Compounds III-V were obtained via the scheme in [11]; aldehyde II was prepared by the method in [12].

1,3,3-Trimethyl-2-(2-thienyl)methyleneindoline (V). A solution of 1.1 g (7.5 mmole) of thiophene-2-carboxylic acid chloride in 7.5 ml of benzene was added to a solution of 2.6 g (15 mmole) of 1,3,3-trimethyl-2-methyleneindoline in 7.5 ml of benzene, and the mixture was refluxed for 1 h. The precipitated 1,2,3,3-tetramethyl-3H-indolium chloride was removed by filtration and washed with benzene, and the filtrate was passed through a column packed with aluminum oxide and evaporated *in vacuo*. The crystalline residue was washed with hexane and removed by filtration to give 0.98 g (46%) of a product with mp 136-137°C (from methanol). Found: C 71.7; H 5.9; N 4.7; S 11.6%. $C_{17}H_{17}NOS$. Calculated: C 72.0; H 6.0; N 4.9; S 11.3%.

LITERATURE CITED

1. E. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill (1962).
2. M. Yu. Kornilov and A. V. Turov, Khim. Geterotsikl. Soedin., No. 10, 1299 (1979).
3. M. Yu. Kornilov, E. D. Matveeva, V. A. Budylin, L. G. Yudin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 1, 139 (1973).
4. R. Radeglia and A. Weber, J. Prakt. Chem., 314, 884 (1972).
5. F. S. Babichev, Nauk. Zap. KDU, Khim. Zb., No. 7, 206 (1956).
6. M. Yu. Kornilov, A. V. Turov, and V. I. Zamkovoi, Ukr. Khim. Zh., 41, 769 (1975).
7. H. M. McConnell and R. E. Robertson, J. Chem. Phys., 29, 1361 (1958).
8. M. Yu. Kornilov, F. S. Babichev, V. I. Zamkovoi, A. N. Kost, G. P. Kutrov, E. D. Matveeva, A. M. Nesterenko, A. V. Turov, A. K. Tyltin, L. G. Yudin, and N. S. Yaremchuk, in: Application of Conformational Analysis in the Synthesis of New Organic Substances. Material from the Republican Conference on Dynamic Stereochemistry and Conformational Analysis [in Russian], Odessa (1975), p. 29.
9. N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, J. Am. Chem. Soc., 71, 3337 (1949).
10. G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, J. Am. Chem. Soc., 95, 6365 (1973).
11. French Patent No. 829442; Compt. Rend., 1, 808 (1939).
12. H. Fritz, Chem. Ber., 92, 1809 (1959).

BISINDOLES.

15.* ACIDIC CONDENSATION OF BIS(2-ETHOXYCARBONYL-5-INDOLYL) OXIDE AND BIS(2-ETHOXYCARBONYL-5-INDOLYL)METHANE WITH AROMATIC ALDEHYDES

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The acidic condensation of bis(2-ethoxycarbonyl-5-indolyl) oxide and bis(2-ethoxycarbonyl-5-indolyl)methane with aromatic aldehydes was studied. Bis(3-chloro) compounds with labile chlorine atoms, by nucleophilic substitution of which the corresponding dimethylamino, hydroxy, methoxy, acetoxy, cyano, and mercapto derivatives were obtained, were isolated.

In connection with the accessibility of bisindoles with various structures [2, 3] it seemed of interest to subject them to acidic condensation with aromatic aldehydes and to ob-

*See [1] for communication 14.

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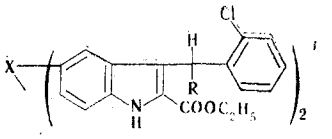
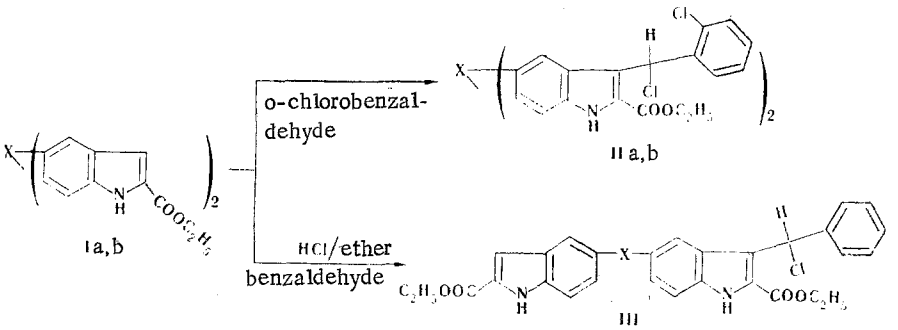
TABLE 1. Characteristics of Bisindole Derivatives



