REACTION OF AROMATIC ALDEHYDES WITH 1-ALKYLINDOLE-2-CARBOXYLIC ACID AND ITS DERIVATIVES

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UDC 547.756

The effect of a substituent in benzaldehydes during reactions with 1-alkylindole-2-carboxylic acid and its esters and anilide is expressed in the formation of either di(3-indolyl)phenylmethanes or 1-alkyl-2-carboxy(carbomethoxy, carbanilido)-3-(α-X-benzyl)indoles. The possibility of replacement of X by OH, OAc, SC_2H_5, and hydrazine groups is shown.

The reaction of aldehydes with indoles in acidic media has been investigated extremely extensively [1], including the reaction of benzaldehydes with 2-carbethoxyindole [2], where it was confirmed that the only reaction products are di(3-indolyl)phenylmethanes. The intermediate — 3-indolyl(α-hydroxybenzyl)indole was isolated during alkaline catalysis [3], and products involving replacement of the hydroxy group (X=SC_2H_5 [4] and NHC_6H_5 [5]) were obtained only by an indirect method, whereas 3-(α-halobenzyl)indoles are unknown.

In the present research we attempted to synthesize 1,2-substituted 3-indolylphenylcarbinols and their derivatives from deactivated (as compared with indole) nucleophiles — 1-alkylindole-2-carboxylic acid and its esters and anilide

We found that 1-alkylindole-2-carboxylic acid and its derivatives react with aromatic aldehydes to give either analogs of the previously known di(3-indolyl)phenylmethanes (Table 1) or the expected 3-indolylphenylcarbinol derivatives (Table 2). The reaction is accomplished under mild conditions in the presence of hydrogen halides (HCl, HBr). The direction

TABLE 1. Di(1-methyl-2-R-3-indolyl)arylmethanes (I-XI)

Compound	Ar	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
I	*p*-$C_6H_4OCH_3$	$COOCH_3$	180	$C_{30}H_{28}N_2O_5$	72,5	5,4	5,6	72,6	5,6	5,6	88
II	*p*-$C_6H_4OCH_3$	COOH	250	$C_{28}H_{24}N_2O_5$	71,6	4,9	5,9	72,0	5,1	6,0	79
III	*o*-C_6H_4OH	$COOCH_3$	194—196	$C_{29}H_{26}N_2O_5$	—	—	5,4	72,2	5,4	5,8	59
IV	3,4-OCH_2-*o*-C_6H_3	$COOCH_3$	190—192	$C_{30}H_{26}N_2O_6$	—	—	5,6	70,6	5,1	5,5	66
V	C_6H_5	$CONH_2$	220	$C_{27}H_{24}N_4O_2$	—	—	12,6	74,0	5,5	12,8	57
VI	9-Anthranyl	$COOCH_3$	240	$C_{37}H_{28}N_2O_4$	—	—	4,7	79,0	5,0	5,0	52
VII	*o*-C_6H_4Cl	$COCH_3$	135	$C_{27}H_{24}ClN_2O_2$*	—	—	6,0	73,0	5,4	6,3	63
VIII	*o*-C_6H_4Cl	CH_2OH	103	$C_{25}H_{20}ClN_2O_2$ †	—	—	6,3	72,5	4,8	6,7	55
IX	1-Naphthyl	$COOCH_3$	210	$C_{33}H_{26}N_2O_4$	—	—	5,1	77,0	5,1	5,5	68
X	*o*-ClC_6H_4	$COOCH_3$	178	$C_{29}H_{25}ClN_2O_4$ ‡	—	—	5,4	69,6	5,0	5,6	78
XI	C_6H_5	COOH	250	$C_{27}H_{22}N_2O_4$	73,5	4,9	6,4	74,0	5,0	6,4	75

