REACTION OF 1-METHYL-2-CYANOINDOLE WITH AROMATIC ALDEHYDES

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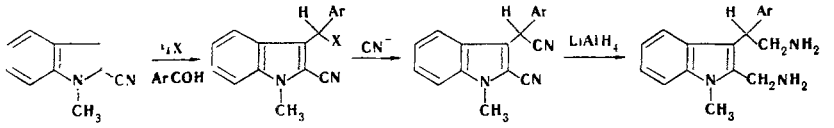
1-Methyl-2-cyanoindoles react with aromatic aldehydes in acidic media to give 1-methyl-2-cyano-3-(α-halobenzyl)indoles. Replacement of the halogen by a cyano group gives (indolyl)-phenylacetonitrile, reduction of which gives the corresponding tryptamine. An attempt to replace the acetoxy group in 1-methyl-2-carbomethoxy-3-(α-acetoxybenzyl)indole by a cyano group was accompanied by rearrangement to give 1-methyl-2-cyano-3-benzylindole.

The reaction of aromatic aldehydes with indoles in acidic media gives both (diindolyl)phenylmethanes and indolenines. In contrast to this, 1-alkylindole-2-carboxylic acids and their esters and amides form 3-(α-X-benzyl)indoles, where X = Cl, Br, and OAlk[1] [1]. We have observed that 1-methyl-2-cyanoindole (I) also forms addition products with aromatic aldehydes:



I II-VI VII, VIII IX

II-VI X = Cl, Br

The UV spectra of 1-methyl-2-cyano-3-(α-halobenzyl)indoles II-VI contain λ_{max} bands at 284-286 nm (log ε 4.505), which are close to the band observed in the spectrum of starting nitrile I [λ_{max} 284 nm (log ε 4.580)]. The band at 2230 cm^{-1} due to the stretching vibrations of the C≡N group is retained in the IR spectrum. The PMR spectrum of II contains signals of aromatic protons (m, 8H; 7.2-7.3 ppm), the signal of a benzyl proton (s, 1H; 6.85 ppm) and the signal of an NCH_3 group (s, 3H; 3.86 ppm); this indicates the inclusion of the aldehyde fragment in the indole molecule. All II-VI are easily crystallized colorless substances (Table 1). An attempt to exchange the halogen in II-VI for a cyano group with potassium and sodium cyanides proceeded in satisfactory yield (65%) only with derivative II to give VII, whereas VIII was isolated in only 30% yield. The use of a less alkaline media by the method in [2] did not improve the yield. The IR spectrum of dinitrile VII contains two bands at 2230 and 2240 cm^{-1} with an intensity ratio of 10:1, respectively, for the aromatic and aliphatic C≡N groups [3]. At the same time, a considerable shift to the strong-field region of the signal of the lone benzyl proton (s, 1H; 6.34 ppm) as compared with chloride II (s, 1H, 6.85 ppm), which indicates replacement of the chlorine atom by the stronger-shielding C≡N group, was observed.

An attempt to obtain 3-(α-cyanobenzyl)indoles in analogy with the synthesis of dinitriles VII and VIII from 1-methyl-2-carbomethoxy-3-(α-acetoxybenzyl)indole was unsuccessful. 1-Methyl-2-cyano-3-benzylindole (X) was isolated unexpectedly in high yield. The same compound (X) was obtained from 1-methyl-2-carboxy-3-(α-chlorobenzyl)indole in 15% yield.

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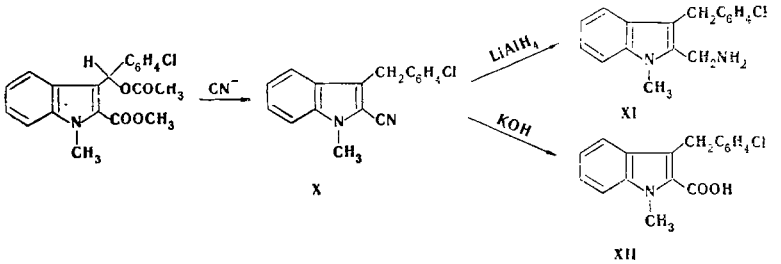

