were prepared. They were found to have no hypoglycemic activity.

We thank the pharmacological laboratory of Leo Pharmaceutical Products for performing the tests for antidiabetic activity.

EXPERIMENTAL

N,N-Dimethylcarbamimidoyl azide (N,N-dimethylguanyl azide). The *hydrochloride* was prepared in the following manner: 2,2-Dimethyl-1-aminoguanidinium iodide [1] (4 g) was dissolved in water (20 ml) and the solution shaken with excess silver chloride until the iodide reaction was negative (*ca.* 1½ h). The solution was filtered; 10 ml of 4 N hydrochloric acid and then 1.2 g of sodium nitrite were added to the cooled solution. The solution was slowly heated and evaporated to dryness on a steam bath. The residue was dried in a desiccator over NaOH and extracted with abs. ethanol. On evaporation of the solution an oil was obtained which crystallized on standing in a vacuum desiccator. Yield 2 g. The product was purified by dissolution in 15 ml of abs. ethanol, filtration and precipitation with 60 ml of ether. Yield 1.1 g (54 %). (Found: C 24.2; H 5.6; Cl 23.3. Calc. for $C_3H_8ClN_5$: C 24.1; H 5.4; Cl 23.8). The compound is very hygroscopic. It melts over the range 112—115°C, solidifies again because of ring-closure to 5-dimethylaminotetrazole, and melts again above 200°C. Its infrared spectrum shows a strong and sharp azide band at 2160 cm^{-1}.

The *hydrobromide* was prepared in a similar way from dimethylaminoguanidinium bromide and sodium nitrite in hydrobromic acid. Yield 60 %. M.p. 135—136°C (decomp.). Infrared spectrum identical with that of the hydrochloride.

Dimethylaminoguanidinium bromide was prepared by shaking a mixture of *S*-ethylthiosemicarbazidium bromide (20 g) and 2 N ethanolic dimethylamine (75 ml) until a clear solution had been obtained, refluxing for 15 min, and cooling in an ice-salt bath. Yield 82 %. M.p. 212—214°C. (Found: C 19.66; H 6.11; Br 42.83. Calc. for $C_3H_{11}BrN_4$: C 19.68; H 6.01; Br 43.69).

Thiosemicarbazidium bromide was prepared by refluxing a mixture of thiosemicarbazide (45.5 g), ethyl bromide (65 g) and ethanol (200 ml) until a clear solution was obtained (*ca.* 18 h). The colourless, crystalline product (93 g, 93 %) obtained by cooling and concentrating the mother liquor was practically pure; the m.p. was 119—120°C after recrystallization from methanol.

N,N-Dimethylcarbamoyl azide (III). 4,4-Dimethylsemicarbazide (8.5 g) was dissolved in 20 ml of 4 N hydrochloric acid and a solution of sodium nitrite (5.5 g) in water (10 ml) was added slowly with cooling. The solution was extracted with ether and the ether solution was dried with sodium sulfate and distilled *in vacuo* (Caution! The compound may explode violently by overheating). Yield 3.7 g (40 %). B.p. 58°C at 14—15 mm Hg. This compound has been prepared earlier from dimethylcarbamoyl chloride and sodium azide by Stollé.[7]

No ring-closure to an oxatriazole could be induced by treatment of the azide with basic catalysts or Lewis acids. No Curtius rearrangement to derivatives of $(CH_3)_2N—NCO$ took place on treatment with alcohols or amines. Refluxing of the azide with aniline resulted in formation of *N,N'*-diphenylurea.

