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SYNTHESIS OF $N_{(1)}$-SUBSTITUTED 5-AMINO-3-METHYLPYRAZOLES

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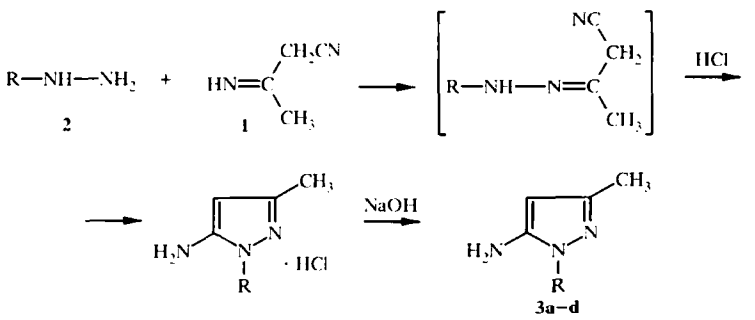
With the aim of preparing new biologically active compounds a series of $N_{(1)}$-substituted 5-amino-3-methylpyrazoles has been obtained from β-aminocrotononitrile and mono-substituted hydrazines.

Keywords: aminopyrazoles, aminocrotononitrile, hydrazines.

We have described the synthesis of diacyl derivatives of 5-amino-3-(*p*-aminophenyl)pyrazole as potentially active pharmacological materials and we have cited data on the physiological activity of pyrazole derivatives [1].

In the present paper the synthesis of $N_{(1)}$-substituted 5-amino-3-methylpyrazoles **3** based on the reaction of β-aminocrotononitrile (**1**) with monosubstituted hydrazines (**2**) is described.



The reactions proceeded in 60-90% yield even in the case of hydrazines containing a sulfur group. Difficulties, which might arise because of the amphoteric nature of such compounds, were not observed because salts of type **3e**, which have poor solubility in water, were formed even in the strongly acidic medium and were readily isolated from the reaction mixture.

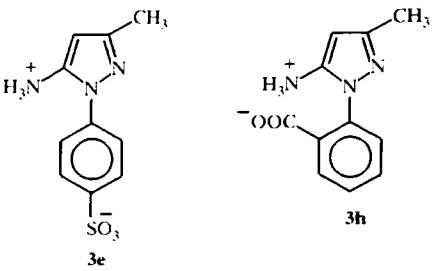


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TABLE 1. Characteristics of 1-Substituted 3-Methyl-5-aminopyrazoles **3**

Compound	R	Empirical formula	Found, % / Calculated, %			UV spectrum*, nm (log ε)	IR spectrum, cm^{-1}
			C	H	N		
3a	C_6H_5	$C_{10}H_{11}N_3$	–	–	–	–	1620, 1580, 1515
3b	H	$C_4H_7N_3$	49.2 / 49.5	7.4 / 7.2	43.6 / 43.3	224 (3.75), 303 (1.72)	1480, 1580, 3200
3c	CH_3	$C_5H_9N_3$	53.7 / 54.1	8.3 / 8.1	37.8 / 37.8	227 (3.77), 304 (1.72)	1390, 1560, 1620, 3200
3d	3-Sulfo-4-phenoxyphenyl	$C_{16}H_{15}N_3O_4S$	55.4 / 55.6	4.4 / 4.3		254 (4.15), 284 (3.41)	1650, 1590, 1495
3e	4-Sulfophenyl	$C_{10}H_{11}N_3O_3S$	47.0 / 47.4	4.6 / 4.3	16.1 / 16.6	256 (4.42)	1650, 1600, 1500, 1460
3f	*o*-Tolyl	$C_{11}H_{13}N_3$	70.3 / 70.2	7.1 / 7.0	22.5 / 22.2	222 (4.06), 267 (3.31)	1620, 1570, 1520
3g	*p*-Tolyl	$C_{11}H_{13}N_3$	70.3 / 70.2	7.0 / 7.0	22.3 / 22.2	246 (4.30)	1620, 1585, 1570, 1520
3h	*o*-Carboxyphenyl	$C_{11}H_{11}N_3O_2$	60.6 / 60.8	4.7 / 5.1	19.9 / 19.4	226 (4.53), 233 (4.59), 260 (4.53)	1690, 1625, 1480
3i	*p*-Carboxyphenyl*²	$C_{11}H_{11}N_3O_2 \cdot HCl$	52.1 / 52.0	4.8 / 4.7	16.9 / 16.5	254 (4.14), 274 (4.26)	1680, 1630, 1590, 1570

* Peak.

*² Hydrochloride.

It is interesting that the internal salt **3h**, rather than the aminopyrazole hydrochloride, was obtained from *o*-carboxyphenylhydrazine, whereas the corresponding aminopyrazole hydrochloride was obtained from *p*-carboxyphenylhydrazine under the same conditions.

EXPERIMENTAL

UV spectra of ethanol solutions were recorded with a Specord M spectrometer. IR spectra of KBr disks were recorded with a Perkin Elmer 577 machine. ^{1}H NMR spectra of DMSO-d_6 solutions were recorded with a Bruker WM-250 instrument.

