REACTION OF A 2-AMINOINDOLE WITH DIFUNCTIONAL COMPOUNDS

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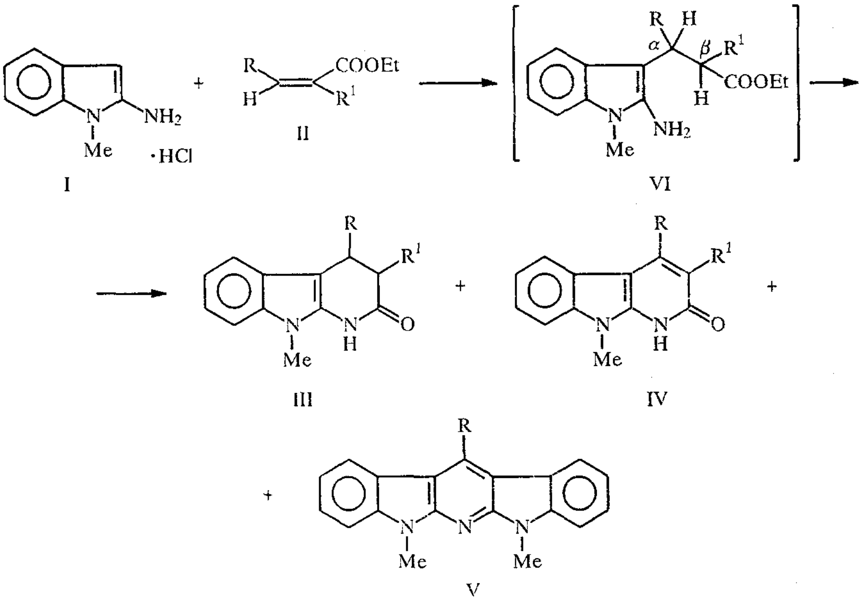
The reaction of a 2-aminoindole with arylidenemalonic and arylidenecyanoacetic esters was studied. The effect of substituents in the benzene ring of the arylidenemalonic ester on the reaction pathway is demonstrated.

We have previously found that 2-aminoindole hydrochloride I readily condenses with ethoxymethylenemalonic ester in the presence of sodium ethoxide to give the sodium salt of ethyl 4-α-carbolone-3-carboxylate [1]. Continuing our research on the synthesis of condensed heterocycles based on a 2-aminoindole, we studied the reaction of 2-aminoindole hydrochloride I with arylidenemalonic esters IIa-d and arylidenecyanoacetic esters IIe-f.



II—VI a R=Ph, R^1=COOEt; b R=p-$MeOC_6H_4$, R^1=COOEt; c R=p-$(Me)_2NPh$, R^1= COOEt; d R=p-$NO_2C_6H_4$, R^1=COOEt; e R=Ph, R^1=CN; f R=p-$MeOC_6H_4$, R^1=CN; g R=p-$(Me)_2NC_6H_4$, R^1=CN; h R=p-$NO_2C_6H_4$, R^1=CN; i R=—$(CH_2)_4$—, R^1=CN

It is known that reactions of this type depend substantially on the conditions under which they are carried out and do not always proceed unambiguously [2, 3]. Thus, in the presence of triethylamine the 2-aminoindole condenses with benzalmalonic ester or ethyl α-cyanocinnamate to give only diindolopyridines V [2]. Since diindolopyridines V have been adequately studied [2, 4], our task was to direct the process to favor the formation of α-carbolines III and IV.

In a study of the reaction of 2-aminoindole I with benzalmalonic ester IIa in the presence of an equimolar amount of sodium methoxide we established that diindolopyridine Va (40%) is formed along with 3-carbethoxy-1-methyl-2-oxo-4-phenyl-

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All-Union Science Center for the Safety of Biologically Active Substances, Kupavna, Moscow Region 142450. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 899-902, July, 1992. Original article submitted January 6, 1991.

