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NEW SYNTHESIS OF DERIVATIVES OF β-[2-ALKOXY-3-INDOLYL]ACRYLIC ACID

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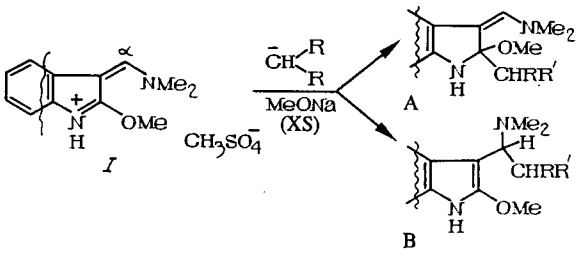
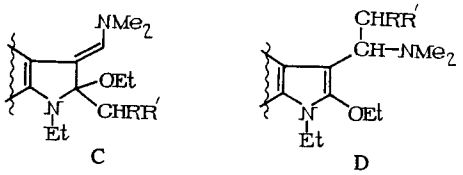
In [1] we studied the transamination of derivatives of 3-dimethylaminomethyleneoxindole with different amines and established the structure of the derivatives obtained by ^1H NMR spectroscopy. The present investigation is dedicated to a study of the reaction of the earlier-obtained [2] methyl sulfate salt of 2-methoxy-3-dimethylaminomethyleneindolenine (I) and the fluoroborate of 1-ethyl-2-ethoxy-3-dimethylaminomethyleneindolenine (II) with compounds having an active methylene component. Since the reaction proceeds in the presence of bases (usually sodium alcoholate), the addition of the anion may be to position 2 of the indole ring or to the α-position of the eneamine fragment. The respective intermediates for the salt I could have the structures A or B,



and for the fluoroborate II, structures C or D,



It is evident that only intermediates B and D are aromatized with the formation of the indole ring, which, as was shown earlier in a study of the polarographic reduction of oxindole and indoxyl eneamines, significantly stabilizes the respective intermediate compounds [3]. Thus, this direction of the reaction, coupled with the substitution of the dimethylamino group of the eneamine fragment, is preferable. Actually, the condensation process selectively proceeds on the α-carbon of salts I and II with formation of derivatives of β-(2-alkoxy-3-indolyl)acrylic acid. Thus, the reaction of methylsulfate I with cyanoacetamide and ethyl cyanoacetate proceeds unambiguously and in good yield to give the corresponding derivatives if 3-indolylacrylic acid (IIIa, b),* since, in the latter case, a transesterification reaction with the formation of the corresponding methyl ester (IIIb) is also observed.

*IIIa also may be obtained from the earlier-described 2-methoxy-3-dimethylaminomethylene indolinine by fusion with cyanoacetamide [2], but in significantly lower yield (See Experimental part).

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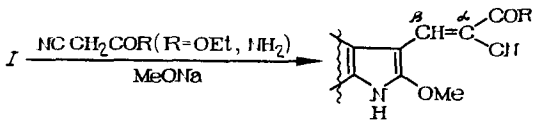
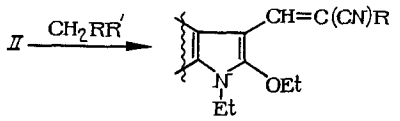


R=NH$_2$(III a), OMe(III b) III a,b

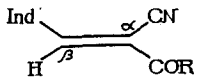
Analogously, in the reaction of fluoroborate II with cyanoacetic ester the main product is the ethyl ester of β-(1-ethyl-2-ethoxy-3-indolyl)-α-cyanoacrylic acid (IVa). In addition to this compound the substituted acrylic acid (IVb) was isolated in minor amount. Under the same conditions the reaction of II with cyanoacetamide gave a high yield of isolated amide (IVc). The condensation of II with malononitrile proceeds in the presence of a catalytic amount of pyridine: the product of reaction is the dinitrile (IVd) (see Tables 1 and 2).



IV a-b

R=COOEt(a), COOH(b), CONH$_2$(c), CN(d).

The structures of the compounds obtained were confirmed by IR and ^{1}H NMR spectroscopy and elemental analysis. The most characteristic signals in the ^{1}H NMR spectra of the compounds obtained are those of the β-protons in the 8.20-8.45 ppm region and the C(4)-H protons in the 8.15-8.39 ppm region (Table 3). The shift of the C(4)-1 signal into the lower field indicates, apparently, the anisotropic influence of the unsaturated substituent in position 3 on the indole ring. On the basis of the comparison of the chemical shift of the β-protons of the symmetrical substituent of compound IVd and the remaining materials and on the basis of earlier-obtained data on the configuration of eneamines with different size substituents on the double bond carbon [4] it is logical to assume that the structure of the compounds obtained corresponds to a *trans*-arrangement of the β-hydrogen and the α-cyano groups, i.e. the smaller-volume cyano group and the indole fragment positioned on one side of the double bond.



