THE CHEMISTRY OF INDOLE

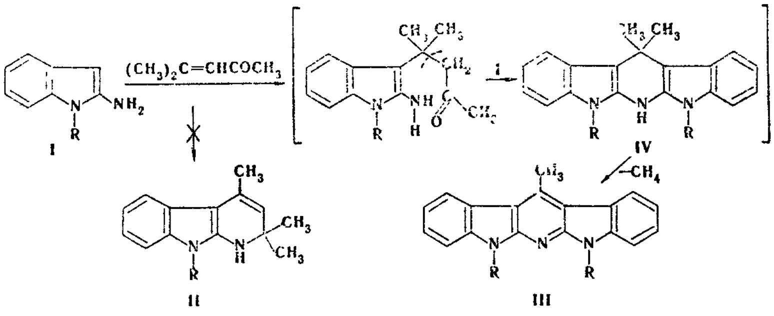
XXXVIII.* CLEAVAGE OF A CARBON–CARBON BOND IN THE REACTION OF 2-AMINOINDOLES WITH DIFUNCTIONAL COMPOUNDS

T. V. Mel'nikova, A. N. Kost,
R. S. Sagitullin, and N. N. Borisov

UDC 547.759.3:542.953.4

The reaction of 2-aminoindole with α,β-unsaturated aldehydes and ketones leads to α-carbolines, the β-carbon atom of the oxo compound attacking C_3 of the indole. In a number of cases, reactions with bifunctional derivatives take place with the cleavage of a carbon–carbon bond and the formation of the pentacyclic system of indolo[2,3-b]-α-carboline. The same substances are obtained from 2-amino-3-(arylmethylene)indoles and 3-(arylmethylene)-oxindoles. The replacement of one molecule of 2-aminoindole by other acceptors did not lead to the formation of unsymmetrical structures.

The condensation of 2-amino-1-methylindole with α,β-unsaturated ketones leads to α-carbolines [2]. On expanding the range of unsaturated oxo compounds and varying the indole part, we found that the reaction of 2-aminoindoles (I) with ethylideneacetone, methyl vinyl ketone, crotonaldehyde and cinnamaldehyde takes place with the formation of 2,4-dimethyl-, 2-methyl-, 4-methyl-, and 4-phenyl-α-carbolines, respectively. In all cases, the β-carbon atom of the unsaturated oxo compound attacks not the amino group (as is the case in the synthesis of quinolines) but the C_3 atom of the indole molecule. No isomeric substances could be detected chromatographically. However, in some cases the condensation of the oxo compound with the participation of two molecules of (I) takes place as a side process or even as the main process. For example, the reaction of (Ia, $R = CH_3$) with mesityl oxide gave not the dihydrocarboline (II), the formation of which could be expected by analogy with the reaction between aniline and mesityl oxide, but 5,7,12-trimethylindolo[2,3-b]-α-carboline (IIIa), identical with the substance obtained from (Ia) and acetaldehyde [3]. In the reaction, a C–C bond is cleaved and, apparently, the gem-dihydro compound (IV) is formed, which, however, could not be isolated and identified since it aromatized with the loss of a molecule of methane, giving IIIa. This hypothesis is confirmed by the formation of the same compound (IIIa) in experiments with mesityl oxide and with diacetone alcohol or 4-hydroxypentan-2-one.



a $R = CH_3$; b $R = CH_2C_6H_5$

Under similar conditions [heating with the hydrochloride of (Ia) in isopropanol in the presence of triethylamine] acetoacetic ester also forms (IIIa). If, however, protonic solvents are excluded and the process is performed in dry pyridine, 2-oxo-α-carboline [4] is obtained.

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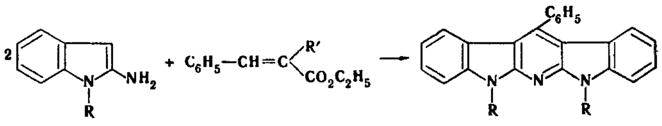
*For Communication XXXVII, see [1].

