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Synthesis of some new hydrazine derivatives of thiazol.

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(Received December 1948.)

In the search for new, more active chemotherapeuticals (1) it deemed of interest to synthesize 2-hydrazino-thiazols and some of their sulfanilyl derivatives, especially as other hydrazine derivatives of sulfanilic acid (2, 3) were found to be effective against different bacteria; e. g. Sulfanilyl thiosemicarbazide proved to be efficient against different Clostridia strains (3). We suggested that ring closure of this molecule to the corresponding 2(2′-sulfanilyl-hydrazino)-4-methyl-thiazol II bring about an increase of antibacterial activity all the more as sulfamethylthiazol proved more active than sulfanilyl thiocarbamide. On the other hand, it seemed worthy to synthesize the 1′-sulfanilyl-isomer of II (IV) in order to compare its antibacterial activity with that of the 2′-sulfanilyl analogue II.

For this reason we attempted to prepare first 2-hydrazino-4-methyl-thiazol. 2-Hydrazino thiazol and its homologues were as yet not described, with the exception of the preparation of its 2′-aryl derivatives (4) and of 2.2′-hydrazino-bis-thiazol (5). Diazonium salts (6) resp. nitrimines (7) from amino thiazols could not yet be isolated (8). In solution these salts copulate normally with phenols, etc. (9), but they tend to give diazoamido compounds (10). Considering their sensibility, their reduction to the corresponding hydrazines was not yet carried out. We reduced the diazonium chloride from 2-amino-4-methyl-thiazol using methods which are suitable for the preparation of primary hydrazines, but we failed to obtain appreciable amounts of the excepted 2-hydrazino-4-methyl-thiazol. Sodium sulfite reduction led to the isolation of the sodium salt of the corresponding hydrazine N-sulfonic acid, however, we did not succeed in removing the sulfonic group without destroying the molecule. On the other hand, our reduction experiments with stannous chloride furnished as a single basic product 2-amino-4-methyl-thiazol, identified through its picrate (11) and acetylsulfanilyl derivative (12). Its formation can be explained, assuming acid hydrolysis of the nitrosimino derivative (tautomeric form of the diazonium hydroxyde) during the reduction. We interrupted these reduction experiments and wanted to build up 2(1′-sulfanilyl-hydrazino)-4-methyl-thiazol in an indirect way.

One plan was to synthesize 2(2′.2′dibenzylhydrazino)-4-methyl-thiazol (Va) in which only the nitrogen atom in 1′position would be able to react with an acyl chloride to secure a sulfanilyl-hydrazine Vb, closely related chemically and perhaps pharmacologically too, to sulfamethyl-thiazol. It was anticipated that benzyl groups would be removed by hydrogenolyiss to furnish IV.

Va was synthesized by converting as-dibenzyl-hydrazine (13) (VI) by means of hydrogene thiocyanate, resp. with thiocarbamide

into the oily 1.1-dibenzyl-thiosemicarbazide (VII); this was condensed in turn with monochloro acetone to Va. Another method consisted of a condensation of VI with thiocyano acetone (14) to Va. Acylation of the latter gave an acetyl derivative Vc, however, with benzene sulfonyl chloride it failed. This was attributed to steric hindrance, caused by the two benzyl groups and by the thiazol nucleus. A prototropic change (15) of Va into a thiazolon-hydrazone, like Vd, would not cause the failure of the reaction (16).

In the presence of palladized charcoal Va absorbed only up to 1 mole of hydrogen instead of 2 moles, so that the preparation of 2-hydrazino-4-methyl-thiazol could not be realized in this way.

