CHEMISTRY OF INDOLE. XIX†. CONDENSATION OF 1-ALKYL-2-AMINOINDOLES WITH MALONIC AND SUBSTITUTED MALONIC ESTERS

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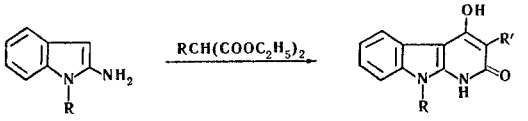
UDC 547.759.3:542.953:543.422.4.6:541.67

Condensation of 1-alkyl-2-aminoindoles with malonic ester gives α-carbonyl derivatives which, on the basis of the their UV, IR, and NMR spectra, and their chemical properties, are assigned the 2-oxo-4-hydroxy-α-carboline structure.

It has been shown [2, 3] that 1-alkyl-2-aminoindoles react smoothly with β-diketones to give α-carbolines. In the present paper, we describe the analogous condensation of 1-methyl and 1-benzyl-2-aminoindoles with malonic and substituted malonic esters. The condensation requires heating at 200-230°, and the 2-aminoindole salt used as starting material was converted into the free base by adding a small excess of triethylamine. The resulting triethylamine hydriodide or hydrochloride functions as a proton donor, facilitating polarization of the ethoxycarbonyl group, or ensuring proton transfer. However, the electrophilicity of the carbonyl carbon atom is much lower than in ketones, and the reaction requires much more vigorous conditions thanwith β-diketones [2, 3]. In order to attain the required temperature, it is best to use diphenyl ether, which is usually used in such reactions [4]. In this way, we condensed 1-methly- and 1-benzyl-2-aminoindole with malonic and acetylmalonic esters.

In the latter case, the carbonyl group is almost completely enolized, and this, together with steric hindrance, limits its participation in the condensation. On the other hand, with the esters of methyl-, butyl-, and diethylmalonic acids, and also with 1,1-diethoxycarbonylcyclopropane, the ethoxycarbonyl group no longer reacts, and consequently, α-carboline derivatives are not formed, even under forcing conditions.



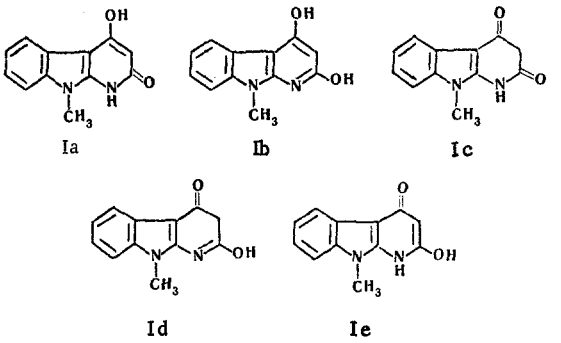
I–IV

I $R=CH_3$, $R'=H$; II $R=CH_2C_6H_5$, $R'=H$; III $R=CH_3$, $R'=COCH_3$; IV $R=CH_2C_6H_5$; $R'=COCH_3$

In the simplest case, condensation of 1-methyl-2-aminoindole with diethyl malonate gives I, which may possess structures Ia-e. In the PMR spectrum (in trifluoroacetic acid), the compound shows a clear band at δ 6.09 ppm due to a single proton at C_3, and at δ 3.48 ppm due to the $N-CH_3$ group. This excludes structures Ic and Id (in every case, in acid media). In the PMR spectrum of III, the C_3 proton peak is absent

† For Part XVIII, see [1].

Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1207-1211, September, 1970. Original article submitted June 9, 1969.