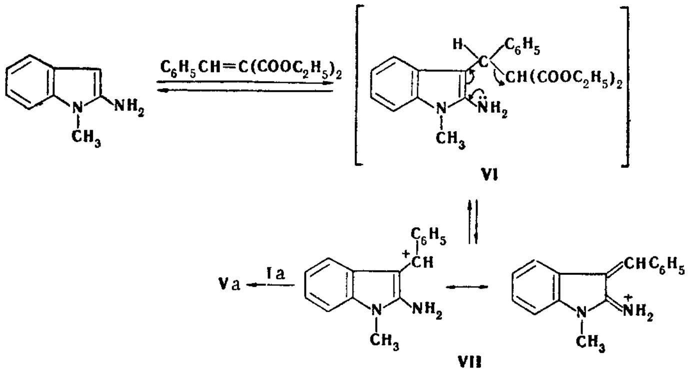
M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1273-1278, September, 1973. Original article submitted September 19, 1972.

The reactions described take place fairly slowly and are accompanied by considerable resinification, which is evidently responsible for the low yields of (IIIa). If, however, ethyl α-cyanocinnamate or benzylidenemalonic ester is caused to react with (I) in the presence of isopropanol, compounds (V) are formed rapidly (in 15-20 min) and in good yields.

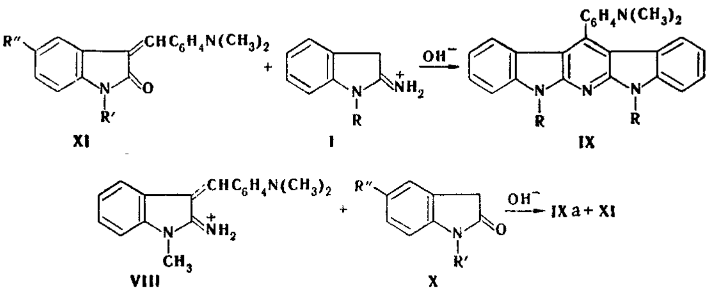


$R'=CN, COOC_2H_5$ Va $R=CH_3$; b $R=CH_2C_6H_5$

Here the strong influence of the two electron-accepting groups facilitates both the process of addition to the double carbon–carbon bond and also solvolysis and aromatization. It may be considered that in these cases cleavage takes place in the manner of a retroaldol or a retro-Claisen condensation. For such models, the formation of (V) apparently does not require the obligatory participation of a protonic solvent or the appearance of a kinetically independent molecule of aldehyde. Then an alternative reaction mechanism approximates to the type of a reverse Michael reaction [5] and includes the formation of the intermediate compound (VI), which is cleaved heterolytically, giving the diarylmethane cation (VII) which then attacks a second molecule of 2-aminoindole with the formation of the indolo-α-carboline (V).



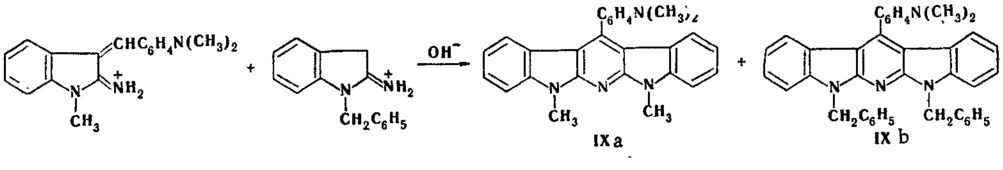
The formation of a cation of similar structure in the 2-aminothiophene series has been suggested previously [6]. Correspondingly, we have observed [7] that in the reaction of a salt of (Ia) with p-dimethylaminobenzaldehyde the resulting 2-amino-3-(arylmethylene)indole (VIII) is capable, under alkaline conditions, of condensing with (Ia), giving (IXa). In an attempt to replace the (Ia) in this reaction by the more readily available 1-methyloxindole (Xa) we again obtained (IXa), but in low yield. The same low yield of (IX) was obtained in the reaction of (I) with the 3-(arylmethylene)oxindole (XI). If a compound (X) or (XI), differing by the substituents in the benzene ring and on the nitrogen atom from the 2-aminoindole molecule was used, in neither case was a substance (IX) of unsymmetrical structure obtained. The structure of the product was always determined by that of the initial 2-aminoindole. Thus, in the case of the oxindole derivatives no direct cyclization took place. Only the migration of the arylmethylene group into the molecule of the 2-aminoindole and then its reaction with a second molecule of (I) was observed. When (VIII) was condensed with (X), it was possible to isolate and identify compound (XI), in addition to (IXa).



