ARYLAMIDES OF SUBSTITUTED THIOACETIC ACIDS

IV. Reaction of Arylamides of Monoacetylthioacetic Acid with Nucleophilic Reagents*

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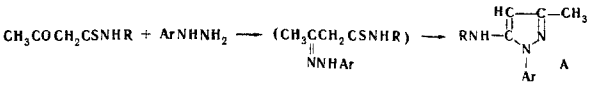
The reaction of arylamides of monoacetylthioacetic acid with arylhydrazines and hydrazine hydrate has given, respectively, 1-aryl-5-arylamino-3-methylpyrazoles and 5-arylamino-3-methylpyrazoles, the structures of which have been confirmed by independent synthesis and by their IR and UV spectra. It has been shown that, on reacting with arylamides of monoacetylthioacetic acid, nitrogen bases attack first the carbonyl and then the thiocarbonyl group of these compounds, forming substituted pyrazoles.

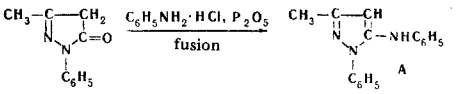
We have previously [1–3] reported reactions of arylamides of monoacetylthioacetic acid with electrophilic agents. The reaction of arylamides of monoacetothioacetic acid with nucleophilic reagents has been studied little. According to Worral [4], arylamides of diacetyl- and monoacetylthioacetic acids react with hydroxylamine to form 3-arylamino-5-methylisoxazoles. It is also known that when diacetylthioacetanilide is boiled with phenylhydrazine in aqueous ethanol, pronounced resinification of the reaction mixture takes place [4]. Both in the case of the reaction with hydroxylamine and in the case of the reaction with phenylhydrazine, it was assumed that the nitrogen bases first attack the thiocarbonyl group [3]. The oxime or hydrazine so formed subsequently cyclizes into an isoxazole or pyrazole, respectively. It has recently been shown that, in their reaction with benzoylthioacetamide, arylhydrazines and hydroxylamines first attack the carbonyl and not the thiocarbonyl carbon atom [5].

*For part III, see [3].

In view of this, we have again studied the reaction of arylamides of monoacetylthioacetic acid with arylhydrazines.



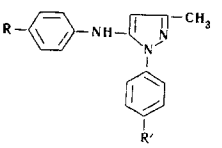
This reaction was carried out in glacial acetic acid at room temperature. The structure of the 1-arylpyrazoles A obtained were shown by independent synthesis. Thus, 3-methyl-1-phenylpyrazole-5-one was first obtained by the reaction of acetoacetic ester with phenylhydrazine. This was then treated with aniline hydrochloride to form 5-anilino-3-methyl-1-phenylpyrazole, which proved to be identical with the material obtained from antipyrine [6] or from the aniline of monoacetylthioacetic acid and phenylhydrazine:



On this basis, it may be concluded that phenylhydrazine, on reacting with monoacetylthioacetanilide, first attacks the carbonyl group, and that cyclization to form a pyrazole ring takes place even at this stage. Thus, the carbonyl group is more reactive than the thioanilide group. The reaction products A (Table 1) were isolated by diluting the acetic acid solution with water. Sometimes on dilution with water the 1-arylpyrazoles A separated in the form of oils which rapidly

Table 1

1-Aryl-5-arylamino-3-methylpyrazoles



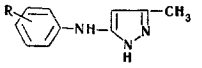
Compound	R	R′	Mp, °C	Empirical formula	N, % found	N, % calculated	Yield, %
I	OCH_3	H	87—88	$C_{17}H_{17}N_3O$	15.05; 15.21	15.04	92
II	OC_2H_5	H	88—89	$C_{18}H_{19}N_3O$*	14.12; 14.10	14.33	70
III	CH_3	SO_3H	313—314	$C_{17}H_{17}N_3O_3S$	12.15; 12.14	12.24	73
IV	CH_3	SO_2NH_2	208—209	$C_{17}H_{18}N_4O_2S$	16.76; 16.62	16.86	60
V	OC_2H_5	SO_2NH_2	206—207	$C_{18}H_{20}N_4O_3S$	15.44; 15.38	15.04	55
XIII	CH_3	H	112—112.5**	$C_{17}H_{17}N_3$	15.99; 16.10	15.95	70

*Picrate—mp 156–157° C (from ethanol). Found, %: N 16.27, 16.40. Calculated for $C_{18}H_{19}N_3O \cdot C_6H_3N_3O_7$, %: N 16.08.