5-Dimethylaminotetrazole (I). The method originally used[1] (a) is not convenient for the preparation of larger amounts of 5-dimethylaminotetrazole because it is necessary to convert dimethylaminoguanidinium iodide into the chloride before nitrosation. An attempt to start the preparation by methylating thiosemicarbazide with dimethyl sulfate was made, but yields were unsatisfactory. Excellent yields were, however, obtained from *S*-ethyl thiosemicarbazidium bromide (b). An alternative method is to react *N,N*-dimethylcyanamide with lithium azide (c).

a) An aqueous solution of the hydrochloride of the azide was prepared as described above and sodium acetate was added until the pH of the solution was 6. The solution was evaporated to dryness *in vacuo*, and the residue extracted with ethanol several times; the ethanolic solutions were evaporated to dryness and the residue recrystallized from water. Yield 40—50 %, based on 2,2-dimethyl-1-aminoguanidinium iodide. M.p. 242—244°C (closed capillary tube).

b) Dimethylaminoguanidinium bromide (15 g) was dissolved in 60 ml 2 N hydrobromic acid and, while keeping the temperature between 0 and 5°C, a solution of sodium nitrite (5.7 g) was added. Stirring was continued for 15 min at 0°C and then for ½ h at room temperature. The solution was cooled again to 0°C, 4 N NaOH was added until the pH of the solution was 4—5 and then a concentrated solution of sodium acetate was added until the pH was 6. The solution was stirred for ½ h at room temperature, heated to boiling and left overnight at room temperature, when colourless crystals of 5-dimethylaminotetrazole had separated. The solution was cooled for 2 h in an ice-salt bath before filtering. Yield 6.75 g; an additional crop of 0.70 g was obtained from the mother liquor, making the total yield 80 % (or 61 % based on thiosemicarbazide).

c) A well-stirred suspension of sodium azide (9.75 g), lithium chloride (6.36 g) and dimethylcyanamide (7.0 g) in 300 ml of glycol monomethyl ether was boiled for 48 h. After removing the solvent *in vacuo*, the residual solid was dissolved in 300 ml of water and 8.4 ml of conc. hydrochloric acid was added. The colourless precipitate was filtered and washed with water. Yield 3.0 g. M.p. 239—241°C. By concentrating the combined filtrates *in vacuo* to 50 ml and cooling in ice another 4 g were obtained, making the total yield 62 %.

5-Dimethylaminotetrazole also crystallizes from a solution of dimethylcyanamide in aqueous hydrazoic acid. However, the reaction is too slow to be of preparative importance (after standing of a solution at room temperature for 20 days a yield of 18 % was obtained).

(1-p-Toluenesulfonyl-4,4-dimethylcarbamohydrazonoyl)pyridinium chloride (VII). 5-Dimethylaminotetrazole (5.7 g) and *p*-toluenesulfonyl chloride (9.5 g) were dissolved

in dry pyridine (20 ml). The mixture became warm and the temperature was kept at 45°C by slight cooling. After 10—15 min the mixture solidified. After cooling, dry ether was added to the mixture and the crystalline precipitate filtered and washed with ether. To remove a possible excess of pyridinium chloride it was digested several times with warm chloroform. The compound forms light yellow crystals. Yield 10.1 g (57 %). (Found: C 49.50; H 5.28; N 15.80; Cl 9.79. Calc. for $C_{15}H_{19}ClN_4O_2S$: C 50.80; H 5.37; N 15.82; Cl 9.99). In later experiments the product was only washed with ether and yields as high as 95 % have been obtained. It is only slightly soluble in most solvents but could be recrystallized from abs. ethanol (without boiling), but with great loss; 0.3 g recrystallized twice from 2 ml of ethanol yielded 0.05 g with m.p. 136—136.5°C.

(1-Methanesulfonyl-4,4-dimethylcarbamohydrazonoyl)pyridinium chloride (VII b). 5-Dimethylaminotetrazole (1.5 g) was suspended in pyridine (10 ml) and 1 ml of methanesulfonyl chloride was added with stirring. The reaction proceeded readily at room temperature with nitrogen evolution and the temperature rose to *ca.* 50°C. The temperature was kept at 45°C for ½ h, 15 ml of chloroform was added and the solution cooled. A crystalline precipitate separated; it was filtered and washed with chloroform and finally extracted with boiling chloroform. The compound contained chloroform which proved difficult to remove: fairly satisfactory analyses were only obtained after the substance had been kept for 16 h in vacuum at 50°C. (Found: C 36.8; H 5.1; N 19.5; S 11.5; Cl 12.3. Calc. for $C_9H_{14}ClN_4O_2S$: C 38.9; H 5.1; N 20.2; S 11.5; Cl 12.8).

