INDOLES

XLVI.* SALTS OF ARYLHYDRAZINES AND BISULFITE DERIVATIVES OF γ-HALO CARBONYL COMPOUNDS IN THE SYNTHESIS OF TRYPTAMINES

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UDC 547.752.07

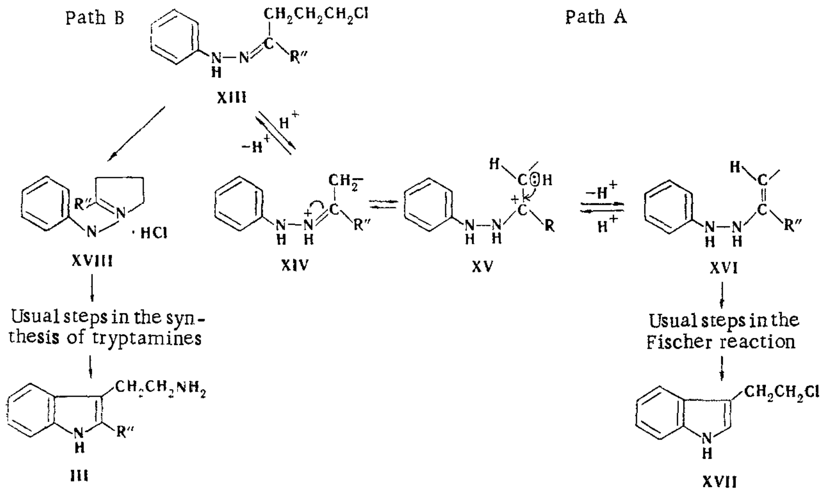
The formation of tryptamines instead of the usual Fischer cyclization is observed when salts of arylhydrazines are heated with γ-halo carbonyl compounds. Bisulfite derivatives of γ-halo carbonyl compounds with both arylhydrazines themselves and with their salts can also be used in the synthesis of the tryptamines.

In an investigation of the possibility of the use of the method in [2, 3] for the synthesis of tryptamines based on the condensation of arylhydrazines with γ-halo carbonyl compounds we observed that the salts of arylhydrazines (I), which are more stable than the corresponding bases (Table 1, path A), can also be used as the starting compounds.

At first glance, the results may seem unexpected. It is known that the salts of arylhydrazines undergo Fischer cyclization to indoles on heating with carbonyl compounds. In particular, the arylhydrazones of γ-halo carbonyl compounds form 3-(β-chloroethyl)indoles (XVII) under acidic conditions [7-10]. This also might have been expected in our case, inasmuch as arylhydrazones XIII are formed very rapidly when salts I are mixed with carbonyl compounds II [3].

The rate of the Fischer reaction (path A) is determined primarily by protonation of the arylhydrazone [11, 12] or, more precisely, by the rate of formation of the enehydrazine [13].

The arylhydrazones of carbonyl compounds are weak bases with pK_a values of the conjugate acids of ~1.5 [14].



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*For Communication XLV see [1].

K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1085-1088, August, 1974. Original article submitted October 16, 1973.

TABLE 1. Characteristics of the Compounds Obtained

Compound	R	R′	R″	mp, °C	bp, °C (mm)	A (from salts I · HX)		B (from bisulfite derivatives of II) yield, %
						X	Yield, %	
III	H	H	H	113—115[2]	185—187 (0,5)	Cl	78	78
IV	CH_3	H	H	—	135—136[2] (2) n_D^{20} 1,6021	HSO_4	78	83
V	$CH_2C_6H_5$	H	H	93—94[2]	157—161 (0,1)	—	—	78
VI	H	5-CH_3	H	95—96[2]	150—155 (0,1)	HSO_4	45	—
VII	H	5-$OCH_2C_6H_5$	H	84—86[4]	—	—	—	62
VIII	H	H	CH_3	108[5]	214—216 (1,5)	Cl	74	74 (91*)
IX	CH_3	H	CH_3	54—55[6]	170—172 (0,2)	HSO_4	75	80 (60†)
X	H	5-CH_3	CH_3	100—101[5]	210—212 (8)	HSO_4	71	—
XI	H	7-CH_3	CH_3	160—161[5]	209—211 (7)	Cl	64	—
XII	$CH_2C_6H_5$	H	CH_3	54—55[6]	170—172 (0,5)	Cl	74	—

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*Obtained by heating in a sealed ampul in 90% methanol at 170-180° for 2 h.

