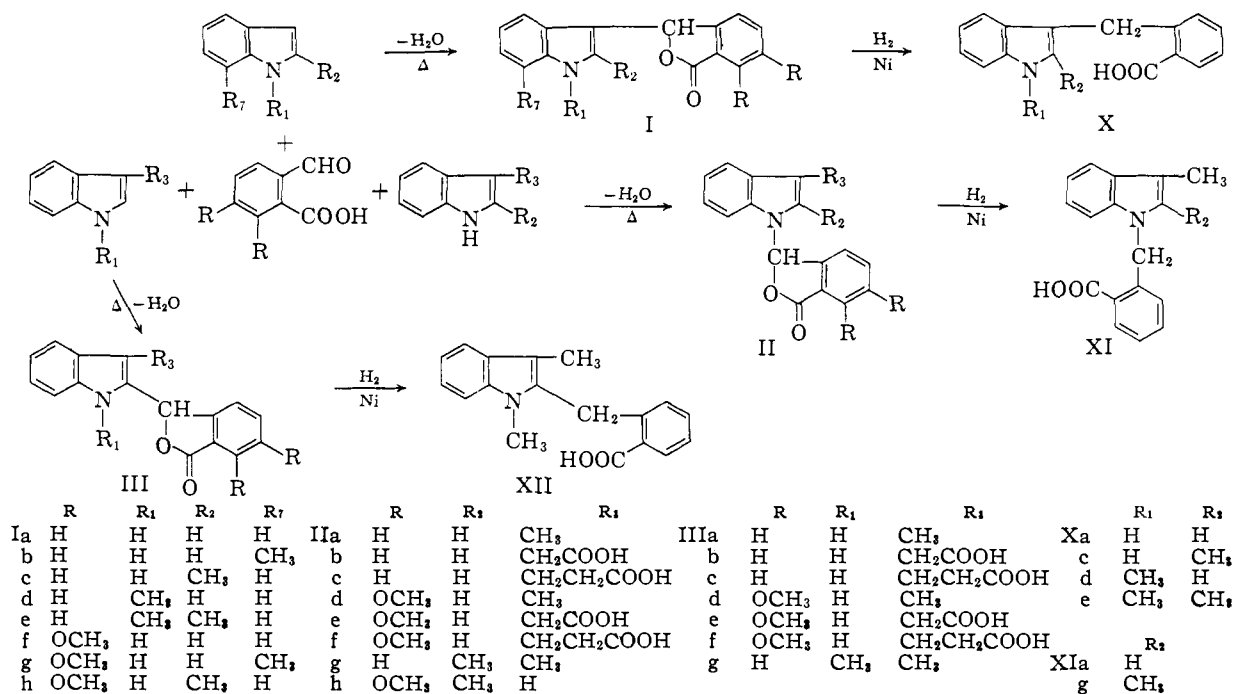# 3-(Indolyl)-Phthalides and (2-Carboxybenzyl)-Indoles

BY WAYLAND E. NOLAND AND JAMES ELVER JOHNSON[1,2]
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New chemical and spectral evidence is presented concerning the structures of phthalides derived from fusion of indoles with phthalaldehydic or opianic acids. The phthalides derived from indole and 7-methylindole are assigned the 3-substituted indole structures Ia, If and Ib, Ig. The phthalides derived from skatole and its derivatives are reassigned the 1-substituted indole structures IIa—IIf. The phthalide derived from 2-methylindole and opianic acid, about which conflicting reports appear in the literature, is assigned the 3-substituted indole structure Ih, analogous to the phthalide (Ic) from 2-methylindole and phthalaldehydic acid. New phthalides are described from the reactions of phthalaldehydic acid with 1-methylindole (Id), 1,2-dimethylindole (Ie), 2,3-dimethylindole (IIg) and 1,3-dimethylindole (IIIg). The structures of all the products studied indicate that the tendency to form phthalides at available positions of the indole nucleus is in the order 3 > 1 > 2. Structures VIII and possibly IX are proposed for by-products from the reactions of phthalaldehydic acid with 1-methylindole and skatole, respectively. The (indolyl)-phthalides have been found to undergo hydrogenolysis under low pressure hydrogenation. This constitutes a general synthetic route to (2-carboxybenzyl)-indoles of all three types: 1-, 2- and 3-substituted indoles.