0009-3122/92/2807-0746$12.50

TABLE 1. Correlation of the Yields of the Products of Condensation of 2-Amino-1-methylindole Hydrochloride with Arylidenemalonic Esters

Type of condensation product	Substituent R in the arylidenemalonic ester, yield, %			
	$C_6H_4(p\text{-}OCH_3)$	C_6H_5	$C_6H_4(p\text{-}N(CH_3)_2)$	$C_6H_4(p\text{-}NO_2)$
		pH 7		
III	17	35	—	41
IV	—	13	—	—
V	72	40	88	56
		pH 11		
III	71	64	59	83
IV	4	18	—	—
V	9	5	16	—

TABLE 2. IR and PMR Spectra of α-Carboline Derivatives III and IV

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
IIIa*	3220, 3140, 3050, 1750, 1685	1,02 (3H, t, CH_3); 3,29 (3H, s, NCH_3); 3,50 (1H, d 3-H); 3,68 (2H, q OCH_2); 4,30 (1H, d 4-H); 5,88...6,49 (9H, m Ar); 8,88 (1H, br.s, NH)
IIIb	3220, 3140, 1745, 1670	0,98 (3H, t, CH_3); 3,61 (3H, s, NCH_3); 3,67 (3H, s OCH_3); 3,81 (1H, d 3-H); 3,96 (2H, q, OCH_2); 4,54 (1H, d 4-H); 6,37...7,30 (8H, m Ar)
IIIc	3700...3100, 1740, 1660	1,05 (3H, t CH_3); 2,87 (6H, s $N(CH_3)_2$); 3,67 (3H, s NCH_3); 3,82 (1H, d 3-H); 4,02 (3H, q OCH_2); 4,52 (1H, d 4-H); 6,47...7,36 (8H, m Ar),; 10,99 (1H, br.s NH)
IIId	3550...2600, 1660	0,83 (3H, t, CH_3); 4,0 (3H, s, NCH_3); 4,1 (2H, q, OCH_2); 6,4 (1H, d 3-H); 6,53 (1H, d, 4-H); 7,26...7,70 (8H, m, Ar)
IVa	1650, 1630	0,84 (3H, t CH_3); 3,87 (3H, s, NCH_3); 3,95 (2H, кв, OCH_2); 6,69...7,61 (9H, m Ar)
IVb	3600...3100, 1660	0,91 (3H, t, CH_3); 3,29 (3H, s, NCH_3); 3,87 (3H, s., OCH_3); 3,94 (2H, q OCH_2); 6,91...7,61 (8H, m Ar)
IVe**	3700...2400, 2260, 1760, 1660	3,64 (3H, s NCH_3); 6,41...7,11 (9H, m, Ar)
IVf	3600...3100, 2200, 1610	3,83 (3H, s, NCH_3); 3,89 (3H, s, OCH_3); 6,96...7,61 (8H, m Ar)
IVg	3500...3200, 2700...2400, 2200, 1650	3,04 (6H, s, $N(CH_3)_2$); 3,83 (3H, s, NCH_3); 6,85...7,51 (8H, m Ar)
IVh	2210, 1650	3,9 (3H, s, NCH_3); 6,85...8,6 (8H, m, Ar)

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*The PMR spectra were obtained from solutions in d_6-DMSO, except for this compound, the PMR spectrum of which was obtained from a solution in $CDCl_3$.

**The PMR spectrum of this compound was obtained from a solution in deuterotrifluoroacetic acid.

α-carboline IVa (13%) and its 3,4-dihydro derivative IIIa (35%). The use of a twofold excess of sodium methoxide in the reaction with benzalmalonic ester makes it possible to obtain 3,4-dihydro-α-carboline IIIa in 64% yield; α-carboline IVa (5%) and diindolopyridine Va (18%) are also formed. The use of a tenfold excess of sodium methoxide makes it possible to completely exclude the formation of diindolopyridine V but leads to resinification of the reaction mass and does not give a substantial increase in the yields of α-carbolines IIIa and IVa. The nature of the substituent in the benzene ring of the arylidenemalonic ester also affects the reaction pathway. Thus, in carrying out the reaction with p-nitrobenzylidenemalonic ester IId at pH 11 we did not observe the formation of diindolopyridine Vd, while in the case of p-methoxybenzylidenemalonic ester (IIb) and p-dimethylaminobenzylidenemalonic ester (IIc) at pH 11 the yields of diindolopyridines Vb and Vc were 19% and 16%, respectively (Table 1).

The presence of a strong acceptor such as a nitro group in substituent R of intermediate adduct VId evidently hinders heterolytic cleavage of the α—β bond by destabilizing the carbonium ion of the benzyl type that is formed in this sort of cleavage, and this leads to the primary formation of α-carbolines IIId and IVd. The electron-donor effect of methoxy and dimethylamino groups makes the formation of diindolopyridines Vb and Vc possible by promoting heterolytic cleavage of the α—β bond in intermediate VI.