Ind = indole group

The possibility of using salts of the types I and II in organic synthesis is not limited by reactions between amines and active methylene components. An example of this is available within the framework of our work on the condensation of fluoroborate II with the diethyl acetal of dimethylacetamide (V) which takes place analogously with the reaction of acetal V with eneaminodicarbonyl compounds [5]. The resulting dienediamines (VI) had ^{1}H NMR spectra (in DMF-d$_7$), δ, ppm: 1.39 (t, NCH_2CH_8); 4.28 (q, NCH_2CH_3); 1.53 (t, OCH_2CH_3); 4.52 (q, OCH_2CH_3); 3.35 (s, NMe_2); 6.46 (d, J = 15.8 Hz, β-CH); 7.78 (d, $J_{\alpha\beta}$ = 15.8 Hz, α-CH); 7.24-7.65 (m, 5,6,7-CH), 8.02 (q, 4-CH). The process appears to take the form of the following scheme:

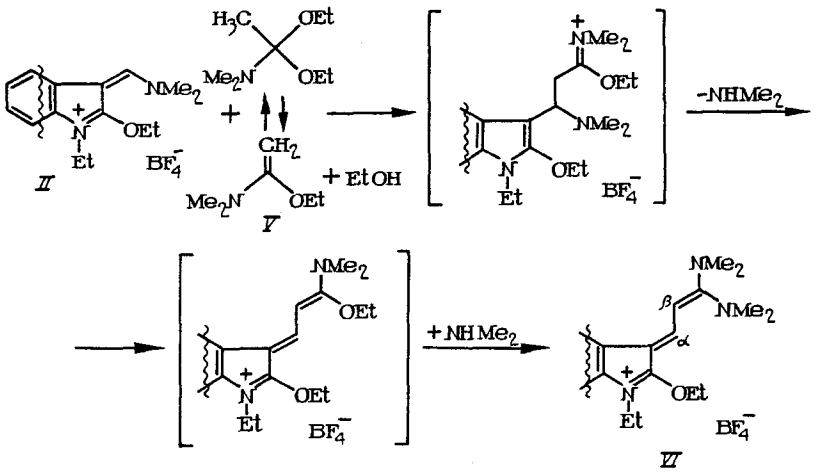


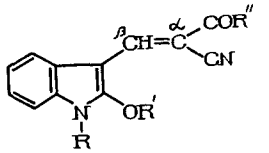
TABLE 1. Properties of the Synthesized Compounds

Compound	mp, °C	Solvent	Empirical Formula	Yield, %
IIId	226—8	Methanol	$C_{13}H_{11}N_3O_2$	8 (Method) A
IIIb	240—2	»	$C_{14}H_{12}N_2O_3$	62 (Method) A 81 (Method) B
IVa	64—5	Heptane	$C_{18}H_{20}N_2O_3$	70
IVb	174—6	Ethyl Acetate	$C_{16}H_{16}N_2O_3$	8
IVc	175—6	Methanol	$C_{16}H_{17}N_3O_2$	82
IVd	98—8,5	Ethanol	$C_{16}H_{15}N_3O$	69
VI	140,5—1,5	»	$C_{19}H_{28}N_3OBF_4$	83

TABLE 2. IR Spectra of Compounds III and IV

Compound	IR Spectra, ν_{max}, cm^{-1}		
	NH_2, NH	CN	CO
IIIa	Broad. 3100, 3360, 3490	2190	1665
IIIb	Broad. 3150	2200	1705
IVa	—	2205	1695
IVc	3160, 3310, 3400	2210	1680
IVd	—	2205	

TABLE 3. ^1H NMR Spectral Data for Compounds III and IV in DMF-d_7



Compound	Chemical Shift, δ, ppm					
	β-CH	R	R'	R''	C(4)-H	C(5), C(6), C(7)-H
IIIa	8,38	7,33 (NH)	4,28 (OMe)	7,33 (NH_2)	8,25	7,10—7,45
IIIb	8,33	—*	4,33 (OMe)	3,83 (OMe)	8,39	7,15—7,45
IVa	8,44	1,42, 4,31 (NEt)	1,55, 4,58 (2-OEt)	1,35, 4,33 (OEt)	8,33	7,25—7,65
IVb	8,44	1,42, 4,30 (NEt)	1,54, 4,50 (2-OEt)	—*	8,32	7,20—7,65
IVc	8,45	1,40, 4,29 (NEt)	1,52, 4,46 (OEt)	—*	8,16	7,20—7,65
IVd	8,20	1,42, 4,30 (NEt)	1,55, 4,59 (OEt)	—	8,15	7,25—7,68

*The NH and OH signals were not visible in these structures.