† From arylhydrazine salt I and bisulfite derivative of IIb by refluxing in 60% methanol.

Such low basicities are responsible for the fact that the salt⇌base (XIII-XIV) equilibrium under our conditions of aqueous alcohol solutions (their pH is ~1.75) is shifted to favor the unprotonated hydrazone (XIII) (~70% of this form is present).

In this connection, the usual Fischer reaction (path A) does not occur, but a competitive process – quaternization at the β-nitrogen atom in hydrazone XIII to give N-anilinopyrroline XVIII and final conversion to tryptamine III (path B) – does take place.

An increase in the acidity [7-10] shifts the equilibrium to favor protonated hydrazone XIV, decreasing the possibility of quaternization, and, in addition, increases the rate of conversion of hydrazone XIII to enehydrazone XVI (which is removed from the reaction), increasing the rate of indolization [15] (path A).

Only the formation of enehydrazine XVI can lead to indole XVII, but apparently does not occur during each act of its development, inasmuch as the enehydrazine form is extremely unfavorable [16] and is rapidly converted to hydrazone XIII through the same steps via the above-indicated scheme (XVI-XV-XIV-XIII).

However, in the case of quaternization, structure XVIII, which is ideal for the subsequent sigmatropic [3,3] shift [3], is formed. Shifting of the double bond to the nitrogen atom in the molecule of unprotonated base cannot occur here, and the reaction proceeds readily along the path of formation of the tryptamine (path B).

The kinetic data should also be taken into account. The rate-determining step in the synthesis of tryptamines is quaternization of the β-nitrogen atom of hydrazone XIII [12].

It follows from a comparison of the rate constants of Fischer reactions catalyzed by acids [17] and proceeding under the influence of allyl bromide [12] under comparable conditions that these rates are first-order values (K $10.5 \cdot 10^{-3}$ and $4.7 \cdot 10^{-3}$, min^{-1}, respectively).

The difference between our reaction and the above reactions consists in the fact that quaternization of the β-nitrogen atom proceeds intramolecularly, i.e., the probability factor, which always promotes an intramolecular reaction, should also be taken into account.

We were also able to find another variant of the method for the synthesis of tryptamines III based on the use of the stable bisulfite [18] derivatives of γ-halo carbonyl compounds (XX). This is particularly important for the synthesis of 2-unsubstituted tryptamines, inasmuch as γ-chlorobutyraldehyde itself (IIa) is an extremely unstable compound.

Derivatives XX are readily obtained via the usual scheme [18]. Condensation of the latter with arylhydrazines XIX occurs when the compounds are refluxed in 60% methanol in a neutral medium (no resinification is observed). The yields of the tryptamines (Table 1, path B) are basically even higher than when free γ-halo carbonyl compounds are used [2]. In this case, carrying out the reaction at higher temperatures (by heating in a sealed ampul at 170-180° for 2 h) promotes a further increase in the yields (Table 1, path B, compound VIII).

Salts of arylhydrazines I can also be used in this same reaction, but, despite variations in the conditions (changes in the temperature and the reagent ratios), the yields of the tryptamines are considerably lower (Table 1, path B, compound IX).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions were recorded with an EPS-3T spectrophotometer. Thin-layer chromatography (TLC)was carried out on Silufol UV-254 in isopropyl alcohol–25% ammonia (90 : 15) (R_f); paper chromatography was carried out on Volodarskii "fast" paper in n-butanol–acetic acid–water (4 : 1 : 5) (R_f). The chromatograms were developed with Erlich's reagent.

γ-Chlorobutyraldehyde (IIa). This compound was obtained by Rosemund reduction [18] of γ-chlorobutyryl chloride in tetralin at 130-140°.