Fusion of indoles having an open 2- or 3-position with phthalaldehydic acid or opianic acid (5,6-dimethoxyphthalaldehydic acid) at 120–160° has been shown to proceed with steam evolution and the skatole (IIIa,IIId) or its derivatives (IIIb-c,IIIe-f) on the basis that the ester structure could be established through saponification by "warm titration" of an alcoholic solution with 0.1 N sodium hydroxide

	R	R₁	R₂	R₇		R	R₃	R₁		R	R₁	R₁		R₁	R₁
Ia	H	H	H	H	IIa	H	H	CH₃	IIIa	H	H	CH₃	Xa	H	H
b	H	H	H	CH₃	b	H	H	CH₂COOH	b	H	H	CH₂COOH	c	H	CH₃
c	H	H	CH₃	H	c	H	H	CH₂CH₂COOH	c	H	H	CH₂CH₂COOH	d	CH₃	H
d	H	CH₃	H	H	d	OCH₃	H	CH₃	d	OCH₃	H	CH₃	e	CH₃	CH₃
e	H	CH₃	CH₃	H	e	OCH₃	H	CH₂COOH	e	OCH₃	H	CH₂COOH			
f	OCH₃	H	H	H	f	OCH₃	H	CH₂CH₂COOH	f	OCH₃	H	CH₂CH₂COOH			
g	OCH₃	H	H	CH₃	g	H	CH₃	CH₃	g	H	CH₃	CH₃	XIa	H	
h	OCH₃	H	CH₃	H	h	OCH₃	CH₃	H						R₁	
													g	CH₃	

formation in unstated yield of 1:1 condensation products.[3] Phthalide structures were assigned to the products from 2-methylindole (Ic,Ih) and from

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(2) A part of the work described in this paper was carried out by students in the advanced organic laboratory course at the University of Minnesota. In particular, we are indebted to: (a) Francis A. Schurb, (b) William M. Bogart, (c) Robert G. Rainey, (d) Ping-Yueh Peng, (e) Abdel-Moneim M. Makky, (f) Marvin L. Lewbart, (g) Piroska Nemeth, (h) Roxy Ru-Jien Ni, as well as to (i) Allan M. Huffman.[1]

(3) A. Ludwig and S. Tache, Soc. Chim. Romånia Sect. Soc. romåne Stiinte, Bul Chim. purå apl., [2]3A, 3 (1941–1942) [Chem. Zentr., 114, II, 1275 (1943); C. A., 38, 5499 (1944)]. A microfilm of this paper was kindly provided by La Maison de la Chimie, Paris, France. We are grateful to Dr. Gabriel Mureşan of ICECHIM, Chemical Research Institute, Bucharest, Romania, for sending us a complete photoprint of the paper.

solution. The corresponding phthalide structures for the products from indole (Ia,If) and 7-methylindole (Ib,Ig) were rejected because the products could not be saponified by "warm titration" as in the preceding cases. The possibility that the products from indole or 7-methylindole might saponify at a slower rate than those from 2-methylindole or skatole and its derivatives, thus making them unresponsive to the technique of "warm titration," does not seem to have been considered.

We have re-examined the saponification of the products from indole and 2-methylindole, as well as new products from 1-methylindole, 1,2-dimethylindole, 2,3-dimethylindole and 1,3-dimethylindole, with phthalaldehydic acid under the more usual conditions for determination of saponification equivalents: refluxing with an excess of 0.1 N etha-