On heating with water this substance was transformed into *1-methanesulfonyl-4,4-dimethylsemicarbazide*, (IV b) identical with the product prepared from 4,4-dimethylsemicarbazide and methanesulfonyl chloride in a similar way as the corresponding *p*-toluenesulfonyl derivative (IV), except that ethanol was used for recrystallization (the residue from the evaporation of the pyridine may form an oil, but this crystallizes on cooling). M.p. 142—143°C. (Found: C 26.70; H 6.20; N 23.14. Calc. for $C_4H_{11}N_3O_3S$: C 26.52; H 6.13; N 23.20).

*4,4-Dimethyl-1-*p*-toluenesulfonylsemicarbazide (IV).* a) Compound VII (1.49 g) was dissolved in 12 ml of water and the solution slowly heated to boiling. There was a slight evolution of gas (identified as CO_2) and the solution became turbid. On cooling a crystalline precipitate separated. It was filtered and washed with a little cold water. Yield 0.94 g (87 %). M.p. after recrystallization from ethanol-water 146—148°C. (Found: C 46.50; H 6.05; N 16.22. Calc. for $C_{10}H_{15}N_3O_3S$: C 46.69; H 5.88; N 16.34).

The evolution of CO_2 indicates some hydrolysis during the formation of the semicarbazide and in accordance with this the mother liquor from the crude product contained a compound which reduced copper(II) sulfate with nitrogen evolution, probably hydrazine or *p*-toluenesulfonylhydrazine. No *p*-toluenesulfonamide, which might have arisen from the isomer (V), could be detected by thin-layer chromatography.

Identity of this product with authentic 4,4-dimethyl-1-toluenesulfonylsemicarbazide, prepared by method b), was proved by comparison of the infrared spectra of the two products.

b) 4,4-Dimethylsemicarbazide (1 g) was dissolved in pyridine (10 ml) and *p*-toluenesulfonyl chloride (1.9 g) was added with stirring to the ice-cooled solution. After stirring the solution for ½ h it was heated to reflux for 5 min and the pyridine was removed by evaporation *in vacuo*, addition of water and renewed evaporation; 5 ml of water were added to the residue, the crystalline solid was isolated by filtration and recrystallized from ethanol-water. Yield 1.9 g (74 %). M.p. 146—149°C (decomp.). (Found: C 46.80; H 5.64; N 16.18. Calc. for $C_{10}H_{15}N_3O_3S$: C 46.69; H 5.88; N 16.34).

In a similar way the following compounds (colourless crystals from ethanol-water) were prepared from ethoxycarbonylhydrazine, ethoxythiocarbonylhydrazine, and methoxythiocarbonylhydrazine:

*1-Ethoxycarbonyl-2-*p*-toluenesulfonylhydrazine.* Yield 80 %. M.p. 106—107°C. (Found: C 46.57; H 5.43; N 11.56. Calc. for $C_{10}H_{14}N_2O_4S$: C 46.51; H 5.47; N 10.85).

*1-Ethoxythiocarbonyl-2-*p*-toluenesulfonylhydrazine.* Yield 40 %. M.p. 97—98°C. (Found: C 43.62; H 5.13; N 10.29. Calc. for $C_{10}H_{14}N_2O_3S_2$: C 43.80; H 5.15; N 10.22).

*1-Methoxythiocarbonyl-2-*p*-toluenesulfonylhydrazine.* Yield 66 %. M.p. 123—125°C. (Found: C 41.46; H 4.78; N 10.78. Calc. for $C_9H_{12}N_2O_3S_2$: C 41.54; H 4.65; N 10.77).

*1,1-Dimethyl-4-*p*-toluenesulfonylsemicarbazide (V).* A solution of 1 g of *p*-toluenesulfonyl isocyanate[8] in 10 ml of ether was added slowly with cooling to a solution of 0.5 g of 1,1-dimethylhydrazine in 10 ml of ether. There was an immediate reaction with forma-

tion of a crystalline precipitate. This was filtered and recrystallized twice from ethanol. Yield 0.5 g (40 %). Some higher homologues were prepared in a similar way; melting points and analyses are given in Table 2.

