soluble in boiling ethyl alcohol, and gives a yellow color with a green fluorescence when treated with sulfuric acid.

(b). Vb and Vd were prepared from the condensation of *p*-cresol and *o*-cresol with *o*-chlorobenzoic acid, respectively, as described above without the isolation of the intermediate substituted phenoxy-*o*-benzoic acid, and proved to be identical with samples, prepared after Ullmann and Zlokasoff[21]; the yield was 69% and 73%, respectively.

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[21] F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2111 (1905).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Mixed Indole Dimers, Trimers, and Their Acyl Derivatives[1]

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The synthesis of the first mixed indole and indole:pyrrole dimers is described. They are derived from an A component (an indole having an open 2-position) and a B component (an indole or pyrrole more nucleophilic than the A component). Included are the dimers from indole with 2-methylindole (Ib), 1,2-dimethylindole (Ic), 2-phenylindole (Id), or 2,5-dimethylpyrrole (XIIa), and the dimer from skatole with 2-methylindole (IIIa). Structures are assigned on the basis of spectral data and by analogy with the proven structure of diindole (Ia). The competitive dimerization reaction of indole and 1-methylindole permitted isolation, after acylation with maleic anhydride, of only maleyldiindole (XVa). The competitive reaction of indole and skatole proceeded in rather clean-cut stepwise fashion with formation first of diindole hydrochloride and then of diskatole hydrochloride. A new homodimer, 1,3-dimethylindole dimer (VIb), has been prepared. Evidence is presented concerning the structure of diskatole (VIa). As byproducts in the preparation of the mixed dimers, the first mixed trimers have been prepared. Included are diindole:2-methylindole trimer (IIc); diindole:1,2-dimethylindole trimer (IId); and indole:di-2,5-dimethylpyrrole trimer (XIII). Diindole: 1,2-dimethylindole trimer (IId) is different from the dimethyltriindole obtained by methylation of triindole (IIa). Evidence is presented that, contrary to a previous report, the latter dimethyltriindole is in reality an *N,N*-dimethylaniline derivative (IIb) resulting from dimethylation of the primary amino group of triindole. Acyl derivatives of the mixed dimers and trimers have been prepared from maleic, succinic, itaconic, and citraconic anhydrides. Whereas acylation of diindole, indole:2-phenylindole dimer, and indole:2,5-dimethylpyrrole dimer with maleic anhydride gave only the maleyl derivatives, the corresponding reactions with indole:2-methylindole dimer and indole:1,2-dimethylindole dimer gave not only the maleyl derivatives (XVb–c) but also lesser amounts of the fumaryl derivatives (XVI b–c). In the two cases where both maleyl and fumaryl derivatives were obtained, hydrogenation of these stereoisomers gave the succinyl derivatives (XVIIb–c), which were also prepared independently by acylation of the dimers with succinic anhydride. Skatole:2-methylindole dimer with maleic anhydride gave the maleyl derivative (IIIb), but in more polar solvents an isomer was obtained to which the spiro indolenine structure XXI is assigned.

Mixed indole dimers and trimers. Although homodimers of indole,[4–7] skatole,[8,9] 1-methylindole,[10] and 7-methylindole[10] are known, and 2-methylindole dimer has been prepared by a method other than dimerization,[11] there appear to be no published reports of the synthesis of mixed indole dimers or their derivatives.[12] The mechanism proposed[6] for the formation of diindole (Ia) offered hope for the synthesis of mixed indole dimers. Requirements for indole dimerization appear to include a protonated indole with an open 2-position (which we shall designate as the A component) and an indole with a nucleophilic position, usually an open 3-position (B component). Consequently, although its dimer has been prepared by another synthetic route,[11] 2-methylindole does not undergo

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[1] Presented in part as Paper 26 before the Organic Division at the 134th National Meeting of the Am. Chem. Soc., Chicago, Ill., Sept. 8, 1958, Abstracts, p. 14P.

[2] We are indebted to the Graduate School of the University of Minnesota for a 1957 Faculty Summer Research Appointment.

