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CO-CONDENSATION OF 2-AMINOPYRIDINE, AROMATIC ALDEHYDES, AND KETONES

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The co-condensation of 2-aminopyridine with aromatic aldehydes and ketones proceeds via the initial formation from the amine and the benzaldehydes of (2-pyridylamino)aryl carbinols, which then react with p-nitroacetophenone to give 3-aryl-1-(4-nitrophenyl)-3-(2-pyridylamino)-1-propanones and 3-aryl-1-nitrophenylprop-2-en-1-ones, or with antipyrine to give (2-pyridylamino)aryl-(4-antipyryl)methanes and aryl(diantipyryl)methanes.

The co-condensation of amines, aldehydes, and ketones (the Bayer—Döbner—Mannich reaction [1]) has been used extensively for the synthesis of heterocyclic compounds and aminoketones, but the mechanism of these reactions has been little studied. The Mannich reaction is said to occur via the intermediate formation of the Schiff base [2]. We, too, have observed the intermediate formation of Schiff bases in the synthesis of benzo[f]quinolines from 2-amino-8-naphthol-6-sulfonic acid, aromatic aldehydes, and ketones [3].

We have now examined the behavior of 2-aminopyridine (I) on co-condensation with aldehydes and ketones. It was of interest to investigate the reactions taking place, since the formation of Schiff bases by reaction of the amine (I) with aldehydes in solution has been disputed by many workers [4-6]. For example, the products of the reaction of 2-aminopyridine with aromatic aldehydes in alcohol, toluene, or xylene have been assigned [4, 5], without clear proof, the arylidenepyridylimine structure. With this in mind, we set ourselves the initial task of examining the reaction of the amine (I) with benzaldehydes (IIa-c) and establishing the precise structure of the products, which we required as reference samples in the study of the co-condensation of 2-aminopyridine, benzaldehydes, and ketones.

It was found that brief heating of equimolar amounts of (I) and (II) in alcohol gave the 2-pyridylaminoaryl carbinols (IIIa-c). The UV spectra of these compounds show the absence of a highly conjugated chromophore (Fig. 1). The IR spectra show a narrow absorption band of medium intensity at 3400-3410, and a broad band at 3200-3300 cm^{-1} attributed to absorption of the secondary amino group and the intramolecularly hydrogen-bonded hydroxyl group. Absorption at 1600-1670 cm^{-1}, which would indicate the presence of the azomethine group, was absent. In the PMR spectrum, the signal for the methine proton was seen at 6.12-6.16 ppm. Stability is probably conferred on these compounds by the presence of a strong hydrogen bond between the heteroatom of the pyridine ring and the hydroxyl group.

When the amine (I) was reacted with the aldehyde (IIa) in benzene with azeotropic removal of the water formed by the solvent, a product was obtained which had a higher melting point than (IIIa). From its UV, IR, and PMR spectra, this compound is assigned the structure represented by formula (IV).

This compound (IV) is quite stable, crystallizing from benzene without any changes in its physicochemical constants. Cryoscopic measurement of its molecular mass gave a value close to theoretical. The UV spectrum indicates the presence of a chromophore with a longer conjugated chain than in (IIIa). In the IR spectrum, the absorption at 3200-3500 cm^{-1} was still present, and in addition a weak band at 1670 and a medium band at 1700 cm^{-1} appeared,

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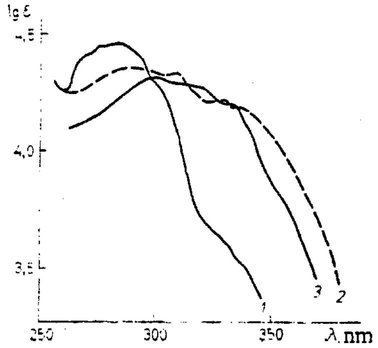
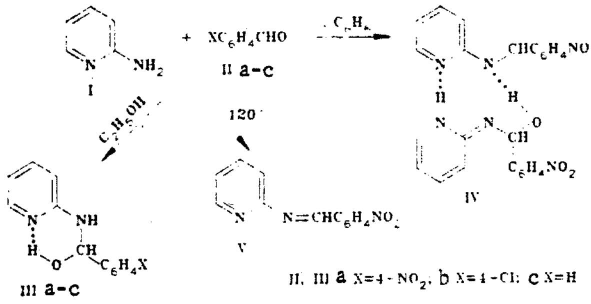


Fig. 1. UV spectra of: 1) 2-pyridylamino-4-nitrophenyl carbinol (IIIa); 2) the molecular compound of 2-pyridylamino-4-nitrophenyl carbinol with 2-(4-nitrobenzylideneamino)pyridine (IV); 3) 2-(4-nitrobenzylideneamino)pyridine (V).

