NEW SYNTHESIS OF SUBSTITUTED GRAMINES

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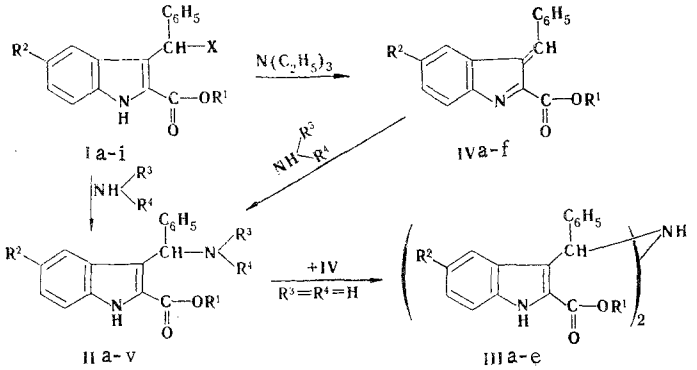
A method for the preparation of substituted gramines, viz., 3-(α-aminobenzyl)-2-carbethoxyindoles, by alkylation of amines with 3-(α-halobenzyl)-2-carbethoxyindoles was developed. Ammonia, primary and secondary amines, and pyridine were used. Anhydronium bases, viz., 3-indolidenephenylmethanes, were isolated and characterized.

Gramines are used as alkylating agents for the introduction of a skatyl grouping in CH acids [1] and to obtain indolylacetonitrile [2] and other indole derivatives [3, 4]. Compounds that have hypoglycemic action have been detected in the gramine series [5]. Methods for the preparation of 3-(α-aminomethyl)indoles by the Mannich reaction [6] or by the reaction of indoles with aldimines [7] are known. The synthesis of gramines that are substituted at a carbon atom of the side chain requires severe conditions [8]. We propose the preparation of gramines by alkylation of ammonia and primary, secondary, and tertiary amines with 3-(α-halobenzyl)-2-carbethoxyindoles [9, 10]. The latter already contain the carbon skeleton of gramine, and replacement of the halogen by an amino group proceeds under mild conditions via the scheme



The reaction is carried out in an aprotic solvent (ether, benzene, dichloroethane, and methylene chloride) at 0-20°C. Addition takes place virtually instantaneously. Substituted amines react with 3-(α-halobenzyl)indoles I to give only 3-(α-aminobenzyl)indoles II. Mixtures of II and bis[α-(3-indolylbenzyl)]amines III are formed when I are added to ether saturated with ammonia (see the scheme presented above). Reverse addition, i.e., passage of ammonia through solutions of I, leads to exclusively diskatylamines III. The mechanism of alkylation of amines includes the formation of unsaturated indolidene derivatives IV, which add the amine to give 3-(α-aminobenzyl)indoles II. In the alkylation of substituted amines the reaction stops at this step. In the case of ammonia III are primary amines that are capable of adding to intermediates IV to give secondary amines III. Bulky substituents, viz., indolylphenylmethyl groups, interfere with the subsequent addition of amines III to unsaturated IV. The formation of IV is confirmed by the development of coloration when halides I are treated with tertiary amines (triethylamine and others) and the UV spectra of the solutions with λ_{max} at 368-373 nm (log ε 3.9-4.9), which is characteristic for indolidene structures [11]. The coloration vanishes when a primary or secondary amine is added to the solutions.

In the case of primary amines aliphatic amines (methylamine and isopropylamine), including one that has the high biological activity of phenylisopropylamine (phenamine), an acyclic amine (cyclohexylamine), an aromatic amine (p-toluidine), an amino alcohol (aminoethanol), and

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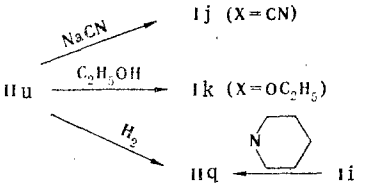
amino acids (p-aminobenzoic acid and glycine ethyl ester) added to give the products in high yields. Dimethylamine and cyclic amines (piperidine and morpholine) were used as the secondary amines. The alkylation of pyridine leads to the formation of a quaternary pyridinium salt with a structure that is similar to the structure of quaternary gramine salts. The latter are alkylating agents in diverse indole syntheses [6]. We tested the alkylating abilities of pyridinium salts in the synthesis of 3-indolylacetonitrile. Brief refluxing (3-5 min) of the pyridinium salts in ethanol leads to the formation of 3-(α-ethoxybenzyl)-indoles. The pyridinium salt is reduced with hydrogen at atmospheric pressure on a PtO_2 catalyst to give the corresponding piperidine derivative, which was also obtained by alternative synthesis from 3-(α-chlorobenzyl)indole and piperidine.