4,4-Dimethyl-1-p-toluenesulfonylthiosemicarbazide (VIII). a) Compound VII (1 g) was dissolved in water (10 ml) and hydrogen sulfide was bubbled through the solution for 2—3 h. A yellow product, which was isolated by centrifugation and dried over P_2O_5, separated. Yield 0.5 g (68 %). (Found: C 43.88; H 5.62; N 15.27. Calc. for $C_{10}H_{15}N_3O_2S_2$: C 43.95; H 5.53; N 15.38).

The product was shown to be identical with authentic 4,4-dimethyl-1-*p*-toluenesulfonylthiosemicarbazide, prepared by method b), by comparison of their infrared spectra. However, it contained a small amount of a yellow impurity which could not be removed by recrystallization. The presence of this impurity could not be seen in the infrared spectrum, but in the visible spectrum it made itself conspicuous by an absorption band at 440—450 mμ when solutions of sufficiently high concentrations were measured. On addition of NaOH the colour changed to violet (reversibly) and the absorption maximum moved to 570—575 mμ.

b) 4,4-Dimethylthiosemicarbazide (1.2 g) was dissolved in pyridine (10 ml) and *p*-toluenesulfonyl chloride (1.9 g) was added with shaking to the cooled solution. Then the solution was heated on a steam-bath for 5 min. The pyridine was removed by evaporation *in vacuo*, addition of water and renewed evaporation. The residue was crystallized from ethanol. Yield 2.6 g (95 %). M.p. 146—147°C (decomp.). (Found: C 43.82; H 5.38; N 15.21. Calc. for $C_{10}H_{15}N_3O_2S_2$: C 43.95; H 5.53; N 15.38).

4,4-Dimethyl-1-p-toluenesulfonylaminoguanidine (X). Compound VII (0.5 g) was added in small portions to 20 ml of ethanol containing excess ammonia. The solid dissolved with a red-brown colour which rapidly disappeared. After addition of ether until the solution became turbid it was cooled for 3 h at 0°C and the precipitate filtered, washed with ether, then with water and dried over P_2O_5. Yield 0.15 g (42 %). M.p. 162—164°C. (Found: C 46.70; H 6.35; N 21.35. Calc. for $C_{10}H_{16}N_4O_2S$: C 46.87; H 6.29; N 21.87).

5-Dimethylamino-1-p-toluenesulfonamidotetrazole (XI). Compound VII (0.3 g) was dissolved in 2 ml of water and a solution of 0.5 g of sodium azide in 2 ml of water was added. The mixture turned light red and a white precipitate was immediately formed. After filtering, washing and drying it weighed 0.15 g (63 %). M.p. after recrystallization from ethanol-water 204—205°C (decomp.). (Found: C 42.40; H 5.16; N 29.42. Calc. for $C_{10}H_{14}N_6O_2S$: C 42.55; H 5.00; N 29.78).

1,1-Dimethyl-4-p-toluenesulfonylthiosemicarbazide (IX). A solution of 0.60 g 1,1-dimethylhydrazine was added with cooling and stirring to a solution of 2.13 g of *p*-toluenesulfonyl isothiocyanate [9] in 10 ml of methylene chloride. There was immediate reaction with formation of a precipitate. The mixture was left for ½ h at room temperature, the solvent was removed by evaporation and the residue recrystallized from ethanol and then from benzene-petroleum ether. Yield 1.1 g (40 %). M.p. 176—177°C. (Found: C 44.00; H 5.39. Calc. for $C_{10}H_{15}N_3O_2S_2$: C 43.95; H 5.53).

