THE CHEMISTRY OF INDOLE

XIV. Formation of 1-(3-Aminopropyl)indoles from 1-Arylpyrazolidines*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 3, pp. 371–376, 1970

UDC 547.752'772.2

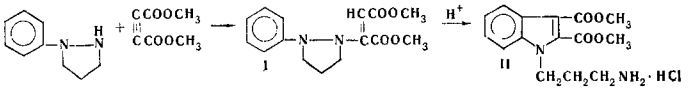
The opening of the pyrazolidine ring at the nitrogen—nitrogen bond in 1-arylpyrazolidine under the influence of acidic agents which leads to the formation of N-(3-aminoalkyl)indoles is described. The method enables one to obtain indoles with branched aminoalkyl radicals.

The nitrogen—nitrogen bond in hydrazine, which is comparatively stable to thermolysis and even to the action of acidic agents, when conjugated with multiple bonds or with an aromatic sextet of π electrons is cleaved fairly readily. In extreme cases, for example, in tetraarylhydrazines, free diarylimine radicals exist in equilibrium [2]. Acylhydrazones in which the carbonyl group is conjugated with the nitrogen—nitrogen bond disproportionate with the formation of pyridine and 1,2-diacylhydrazine [3].

Arylhydrazones rearrange in the manner of a Fischer reaction to form the corresponding indoles under the action of acidic agents, and sometimes alkalis [5] or simply heat [6]. This rearrangement, as it may be considered, is preceded by a shift of the double bond with the formation of an enehydrazine [7]. In actual fact, enehydrazine structures obtained by independent methods are converted into indoles under similar conditions with the cleavage of the nitrogen—nitrogen bond [8, 9].

In a study of five-membered cyclic hydrazines (pyrazolidines and pyrazolines) we have noted the unusual stability of the nitrogen—nitrogen bond in these substances [10]. In the present work we have succeeded in showing that the introduction of a vinyl group as a substituent on the second nitrogen atom of 1-arylpyrazolidine creates adequate conditions for the lability of the nitrogen—nitrogen bond. Under the action of acidic agents a rearrangement of the Fischer type takes place leading to 1-(3-aminoalkyl)indoles. In contrast to the usual Fischer syntheses the reaction takes place without the loss of a molecule of ammonia, since there is a hydrocarbon bridge between the hydrazine nitrogen atoms. This is similar to the recently developed synthesis of tryptamines [11].

The reaction takes place under fairly mild conditions. Thus, dimethyl acetylenedicarboxylate adds to 1-phenylpyrazoline with the formation of the adduct I (yield 30%) in ethereal solution at room temperature in 4–5 hr. Substance I has been ascribed the cis structure on the basis of its IR spectrum, PMR spectrum (chemical shift of the vinyl proton $\tau = 5.19$ ppm) and by analogy with the literature [12, 13].



I II

The conversion of the adduct I into a compound of the indole series II takes place when an ethanolic solution of I is saturated with hydrogen chloride at 0° C. The purity of the 1-(3-aminopropyl)-2,3-dimethoxycarbonylindole was checked by chromatography. The UV spectrum of the compound II which was obtained correspond to that of 1-methyl-2,3-dimethoxycarbonylindole, which has been described in the literature [14].

Similar reactions were carried out with 3- and 4-methyl-1-phenylpyrazolidine. The introduction of a substituent (chlorine or bromine) into the phenyl nucleus of the 1-arylpyrazolidine had no substantial effect on the addition and cyclization processes.

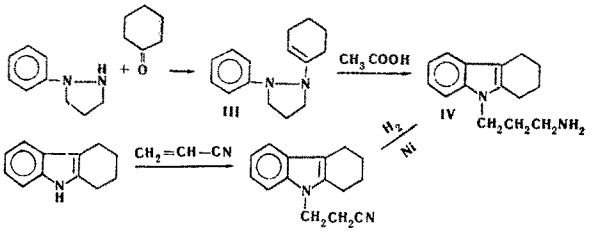
Subsequently we did not carry out the isolation and purification of the intermediate enehydrazines. However, the

*For part XIII see [1].

presence of such an enehydrazine in the reaction mixture was easily shown by chromatography on alumina: the compounds had R_f 0.44 in a chloroform–hexane (4 : 1) system and R_f 0.1 in a benzene–cyclohexane (1 : 1) system. In 1,5-diphenylpyrazolidine, as an example, it was shown that the presence of a second aromatic substituent in the pyrazolidine nucleus markedly lowers the yield of reaction product, interfering with addition to the carbon—carbon triple bond and with cyclization to the indole. The corresponding indole was isolated in a very small amount in the form of the 3,5-dinitrobenzoate with mp 210° C [λ_{max} 233, 295 nm (log ε 4.43, 3.77)], R_f 0.56 in a methanol–acetone (1 : 10) system on silica gel.