** Mp 111° C [7].

Table 2

5-Arylamino-3-methylpyrazoles



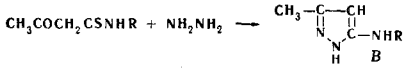
Compound	R	Mp, °C	Empricial formula	N, % found	N, % calculated	Yield, %
VII	H	132—134	$C_{10}H_{11}N_3$*	24.52; 24.69	24.27	70
VIII	*p*-CH_3	149—150	$C_{11}H_{13}N_3$	22.10; 21.93	22.35	78
IX	*p*-OCH_3	136—137	$C_{11}H_{13}N_3O$	20.30; 20.43	20.67	66
X	*o*-OCH_3	108—110	$C_{11}H_{13}N_3O$	20.63; 20.73	20.67	66
XI	*p*-OC_2H_5	134—135	$C_{12}H_{15}N_3O$	19.07; 19.14	19.32	75
XII	*p*-Cl	183—184	$C_{10}H_{10}ClN_3$	20.44; 20.54	20.23	73

*Found, %: C 70.22; 70.32; H 6.48; 6.51. Calculated, %: C 70.53; H 6.40.

crystallized. Only in the case of compound II was an oily reaction product obtained; this crystallized after being chromatographed twice on a column of alumina and left to stand for 4 months.

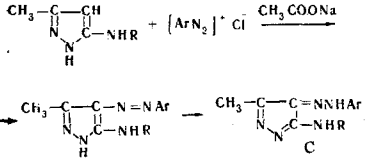
With concentrated sulfuric acid, the 1-arylpyrazoles that we synthesized form colored solutions. For example, a solution of I in sulfuric acid has a violet color, a solution of 3-methyl-1-phenyl-5-toluidinopyrazole (VI) a faint red-violet color, and solutions of II and III a faint yellow color. The absorption bands of the free NH groups in the IR spectra of solutions of compounds A in chloroform are found at 3430 cm^{-1}. The UV spectrum of VI in ethanol is characterized by a maximum at 267 nm, log ε 4.3, and by an inflection in the 280–290 nm region (log ε 4.0). Compound II in ethanol absorbs within the same wavelength ranges.

The reactions of arylamides of monoacetylthioacetic acid with hydrazine hydrate were carried out in glacial acetic acid at room temperature.



The compounds B that we synthesized are listed in Table 2.

To confirm the structure of compounds B, we treated them with aryldiazonium chlorides:



The 5-anilino-3-methyl-4-phenylazopyrazole obtained in this way proved to be identical with an authentic sample [3]. This confirms the structure of the compounds C and of the compounds B synthesized.

The IR spectra of solutions of the pyrazoles B have two bands of a free NH group: at 3480 and 3440 cm^{-1}. Taking into account the fact that in the IR spectrum of a solution of pyrazole in CCl_4 the ν_{NH} band of the ring is located at 3480 cm^{-1} [8], we ascribed the 3480 cm^{-1} band in the IR spectrum of the pyrazoles B to the stretching vibrations of the NH group of the ring. We ascribed the 3440 cm^{-1} band to the stretching vibrations of a secondary arylamino group on the basis that the ν_{NH} band of compounds A is located in approximately the same region.

The IR spectrum of an ethanolic solution of compound VII has an absorption maximum at 267 nm (log ε 4.31).

EXPERIMENTAL

5-Anilino-3-methyl-1-phenylpyrazole. a) A solution of 2 g (~0.01 mole) of monoacetylthioacetanilide in 20 ml of glacical acetic acid was treated with 2.2 g (0.02 mole) of phenylhydrazine. There was a vigorous evolution of hydrogen sulfide. The mixture was kept at room temperature for 24 hr and was then diluted twofold with water. An oil precipitated at first, and after 20–30 min this crystallized. The reaction product was filtered off, washed with water, and dried. Yield 2 g (77%). Mp 120° C (from ethanol). Found, %: N 17.06, 17.10. Calculated for $C_{16}H_{15}N_3$, %: N 16.92.