I, IX a $R=CH_3$; b $R=CH_2C_6H_5$; X, XI a $R'=CH_3$, $R''=H$; b $R'=C_2H_5$, $R''=H$; b $R'=CH_3$, $R''=Br$

When the initial oxindole (X or XI) contained halogen in position 5, halogen was absent from the (IX) obtained. Consequently, the formation of (IX) takes place through a molecule of 2-aminoindole and the arylmethylene group from (XI). When 2 moles of (Ia) per 1 mole of (XI) was used, the yield of (IX) was accordingly doubled.

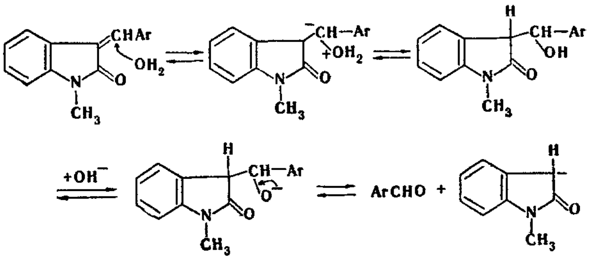
In the condensation of (VIII) with 2-amino-1-benzylindole (Ib), instead of the expected unsymmetrical substance a mixture of the symmetrical indolo-α-carbolines (IXa and IXb) was obtained, their structures being shown by the identity of their IR spectra with the respective authentic samples and by mass spectrometry.



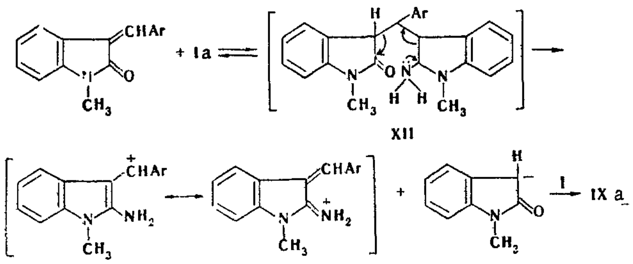
In an attempt to obtain an unsymmetrical structure starting from 4-benzylidene-3-methyl-1-phenylpyrazolin-5-one and (Ia), we again isolated only the indolo-α-carboline (Va). The pyrazolinone structure did not take part in the condensation.

Thus, here, as well, apparently, the reversibility of the process leads to the situation that heterocyclization takes place in the direction of the formation of the thermodynamically more stable symmetrical systems.

In alkaline media, solvolysis goes to completion and from the 3-benzylidene derivatives of oxindole- or 2-aminoindole, after boiling in ethanolic caustic potash solution, we isolated the aldehyde in the form of the 2,4-dinitrophenylhydrazone.



In favor of the proposed scheme is also the fact that compound (IX) is formed simply by boiling (VIII) in alcoholic alkali without the addition of an acceptor of the arylmethylene residue (as which we previously added oxindole derivatives); but under these conditions the yield of (IXa) is halved (falling from 80 to 40%). Alternatively, it is possible that addition first takes place in the manner of a Michael reaction, and then the intermediate structure (XII) undergoes solvolysis.



Experiment did not contradict this mechanism, either. When the reaction was performed in absolute acetonitrile in the presence of dry triethylamine, an indolo-α-carboline (IX) was formed, although the yield was halved. It may be assumed that the two processes take place in parallel.

There is information in the literature on the heterolytic cleavage of the double carbon–carbon bond of similar structures [8-11].