The structures of all of the synthesized α-carbolines III and IV were confirmed by the set of spectral data. For example, the PMR spectrum of a solution of IVa in d_6-DMSO contains signals of NCH_3 protons (3.87 ppm), OC_2H_5 protons (0.84 and 3.95 ppm), and aromatic protons (6.69-7.61 ppm). In addition to signals of protons of NCH_3 and OC_2H_5 groups and aromatic protons, the PMR spectrum of a solution of IIIa in $CDCl_3$ also contains characteristic 3-H and 4-H doublets at 3.50 and 4.30 ppm. The electron-donor effect of the methoxy and dimethylamino groups in the case of IIIb and IIIc weakens the deshielding effect of the benzene ring in the 4α position of the carboline ring and gives rise to a shift of the signals of these protons to the strong-field region: the 3-H signals are located at 3.96 and 3.82 ppm, and the 4-H signals are found at 4.54 and 4.52 ppm, respectively. In the case of IIId the strong electron-acceptor effect of the nitro group causes a shift of the signals of the protons to the weak-field region — 6.40 ppm for 3-H, and 6.53 ppm for 4-H. The absence of 3-H and 4-H signals in the PMR spectra of IV confirms the aromatic structure of these α-carbolines. The molecular-ion peaks M^+ and the $[M - 2H]^+$ and $[M - OC_2H_5]^+$ ion peaks are the most intense peaks in the mass spectra of III, while the M^+ and $[M - OC_2H_5]^+$ ion peaks are the most intense peaks in the mass spectra of α-carbolines IV.

The reaction of 2-aminoindole I with arylidenemalonic esters IIe-i leads to 3-cyano-α-carbol-2-ones IIIi and IVe-h. The presence in the IR spectra of these compounds of an absorption band of a cyano group at 2200-2260 cm^{-1} constitutes evidence that the formation of a pyridine ring proceeds with the participation of the carbethoxy group. The use of excess sodium methoxide in the condensation of the 2-aminoindole with arylidenecyanoacetic esters makes it possible to completely exclude the formation of diindolopyridine V and to obtain 3-cyano-α-carbol-2-ones in good yields.

α-Carbolines cannot be obtained even in low yields in the reaction of the 2-aminoindole with arylidenemalonic acid dinitriles. Diindolopyridines V are obtained in virtually quantitative yields under various conditions (pH 7-14). This can be explained by the fact that the two cyano groups, being stronger acceptors than carbethoxy groups (Hammett σ constants 0.66 and 0.45, respectively), stabilize to a greater extent the leaving carbonium ion formed in the heterolytic cleavage of intermediate VI, and this shifts the reaction pathway to favor the formation of diindolopyridines V.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Specord 75-IR spectrometer. The PMR spectra were recorded with a Tesla BS-587A spectrometer at 90 MHz with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with an MKh-1321A mass spectrometer at an ionizing voltage of 70 eV. The progress of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in a benzene—isopropyl alcohol (10:1) system.

Condensation of 1-Methyl-2-aminoindole Hydrochloride (I) with Benzalmalonic Ester IIa. A. A 1.3-ml sample of a 1 N solution of sodium methoxide in methanol was added to a mixture of 0.2 g (1.1 mmole) of 2-amino-1-methylindole hydrochloride (I) and 0.27 g (1.1 mmole) of benzalmalonic ester IIa in 10 ml of alcohol, and the mixture was refluxed for 40 min. It was then cooled, and the resulting precipitate was removed by filtration, washed with water and alcohol, dried, and dissolved in chloroform—methanol. This solution was applied to a column packed with Silpearl adsorbent and eluted with chloroform—ethanol (30:1) to give 0.11 g (30%) of 3,4-dihydro-3-carbethoxy-9-methyl-4-phenyl-α-carbol-2-one (IIIa) and 0.07 g (35%) of 5,7-dimethyl-12-phenyldiindolo[2,3-b;3',2'-e]pyridine (Va) with mp 289-290°C (mp 288-290°C [4]). The aqueous filtrate was extracted with chloroform, the chloroform extract was combined with the alcoholic filtrate, the mixture was evaporated, and the residue was chromatographed with a column [Silpearl, chloroform—ethanol (30:1)] to give another 0.02 g (5%) of dihydro-α-carbolone IIIa, 0.01 g (5%) of diindolopyridine Va, and 0.05 g (13%) of 3-carbethoxy-9-methyl-4-phenyl-α-carbol-2-one (IVa).