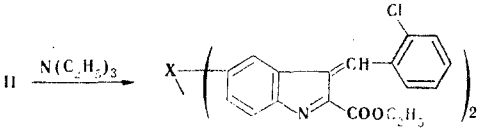
Compound	X	R	mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
				Cl	N		Cl	N	
IIa	O	Cl	140—141	19,72	7,48	$C_{36}H_{28}Cl_4N_2O_5$	20,0	7,89	87
IIb	CH_2	Cl	145—146	19,23	3,90	$C_{37}H_{30}Cl_4N_2O_4$	20,01	3,95	90
Va	O	$N(CH_3)_2$	175—176	9,28	7,24	$C_{40}H_{40}Cl_2N_4O_5$	9,76	7,70	95
Vb	CH_2	$N(CH_3)_2$	110—112	9,72	7,48	$C_{41}H_{42}Cl_2N_4O_4$	9,79	7,72	92
VIIa	O	OCH_3	119—120	9,81	3,67	$C_{38}H_{34}Cl_2N_2O_7$	10,12	3,99	84
VIIb	CH_2	OCH_3	110—111	9,83	3,74	$C_{39}H_{36}Cl_2N_2O_6$	10,15	4,01	81
VIIIa	O	$OCOCH_3$	115—116	9,03	3,23	$C_{40}H_{34}Cl_2N_2O_9$	9,40	3,70	80
VIIIb	CH_2	$OCOCH_3$	155—156	9,08	3,71	$C_{41}H_{36}Cl_2N_2O_8$	9,40	3,70	80
IX	CH_2	SC_2H_5	135—136	S 8,15	3,60	$C_{41}H_{40}Cl_2N_2O_4S_2$	S 8,43	3,69	85
X	CH_2	CN	134—135	9,94	7,89	$C_{39}H_{30}Cl_2N_4O_4$	10,30	8,12	71

tain compounds with polymeric structures or bis(3-chloroindolyl) compounds. It was established experimentally that 3,3'-disubstituted bisindoles IIa,b are formed when bisindoles Ia and Ib are treated with o-chlorobenzaldehyde by the method in [4], while the reaction with benzaldehyde gives mixtures of substances containing bisindoles III.



I-II a X=O; b X=CH_2

The use of o- and p-nitro- and p-methoxybenzaldehydes also gave complex mixtures of substances. An attempt to obtain monoalkylated bisindoles III at an o-chlorobenzaldehyde:bisindole ratio of 1:1 was unsuccessful. A mixture of the starting bisindole and its mono- and dialkyl derivatives was obtained.



IV a X=O; b X=CH_2

Dichlorides IIa,b were obtained in 70-85% yields in ether saturated with HCl. The dichlorides evolve HCl when they are heated. Treatment of benzene solutions of the dichlorides with triethylamine leads to the development of a yellow-green coloration due to the indolenine form.

Indolenine derivatives IVa,b are extremely reactive compounds. They readily add water, alcohol, and amines. Secondary amines add instantaneously, and we used this fact for the titration of the indolenine form with morpholine. The aim of the titration was to determine the number of benzylidene double bonds. It must be noted that the color of the indolenine form of oxide IVa is deeper and more intense than in the case of methane IVb due to the presence of an oxygen atom in the molecule.

The halogen in IIa,b is readily replaced by dimethylamino, hydroxy, methoxy, acetoxy,

cyano, and mercapto groups upon treatment with, respectively, amines, aqueous alkali, sodium methoxide, acetic anhydride, sodium cyanide, and ethyl mercaptan.

The UV spectra of solutions of IIa,b, V-VIIIa,b, IX, and X in benzene are similar to the spectra of the starting bisindoles (λ_{max} 298 nm), which indicates the absence of conjugation with the aldehyde fragments included in the molecule, and maxima in the visible region at 370 and 357 nm appear in the spectra of IVa,b along with maxima at 294 and 296 nm; this indicates the presence of a side double bond conjugated with the double bond of the indolenine form of the bisindoles.

A characteristic absorption band of an ester group at 1690 cm^{-1}, which is similar to the band in the spectra of the bisindoles (1685 cm^{-1}), and bands at 3330-3400 cm^{-1} (NH) are observed in the IR spectra.

The PMR spectra, which contain signals of protons of alkylamino, hydroxyalkyl, and acetoxy groups, are most informative. As a consequence of the presence of two asymmetric carbon atoms in the bis[2-ethoxycarbonyl-3-(o-chlorobenzyl)-5-indolyl] oxide and bis[2-ethoxycarbonyl-3-(α,o-dichlorobenzyl)-5-indolyl]methane molecules, IIa,b are the inseparable meso form and the racemate. We were unable to separate them by either crystallization or chromatography. Doubled signals with equal intensities of the protons of the acetoxy groups at 1.8 and 1.6 ppm and of the methylene protons of the SC_2H_5 groups at 3.45 and 3.43 ppm are, however, observed in the PMR spectra.

The dependence of the chemical shifts of the methylidyne benzyl proton on substituent R in II-X is significant. Electron-donor substituents shift the signal to the strong-field region: For example, it is observed at 5.7 ppm when R = $N(CH_3)_2$. Acetoxy (7.90 ppm) and chloro (7.55 ppm) substituents give the greatest shifts to weak field. The remaining substituents occupy an intermediate position.

Thus the facile acidic condensation of bisindoles with aromatic aldehydes leads to highly active compounds with two electrophilic centers.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in benzene were recorded with a Specord spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard.