This lack of success prompted us to synthesize 2(2′-benzylhydrazino)-4-methyl-thiazol (type Va) from benzyl-hydrazine *via* 1-benzyl-thiosemicarbazide VIII. Condensation of thiosemicarbazide itself with a chloro ketone was not attempted as the formation of thiodiazines in similar reactions could never be avoided (17). This thiosemicarbazide showed a higher melting point than its 2-benzyl isomer (IX) (18) and did not react with benzaldehyde, supporting structure VIII. The well known thermic rearrangement of 1-substituted thiosemicarbazides into 2-substituted derivatives can in our opinion rather be explained by assuming a migration of the thiocarbaminyl i. e. acyl group, than by a shift of an aryl, resp. aralkyl radical.

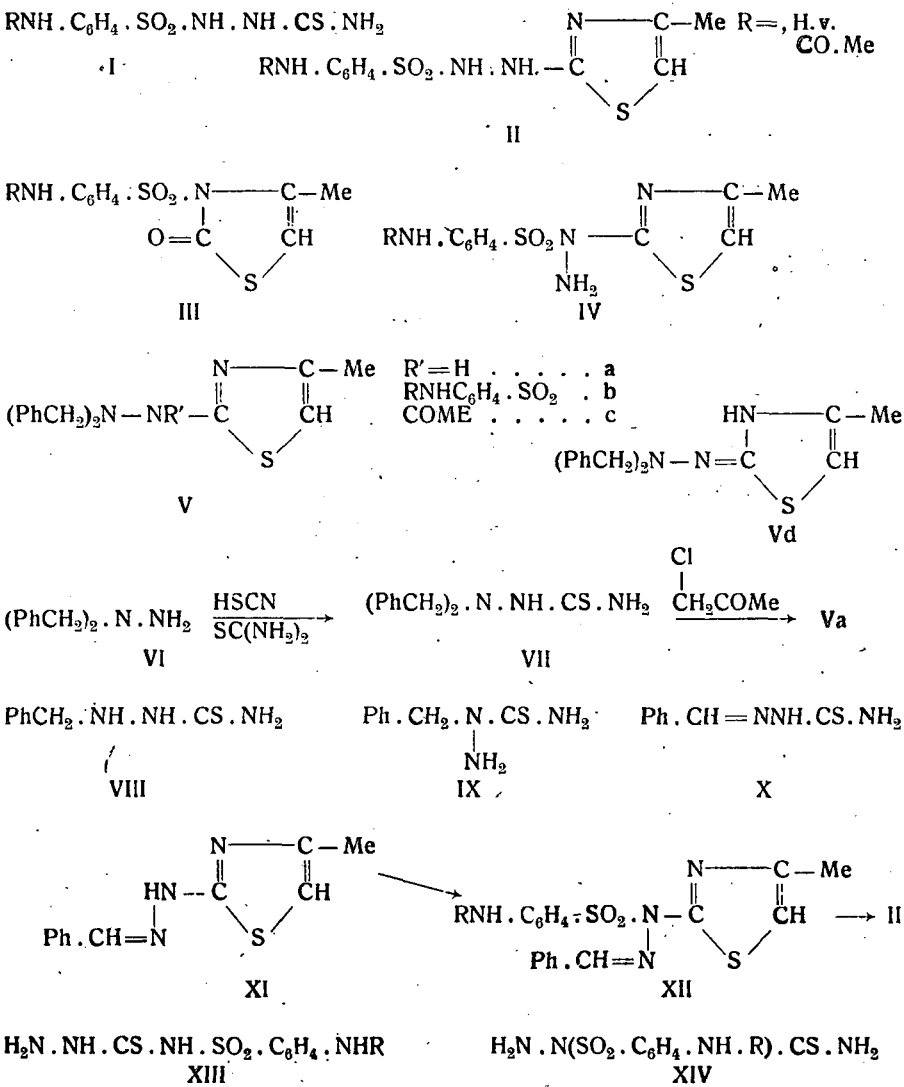
The crystalline 2(2′-benzyl-hydrazino)-4-methyl thiazol was obtained smoothly from VIII with monochloro acetone; it could be acylated with benzene sulfonyl chloride, as elimination of a benzyl group from Va resulted obviously in an abolition of steric hindrance. However, neither the base, nor its acyl derivative were able to undergo hydrogenolysis. This failure can be attributed to the formation of a sulphur containing catalyst poison, or to a relatively great stability of the benzyl group at the nitrogen.