[3] From the Ph.D. thesis of Charles F. Hammer, May 1959. Research Corporation Research Assistant 1956–1959, Upjohn Company Summer Fellow 1958. We are indebted to the Research Corporation for a Frederick Gardner Cottrell Grant in support of this research, and to the Upjohn Company for a summer fellowship.

[4] O. Schmitz-Dumont and B. Nicolojannis, *Ber.*, **63**, 323 (1930).

[5] O. Schmitz-Dumont, K. Hamann, and K. H. Geller, *Ann.*, **504**, 1 (1933).

[6] G. F. Smith, *Chem. and Ind.* (London), 1451 (1954).

[7] H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957).

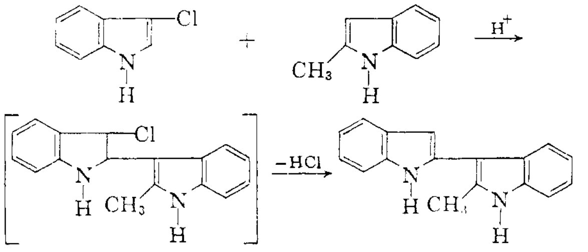
[8] B. Oddo and G. B. Crippa, *Gazz. chim. ital.*, **54**, 339 (1924).

[9] O. Schmitz-Dumont, *Ann.*, **514**, 267 (1934).

[10] O. Schmitz-Dumont and K. H. Geller, *Ber.*, **66**, 766 (1933).

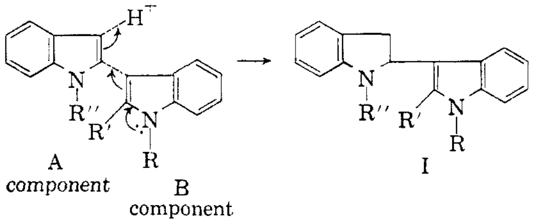
[11] B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

[12] Dr. G. F. Smith of the University of Manchester, England, has kindly informed us in a private communication (Nov. 22, 1957) that he has prepared a mixed diindolyl (corresponding to indole:2-methylindole dimer), the formation of which almost certainly involves an unstable mixed indole dimer as an intermediate:

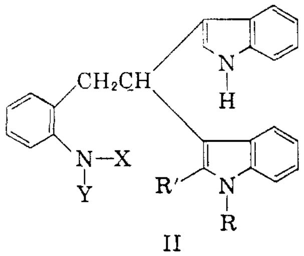


acid-catalyzed dimerization[9,13a] (an observation we have confirmed under our conditions), presumably because of the blocking methyl group in the 2-position of the A component. 2-Methylindole, however, is more nucleophilic at the 3-position than indole for the same reason that the *o*-positions of toluene are more reactive than any position of benzene. It was hoped, therefore, that 2-methylindole would be sufficiently better as a B component than indole so that isolation of a mixed dimer would be possible.

When dry hydrogen chloride was passed slowly into an equimolar solution of indole and 2-methylindole in dry ether, the mixed dimer hydrochloride precipitated in quantitative yield. The free indole: 2-methylindole dimer (Ib), an oil, was characterized by acylation, which yielded crystalline amide derivatives in up to 57% yield. On some occasions, usually when hydrogen chloride was passed *rapidly* into an ether solution of the reactants, or else when moisture was present (possibly causing some of the dimer hydrochloride to dissolve and permit further reaction) during the passing in of hydrogen chloride, there was also isolated, in up to 15% yield as the succinyl derivative, and 62% yield as the citraconyl derivative, a mixed trimer, diindole:2-methylindole trimer (IIc). The structure of this mixed trimer is assigned from analogy with the structure of triindole (IIa)[6,13b] and on the basis of the elemental analyses of the succinyl and citraconyl derivatives and the neutralization equivalent of the succinyl derivative.