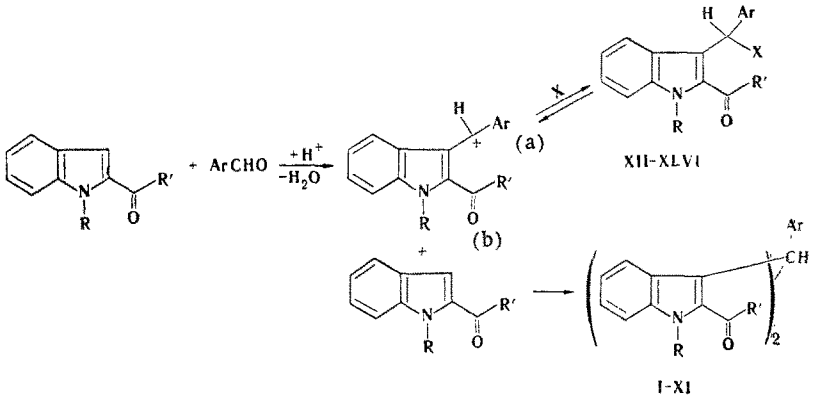
*Calculated: Cl 8.0%. Found: Cl 7.7%.
†Calculated: Cl 8.6%. Found: Cl 8.2%.
‡Calculated: Cl 7.1%. Found Cl 7.5%.

Leningrad Pharmaceutical-Chemistry Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 504-508, April, 1975. Original article submitted May 6, 1974.

TABLE 2. 1-Alkyl-3-(α-X-benzyl)indole-2-carboxylic Acid Derivatives

No.	R′	X	Ar	R	No.	R′	X	Ar	R
XII	OCH_3	Br	H	CH_3	XXX	OCH_3	O—Ac	H	CH_3
XIII	OCH_3	Br	*p*-NO_2	CH_3	XXXI	OCH_3	O—Ac	*p*-NO_2	CH_3
XIV	OCH_3	Br	*o*-Cl	CH_3	XXXII	OCH_3	O—Ac	*o*-NO_2	CH_3
XV	OCH_3	Cl	*o*-NO_2	CH_3	XXXIII	OCH_3	O—Ac	*o*-Cl	CH_3
XVI	OCH_3	Cl	*p*-NO_2	CH_3	XXXIV	OH	OH	*o*-Cl	CH_3
XVII	OCH_3	Cl	*o*-Cl	CH_3	XXXV	OH	*p*-NO_2	*p*-NO_2	CH_3
XVIII	OCH_3	Cl	2,4-Cl	CH_3	XXXVI	OH	OH	*o*-NO_2	CH_3
XIX	OH	Cl	H	CH_3	XXXVII	OH	OH	H	CH_3
XX	OH	Cl	*o*-Cl	CH_3	XXXVIII	NHC_6H_5	Cl	*o*-Cl	CH_3
XXI	OH	Cl	*o*-NO_2	CH_3	XXXIX	NHC_6H_5	Br	*o*-Cl	CH_3
XXII	OH	Cl	*p*-NO_2	CH_3	XL	OCH_3	Cl	*o*-Cl	$C_6H_5CH_2$
XXIII	OCH_3	OC_2H_5	H	CH_3	XLI	OCH_3	O—Ac	*o*-Cl	$C_6H_5CH_2$
XXIV	OCH_3	OC_2H_5	*o*-Cl	CH_3	XLII	OCH_3	HN—N(CH_3)×$\times C_6H_5$	*p*-NO_2	CH_3
XXV	OCH_3	OCH_3	*o*-Cl	CH_3					
XXVI	OCH_3	OC_2H_5	*o*-NO_2	CH_3	XLIII	OCH_3	SC_2H_5	*o*-Cl	CH_3
XXVII	OCH_3	OC_2H_5	*p*-NO_2	CH_3	XLIV	OH	SC_2H_5	*o*-Cl	CH_3
XXVIII	OH	OC_2H_5	*o*-Cl	CH_3	XLV	OH	SC_2H_5	H	CH_3
XXIX	OH	OCH_3	*o*-Cl	CH_3	XLVI	OCH_3	OC_2H_5	*o*-Cl	$C_6H_5CH_2$

of the reaction is determined completely by the substituent in the aromatic aldehyde: electron-donor substituents lead to diindolylphenylmethanes, and electron-acceptor substituents lead to indolylphenylcarbinol derivatives. The use of 1-methylindole-2-carboxylic acid esters in place of the acid itself slightly facilitates the formation of the former structure, hydrogen halide does not affect the structure of the reaction products, and the use of 1-unsubstituted acid is accompanied by resinification. The determining effect of the substituent in the aldehyde on the direction of the reaction is explained, in our opinion, by the development in acidic media of an indolylphenylmethyl cation, which undergoes parallel reactions with all of the nucleophiles present in solution via the scheme



Halides (X=Cl, Br) are formed when the reaction is carried out in a solution of hydrogen halides in ether or acetic acid, whereas alkoxy derivatives (X=OAlk) of 3-indolylphenylmethylcarbinol are formed in alcohols.