We succeeded finally in synthesizing the required derivatives of 2-hydrazino thiazol, starting with benzal-thiosemicarbazide (X) (19). Its condensation with monochloro acetone gave the 2′-benzal derivative of 2-hydrazino-4-methyl-thiazol (XI) with a very good yield. This compound is very resistant towards acid hydrolysis. It could be acylated by means of acetyl-sulfanilyl chloride in pyridine yielding 2(2′-benzal-1′-acetylsulfanilyl-hydrazino)-4-methyl-thiazol (XII) (benzalderivative of IV). XII is insoluble in alkali, supporting the correctness of this formula.

Simultaneous removal of the benzal and acetyl groups by acid hydrolysis gave a crystalline compound with the analytical data calculated for the expected 2-(sulfanilyl-hydrazino)-4-methyl-thiazol. IV. However, it is readily soluble in diluted acids and alkalis. This amphoteric character can only be explained by suggesting for it structure II, of the isomeric 2′-sulfanilyl derivative. This interesting example of the migration of an arylsulfonyl group will be investigated more intensively later.

Another synthesis of II was attempted by allowing acetyl-sulfanilyl-thiosemicarbazide I to react with monochloro acetone. Analytical data of the obtained crystalline product as well as its neutral character suggest the structure of 3-acetyl-sulfanilyl-4-methyl-thiazolon-2 (III). Its formation can be explained in 2 ways either by assuming structure of 4-acetylsulfanilyl-thiosemicarbazide

for the starting material, and subsequent hydrolysis of the primarily formed 3-acetylsulfanilyl-4-methyl-thiazolon-2-hydrazone, or by supposing migration of the arylsulfonyl group of 2(2'-acetylsulfanilyl--hydrazino)-4-methyl-thiazol to the nitrogen at position 3 of the thiazol ring, with subsequent hydrolytic splitting off of hydrazine. As in our experiments acetylsulfanilyl thiosemicarbazide did not react



with benzaldehyde, a primary amino group, as in the case of XIII can not be present. Since acetylsulfanilyl thiosemicarbazide is easily soluble in dilute alkali, the possibility of a structure like XIV can also be regarded as very improbable. Consequently, acetylsulfanilyl thiosemicarbazide possesses structure I. so that the first assumption can be disregarded in favor of the second one.

This observation is surprising as similar *intra*molecular migration of an arylsulfonyl radical has not yet been reported. *Inter*molecular migration of an arylsulfonyl group from the ring nitrogen of some 2-acylimido-3-acyl-thiazolons to the amino nitrogen of amino-thiazol have already been described (16).

Rearrangement of IV to IIb, resp. conversion of I to III. will be the subject of systematic investigations.

Domagk (20) recorded recently on the strong tuberculostatic action of benzaldehyde thiosemicarbazon. In this regard compound XI can also receive some attention as it is to investigate, whether ring closure of benzaldehyde thiosemicarbazon to XI effect enhancement or diminution of the antibacterial activity. XI, and 2-sulfanilylhydrazino-4-methyl-thiazol will be assayed by Prof. G. Iványovics for antibacterial, especially for tuberculostatic activity.

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The author is very obliged to Mr. George Wilheim for his assistance in a part of this experimental work.

Summary.

Several attempts were made for the synthesis of sulfanilyl-hydrazino-methyl-thiazols. 2(2'-Sulfanilylhydrazino)-4-methyl-thiazol II was synthesized starting from benzaldehyde thiosemicarbazon *via* XI → IVa. Acid hydrolysis of the protecting benzal group from the primary hydrazino group effected a simultaneous shift of the arylsulfonyl radical from the secondary aminogroup to the liberated primary amino group. Condensation of acetylsulfanilyl thiosemicarbazide with monochloro acetone caused splitting off of hydrazine. XI and II may receive attention as antibacterials, their bioassay is in progress.