TABLE I

3-(INDOLYL)-PHTHALIDES

	R₁ R₂ -phthalide	R	Mol. formula Yield, %	M.p., °C. Reported Found	Recrystn. solvent	Sapon. equiv. Calcd. Found	C, %	Calcd. Found H, %	N, %
Ia	H H 3-(3-Indolyl)-	H	C₁₆H₁₁NO₂ 66[b]	176[a] 176	EtOH[a] EtOH	249.26 250	77.09 ...[a]	4.45 ..[a]	5.62 5.69
Ic	H CH₃ 3-(2-Methyl-3-indolyl)-	H	C₁₇H₁₃NO₂ 88[c]	196[a] 197	EtOH[a] EtOH	263.28 272	77.55 ...[a]	4.98 ..[a]	5.32 5.29
Id	CH₃ H 3-(1-Methyl-3-indolyl)-	H	C₁₇H₁₃NO₂ 70[d]	.. 128	... CH₂Cl₂-LP[e]	263.28 268	77.55 77.39	4.98 5.06	5.32 5.35
Ie	CH₃ CH₃ 3-(1,2-Dimethyl-3-indolyl)-	H	C₁₈H₁₅NO₂ 100	.. 204–206	... C₆H₆	277.31 298	77.96 78.01	5.45 5.47	5.05 4.96
Ih	H CH₃ 3-(2-Methyl-3-indolyl)-6,7-dimethoxy-	OCH₃	C₁₉H₁₇NO₄ 100	194[f] 203[a] 203–205	EtOH[f] AcOH[a] AcOH	323.33 ....[a]	70.57 ...[a,f] 70.38	5.30 ..[a,f] 5.34	4.33 .. 4.53
IIa	.. H ... 3-(3-Methyl-1-indolyl)-		C₁₇H₁₃NO₂ 47[g]	140–141[a] 140–141[h] 155–156[h,i]	EtOH[a] CH₂Cl₂-LP[e] EtOH	263.28 263	77.55 ...[a] 77.51	4.98 ..[a] 4.98	5.32 5.58 5.35
IIg	.. CH₃ ... 3-(2,3-Dimethyl-1-indolyl)-		C₁₈H₁₅NO₂ 21[j]	.... 154.5–155.5	... MeOH–H₂O	277.31	77.96 78.21	5.45 5.33	5.05 5.10
IIIg	CH₃ .. ... 3-(1,3-Dimethyl-2-indolyl)-		C₁₈H₁₅NO₂ 90	 177–179	... EtOH	277.31 263	77.96 78.03	5.45 5.54	5.05 5.31

[a] Ref. 3.   [b] Ref. 2d.   [c] Ref. 2e.   [d] Ref. 2a and 2g.   [e] LP = light petroleum (b.p. 60–68°).   [f] Ref. 7.   [g] Ref. 2f.   [h] Dimorphic forms.   [i] Ref. 2h.   [j] Ref. 2b.

nolic alkali, followed by back titration of the excess alkali with 0.1 N ethanolic hydrochloric acid. Under these conditions all of the products yielded saponification equivalents corresponding to the expected 1:1 condensation products (see Table I.) Now that the objection to the phthalide structures has been removed, we feel justified in assigning structures Ia and If to the products from indole with phthalaldehydic acid and opianic acid, respectively, and structures Ib and Ig to the analogous products from 7-methylindole. Similarly, structures Id and Ie are assigned to the new products from 1-methylindole and 1,2-dimethylindole with phthalaldehydic acid. Further confirmation of the phthalide structures is provided by the presence of the typical strong lactone carbonyl band at 1730–1770 cm.⁻¹ in the infrared spectra of all the 1:1 condensation products of indoles with phthalaldehydic acid which we have examined (see Table Ia). The position of these bands is in good agreement with that reported for phthalide[4] at 1770 cm.⁻¹ in carbon tetrachloride solution, or for 3-aminophthalides[5] at 1715–1778 cm.⁻¹.

The infrared spectra of the skatole–phthalaldehydic acid product contain no NH band, thus indicating that condensation has taken place in the 1-

(4) F. Pristera, *Anal. Chem.*, **25**, 855 (1953).

(5) D. D. Wheeler, D. C. Young and D. S. Erley, *J. Org. Chem.*, **22**, 547 (1957).