γ-Chloropropyl Methyl Ketone (IIb). This compound was obtained in 66% yield by the method in [19] by refluxing acetylpropyl alcohol with excess concentrated HCl.

Bisulfite Derivative of γ-Chlorobutyraldehyde (XXa). This compound was obtained in 96% yield by the method in [18] and was 90% pure.

Bisulfite Derivative of γ-Chloropropyl Methyl Ketone (XXb). This compound was similarly prepared in 92% yield and was 95% pure.

p-Benzyloxyphenylhydrazine. A total of 143 g (0.625 mole) of p-nitrophenol benzyl ether was added gradually in 10-15-g portions (until all of the solid had dissolved) to a refluxing mixture of 400 ml of methanol, 400 ml of hydrazine hydrate, and 3 g of Raney nickel (type W-2 [20]), after which the mixture was refluxed for 1 h. The hot solution was decanted away from the catalyst, and the alcohol was removed by vacuum distillation. The crystalline residue was removed by filtration and washed with 600 ml of hot water (in 200-ml portions). The moist, well-squeezed solid was dissolved in 500 ml of hot isopropyl alcohol, and concentrated HCl was added until the mixture was acid to Congo red (~ 50 ml). The precipitated crystalline salt (~ 100 g) was removed by filtration and washed with ether. The filtrate was then vacuum evaporated until a precipitate began to form. An additional 32 g of p-aminophenol benzyl ether hydrochloride was obtained. The overall yield was 132 g (90%); mp 210-212° (from aqueous isopropyl alcohol [22].

The diazonium salt from p-aminophenol benzyl ether was reduced with stannous chloride in hydrochloride. The yield of the hydrazine was 70%; mp 106-107° [22].

General Method for the Preparation of Tryptamines (III). A) A solution of 0.05 mole of γ-chlorobutryaldehyde (IIa) or γ-chloropropyl methyl ketone (IIb) in 10 ml of methanol was added to a refluxing solution of an equimolar amount of arylhydrazine salt I in 60 ml of 90% methanol, and the mixture was refluxed for 10 h. The alcohol was then removed by distillation, and the residue was dissolved in 50 ml of water. The neutral impurities were extracted with ether (two 20-ml portions). The aqueous solution was cooled and made alkaline, and the resulting oil was extracted with benzene (three 20-ml portions). The extract was dried with fused KOH and vacuum distilled. The crystalline compounds were additionally purified by crystallization.

B) A solution of 0.05 mole of arylhydrazine XIX or its salt (I) in the minimum amount of methanol was added all at once to a refluxing solution of 0.05 mole (based on the principal product) of bisulfite derivative XX in 100 ml of 60% methanol, and the mixture was refluxed on a water bath for 14 h. The alcohol was removed with a rotary evaporator, and the residue was dissolved in 50 ml of 1 N HCl. The reaction mixture was then worked up as in the preceding method (A).

The individuality of all of the tryptamines obtained (III) was monitored by chromatography on Silufol. The identification of the crystalline compounds was established by means of mixed melting point determinations.

5-Benzyloxytryptamine (VII). This compound, with mp 84-86° [4], was obtained in a yield that was 62% of that expected from theory B (it began to crystallize after evaporation of the benzene extract, which had first been filtered through a layer of aluminum oxide): R_f 0.60, R_f 0.86. Found: C 76.7; H 6.8%. $C_{17}H_{18}N_2O$. Calculated: C 76.7; H 6.8%. IR spectrum: 3350, 3290 (NH); 1620, 1590, and 1490 cm^{-1} (ring). UV spectrum, λ_{max}, nm (log ε): 277 (3.67), 285 (3.62), and 291 (3.57). The picrate, with mp 222.5-224° (dec.), was obtained in absolute ether with a molar amount of picric acid and was recrystallized from the minimum amount of alcohol. Found: N 14.1%. $C_{17}H_{18}N_2O \cdot C_6H_3N_3O_7$. Calculated: N 14.2%.

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