5-Amino-3-methyl-1-phenylpyrazole (3a). A mixture of conc. HCl (100 ml) and water (200 ml) was placed in a 2 liter container. Freshly distilled phenylhydrazine (108 g, 1 mol) was added dropwise over 10 min with stirring by a Hirschberg stirrer. β-Aminocrotononitrile (diacetonitrile) (82 g, 1 mol) was added to the sticky mixture over 10 min. Phenylhydrazine hydrochloride dissolved and the oily solid phenylhydrazone separated. More conc. HCl (300 ml) was added to the mixture which was boiled with stirring for 2 h. The mixture was cooled and carefully neutralized with solid NaOH. Crystals of the aminopyrazole formed immediately. The crystals were separated after cooling the mixture and were washed with water, and then boiled under reflux with stirring with water (400 ml) for 30 min, cooled again, filtered off and carefully dried. For further purification the aminopyrazole was dissolved in boiling benzene (150 ml), about 50 ml of the wet benzene was distilled off, and the residue obtained on cooling was treated by slow addition of hexane (250 ml) with vigorous stirring. After cooling, the aminopyrazole crystals were filtered off, washed with cold hexane (100 ml) and dried to give 5-amino-3-methyl-1-phenylpyrazole (153 g, 88%); mp 111°C [2]. ^{1}H NMR spectrum: 2.11 (3H, s, 3-CH_3); 5.36 (1H, s, 4-H); 5.3 (2H, br. s, NH_2); 7.6 (2H, m, J = 6Hz, *o*-Ph); 7.45 (2H, dd, *m*-Ph); 7.26 ppm (1H, t, *p*-Ph).

5-Amino-3-methylpyrazole (3b). β-Aminocrotononitrile (24.6 g, 0.3 mol) and 85% hydrazine hydrate (50 ml) were refluxed for 8 h. Vacuum distillation of the reaction mixture gave 5-amino-3-methylpyrazole (22.6 g, 77.6%); bp 152-153°C/6 mm Hg, which crystallized on standing; mp 49°C.

5-Amino-1,3-dimethylpyrazole (3c). Methylhydrazine sulfate (47.5 g, 0.33 mol) was mixed with water (20 ml) and isopropanol (20 ml). β-aminocrotononitrile (24.6 g, 0.3 mol) was added and the mixture was refluxed for 1 h. The reaction was evaporated to dryness in a rotary evaporator, then conc. HCl (60 ml) was added to the residue and the mixture was refluxed for 6 h. The reaction mixture was again evaporated to dryness on the rotary evaporator, neutralized with an excess of NH_4OH, and once more evaporated to dryness. The dry residue was further dried in vacuum and then Soxhlet extracted with absolute isopropanol. Removal of isopropanol from the extract gave 5-amino-1,3-dimethylpyrazole (19.3 g, 58%); bp 121-123°C/9 mm Hg, which crystallized on standing; mp 54°C.

5-Amino-3-methyl-1-(3-sulfo-4-phenoxyphenyl)pyrazole (3d). A mixture of 4-phenoxyphenyl-3-sulfohydrazine (14 g, 0.05 mol) and β-aminocrotononitrile (4.1 g, 0.05 mol) was refluxed for 1 h. The reaction mixture was taken to dryness on a rotary evaporator, conc. HCl (25 ml) was added to the residue and the mixture was boiled for 2 h and then kept in the refrigerator for a day. The precipitated aminopyrazole was filtered off, washed on the filter with cold water and then refluxed with absolute CH_3OH (40 ml). After cooling, aminopyrazole was filtered off on a sintered glass funnel and dried to give compound **3d** (13 g, 75.4%); mp 278°C (dec.). ^1H NMR spectrum: 2.28 (3H, s, 3-CH_3); 5.7 (1H, s, 4-H); 7.92 (1H, s, *o*-Ph); 7.15-7.39 (5H, m, OPh); 6.94 (1H, d, J = 6 Hz, *m*-Ph); 7.08 ppm (1H, d, J = 6 Hz, *o'*-Ph).

5-Amino-3-methyl-1-(4-sulfophenyl)pyrazole (3e) was prepared as for compound **3d** in 85.6% yield; mp ~345°C (dec.).

5-Amino-3-methyl-1-*o*-tolylpyrazole (3f). A mixture of β-aminocrotononitrile (7.4 g, 0.09 mol) and *o*-tolylhydrazinium chloride (13.5 g, 0.09 mol) in water (30 ml) and ethanol (15 ml) was refluxed for 1 h. The solvents were removed with a rotary evaporator, conc. HCl (25 ml) was added to the residue and the mixture was again refluxed for 4 h. The mixture was made basic with an excess of ammonia and extracted with hot benzene. The benzene extract was distillated in vacuum to give aminopyrazole (11.2 g, 60%); bp 153-154°C/4 mm Hg.

5-Amino-3-methyl-1-*o*-tolylpyrazole (3g) was obtained analogously to compound **3f** in a yield of 62%; bp 187-189°C/6 mm Hg.

5-Amino-3-methyl-1-*p*-carboxyphenylpyrazole (3i). A mixture of *p*-carboxyphenylhydrazine (4.56 g, 0.03 mol) and β-aminocrotononitrile (2.46 g, 0.03 mol) was heated to boiling in a mixture of water (5 ml) and methylcellosolve (10 ml), evaporated to dryness on a rotary evaporator, conc. HCl (10 ml) was added and the mixture was boiled for a further 3 h. After cooling the reaction mixture water (20 ml) was added, the crystals were filtered off, washed with water (10 ml), methanol, ether, and then dried to give 5-amino-3-methyl-1-*p*-carboxyphenylpyrazole hydrochloride (6.5 g, 78%); mp 232°C (see Table 1).

5-Amino-3-methyl-1-*o*-carboxyphenylpyrazole (3h) was obtained analogously to compound **3i** from *o*-carboxyphenylhydrazinium chloride (5.7 g, 0.03 mol) and β-aminocrotononitrile (2.46 g, 0.3 mol). Crystals of the internal salt of 5-amino-1-*o*-carboxyphenyl-3-methylpyrazole were obtained (5.4 g, 71%); mp 254°C (see Table 1).

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