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HETEROCYCLIZATION OF *N*-PHENYLAMINO-2-PYRROLIDONES

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Heterocyclization of N-*phenylamino-2-pyrrolidones with solutions of phosgene takes place with the formation of dihydropyrrolo[2,3-*b*]indoles, which on acid cleavage give 2-oxotryptamines or their derivatives.*

The rearrangement of carboxylic acid arylhydrazides by treatment with phosphorus halides is the principal method for synthesizing 2-aminoindole derivatives [1]. Up to the present time there have been detailed studies of the rearrangement of arylhydrazides of alkyl- and aralkyl-carboxylic acids, and also of a series of 1-aryl-2-acylpyrazolidines, which are carbocyclic analogues of hydrazines [2]. The heterocyclization of arylhydrazides containing a cyclic residue in the amide part of the molecule of *N*-arylamino-2-pyrrolidones and the reactivity of the reaction products have not previously been studied.

In a brief communication [3] we published the preliminary results of the reaction between *N*-alkyl-*N*-phenylamino-2-pyrrolidones and phosphorus oxychloride, resulting in the isolation of 2-oxotryptamine derivatives after treatment of the reaction mixtures. This can be accounted for by decomposition of unstable tricyclic structures that are related to eserine systems, the formation of which follows logically from application of the reaction mechanism to these models. We have previously demonstrated that chloroformic acid derivatives, and in particular solutions of phosgene in benzene, are mild and efficient heterocyclization reagents [4].

In connection with the above, it was of interest to study the reaction between *N*-phenylamino-2-pyrrolidones and solutions of both phosgene and phosphorus oxychloride and the properties of the compounds thus obtained.

In the present study the compounds to be investigated are *N*-phenylamino-2-pyrrolidones (Ia-d). We have previously developed a method for their synthesis by intramolecular alkylation of arylhydrazides of γ-chlorobutyric acid in the presence of sodium ethoxide [5].

Heterocyclization of pyrrolidones Ia-c on treatment with solutions of phosgene in benzene results in the formation of compounds that can be assigned the structure of dihydropyrrol[2,3-*b*]indoles (IIa-c) on the basis of their physicochemical data. Thus, in the mass spectra of these compounds there are peaks due to ions with *m/z* equal to M + H from their bases. In the PMR spectra, in addition to signals from the protons of the aromatic and dihydropyrrole rings and the substituent on the nitrogen atom there is a signal due to the proton at the 3a-position of the molecule in the form of a double doublet at about 4.8 ppm.

Dihydropyrrolo[2,3-*b*]indoles (IIa-c) are fairly unstable and on standing in aqueous alcohol solutions or on heating for a short time in the presence of hydrochloric acid they are converted to the corresponding 2-oxotryptamines IIIa-c, corresponding to those obtained previously [3]. On heating in ethanol the amidine group of the tricyclic systems undergoes cleavage, 2-ethoxyindole derivatives IVb and IVc being formed, for example, from compounds IIb and IIc.

Acetylation of dihydropyrrolo[2,3-*b*]indoles IIa-c leads to the corresponding *N*-acetyl derivatives Va-c. In their IR spectra there are absorption maxima due to the carbonyl groups at about 1650 cm^{-1}. In some cases (compounds Vb and Vc) peaks appear in the mass spectra due to products from the reaction between the compounds and ethanol in the glycerine matrix (M + EtOH + H) in addition to molecular ion peaks. They probably result from a form of cleavage of the tricyclic structures of IIb and IIc with ethanol. In contrast to the spectra of *N*-acetyl-2-oxotryptamines VIa-c (see below), in the PMR spectra of compounds Va-c the signals due to the protons of the dihydropyrrole ring are recorded as two triplets (J = 8 Hz) at about 3 and 4-4.5 ppm.

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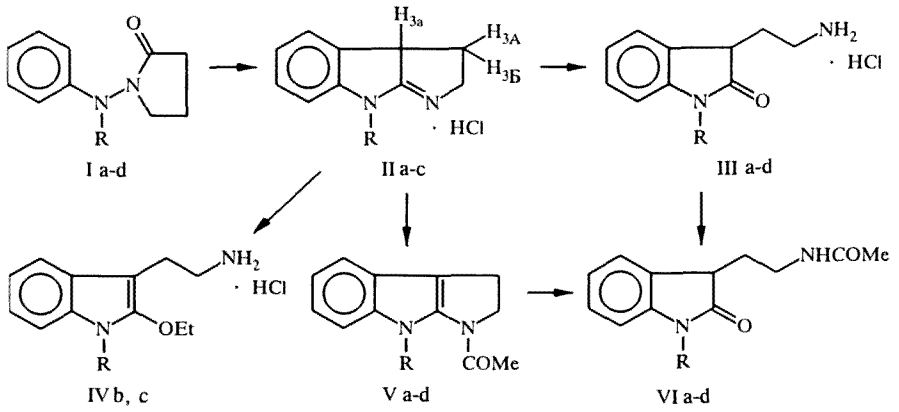