Of all the paths of consumption of the carbonium ion, only path b is irreversible, and in the case of thermodynamic control of the process diindolylphenylmethane should therefore be the only reaction product. Equilibrium (a) is determined by the stability of the carbonium ion, an increase in which leads to a shift in the equilibrium to the left and subsequent formation of diindolylphenylmethanes, which is accomplished by reaction of the carbonium ion with both the 3-unsubstituted indole and with 3-(α-X-benzyl)indole. In the latter case, an aldehyde molecule is liberated. The unstable highly reactive carbonium ions form a stronger carbon—halogen (oxygen) bond, and this leads to a shift in equilibrium (a) to the right and to the liberation of 3-(α-X-benzyl)indoles. A more stable carbonium ion than that formed in the reaction of p- and o-nitrobenzaldehyde and p- and o-chlorobenzaldehyde [6] should form in the reaction of p-hydroxy- and p-methoxybenzaldehyde, 1-naphthaldehyde, and 9-anthraldehyde with 1-alkylindole-2-carboxylic acid and its derivatives. In fact, the former gives diindolyl-

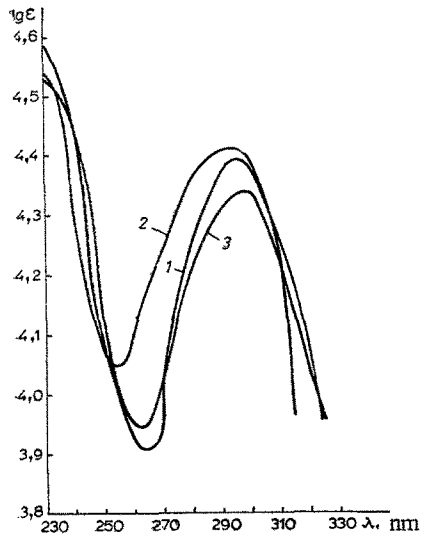


Fig. 1. UV spectra of: 1) XX; 2) XXII; 3) XI in octane (solution concentration $3 \cdot 10^{-5}$ mole/liter).

phenylmethanes (Table 1), whereas the latter gives 3-indolylphenylcarbinol derivatives (Table 2). A carboxyl group in the 2 position of indole also promotes an increase in the reactivity of the cation, whereas 1-methyl-2-acetyl- and 1-methyl-2-hydroxymethylindole react with aromatic aldehydes to give exclusively di-3-indolylphenylmethanes (VII, VIII).

The UV spectra of XI — a representative of the diindolylphenylmethane class — and of indolylphenylcarbinol derivatives XX and XXII are presented in Fig. 1. The close λ_{max} absorption (300 nm) and the close extinction (from a calculation per equivalent weight) both between themselves and in comparison with 2-carboxyindole (λ_{max} 300 nm, log ε 4.40) and the absence of substituent effect on the λ_{max} position constitute evidence for retention of the 2-carboxyindole chromophore in the synthesized compounds.

Features common to the IR spectra of XII-XLVI are the $\nu_{C=O}$ bands at 1675-1685 cm^{-1} for the acids (XIX-XXII) and at 1710-1715 cm^{-1} for the esters (XV-XVIII).

The PMR spectra, which are typical for halides, contain a multiplet of aromatic protons (8H, 7.3 ppm) and two singlets of two methyl groups — N—CH_3 (3H, 3.97 ppm) and O—CH_3 (3H, 3.79 ppm); additional bands due to the ethoxy groups — a quartet (2H, 3.53 ppm) and a triplet (3H, 1.19 ppm) — appear in the spectra of the alkoxy derivatives. The position of the singlet of the single proton of the benzyl group depends on the character of the substituent attached to the same carbon atom and ranges from 6.34 ppm in ethylmercapto derivative XLIII to 6.84 ppm in ethoxy derivative XXIV, 7.35 ppm in chloride XVII, and up to 7.6 ppm in acetoxy derivative XXXIII.