Thus, β-hydroxy ketones, α,β-unsaturated ketones, and esters of β-oxo acids and of α,β-unsaturated acids, on reaction with 2-aminoindoles, either form α-carbolines or are converted with cleavage of a carbon–carbon bond and the participation of a second molecule of aminoindole into indolo-α-carbolines. The second process takes place more slowly, under more severe conditions, and apparently by two different routes in which all the stages are equilibrium processes with the exception of the last one – aromatization.

EXPERIMENTAL

The IR spectra were taken on an IKS-22 instrument in paraffin oil. The mass spectra were taken on an MKh-1303 instrument. The identity of compounds (III, V, IX, and XI) with the respective authentic samples was shown by comparing their chromatographic mobilities, melting points, and IR spectra, and also mass-spectrally.

2,4-Dimethyl-α-carboline. A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.052 g (0.62 mmole) of ethylideneacetone, and 0.14 ml (1 mmole) of triethylamine in 1.5 ml of isopropanol was boiled in a current of nitrogen for 30 min. After cooling, water was added, and the precipitate that deposited was filtered off and washed with ethanol. This gave 0.06 g (61%) of 2,4-dimethyl-α-carboline with mp 222-224°C (from methanol). According to the literature [16], mp 222-222.5°C. UV spectrum: λ_{max} 218, 239, 261, 296, 332 nm (log ε 4.45, 4.26, 4.02, 4.13, 3.60).

2-Methyl-α-carboline. A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.1 g (1.5 mmole) of methyl vinyl ketone, and 0.14 ml (1 mmole) of triethylamine in 1.5 ml of isopropanol was boiled in a current of nitrogen for 1 h. The solvent was evaporated off and the residue was dissolved in benzene and separated preparatively on alumina (activity grade II) in the benzene–ethyl acetate (3 : 1) system. This gave 0.027 g (30%) of 2-methyl-α-carboline with mp 252°C. According to the literature [14], mp 252-254°C.

4-Methyl-α-carboline. Similarly, 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.1 g (1.5 mmole) of crotonaldehyde, 0.14 ml (1 mmole) of triethylamine, and 1.5 ml of isopropanol (boiled in a current of nitrogen for 4 h) gave 0.03 g (33%) of 4-methyl-α-carboline with mp 216°C (from methanol). According to the literature [14], mp 217-219°C.

4-Phenyl-α-carboline. As in the preceding case, 0.5 g (3 mmoles) of 2-aminoindole hydrochloride, 0.4 g (9 mmoles) of cinnamaldehyde, 6 ml of isopropanol, and 0.084 ml (6 mmoles) of triethylamine, after being boiled for 3 h, gave 0.13 g (18%) of 4-phenyl-α-carboline [system for preparative separation: toluene–ethyl acetate (3 : 2)], with mp 223-225°C. UV spectrum: λ_{max} 218, 247, 300 nm (log ε 4.63, 4.26, 4.09). PMR spectrum (in dimethyl sulfoxide): doublet (3-H), δ 7.0 ppm ($J_{2,3}$ = 5 Hz). Found, %: C 83.9; H 5.5. $C_{17}H_{12}N_2$. Calculated, %: C 83.6; H 5.0.

5,7,12-Trimethylindolo[2,3-b]-α-carboline (IIIa). a) From diacetone alcohol. A mixture of 0.55 g (2 mmoles) of 2-amino-1-methylindole (Ia), 0.23 g (2 mmoles) of diacetone alcohol, and 0.42 ml (3 mmoles) of triethylamine in 4 ml of dimethylformamide was boiled for 7 h. The dark transparent solution was cooled to 10°C, and the crystalline precipitate that deposited was filtered off and washed first with dimethylformamide and then with water. After drying, 0.13 g (43%) of (IIIa) was obtained with mp 265-266°C [3]. Found, %: C 80.6; H 5.3; N 14.0. $C_{20}H_{17}N_3$. Calculated, %: C 80.2; H 5.7; N 14.0.

b) From 4-hydroxypentan-2-one. A mixture of 0.14 g (0.5 mmole) of the hydriodide of (Ia), 0.1 g (1 mmole) of 4-hydroxypentan-2-one, and 0.11 ml (0.75 mmole) of triethylamine was boiled in 3 ml of isopropanol for 3 h. The reaction mixture was evaporated in vacuum to dryness, and the residue was carefully triturated with 3 ml of methanol and filtered off. The substance was washed with more methanol on the filter, giving 0.04 g (54%) of the same (IIIa).

c) From mesityl oxide. Similarly, 0.14 g (0.5 mmole) of the hydriodide of (Ia) and 0.1 g (1 mmole) of mesityl oxide, on being boiled in isopropanol for 3 h, gave 0.01 g (13%) of (IIIa), mp 260-262°C (from acetone).