Experimental.

Benzyl hydrazine. 91 g. (0.44 mole) of benzaldazine were dissolved under stirring in 76 ml. (1.52 mole) of hot hydrazine hydrate. The solution was cooled back, extracted with a total of 250 ml. of ether, the solvent blown off, the residual (94.8 g.) oil distilled b. p. 92—104° (1 mm). Yield, 72 g. of benzal hydrazine. 36 g. (0.30 mole) of this product were hydrogenated in 250 ml. of alcohol with 1 g. Pd- charcoal (20% Pd), the uptake of hydrogene stopped after absorption of 8660 ml., i. e. 7680 n-ml (calcd. 6726 ml.). The solution was then evaporated and the remainder distilled, b. p. 80—81.5° (1.4 mm.), yield, 10.1 g. benzyl hydrazine, which has been converted into 14.8 g. of the hydrochloride, m. p. 148°.

Anal. Calcd. for $C_7H_{10}N_2$ 2HCl : Cl, 36.5; Found: Cl, 36.2.

1-Benzyl-thiosemicarbazide (VIII). 14.1 g. (0.07 mole) of the hydrochloride obtained above were dissolved in 15 ml. of water, 32.8 ml. of 2.1 N-sodium hydroxide (0.07 mole) solution then 7 g. (0.07 mole) of potassium thiocyanate were added and the whole boiled for 2 hours. Water was removed, the residue extracted by boiling four time with a total of 400 ml. of ethyl acetate. On cooling 1.4 g. of crystals separated, m. p. 175°; the residue of the solution (9.5 g.) showed the same m. p.

Anal. Calcd. for $C_8H_{11}N_3S$: S, 17.7. Found: S, 17.5.

2-2'-Benzylhydrazino-4-methyl thiazol. 1.81 g. (0.01 mole) of 1-benzylthiosemicarbazide in 10 ml. of 50% ethanol was condensed with 0.95 ml. monochloroacetone (0.01 mole) by refluxing for two hours. The solvent was then removed,

the sticky residue (2.9 g.) converted into the picrate, yield, 3.5 g. (78%). m. p. 135—136°, which raised on recrystallisation from ethanol to 143°. 1.7 g. of this picrate were treated with 2N-sodium hydroxide, the free base extracted with ether, yield, 0.6 g. thiazol derivative m. p. 44°.

Anal. Calcd. for $C_{11}H_{13}N_3S$: N, 19.2; S, 14.6. Found: N, 19.4; S, 14.5.

1.1-Dibenzyl-hydrazine (VI), was prepared according to *Busch* and *Weiss* (13), but some changes were undertaken to which we shall refer below. 156.2 g. (3.12 mole) of hydrazin hydrate was diluted with a mechanical stirrer, thermometer, dropping funnel and reflux condenser. Then 200 g. (1.58 mole) of benzyl chloride in 1 L. ethanol were added drop by drop under stirring in 40 min, meanwhile the temperature was maintained at 50°, and the whole refluxed for 2 hours under stirring. The solvent (870 ml.) was distilled off, the residue cooled in an ice-salt mixture. The separated crystals (consisting of the hydrochlorides of dibenzylhydrazine and of hydrazine) were collected on a filter, washed with some ice-cold alcohol and dried in a desiccator, yield, 87 g. Treatment with alkali afforded 41 g. of pure dibenzyl hydrazine. The filtrate was diluted with 500 ml. water, and extracted twice with a total of 800 ml. of ether, the dried ether solution was concentrated to a small volume, treated with 200 ml. of 15% hydrogene chloride in alcohol, yield, 70 g., m. p. 180° (not sharp). *Busch* suggested for this substance to be dibenzyl hydrazine bis-hydrochloride. We found, however, that always a mixture of hydrazine hydrochloride with the monohydrochloride of dibenzyl hydrazine was present. This assumption was proved by treatment of the product with alkali, when only a part of the calculated amount of dibenzyl hydrazine could be obtained, on the other hand by treatment of pure as-dibenzyl hydrazine even with a great excess of alcoholic HCl, only the mono-hydrochloride was formed. *Kenner* and *Wilson* also reported (13) the formation of the monohydrochloride. 1.1-Dibenzylhydrazine yield, 60% (calculated upon benzyl chloride used); m. p. 65°.