Three signals of methyl groups — 3.9 ppm (N—CH_3, 6H), 3.69 ppm (O—CH_3, 3H), and 3.57 ppm (OCH_3, 6H) — are observed in the PMR spectra of di(1-ethyl-2R-3-indolyl)phenylmethanes (I-XI) (for example, for II). The intensity ratio of 2:1:2 indicates that the molecule includes two indole fragments and one p-methyoxybenzaldehyde fragment.

The indolylphenylcarbinol derivatives (Table 2) are capable of exchanging the X group. Thus when halides XII and XVII are heated in alcohol, they give alkoxy derivatives XXIII and XXIV, whereas heating XIII-XIX and XX with ethyl mercaptan in benzene gives ethylmercapto derivatives XLIII-XLV, during which hydrogen halide is evolved. Brief refluxing of halides XV-XVII and alkoxy derivative XXIII in acetic anhydride is sufficient to obtain acetates XXXI-XXXIII and XXX, respectively. When both chloride XVI and acetate XXXI are heated to 160° for 1 h in ethylene glycol with α-methylphenylhydrazine, 1-methyl-2-carbomethoxy-3-[α-(2-methyl-2-phenylhydrazino)benzyl]indole (XLII) [7] is formed.

Carbinols XLIV-XLVII were obtained by dissolving carboxyl derivatives XIX-XXII in dilute alkali at room temperature. Colorless crystals of the carbinols were isolated when the solutions were acidified with acetic acid; on standing in air, they were rapidly converted to crimson substances, but in the absence of oxygen they can be stored satisfactorily. Ether solutions of the carbinols are also stable for a long time. Heating alkaline solutions of the carbinols to 80-100° leads to diindolylphenylmethanes with the liberation of an equimolar amount of aldehyde.

The ability to undergo condensation to give diindolylphenylmethanes and aldehydes is characteristic for all of the synthesized derivatives (Table 2). High temperatures, polar solvents, and electron-donor substituents in the aldehyde fragment promote the condensation. According to our observations, the effect of the X group on the resistance to condensation increases in the order OH < Cl, Br < OAlk < SAlk < OAc. The thermal instability of the indolylphenylcarbinol derivatives (Table 2) hinders purification of the products by crystallization in a number of cases.

EXPERIMENTAL METHOD

The PMR spectra of CCl_4 solutions of the compounds were recorded with a Varian spectrometer (100 MHz). The IR spectra of mineral-oil suspensions were recorded with a UR-22 spectrometer. The UV spectra of alcohol solutions were recorded with an SR-16 spectrophotometer. An investigation of the homogeneity of the compounds in cyclohexane–ethyl acetate (3:1) on Silufol with a phosphorescence coating showed that derivatives of indole-2-carboxylic acid esters are observed as a single distinct dark spot (R_f 0.7-0.8), which is sometimes accompanied by a very low-intensity spot of a diindolylphenylmethane impurity, the chromatographic mobility of which is lower than that of the indolylphenylcarbinol derivatives (R_f 0.6-0.7).

We have previously described XII-XXXVII [8].

Di(1-methyl-2-carbomethoxy-3-indolyl)-p-methoxyphenylmethane (I). A 1.89-g (0.01 mole) sample of methyl 1-methylindol-2-carboxylate and 1.36 g (0.01 mole) of anisaldehyde were mixed, and 20 ml of ether saturated with HCl was added. When the mixture was stirred, the solid dissolved, and after 5-6 min, I precipitated. Workup of the mixture gave 2.2 g (88%) of product. The same method was used to obtain II-IX.

Di(1-methyl-2-carbomethoxy-3-indolyl)-o-chlorophenylmethane (X). A 1-g (2.5 mmole) sample of 1-methyl-2-carbomethoxy-3-(α-bromo-o-chlorobenzyl)indole (XIV) was refluxed in 10 ml of acetonitrile for 1 h. The mixture was then cooled, and the precipitated X was removed by filtration to give 0.6 g (95%) of a product with mp 178°. The same method was used to obtain XI from XIX.