TABLE Ia

SPECTRAL DATA ON 3-(INDOLYL)-PHTHALIDES

	Ultraviolet[a]				Infrared, frequencies in cm.⁻¹ NH In CHCl₃ In Nujol	C=O In CHCl₃ In Nujol
Ia	217 (4.71)	271 (3.90)	276[b] (3.90)	287 (3.74)	3500 3330	1756 1734
Ic	220 (4.64)	273 (3.93)	279[c] (3.92)	286[c] (3.77)	3460 3360	1750 1731
Id	221 (4.78)	274 (3.93)	280 (3.94)	293 (3.80)	None	1755 1737,[d] 1759
Ie	223 (4.68)	275 (3.97)	281 (3.99)	290 (3.85)	None	1750 1748
Ih	217 (4.74)	277[c] (3.92)	280 (3.93)	288[e] (3.89)	3480 3340	1750 1725
IIa	224 (4.60)	267 (3.86)	278[c] (3.81)	290 (3.54)	None	1770 1760
IIg	226 (4.58)	270 (3.97)	279[c] (3.92)	290[c] (3.62)	None	1763 1740
IIIg	228 (4.71)	..	280 (4.06)	..	None	1760 1755

[a] Wave lengths of maxima in 95% ethanol are given in mμ with intensities in log ε beneath them in parentheses. We are indebted to James A. Elberling for determining several of the ultraviolet and infrared spectra reported here. [b] Also 279[d] (3.89). [c] Inflection. [d] Stronger band. [e] Also maximum at 307 (3.59).

position, rather than in the 2-position of the skatole nucleus (IIIa), as had been assumed previously,[3] and as might have been expected on the basis of the structure of the bisindole from skatole and benzal-

dehyde.[6] Consequently, structures IIa and IId are now assigned to the products from skatole with phthalaldehydic and opianic acids, respectively. By analogy, it appears justified to assign the corresponding structures IIb,IIe and IIc,IIf to the products from 3-indoleacetic and 3-indolepropionic acids with phthalaldehydic and opianic acids, respectively. The validity of this analogy is strengthened by the fact that decarboxylation of the products from 3-indoleacetic acid with phthalaldehydic (IIb) or opianic (IIe) acids has been shown previously[3] to yield the corresponding skatole products (IIa and IId). Further confirmation is provided by the fact that 2,3-dimethylindole, which would be expected to condense only in the 1-position of the indole nucleus, yields a phthalide condensation product (IIg) with phthalaldehydic acid. The infrared spectra of this product contain no NH band. The formation of 1:1 condensation products from isatin with phthalaldehydic or opianic acids has been mentioned previously.[3] Here again, condensation is most likely to have occurred on nitrogen at the 1-position. Condensation can be forced at the 2-position, however, when both the 1- and 3-positions are blocked, as in 1,3-dimethylindole, which forms the corresponding (2-indolyl)-phthalide (IIIg) smoothly under the fusion conditions.
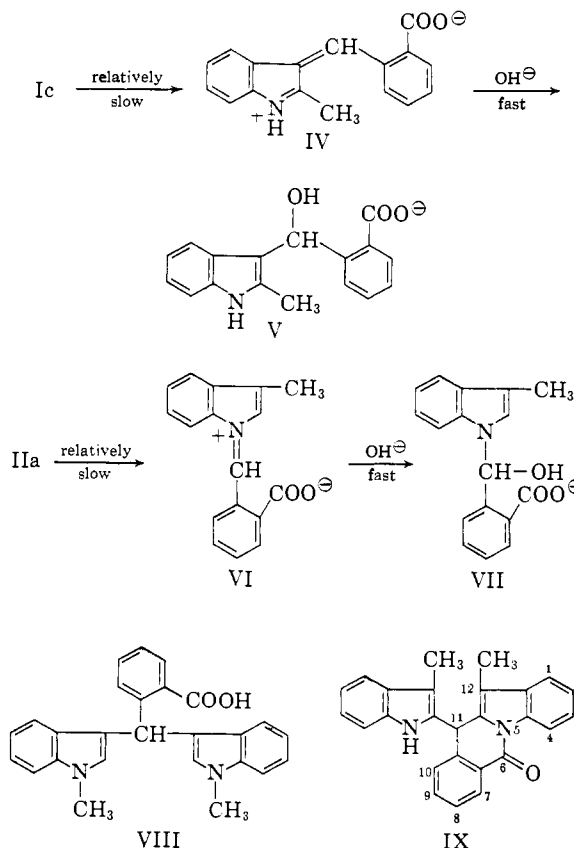
The reaction of 2-methylindole with opianic acid in alcohol solution at room temperature is reported to give a 1:1 condensation product, m.p. 194°, for which the (1-indolyl)-phthalide structure IIh was proposed.[7] Fusion of 2-methylindole with opianic acid, or boiling the reactants in acetic acid, is also reported to give a 1:1 condensation product, m.p. 203°.[3] This 203° compound underwent "warm titration" in the manner expected of the (3-indolyl)-phthalide Ih, and was said to be different from the 194° compound,[3] apparently because of the difference in melting points. We have repeated the preparations, both in ethanol solution (97% yield) and by the fusion procedure (100% yield), and have shown by mixed melting point and infrared comparisons in Nujol that the products, m.p. 203–205°, are identical. The presence of NH absorption in the infrared spectra (see Table Ia) shows that condensation has not occurred at the 1-position of the indole nucleus; hence, structure Ih must be correct.