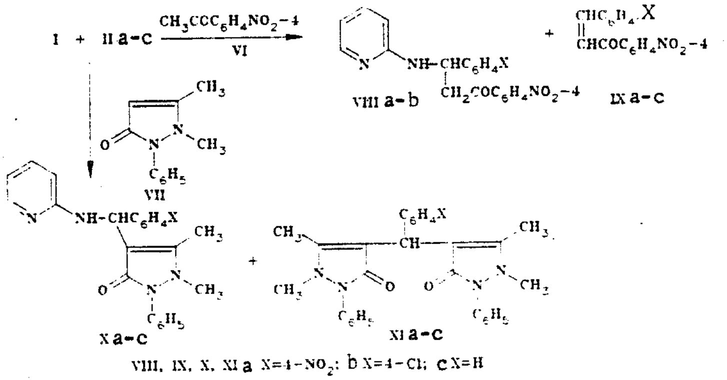
assigned to vibrations of the C=N groups in the Schiff base and the pyridonimine system.

The PMR spectrum contained a complex multiplet consisting of three groups of signals for the aromatic protons: 6.3-6.8 and 7.2-7.5 (protons of both pyridine systems), and 7.7-8.7 ppm (signals for the benzene rings and the pyridine system). The signal at 6.16 ppm was retained, and in addition a signal for the azomethine group appeared with a chemical shift of 9.8 ppm. The elemental composition of (IV) corresponded to that given in [5] for the product of the reaction of 2-aminopyridine with p-nitrobenzaldehyde in toluene or xylene, which the authors regarded as the hemihydrate of the Schiff base, although the melting point of the latter is 105°C [5], and that of (IV) is 118°C.

On fusing 2-aminopyridine with p-nitrobenzaldehyde, the Schiff base (V) is obtained, this having a higher melting point than (IIIa) or (IV) and a different UV spectrum (Fig. 1). Its IR spectrum shows medium absorption at 1670 cm^{-1} (C=N). The PMR spectrum contains a one-proton signal for the methine group at 9.8 ppm, the signals for the aromatic protons being grouped together as a complex multiplet at 7.2-8.7 ppm.



In examining the co-condensation of the amine (I), aldehydes (IIa-c), and ketones in alcohol, the ketones used were p-nitroacetophenone (VI) and antipyrine (VII). As would be expected from what has been said above, the condensation commences with the formation of the aminoalcohols (IIIa-c). In the case of ketone (VI), the final products were the aminoketones (VIIIa, b) and the unsaturated ketones (IXa-c), identical with authentic samples [7], and with the ketone (VII), (2-pyridylamino)aryl-(4-antipyryl)methanes (Xa-c) and the known aryl-(diantipyryl)methanes (XIa-c) [8].



The IR spectra of (VIIIa, b) show strong absorption at 1690 (C=O) and a band of medium intensity at 3410-3430 cm^{-1} (NH). The PMR spectra show a complex multiplet for the aromatic protons at 6.7-8.5 ppm, a doublet with a chemical shift of 4.8 (CH_2), and a triplet at 5.8 ppm (CH).

The IR spectra of (Xa-c) possess characteristic absorption for C=O at 1650 cm^{-1} and for stretching vibrations of the NH group at 3340 cm^{-1}. The PMR spectra show signals for the methine proton (6.15 ppm), two three-proton singlets at 2.25 and 2.95 ppm (2 CH_3), and a complex multiplet for the aromatic protons (6.45-8.07 ppm). The mass spectra contain strong peaks (80%) for the molecular ions. Common to all the spectra of these compounds are relatively strong peaks (30-50%) corresponding to the ions $C_6H_4X^+$ (X = H, Cl, NO_2), $C_5H_5N^+$, $C_5H_5NNH_2{}^+$, ions formed by the elimination of these ions, the $C_6H_5NCO^+$ ion formed from the antipyrine system, and the molecular ion apparently arising from elimination of $C_6H_5NCO^+$ followed by rearrangement to 5-methyl-1-phenyl-3-aryl-2-pyridyl-2,3-dihydropyrazole (the most intense peak).

Increasing the acidity of the medium to more than 0.1 N shifts the reaction toward the preferential formation of (IXa-c) and (XIa-c). These products could be formed directly from the reaction of aldehydes (IIa-c) with ketones (VI) and (VII), but under the conditions in which the co-condensation was carried out (as shown by separate experiments), the unsaturated ketones (IXa-c) are not formed, and the rate of synthesis of the aryldiantipyrylmethanes (XIa-c) is much lower than in the condensation of (I), (II), and (VII). We consider that the suggestion of Kozlov et al. [9] is the most likely explanation, namely that such products result from the cleavage of the initially formed aminoketones [in the present case, (VIIIa, b) and (Xa, b)]. Confirmation of this suggestion is provided by the fact that reaction of ketones (VI) and (VII) with aminoalcohols (IIIa-c) also affords (VIIIa, b), (IXa-c), and (XIa-c).

Hence, the co-condensation of 2-aminopyridine with benzaldehydes and ketones initially gives (2-pyridylamino)aryl carbinols. With p-nitroacetophenone, these give aminoketones and unsaturated ketones, and with antipyrine, aminoketones and aryldiantipyrylmethanes.

