

Studies of Polarized Ethylenes

Part III.* Reactions of 1-Dimethylamino-1-methylthio- and 1,1-Bis-(methylthio)-2-acylethylenes with Hydrazines

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The reactions of hydrazines with 1-dimethylamino-1-methylthio-2-acylethylenes (I) give elimination of dimethylamine with the formation of methylthiopyrazoles (III) instead of the expected dimethylaminopyrazoles. The same products are formed from the 1,1-bis(methylthio) analogs (II) with the exception of the 2,2-diacetyl compound (IIb), which gives trimethyl-3,5-dimethylpyrazole-4-*ortho*-trithiocarboxylates (V). The structures of the 1-substituted pyrazoles, with the methylthio group in position 3, are demonstrated by preparative and spectroscopic evidence.

Ethylenes with thiol or thioether functions on C¹ and carbethoxy or cyano groups on C² have been valuable starting materials for the synthesis of various heterocyclic compounds. Thus Hartke and Pesker¹ obtained isothiazoles by reaction between 1-mercapto-2,2-dicyano-ethylene anions and chloramine, and Gompper and Töppf² have prepared aminopyrazoles, pyrazolones, and aminoisoxazoles by reaction of hydrazine and hydroxylamine with 1,1-bis(methylthio)-2,2-dicyano-ethylene and its 2-carbethoxy-2-cyano analog. Gompper *et al.*³ have also developed a thiophene synthesis by Dieckmann type condensations of 1,1-bis(carboxymethylthio)-2-carboxymethyl-ethylenes and analogous compounds. Reactions of 1,1-bis(methylthio)-2-cyano- and -2-carbethoxy-ethylenes with 2-aminopyridine and its analogs gives, *e.g.*, pyrido[1,2-*a*]-pyrimidines.⁴

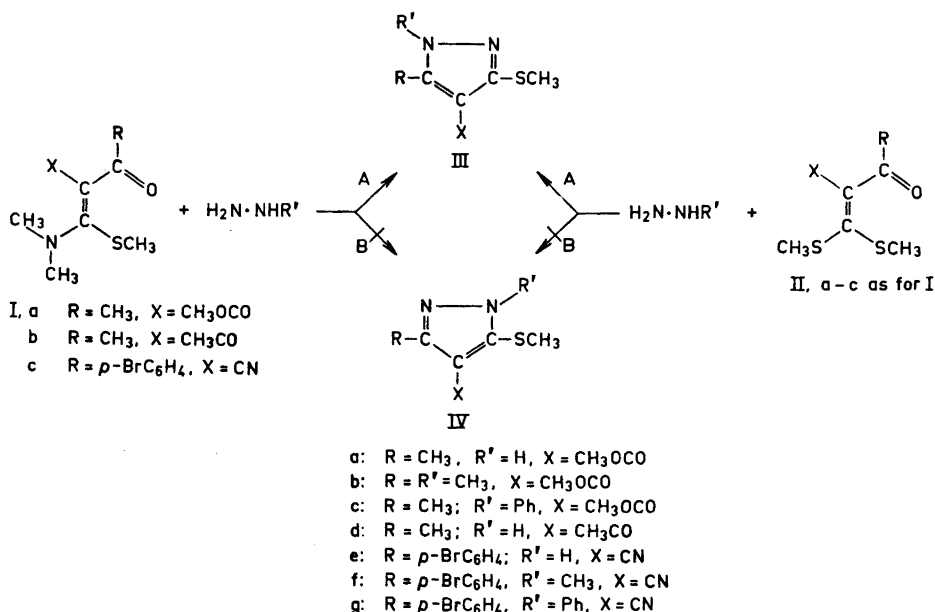
The purpose of the present investigation was to prepare 3- or 5-dimethylaminopyrazoles with electron-attracting groups in position 4 for a study of the internal rotation of the dimethylamino group. It was expected that reaction of compounds I with hydrazines should provide a suitable method, since generally the alkylthio group is the better leaving group in systems of

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this kind.⁵ However, in the reactions studied here, invariably dimethylamine was eliminated, and methylthiopyrazoles were formed. The same products were obtained, with the exception discussed later, in reactions of hydrazines with 1,1-bis(methylthio)-2-acylethylenes (II).