B. A 3-ml sample of a 1 N solution of sodium methoxide in methanol was added to a mixture of 0.25 g (1.35 mmole) of 2-aminoindole hydrochloride I and 0.33 g (1.35 mmole) of benzalmalonic ester IIa in 10 ml of alcohol, and the mixture was refluxed for 1 h. It was then evaporated, 20 ml of water was added to the residue, the aqueous mixture was acidified to pH 5, and the resulting precipitate was removed by filtration, washed with water, dried, and dissolved in chloroform—methanol. This solution was chromatographed with a column [Silpearl, chloroform—ethanol (30:1)] to give 0.3 g (64%) of IIIa, 0.087 g (18%) of IVa, and 0.013 g (5%) of diindolopyridine Va.

The condensations of 2-aminoindole hydrochloride with arylidenemalonic esters IIb-d were carried out similarly. The overall yields are presented in Table 1. The IR and PMR spectra of the compounds are presented in Table 2.

9-Methyl-4-(p-nitrophenyl)-3-cyano-α-carbol-2-one (IVh, $C_{19}H_{14}N_4O_3$). A solution of 11 mmole of sodium ethoxide in 10 ml of alcohol was added to a mixture of 1.0 g (5.4 mmole) of 2-amino-1-methylindole hydrochloride (I) and 1.33 g (5.4 mmole) of 4-nitrobenzylidenecyanoacetic ester (IIh) in 40 ml of ethanol, and the mixture was refluxed for 2.5 h. It was then evaporated, 10 ml of water was added to the residue, and the aqueous mixture was acidified to pH 5 with dilute hydrochloric acid. The resulting precipitate was removed by filtration and crystallized from alcohol to give 1.6 g (76%) of 3,4-dihydro-1-methyl-4-(p-nitrophenyl)-3-cyano-α-carbol-2-one (IIIh) with mp 357°C and M^+ 346. IR spectrum: 2210 (CN), 1650 cm^{-1} (CO).

4-(p-Dimethylaminophenyl)-9-methyl-3-cyano-α-carbol-2-one (IVg, $C_{21}H_{18}N_4O$). This compound was obtained in the same way as IVh from 1 g (5.4 mmole) of 2-aminoindole I and 1.32 g (5.4 mmole) of p-dimethylaminobenzylidenecyanoacetic ester (IIg) in the presence of 0.06 mole of sodium ethoxide. The product had mp 375-377°C and M^+ 342. IR spectrum: 3200-3500, 2400-2700, 2200 (CN), 1650 cm^{-1} (CO). The yield was 1.5 g (81%).

9-Methyl-4-(p-methoxyphenyl-3-cyano-α-carbol-2-one (IVf, $C_{20}H_{15}N_3O_2$). This compound was obtained in the same way as IVh from 0.5 g (2.7 mmole) of 2-aminoindole I and 0.62 g (2.7 mmole) of p-methoxybenzylidenecyanoacetic ester IIf in the presence of 0.03 mole of sodium ethoxide and had mp 352-355°C and M^+ 329. IR spectrum: 3100-3600 (NH), 2200 (CN), 1610 cm^{-1}. The yield was 0.65 g (73%).

9-Methyl-4-phenyl-3-cyano-α-carbol-2-one (IVe, $C_{19}H_{13}N_3O$). This compound was obtained in the same way as IVh from 0.5 g (2.7 mmole) of 2-aminoindole I and 0.54 g (2.7 mmole) of benzalcyanoacetic ester in the presence of 8.2 mmole of sodium ethoxide and had mp 354-356°C and M^+ 299. IR spectrum: 2400-3700, 2260, 1760, 1660 cm^{-1}. The yield was 0.6 g (75%).

9-Methyl-4,4-tetramethylene-3-cyano-α-carbol-2-one (IVi, $C_{17}H_{17}N_3O$). This compound was obtained in the same way as IVh from 1 g (5.4 mmole) of 2-aminoindole I and 0.96 g (5.4 mmole) of cyclopentylidenecyanoacetic ester (IIi) in the presence of 0.06 mole of sodium ethoxide and had mp 218-220°C and M^+ 279. IR spectrum: 3000-3700 (NH), 2250 (CN), 1690 cm^{-1}. The yield was 0.74 g (50%).

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