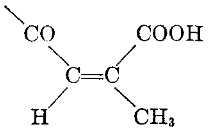
I



II

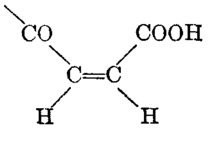
Ia. R = R′ = R″ = H
Ib. R = R″ = H, R′ = CH$_3$
Ic. R = R′ = CH$_3$, R″ = H
Id. R = R″ = H, R′ = C$_6$H$_5$
Ie. R = CH$_3$, R′ = R″ = H
If. R = R′ = H, R″ = CH$_3$
Ig. R = R″ = CH$_3$, R′ = H
IIa. R = R′ = X = Y = H
IIb. R = R′ = H, X = Y = CH$_3$
IIc. R = X = Y = H, R′ = CH$_3$
IId. R = R′ = CH$_3$, X = Y = H
IIe. R = X = H, R′ = CH$_3$
Y = COCH$_2$CH$_2$COOH
IIf. R = X = H, R′ = CH$_3$,

Y =



IIg. R = R′ = CH$_3$, X = H

Y =



Similarly prepared were indole:1,2-dimethylindole dimer (Ic), m.p. 134–135°, also obtained in good yield, and the corresponding mixed trimer, diindole:1,2-dimethylindole trimer (IId), in 11% yield as the maleyl derivative, and in up to 14% yield as the free base along with 26% of unchanged 1,2-dimethylindole. The trimer has a melting point of 165–166°. A dimethyltriindole, m.p. 165–166°, from reaction of triindole with methyl iodide in the presence of potassium carbonate, has been described previously.[14] We have repeated the preparation of this dimethyltriindole. It depresses the melting points of diindole:1,2-dimethylindole trimer (IId), mixed m.p. 142–145°, and of trindole (m.p. 170–171°) mixed m.p. 146–149°.

On the basis of the incorrect assumption that no more than one methyl group would become attached to any single nitrogen atom of triindole, and the fact that reaction with cyanogen bromide replaced only one methyl group of the dimethyl derivative, it was claimed[14] that dimethyltriindole contains one C-methyl as well as one *N*-methyl group. The discovery that triindole contains a primary amino group,[6] however, permits the likely assumption that during methylation both methyl groups have become attached to the primary amino nitrogen, the most nucleophilic site in the triindole molecule. All of the reported[14] reactions of dimethyltriindole are consistent with this hypothesis.

We have examined the visible absorption maxima of solutions resulting from reaction of *p*-dimethylaminobenzaldehyde (Ehrlich reagent) with aniline derivatives in 95% ethanol containing perchloric acid. The Ehrlich reagent has its longest wave-length maximum in the ultraviolet region, at 340 mμ. With aniline there results an intense Schiff base maximum at 435 mμ. With *N*-methylaniline there is a less intense maximum at 406 mμ, and with *N*,*N*-dimethylaniline, which is incapable of forming a Schiff base-type product, there is no absorption maximum in the visible region.

Triindole (IIa) gives an intense Schiff base maximun at 421 mμ (the Schiff base maximum for the

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[13] (a) B. Oddo, *Gazz. chim. ital.*, **43**, I, 385 (1913). (b) The structures of triindole (IIa) and of indole: di-2,5-dimethylpyrrole trimer (XIII) have recently been proved by an independent synthesis: W. E. Noland and W. C. Kuryla, *J. Org. Chem.*, **25**, 486 (1960).

[14] O. Schmitz-Dumont, J. ter Horst, and H. Müller, *Ann.*, **538**, 261 (1939).

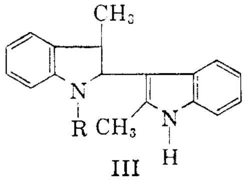
simple benzylidene derivative of triindole is at 324 mμ[6]), and less intense Ehrlich dye[15] absorption at 540 (inflection) and 566 mμ (maximum), attributed to condensation at the open 2-positions of the intact indole nuclei of triindole. Similarly, diindole:-1,2-dimethylindole trimer (IId) gives an intense Schiff base maximum at 417 mμ and less intense Ehrlich dye absorption at 545 mμ. Dimethyltriindole, on the other hand, gives no Schiff base maximum but only Ehrlich dye absorption at the corresponding positions (540, inflection, and 564 mμ, maximum). We conclude, therefore, that dimethyltriindole is an *N*,*N*-dimethylaniline derivative and we assign to it structure IIb.