Anal. Calcd. for $C_{14}H_{16}N_2$: N, 13.2. Found: N, 13.5.

1.1-Dibenzyl-thiosemicarbazide. (VII.) *a. From 1.1-dibenzyl hydrazine.* A solution of 4.6 g. (0.019 mole) of 1.1-dibenzyl hydrazine monohydrochloride and 2.3 g. (0023 mole) of potassium thiocyanate was refluxed for 12 hours, the alcohol evaporated, the residue taken up in 200 ml. of ethyl acetate, washed with 50 ml. of water then with 73 ml. of 1% hydrochloric acid (to remove dibenzylhydrazine, as dibenzyl thiosemicarbazide is insoluble in such a dilute acid.) Ethyl acetate was blown off, to give 3.6 g. of an yellowish oil which gave on treatment with hydrogen chloride in ethyl acetate, a hydrochloride. The base is sufficiently pure for transformation into the thiazol derivate.

Anal. Calcd. for $C_{35}H_{18}N_3SCl$: N, 13.6. Found: N, 12.9.

b) From thiocarbamide. A mixture of 0.75 g. (0.01 mole) of thiocarbomide and of 2.1 g. (0.01 mole) of 1.1-dibenzyl hydrazine was heated to 160° for three hours, a vigorous evolution of ammonia was observed. The sirupy residue weighed 2.75 g; this was extracted with boiling petroleum ether, then dissolved in 50 ml. of ethyl acetate, washed with two portions of N/2 hydrochloric acid, then evaporated. This oil, 1.4 g. (51.9% calcd. upon the amount of dibenzyl hydrazine) gave approximately the expected analytical data. Calcd. S, 11.8. Found: S, 13.6. It is satisfactorily pure for condensation reaction.

c) The best method leading to 1.1-dibenzyl-thiosemicarbazide was the *rearrangement of dibenzyl hydrazine thiocyanate* in aqueous alcoholic solution, as follows: A mixture of 54 g. (0.22 mole) of 1.1-dibenzyl hydrazine monohydrochloride, 250 ml. of alcohol, 41 g. (0.42 mole) of potassium thiocyanate and 50 ml. of water was heated for 12 hours in a steam bath, the solvent evaporated

and the residue worked up as described under a.) Yield, 39.4 g. (67.6%) of a pale-yellow colored oil.

Anal. Calcd. for $C_{35}H_{17}N_3S$: S, 11.8. Found: S, 12.6.

2-(2'.2'-Dibenzyl-hydrazino)-4-methyl-thiazol. (Va.) a) From 1.1-Dibenzyl-thiosemicarbazide. A solution of 40.4 g. (0.15 mole) of crude 1.1-dibenzyl-thiosemicarbazide and of 13.8 g. (0.15 mole) of monochloro acetone in 200 ml of ethanol (96%) was refluxed for two hours, the solvent evaporated, the residual amorphous mass weighed 45.5 g. Then 300 ml. of a concentrated alcoholic solution of picric acid was added. Its yellow colored picrate (48 g.) showed m. p. 190°; the mother liquor furnished a further crop, 16.3 g. melting from 145 till 155°. The first portion obtained was dissolved in 300 ml. of chloroform, washed three times with a total of 350 ml. of 3% sodium hydroxide, dried and the solvent removed. Yield, 18.3 g. of colourless crystals of the thiazol derivative, m. p. 158—159°.