Attempts to extend this reaction to a number of other compounds which have a triple bond (esters of propiolic, tetrolic, and phenylpropiolic acids) were unsuccessful. No formation of enehydrazines was observed even under more severe conditions, which is possibly due to the lower polarization of the triple bond in these compounds. Thus, the possibility of obtaining aminoalkylindoles by this method has proved to be a limited one.

The condensation of 1-arylpyrazolidines with cyclohexanone, cyclopentanone, and acetoacetic ester takes place considerably better, at room temperature in absolute benzene for 4–5 hr.



The N-anilinoenamines obtained by this method readily cyclize into the corresponding aminopropylindoles (IV) when a small amount of glacial acetic acid is added and the mixture is boiled for 2–3 hr. If acetoacetic ester is used as the keto component, cyclization takes place after an ethanolic solution has been saturated with hydrogen chloride at 0° C.

We encountered great difficulties in the isolation and purification of the aminoalkylindoles. The bases obtained are liquids which decompose on distillation, their N-acetyl derivatives are oils, their hydrochlorides are generally hygroscopic, the picrates decompose on crystallization, and oxalic acid forms salts of variable composition. Consequently the majority of the aminoalkylindoles were characterized in the form of their 3,5-dinitrobenzoates, the individuality of which was checked by chromatography on silica gel in a methanol–acetone (1 : 1) system.

All the aminoalkylindole salts obtained in this way had a broad band in the 2600–3300-cm^{-1} region of the IR spectrum which is characteristic for a protonated amino group.

The UV spectra of both the hydrochlorides and the 3,5-dinitrobenzoates have a strong maximum in the 230–234-nm region (log ε 4.4–4.8) and a weaker band, or even simply an inflection, in the 282–290-nm region (log ε 3.7–4.0). However, it must be pointed out that for 3,5-dinitrobenzoic acid itself λ_{max} 233 nm (log ε 4.29). Thus, overlapping of one of the maxima takes place in the spectra of the 3,5-dinitrobenzoates, which considerably lowers the value of these spectral characteristics.

The free aminoalkylindoles give an intense coloration with ninhydrin, which may serve as a method for checking the completeness of the cyclization reaction with acetic acid in benzene.

The reaction of the arylpyrazolidines with aliphatic ketones (noncyclic), for example, with methyl ethyl ketone, leads to the formation of enehydrazines in very low yield. In this case we were unable to obtain appreciable amounts of the indole.

To check the structure of the compounds obtained we carried out an independent synthesis of the aminoalkylindole IV by reducing 9-(β-cyanoethyl)-1,2,3,4-tetrahydrocarbazole [15]. The 3,5-dinitrobenzoyl derivatives of the 9-(3-aminopropyl)-1,2,3,4-tetrahydrocarbazole produced in this manner and of the compound obtained by the reaction of 1-phenylpyrazolidine with cyclohexanone and subsequent cyclization were identical.

Thus, we have described a new opening of the pyrazolidine ring at the nitrogen—nitrogen bond under the action of

acidic agents and, simultaneously, a new synthesis of 1-(aminoalkyl)indoles from 1-arylpyrazolidines. This method enables the production of indoles with branched side chains.

EXPERIMENTAL

The UV spectra were taken on a Sagu instrument in ethanol and the IR spectra on a UR-20 instrument in paraffin oil or hexachlorobutadiene. Chromatography was carried out in a thin layer of alumina of activity grade II (50–150 mesh) and on KSK silica gel (200 mesh).

3-Methyl-1-phenylpyrazolidine was obtained by the method of Bouchet et al. [16]; the synthesis of the other initial pyrazolidines is the subject of a future paper.

2-(1,2-Dimethoxycarbonylvinyl)-1-phenylpyrazolidine (I). A mixture of 1.15 g (0.008 mole) of dimethyl acetylenedicarboxylate and 1.2 g (0.008 mole) of 1-phenylpyrazolidine dissolved in ether was kept at room temperature for 4–5 hr. After the ether had been distilled off in vacuo, 0.6 g (30%) of compound I was obtained with mp 73–74° C (from hexane). UV spectra (in methanol) λ_{max}, nm: 237, 278 (log ε 4.02, 4.16); IR spectrum (paraffin oil), 1695 and 1746 cm^{-1}. Found, %: C 62.58, 62.82; H 6.28, 6.31. Calculated for $C_{15}H_{18}N_2O_4$, %: C 62.02; H 6.21.