Indole and 2-phenylindole also give a mixed dimer (Id), which was isolated in 23% yield as the maleyl derivative. There was no evidence for a mixed trimer analogous to those from the reactions of indole with 2-methylindole or 1,2-dimethylindole.

Our results suggest the generalization that indole will form mixed dimers with 2-substituted indoles more nucleophilic than indole itself. Presumably, however, at some point the steric hindrance of increasingly large substituents in the 2-position will so inhibit the formation of mixed dimers that diindole, which is also formed rapidly, will become the favored product. A comparable situation exists between indole and 1-methylindole, which is believed to be less nucleophilic than indole. In a competitive reaction between equimolar amounts of indole and 1-methylindole, a hydrochloride precipitated in a quantity which accounted for 84% of the mixed indoles used (calculated as the mixed dimer hydrochloride). From this hydrochloride, only diindole was isolated, as the maleyl derivative, in 52% yield of the indole used. The failure to isolate any other dimer as the maleyl derivative shows the absence of indole:1-methylindole dimer (Ie), which would have an acylable basic N—H group, but does not exclude the possible presence of 1-methylindole:indole dimer (If) or of 1-methylindole dimer,[10] to which the structure Ig is assigned by analogy with the structure of diindole.

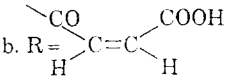
A similar situation exists between indole and skatole. The competitive reaction of equimolar amounts of indole and skatole proceeded in rather clean-cut stepwise fashion. After dry hydrogen chloride gas had been passed into the ether solution for seven minutes, a quantitative precipitate of diindole hydrochloride was filtered off. Passing in hydrogen chloride was resumed and after thirty-eight more minutes an 85% yield of diskatole hydrochloride was filtered off. This stepwise formation of the homodimers shows that indole is more reactive than skatole, both as an A component and as a B component.

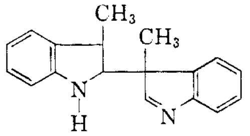
As skatole has an open 2-position, it should be capable of forming a mixed dimer with 2-methylindole. Furthermore, as 2-methylindole is much more nucleophilic (thus making it a better B component) than skatole, the mixed dimer might form in preference to diskatole. In accordance with this prediction skatole:2-methylindole dimer (IIIa) was obtained, in up to 37% yield as the maleyl derivative, but diskatole was also obtained, in up to 10% yield as the maleyl derivative, along with unchanged 2-methylindole, which was isolated in up to 30% yield in the form of its reaction products with maleic anhydride.[16] These results show that the rates of reaction of skatole with 2-methylindole and with itself are of comparable magnitude.



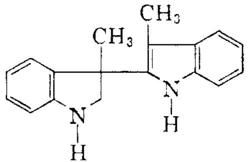
III

IIIa. R = H

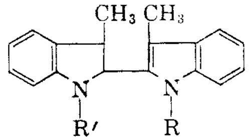
IIIb. R =

$$R = \overset{\diagdown}{}CO\text{-}CH{=}CH\text{-}COOH$$



IV

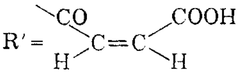


V

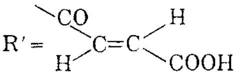


VI

VIa. R = R′ = H
VIb. R = R′ = CH₃
VIc. R = H,


$$R' = CO\text{-}CH{=}CH\text{-}COOH$$

VId. R = H,


$$R' = CO\text{-}CH{=}CH\text{-}COOH$$

A proof of structure for diskatole has not yet been published.[17] If the mechanism of skatole dimerization parallels that of indole,[6] then diskatole would have the dibasic indolenine structure IV, no longer containing an indole chromophore. The ultraviolet spectra of diskatole and several of its derivatives (Table I), however, contain the indole chromophore. Furthermore, diskatole,[18,19] like diindole,[4,13,20–22] forms a monohydrochloride. The infrared spectrum (in Nujol) of maleyldiskatole[16] (VIc) contains an NH band at 3320 cm^{-1}. Consequently, the indolenine structure IV is not valid

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[15] A. Treibs and E. Herrman, *Z. physiol. Chem., Hoppe-Seyler's*, **299**, 168 (1955).

