[Contribution from the Chemical Laboratory of the Rice Institute]

FORMALDEHYDE CONDENSATION IN THE PYRAZOLE SERIES

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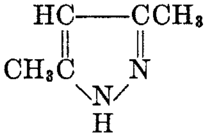
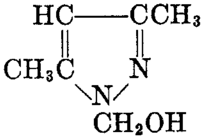
A study of the reaction of several representative pyrazoles with formaldehyde has shown that those compounds in which the 1-position of the heterocyclic ring is unsubstituted react in both neutral and acidic media to give the corresponding 1-carbinols. Furthermore, the same nuclei react with formaldehyde in acid medium to form alcohols resulting from condensation in the 4-position. Pyrazoles containing a substituent in the 1-position undergo no reaction in neutral solution, but condense with the aldehyde in the presence of acid to yield the 4-carbinols. No product of the condensation of formaldehyde with a side-chain methyl group could be obtained, even in basic solution.

The investigation described here had its origin in the work of Landua (1) on the chloromethylation of 3,5-dimethylpyrazole (I). Landua studied the reaction

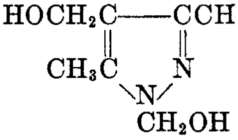


I

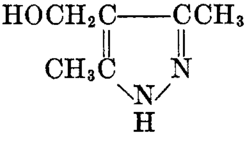
of this compound with paraformaldehyde and hydrochloric acid in the absence of a catalyst under a variety of conditions. By successive extraction of the basic reaction mixtures with ether and alcohol he obtained three products, which have subsequently been shown to be 3,5-dimethylpyrazole-1-carbinol (II), 3,5-dimethylpyrazole-1,4-dicarbinol (III), and 3,5-dimethylpyrazole-4-carbinol (IV). These results of the attempted chloromethylation of I suggested a systematic study of the reaction of the pyrazole nucleus with formaldehyde.



II



III



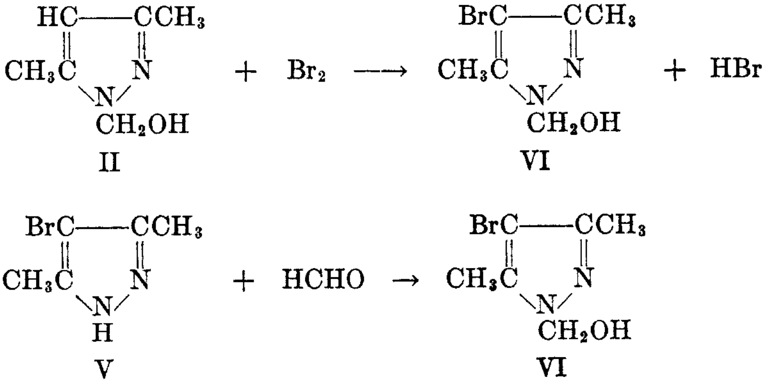
IV

The reaction between equimolar proportions of I and formalin at room temperature was found to result in a 71% yield of II. Higher condensation products could not be obtained by the use of an excess of formalin. The effect of a higher temperature on the reaction was studied by allowing a molten mixture of equivalent amounts of I and paraformaldehyde to react at 110–120°. The 1-carbinol was again obtained, this time in a yield of 90%. An excess of paraformaldehyde gave identical results.

Since no product other than II could be obtained from I and formaldehyde alone, the effect of acid on the reaction was determined. Inasmuch as II is formed both in the presence and in the absence of hydrochloric acid, a reaction was carried out between the 1-carbinol, paraformaldehyde, and hydrochloric acid. From these reactants there was obtained III in a yield of 24%.

Several experiments in which I was allowed to react with paraformaldehyde and hydrochloric acid at room temperature were carried out. The mixture of products consisted predominantly of II; smaller amounts of III were formed, and only traces of IV could be isolated. At higher temperatures, the reaction yielded polymeric substances from which no definite compounds could be isolated. The introduction of acid catalysts, such as zinc and stannic chlorides, produced a similar effect.

The presence of the alcoholic groups in the above compounds was verified by combustion analysis, but the determination of their positions required further study. Direct bromination of II yielded a new compound (VI). It was found also that 4-bromo-3,5-dimethylpyrazole (V) reacts with formalin to give the same product (VI). Combustion analysis of the common product indicated that it is a bromodimethylpyrazolecarbinol. The carbinol group is excluded from the 4-position because of the presence of the bromine atom; it is therefore located either in the 1-position or on the side chain. The distinction between the latter two possibilities was based upon a characteristic property of pyrazoles which contain an unsubstituted imino hydrogen atom—the formation of a nitric acid-soluble precipitate with silver nitrate solution. It was found that I and V react with alcoholic silver nitrate immediately, while II and VI give a precipitate only on standing. The slow formation of the precipitates by the two carbinols suggests that the alcoholic group is located in the 1-position and not on the side chain, and that the precipitates resulted from displacement of formaldehyde by silver ion. This explanation is supported by the fact that II on treatment with ammoniacal silver nitrate slowly formed both a precipitate and a silver mirror. Posner (2) has observed that 3,5-dimethylpyrazole-1-carbonamide also gives a precipitate with silver nitrate. It follows, therefore, that VI is 4-bromo-3,5-dimethylpyrazole-1-carbinol, and that it was formed according to the equations



The 4-carbinol (IV) was prepared independently of formaldehyde condensation by reduction of 4-carbethoxy-3,5-dimethylpyrazole with lithium aluminum hydride. The product thus obtained was shown by a mixed-melting point test to be identical with the compound which resulted from formaldehyde condensation.