Bis[2-ethoxycarbonyl-3-(α,o-dichlorobenzyl)-5-indolyl] Oxide (IIa). A 4.21-g (30 mmole) sample of o-chlorobenzaldehyde and 50 ml of ether saturated with HCl were added to 3.92 g (10 mmole) of bis(50-indolyl) oxide Ia, and the mixture was stirred at room temperature for 1 h. It was then poured into 50 ml of petroleum ether (70-100°C), and the white precipitate was removed by filtration, washed with petroleum ether, and dried.

Compound IIb was similarly obtained.

Bis[2-ethoxycarbonyl-3-(o-chlorobenzylidene)-5-indolyl] Oxide (IVa). Compound IIa was dissolved in benzene, excess triethylamine was added, and the precipitated triethylamine hydrochloride was removed by filtration. The clear solution was poured into petroleum ether, and the resulting yellow precipitate was removed by filtration, washed with petroleum ether, and dried in a vacuum desiccator to give a product with mp 137-138°C (dec.) in 95% yield.

Compound IVb, with mp 170-171°C, was similarly obtained in 92% yield.

Titration of Indolenine Compounds IV with Morpholine. A 0.1 M solution of morpholine in anhydrous benzene was prepared. A 0.05-sample (m) of dichloride II was dissolved in 5 ml of benzene with the addition of 0.2 ml of triethylamine; the solution turned greenish yellow and contained precipitated triethylamine hydrochloride. The 0.1 M morpholine solution was added dropwise with shaking from a burette to the colored benzene solution until it became colorless; 1.2-1.5 ml (V) of this solution was consumed in the process. The number of benzylidene double bonds in the molecule was calculated from the formula number of double bonds = (V·0.1M)/(100·m), where M is the molecular mass of dichlorides IIa,b.

Bis[2-ethoxycarbonyl-3-(α-dimethylamino-o-chlorobenzyl)-5-indolyl] Oxide (Va). Dimethylamine was passed through a solution of 0.7 g (1 mmole) of IVa in 10 ml of benzene until it was colorless, and the mixture was then poured into petroleum ether. The precipitated white crystals were removed by filtration, washed with petroleum ether, and dried.

Compound Vb was similarly obtained.

Bis[2-ethoxycarbonyl-3-(α-hydroxy-o-chlorobenzyl)-5-indolyl] Oxide (VIa). A 2-ml sample of 45% KOH was added to a solution of 0.71 g (1 mmole) of Ia in alcohol, and the mixture was stirred for 30 min and treated with water. The resulting precipitate was removed by filtration, washed with water, and dried to give a product with mp 122-123°C in 90% yield.

Compound VIb, with mp 98-100°C, was similarly obtained in 91% yield.

Bis[2-ethoxycarbonyl-3-(α-methoxy-o-chlorobenzyl)-5-indolyl] Oxide (VIIa). Excess triethylamine was added to 0.71 g (1 mmole) of IIa in benzene, and 2 ml of a solution of sodium methoxide was added to the resulting solution (the yellow coloration vanished when the mixture was stirred). The mixture was extracted with ether, and the extract was washed with water and dried with Na_2SO_4. The ether was evaporated, and the residual white crystals were washed with petroleum ether and dried.

Compound VIIb was similarly obtained.

Bis[2-ethoxycarbonyl-3-(α-acetoxy-o-chlorobenzyl)-5-indolyl]methane (VIIIa). A 3-ml sample of acetic anhydride was added to 0.67 g (1 mmole) of VIa, and the mixture was refluxed for 10 min. The precipitate that formed after cooling was dissolved in alcohol and precipitated with water. The precipitated white crystals were removed by filtration and dried.

Compound VIIIb was similarly obtained.

Bis[2-ethoxycarbonyl-3-(α-diethylmercapto-o-chlorobenzyl)-5-indolyl]methane (IX). A 0.5-g (8 mmole) sample of ethyl mercaptan was added to 0.71 g (1 mmole) of IIb in benzene, and the mixture was refluxed for 1 h. It was then cooled and poured into petroleum ether, and the resulting precipitate was removed by filtration, washed with petroleum ether, and dried.

Bis[2-ethoxycarbonyl-3-(α-cyano-o-chlorobenzyl)-5-indolyl]methane (X). A 0.3-g sample of NaCN was added to a solution of 0.71 g (1 mmole) of IIb in 10 ml of dimethyl sulfoxide, and the reaction mixture was heated with stirring at 100°C for 1 h. It was then cooled and extracted with ether, and the extract was washed with water and dried with Na_2SO_4. The ether was evaporated, and the residue was crystallized from alcohol.

LITERATURE CITED

1. Sh. A. Samsoniya, D. M. Tabidze, Dzh. A. Kereselidze, and N. N. Suvorova, Khim. Geterotsikl. Soedin., No. 1, 55 (1983).
2. Sh. A. Samsoniya, D. M. Tabidze, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 57 (1981).
3. Sh. A. Samsoniya, I. Sh. Chikvaidze, N. N. Suvorov, and I. M. Gverdtsiteli, Soobshch. Akad. Nauk Gruz. SSR, 91, No. 3, 609 (1978).
4. N. A. Kogan, Khim. Geterotsikl. Soedin., No. 4, 504 (1975).