A STUDY OF THE INTRAMOLECULAR CYCLIZATION OF ESTERS OF 3-ARYLAZOINDOL-2-YLACETIC ACIDS

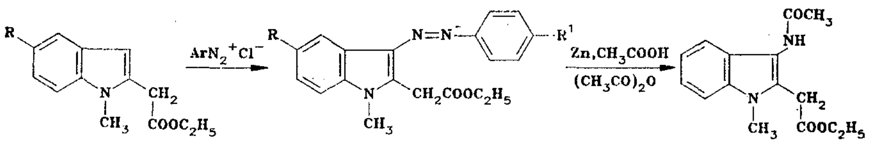
F. A. Trofimov, V. I. Garnova, and
N. G. Tsyshkova

UDC 547.757'754.04'852.9.07:542.953.7

A method is proposed for the synthesis of the new heterocyclic system pyridazino-[4,3-b]indole which is based on the intramolecular condensation of ethyl 3-arylazoindol-2-ylacetates in the presence of bases.

Continuing a study of the chemical properties of esters of the indol-2-ylacetic acids (Ia-c) with a free position 3 [1, 2], we have considered the azo-coupling reaction and the possibility of obtaining the corresponding 3-amino-2-ylacetic acid derivatives from 3-arylazoindoles. The azo-coupling reaction took place most successfully in neutral or weakly alkaline media. In the IR spectra of the ethyl 3-arylazoindol-2-ylacetates (IIa-g) obtained, the frequency of the vibrations of the carbon group appeared in the 1740-1760 cm^{-1} region and there was a strong band in the 1400 cm^{-1} region due to the stretching vibrations of the azo group (Table 1). In the electronic spectra, this group had a characteristic long-wave absorption maximum at 380-440 nm. The PMR spectra of compounds (IIa-g) lacked the signal of the 3-H proton of the indole ring that was present in the initial compounds (Ia-c), which confirmed the direction of the azo-coupling reaction.

The reduction of the 3-arylazoindoles (IIa-g) took place ambiguously and, depending on the type of reducing agent and the pH of the medium, led either to derivatives of 3-aminoindol-2-ylacetic acid (III) or to compounds with the previously unknown heterocyclic system of 2-aryl-5-methyl-3-oxo-2,3-dihydropyridazino[4,3-b]indoles (Iva-f) — the aza analogs of tetrahydro-γ-carbolines. Under the conditions of the reductive acetylation reaction [3, 4], ethyl 3-acetylamino-1-methylindol-2-ylacetate (III) was obtained with a 59% yield.



Ia-c IIa-g III

Ia, IIa–e R=H; Ib, IIf $R=CH_3$; Ic, IIg $R=OCH_3$; II a, f, g $R^1=H$; b $R^1=CH_3$; c $R^1=OCH_3$; d $R^1=Cl$; e $R^1=NO_2$

An investigation of the possibility of obtaining indoles with free amino groups by the reduction of compounds (IIa-g) with sodium hydrogen sulfide [5, 6] showed that in a neutral medium the reaction did not proceed, and in an alkaline medium it led to the pyridazino[4,3-b] indoles (IVa-f). The structures of the pyridazino[4,3-b]indoles (IVa-f) were unambiguously confirmed by their spectral characteristics (Table 1). The peaks of the molecular ions corresponded to the calculated values. When compounds (IIa-f) were converted into compound (IVa-f), the following changes appeared in their IR, UV, and PMR spectra: in the electronic spectra, an absorption band at 380-440 nm disappeared and so, correspondingly, did the band of a carbonyl group in the IR spectrum (1740-1760 in $CH_2COOC_2H_5$), and characteristic bands corresponding to the vibrations of C═N groups (1620-1640 cm^{-1}) and amide C═O groups (1660-1670 cm^{-1}) appeared. In the PMR spectra of compounds (IVa-c, f), there was no signal of the protons for a CH_2 group (in $CH_2COOC_2H_5$) at 4.26-4.38 ppm, and singlets relating to the 4-H proton of the pyridazine ring appeared at 6.32-6.36 ppm.

Scientific-Research Institute of Medical Radiology, Academy of Medical Sciences of the USSR, Obninsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 640-643, May, 1985. Original article submitted May 21, 1984.