In [4] it was observed that anionotropic rearrangement of the benzoyl group to the 2 position of the indole ring occurs during substitution of the halogen in β-(3-indolyl)-β-halopropionic acid under the influence of silver benzoate. In 1972 Rusinova and co-workers [5] showed that the cyano group initially attacks the benzyl carbon atom in the reaction of KCN with 3-(α-methylaminobenzyl)indole, after which it migrates to the 2 position of the indole ring as a result of oxidative rearrangement. The stability of X with respect to oxidation that we observed in this study is explained by the presence of a methyl substituent attached to the nitrogen atom, whereas the formation of 2-cyanoindole X may be realized through the (3-indolyl)phenylmethyl cation that is generated due to dissociation of the carbon–oxygen or carbon–chlorine bond. The resonance structures with a positive charge on the α-carbon atom of the indole ring and on the benzyl carbon atom make a considerable contribution to the structure of the (indolyl)phenylmethyl cation. The attack of the cyanide ion proceeds primarily at the more electrophilic (due to the carbomethoxy group) α position of the indole ring, and this leads to the formation of geminal cyano and carbomethoxy groups, of which the latter is readily split out after hydrolysis. The difference in the behavior of 1-methyl-2-cyano-3-(α-chlorobenzyl)indoles II and V and the behavior of 1-methyl-2-carbomethoxy-3-(α-chlorobenzyl)indole in the reaction with KCN consists in the fact that the fact that the cyano group in the 2 position is not eliminated as readily as the carboxyl group, and the newly introduced cyano group remains in the benzyl grouping. Dinitrile VII was reduced with $LiAlH_4$ to tryptamine IX, which was isolated in the form of the base and the picrate, whereas nitrile X was reduced by the same method to amine XI and saponified to acid XII with KOH in ethylene glycol.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with an SF-16 spectrophotometer. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra of CCl_4 solutions were obtained with a Varian-100 spectrometer.

1-Methyl-2-cyanoindole (I). A mixture of 17.5 g (0.1 mole) of 1-methylindole-2-carboxylic acid, 25 g of phosphorus pentachloride, and 750 ml of absolute ether was stirred for 3 h, after which the solution was decanted away from the undissolved solid, and a strong stream of ammonia was bubbled through the ether solution until precipitation ceased. The precipitate was removed by filtration, and washed on the filter with water to remove the inorganic salts to give 15.6 g (90%) of 1-methylindole-2-carboxamide with mp 170° (mp 171° [6]). The amide was refluxed in 100 ml of phosphorus oxychloride for 10 min, after which the excess phosphorus

TABLE 1. 1-Methyl-2-R-3-(α-X-benzyl)indoles (II-XII)

Compound	R	R′	X	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
						Cl	N	Cl	N	
II	CN	o-Cl	Cl	154	$C_{17}H_{12}Cl_2N_2$	22,4	8,6	22,6	8,9	83
III	CN	o-NO_2	Cl	134	$C_{17}H_{12}ClN_3O_2$	11,5	12,5	10,9	12,9	58
IV	CN	p-NO_2	Cl	126	$C_{17}H_{12}ClN_3O_2$	10,9	12,3	12,9	12,9	61
V	CN	p-Cl	Cl	98	$C_{17}H_{12}Cl_2N_2$	21,9	8,8	22,6	8,9	55
VI	CN	p-Cl	Br	128	$C_{17}H_{23}BrClN_2$	28,8	7,2	29,3	7,8	50
VII	CN	o-Cl	CN	171	$C_{18}H_{12}ClN_3$	12,1	14,1	11,6	13,8	65
VIII	CN	p-Cl	CN	156	$C_{18}H_{12}ClN_3$	11,0	12,8	11,6	13,8	30
IX	CH_2NH_2	o-Cl	CH_2NH_2	110	$C_{18}H_{20}ClN_3$	10,7	12,7	11,3	13,4	56
X	CN	o-Cl	H	108	$C_{17}H_{13}ClN_2$	12,6	9,9	12,7	10	85
XI*	CH_2NH_2·HCl	o-Cl	H	254	$C_{17}H_{17}ClN_2 \cdot HCl$	21,9	8,6	22,2	8,7	75
XII	COOH	o-Cl	H	220	$C_{17}H_{14}ClNO_2$	11,8	4,4	11,9	4,7	60