[16] O. Diels, K. Alder, and W. Lübbert, *Ann.*, **490**, 277 (1931).

[17] Structure VIa has been proved for diskatole by degradation, G. F. Smith and A. E. Walters, unpublished work, University of Manchester, England (private communication, Oct. 16, 1958).

[18] M. Wenzing, *Ann.*, **239**, 239 (1887).

[19] R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 976 (1952).

[20] K. Keller, *Ber.*, **46**, 726 (1913).

[21] O. Schmitz-Dumont, B. Nicolojannis, E. Schnorrenberg, and H. H. Saenger, *J. prakt. Chem.*, **131**, 146 (1931).

[22] O. Schmitz-Dumont and H. H. Saenger, *J. prakt. Chem.*, **132**, 39 (1931).

TABLE I

Spectral Data on Indole Dimers and Trimers, and Related Compounds

	Ultraviolet			Infrared	
Compound	Wave lengths of maxima in mμ with intensities (log ε). Solvent: 95% ethanol			Frequencies in cm.$^{-1}$ NH	Medium
Indoline[a]	[b] 240 (3.83)	—	292 (3.35)	3400	liquid
2-Methylindoline[a]	[b] 241 (3.84)	—	293 (3.34)	3390	liquid
Ia[c]	221 (4.61)	283 (3.92)	290 (3.91)	3410	KBr
Ia·HCl[d]	221 (4.56)	283 (3.94)	290 (3.94)	3330,[e] 2590, 2490, 3460[e], 2600, 2520	KBr Nujol
Di-2-methylindole[f]	226 (4.54)	284 (3.92)	291 (3.92)	3420,[e] 3330	$CHCl_3$
Ib·HCl[g]	225 (4.55)	281 (3.99)	288 (3.95)	3340, 3220,[e] 2770, 2540, 2480	Nujol
Ic	228 (4.57)	288 (3.97)	294 (3.98)	3420 3400	$CHCl_3$ Nujol
Ic·HCl	219 (4.78)	281 (4.09)	287 (4.04)	3380, 2490[e]	Nujol
VIa	228 (4.60)	285 (4.09)	293 (4.06)	3470,[e] 3400 3420,[e] 3380 3450, 3400[e]	$CHCl_3$ KBr Nujol
VIa·HCl[h]	228 (4.59)	285 (4.08)	293 (4.06)	3320 3270	KBr Nujol
Bisdiskatole oxalate	228 (4.60)[i]	285 (4.08)[i]	293 (4.06)[i]		
VIb	229 (4.63)	249[j] (4.16)	289 (4.07)	none	Nujol
VIb·HCl	229 (4.65)	249[j] (4.16)	289 (4.07)	2280	Nujol
XIIa·HCl	[b]	280 (3.82)	288 (3.81)	3250,[e] 3180, 2670, 2580, 2500	Nujol
IIb	225 (4.85)	283 (4.10)	291 (4.05)	3540,[e] 3480 3450	$CHCl_3$ Nujol
IId	225 (4.82)	284 (4.14)	290 (4.12)	3420, 3350, 3260[e]	Nujol
XIII	[b]	283 (3.36)	—	3370,[e] 3300, 3220	Nujol

[a] Prepared as described in ref. 32. [b] Rising end absorption. [c] Ref. 33. [d] Obtained in 82% yield, m.p. 172–173°, by the method of ref. 13. Reported m.p. 180°,[13] >150°.[4] [e] Strongest NH band. [f] Sample kindly provided by Dr. Bernhard Witkop. See ref. 11 for preparation and source of infrared data. [g] Prepared and determined by George J. Meisters. [h] The m.p. 183–184° of our sample[8] was higher than that reported: 167–168°,[18] 173°,[8] 180°.[19] [i] Log ε/2. [j] Inflection.