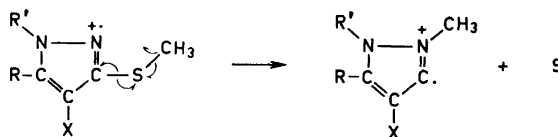
With methylhydrazine and phenylhydrazine, the resulting pyrazoles could be 3-methylthio (path A) or 5-methylthio (path B) derivatives. In all cases only one product was isolated, and for all of them structure III could be ascertained by a combination of spectroscopic and preparative arguments.

The pyrazole from Ia and methylhydrazine was desulphurized by Raney nickel to methyl 1,5-dimethylpyrazole-4-carboxylate, and this was transformed by hydrolysis and decarboxylation to 1,5-dimethylpyrazole, identified as its picrate, m.p. 172°. von Auwers reports m.p. 172° for this picrate, whereas the



picrate of the 1,3-isomer has m.p. 137°.⁶ The structure of the 1,5-dimethylpyrazole of von Auwers has been firmly established by Allemagna and Barbetta.⁷

Previous studies of mass spectra of pyrazoles indicate that the dominant fragmentation modes require fission of the N₁ - N₂ bond.^{8,9} In agreement with this, the mass spectrum of IIIb shows a prominent peak at *m/e* 56, corresponding to the ion CH₃N⁺≡C-CH₃. However, the molecular ion gives the base peak, and prominent peaks are also found at *m/e* 168 (M⁺-S) and *m/e* 169 (M⁺-OCH₃), so obviously fission of the pyrazole ring is not a dominant mode in this compound. The (M-S) peak is given by all pyrazoles III, and it must be due to a molecular rearrangement, possibly as follows:



The pyrazole from Ia and phenylhydrazine was shown to be IIIc by comparison with ethyl 1-phenyl-3-methylthio-5-methylpyrazole-4-carboxylate, which has been prepared in an unequivocal way from methyl 3-phenyldithiocarbazate and ethyl α -chloroacetoacetate.¹⁰ The two esters on hydrolysis give the same acid, as shown by identity of IR spectra and melting points. The mass spectrum of IIIc shows the expected prominent peaks at m/e 118 ($C_6H_5 - \overset{+}{N} \equiv C \cdot CH_3$), 230 ($\overset{+}{M} - S$), and 231 ($\overset{+}{M} - OCH_3$).

The expected pyrazole was obtained by reaction between Ib and hydrazine, but with methylhydrazine and phenylhydrazine no definite products were obtained.

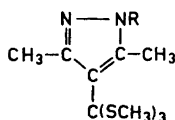
Ic and IIc gave the expected three pyrazoles. Reaction with hydrazine gave IIIe/IVe, the *p*-bromophenyl group of which shows a strongly coupled AA'BB' spectrum (100 MHz, in acetone) with the center of gravity of the "doublets" at δ 7.70 and 7.80 ppm. The 1-methyl analog displays a more separated AA'BB' spectrum at δ 7.55 and 7.76 ppm. It is unlikely that such a large upfield shift of the protons *meta* to bromine should be caused by the inductive and hyperconjugative effect of the 1-methyl group. A more reasonable explanation is that the *p*-bromophenyl group is in position 5 (IIIIf), where it is twisted out of the plane of the pyrazole ring by the steric effect of the 1-substituent. In this conformation, the mesomeric electron withdrawal by the cyano group is diminished as is the deshielding effect of the ring current in the pyrazole ring. Structure IIIIf for this compound is also supported by its mass spectrum, which shows an intense doublet at m/e 196 and 198 ($p\text{-Br} - C_6H_4C \equiv \overset{+}{N}CH_3$), and only a low intensity peak at m/e 88, where structure IVf would display the corresponding fragment ion ($CH_3S - C \equiv \overset{+}{N} - CH_3$).