Ia Ib Ic

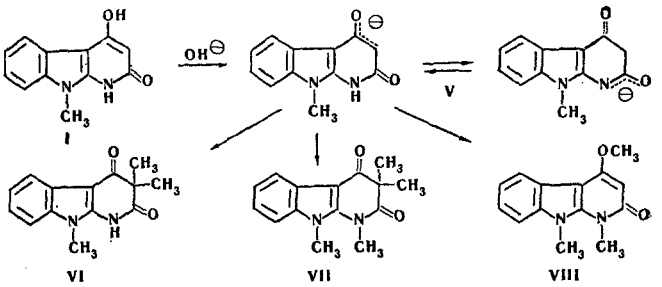
Id Ie

(in the aliphatic region, only two singlets appear, due to the methyl groups, at δ 2.55 and 3.40 ppm). Thus, on introduction of the electron-accepting acetyl group in the 3-position, in acid media (which suppresses possible dissociation of the phenolic hydroxyl), structures of types Ic and Id are likewise ruled out.

Reaction of methyl iodide in aqueous alkali with I initially gives the anion V, which undergoes double alkylation on carbon to give 3, 3, 9-trimethyl-2, 4-dioxo-1, 2, 3, 4-tetrahydro-α-carboline (VI).

The PMR spectrum of this compound displays a single peak due to the two CH_3 (δ 1.67 ppm), and a peak due to the N–CH_3 group (δ 3.71 ppm). In the IR spectrum (in Vaseline oil), two strong bands are observed at 1695 and 1645 cm^{-1}, which may be assigned to the ketone and amide carbonyl group frequencies, respectively, and also a wide band in the 3300-2600 cm^{-1} region, which disappears on dilution (in $CHCl_3$), a weak band appearing at 3410 cm^{-1}. Such behavior is typical of intermolecular hydrogen bonding of amide groups.

Methylation of the carboline I with methyl iodide in more strongly alkaline solution (alcoholic alkoxide) results in the replacement of a hydrogen atom at the NH group, to give 1, 3, 3, 9-tetramethyl-2, 4-dioxo-1, 2, 3, 4-tetrahydro-α-carboline (VII). If the methylation is carried out with dimethyl sulfate (in aqueous alkali), the intermediate ion V is methylated, not on carbon, but on nitrogen and oxygen, giving 1, 9-dimethyl-2-oxo-4-methoxy-α-carboline (VIII).



I V

VI VII VIII

In the PMR spectrum of VII, no signal due to a proton at C_3 is found, but clear singlets due to the N–CH_3 groups are seen (δ 3.77 and 4.02 ppm), and also a singlet due to the two CH_3 groups in the 3-position (δ 1.67 ppm). Accordingly, in the IR spectrum of VIII, bonds due to the amide carbonyl (1635 cm^{-1}) and conjugated C=C bond (1600 cm^{-1}) are present, but no NH or OH absorption is seen.

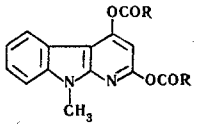
The mode of alkylation of 2-oxo-4-hydroxy-α-carboline, therefore, depends less on the alkalinity of the medium than on the nature of the attacking reagent. From the preparative point of view, formation of C-alkylated compounds of type IV are of the greatest interest, since these are not accessible by direct condensation of 1-methyl-2-aminoindole with dimethylmalone ester.

Comparison of the UV spectra (see Table 1) shows that compounds of types I and II differ substantially in the nature of their absorption from the ketonic structures VI and VII, which again confirms the PMR spectral results. The acetylation and benzoylation products (IX and X) exhibit absorption spectra typical of the fully aromatic α-carbolines [2, 3, 5], and consequently, in both cases, acylation takes place at the oxygen.

TABLE 1. IR and UV Spectral Data

Compound	IR Spectrum, ν_{max}, cm^{-1}	UV Spectrum			
		dimethylformide		methanol	
		λ_{max}, nm	log ε	λ_{max}, nm	log ε
I	3300—2400 (N—H or O—H) 1665 (amide)	264 290 300*	4,51 4,45 4,31	—	—
VI	3300—2600 (N—H or O—H) 1695 (C=O) 1645 (amide)	254 274 323	4,69 4,30 3,93	225 255 329	2,92 3,28 2,57
VII	1700 (C=O) 1640 (amide)	278 332	3,97 3,74	256 277 337	3,51 3,15 2,89
VIII	1635 (amide)	264 292 330	4,19 4,12 3,44	233 263 290 303	5,29 4,14 4,09 3,81
IX	1770 (COOR)	265 295 327	4,65 4,20 3,61	235 265 294 326	4,36 4,28 4,18 3,60
X	1740 (COOR)	262 296 329	4,51 4,30 3,65	— — —	— — —

* Inflexion



IX R=CH_3; X R=C_6H_5

The UV spectra of I and VIII are very similar, which supports structure Ia. The slight divergence between the spectra of VII and VI in methanol may be explained by amide-imidol tautomerism in the latter.

