

Pyrazoles V: Di-(1,3,5-trimethyl-4-pyrazolylmethyl) Ether,
a Product of the "Chloromethylation" of 1,3,5-Trimethylpyrazole (1)

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There are only a few examples in the literature of the isolation of an ether from the chloromethylation of an aromatic compound (2,4) and these are all heterocyclic compounds. We wish to report the isolation of di-(1,3,5-trimethyl-4-pyrazolylmethyl) ether from the condensation of paraformaldehyde with 1,3,5-trimethylpyrazole. From the reaction mixture in the presence of hydrochloric acid no 4-chloromethyl-1,3,5-trimethylpyrazole could be isolated; the second reaction product was di-(1,3,5-trimethylpyrazolyl)methane. In the presence of sulfuric acid 4-hydroxymethyl-1,3,5-trimethylpyrazole was also formed.

Grandberg, Vasina and Kost (5) investigated the hydroxy- and chloromethylation of 1-substituted pyrazoles and reported the isolation of 4-hydroxymethylpyrazoles and dipyrazolylmethanes, however no mention was made of the formation of dipyrazolyl-methyl ethers.

The structural assignments of di-(1,3,5-trimethyl-4-pyrazolylmethyl) ether and di-(1,3,5-trimethyl-4-pyrazolyl)methane were based on molecular weight determinations and PMR and IR spectra. The PMR spectrum of the ether (see Table I, compound No. 1) differs from that of the methane (compound No. 2) and resembles that of the

4-hydroxymethyl-1,3,5-trimethylpyrazole (compound No. 3). 4-Hydroxymethyl-1,3,5-trimethylpyrazole was obtained both from a hydroxymethylation reaction with paraformaldehyde in 50% sulfuric acid solution and from a sodium borohydride reduction of 4-formyl-1,3,5-trimethylpyrazole. The IR spectrum of the ether shows a strong absorption at 1040 cm^{-1} corresponding to a C-O stretching vibration and no absorption between 3000 and 3600 cm^{-1} of an O-H absorption.

The condensation reaction of paraformaldehyde and 1,3,5-trimethylpyrazole with dry hydrogen chloride in dichloroethane solution or in concentrated hydrochloric acid solution gave mixtures of di-(1,3,5-trimethyl-4-pyrazolyl)methane and di-(1,3,5-trimethyl-4-pyrazolylmethyl) ether. A mixture of these two compounds and 4-hydroxymethyl-1,3,5-trimethylpyrazole was formed during the reaction with paraformaldehyde in 50% sulfuric acid solution. The composition of these mixtures was deduced from PMR spectra and thin layer chromatograms. On prolonged heating under vacuum of 4-hydroxy-1,3,5-trimethylpyrazole in a sublimation experiment a small amount of the ether was detected in the

TABLE I

Proton Magnetic Resonance Spectra

No.	Compound	Chemical Shifts (δ) in p.p.m. (a)		
		1 CH ₃	3/5 CH ₃	4 CH ₂ (4 CH)
1	Di-(1,3,5-trimethyl-4-pyrazolylmethyl) ether	3.65	2.18	4.25
2	Di-(1,3,5-trimethyl-4-pyrazolyl)methane	3.38	2.05	3.64
3	4-Hydroxymethyl-1,3,5-trimethylpyrazole	3.58	2.16	4.37
4	4-Formyl-1,3,5-trimethylpyrazole	3.63	2.29/2.41	9.75

(a) Only compound 4 gave separate singlet peaks for the two methyl groups in these spectra taken using a 1000 cycle chart-width. Peak integrations are consistent with peak assignments.

residue. The ether formation under the reaction conditions for the chloromethylation might be due to the high reactivity of the chloromethylpyrazoles. In the few cases that 4-chloromethylpyrazoles were studied the compounds appear to be very reactive (4,6).

EXPERIMENTAL

Di-(1,3,5-trimethyl-4-pyrazolylmethyl) Ether.

A stream of dry hydrogen chloride was passed through a solution of 11 g. of 1,3,5-trimethylpyrazole and 3.5 g. of paraformaldehyde in 25 ml. of 1,1-dichloroethane for 2 hours while the temperature was maintained at 50-55°. Subsequently the reaction mixture was refluxed for 2½ hours. Concentrated hydrochloric acid (25 ml.) was added, and the water layer was separated and extracted with chloroform. The residue obtained after evaporation of the solvent was distilled under reduced pressure, b.p. 160-180°/1-2 mm. (6.2 g.); m.p. 60-62°. No chlorine could be detected with the copper halide test. The ether was purified by means of several crystallizations from ligroine, m.p. 83°; mol. wt. 261 ± 5; $\nu(\text{C-O})$ 1040 cm^{-1} ; no absorption between 3000-3600 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_4\text{O}$: C, 64.09; H, 8.45; N, 21.36. Found: C, 63.52; H, 8.43; N, 21.15.