0009-3122/85/2105-0538$09.50

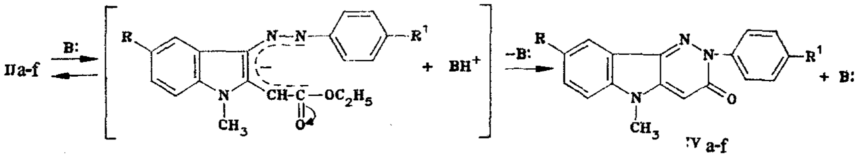
TABLE 1. Spectral Characteristics of the Ethyl 1-Methyl-3-arylazoindolyl-2-acetates (IIa-g) and of the 3-Oxo-5-methyl-2,3-dihydropyridazino[4,3-b]indoles (IVa-f)

Compound	PMR spectrum*, δ, ppm, multiplicity (number of protons)	IR spectrum, ν, cm^{-1}	
		C=O	N=N†
IIa	1,21, t (3H); 3,64, s (3H); 4,28, q (2H); 4,36, s (2H); 6,86—8,02, m (9H)	1740	1400
IIb	1,20, t (3H); 2,30, s (3H); 3,52, s (3H); 4,26, q (2H); 4,38, s (2H); 6,84—7,96, m (8H)	1750	1410
IIc	1,21, t (3H); 3,64, s (3H); 3,87, s (3H); 4,15, q (2H); 4,40, s (2H); 6,89—8,06, m (8H)	1760	1420
IId	1,21, t (3H); 3,52, s (3H); 4,10, q (2H); 4,26, s (2H); 7,20—7,96, m (8H)	1750	1410
IIe	1,12, t (3H); 3,38, s (3H); 4,10, q (2H); 4,26, s (2H); 7,22—8,30, m (8H)	1750	1410
IIf	1,25, t (3H); 2,46, s (3H); 3,72, s (3H); 4,18, q (2H); 4,38, s (2H); 7,20—8,02, m (8H)	1750	1410
IIg	1,21, t (3H); 3,64, s (3H); 3,87, s (3H); 4,15, q (2H); 4,28, s (2H); 6,89—8,06, m (8H)	1760	1420
IVa	3,44, s (3H); 6,38, s (1H); 7,00—7,94, m (9H)	1660	1620
IVb	2,35, s (3H); 3,44, s (3H); 6,36, s (1H); 7,02—7,96, m (8H)	1670	1630
IVc	3,66, s (3H); 3,86, s (3H); 6,34, s (1H); 6,87—8,04, m (8H)	1670	1640
IVd		1660	1620
IVe		1660	1620
IVf	2,36, s (3H); 3,30, s (3H); 6,32, s (1H); 6,98—7,78, m (8H)	1670	1640

---

*The PMR spectrum of compounds (IVd, e) could not be recorded because of their inadequate solubility in $CDCl_3$.

†For compounds (IVa-f), C=N.



IV a–e R=H; f R=CH_3; a, f R^1=H; b R^1=CH_3; c R^1=OCH_3; d R^1=Cl; e R^1=NO_2

In order to study the laws of the formation of the pyridazinoindoles, kinetic investigations were performed in the presence of catalytic amounts of sodium ethanolate. The course of the reaction was followed spectrophotometrically from the decrease in the intensity of the absorption of the initial compounds (IIa-f) in the 380-440 nm region and from the accumulation of the final substance (IVb), absorbing in the 260 nm region. The reaction was of the first order with respect to the compounds (IIa-f), the rate constants were calculated from the decrease in the amount of the initial compound (IIb) and from the accumulation of the final compound (IVb) proving to be equal. This showed the unambiguous nature of the direction of the process being studied, the motive force of which is the formation of the aromatic system of pyridazinoindole. An analysis of the dependence of the rate constant on the concentration of catalyst in logarithmic coordinates showed that the reaction was also first-order with respect to the base (Fig. 1).

The formation of pyridazinoindoles does not take place in the presence of acidic catalysts.

According to Table 2, the formation of pyridazinoindoles is considerably accelerated on passing from electron-donating substituents R_1 to electron-accepting substituents in the arylazo group. The comparatively small difference in the numerical values of the rate constants in this series can apparently be explained by the fairly good conductivity of the system. These facts give grounds for the assumption that the transition state has a carbanionic nature. The presence of a methyl group in position 5 of the initial indole (IIf) lowered the rate of the reaction as compared with the unsubstituted compound (IIa), while a methoxy group present in the same position exerted such a strong destabilizing action on the carbanion that no intramolecular condensation took place. We have shown a similar influence of an electron-donating substituent in a study of the formation of γ-carbolines from isotryptamines by the Mannich reaction [2].