for diskatole. If, in the formation of diskatole, protonation of skatole occurs at the 2-position, which appears to be the most nucleophilic center,[23] followed by attack at the 3-position by the B component from its 2-position, then diskatole would have structure V, requiring the formation of a quaternary carbon atom. If, however, skatole is protonated at the 3-position, followed by attack at the 2-position by the B component from its 2-position, then the least possible sterically hindered structure (VIa) for diskatole would result. Consistent with the formulation of diskatole as V or VIa is the fact that in the Ehrlich test diskatole gives Schiff base-type absorption at 442 (inflection) and 457 mμ (maximum) but no Ehrlich dye maximum, indicating the absence of an open 2- or 3-position in an indole nucleus. Diindole, in contrast, gives both the intense Schiff base-type absorption at 442 (inflection) and 453 mμ (maximum) and the Ehrlich dye maximum at 568 mμ, in agreement with the open 2-position in the indole nucleus of diindole. Indole itself gives only Ehrlich dye absorption at 540 (inflection) and 567 mμ (maximum), and skatole similarly gives maxima at 545 and 578 mμ, the latter maxmum being the more intense of the two.

Diskatole sublimes unchanged at 125–126° (0.2 mm.), and diskatole hydrochloride could even be sublimed without decomposition. Nevertheless, the reversion of diskatole hydrochloride into skatole upon warming with alkali[8,18] appears to rule out the possibility of carbon skeletal rearrangements occurring during its formation. It is interesting to note that 3-ethylindole, in contrast to skatole, has been reported not to dimerize,[10] but this report appears to be in error.[24]

The bisdiskatole oxalate, m.p. 180°, of Oddo and Crippa[8] was reinvestigated since the nitrogen analysis, which constituted the sole characterization, was in better agreement with $C_{38}H_{34}N_4O_2$, bisdiskatole oxamide, than with the formula $C_{38}H_{38}N_4O_4$ proposed. Our carbon, hydrogen, and nitrogen analyses, however, are in agreement with the bisdiskatole oxalate formula originally proposed.

1,3-Dimethylindole forms a homodimer (VIb), m.p. 124–125.5°, analogous to diskatole, but the

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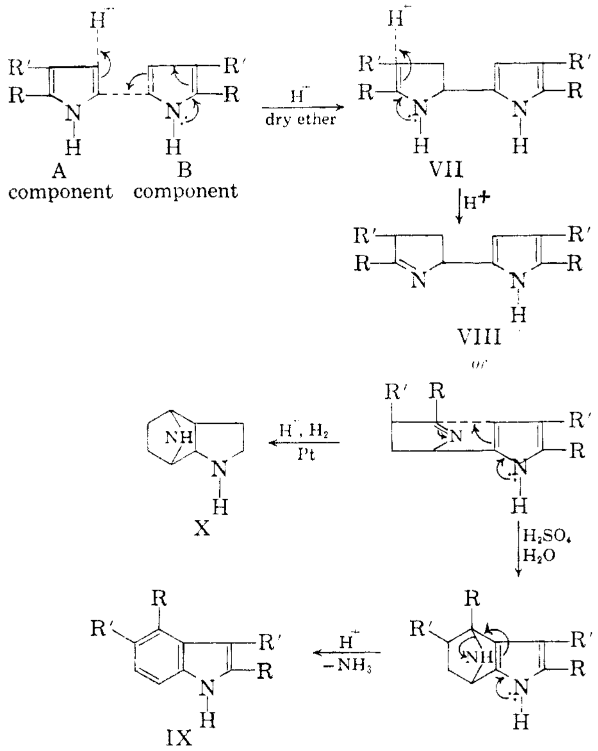
(23) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(24) Dr. G. F. Smith of the University of Manchester, England, has kindly informed us in a private communication (April 28, 1957) that he has found 3-*n*-propylindole to form a beautifully crystalline dimer hydrochloride at about the same rate as skatole dimerizes. On the other hand, he has prepared pure crystalline 3-t-butylindole and shown that it is completely unaffected by hydrochloric acid under conditions which lead to the rapid dimerization of skatole and 3-*n*-propylindole.