The important properties of all the 3-(indolyl)-phthalides studied in this work are described in Tables I and Ia. They are all colorless compounds. The structures of the products indicate that the tendency to form phthalides at available positions of the indole nucleus is in the order 3 > 1 > 2. The reaction of 2-phenylindole with phthalaldehydic acid under fusion conditions gave no crystalline product, only a dark brown polymer.

The relatively slow rate of saponification of the phthalides from indole and 1-methylindole relative to the phthalide derived from 2-methylindole, which, like the skatole derivative, can be saponified even under conditions of "warm titration," is contrary to expectations if steric hindrance on the indole nucleus to hydrolytic acyl–oxygen fission were

(6) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(7) C. Liebermann, *Ber.*, **29**, 2030 (1896).

the governing factor. Instead, the relative rates of saponification of the 3-(3-indolyl)-phthalides seem to be qualitatively in accord with the increasing electron-releasing power at the 3-position of the indole nuclei involved.[8] The phthalide derived from skatole is a carbinolamine derivative, and, thus, should be readily subject to alkyl-oxygen fission. These facts provide strong evidence that, at least in the two cases which can be saponified by "warm titration," solvolysis by alkyl–oxygen fission (Ic → IV → V and IIa → VI → VII), rather than hydrolysis by acyl–oxygen fission, is the rate-determining step. It seems likely that phthalide formation involves essentially the reverse of this process, so that all of the oxygen atoms incorporated in the phthalide would be derived from the carboxyl group, and none from the aldehyde carbonyl (or lactol hydroxyl) of phthalaldehydic acid.

From the reaction of 1-methylindole with phthalaldehydic acid, in addition to 3-(1-methyl-3-indolyl)-phthalide (Id), there was isolated on one occasion a small amount of an acidic 2:1 condensation product, m.p. 217–219°. The properties of this acidic product are consistent with the structure 1,1'-dimethyl-3,3'-(2-carboxybenzylidene)-bisindole (VIII). From the reaction of skatole with phthalaldehydic acid, besides 3-(3-methyl-1-indolyl)-phthalide (IIa), which was obtained in dimorphic forms, m.p. 140–141° and 155–156°, there was usually also isolated a 2:1 condensation product, m.p. 243–244°, in yields as high as 9%. This

(8) W. E. Noland and R. F. Lange, THIS JOURNAL, **81**, 1203 (1959).