The phenyl analog shows an NMR spectrum similar to that of IIIIf, though with the *p*-bromophenyl "doublets" at δ 7.31 and 7.61 ppm. The upfield shifts of both "doublets" compared to those of IIIIf are understandable if the *p*-bromophenyl ring is in position 5, and both aromatic rings are twisted with respect to the pyrazole ring. Then all four protons of the *p*-bromophenyl ring are in the shielding region of the 1-phenyl ring. The mass spectrum of this pyrazole shows the prominent doublet at m/e 258 and 260 ($p\text{-Br} - C_6H_4C \equiv \overset{+}{N}C_6H_5$) required by structure IIIIg, whereas the corresponding peak for IVg at m/e 150 ($CH_3S - C \equiv \overset{+}{N} - C_6H_5$) is absent. The molecular ion gives the base peak.

The formation of 3-methylthiopyrazoles on reaction of I or II with methylhydrazine as well as with phenylhydrazine is unexpected, since in methylhydrazine the $NHCH_3$ group and in phenylhydrazine the NH_2 group is the

more nucleophilic part. It is perhaps premature to attempt a rationalization of these results at present.

Reaction of 1,1-bis-(methylthio)-2,2-diacetyl-ethylene (IIb) with hydrazine gives a product, $C_8H_{16}N_2S_3$, which by mass and NMR spectra and elemental analysis has been identified as trimethyl 3,5-dimethylpyrazole-4-*ortho*-trithiocarboxylate (Va). The mass spectrum shows no molecular ion, but intense peaks appear at m/e



V, a. R = H
b. R = Ph

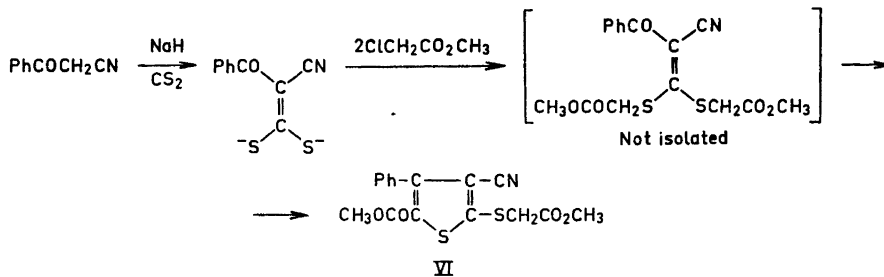
201 ($\overset{+}{M} - \text{CH}_3\text{S}$), m/e 186 ($\overset{+}{M} - \text{CH}_3\text{S} - \text{CH}_3$), and m/e 139 ($\overset{+}{M} - 2\text{CH}_3\text{S} - \text{CH}_3$). The NMR spectrum of Va shows two signals at δ 2.55 and 2.01 in the intensity ratio 2:3. The structure of Va was further ascertained by Raney nickel desulphurisation to 3,4,5-trimethylpyrazole, identified as

the picrate, which had the same melting point and IR spectrum as an authentic specimen.

Reaction of IIb with phenylhydrazine gave Vb in moderate yield. Its mass spectrum showed intense peaks at m/e 277 ($\overset{+}{M} - \text{SCH}_3$), 262 ($\overset{+}{M} - \text{SCH}_3 - \text{CH}_3$), and 215 ($\overset{+}{M} - 2\text{SCH}_3 - \text{CH}_3$). The NMR spectrum shows a broad singlet at δ 7.36 (5H), and sharp singlets at δ 2.58 (3H), 2.51 (3H), and 2.05 (9H).

The mechanism for the formation of the *ortho*-trithio esters V is not clear to us. It is possible that the hydrazine reacts with IIb to give a reactive intermediate, which then adds methanethiol formed in a competing reaction. The latter reaction is probably not an alkaline hydrolysis of IIb, since the yield of Va is not affected by addition of an excess of acetic acid to the reaction mixture. The reaction is currently being investigated.

Attempts were made to increase the leaving tendency of the alkylthio group in analogs of I. However, the benzylthio analog of Ia gave the 3-benzylthio analog of IIIa/IVa on reaction with hydrazine. Attempts to replace the methylthio group by the more readily eliminated carbomethoxymethylthio group failed at an early stage because the intermediate 1,1-bis(carbomethoxymethylthio)-2-benzoyl-2-cyanoethylene underwent a Dieckmann type cyclisation under the reaction conditions to give methyl 2-carbomethoxymethylthio-3-cyano-4-phenyl-thiophene-5-carboxylate (VI).