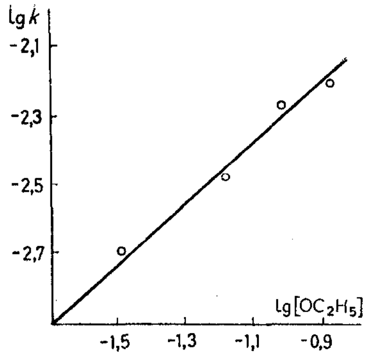


Fig. 1. Dependence of the rate constant of the cyclization of ethyl 1-methyl-3-phenylazoindol-2-ylacetate (IIa) on the concentration of catalyst.

TABLE 2. Rate Constants of the Cyclization of Ethyl 3-Arylazoindol-2-ylacetates to Pyridazino[4,3-b]indoles

Compound	R	R¹	$k \cdot 10^3$ sec^{-1}
IIa	H	H	9,28
IIb	H	CH_3	4,69
IIc	H	OCH_3	3,06
IId	H	Cl	28,2
IIe	H	NO_2	251,0
IIf	CH_3	H	7,46
IIg	OCH_3	H	No reaction

The qualitative influence of the substituent R^1 on the rate of the reaction was analyzed with the aid of Hammett's equation [7]. In the coordinates of the equation, a good linear relationship with a positive angular coefficient was observed ($\rho = 1.9$; $r = 0.98$).

At the same time, these results do not give grounds for considering that the rate of the reaction is limited only by the stage of the transfer of a proton from the methylene group (of $CH_2COOC_2H_5$) to the catalyst or only by the stage of the intramolecular cyclization of the anion formed. However, the possibility of the occurrence of the process when an electron-donating substituent — a methoxy group — is introduced into position 5 of compounds (II) may be an argument in favor of the assumption that the limiting stage of the reaction under consideration is the transfer of a proton to the catalyst. Apparently, the pyridazinoindole-forming reaction is the simplest analogy of a sigmatropic [1,5]-rearrangement.

EXPERIMENTAL

IR spectra were obtained on a UR-10 instrument (in KBr tablets or in chloroform solution), UV spectra (ethanolic solutions) on a Unicam SP-8000 spectrophotometer, and PMR spectra on a JNM-4H-100 and C-60H instrument (in $CDCl_3$ with TMS as internal standard). Mass spectra were recorded on a RMN-6 instrument (Hitachi, Japan) with direct introduction of the sample into the ion source at a temperature of 150-200°C and with an energy of the ionizing electrons at 70 eV.

The kinetics of the intramolecular cyclization of compounds (IIa-f) in a concentration of $2.5 \cdot 10^{-2}$ mM were studied in 31.25-250 mM ethanolic solutions of sodium ethanolate at 28°C in a thermostated cell in the Unicam SP-8000 spectrophotometer.

The ethyl indol-2-ylacetates (Ia-c) were obtained as described previously [1, 2].

The characteristics of compounds (II) and (IV) are given in Table 3.

Ethyl 1-Methyl-3-phenylazoindol-2-ylacetate (IIa). The diazonium salt obtained by the usual method from 0.93 g (10 mmole) of aniline, 3 ml of concentrated HCl, 4.5 ml of water, and 0.7 g (10 mmole) of $NaNO_2$ was kept at 0°C for 20 min and was then neutralized with sodium acetate to a weakly alkaline reaction. With stirring, the diazonium salt solution was added to a solution of 2.2 g (10 mmole) of compound (Ia) in 30 ml of methanol at 0°C. The reaction mixture was stirred in the cold for 1 h and then the precipitate that had deposited was filtered off and washed with water. The yield of azo compound (IIa) was 2.37 g (74%), mp 101-103°C (from methanol). IR spectrum, cm^{-1}: 1400 (N=N), 1740 (C=O). UV spectrum (in ethanol), λ_{max}, nm (log ε): 227 (4.28), 285 (4.11), 380 (4.37). PMR spectrum, ppm: 1.21 (t, $CH_2COOCH_2C\underline{H}_3$); 3.64 (s, $N{-}CH_3$); 4.28 (q, $CH_2COOC\underline{H}_2CH_3$); 4.36 (s, $C\underline{H}_2COOCH_2CH_3$); 6.86-8.02 (m, 9 H, aromatic protons). Found: C 70.7; H 5.9; N 12.8%. $C_{19}H_{19}N_3O_2$. Calculated: C 71.0; H 6.0; N 13.1%.

Compounds (IIb-g) were obtained similarly.