TABLE II
(2-CARBOXYBENZYL)-INDOLES
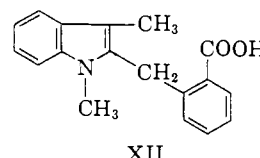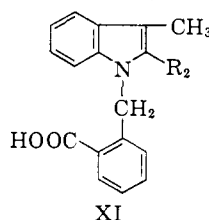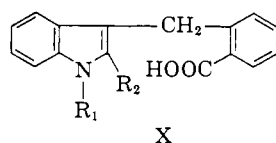
	R₁	Rₛ -indole	Mol. formula Yield, %	M.p., °C. Recrystn. solvent	Neut. equiv. Calcd. Found	C, %	Calcd. Found H, %	N, %
Xa	H	H	C₁₆H₁₃NO₂	210–212ᵃ	251.27	76.47	5.22	5.57
		3-(2-Carboxybenzyl)-	91	EtOH–H₂O	241	76.48	5.24	5.48
Xc	H	CH₃	C₁₇H₁₅NO₂	174	265.30	76.96	5.70	5.28
		2-Methyl-3-(2-carboxybenzyl)-	84ᵇ	C₆H₆	276ᶜ	77.54ᶜ	5.83ᶜ	5.42ᶜ
Xd	CH₃	H	C₁₇H₁₅NO₂	189–190	265.30	76.96	5.70	5.28
		1-Methyl-3-(2-carboxybenzyl)-	56	C₆H₆	257, 253	77.18	5.71	5.23
Xe	CH₃	CH₃	C₁₈H₁₇NO₂	223–226	279.32	77.39	6.13	5.01
		1,2-Dimethyl-3-(2-carboxybenzyl)-	78	CH₃CN	275ᶜ	77.80ᶜ	6.14ᶜ	5.58ᶜ
XIa	..	H	C₁₇H₁₅NO₂	168–169	265.30	76.96	5.70	5.28
		3-Methyl-1-(2-carboxybenzyl)-	84ᵈ	EtOH–H₂O	273	76.75	5.49	5.18
XIg	..	CH₃	C₁₈H₁₇NO₂	230–232	279.32	77.39	6.13	5.01
		2,3-Dimethyl-1-(2-carboxybenzyl)-	ᵉ	MeOH–H₂O	264	77.43	6.33	5.13
XII	..	..	C₁₈H₁₇NO₂	237–245	279.32	77.39	6.13	5.01
		1,3-Dimethyl-2-(carboxybenzyl)-	90	AcOH–H₂O	270	77.19	6.16	5.20

ᵃ Ref. 2d. ᵇ Ref. 2e. ᶜ The 2-methylindole acids were notably electrostatic; accurate weighing of the analytical samples was difficult. ᵈ Ref. 2c. ᵉ Ref. 2b; yield not determined. The compound turns pink rapidly on exposure to air.

yellow crystalline compound has a complex ultraviolet spectrum, with principal bands at 227, 271 and 342 mμ, the latter being indicative of considerably more conjugation than is present in an isolated indole nucleus. The infrared spectrum in Nujol contains both an NH band (at 3320 cm.⁻¹) and a conjugated carbonyl band (at 1667 cm.⁻¹), which could be attributed either to an amide or to a diaryl ketone structure. The ketone possibility appears to be ruled out because the compound did not form an oxime or 2,4-dinitrophenylhydrazone. During attempted oximation in pyridine–ethanol solution this yellow compound yielded a white crystalline transformation product which is either a dimorphic or isomeric form. The ultraviolet spectrum of this new form is essentially identical, but in the Nujol infrared spectrum the single carbonyl band at 1667 cm.⁻¹ is replaced by two bands of slightly lower intensity at 1652 and 1635 cm.⁻¹; the lower frequency part of the infrared spectrum is also quite different. The fact that skatole can undergo electrophilic substitution at the 2-position as well as at the 1-position, as illustrated by the bisindole from skatole and benzaldehyde,⁶ leads to the proposal that our yellow condensation product has the amide structure, 6,11-dihydro-12-methyl-11-(3-methyl-2-indolyl)-dibenzo[b,f]-6-pyrrocolone (IX), or a tautomeric variation of this structure. An amide structure very similar to IX, specifically 1,2,3,4-tetrahydro-3,5-dimethyl-4-(3-methyl-2-indolyl)-benzo[b]-1-pyrrocolone, has been proposed for the colorless neutral 2:1 product, m.p. 220°, from the acid-catalyzed condensation of skatole with levulinic acid.⁹ The ultraviolet spectrum of this product contains only indole bands at 230 mμ (log ε

(9) R. Robinson and J. E. Saxton, J. Chem. Soc., 3136 (1950).

4.16) and 281 (3.53), without the long wave length maximum, but here, in contrast to the present case, the carbonyl is not conjugated with benzenoid unsaturation.