5,7-Dimethyl-12-phenylindolo[2,3-b]-α-carboline (Va). a) From benzylidenemalonic ester. To 0.14 g (0.5 mmole) of the hydriodide of (Ia) in 5 ml of isopropanol were added 0.25 g (1 mmole) of benzylidenemalonic ester and 0.11 ml (0.75 mmole) of triethylamine, and the mixture was boiled for 15 min. Then it was cooled with water, and the crystalline precipitate that had formed was filtered off and washed with isopropanol. This gave 0.08 g (89%) of (Va), mp 292-294°C°

b) From ethyl 2-cyanocinnamate. In a similar manner to the preceding case, 0.14 g (0.5 mmole) of the hydriodide of (Ia) and 0.2 g (1 mmole) of ethyl 2-cyanocinnamate gave 0.09 g of (Va). Yield quantitative.

c) From (Ia) and 4-benzylidene-3-methyl-1-phenylpyrazolin-5-one. With heating in an inert-gas atmosphere, 2 ml (0.36 mmole) of an 0.2 N ethanolic solution of caustic potash was added to a mixture of 0.094 g (0.36 mmole) of 4-benzylidene-3-methyl-1-phenylpyrazolin-5-one and 0.1 g (0.36 mmole) of the hydriodide of (Ia) in 3 ml of ethanol, and then the mixture was boiled for 20 min. After cooling, the crystals that had deposited were filtered off with suction and washed with ethanol. This gave 0.04 g (61%) of (Va), calculated on the (Ia), mp 288-290°C. According to the literature [3], mp 288-290°C.

5,7-Dibenzyl-12-phenylindolo[2,3-b]-α-carboline (Vb). As in the preceding case, 0.26 g (1 mmole) of the hydrochloride of (Ib) and 0.2 g (1 mmole) of ethyl 2-cyanocinnamate, by being boiled in 5 ml of isopropanol for 30 min, gave 0.2 g (78%) of (Vb), mp 286-288°C.

5,7-Dibenzyl-12-(p-dimethylaminophenyl)indolo[2,3-b]-α-carboline (IXb). With heating, 0.093 g (0.36 mmole) of the hydrochloride of (Ib) was dissolved in 3 ml of ethanol containing 0.02 g of caustic potash. Then 0.05 g (0.36 mmole) of p-dimethylaminobenzaldehyde was added, and the flask was filled with inert gas and left to stand at room temperature for 12 h. The crystals that deposited were filtered off and washed with ethanol. This gave 0.06 g (60%) of (IXb), mp 236-238°C (from benzene). Found, %: C 84.3; H 5.8. $C_{39}H_{32}N_4$. Calculated, %: C 84.1; H 5.7.

12-(p-Dimethylaminophenyl)-5,7-dimethylindolo[2,3-b]-α-carboline (IXa). a) From 3-(p-dimethylaminobenzylidene)oxindoles (XIa-c) and (Ia). General procedure. With heating in an inert-gas atmosphere, 2 ml (0.36 mmole) of an 0.2 N ethanolic solution of caustic potash was added to a mixture of 0.36 mmole of (XI), 0.36 mmole of (Ia), and 3 ml of ethanol, and the resulting mixture was boiled for 30 min. After cooling, the crystals that had deposited were filtered off and were washed with ethanol, dissolved in benzene and chromatographed on a column (2 × 50) of alumina (activity grade II), being eluted with benzene. The solvent was evaporated off and the residue was recrystallized from benzene. This gave (IXa) with a yield of 60-62% calculated on the (Ia).