N,N-*Dimethyl*-N′-p-*toluenesulfonyl*-S-*ethylisothiourea (XII).* To a suspension of 2.13 g of *N,N*-dimethyl-*S*-ethylthiouronium bromide in 5 ml of pyridine was added 1.90 g of *p*-toluenesulfonyl chloride and the mixture was boiled for 30 min. After evaporation of the solvent *in vacuo* 40 ml of 1 N hydrochloric acid was added and the mixture was left in a refrigerator overnight. After filtration, washing with water, drying, washing with 3 times 5 ml of diethyl ether and re-drying the light brown product weighed 1.05 g (37 %). M.p. after recrystallization from water-ethanol (4:1) 80.5—81°C. (Found: N 9.58. Calc. for $C_{12}H_{18}N_2O_2S_2$: N 9.79).

4,4-Dimethyl-3-p-toluenesulfonylaminoguanidine (XIII). One g of recrystallized (XII) was dissolved in 5 ml of 1 M ethanolic hydrazine by gentle heating. The mixture was left at room temperature for 48 h and the crystalline precipitate was filtered and washed with ethanol (4 ml) and with ether. Yield 0.70 g (78 %). M.p. after recrystallization from ethanol 141.5—142°C. (Found: N 22.10. Calc. for $C_{10}H_{16}N_4O_2S$: N 21.87).

N,N-*Dimethyl*-N′-p-*toluenesulfonylcarbamimidoyl azide (II).* Compound XIII (0.5 g) was dissolved in 10 ml of 2 N hydrochloric acid and a solution of sodium nitrite (0.15 g) in water (5 ml) was added slowly with stirring and cooling in ice. The product was filtered and washed with water. Yield 0.44 g (84 %). Purification was attained by dissolving the product in ethanol (2 ml) and precipitating by addition of water (2 ml). M.p. 73—73.5°C. (Found: C 44.96; H 4.64; N 26.07. Calc. for $C_{10}H_{13}N_5O_2S$: C 44.94; H 4.90; N 26.21).

The infrared spectrum recorded in CCl_4 exhibited a strong absorption at 2160 cm^{-1} which shows that the compound is an azide and not a tetrazole. On heating, the compound started to give off nitrogen above 80°C and at about 110°C it was transformed into a reddish product in a few minutes. It could, however, be treated with boiling benzene without nitrogen evolution. After 10 min most of it had dissolved. The residue was shown by its infrared spectrum to be unchanged azide. The benzene solution left, on evaporation, a crystalline residue which was recrystallized from hexane. Analyses showed essentially the same composition as the azide but its infrared spectrum showed no azide bands, thus ring-closure to 1-*p*-toluenesulfonyl-5-dimethylaminotetrazole may have occurred. However, only a few mg of the azide were available for this experiment, so that further work is necessary to establish the nature of this product.

S-*Ethyl*-N-(p-*toluenesulfonyl)thiobenzimidate*. *S*-Ethyl thiobenzimidate hydrochloride (1 g) was dissolved in pyridine (5 ml) and *p*-toluenesulfonyl chloride (0.95 g) was added. The mixture was heated to boiling for 3 min, kept at room temperature for one hour, and poured into 50 ml of water; an oil which solidified on scratching, separated. Yield 1 g (63 %). M.p. after recrystallization from ethanol 99—101°C. (Found: C 60.00; H 5.27; N 4.09. Calc. for $C_{16}H_{17}NS_2O_2$: C 60.18; H 5.37; N 4.39).

When hydrazine was added to an ethanolic solution of this compound there was at once formation of ethanethiol and the solution slowly turned red. After standing in air for 24 h, the solution was dark red and a good yield of 3,6-diphenyl-1,2,4,6-tetrazine, but no benzohydrazide *p*-toluenesulfonylimide, could be isolated.

3,5-Diphenyl-1,2,4-triazole. The *N*-benzoyl derivative of *S*-ethyl benzimidate was prepared in the same way as the toluenesulfonyl derivative, but could not be induced to crystallize. When aqueous hydrazine was added to the oily product it was rapidly transformed into a white solid which was filtered and recrystallized from ethanol. Yield 95 %. M.p. 190—192°C. (Found: C 76.05; H 4.95; N 18.87. Calc. for $C_{14}H_{11}N_3$: C 75.99; H 5.05; N 18.99).

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