The 3-(α-aminobenzyl)indoles that we synthesized are insoluble in water in the base form, whereas 1-3% aqueous solutions (pK 3.0-3.3) are formed from the hydrochlorides. The quaternary pyridinium salts have the highest solubilities and give 10-15% solutions.

The UV spectra of structures II and III have the absorption maximum at 300 nm (log ε 4.1-4.5) that is peculiar to ethyl indole-2-carboxylates. The substituents of the side chain in the 3 position, which are separated from the aromatic indole system by a —CH—X bridge, do not affect the position of λ_{max} and the molar extinction. The IR spectra of the hydrochlorides are characterized by an intense band of CO stretching vibrations at 1675-1720 cm^{-1}. The stretching vibrations of the primary and secondary amino groups are overlapped by the indole νNH band and give one band at 3200-3400 cm^{-1}. The PMR spectrum of methylamine derivative IIe contains signals of a benzyl proton at 5.77 ppm, of the proton of the indole NH group at 9.27 ppm, and of the proton of the $NHCH_3$ group at 1.73 ppm, as well as a singlet of the protons of a methyl group at 2.41 ppm. In the PMR spectrum of dimethylamine derivative IIo the singlet of the methyl protons of the $N(CH_3)_2$ group with an integral intensity of 6H lies at 1.9 ppm, and the signal of the benzyl proton is located at 5.7 ppm.

Two asymmetric carbon atoms separated by a nitrogen atom in diskatylamines IIIa-e make the existence of diastereoisomers possible. As a consequence of identical substituents attached to the asymmetric carbon atoms, the enantiomers may be the unresolvable meso form and a racemic mixture of enantiomers.

In the preparation of bis[α-(5-methoxy-2-carbethoxy-3-indolyl)-p-nitrobenzyl]amine was isolated two substances with mp 208-209°C (IIIa) and mp 227-228°C (IIIb) with identical elementary compositions but different solubilities in ether and chloroform and different IR spectra. One νCO band at 1690 cm^{-1} is observed in the IR spectrum of IIIa (νNH is at 3315 cm^{-1}), whereas the spectrum of IIIb contains two νCO bands at 1680 and 1708 cm^{-1} (νNH at 3330 and 3445 cm^{-1}). The single νCO band of IIIa is evidently due to the symmetrical orientation of the $COOC_2H_5$ group, and the configuration of the meso form can be assigned to it, while IIIb can be considered to be the racemate of the threo form.

The isolated 3-indolidenephenylmethane bases IVa-f (Table 4) are crystalline substances with colors ranging from yellow to red. The IR spectra of IV contain a carbonyl band of an ester group that is not tied up in an intramolecular hydrogen bond (1720-1725 cm^{-1}), but absorption at 3100-3600 cm^{-1} is absent. In addition to signals of an ethoxy group, a complex multiplet of aromatic protons, which overlaps the signal of the lone proton of the —C=CH—Ph group at 6.6-7.2 ppm, is observed in the PMR spectrum of IVb; this indicates participation of the enamine fragment in conjugation with the phenyl group of the side chain.

The 3-indolidenephenylmethanes are highly active compounds that readily add amines. Thus IIs was prepared from IVb by mixing ether solutions of IVb and glycine ethyl ester.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of mineral

TABLE 1. 2-Carbethoxy-5-R-3-(α-halobenzyl)indoles (Ia-i)