The structure was demonstrated by elemental analysis and by the IR spectrum, which showed ν_{CN} at 2220 cm^{-1} and ν_{CO} at 1740 and 1730 cm^{-1} . The NMR spectrum was in agreement with structure VI.

In attempts to prepare 3(5)-dimethylaminopyrazoles, 1,1-bis(dimethylamino)-2-acylethylenes¹¹ were treated with hydrazine under various conditions, but no reaction took place.

EXPERIMENTAL

The 1-dimethylamino-1-methylthio-ethylenes (I) were prepared by reaction between bis-(methylthio)-ethylenes (II) and dimethylamine (cf. Refs. 4, 12). Of the latter compounds, IIa and IIb were described in Part I, and 1,1-bis(methylthio)-2-p-bromobenzoyl-2-cyanoethylene (IIc) was prepared in the same way by reaction between *p*-bromobenzoyl acetonitrile,¹³ sodium hydride, and carbon disulphide in benzene-dimethylformamide, followed by methylation with dimethyl sulphate. Work-up in the usual way (see Part I) gave IIc as pale yellow prisms (41 % yield), m.p. $105-106^\circ$ after recrystallization from toluene. (Found: C 44.2; H 3.21; Br 24.4; N 4.26; S 19.5. $\text{C}_{12}\text{H}_{10}\text{BrNOS}_2$ (328.27) requires C 43.9; H 3.07; Br 24.3; N 4.27; S 19.5.)

1,1-Bis-(benzylthio)-2-acetyl-2-carbomethoxy-ethylene was prepared in the same way as IIc from methyl acetoacetate, sodium hydride, carbon disulphide, and benzyl chloride in benzene-dimethylformamide. The colourless product (32 % yield) crystallized from 1-butanol as colourless prisms, m.p. $47.5-49^\circ$. (Found: C 64.6; H 5.44; S 17.1. $\text{C}_{20}\text{H}_{20}\text{O}_3\text{S}_2$ (372.51) requires C 64.5; H 5.41; S 17.2.)

1-Dimethylamino-1-methylthio-2-acetyl-2-carbomethoxyethylene (Ia) was obtained in nearly quantitative yield when IIa reacted with one equivalent of dimethylamine in benzene at room temperature. Part of the product crystallized from the solution, and the remainder was obtained on evaporation. Recrystallization from acetone at low temperature gave yellow prisms, m.p. $132-133^\circ$. (Found: C 49.9; H 7.12; N 6.53; S 14.9. $\text{C}_9\text{H}_{15}\text{NO}_3\text{S}$ (217.29) requires C 49.8; H 6.96; N 6.45; S 14.8.)

1-Dimethylamino-1-methylthio-2,2-diacetyl-ethylene (Ib) was prepared as above. For a good yield of pure product it was found essential to cool the reactants to $+5^\circ$ before mixing. The product was obtained as yellow, deliquescent prisms (57 % yield), m.p. $92-94^\circ$ after recrystallization from toluene-ligroin. (Found: C 53.4; H 7.70; N 7.14; S 15.8. $\text{C}_9\text{H}_{15}\text{NO}_3\text{S}$ (201.29) requires C 53.7; H 7.51; N 6.96; S 15.9.) This compound has also been prepared by reaction between sodium acetylacetonate and dimethylamino-bis-(methylthio)-carbonium perchlorate.¹⁴

1-Dimethylamino-1-methylthio-2-p-bromobenzoyl-2-cyano-ethylene (Ic) was obtained in 67 % yield when IIc reacted with one equivalent of dimethylamine in benzene at room temperature, and it crystallized from benzene as colourless prisms, m.p. $167-168^\circ$. (Found: C 48.1; H 4.17; Br 24.6; N 8.65; S 9.91. $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{OS}$ (325.23) requires C 48.0; H 4.03; Br 24.6; N 8.61; S 9.86.)

1-Benzylthio-1-dimethylamino-2-acetyl-2-carbomethoxy-ethylene was prepared in high yield from the bis-benzylthio compounds in the same way as Ia. Recrystallization from toluene gave yellow prisms, m.p. $115-116^\circ$. (Found: C 61.4; H 6.69; N 4.89; S 10.9. $\text{C}_{15}\text{H}_{19}\text{NO}_3\text{S}$ (293.37) requires C 61.4; H 6.53; N 4.77; S 10.9.)