Compounds **I–VI** were obtained similarly as colorless crystalline substances soluble in ethanol and methanol and sparingly soluble in benzene.

b) With ice water cooling, 5.5 ml of phenylhydrazine was added dropwise to a solution of 7.8 g (0.06 mole) of acetoacetic ester in 5 ml of 60% aqueous ethanol. Starting 30 min after the addition of the phenylhydrazine, the reaction mixture was heated in the boiling water bath for 1 hr. The cooled solution was treated with 30–50 ml of ether, the mixture was shaken, and the precipitate that deposited was filtered off and was washed with water and ether. The yield of 3-methyl-1-phenylpyrazol-5-one was 8 g (40%), mp 125–127° C (from aqueous ethanol). The melting point given in the literature [9] is 127° C. A mixture of 1.74 g (0.01 mole) of 3-methyl-1-phenylpyrazole-5-one, 1.35 g (0.011 mole) of aniline hydrochloride, and 0.7 g (0.005 mole) of phosphorus pentoxide was heated in an oil bath at 210–220° C for 1 hr 30 min. The cooled solid mass was treated with 15–20 ml of glacial acetic acid, the contents of the flask were triturated until dissolution was achieved, and the resulting solution was poured into 25 ml of cold water. The precipitate was filtered off, washed with water, and dried. Yield 1.2 g (50%); mp 119–120° C (from ethanol). According to the literature [6], mp 120° C. This substituted 1-arylpyrazole gave no depression of the melting point in admixture with a sample of the 5-anilino-3-methyl-1-phenylpyrazole obtained by the reaction of acetylthioacetanilide with phenylhydrazine.

5-Anilino-3-methylpyrazole (VII). A solution of 4 g (~0.02 mole) of acetylthioacetanilide in 25 ml of acetic acid was treated with 2.8 ml of hydrazine hydrate, leading to a vigorous evolution of hydrogen sulfide. The solution was kept at 18–20° C for 24 hr, and then diluted with water and neutralized with 10% caustic soda solution. The precipitate was filtered off, washed with water, and dried. Yield 2.45 g mp 132–134° C (from benzene and ethanol).

The other 5-arylamino-3-methylpyrazoles (Table 2) were obtained under similar conditions. They are colorless crystalline compounds readily soluble in ethanol and methanol and sparingly soluble in benzene and dioxane. For the synthesis of compound **XII** we first obtained the p-chloroanilide of acetylthioacetic acid by Worral's method [4]. Yield 70%; mp 95–96° C (from ethanol). Found, %: Cl 15.79, 15.80. Calculated for $C_{10}H_{10}ClNOS$, %: Cl 15.57.

5-Anilino-3-methyl-4-phenylazopyrazole. A suspension of 1.8 g (0.01 mole) of 5-anilino-3-methylpyrazole in 23 ml of ethanol and 18 ml of water was treated with 10 g of sodium acetate and, with ice water cooling, a solution of benzenediazonium chloride prepared from 0.95 g (0.01 mole) of aniline, 0.75 g (0.011 mole) of sodium nitrite, and 5.5 ml of 19% hydrochloric acid was slowly added. The suspension was stirred for 1 hr, and the yellow precipitate was filtered off. Mp was 233–234° C (from ethanol). A mixture of this pyrazole with an authentic sample [3] gave no depression of the melting point.

Under similar conditions we obtained 5-anilino-4-p-carboxyphenylazo-3-methylpyrazole [yield 80%, mp 308–310° C (from ethanol). Found, %: N 21.81, 21.89. Calculated for $C_{17}H_{15}N_2O_2$, %: N 22.05] and 5-anilino-3-methyl-4-p-sulfamoylphenylazopyrazole [yield 49%, mp 280–281.5° C (chromatographed on a column of Al_2O_3 in ethanolic solution and subsequently crystallized from ethanol). Found, %: N 23.40, 23.38. Calculated for $C_{16}H_{16}N_6O_2S$, %: N 23.57].

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