Compound	R^1	R^2	Ph	X	mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
						Cl	N		Cl	N	
Ia	C_2H_5	OCH_3	*p*-NO_2	Cl	165—167	9,0	7,2	$C_{19}H_{17}ClN_2O_5$	9,1	7,2	70
Ib	C_2H_5	H	*p*-NO_2	Cl	85—88	9,8	7,8	$C_{18}H_{15}ClN_2O_4$	9,9	7,8	68
Ic	C_2H_5	H	*p*-NO_2	Br	91—93		6,8	$C_{18}H_{15}BrN_2O_4$[a]		6,9	70
Id	C_2H_5	H	*o*-Cl	Br	154—156	8,8	3,4	$C_{18}H_{15}ClBrNO_2$[b]	9,0	3,5	70
Ie	C_2H_5	Cl	*p*-NO_2	Cl	171—173	17,8	7,0	$C_{18}H_{14}Cl_2N_2O_4$	18,0	7,1	72
If	C_2H_5	Cl	H	Cl	128—130	20,1	3,9	$C_{18}H_{15}Cl_2NO_2$	20,4	4,0	75
Ig	C_2H_5	$OCH_2C_6H_5$	*p*-NO_2	Cl	163—165	7,5	6,0	$C_{25}H_{21}ClN_2O_5$	7,6	6,0	65
Ih	C_2H_5	H	H	Cl	110—115	11,2	4,4	$C_{18}H_{16}ClNO_2$	11,3	4,4	68
Ii	CH_3	H	H	Cl	143—145	11,7	4,6	$C_{17}H_{14}ClNO_2$	11,8	4,6	70

[a]Found, %: Br 19.6. Calculated, %: Br 19.8. [b]Found, %: Br 20.1. Calculated, %: Br 20.4.

oil suspensions of the compounds were recorded with a UR-22 spectrometer. The UV spectra of solutions in ethanol and benzene were recorded with an SF-16 spectrophotometer. The purity of the isolated substances was verified by thin-layer chromatography (TLC) in an ethyl acetate—hexane system (3:1).

Compounds Ia-i (Table 1) were obtained by the method in [10].

2-Carbethoxy-5-methoxy-3-(α-amino-p-nitrobenzyl)indole (IIa). A solution of 1.9 g (5 mmole) of Ia in 60 ml of ether was added dropwise with cooling (with a mixture of water and ice) to 30 ml of anhydrous ether saturated with NH_3, and the precipitated NH_4Cl was removed by filtration. The filtrate was evaporated *in vacuo* to 0.1 of its original volume, and the precipitated mixture [0.9 g (50%)] of diastereoisomers of diskatylamine (IIIa, b) was removed by filtration. The addition of ether saturated with HCl to the filtrate precipitated the hydrochloride of IIa, which was converted to the base by dissolving it in 200 ml of water, filtering the solution to remove the insoluble impurities, and alkalization of the filtrate with NH_4OH. Workup gave 0.49 g (27%) of IIa with mp 82-85°C. IR spectrum of the hydrochloride of IIa: 1675 (C=O) and 3250-3260 cm^{-1} (NH, NH_2).

Gramines IIb and IId were similarly obtained. Compound IIe was synthesized by the same method, except that methylamine was used in place of ammonia. Compound IIc was obtained by the method used to prepare IIa, but after the addition of a suspension of 1 g in ether to ether saturated with NH_3, the mixture was washed with water to remove the ammonia, the ether solution was shaken with 2-5% HCl solution, and the precipitated hydrochloride of IIc, which was only slightly soluble in water, was removed by filtration and converted to the base by the action of NH_4OH on a very dilute solution of it.

Indoles II and III were purified by reprecipitation from aqueous or aqueous alcohol solutions of their hydrochlorides by means of ammonia. The bases were again dissolved in ether and precipitated in the form of salts by means of ether saturated with HCl.

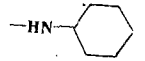
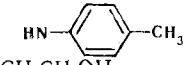
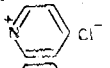
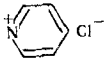
2-Carbethoxy-5-chloro-3-[α-isopropylamino(p-nitrobenzyl)]indole (IIf). A solution of 1.18 g (3 mmole) of indole Ie in 50 ml of anhydrous ether was added with cooling (with ice water) to a solution of 0.55 ml (6.5 mmole) of isopropylamine in 10 ml of anhydrous ether. After 30 min, ether saturated with HCl was added to the reaction mixture until the amines had precipitated completely. To obtain base IIf the precipitate was dissolved in water, and the base was precipitated by the addition of NH_4OH to give 0.94 g (75%) of IIf with mp 75-77°C.