Ethyl 3-Acetylamino-1-methylindol-2-ylacetate (III). In portions, 1 g of zinc dust was added to a solution of 0.8 g (2.5 mmole) of compound (IIa) in a mixture of 10 ml of glacial

TABLE 3. Characteristics of Compounds (IIb-g) and (IVb-f)

Compound	R	R¹	mp,* °C	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
IIb	H	CH_3	106—107	71,6	6,5	12,6	$C_{20}H_{21}N_3O_2$	71,6	6,3	12,5	72
IIc	H	OCH_3	111—112	68,6	6,4	12,4	$C_{20}H_{21}N_3O_3$	68,4	6,0	12,0	65
IId	H	Cl	143	64,3	5,2	11,8	$C_{19}H_{18}ClN_3O_2$	64,1	5,1	11,8	73
IIe	H	NO_2	166—168	61,9	5,1	15,5	$C_{19}H_{18}N_4O_4$	62,3	4,9	15,3	66
IIf	CH_3	H	104—106	71,3	6,4	12,5	$C_{20}H_{21}N_3O_2$	71,6	6,3	12,5	72
IIg	OCH_3	H	168—169	68,3	5,9	12,2	$C_{20}H_{21}N_3O_3$	68,4	6,0	12,0	54
IVb	H	CH_3	212—213	74,9	5,4	14,6	$C_{18}H_{15}N_3O$	74,6	5,2	14,5	83
IVc	H	OCH_3	221—222	70,6	5,3	13,3	$C_{18}H_{15}N_3O_2$	70,8	5,0	13,7	65
IVd	H	Cl	291—292	65,9	4,0	13,2	$C_{17}H_{12}ClN_3O$	65,9	3,9	13,6	91
IVe	H	NO_2	338—340	63,7	4,1	17,9	$C_{17}H_{12}N_4O_3$	63,7	3,8	17,5	95
IVf	CH_3	H	207—208	74,8	5,3	14,4	$C_{18}H_{15}N_3O$	74,6	5,2	14,5	73

*Compounds (IIb-d, f, g) were crystallized from methanol, (IIe) from chloroform, (IVb-d, f) from ethanol, and (IVe) from ethanol—chloroform (1:1).

acetic acid and 0.6 ml of acetic anhydride heated to 90°C. The mixture was boiled for 1 h, and the sludge was filtered off and washed with hot acetic acid. The filtrate was evaporated to dryness, water was added to the residue, and the solid matter was filtered off. The yield of compound (III) was 0.41 g (59%), mp 136-137°C (from ethanol). IR spectrum, cm^{-1}: 1670 (C=O); 1740 (C=O in $CH_2COOC_2H_5$); 3250 (NH). UV spectrum, λ_{max}, nm (log ε): 225 (4.55); 280 (3.94). Found: C 65.5; H 6.7; N 10.6%. $C_{15}H_{18}N_2O_3$. Calculated: C 65.7; H 6.6; N 10.3%.

5-Methyl-3-oxo-2-phenyl-2,3-dihydropyridazino[4,3-b]indole (IVa). A solution of 1.6 g (5 mmole) of ethyl 1-methyl-3-phenylazoindol-2-ylacetate (IIa) in 50 ml of ethanol was treated with 10 ml of a 250 mM solution of sodium ethanolate, and the mixture was kept at 50°C for 10-15 min. Then the solvent was evaporated off in vacuum until a precipitate began to form, which was then filtered off, washed with water, and dried. The yield of compound (IVa) was 1.1 g (82%); mp 218-219°C (from ethanol). IR spectrum ($CHCl_3$), cm^{-1}: 1600, 1625 (C=O, amide I and II). UV spectrum (in ethanol), λ_{max}, nm (log ε): 223 (4.28); 275 (4.46). PMR spectrum ($CDCl_3$), ppm: 3.44 (s, N—CH_3); 6.38 (s, 4-H of the pyridazine ring); 7.0-7.94 (m, 9 H, aromatic protons). Found: C 74.2, H 4.8, N 15.4%. $C_{17}H_{13}N_3O$. Calculated: C 74.2; H 4.8; N 15.3%.

Compounds (IVb-f) were obtained similarly.

LITERATURE CITED

1. F. A. Trofimov, N. G. Tsyshkova, V. I. Garnova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 1, 1254 (1975).
2. F. A. Trofimov, V. I. Garnova, N. G. Tsyshkova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 1, 72 (1979).
3. G. N. Kurilo, O. N. Boyarintseva, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 12, 1654 (1973).
4. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 8, 1096 (1975).
5. K. Senda, M. Icluda, H. Kanazawa, and S. Nischigaki, Synthesis, No. 4, 264 (1977).
6. F. C. Cooper, J. Chem. Soc., No. 11, 4222 (1958).
7. C. D. Johnson, The Hammett Equation, Cambridge University Press (1973).