I—VI a R = H, b R = Me, c R = CH_2Ph, d R = Ph

We were not able to isolate the respective pyrroloindole from the reaction between *N*-diphenylamino-2-pyrrolidone (Id) and phosgene, and only after acetylation of the impure compound was its *N*-acetyl derivative Vd isolated in low yield, thus suggesting that the heterocyclization process was not clearly defined. The low yields of the acetylation products Va-c can be attributed to the low stability of the pyrroloindoles themselves and also of the products obtained, which, for example, when chromatographed on silica gel decompose to *N*-acetyl-2-oxotryptamines that are identical to those described above.

The reaction between compounds Ia-d and solutions of phosphorus oxychloride in dioxane combines heterocyclization with subsequent decomposition and leads to a mixture of compounds, from which it was possible to isolate and characterize 2-oxotryptamine hydrochlorides IIIa-d. These compounds have UV spectra that are typical of oxindoles — absorptions at 213-218 nm, 253-260 nm, and 280 nm (shoulder) [6]. In the IR spectra of the hydrochlorides IIIa-d there are broad absorption maxima from the salt-like ammonium group at about 3250-2500 cm^{-1} and the carbonyl group at 1700-1710 cm^{-1} [6]. In the PMR spectra a multiplet due to the 3-H methine proton occurs at 3.6-3.8 ppm. In the mass spectra of these compounds there are intense molecular ion peaks with *m/z* values equal to M^+ from their free bases. It is clear that reactions similar to those described above for pyrroloindoles have also taken place on treatment of the reaction mixtures with alcohols in the presence of phosphorus oxychloride after heterocyclization. We incorporated acidic cleavage after rearrangement, so that the yields of 2-oxotryptamines could be increased substantially.

When 2-oxotryptamines IIIa-d are acetylated, their monoacetyl derivatives VIa-d are formed. In the IR spectra of these compounds there are absorption bands due to the NH of the amide group at 3280-3310 cm^{-1} and also absorption maxima due to the carbonyl group of the oxindole ring at about 1700 cm^{-1}. The molecular ion peaks are present in the mass spectra.

Thus, heterocyclization of *N*-phenylamino-2-pyrrolidones with solutions of phosgene in benzene is a convenient preparative method for the synthesis of dihydropyrrolo[2,3-*b*]indoles, acid treatment of which leads to 2-oxotryptamines.

EXPERIMENTAL

The IR spectra were recorded as suspensions in vaseline oil on a Specord 1R-75 instrument. The PMR spectra were recorded on a Tesla BS 487C instrument in DMSO-D_6, with TMS as internal standard. The mass spectra of compounds IIa-c, IVb, IVc, and Va-d were recorded in a glycerine matrix on an MI 1201É instrument by bombardment with accelerated argon atoms; the electron impact spectra for compounds IIIa-d and VIa-d were recorded on an MX-1303 instrument with an electron ionization energy of 70 eV with direct introduction of the sample. The properties of the compounds synthesized are listed in Table 1.

The elemental analysis data of the compounds synthesized corresponded to the calculated values.

Dihydropyrrolo[2,3-*b*]indole Hydrochlorides (IIa-c). To 0.02 mole of the respective pyrrolidone [5] was added 18-20 ml of a solution of phosgene in benzene (0.04 mole). When the foaming had ceased the reaction mixture was agitated at room temperature for 24 h. The precipitate of dihydropyrrolo[2,3-*b*]indoles dihydrochlorides IIa-c that formed was triturated, filtered off, and washed on the filter with dry ether. The product was dried under vacuum.