EXPERIMENTAL

The IR spectra were recorded on IKS-22 and UR-20 instruments in hexachlorobutadiene and Vaseline oil. The PMR spectra were taken on an RS-60 (60 MHz) instrument, using trifluoroacetic acid as solvent.

9-Methyl-2-oxo-4-hydroxy-α-carboline (I). To a suspension of 0.27 g (1 mmole) of 1-methyl-2-aminoindole hydriodide in 5 ml of diphenyl ether was added 0.32 g (2 mmole) of diethyl malonate and 0.15 g (1.5 mmole) of dry triethylamine. The mixture was heated in a current of inert gas for 1.5-2 h at 200-220°, then cooled to room temperature and diluted with 10 ml of light petroleum. The resulting precipitate was filtered off, and washed with light petroleum followed by water, to give 0.17 g (80%) of the carboline I. Recrystallization from aqueous dimethylformamide with the addition of activated charcoal gave fine, colorless crystals, mp 354-358° (decomp.). Found: C 67.08; 67.22; H 4.90; 5.1%. $C_{12}H_{10}N_2O_2$. Calculated: C 67.27; H 4.71%.

9-Benzyl-2-oxo-4-hydroxy-α-carboline (II). A mixture of 0.35 g (1.2 mmole) of 1-benzyl-2-aminoindole hydrochloride, 6 ml of diphenyl ether, 0.32 g (2 mmole) of diethyl malonate, and 0.15 g (1.5 mmole) of dry triethylamine was heated in a current of inert gas for 1 h at 220-230°. The mixture was cooled to room temperature and diluted with 14 ml of light petroleum. The oily residue was separated, washed with light petroleum, and dissolved in the minimum amount of acetone. The acetone solution was stirred with activated charcoal, filtered, and diluted with water to give 0.15 g (38%) of the carboline II as light acicular crystals, mp 287-289° (from glacial acetic acid). Found: C 74.12; 74.36; H 4.75; 4.91%. $C_{18}H_{14}N_2O_2$. Calculated C 74.46; H 4.87%.

9-Methyl-3-acetyl-2-oxo-4 hydroxy-α-carboline (III). To a suspension of 0.55 g (2 mmole) of 1-methyl-2-aminoindole hydriodide and 0.3 g (3 mmole) of dry triethylamine in 10 ml of diphenyl ether, heated to 120°, was added with stirring a hot (about 120°) solution of 0.81 g (4 mmole) of diethyl acetylmalonate in 2 ml of diphenyl ether. The mixture was heated for an hour at 200-220°, then cooled to room temperature

and diluted with 25 ml of light petroleum. The precipitate was filtered off, and washed with light petroleum, followed by water to give 0.33 g (64%) of fine, bright orange crystals, mp 346-349° (with decomp., from glacial acetic acid). Found: C 65.92; 66.01; H 4.59; 4.59%. $C_{14}H_{12}N_2O_3$. Calculated: C 65.61; H 4.73%.

9-Benzyl-3-acetyl-2-oxo-4-hydroxy-α-carboline (IV). Obtained similarly to the above, from 0.7 g (2.5 mmole) of 1-benzyl-2-aminoindole hydrochloride, 0.81 g (4 mmole) of diethyl acetylmalonate, and 0.3 g (3 mmole) of dry triethylamine in 12 ml of diphenyl ether. Yield 0.52 g (58%) of lustrous crystals, mp 326-329° (with decomp., from tetrahydrofuran). Found: C 72.56; 72.53; H 5.00; 5.23; N 14.45; 14.47%. $C_{20}H_{16}N_2O_3$. Calculated: C 72.27; H 4.86; N 14.44%.