Compounds IIg-r were similarly obtained.

2-Carbethoxy-3-[α-carbethoxymethylamino(o-chlorobenzyl)]indole (IIs). A 0.48-ml (3.5 mmole) sample of triethylamine was added with cooling (with ice water) to suspension of 1.17 g (3 mmole) of indole Id in 30 ml of anhydrous ether, and this mixture was added to 30 ml of an ether solution of 0.31 g (3 mmole) of ethyl aminoacetate. After 30 min, the mixture was worked up as in the case of IIf to give 0.93 g (75%) of IIs with mp 93-95°C.

2-Carbomethoxy-3-[α-(p-carboxyphenylamino)benzyl]indole (IIt). A 1.19-g (4 mmole) sample of indole Ii and 1.16 g (8.5 mmole) of p-aminobenzoic acid were dissolved in 25 ml of dimethyl sulfoxide (DMSO), and the mixture was maintained at room temperature for 24 h. It was then

TABLE 2. 5-R^2-2-Carbethoxy-3-(α-aminobenzyl)indoles (IIa-v)

Compound	R^2	Ph	NR^3R^4	mp, °C		Found, %				Empirical formula	Calc., %				Yield, %
				base	hydrochloride	C	H	Cl	N		C	H	Cl	N	
IIa	OCH_3	*p*-NO_2	NH_2	82—85	215—217	61,5	5,2		11,5	$C_{19}H_{19}N_3O_5$	61,8	5,14		11,4	27
IIb	H	*p*-NO_2	NH_2	80—82	208—210	63,7	5,0		12,3	$C_{18}H_{17}N_3O_4$	63,7	5,01		12,4	32
IIc	H	*o*-Cl	NH_2	62—65	240—242	65,6	5,2	10,7	8,6	$C_{18}H_{17}ClN_2O_2$	65,7	5,17	10,8	8,52	73
IId	Cl	*p*-NO_2	NH_2	128—130	186—190	57,7	4,3	9,3	11,2	$C_{18}H_{16}ClN_3O_4$	57,8	4,28	9,5	11,2	42
IIe	Cl	H	$NHCH_3$	74—77	185 (dec.)	66,7	5,6	10,4	8,3	$C_{19}H_{19}ClN_2O_2$	66,6	5,54	10,4	8,2	66
IIf	Cl	*p*-NO_2	$NHCH(CH_3)_2$	75—77	186—188	60,4	5,2	8,5	9,9	$C_{21}H_{22}ClN_3O_4$	60,6	5,29	8,54	10,1	75
IIg	$OCH_2C_6H_5$	*p*-NO_2	$NHCH(CH_3)_2$		188—190	68,7	5,9		8,5	$C_{28}H_{29}N_3O_5$	68,9	5,95		8,62	65
IIh	H	H	$NHCH(CH_3)_2$	78—80	189—192	74,7	7,0		8,3	$C_{21}H_{24}N_2O_2$	75,0	7,14		8,33	80
IIi	H	*p*-NO_2	$NHCH(CH_3)CH_2C_6H_5$	65—67	158—160	70,7	5,9		9,3	$C_{27}H_{27}N_3O_4$	70,9	5,9		9,2	75
IIj[a]	$OCH_2C_6H_5$	*p*-NO_2	$NHCH_2CH_2N(C_2H_5)_2$		167—169	68,1	6,6		10,0	$C_{31}H_{36}N_4O_5$	68,4	6,6		10,3	65
IIk	H	*p*-NO_2		68—70	181—183	68,2	6,4		10,1	$C_{24}H_{27}N_3O_4$	68,4	6,4		9,97	70
IIl	H	*p*-NO_2		95—97	135—138	69,8	5,4		9,7	$C_{25}H_{23}N_3O_4$	69,9	5,36		9,79	70
IIm	H	*o*-Cl	$NHCH_2CH_2OH$	67—70	222—225	64,3	5,6	9,4	7,5	$C_{20}H_{21}ClN_2O_3$	64,4	5,63	9,53	7,5	75
IIn	$OCH_2C_6H_5$	*p*-NO_2	$NHCH_2CH_2OH$		162—164	65,9	5,6		8,4	$C_{27}H_{27}N_3O_6$	66,2	5,52		8,58	65
IIo	H	*o*-Cl	$N(CH_3)_2$	150—151	203—205	67,1	6,0	9,8	7,8	$C_{20}H_{21}ClN_2O_2$	67,3	5,89	9,95	7,85	70
IIp	H	*p*-NO_2		93—96	165—168	67,7	6,1		10,2	$C_{23}H_{25}N_3O_4$	67,8	6,14		10,3	88
IIq[b]	H	H		148—150	194—197	75,7	7,0		8,0	$C_{22}H_{24}N_2O_2$	75,8	6,9		8,04	70
IIr	H	*o*-Cl		80—82	166—168	66,1	5,8	8,9	6,9	$C_{22}H_{23}ClN_2O_3$	66,2	5,77	8,9	7,03	80
IIs	H	*o*-Cl	$NHCH_2COOC_2H_5$	93—95	214—216	63,5	5,6	8,4	6,7	$C_{22}H_{23}ClN_2O_4$	63,7	5,54	8,56	6,75	75
IIt[b]	H	H	NHC_6H_4COOH	225—228		72,1	5,0		6,9	$C_{24}H_{20}N_2O_4$	72,0	5,0		7,0	60
IIu[b]	H	H			135—137	69,5	5,0	9,2	7,3	$C_{22}H_{19}ClN_2O_2$	69,7	5,02	9,38	7,39	66
IIv	H	*p*-NO_2			137—140	63,0	4,6	8,0	9,5	$C_{23}H_{20}ClN_3O_4$	63,1	4,57	8,11	9,6	70