The synthesis was also performed in 1,2-dichloroethane, giving 4 g. of the ether, b.p. 160-170°/0.7-1 mm; twice crystallized from ligroine, m.p. 83°. The picrate was obtained from ethanol, m.p. 90°.

4-Formyl-1,3,5-trimethylpyrazole.

The procedure of Finar and Lord (7) for the preparation of 4-formyl-1-methylpyrazole was followed. Distillation under reduced pressure gave the desired compound, b.p. 132°/12 mm; m.p. 77-78°; after sublimation, m.p. 79°; $\nu(\text{C=O})$ 1668 cm^{-1} .

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.70; H, 7.74; N, 20.41.

The picrate crystallized from ethanol, m.p. 100°. A solution of 0.5 g. of the pyrazole in 10 ml. of water treated in the cold with 0.4 g. of potassium permanganate gave 0.3 g. of 1,3,5-trimethylpyrazole-4-carboxylic acid. The product was recrystallized from water and then from ethanol/water, m.p. 217° (lit. (8) 217°).

4-Hydroxymethyl-1,3,5-trimethylpyrazole.

A solution of 0.7 g. of the above aldehyde in 7 ml. of water was treated with a solution of 0.2 g. of sodium borohydride in 2.5 ml. of water. After standing for two hours at room temperature the excess sodium borohydride was removed with 4 *N* hydrochloric acid and the solution was extracted with chloroform. The product obtained after evaporation of the dried solution was a colorless, viscous oil (0.58 g.). On two weeks standing the compound crystallized, m.p. after sublimation 79°; $\nu(\text{C-O})$ 1003 cm^{-1} ; $\nu(\text{O-H})$ 3250 cm^{-1} .

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{N}_2\text{O}$: C, 59.97; H, 8.63; N, 19.80. Found: C, 59.47; H, 8.88; N, 19.99.

The picrate crystallized from ethanol, m.p. 89°.

Di-(1,3,5-trimethyl-4-pyrazolyl)Methane

A stream of dry hydrogen chloride was passed through a mixture of 11 g. of 1,3,5-trimethylpyrazole and 30 ml. of concentrated hydrochloric acid. The temperature was brought to 50° and after 15 minutes 3.5 g. of paraformaldehyde was added. The mixture was kept at 60° for 4 hours while a stream of dry hydrogen chloride was passed through the solution. Then the mixture was made

alkaline and extracted with 1-butanol. The extracts were dried, evaporated and distilled under reduced pressure, b.p. 200°/1 mm. (3.2 g.). According to the PMR spectrum the product was a mixture of di-(1,3,5-trimethyl-4-pyrazolyl)methane and di-(1,3,5-trimethyl-4-pyrazolylmethyl) ether; no resonance peak at 4.37 p.p.m. of the 4-hydroxymethyl derivative was present. No chlorine could be detected with the Beilstein test. The pure methane was obtained by several crystallizations from benzene/ligroine, m.p. 83°; mol. wt. 242 ± 3.

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_4$: C, 67.20; H, 8.68; N, 24.12. Found: C, 67.37; H, 8.52; N, 24.04.

The picrate crystallized from ethanol, m.p. 189°.

Condensation of 1,3,5-Trimethylpyrazole and Paraformaldehyde in Sulfuric Acid Medium.

Eleven g. of the pyrazole and 6 g. of paraformaldehyde in 20 ml. of 50% sulfuric acid were refluxed for 5 hours. Then the reaction mixture was cooled, neutralized and extracted with 1-butanol. Evaporation of the solvent and crystallization of the residue from petroleum ether (b.p. 60-80°) gave 2.2 g. of 4-hydroxymethylpyrazole, m.p. 73°. The IR spectrum was identical with that of the hydroxymethyl compound from the sodium borohydride reduction. The picrate crystallized from ethanol, m.p. 90°.

In another experiment the reaction mixture was refluxed for 20 hours; the composition of the residual oil, obtained after the crystallization of the 4-hydroxymethyl compound was analyzed. The PMR spectrum showed that it consisted of a mixture of the ether, the methane and the 4-hydroxymethyl derivative. This was confirmed by thin layer chromatography (on silica-gel, G. F. 254 Merck, in chloroform/methanol=9/1; Barton and permanganate positive).

Measurements.

All melting points are uncorrected. Elemental analyses were performed in the Micro-Analytic Department, University of Amsterdam. Molecular weights were determined cryoscopically in benzene. PMR spectra were recorded on a Varian HA-100 spectrometer. Chemical shifts are given relative to tetramethylsilane, deuteriochloroform was used as solvent. IR spectra were determined in potassium bromide disks with a Beckman IR-10 spectrophotometer.

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