3, 3, 9-Trimethyl-2, 4-dioxo-1, 2, 3, 4-tetrahydro-α-carboline (VI). To a solution of 0.21 g (1 mmole) of the carboline I in 3 ml of 2% aqueous sodium hydroxide was added 2.84 g (20 mmole) of methyl iodide, and the mixture was boiled with stirring for 4 h. The mixture was cooled, and acidified with 2N hydrochloric acid. The precipitate was filtered off and washed with water, to give 0.23 g (97%) of VI. Colorless needles from methanol, mp 293-295°. Found: C 60.66, 69.75; H 6.07, 5.92%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.39; H 5.84%.

1, 3, 3, 9-Tetramethyl-2, 4-dioxo-1, 2, 3, 4-tetrahydro-α-carboline (VII). To a solution of sodium ethoxide (from 0.1 g of sodium and 3 ml of absolute alcohol) was added 0.21 g (1 mmole) of the carboline I and 2.28 g (16 mmole) of methyl iodide, and the mixture was heated with stirring for 7 h. The alcoholic solution was concentrated to half its volume, diluted with water, and the resulting precipitate was filtered off to give 0.2 g (78%) of VII. Transparent plates from toluene, mp 254-256°. Found: C 70.52; 70.61; H 6.35; 6.21%. $C_{15}H_{16}N_2O_7C$ 70.28; H 6.30%.

Acidification of the aqueous-alcoholic solution with 2N hydrochloric acid precipitated 0.04 g (17%) of the carboline VI, identical with that obtained above.

1, 9-Dimethyl-2-oxo-4-methoxy-α-carboline (VIII). To a solution of 0.43 g (2 mmole) of the carboline I in 25 ml of 2N aqueous sodium hydroxide was added during 3 h 5.04 g (40 mmole) of dimethyl sulfate The mixture was stirred and heated under reflux at 100° during this time. The resulting precipitate was filtered off and washed with water, then it was dissolved in benzene, and the solution was filtered through a layer of alumina 70 mm thick. The benzene solution was evaporated, giving 0.3 g (59%) of VIII. Colorless plates from hexane, mp 110-112°. Found: C 69.40; 69.62; H 5.90; 5.80%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.39; H

Acidification of the alkaline solution with 2N hydrochloric acid precipitated 0.11 g (23%) of the carboline VI, identical with that obtained previously.

9-Methyl-2, 4-diacetoxy-α-carboline (IX). A suspension of 0.32 g (1.5 mmole) of the carboline I in 4 ml of acetic anhydride was boiled for 30 min under reflux. The mixture was evaporated in vacuo, and the oily residue was treated with 5 ml of toluene. After heating and separating from the dark residue, the toluene solution was evaporated to give 0.42 g (94%) of IX. Long bright yellow plates from a mixture of toluene and hexane (1:3), mp 127.5-129°. Found: C 64.51; 64.78; H 4.61; 4.73%. $C_{16}H_{14}N_2O_4$. Calculated: C 64.41; H 4.74%.

9-Methyl-2, 4-dibenzoyloxy-α-carboline (X). To a solution of 0.64 g (3 mmole) of the carboline I in 18 ml of 2N aqueous sodium hydroxide was added portionwise 3.22 g (23 mmole) of benzoyl chloride, and the mixture was stirred vigorously at room temperature for 10 h. The solid was filtered off and washed with alkali followed by water, to give 0.91 g (72%) of the carboline X, mp 172-174° (from acetone). Found: C 73.85; 73.98; H 4.29; 4.45%. $C_{26}H_{18}N_2O_4$. Calculated: C 73.91; H 4.30%. Acidification of the alkaline solution to pH 7.5 precipitated 0.15 g (23%) of unreacted I.

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