Methyl 3(5)-methylthio-5(3)-methylpyrazole-4-carboxylate (IIIa or IVa). Hydrazine hydrate (0.5 g) was added to a solution of IIa (2.17 g) in ethanol (10 ml). On the following day the product (0.78 g, 42 % yield) was precipitated with water (150 ml) and crystallized from toluene as colourless prisms, m.p. $126-127^\circ$. (Found: C 45.6; H 5.61; N 15.0; S 17.5. $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ (186.26) requires C 45.1; H 5.41; N 15.0; S 17.2.) When the reaction was performed with Ia, the same pyrazole was obtained in 59 % yield, identified by NMR and IR spectra.

Methyl 1,5-dimethyl-3-methylthiopyrazole-4-carboxylate (IIIb) was obtained in 40 % yield by reaction of IIa with methylhydrazine in ethanol. Recrystallization from toluene gave colourless prisms, m.p. $115-116.5^\circ$. (Found: C 48.1; H 6.08; N 13.8; S 16.0. $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (200.26) requires C 48.0; H 6.04; N 14.0; S 16.0.) The same product was obtained in 45 % yield when methylhydrazine reacted with Ia as described above.

This pyrazole (2.7 g) was refluxed with Raney nickel (30 g) in methanol (150 ml) for 1 h. The solution was filtered and evaporated, and the residue was refluxed for 5 h in 0.5 N methanolic potassium hydroxide (25 ml). Evaporation of the solution, dissolution of the residue in water and acidification of the solution gave *1,5-dimethylpyrazole-4-carboxylic acid* (64 % yield), m.p. 179–181° after vacuum sublimation. (Found: C 51.0; H 6.06; N 19.6; O 22.4. $C_8H_{10}N_2O_2$ (140.14) requires C 51.4; H 5.75; N 20.0; O 22.8.)

A sample of this acid was kept at 200° until the evolution of carbon dioxide had ceased, and the remaining oil was distilled and added to a solution of picric acid in ethanol. A picrate separated, m.p. 172° after recrystallization from water.

Methyl 1-phenyl-3-methylthio-5-methylpyrazole-4-carboxylate (IIIc) was obtained in 33 % yield on reaction of IIa with phenylhydrazine in ethanol, and it crystallized from toluene as colourless prisms, m.p. 134–135°. (Found: C 58.8; H 5.08; N 10.6; S 12.3. $C_{13}H_{14}N_2O_2S$ (262.33) requires C 59.5; H 5.38; N 10.7; S 12.2.) Reaction of Ia with phenylhydrazine gave the same compound in 34 % yield. Hydrolysis of this pyrazole ester gave *1-phenyl-3-methylthio-5-methylpyrazole-4-carboxylic acid*, identical with the acid described in Ref. 10.

Methyl 3-benzylthio-5-methylpyrazole-4-carboxylate. *1-Benzylthio-1-dimethylamino-2-acetyl-2-carbomethoxyethylene* (2.93 g) and hydrazine hydrate (0.5 g) in ethanol (20 ml) were left at room temperature for 24 h. After evaporation of the solvent, the remaining oil crystallized on cooling and scratching, and recrystallization from ligroin-toluene gave colourless prisms (1.2 g, 41 % yield), m.p. 113–114°. (Found: C 59.6; H 5.66; N 10.6; S 11.7. $C_{13}H_{14}N_2O_2S$ (262.33) requires C 59.5; H 5.38; N 10.7; S 12.2.)

3(5)-Methyl-4-acetyl-5(3)-methylthio-pyrazole (IIIId/IVd). Hydrazine hydrate (0.5 g) was added to a solution of Ib (2.0 g) in ethanol (20 ml). After 24 h at room temperature the solvent was evaporated, and the residue crystallized on trituration with water. Recrystallization from toluene gave colourless prisms (0.59 g, 35 % yield), m.p. 139–140°. (Found: C 48.4; H 6.29; N 16.2; S 18.4. $C_7H_{10}N_2OS + 1/6 H_2O$ (173.23) requires C 48.5; H 6.01; N 16.2; S 18.5.)