*Found: Cl′ 11.1%. Calculated: Cl′ 11.1%.

oxychloride was removed by vacuum distillation, and the residue was poured into ammonium hydroxide containing ice. The liberated oil immediately began to crystallize. The crystals were separated, dried, and purified by crystallization from aqueous ethanol to give 10.6 (68%) of nitrile I with mp 71°. Calculated: C 76.2; H 4.8; N 17.8%. $C_{10}H_8N_2$. Calculated: C 76.9; H 5.1; N 17.9%. UV spectrum: λ_{max} 284 nm (log ε 4.504). IR spectrum: 2250 cm^{-1} (CN).

1-Methylindole-2-carboxylic Anhydride. Evaporation of an ether solution of 1-methylindole-2-carboxylic acid chloride obtained from the preceding step gave crystals, which were removed by filtration and dried to give 10 g (62%) of a product with mp 85° (from ether). UV spectrum: λ_{max} 314 nm (log ε 4.356). IR spectrum: 1750 cm^{-1} (CO). PMR spectrum: 7.2 ppm (8H, aromatic protons) and 3.80 ppm (NCH_3, s, 6H).

1-Methyl-2-cyano-3-(α-chloro-o-chlorobenzyl)indole (II). A 1.56-g (0.01 mole) sample of I was mixed with 1.54 g (0.011 mole) of o-chlorobenzaldehyde, 10 ml of ether saturated with hydrogen chloride was added, and the mixture was stirred and allowed to stand at room temperature overnight. The resulting precipitate was removed by filtration to give 2.6 g (83%) of a product with mp 154° (from acetonitrile).

The method described above was used to obtain III, IV, and V. Compound VI was obtained by replacement of ether saturated with HCl by acetic acid saturated with HBr.

After purification from acetonitrile, II-VI displayed one spot with R_f 0.7-0.8 on their thin-layer chromatograms [Silufol, elution with cyclohexane–ethyl acetate (3 : 1)].

1-Methyl-2-cyano-3-(α-cyano-o-chlorobenzyl)indole (VII). A mixture of 1.56 g (0.005 mole) of II and 0.49 g (0.01 mole) of NaCN in 30 ml of alcohol was refluxed for 1 h, after which 5 ml of water was added, and the mixture was refluxed for another hour. The mixture was then allowed to stand at room temperature for 12 h, and the resulting precipitate was removed by filtration and crystallized from ethanol to give 0.98 g (65%) of a product with mp 171°.

Compound VIII, which was obtained by a procedure similar to that used to prepare VII, was isolated by the addition of water to the reaction mixture, after which it was dissolved in ether and purified with a column filled with Al_2O_3. The fractions were monitored by means of TLC. The ether solution was evaporated to give an individual product with mp 156°.

1-Methyl-2-aminomethyl-3-(α-aminomethyl-o-chlorobenzyl)indole (IX). An ether solution of 0.61 g (0.002 mole) of dinitrile VII was added dropwise to a suspension of 0.3 g of $LiAlH_4$ in ether, and the mixture was heated for 1.5 h. The color of the solution at the start of the reaction changed from red to greenish. The excess $LiAlH_4$ was decomposed with water, the mixture was filtered, and the filtrate was dried with anhydrous Na_2SO_4 and evaporated to dryness to give a free-flowing residue. The residue was dissolved in 10 ml of dilute (1 : 20) HCl, and the solution was filtered with charcoal. The base was precipitated from the filtrate by the addition of ammonia to give 0.3 g (50%) of IX with mp 110°. The picrate of IX had mp 265°. Found: N 15.0%. $C_{18}H_{20}ClN_3 \cdot C_6H_2(NO_2)_3OH$. Calculated: N 15.5%.