1-Benzyl-2-carbomethoxy-3-(α-chloro-o-chlorobenzyl)indole (XL). Ether (20 ml) saturated with HCl was added to a mixture of 2.65 g (0.01 mole) of 1-benzyl-2-carbomethoxyindole and 1.4 g (0.01 mole) of o-chlorobenzaldehyde. When stirring was commenced, the solids began to dissolve, and XL precipitated after 5-6 min. Workup of the mixture gave 3.05 g (75%) of a product with mp 178°. Calculated: Cl 16.8; N 3.3%. $C_{24}H_{19}Cl_2NO_2$. Found: Cl 16.5; N 3.2%.

1-Benzyl-2-carbomethoxy-3-(α-ethoxy-o-chlorobenzyl)indole (XLVI). When XL [0.42 g (1 mmole)] was refluxed for 3 min in 5 ml of ethanol it began to dissolve, and cooling of the solution precipitated XLVI. Workup gave 0.35 g (83%) of product. Calculated: Cl 8.2; N 3.2%. $C_{24}H_{24}ClNO_3$. Found: Cl 7.8; N 3.1%.

1-Benzyl-2-carbomethoxy-3-(α-acetoxy-o-chlorobenzyl)indole (XLI). Refluxing 4.2 g (1 mmole) of XL in 10 ml of acetic anhydride for 5 min and subsequent cooling of the mixture gave crystals of indole derivative XLI with mp 135°. The yield was 2.5 g (60%). Calculated: Cl 7.9; N 3.1%. $C_{26}H_{22}ClNO_4$. Found: Cl 7.6; N 3.0%. This compound was obtained from XLVI by the same method.

1-Methyl-2-carboxyl-3-(α-ethylthiobenzyl)indole (XLV). A mixture of 1.5 g (5 mmole) of chloride XIX and 0.5 g (8 mmole) of ethyl mercaptan in 10 ml of benzene was refluxed until hydrogen chloride evolution ceases (1.5 h). Cooling of the solution gave crystals of XLV with mp 160°. The yield was 1 g (62%). Calculated: S 9.8; N 4.3%. $C_{19}H_{19}NO_2S$. Found: S 9.3; N 4.3%. Compounds XLIII and XLIV were similarly obtained and were isolated from the reaction mixtures by adding pentane to the benzene solution until crystallization began. The products were crystallized from 80% ethanol.

Compound XLIII. This compound was obtained in 67% yield and had mp 117°. Calculated: S 8.6; Cl 9.5%. $C_{20}H_{20}ClNO_2S$. Found: S 8.05; Cl 9.2%. PMR spectrum: 7.2 ppm (aromatic protons, 8H), 1.22 ppm (triplet, 3H), 3.50 ppm (quartet, 2H), 3.85 ppm (N–CH_3, singlet, 3H), 3.97 ppm (O–CH_3, singlet, 3H), and 6.34 ppm (benzyl proton, singlet, 1H).

Compound XLIV. This compound was obtained in 68% yield and had mp 171°. Calculated: S 8.9; Cl 9.9%. $C_{19}H_{18}ClNO_2S$. Found: S 8.3; Cl 9.6%.

1-Methyl-2-carbanilido-3-(α-chloro-o-chlorobenzyl)indole (XLVIII). Ether (20 ml) saturated with HCl was added to a mixture of 2.5 g (10 mmole) of 1-methylindole-2-carboxylic acid anilide and 2.1 g (15 mmole) of o-chlorobenzaldehyde. Five minutes after the solids had dissolved, XXXVIII precipitated. The yield of product with mp 160° was 3.1 g (76%). Calculated: Cl 16.4; N 6.8%. $C_{23}H_{19}ON_2Cl_2$. Found: Cl 16.2; N 6.5%. "Bromide" XXXIX, with mp 169°, was similarly obtained in 70% yield. calculated: halida 25.4; N 6.2%. $C_{23}H_{19}BrClN_2O$. Found: halide 24.9; N 6.0%.

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