1-(3-Aminopropyl)-2,3-dimethoxycarbonylindole (II). A solution of 220 mg of the adduct I in 15 ml of absolute methanol was saturated with dry hydrogen chloride at 0° C and was left for a day at 0° C. The crystals that deposited were filtered off with suction and washed with absolute acetone, giving 200 mg (80%) of **II**, mp 221° C (from absolute methanol), R_f 0.48 on silica gel in a methanol–acetone (1 : 10) system. UV spectrum, λ_{max}, nm: 235, 290 (log ε 4.5, 4.1). Found, %: C 55.34, 55.24; H 5.85, 5.76; N 8.25, 8.40. Calculated for $C_{15}H_{18}N_2O_4 \cdot HCl$, %: C 55.31; H 5.84; N 8.58.

1-(3-Aminoalkyl)-2,3-dimethoxycarbonylindoles. A mixture of 0.004 mole of each 1-arylpyrazolidine and dimethyl acetylenedicarboxylate in 30 ml of absolute ether was left at room temperature for 5–6 hr. The ether was evaporated off, the residue was treated with 20 ml of absolute methanol, and a current of dry hydrogen chloride was passed through at 0° C until saturation. The excess methanol was evaporated off and the resulting indole was isolated in the form of its hydrochloride or 3,5-dinitrobenzoate. The constants and methods of obtaining the substances are given in the table (compounds 1–7).

1-(3-Aminoalkyl)-2,3-dialkylindoles. To a mixture of 0.004 mole of each 1-arylpyrazolidine and a ketone were added 30 ml of absolute benzene and a little calcined sodium sulfate. After 5–6 hr* the sodium sulfate precipitate was filtered off, 5 ml of acetic acid was added to the filtrate, and the mixture was boiled for 3 hr. The benzene solution was washed twice with water, and the aqueous layer was made alkaline and extracted with ether, and the extract was dried with potassium carbonate. After the elimination of the ether, the substance was rapidly converted into its hydrochloride or 3,5-dinitrobenzoate. For constants and yields, see table (compounds 8–15).

In ketoesters, (see compounds 16–18 in the table), cyclization was carried out by passing a current of hydrogen chloride into a solution of the enehydrazine in absolute ethanol.

9-(β-Cyanoethyl)-1,2,3,4-tetrahydrocarbazole. Sodium, 100 mg, was dissolved in 30 ml of tert-butanol, 5 g of 1,2,3,4-tetrahydrocarbazole was added and, with stirring, 3.2 g of acrylonitrile was added dropwise to the mixture. Stirring was continued for 5 hr and the mixture was left for 12 hr. Then it was treated with a large volume of water and acidified with acetic acid. The crystals were filtered off with suction, washed with water, and recrystallized from ethanol. Yield 2.65 g (40%), mp 114° C, R_f 0.30 [Al_2O_3, acetone–petroleum ether (1 : 10)]. According to the literature [17], mp 115–116° C.

1-(3-Aminopropyl)-1,2,3,4-tetrahydrocarbazole. 9-(β-Cyanoethyl)tetrahydrocarbazole was hydrogenated in ethanol over Raney nickel in an autoclave at 10 atm for 6 hr. The nickel was filtered off and the ethanol was evaporated off. This gave 1.4 g (83%) of a light-green oil. **3,5-Dinitrobenzoyl derivative,** mp 158° C, R_f 0.55 [Al_2O_3, benzene–acetone (5 : 1)]. Yield 31%. Found, %: C 62.50, 62.74; H 5.23, 5.30. Calculated for $C_{22}H_{22}N_4O_5$, %: C 62.60; H 5.21. UV spectrum, λ_{max}, nm: 230, 287 (log ε 4.26, 3.34). It was identical with the dinitrobenzoyl derivative obtained from

*The end of the reaction is easy to determine chromatographically on alumina in a benzene–cyclohexane (1 : 1) system from the completeness of the disappearance of the spot of the initial pyrazolidine, R_f 0.41–0.42, and the appearance of a spot for the enehydrazine stretching from the start and poorly revealed by iodine.