TABLE 1. Properties of Compounds Synthesized

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	Mass spectrum, m/z	PMR spectrum, δ, ppm, J, Hz	Yield, %
1	2	3	4	5	6	7
IIa	$C_{10}H_{10}N_2 \cdot HCl$	127...130	3600...2700, 1700, 1610	159 $[M-HCl+H]^+$	1,7...3,0 (2H, m, CH_2), 3,7...4,2 (2H, m, CH_2), 4,8 (d.d, 3a-H, $J_1 = 14$, $J_2 = 8$), 7...7,7 (4H, m, arom), 11,6, 13 (NH, br.)	72
IIb	$C_{11}H_{12}N_2 \cdot HCl$	220 (dec.)	2700...2600, 1700, 1610	173 $[M-HCl+H]^+$	1,9...3,0 (2H, m, CH_2), 3,53 (3H, s, CH_3), 3,9...4,2 (2H, m, CH_2), 4,8 (d. d, 3a-H, $J_1 = 15$, $J_2 = 8$), 7...7,6 (4H, m, arom), 12,1 (NH, br.)	89
IIc	$C_{17}H_{16}N_2 \cdot HCl$	180...182 (dec.)	2600...2500, 1680, 1600	249 $[M-HCl+H]^+$	1,9...3,0 (2H, m, CH_2), 3,8...4,3 (2H, m, CH_2), 4,7...5,6 (3H, m, 3a-H, $CH_2C_6H_5$), 7...7,6 (9H, m, arom), 8,5 (NH, br.)	94
IIIa	$C_{10}H_{12}N_2O \cdot HCl$	234...237*	3250...2500, 3140, 1705	176 $[M-HCl]^+$	1,9...2,4 (2H, m, CH_2), 2,8...3,2 (2H, m, CH_2), 3,7 (m, 3-H), 7...7,4 (4H, m, arom), 8,3, 10,6 (NH, br.)	54
IIIb	$C_{11}H_{14}N_2O \cdot HCl$	212...215*	3210...2500, 1710	190 $[M-HCl]^+$	2,4...2,8 (2H, m, CH_2), 3,1 (2H, m, CH_2), 3,5 (3H, s, CH_3), 3,8 (t, 3-H, $J = 7$), 7,2...7,9 (4H, m, arom)	57
IIIc	$C_{17}H_{18}N_2O \cdot HCl$	222...224	3150...2500, 1710	266 $[M-HCl]^+$	2,0...2,4 (2H, m, CH_2), 2,9...3,4 (2H, m, CH_2), 3,6 (m, 3-H), 4,6 (2H, s, $CH_2C_6H_5$), 6,4...7,4 (9H, m, arom)	81
IIId	$C_{16}H_{16}N_2O \cdot HCl$	217...219	3150...2500, 1710	252 $[M-HCl]^+$	2,0...2,5 (2H, m, CH_2), 2,8...3,5 (2H, m, CH_2), 3,9 (m, 3-H), 6,5...7,8 (9H, m, arom)	75
IVb	$C_{13}H_{18}N_2O \cdot HCl$	166 (dec.)	3400...2700, 1550	219 $[M+H]^+$	1,33 (3H, t, $J = 7$, CH_3CH_2), 3,0 (4H, br., 2-CH_2), 3,57 (3H, s, NCH_3), 4,16 (2H, q, $J = 7$, CH_3CH_2), 6,7...7,6 (4H, m, arom), 8,35 (NH_2, br.)	37
IVc	$C_{19}H_{22}N_2O \cdot HCl$	175 (dec.)	3300...2800, 1620, 1570	295 $[M+H]^+$	1,27 (3H, t, $J = 7$, CH_3CH_2), 3,0 (4H, br., 2-CH_2), 4,14 (2H, q, $J = 7$, CH_2CH_3), 5,27 (2H, s, $CH_2C_6H_5$), 6,7...7,7 (9H, m, arom), 8,34 (NH_2, br.)	72
Va	$C_{12}H_{12}N_2O$	214...215	3320, 1640, 1600, 1570	201 $[M+H]^+$	2,17 (3H, s, $COCH_3$), 3,07 (2H, t, $J = 8$, 3-CH_2), 4,47 (2H, t, $J = 8$, 2-CH_2), 6,7...7,6 (4H, m, arom), 11,2 (NH, br.)	35
Vb	$C_{13}H_{14}N_2O$	151...153	1650, 1600, 1560	261 $[M+EtOH+H]^+$, 215 $[M+H]^+$	2,2 (3H, s, $COCH_3$), 2,72 (2H, t, $J = 8$, 3-CH_2), 3,97 (3H, s, NCH_3), 4,34 (2H, t, $J = 8$, 2-CH_2), 7...7,1 (4H, m, arom)	32

TABLE 1 (continued)