[a]The salt was hygroscopic. [b]2-Carbomethoxyindole derivatives.

TABLE 3. Bis[α-(2-carbethoxy-5-R²-3-indolyl)benzyl]amines (IIIa-e)

Compound	R²	Ph	mp of the base, °C	IR spectrum, cm⁻¹ νCO	IR spectrum, cm⁻¹ νNH	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIIa	OCH_3	*p*-NO_2	208—209	1690	3315	63,1	4,8	9,6	$C_{38}H_{35}N_5O_{10}$	63,2	4,8	9,7	26
IIIb	OCH_3	*p*-NO_2	227—228	1680 1708	3330 3445	63,2	4,8	9,6	$C_{38}H_{35}N_5O_{10}$	63,2	4,8	9,7	60
IIIc	Cl	H	125—128	1693	3340	67,3	4,9	6,4	$C_{36}H_{31}Cl_2N_3O_4$[a]	67,5	4,8	6,56	80
IIId	Cl	*p*-NO_2	167—168	1685	3310	59,0	4,0	9,5	$C_{36}H_{29}Cl_2N_5O_8$[b]	59,2	3,97	9,58	85
IIIe	H	*p*-NO_2	272—273	1680 1715	3340 3360	65,2	4,6	10,6	$C_{36}H_{31}N_5O_8$	65,3	4,68	10,6	75

[a]Found, %: Cl 10.9. Calculated, %: 11.1. [b]Found, %: Cl 9.6. Calculated, %: Cl 9.7.

TABLE 4. 2-Carbethoxy-5-R²-3-indolidenephenylmethanes (IVa-f)

Compound	R¹	R²	Ph	mp, °C	IR spectrum, νCO, cm⁻¹	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, %
IVa	CH_3	H	*o*-Cl	120—122		68,5	4,0	4,7	$C_{17}H_{12}ClNO_2$[a]	68,6	4,0	4,7	90
IVb	C_2H_5	H	*o*-Cl	118—119		69,1	4,5	4,5	$C_{18}H_{14}ClNO_2$[b]	69,3	4,5	4,5	92
IVc	C_2H_5	Cl	H	113—115	1725	69,2	4,5	4,5	$C_{18}H_{14}ClNO_2$[c]	69,3	4,5	4,5	90
IVd	C_2H_5	OCH_3	*p*-NO_2	150—152	1720	64,7	4,5	7,8	$C_{19}H_{16}N_2O_5$	64,8	4,5	7,9	90
IVe	CH_3	H	*m*-NO_2	132—134	1720	66,0	3,9	8,9	$C_{17}H_{12}N_2O_4$	66,2	3,9	9,1	92
IVf	C_2H_5	H	H	112—113	1725	77,8	5,4	5,0	$C_{18}H_{15}NO_2$	77,9	5,4	5,0	90

[a]Found, %: Cl 11.8. Calculated, %: Cl 11.9. [b]Found, %: Cl 11.3. Calculated, %: Cl 11.4. [c]Found, %: Cl 11.4. Calculated, %: Cl 11.4.

poured into water, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized from alcohol to give 0.95 g (60%) of IIt with mp 225-228°C.