3-p-Bromophenyl-4-cyano-5-methylthiopyrazole (IIIe/IVe). Hydrazine hydrate and Ic reacted as in the preceding experiment and gave colourless prisms (41 % yield), m.p. 174–175° after recrystallization from ligroin-toluene. (Found: C 45.1; H 3.00; Br 27.0; N 14.3; S 10.6. $C_{11}H_8BrN_2S$ (294.19) requires C 44.9; H 2.74; Br 27.2; N 14.3; S 10.9.)

1-Methyl-3-methylthio-4-cyano-5-p-bromophenylpyrazole (IIIIf). Substitution of methylhydrazine for hydrazine hydrate in the preceding experiment gave a 62 % yield of colourless prisms, which crystallized spontaneously from the reaction mixture, m.p. 154–155° after one recrystallization from ethanol. (Found: C 46.9; H 3.20; Br 25.9; N 13.7; S 10.3. $C_{11}H_{10}BrN_2S$ (308.22) requires C 46.8; H 3.27; Br 25.9; N 13.6; S 10.4.)

1-Phenyl-3-methylthio-4-cyano-5-p-bromophenylpyrazole (IIIIf). Reaction between Ic and phenylhydrazine in ethanol gave colourless prisms in 30 % yield after recrystallization from ethanol, m.p. 140–141°. (Found: C 55.3; H 3.35; Br 21.6; N 11.3; S 8.45. $C_{17}H_{12}BrN_2S$ (370.29) requires C 55.1; H 3.27; Br 21.6; N 11.4; S 8.66.)

The three pyrazoles IIIe/IVe, IIIIf, and IIIIf were also obtained by reaction of IIc with the appropriate hydrazines.

Trimethyl 3,5-dimethylpyrazole-4-orthotriithiocarboxylate (Va). Hydrazine hydrate (0.5 g) was added to a solution of Ib (2.04 g) in ethanol (20 ml). After 24 h the mixture was poured into water (150 ml), and colourless prisms were precipitated (0.81 g, 65 % yield based on Ib), m.p. 119.5–120.5° after recrystallization from aqueous ethanol. (Found: C 43.5; H 6.43; N 12.0; S 38.6. $C_9H_{10}N_2S_3$ (248.43) requires C 43.5; H 6.49; N 11.3; S 38.7.)

This pyrazole was refluxed for 1 h with the tenfold quantity of Raney nickel in methanol. After filtration and cooling a solution of picric acid was added, and a yellow crystalline precipitate was formed, m.p. 234–235° after recrystallization from ethanol. This picrate was identical in m.p., mixed m.p., and IR spectrum with a specimen prepared from authentic 1,3,5-trimethylpyrazole¹⁵ and picric acid.

Trimethyl 1-phenyl-3,5-dimethylpyrazole-4-orthotriithiocarboxylate (Vb). Phenylhydrazine (2.16 g) was added to a solution of Ib (4.08 g) in ethanol (40 ml). After 24 h at room temperature the mixture was evaporated, and the remaining oil crystallized on trituration with water. Recrystallization from aqueous ethanol gave colourless prisms (0.8 g, 25 % yield), m.p. 90–91°. (Found: C 55.3; H 6.29; N 8.71; S 29.6. $C_{15}H_{20}N_2S_3$ (324.53) requires C 55.5; H 6.21; N 8.63; S 29.6.)

Methyl 2-carbomethoxymethylthio-3-cyano-4-phenylthiophene-5-carboxylate (VI). Benzoylacetonitrile (29 g) reacted with sodium hydride (5.0 g) and carbon disulphide (17 g) in benzene (300 ml) and dimethylformamide (100 ml) for 3 h at room temperature and 0.5 h at 70°C. Methyl chloroacetate (43.5 g) was added dropwise with stirring, and on the following day the mixture was poured into much water. The benzene layer was extracted twice with water, and after evaporation it gave a colourless oil, which crystallized on trituration with ethanol. The product (9.7 g, 14 % yield) crystallized from ethanol as colourless prisms, m.p. 100.5–101.5°. (Found: C 55.0; H 3.80; N 4.12; S 18.3. $C_{16}H_{13}NO_4S_2$ (347.41) requires C 55.3; H 3.77; N 4.03; S 18.5.)

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