EXPERIMENTAL

UV spectra were obtained on an SF-4A spectrophotometer in dioxane, and IR spectra on a UR-20 in Vaseline oil. PMR spectra were recorded on an NMR-5535 apparatus (40 MHz) in deuterochloroform, internal standard HMDS. Mass spectra were obtained on an LKN-2091 instrument, with direct introduction of the sample into the ion source, ionization energy 70 eV, temperature 0-200°C.

The properties of the products are shown in Table 1.

The progress of the condensations was followed by TLC (silica gel, tetrahydrofuran–benzene, 1:10), as follows: at intervals of 1, 5, 10, and 20 min, then every 20 min until the reaction was complete, 0.1 ml samples were withdrawn from the reaction mixture, 1 drop of 30% ammonia and 0.5 ml of acetone added, and the resulting solution applied with a capillary to the chromatographic plate. Acetone solutions of the reference compounds were applied alongside.

2-Pyridylamino-4-nitrophenyl Carbinol (IIIa). A mixture of 0.94 g (0.01 mole) of the amine (I) and 1.51 g (0.01 mole) of the aldehyde (IIa) in 20 ml of alcohol was boiled for 10 min, cooled, and the solid which separated was filtered off and recrystallized from alcohol. Compounds (IIIb, c) were obtained similarly, from (I) and aldehydes (IIb, c).

Molecular Compounds of 2-(4-Nitrobenzylideneamino)pyridine and 2-Pyridylamino-4-nitrophenyl Carbinol (IV). In a flask fitted with a condenser for distillation a mixture of 0.94 g (0.01 mole) of the amine (I), 1.51 g (0.01 mole) of the aldehyde (IIa), and 80 ml of benzene was heated on a water bath, the benzene being slowly distilled off. When 75 ml of benzene had distilled over, the mixture was cooled, and the crystals which separated were filtered off and recrystallized from dry benzene.

2-(4-Nitrobenzylideneamino)pyridine (V). A mixture of 0.94 g (0.01 mole) of the amine (I) and 1.51 g (0.01 mole) of the aldehyde (IIa) was heated for 20 min at 120°C (bath temperature), and the melt was then cooled and recrystallized from dry benzene.

Co-condensation of 2-Aminopyridine, Aromatic Aldehyde, and Ketone. A. A mixture of 0.47 g (5 mmole) of the amine (I), 0.75 g (5 mmole) of the aldehyde (IIa), 0.83 g (5 mmole) of the ketone (VI), 30 ml of alcohol, and 2 drops of concentrated HCl was boiled for 1 h 30

TABLE 1. Properties of Compounds Obtained

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIIa	83	58.6	4,2	17.0	$C_{12}H_{11}N_3O_3$	58.8	4.5	17,4	93
IIIb	80	61.4	4.6	11.8	$C_{12}H_{11}ClN_2O$	61.5	4.7	12.0	92
IIIc	85	—	—	13.7	$C_{12}H_{12}N_2O$	72.0	6.0	14.0	88
IV	118	60.9	4,1	17.5	$C_{24}H_{20}N_6O_5$	61.0	4.2	17.8	89
V	149	63.3	3.7	18.2	$C_{12}H_9N_3O_2$	63,4	4.0	18.5	84
VIIIa	164	61,0	3.8	14.0	$C_{20}H_{16}N_4O_5$	61.3	4.1	14.3	31
VIIIb	119	62,8	4.2	10.9	$C_{20}H_{16}ClN_3O_3$	63.0	4.2	11.0	30
Xa	190	65.4	5,1	17,4	$C_{22}H_{21}N_5O_3$	65.6	5.2	17.4	64
Xb	158	67,1	5,1	14.3	$C_{22}H_{21}ClN_4O$	67.3	5.3	14,3	51
Xc	171	74,1	5,9	15,5	$C_{22}H_{22}N_4O$	74,1	6.2	15,7	50

min, cooled, 1 ml of concentrated HCl added, and the mixture kept for 1 day in the refrigerator. The solid which separated was boiled with 20 ml of benzene, and the mixture filtered hot. On cooling, there separated from the filtrate 0.6 g (40%) of 1,3-di-(4-nitrophenyl)prop-2-en-1-one (IXa). The solid residue was treated with aqueous ammonia, and crystallized from toluene to give 1,3-di-(4-nitrophenyl)-3-(2-pyridylamino)propan-1-one (VIII).

B. A mixture of 0.47 g (5 mmole) of the amine (I), 0.75 g (5 mmole) of the aldehyde (IIa), 0.94 g (5 mmole) of antipyrine, and 2 drops of concentrated HCl in 30 ml of alcohol was boiled for 2 h. It was then cooled, 50 ml of 10% HCl added, and kept at 20°C. The crystalline salt of (XIa) which separated was filtered off and treated with aqueous ammonia followed by crystallization from alcohol, to give 0.3 g (12%) of 4-nitrophenyldiantipyrylmethane (XIa). To the filtrate was added 10 ml of 30% ammonia, and the mixture placed in the refrigerator. The solid which separated was filtered off and crystallized from alcohol, to give 2-pyridylamino-4-nitrophenyl-4-antipyrylmethane (Xa).

Condensations with the other aldehydes (IIb, c) were carried out similarly.

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