1	2	3	4	5	6	7
V c	$C_{19}H_{18}N_2O$	166...167	3060, 1640, 1610, 1600	337 $[M+EtOH+H]^+$	2,17 (3H, s, $COCH_3$), 3,0 (2H, t, J = 8, 3-CH_2), 4,34 (2H, t, J = 8, 2-CH_2), 5,78 (2H, s, $\underline{CH_2}C_6H_5$), 7,1 (9H, m, arom)	65
V d	$C_{18}H_{16}N_2O$	136...137	1650, 1590, 1570	277 $[M+H]^+$	1,87 (3H, s, $COCH_3$), 3,1 (2H, t, J = 7, 3-CH_2), 4,57 (2H, t, J = 7, 2-CH_2), 6,8...7,6 (9H, m, arom)	10
VI a	$C_{12}H_{14}N_2O_2$	130...134*	3300, 1700, 1640	218 $[M]^+$	–	–
VI b	$C_{13}H_{16}N_2O_2$	117...120	3280, 1700, 1640	232 $[M]^+$	1,8...2,5 (5H, m, CH_2, $COCH_3$), 3,2 (3H, s, NCH_3), 3,2...3,7 (3H, m, 3-H, CH_2), 6,6...7,6 (4H, m, arom)	72
VI c	$C_{19}H_{20}N_2O_2$	115...117	3310, 1700, 1640	308 $[M]^+$	1,9...2,4 (5H, m, CH_2, $COCH_3$), 3,2...3,7 (3H, m, 3-H, CH_2), 4,9 (2H, s, $\underline{CH_2}C_6H_5$), 6,5...7,5 (9H, m, arom)	77
VI d	$C_{18}H_{18}N_2O_2$	115...116	3280, 1700, 1630	294 $[M]^+$	1,9 (3H, s, $COCH_3$), 2...2,5 (2H, m, CH_2), 3,3...3,9 (3H, m, 3-H, CH_2), 6,6...7,9 (9H, m, arom)	61

*Literature data: mp, °C: IIIa) 235-239 [7]; IIIb) 193-194 [8]; VIa) 130-133 [7].

2-Oxotryptamine Hydrochlorides (IIIa-d). **A**. To a solution of 0.01 mole of the respective *N*-phenylamino-2-pyrrolidone (Ia-d) in 20 ml of absolute dioxane was added 0.02 mole of phosphorus oxychloride and the mixture was agitated at 60°C until (according to TLC) the initial compound had disappeared (6-40 h). The reaction mixture was evaporated under vacuum, 10 ml of dry toluene was added to the residue, and further evaporation under vacuum was carried out. To the oily residue was added 10 ml of water and 0.3 g of activated carbon, the mixture was kept at 55-60°C for 0.5 h and then filtered off, and the carbon was washed with 2 ml of water. The filtrate was evaporated under vacuum and the residue was triturated in cold ethanol. The crystalline precipitate of 2-oxotryptamine salt was filtered off, washed on the filter with dry ether (2 × 5 ml), and recrystallized from ethanol.

B. A mixture of 0.001 mole of dihydrochlorides IIa-d, 5 ml of methanol, and 5 ml of water was left for 24 hours at room temperature; it was then evaporated, and the residue was triturated in dry ether and filtered off. The IR spectra and melting point of the compounds obtained were consistent with those obtained by method A for the corresponding 2-oxotryptamine hydrochlorides IIIa-d.

***N*-Acetyl-2-oxotryptamines (VIa-d).** To a solution of 0.005 mole of 2-oxotryptamine hydrochloride IIIa-d in 15 ml of dry chloroform with agitation and cooling to 0-5°C was added dropwise 0.015 mole of triethylamine, then 0.01 mole of acetic anhydride, and the mixture was agitated at room temperature for 2 h. The reaction mixture was diluted to 100 ml with chloroform, washed with water (2 × 100 ml), and dried over sodium sulfate. The chloroform evaporated under vacuum, and the residue was triturated in hexane, filtered off, and dried in the air.

***N*-Acetyldihydropyrrolo[2,3-*b*]indoles (Va-c)**. To a suspension of 0.001 mole of hydrochloride IIa-c in 5 ml of dry chloroform on cooling to 0-5°C was added 0.05 mole of acetic anhydride and 0.01 mole of triethylamine was then added dropwise. The reaction mixture was agitated at room temperature for 24 h and the precipitate was filtered off, washed on the filter with a small quantity of cold water, and dried under vacuum. When the reaction mixtures containing the acetylation products were chromatographed on silica gel to purify them, *N*-acetyl-2-oxotryptamines which were identical to those obtained previously were formed.

1-Acetyl-8-phenyl-2,3-dihydro[1H,8H]pyrrolo[2,3-*b*]indole (Vd). A mixture of 0.01 mole of *N*-diphenylamino-2-pyrrolidone (Id) and 20 ml of a solution of phosgene in benzene (0.04 mole) was agitated for 3 days at room temperature, then evaporated under vacuum, triturated in ether, and repeatedly decanted. The residue was acetylated according to the above procedure. Pyrrolo[2,3-*b*]indole Vd was obtained.

2-Ethoxytryptamine Hydrochlorides (IVb, IVc). A solution of 0.004 mole of compound IIb or IIc in 2 ml of absolute ethanol was refluxed for 0.5-1 h and then cooled. The precipitate of IVb or IVc that formed was filtered off and recrystallized from ethanol.

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