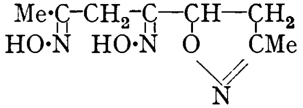
51. *5-Amino-1-aryl-3-methylpyrazoles.*

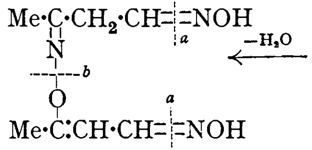
By Frank Bell.

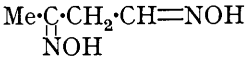
5-Amino-1-phenyl-3-methylpyrazole has been prepared by several distinct methods, but it is not possible from the literature to evaluate the relative efficiencies of these methods or ascertain their suitability for the preparation of analogous compounds. The methods have therefore been resurveyed.

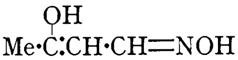
According to Claisen (*Ber.*, 1909, **42**, 67), 5-amino-1-phenyl-3-methylpyrazole is obtained by lengthy boiling of 5-methyl*iso*oxazole with phenylhydrazine. This *iso*oxazole is obtained by heating with N/2-hydrochloric acid the compound $C_8H_{13}O_3N_3$, which is prepared by interaction of sodioacetoacetaldehyde with hydroxylamine hydrochloride (Claisen, *Ber.*, 1891, **24**, 139). It is now found that about 40 g. of sodioacetoacetaldehyde are required to prepare 5 c.c. of 5-methyl*iso*oxazole. This does not accord with Claisen's simple representation (I) of the decomposition of the intermediate "oxymethylene acetonesesquioxime." The formula (II) put forward for this sesquioxime by Scholl (*Ber.*, 1897, **30**, 1292) was rejected by Claisen (*loc. cit.*, p. 64, footnote) on the ground that it cannot be reconciled with the smooth decomposition of the compound by hydrochloric acid. With very dilute acid the product is 5-methyl*iso*oxazole, but with more concentrated acid 3-methyl*iso*oxazole is obtained; 5-methyl*iso*oxazole is not converted into 3-methyl*iso*oxazole by heating with acids. It is now suggested that the sesquioxime is satisfactorily represented by (III), produced by interaction of one molecule of acetoacetaldehydedioxime (IV) with one molecule of acetoacetaldehydemonoxime (V). Hydrolysis of (III) with hydrochloric acid could follow one of two courses: either (i) linkage (*a*) is severed first; when, subsequently, linkage (*b*) is severed, the only *iso*oxazole which can be produced is 3-methyl*iso*oxazole (VI); or (ii) linkage (*b*) is severed first, in which case 5-methyl*iso*oxazole (VII) can be produced from either of the primary decomposition products. The experimental results would indicate that the mode of decomposition is conditioned by the strength of the acid.

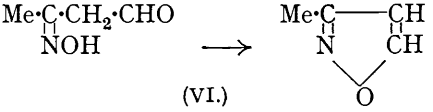
$$C_8H_{13}O_3N_3 + HCl = 2C_4H_5ON + NH_2{\cdot}OH,HCl \quad \text{(I.)}$$

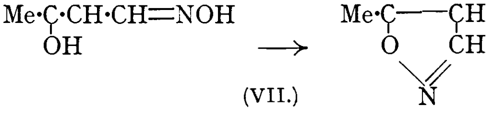

(II.)


(III.)

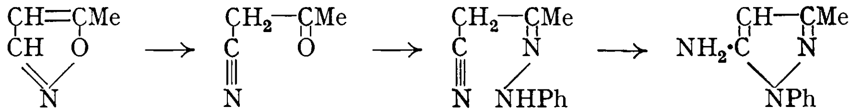

$\mathrm{Me{\cdot}C({:}NOH){\cdot}CH_2{\cdot}CH{=}NOH}$ (IV.)


$\mathrm{Me{\cdot}C(OH){:}CH{\cdot}CH{=}NOH}$ (V.)


(VI.)


(VII.)

The conversion of 5-methyl*iso*oxazole into 5-amino-1-phenyl-3-methylpyrazole by the action of boiling phenylhydrazine is mentioned by Claisen, who added that he would give details in a future communication. It is now found that the conversion goes very unsatisfactorily. Only 0·5 g. of the amine was obtained from 5 c.c. of the *iso*oxazole after this had been boiled with phenylhydrazine for six hours. The probable mechanism of the change (VIII) appears to be that the methyl*iso*oxazole first yields cyanoacetone, which reacts to give cyanoacetonephenylhydrazone, and this undergoes isomerisation to the


(VIII.)

aminopyrazole. If this is so, the yield should be improved by dissolving the methyl*iso*oxazole in warm potassium hydroxide solution to produce cyanoacetone, preparing from this the phenylhydrazone, and then isomerising the latter by hydrochloric acid. Actually 1·5 g. of purified aminopyrazole were obtained from 5 c.c. of methyl*iso*oxazole by this method.