1-(3-Aminoalkyl)-2,3-disubstituted Indoles

No.	Compound	Salt*	Mp, °C	Empirical formula	Found, %		Calculated %		UV spectrum		Yield, %
					C	H	C	H	λ_{max}, nm	lg ε	
1	1-(3-Aminopropyl)-2,3-dimethoxycarbonylindole	HCl	221	$C_{15}H_{18}N_2O_4 \cdot HCl$	55.24 55.34	5.80 5.85	55.31	5.84	235 290	4.5 4.1	68
2	1-(3-Aminobutyl)-2,3-dimethoxycarbonylindole	HCl	183	$C_{16}H_{20}N_2O_4 \cdot HCl$	56.54 56.48	6.40 6.26	56.58	5.19	240 295	4.32 4.22	22.5
3	1-(3-Amino-2-methylpropyl)-2,3-dimethoxycarbonylindole	DNB	194	$C_{16}H_{20}N_2O_4 \cdot C_7H_4N_2O_6$	53.01 53.11	4.73 4.51	53.35	4.67	234 298	4.57 4.00	34
4	1-(3-Aminopropyl)-5-chloro-2,3-dimethoxycarbonylindole	HCl	244	$C_{15}H_{17}ClN_2O_4 \cdot HCl$	49.57 49.84	4.96 4.91	49.86	4.99	224 300	3.94 3.51	31
5	1-(3-Amino-2-methylpropyl)-5-chloro-2,3-dimethoxycarbonylindole	DNB	202	$C_{16}H_{19}ClN_2O_4 \cdot C_7H_4N_2O_6$	49.95 50.09	4.29 4.24	50.18	4.18	221 296	4.46 4.01	19.5
6	1-(3-Aminopropyl)-7-chloro-2,3-dimethoxycarbonylindole	HCl	212	$C_{15}H_{17}ClN_2O_4 \cdot HCl$	50.04 50.11	5.14 5.10	49.86	4.99	224 298	4.26 4.54	30
7	1-(3-Aminopropyl)-7-bromo-2,3-dimethoxycarbonylindole	DNB	201	$C_{15}H_{17}BrN_2O_4 \cdot C_7H_4N_2O_6$	46.43 46.59	4.04 4.21	45.57	3.62	217 227 295	4.76 4.70 4.12	24
8	9-(3-Aminopropyl)-1,2,3,4-tetrahydrocarbazole	HCl	217	$C_{15}H_{20}N_2 \cdot HCl$	68.07 67.98	8.20 8.16	68.31	7.97	228 285	4.42 3.74	38.5
		DNB	212	$C_{15}H_{20}N_2 \cdot C_7H_4N_2O_6$	60.25 60.10	5.62 5.49	60.01	5.46	230 290	4.87 3.96	34
9	9-(3-Aminobutyl)-1-2,3,4-tetrahydrocarbazole	DNB	234	$C_{16}H_{22}N_2 \cdot C_7H_4N_2O_6$	60.73 60.83	5.91 5.87	60.97	5.74	234 287	4.42 3.34	53.5
10	9-(3-Amino-2-methylpropyl)-1,2,3,4-tetrahydrocarbazole	DNB	235	$C_{16}H_{22}N_2 \cdot C_7H_4N_2O_6$	61.35 61.13	5.93 5.88	60.97	5.74	232 280	4.80 4.10	25
11	9-(3-Aminopropyl)-6-chloro-1,2,3,4-tetrahydrocarbazole	DNB	242	$C_{15}H_{19}ClN_2 \cdot C_7H_4N_2O_6$	55.79 55.81	4.92 5.02	55.64	4.84	240 296 300	4.26 3.43 3.45	28
12	9-(3-Amino-2-methylpropyl)-8-bromo-1,2,3,4-tetrahydrocarbazole	DNB	197	$C_{16}H_{21}BrN_2 \cdot C_7H_4N_2O_6$	52.21 52.11	4.97 5.02	51.78	4.69	223 298	3.98 3.45	27.5
13	1-(3-Aminopropyl)-2,3-trimethyleneindole	DNB	193	$C_{14}H_{18}N_2 \cdot C_7H_4N_2O_6$	59.21 59.15	5.27 5.28	59.01	5.17	231 292	4.78 3.95	28.6
14	1-(3-Aminobutyl)-2,3-trimethyleneindole	DNB	205	$C_{15}H_{20}N_2 \cdot C_7H_4N_2O_6$	60.02 60.22	5.45 5.41	60.01	5.45	233 282	4.76 3.98	23.5
15	1-(3-Amino-2-methylpropyl)-2,3-trimethyleneindole	DNB	223	$C_{15}H_{20}N_2 \cdot C_7H_4N_2O_6$	59.98 59.86	5.66 5.84	60.01	5.45	230 282	4.39 3.75	49.3
16	1-(3-Aminopropyl)-3-ethoxycarbonyl-2-methylindole	HCl	258	$C_{15}H_{20}N_2O_2 \cdot HCl$	61.01 61.08	7.25 7.30	60.92	7.09	288	4.28	26
17	1-(3-Aminobutyl)-3-ethoxycarbonyl-2-methylindole	DNB	210	$C_{16}H_{22}N_2O_2 \cdot C_7H_4N_2O_6$	54.96 55.09	5.47 5.54	54.95	5.54	218 231 289	3.99 3.92 3.53	32.5
18	1-(3-Amino-2-methylpropyl)-3-ethoxycarbonyl-2-methylindole	DNB	193	$C_{16}H_{22}N_2O_2 \cdot C_7H_4N_2O_6$	56.92 57.01	5.51 5.52	56.96	5.34	230 283	4.89 4.16	25.5

*DNB = 3,5-dinitrobenzoate

compound IV (compound 8, see table).

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19 July 1969

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