Similarly, in absolute acetonitrile in the presence of an equimolar amount of dry triethylamine, (XIa) and (Ia) gave (IXa) with a yield of 30%. When twice the amount of (Ia) was used, the yield of (IXa) doubled. Likewise, 0.36 mmole of (Ib) and 0.36 mmole of (XIa) gave (IXb) with a yield of 80%.

b) From the hydriodide of 3-(p-dimethylaminobenzylidene)-2-imino-1-methylindoline (VIII) and the substituted oxindoles (Xa-c): 1) From (VIII) and 1-methyloxindole (Xa). With heating in an inert-gas atmosphere, 1.4 ml of an 0.2 N ethanolic solution of caustic potash was added to a mixture of 0.1 g (0.25 mmole) of the hydriodide of (VIII), 0.037 g (0.25 mmole) of 1-methyloxindole, and 2 ml of ethanol, after which the mixture was boiled for 20 min. After cooling, the crystals that had deposited were filtered off with suction and were washed with ethanol. Purification was performed on a column in a similar manner to the experiment described above. This gave 0.04 g (80%), calculated on the VIII) of a product with mp 296-298°C (from benzene). From the filtrate by preparative chromatography on a plate coated with alumina (activity grade II) in the benzene–ethyl acetate (2:1) system, 0.01 g (15%) of 3-(p-dimethylaminobenzylidene)-1-methyloxindole (XIa) with mp 150-152°C (from ethanol) [12] was isolated.

In a similar manner to the preceding experiment, in absolute acetonitrile in the presence of dry triethylamine, (VIII) and (Xa) gave (IXa) with a yield of 40%.

2) From (VIII) and 1-ethyloxindole (Xb). As in the preceding case, 0.1 g (0.25 mmole) of the hydriodide of (VIII) and 0.04 g (0.25 mmole) of 1-ethyloxindole gave 0.034 g (68%) of (IXa) with mp 295-297°C and 0.01 g (15%) of 3-(p-dimethylaminobenzylidene)-1-ethyloxindole (XIb) with mp 149-150°C [13].

3) (VIII) and 5-bromo-1-methyloxindole (Xc). Similarly, 0.1 g (0.25 mmole) of the hydriodide of (VIII) and 0.057 g (0.25 mmole) of 5-bromo-1-methyloxindole gave 0.045 g of yellow-orange crystals of a mixture of (IXa) and (XIc). After preparative separation on a plate coated with alumina in benzene, 0.015 g of (IXa) and 0.03 g of (XIc) with mp 210°C [14] were obtained.

Hydrolysis of (VIII). In an inert-gas atmosphere, 0.05 g (0.125 mmole) of (VIII) in 2 ml of ethanol was boiled with an 0.2 N ethanolic solution of caustic potash (0.7 mole) for 30 min. The crystals of (IXa) that deposited were filtered off. Yield 40% (0.01 g). The filtrate yielded 0.008 g of p-dimethylaminobenzaldehyde 2,4-dinitrophenylhydrazone.

The alkaline hydrolysis of (XIa) took place similarly (p-dimethylaminobenzaldehyde 2,4-dinitrophenylhydrazone was again isolated).

Reaction of 3-(p-Dimethylaminobenzylidene)-2-imino-1-methylindoline (VIII) with 2-Amino-1-benzylindole (Ib). A mixture of 0.1 g (0.25 mmole) of the hydriodide of (VIII), 0.065 g (0.25 mmole) of 2-amino-1-benzylindole hydrochloride (Ib) and 2 ml of ethanol was treated with 2.8 ml (0.5 mmole) of an 0.2 N ethanolic solution of caustic potash, after which the mixture was boiled in an inert-gas atmosphere for 30 min. The precipitate that deposited was filtered off and washed with ethanol. This yielded 0.08 g of a mixture from which, after preparative separation on a plate coated with alumina in the benzene–petroleum ether (1:1) system, (IXa) and (IXb) were obtained with mp 296-298°C and 236-238°C, respectively. They were identical with authentic samples according to their IR and mass spectra.

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