1-Methyl-2-cyano-3-(o-chlorobenzyl)indole (X). A mixture of 3.72 g (0.01 mole) of 1-methyl-2-carbomethoxy-3-(α-acetoxy-o-chlorobenzyl)indole [1] and 0.75 g (0.015 mole) of NaCN was refluxed in 50 ml of 80% ethanol until all of the solid dissolved (1.5h), after which 150 ml of water was added, and the mixture was extracted with benzene. The benzene extracts were evaporated until crystallization began, after which the mixture was worked up to give 2.4 g (85%) of X with mp 108° (from ethanol). PMR spectrum: 7.3 ppm (m, aromatic protons, 8H), 3.98 ppm (s, NCH_3, 3H), and 4.51 ppm (s, CH_2, 2H). IR spectrum: 2250 cm^{-1} (CN); the $\nu C=O$ band was absent.

1-Methyl-2-aminomethyl-3-(o-chlorobenzyl)indole (XI) Hydrochloride. This compound, with mp 254° (from water), was obtained in 75% yield by the standard method by reduction of X with $LiAlH_4$ in ether. UV spectrum: λ_{max} 250 nm (log ε 4.398).

1-Methyl-2-carboxy-3-(o-chlorobenzyl)indole (XII). Nitrile X [1.4 g (0.005 mole)] and 0.56 g (0.01 mole) of KOH were refluxed in 15 ml of ethylene glycol for 10 h until ammonia evolution ceased. The mixture was then diluted with water, and the impurities were extracted with ether. The aqueous layer was acidified with acetic acid to precipitate acid XII. Workup gave 0.9 g (60%) of a product with mp 220° (from 50% ethanol). PMR spectrum: 7.3 ppm (aromatic protons, 8H). 3.68 (s, NCH_3, 3H), and 3.23 ppm (s, CH_2, 2H). IR spectrum: 1680 cm^{-1} (C=O).

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ACETALS OF LACTAMS AND ACID AMIDES.

XVI.* NEW SYNTHESIS OF 4-PYRIDONE DERIVATIVES

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Reaction of N,N-dimethylacetamide and N-methylbutyro-,-valero-, and caprolactam diethylacetals with ethyl β-aminocrotonate gave the corresponding enamidines, through the cyclization of which 2-dimethylamino-6-methyl-4-pyridone, 1,6-dimethyl-4-oxo-2,3,4,7-tetrahydropyrrolo[2,3-b]pyridine, and 1,7-dimethyl-5-oxo-1,3,4,5,8-hexahydro-1,8-naphthyridine were synthesized.

The present research was devoted to a study of the reaction of amide and lactam acetals with ethyl β-aminocrotonate (I) and to the use of the thus obtained enamidines in the synthesis of 4-pyridone derivatives. A prerequisite for the study was the synthesis [2] of condensed 4-quinolones from lactam acetals and ethyl anthranilate. The reaction of the amide acetals with ester I is of independent interest, inasmuch as the literature does not contain data on the reactions of primary enamines with amide acetals.

The reaction of N,N-dimethylacetamide diethylacetal (II) with ester I proceeds smoothly to give N,N-dimethyl-N^1-(α-methyl-β-carbethoxyvinyl)acetamidine (III). N-Methyl-N-(α-methyl-β-carbethoxyvinyl)iminopyrrolidine (VII), -piperidine (VIII), and -hexahydroazepine (IX), respectively, were similarly synthesized from N-methylbutyro- (IV), -valero- (V), and -caprolactam (VI) diethylacetals. Signals of a carbethoxy group (1.20-1.25 and 4.02-4.08 ppm), α-CH_3 and N−CH_3 groups (1.86-2.24 and 2.86-3.01 ppm, respectively), β-C−H protons (4.84-5.14 ppm), and of 3-CH_3 (for III) or CH_2 groups (for cyclic VII-IX) are observed in the PMR spectra (Table 1) of all of the enamidines (III and VII-IX) in CD_3OD. All of the signals in the spectra are doubled (Fig. 1), and this indicates the existence of III and VII-IX in the form of mixtures of two geometrical isomers. The differences in the chemical shifts of the isomers of various groups are not identical; inasmuch as the maximum difference is observed for the chemical shifts of the α-CH_3 and C−H protons, the observed doubling of the signals is associated with cis–trans isomerism about the C=C bond.† The weak-field signal

*See [1] for communication XV.

† The assignment to the cis or trans series was based on the mutual orientation of the CH_3 and COOEt groups.

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