Thus, the present studies have resulted in the development of a new, accessible synthesis for derivatives of the β-(3-indoly)acrylic acids III and IV and the dienamines VI having possible uses as starting compounds for obtaining different indole-containing materials, including condensed indoles†, of interest for biological studies.

EXPERIMENTAL

The ^1H NMR spectra were recorded with a Varian XL-200 spectrometer, using TMS as internal standard. Melting points were obtained with a Boetius hot-stage (GDR). The IR spectra were determined with a Perkin—Elmer 457 instrument in mineral oil. Data from elemental analyses corresponded with the calculated values.

β-(2-Methoxy-3-indoly)-α-cyanoacrylamide (IIIa). Method A. A mixture of 0.5 g (0.0025 mole) of 2-methoxy-3-dimethylaminomethylene indolenine and 0.21 g (0.0025 mole) of cyanoacetamide were heated at bath temperature 100°C for 5 min. The reaction mass was recrystallized from 8 ml of methanol to give 0.05 g of IIIa.

Method B. A mixture of 0.94 g (0.003 mole) of I and 0.25 g (0.003 mole) of cyanoacetamide in 10 ml of sodium methylate solution (from 0.07 g of Na) was stirred at room temperature for 2 h. The reaction mixture was evaporated, the residue was dissolved in 20 ml of water, acidified with 2 N HCl until precipitation was complete (pH ~ 6.5), and 0.45 g of IIIa was filtered off.

†The possibility of this synthesis in presented in a subsequent communication.

Methyl β-(2-Methoxy-3-indolyl)-α-cyanoacrylate(IIIb) was obtained analogously with compound IIIa from I and cyanoacetic ester.

Ethyl β-(1-Ethyl-2-ethoxy-3-indolyl)-α-cyanoacrylate (IVa) and β-(1-Ethyl-2-ethoxy-3-indolyl)-α-cyanoacrylic acid (IVb). A mixture of 1 g (0.003 mole) of compound II and 0.34 g (0.32 ml, 0.003 mole) of cyanoacetic ester in 10 of sodium ethylate solution (from 0.07 g of Na) was stirred at room temperature for 3.5 h. The reaction mixture was filtered and the mother liquor was evaporated. The residue was triturated with petroleum ether and then with ethyl acetate. The precipitate was filtered off, dissolved in water and acidified with 2 N HCl to complete precipitation to give 0.07 g of IVb. The ethyl acetate mother liquor was evaporated, the residue was dissolved in ether and the solution was filtered and evaporated. The residue was triturated with petroleum ether to give 0.66 g of IVa.

β-(1-Ethyl-2-ethoxy-3-indolyl)-α-cyanoacrylamide (IVc). A mixture of 3 g (0.009 mole) of compound I and 0.75 g (0.009 mole) of cyanoacetamide in 30 ml of sodium ethylate solution (from 0.021 g of Na) was stirred at room temperature for 2.5 h. The reaction mixture was cooled and the precipitate was filtered and washed with 20 ml of water to give 2.1 g of IVc.

β-(1-Ethyl-2-ethoxy-3-indolyl)-α-cyanoacrylonitrile (IVd). A mixture of 1 g (0.003 mole) of malononitrile, 10 ml of absolute alcohol, and 2 drops of pyridine was stirred at the boiling point for 45 min. Cooling the reaction mixture and filtration gave 0.55 g of IVd.

Fluoroborate of 1-Ethyl-2-ethoxy-3-(γ,γ-bisdimethylaminopropenylidine)indolenine (VI). A mixture of 2 g (0.006 mole) of compound II and 3.09 g (0.0192 mole) of acetal V in 25 ml of absolute alcohol was stirred at room temperature for 4.5 h. The reaction mixture was evaporated and the residue was triturated with water to give 2 g of VI.

REFERENCES

1. T. V. Golovko, N. I. Mikerova, L. M. Alekseeva, et al., Khim.-farm. Zh., 4 (1994).
2. T. V. Golovko, N. P. Solov'eva, G. A. Bogdanova, et al., Khim. Geterotsikl. Soedin., No. 9, 1190 (1991).
3. M. K. Polievktov, O. A. Petrishcheva, S. Yu. Ryabova, et al., ibid., No. 5, 642-649 (1991).
4. N. P. Kostyuchenko, V. G. Granik, A. M. Zhidkova, et al., ibid., No. 9, 1212-1219 (1974).
5. V. G. Granik, A. K. Shanazarov, N. P. Solov'eva, et al., ibid., No. 11, 1470-1476 (1987).