Anal. Calcd. for $C_{18}H_{19}N_3S$: N, 13.6; S, 10.4. Found: N, 13.55; S, 10.3.

The second crop of picrate gave, after recrystallisation from alcohol and subsequent alkaline treatment further 3.8 g. of the pure hydrazino-thiazol derivative. Total yield, 22.1 g (49%).

b) A solution of 4.57 g. (0.039 mole) of thiocyano acetone (14) and of 8.35 g. (0.039 mole) of 1.1-dibenzyl hydrazine in 15 ml. of ethanol was refluxed for an hour, the brownish coloured solution evaporated to dryness, the residue taken up in chloroform, washed with water, evaporated, then converted into the picrate as reported in the previous experiment to furnish 3.55 g. of a picrate m. p. 185° (after recrystallisation yield 2.5 g.) From this 1.5 g. of the pure hydrazino thiazol derivative could be secured.

2-(1'-Acetyl-2'.2'-dibenzylhydrazino)-4-methyl-thiazol (Vc.) Treatment of 1.04 g. (0.0034 mole) of dibenzyl hydrazino-4-methyl-thiazol in 3 ml. dry pyridine with 1 ml. of acetic anhydride (0.011 mole) furnished in the usual manner 0.95 g. (83%) of the acetyl derivative, m. p. 90°, (after recrystallisation from 25 ml. of 90% methanol.)

Anal. Calcd. for $C_{20}H_{21}ON_3S$: N, 11.95. Found: N, 12.1.

2(2'-benzalhydrazino)-4-methyl-thiazol. (XI.) Forty-six grams of benzaldehyde thiosemicarbazon were dissolved in 184 ml. of acetone and 23 ml. of monochloro acetone added, the mixture refluxed for an hour. The *hydrochloride* of the thiazol derivative separates soon, forming colorless prisms. Yield, 47.5 g; m. p. 186—187° (dec.). Recrystallisation from alkohol-acetone furnish a product, m. p. 193° (dec.). It is very resistant towards acid hydrolysis. Boiling with conc. HCl after cooling the hydrazine derivative was recovered.

Anal. Calcd. for $C_{11}H_{11}N_3S$. HCl : N, 16.55; Found, N, 16.81.

The *base* was liberated by dissolving 25.3 g. hydrochloride in 200 ml of hot methanol and adding 20 ml. of 5N NaOH in abs. methanol. A part crystallizes immediately, another on addition of 500 ml. of water. The base yielded long needles (from alcohol), m. p. 190°.

Anal. Calc. for $C_{11}H_{11}N_3S$: C, 60.79; H, 5.11; N, 19.35.
Found: C, 60.53; H, 5.32; N, 19.16.

2(1'-acetylsulfanilyl-2'-benzal-hydrazino)-4-methyl-thiazol. (XII). Thirteen and half grams of the pure benzal derivative (X) were dissolved in 60 ml. hot pyridine, then 16 g. acetylsulfanilyl chloride added and the reaction mixture heated for an hour in a steam bath. It was then poured into 200 ml. of 5% sulfuric acid, the oily precipitate became suddenly crystalline. Yield, 20 g. of a brown colored solid. Repeated recrystallization from alcohol afforded 5.1 g. of nearly colorless plates; m. p. 171—172°. Insoluble in alkali.

Anal. Calc. for $C_{19}H_{18}O_3N_4S_2$: C, 55.05; H, 4.35; S, 15.5.
Found: C, 54.90; H, 4.82; S, 14.06, 14.0.