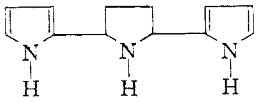
dimerization proceeds less rapidly. Even after hydrogen chloride had been passed into a stirred ether solution of 1,3-dimethylindole for three hours, the dimer hydrochloride was isolated in only 57% yield, and 26% of unchanged 1,3-dimethylindole was recovered after distillation.

Substituted pyrroles have long been known to form monobasic dimer salts under the action of mineral acids in dry ether solutions.[25,26] The structure of 2-phenylpyrrole dimer has been proved to be VIIIa.[25] Unilaterally alkyl-substituted pyrrole dimers are inferred to have analogous structures (such as VIIIb–e), because under the action of dilute sulfuric acid they lose ammonia and form substituted indoles (IX).[26] The indole from 2-methylpyrrole dimer has been proved to be 2,4-dimethylindole (IXb), in agreement with structure VIIIb for 2-methylpyrrole dimer.[26] The action of acid on pyrrole itself yields tripyrrole, which has been proved to have the linear structure XI,[27] as the stable product. The intermediate dipyrrole (VIIIe) has not been isolated, although a salt of the composition $(C_4H_5N)_2SnCl_4$ is known,[28] and dipyrrole has been trapped as the tetrahydro derivative (X) through catalytic hydrogenation of pyrrole in acetic acid or ethanolic hydrochloric acid solutions.[29] The structures VIII for pyrrole dimers are analogous to structure VIa for diskatole, except that the remaining vinylamine double bond of the A component (as in VII) has shifted into the more stable imine position. Such a shift does not occur in diskatole because the vinylamine double bond is already in its most stable position, as part of a benzenoid system.

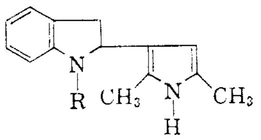


VIIIa. $R = C_6H_5$, $R' = H$
VIIIb, IXb. $R = CH_3$, $R' = H$
VIIIc, IXc. $R = i\text{-}C_3H_7$, $R' = H$
VIIId, IXd. $R = R' = CH_3$
VIIIe, IXe. $R = H$, $R' = CH_3$
VIIIf, IXf. $R = R' = H$

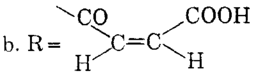
The structures of pyrrole dimers and of tripyrrole show that the 2-position is the point of greatest reactivity in pyrroles, both when they are acting as A components and as B components. It was hoped that blocking both 2-positions of the pyrrole nucleus, as in 2,5-dimethylpyrrole, would inhibit homodimerization of the pyrrole, but leave (or produce) sufficient reactivity as a B component at the 3-position to permit the synthesis of mixed indole:pyrrole dimers. This objective was realized with indole and 2,5-dimethylpyrrole, which gave an almost quantitative precipitate of hydrochlorides, from which indole:2,5-dimethylpyrrole dimer (XIIa) was obtained in up to 67% yield as the maleyl derivative, and indole:di-2,5-dimethylpyrrole trimer (XIII), m.p. 197–199°, was isolated in up to 41% yield.



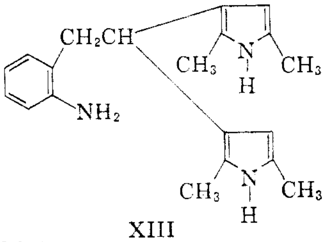
XI



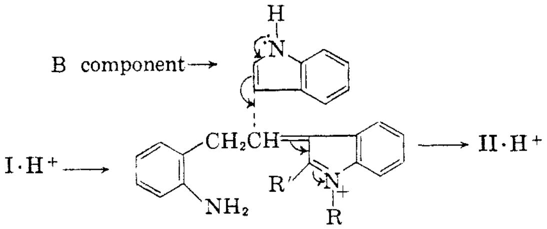
XII
XIIa. R = H

XIIb. R =


$$\text{XIIb. } R = -CO-CH{=}CH-COOH$$



XIII



XIV

Like indole dimers, indole:2,5-dimethylpyrrole dimer forms a monohydrochloride. The infrared spectrum (in Nujol) of the maleyl derivative contains an NH band at 3300 cm.$^{-1}$. Consequently, structures analogous to VIII, in which 2,5-di-

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[25] C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).