3-(Indolyl)-phthalides have been found to undergo hydrogenolysis of the benzyl C—O bond over Raney nickel catalyst under conditions of low pressure hydrogenation. This constitutes a general synthetic route to (2-carboxybenzyl)-indoles of all three types: 1-, 2- and 3-substituted indoles. The important properties of the seven new acids are described in Table II and IIa. The hydrogenolysis

TABLE IIa
SPECTRAL DATA ON (2-CARBOXYBENZYL)-INDOLES

		Ultravioletᵃ		Infrared, frequencies in cm.⁻¹	
				NH In CHCl₃ In Nujol	C=O In CHCl₃ In Nujol
Xa	223	281ᵇ	291	3460	1714
	(4.58)	(3.82)	(3.74)	3480	1684
Xc	226	282	289ᶜ	3500	1695
	(4.61)	(3.94)	(3.87)	3410	1693ᵈ
Xd	227	280ᶜ	289	None	1693
	(4.58)	(3.76)	(3.78)		1688
Xe	229	280ᶜ	286ᵉ	None	1692
	(4.58)	(3.89)	(3.92)		1679
XIa	225		285	None	1690
	(4.59)		(3.85)		1684
XIg	228	280ᶜ	286ᶠ	None	1695
	(4.61)	(3.86)	(3.89)		1690
XII	232	281ᶜ	287ᵍ	None	1691
	(4.66)	(3.90)	(3.94)		1688

ᵃ Wave lengths of maxima in 95% ethanol are given in mμ with intensities in log ε beneath them in parentheses. ᵇ Also 275ᶜ (3.80). ᶜ Inflection. ᵈ In halocarbon oil 1697 cm.⁻¹. ᵉ Also 293ᵉ (3.88). ᶠ 293ᶜ (3.85). ᵍ Also 293ᶜ (3.90).

of 3-(3-indolyl)-phthalides is similar to the reductive alkylation of indole with 2- and 4-pyridinecarboxaldehydes, which yields 2- and 4-skatylpiperidines.[10]

Experimental

Melting points were determined on a calibrated Fisher-Johns hot-stage.

3-(Indolyl)-phthalides (I—III).—Equimolar portions of the indole and phthalaldehydic acid were fused in a Woods' metal- or oil-bath and then heated slowly from 120–160° until steam evolution was complete. In several preparations (Ic, IIg, IIIg) the temperature was raised briefly to 190–200° to ensure completion of the reaction, but it is doubtful if the higher temperatures were necessary. The preparation of Ie was carried out at 200–220°, with a brief, final bath temperature increase to 270°. The preparation of the 3-(indolyl)-phthalides is illustrated by the procedure for 3-(1-methyl-3-indolyl)-phthalide.

3-(1-Methyl-3-indolyl)-phthalide (Id).[2a,2g]—A mixture of 1-methylindole (6.55 g., 0.0499 mole) and phthalaldehydic acid (7.50 g., 0.0500 mole) was placed in a Woods' metal-bath at 75–80°. Steam evolution began immediately, and the temperature was increased gradually and held at 120° for 20 minutes until steam evolution was complete. To ensure completion of the reaction the temperature was increased to 150° during 0.5 hour and held there for an additional 0.5 hour. The reddish glass which resulted on cooling was dissolved in ethanol and set aside overnight. The resulting oil was warmed to redissolve it and then cooled, with scratching, until it crystallized. Five recrystallizations from methylene chloride–light petroleum and one from benzene–light petroleum (b.p. 60–68°) yielded several crops of whitish crystals (8.78 g., 0.0334 mole, 67%), m.p. 126–128°. The analytical sample, m.p. 128°, was prepared by two recrystallizations from methylene chloride–light petroleum (b.p. 60–68°). Analytical and spectral data are given in Tables I and Ia.

From the mother liquors of a similar reaction a small amount of another white crystalline product was obtained.[2a] After recrystallization from methylene chloride–light petroleum (b.p. 60–68°) and from ethanol–water, it had m.p. 217–219°. It is assigned the structure 1,1'-dimethyl-3,3'-(2-carboxybenzylidene)-bisindole (VIII), λ_{max} in 95% EtOH: 226 mμ (log ϵ 4.89), 290 (4.09); ν_{NH} none, ν_{OH} 2630, $\nu_{C=O}$ 1680 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{26}H_{22}N_2O_2$ (394.45): C, 79.16; H, 5.62; N, 7.10. Found: neut. equiv., 392; C, 78.33; H, 5.66; N, 7.01.

Determination of Saponification Equivalents.—A measured amount of ethanolic potassium hydroxide (0.1 N, 5 cc.) was pipetted onto a weighed sample of the 3-(indolyl)-phthalide (0.05 g.). The resulting solution was warmed near reflux temperature until the color began to darken. The warming times, in minutes, for the 3-(indolyl)-phthalides were: Ia, 45; Ic, 15; Id, 80. With Ie and IIIg there was no evidence of color change; warming was discontinued arbitrarily at the end of 90 and 55 minutes, respectively.