Since the dicarbinol (III) was produced by reaction of the 1-carbinol with formaldehyde, one of its two carbinol groups is located in the 1-position. Furthermore, III was found to lose formaldehyde when heated, the residue being IV. It follows that the second alcoholic group is in the 4-position.

EXPERIMENTAL PART

Reaction of 3,5-dimethylpyrazole with formalin. To a solution of 3.27 g. (0.034 mole) of 3,5-dimethylpyrazole, prepared according to the procedure of Knorr and Rosengarten (3), in 58 ml. of water and 5 ml. of ethanol, 3.00 ml. (0.037 mole) of 35% formalin was added. After standing at 30° for 42 hours, the mixture was extracted with three 25-ml. portions of chloroform, and the solvent from the combined extracts evaporated. Recrystallization of the residue from benzene yielded 3.03 g. (71%) of 3,5-dimethylpyrazole-1-carbinol in the form of colorless prisms, m.p. 108–109°.

Anal. Calc'd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99.
Found: C, 57.18; H, 7.76.

Reaction of 3,5-dimethylpyrazole with paraformaldehyde. A mixture of 0.96 g. (0.01 mole) of 3,5-dimethylpyrazole and 0.30 g. (0.01 mole) of paraformaldehyde (Eastman trioxymethylene) was immersed for 20 minutes in an oil-bath maintained at 110–120°. Recrystallization of the solidified melt from benzene yielded 1.13 g. (90%) of 3,5-dimethylpyrazole-1-carbinol.

Reaction between 3,5-dimethylpyrazole-1-carbinol, paraformaldehyde, and hydrochloric acid. A mixture of 1.2 g. (0.01 mole) of 3,5-dimethylpyrazole-1-carbinol and 0.40 g. (0.013 mole) of paraformaldehyde was dissolved in 8.5 ml. (0.10 mole) of conc'd hydrochloric acid. After standing at 30° for one week, the mixture was subjected to distillation at the water-pump until 4 ml. of distillate had been collected. The residue was then carefully neutralized with potassium carbonate, and the potassium chloride removed by filtration. After addition of 15 ml. of ethanol to the filtrate, the solution was saturated with potassium carbonate, and the alcoholic layer separated. Evaporation of the alcohol at room temperature left a solid residue contaminated with inorganic material. The organic product was most readily purified by recrystallization from *n*-propyl alcohol. The yield of white, granular 3,5-dimethylpyrazole-1,4-dicarbinol, m.p. 138–140°, was 0.35 g. (24%).

Anal. Calc'd for $C_7H_{12}N_2O_2$: C, 53.82; H, 7.74.
Found: C, 52.49; H, 7.30.

When heated above its melting point, the dicarbinol evolved formaldehyde and yielded a residue of 3,5-dimethylpyrazole-4-carbinol, m.p. 174–176°.

Anal. Calc'd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99.
Found: C, 57.40; H, 7.79.

Preparation of 4-bromo-3,5-dimethylpyrazole-1-carbinol. (*a*). A solution of 1.16 g. (0.0066 mole) of 4-bromo-3,5-dimethylpyrazole, prepared from 3,5-dimethylpyrazole and N-bromosuccinimide by the method of Ziegler (4), and 5.7 ml. (0.066 mole) of 35% formalin in 5 ml. of water and 3 ml. of ethanol was allowed to stand at 30° for four weeks. The mixture was extracted with three 3-ml. portions of chloroform, and the solvent from the combined extracts evaporated. After two recrystallizations from water the yellow residue furnished 0.88 g. (65%) of 4-bromo-3,5-dimethylpyrazole-1-carbinol in the form of white needles, m.p. 133–134°.

(*b*). A mixture of 0.50 g. (0.004 mole) of 3,5-dimethylpyrazole-1-carbinol and 1.00 g. (0.008 mole) of sodium acetate was dissolved in 10 ml. of water. Dropwise addition of 0.5 ml. (0.009 mole) of bromine to the well-stirred solution resulted in precipitation of a pale-yellow solid. After the excess bromine had been removed by heating on the steam-bath, the white suspension was filtered, and the precipitate recrystallized from water. The weight of the product, m.p. 133–134°, was 0.70 g. (85%).

Anal. Calc'd for $C_6H_9BrN_2O$: C, 35.14; H, 4.42.
Found: C, 34.94; H, 4.38.

Reduction of 4-carbethoxy-3,5-dimethylpyrazole. A solution of 0.98 g. (0.0058 mole) of 4-carbethoxy-3,5-dimethylpyrazole, prepared according to the procedure of Knorr and Rosengarten (3), in 40 ml. of anhydrous ether was placed in a three-necked flask fitted with a dropping-funnel, reflux condenser, and mercury-sealed stirrer. To the stirred solution of the ester, 40 ml. of an ether solution of 0.32 g. (0.0084 mole) of lithium aluminum hydride was added over a period of ½ hour. After decomposition of the excess hydride with 3 ml. of water, the ether was removed by distillation and the residue extracted with 30 ml. of warm ethanol. Evaporation of the solvent from the extract left a crystalline residue, recrystallization of which from ethanol yielded 0.47 g. (64%) of white prisms of 3,5-dimethylpyrazole-4-carbinol, m.p. 179–180°.

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(3) KNORR AND ROSENGARTEN, *Ann.*, **279**, 237 (1894).
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