2-Carbomethoxy-3-[α-(1-pyridinia)benzyl]indole Chloride (IIu). A 0.35-ml (4.3 mmole) sample of pyridine was added with cooling to a solution of 1.19 g (4 mmole) of indole Ii in absolute ether, and salt IIu, which precipitated immediately, was removed by filtration, washed with ether, and dried to give 1.0 g (66%) of a product with mp 135-137°C.

Compound IIv was similarly isolated.

Bis[α-(2-carbethoxy-5-methoxy-3-indolyl)(p-nitrobenzyl)]amine (IIIa, b). A stream of ammonia was passed for 5-8 min with cooling (with ice water) through a solution of 1.9 g (5 mmole) of indole Ia in 60 ml of anhydrous ether, after which the mixture was allowed to stand overnight in a refrigerator. The resulting precipitate was removed by filtration, washed with water to remove the NH_4Cl, and crystallized from dioxane to give 0.46 g (26%) of IIIa (meso form) with mp 208-209°C. The ether extract after separation of isomer IIIa was washed with water and dried. The hydrochloride of IIIb (a racemic mixture of enantiomers) was precipitated from the solution by means of ether saturated with HCl. The salt was washed with water to remove traces of gramine IIa and with chloroform to remove IIIa to give 1.12 g (60%) of IIIb HCl with mp 152-154°C. Base IIIb [1.0 g (57%)], with mp 227-228°C, was isolated by the action of NH_4OH on an alcohol solution of the salt.

Diskatylamines IIIc-e were similarly obtained. Compound IIId was removed by filtration in the base form from an ether solution evaporated to a small volume and was crystallized from carbon tetrachloride.

2-Carbomethoxy-3-(α-cyanobenzyl)indole (Ij). A 1.5-g (4 mmole) sample of pyridinium chloride IIu was heated with 0.49 g (10 mmole) of NaCN in 15 ml of DMSO at 100°C for 2 h, after which the mixture was diluted with water to 100 ml, and the precipitate was removed by filtration and crystallized from alcohol to give 0.72 g (63%) of the cyano compound with

mp 155-156°C. Found, %: N 9.3. $C_{18}H_{14}N_2O_2$. Calculated, %: 9.6.

2-Carbomethoxy-3-(α-ethoxybenzyl)indole (Ik). A 0.38-g (1 mmole) sample of pyridinium chloride IIu was refluxed in 5 ml of ethanol for 10 min, after which the mixture was cooled and diluted with water, and the precipitated ethoxy derivative Ik was removed by filtration to give 0.15 g (50%) of a product with mp 189-190°C. Found, %: N 4.3. $C_{19}H_{19}NO_3$. Calculated, %: N 4.5.

2-Carbomethoxy-3-[α-(1-piperidino)benzyl]indole (IIs). A 0.38-g (1 mmole) sample of pyridinium chloride IIu was hydrogenated over PtO_2 in alcohol at room temperature and atmospheric pressure until 67 ml of hydrogen had been absorbed, after which no more absorption was observed. The catalyst was removed by filtration, and the alcohol was evaporated *in vacuo*. The residue was diluted with water, and the aqueous mixture was made alkaline with ammonium hydroxide to give 0.24 g (70%) of IIs with mp 148-150°C.

2-Carbethoxy-5-methoxy-3-indolidene(p-nitrophenyl)methane (IVd). A 0.5-ml (3.5 mmole) sample of triethylamine was added to a mixture of 1.16 g (3 mmole) of indole Ia in 15 ml of benzene, and the solution was filtered. Compound IVd [0.95 g (90%)], with mp 150-152°C, was precipitated from the filtrate by the addition of petroleum ether.

Compounds IVa-c, e, f were similarly obtained.

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