(10) A. P. Gray, *J. Org. Chem.*, **23**, 1453 (1958).

The excess potassium hydroxide was then back-titrated from a microburet with ethanolic hydrochloric acid (0.1 N), using thymol blue (15 drops) as an indicator (pH 8.0–9.6, yellow to blue).

6,11 - Dihydro - 12 - methyl - 11 - (3 - methyl - 2 - indolyl)-dibenzo [b,f]-6-pyrrocolone (IXa).[2i]—The reaction of skatole and phthalaldehydic acid usually gave, besides 3-(3-methyl-1-indolyl)-phthalide (IIa), an ethanol-insoluble by-product, in yields as high as 9%. After several recrystallizations from benzene the by-product was obtained as small, pale yellow needles, m.p. 243–244° on a hot-stage and 265–267°[2i] in a sealed capillary; λ_{max} in 95% EtOH: 227 mμ (log ϵ 4.82), 249 infl. (4.38), 271 (4.37), 302 infl. (4.01), 324 infl. (3.95), 342 (3.95), 359 infl. (3.82); ν_{NH} 3320, $\nu_{C=O}$ 1667 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{26}H_{20}N_2O$ (376.44): C, 82.95; H, 5.36; N, 7.44. Found[2i]: mol. wt. (Rast), 408; C, 82.96; H, 5.43; N, 7.53.

The compound did not consume alkali under the conditions employed by us for determination of the saponification equivalents of the 3-(3-indolyl)-phthalides. It did not form a 2,4-dinitrophenylhydrazone.[2i] It is transformed by heating above its melting point in a sealed capillary into a white solid, m.p. 301–303°.[2i]

Transformation Product.—A mixture of the yellow needles (0.17 g.), hydroxylamine hydrochloride (1.81 g.), pyridine (5 cc.) and absolute ethanol (5 cc.) was warmed until the solid dissolved and was then refluxed for 2 hours. The solvents were evaporated in a stream of air and the residue was extracted with water (15 cc.). The white crystalline residue (0.20 g., softens at 260°, turns black on the hot-stage at 265–272°) was recrystallized twice from pyridine–absolute ethanol, yielding a white powder having the same m.p. behavior; λ_{max} in 95% EtOH: 227 mμ (log ϵ 4.80), 248 infl. (4.38), 272 (4.34), 306 (3.99), 328 (3.94), 344 (3.94), 358 infl. (3.83); ν_{NH} 3260, $\nu_{C=O}$? 1652, 1635 cm.$^{-1}$ and other double bond bands at lower frequencies. The infrared spectrum is quite different from that of the starting material.

Anal. Calcd. for $C_{26}H_{20}N_2O$ (376.44): C, 82.95; H, 5.36; N, 7.44. Found: C, 82.53; H, 5.33; N, 7.87.

The possibility has not been ruled out that this form may be the same as the thermal transformation product mentioned in the preceding section.

(2-Carboxybenzyl)-indoles (X—XII).—The 3-(indolyl)-phthalides in methanol (Ic, IIg), ethanol (IIa), 2-propanol (Ia) or benzene (Id, Ie, IIIg) solution were hydrogenated at 2 atm. over Raney nickel catalyst, with shaking, in a Parr low-pressure hydrogenation apparatus. The procedure is illustrated by the preparation of 1-methyl-3-(2-carboxybenzyl)-indole.

1-Methyl-3-(2-carboxybenzyl)-indole (Xd).—3-(1-Methyl-3-indolyl)-phthalide (3.95 g., 0.0150 mole) in benzene (150 cc.) was hydrogenated at 2 atm. over Raney nickel catalyst (0.5 teaspoonful), with shaking, for 4 days. Filtration of the catalyst and concentration and cooling of the filtrate produced crystals (2.23 g., 0.00842 mole, 56%), m.p. 185–188°. Four recrystallizations from benzene yielded the analytical sample as colorless plates, m.p. 189–190°. Analytical and spectral data are given in Tables II and IIa.