2(2'-Sulfanilyl-hydrazino)-4-methyl-thiazol. Two grams of the acetylsulfanilyl-benzal derivative, mentioned above, was dissolved in 20 ml. of hot 2N hydrochloric acid and refluxed for an hour. The odor of benzaldehyde became soon remarkable, simultaneously oily drops appeared. Finally charcoal was added and the solution filtered. The filtrate gives on addition of alkali a precipitate which redissolves in an excess of alkali. Ammonia afforded a violet colored solution and a dark colored precipitate. The free base could be obtained by neutralizing the solution with solid sodium bicarbonate. Yield, 0.5 g., m. p. 153—155° (dec.). It is easily soluble in dilute hydrochloric acid and in N. sodium hydroxide, in alcohol, ethyl acetate, slightly soluble in water, insoluble in benzene.

Anal. Calc. for $C_{10}H_{12}O_2N_4S_2$: N, 18.7. Found: N, 18.2.

The *bis-hydrochloride* formed by adding alcoholic hydrogene chloride to the free base. M. p.: over 225°, it decomposes slowly, without melting. It is very soluble in water.

Anal. Calc. for $C_{10}H_{12}N_4O_2S_2 \cdot 2HCl$: Cl, 19.9. Found: Cl, 19.4.

Condensation of 1-acetylsulfanilyl-thiosemicarbazide with monochloro acetone.

Acetylsulfanilyl thiosemicarbazide was prepared according to Roth and Degering (3). It is easily soluble in 2N sodium hydroxide and did not give any precipitate with benzaldehyde. It is therefore neither a 2- nor a 4-acyl derivative.

1. Twenty and six tenth grams of acetylsulfanilyl thiosemicarbazide were heated in a steam bath with 6.7 g. of monochloro acetone and with 12 g. of dry pyridine for an hour. The product was then poured into water which was acidified previously with sulfuric acid. The oily precipitate solidified on triturating with dilute sulfuric acid. Yield, 20 g of dark brown crystals. Recrystallization from 90 ml. of 80% acetone and repeated recrystallization of the product thus obtained afforded 6.7 g. delicate white needles, m. p. 185°. Mixed m. p. with the starting material: 160—175°. It is insoluble in alkali, soluble in hot 20% sulfuric acid.

Anal. Calc. for $C_{12}H_{12}O_4N_2S_2$ (III) : N, 8.97; S. 20.05. Found: N, 8.91, 8.67; S, 19.70.

2. The same product was obtained by heating 2.3 g. I with 0.92 g. of monochloro acetone in 4 ml. of dry pyridine for an hour. Yield, 2.2 g., m. p. 186°, in part 214°. Recrystallization from 80% acetone furnished 1.2 g. colorless crystals, m. p 184—185°, and a further crop, 0.3 g., m. p. 174—177°.

Attempted reduction of diazotized 2-amino-4-methyl-thiazol.

a) A solution obtained by diazotization from 11.4 g. of 2-amino-4-methyl-thiazol in hydrochloric acid solution was treated with 31.5 g. of sodium sulfite according to the preparation of phenylhydrazine (21), but only the sodium salt of an organic sulfonic acid could be separated instead of the expected hydrazine derivative.

b) The solution of the diazonium salt obtained above was treated with a solution of 280 g. stannous chloride in hydrochloric acid at 0°. After stirring for 4 hours a white solid precipitated which contained 24.5% Cl. It was then treated with excess alkali and in turn extracted with chloroform. The resulting oily basic substance was identified 1.) by converting with p-acetamino-benzene-sulfonyl chloride in pyridine into the corresponding acylderivative, m. p. 255°, identical with acetylsulfanilyl-2-amino-4-methyl-thiazol (12). 2.) By converting

with picric acid into the picrate, m. p. 230—232° (11) of the starting material. This latter was analysed:

Anal. Calc. for $C_{10}H_9O_7N_5S$: N, 20.9, Found: N, 20.6.

Acknowledgement. The author is indebted to the Analytical Department of the Chinoin Manufactory and to Miss M. Kovács Oskolás for carrying out the analyses.

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