Cyanoacetonephenylhydrazone is much more easily prepared from diacetonitrile. Moir (J., 1902, **81**, 101) has described the preparation of diacetonitrile. He states that the " yield leaves much to be desired," but does not record the exact percentage. In the present experiments yields were obtained varying between 44 and 49%. Mohr's method (*J. pr. Chem.*, 1909, **79**, 14) of converting this into the phenylhydrazone of cyanoacetone gave yields of 89—92%, and the subsequent conversion of this into 5-amino-1-phenyl-3-methylpyrazole by warm 6N-hydrochloric acid gave a yield of 80%. This satisfactory method of preparing aminopyrazoles was used to obtain 5-*amino*-1-(2'-*chlorophenyl*)- and -1-(2' : 5'-*dichlorophenyl*)-3-*methylpyrazoles.*

Michaelis and Brust (*Annalen*, 1905, **339**, 134) have described the preparation of 5-amino-1-phenyl-3-methylpyrazole by heating 5-chloro-1-phenyl-3-methylpyrazole methochloride (antipyrine chloride) with ammonium carbonate under pressure. They state that the more accessible 5-chloro-1-phenyl-3-methylpyrazole undergoes no reaction with either ammonium carbonate or ammonia–zinc chloride. It is now found that the latter can be recovered unchanged after heating with powdered sodamide for some hours. In contrast with the description given by Michaelis, it was found that, when antipyrine is boiled with phosphorus oxychloride for twelve hours, it is entirely converted into 5-chloro-1-phenyl-3-methylpyrazole-4-phosphinic acid (Michaelis and Pasternack, *Ber.*, 1899, **32**, 2411); with shorter periods of heating, antipyrine chloride was produced together with much 5-chloro-1-phenyl-3-methylpyrazole.

Mohr (*J. pr. Chem.*, 1909, **79**, 16) has recorded that 1-phenyl-3-methyl-5-pyrazolone cannot be converted directly into the 5-aminopyrazole by the Bucherer reaction.

EXPERIMENTAL.

An asterisk indicates microanalysis by Dr. G. Weiler.

o-Chlorophenylhydrazine was prepared by Hewitt's method (J., 1891, **59**, 209; 1893, **63**, 868). Diacetonitrile (16 g.) was added to a solution of *o*-chlorophenylhydrazine (34 g.) in acetic acid (40 c.c.) and water (40 c.c.). The mixture was warmed on a steam-bath for ¼ hour, diluted with water, and kept until the oil which separated had solidified. This *cyanoacetone-*o*-chlorophenylhydrazone* had m. p. 74—77° after two recrystallisations from alcohol (Found* : C, 58·4; H, 4·9. $C_{10}H_{10}N_3Cl$ requires C, 57·8; H, 4·8%). 20 G. of this compound were added to a mixture of concentrated hydrochloric acid (40 c.c.) and water (20 c.c.). The mixture became hot and a clear solution was obtained, which soon began to deposit crystals of the *hydrochloride* of 5-*amino*-1-(2'-*chlorophenyl*)-3-*methylpyrazole*, m. p. 122—125°. Recrystallisation of this from boiling dilute hydrochloric acid gave the compound in transparent, diamond-shaped crystals, m. p. 123—126° (Found : Cl*, 24·3; equiv., 284. $C_{10}H_{10}N_3Cl,HCl,2H_2O$ requires Cl, 25·3%; equiv., 280).

2 : 5-Dichlorophenylhydrazine was prepared by the method of Noelting and Kopp (*Ber.*, 1905, **38**, 3510). 12 G. were mixed with ethyl acetoacetate and warmed on the steam-bath for several hours. The product, which was solid at room temperature, on recrystallisation from alcohol gave *ethyl acetoacetate* 2 : 5-*dichlorophenylhydrazone* in plates (13·3 g.), m. p. 66—68° (Found* : C, 50·6; H, 4·9. $C_{12}H_{14}O_2N_2Cl_2$ requires C, 49·8; H, 4·8%). When this compound was heated with phosphorus oxychloride, the mixture soon changed to a brown plastic mass. After cooling, ice was added, and the product extracted with ether. The extract was dried with potassium carbonate and distilled under diminished pressure, yielding 5-*chloro*-1-(2' : 5'-*dichlorophenyl*)-3-*methylpyrazole*, b. p. 195°/25 mm. or 303—305°/760 mm., m. p. 44° (Found* : Cl, 40·8. $C_{10}H_7N_2Cl_3$ requires Cl, 40·7%).

2 : 5-Dichlorophenylhydrazine with diacetonitrile in aqueous acetic acid gave a 70% yield of *cyanoacetone*-2 : 5-*dichlorophenylhydrazone*, which crystallised from alcohol in needles, m. p. 112—114° (Found* : C, 50·3; H, 3·8. $C_{10}H_9N_3Cl_2$ requires C, 49·6; H, 3·7%); the mother-liquor furnished acetyl-2 : 5-dichlorophenylhydrazine, m. p. 160°. Cyanoacetonedichlorophenylhydrazone (13 g.) with hydrochloric acid (52 c.c.) soon yielded a warm clear solution; this subsequently deposited prisms, m. p. 214—220°, of the *hydrochloride* of 5-*amino*-1-(2' : 5'-

dichlorophenyl)-3-*methylpyrazole*, which could be readily recrystallised from boiling dilute hydrochloric acid (Found: Cl*, 37·9; equiv., 283. $C_{10}H_9N_3Cl_2,HCl$ requires Cl, 38·2%; equiv., 279).

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