[26] C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.*, **2**, 235, 400 (1937).

[27] H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).

[28] O. Schmitz-Dumont, *Ber.*, **62**, 226 (1929).

[29] C. D. Nenitzescu and V. Ioan, *Revue de chimie*, **1**, 55 (1956).

TABLE II

SPECTRAL DATA ON ACYL DERIVATIVES OF MIXED INDOLE DIMERS AND TRIMERS, AND RELATED COMPOUNDS

	Ultraviolet					Infrared			
	Wave lengths of maxima in mμ with intensities (log ε). Solvent: 95% ethanol					Frequencies, cm.$^{-1}$	C=O		
Compound						NH	COOH	CON	Medium
Acetyl-*N*-methyl-*o*-toluidine	[a]	263 (2.57)	270 (2.50)	—	—	none	none	1640	$CHCl_3$
								1642	KBr
1-Maleylindoline[b]	[c]	255 (4.05)	283 (3.87)	292[d] (3.84)	—	none	1710	1625	$CHCl_3$
							1701	1611[e]	KBr
1-Succinylindoline[b]	[c]	252 (4.19)	281 (3.65)	290 (3.58)	—	none	1705	1653	Nujol
1-Maleyl-2-methylindoline[b]	[c]	250 (4.04)	282 (3.75)	289 (3.74)	—	none	1704	1623	Nujol
XVa[f]	218 (4.67)	264 (4.17)	282 (4.13)	290 (4.07)	—	3480	1710	1623	$CHCl_3$
						3280	1703	1620	KBr
XVIIa[g]	219[d] (4.66)	254 (4.21)	281 (4.03)	290 (3.96)	—	3350	1705	1650	Nujol
XVIIIa	[c]	255 (4.21)	280 (4.05)	289 (3.98)	—	3380	1699	1652	Nujol
XXa	218 (4.69)	271 (4.03)		288 (3.92)	—	3400	1347[h]	1164[h]	KBr
XVb	219 (4.64)	262 (4.19)	282 (4.14)	289 (4.09)	—	3480	1709	1623	$CHCl_3$
						3390	1707	1622	KBr
XVIb	224 (4.68)	—	282 (4.07)	289 (4.05)	323 (3.88)	3350	1691	1630	KBr
						3360	1694	1635	Nujol
XVIIb	223 (4.60)	256 (4.19)	282 (4.06)	290 (3.98)	—	3340	1708	1633	Nujol
XVIIIb	222[d] (4.60)	257 (4.22)	282 (4.09)	290 (4.02)	—	3390	1687	1615[i]	Nujol
XIXb	221 (4.66)	269 (4.22)	281 (4.21)	288[d] (4.16)	—	3330	1693	1618	Nujol
XVc	225 (4.61)	259 (4.16)	284 (4.14)	292 (4.10)	—	none	1709	1621	$CHCl_3$
						none	1714[j]	1615[j]	KBr
						none	1714[k]	1613[k]	Nujol
XVIc	226 (4.68)	—	285 (4.05)	291[d] (4.04)	318 (3.83)	none	1683	1619[l]	KBr
						none	1685	1621[m]	Nujol
XVIIc	226 (4.60)	255 (4.18)	283 (4.07)	291 (4.02)	—	none	1693	1648	Nujol
XVd	235[d] (4.48)	—	294 (4.34)	302[d] (4.31)	—	3440	1703	1618	$CHCl_3$
						3260	1697	1621	KBr
						3260	1698	1620	Nujol
IIIb	[c]	261(4.22)	280[d](4.15)	288[d](4.09)	—	3500	1715	1629	$CHCl_3$
						3290	1716	1624	Nujol
						3370[d]			
VIc	225 (4.63)	263 (4.20)	283 (4.21)	291[d] (4.09)	—	3310	1689	1622[n]	KBr
						3320	1689	1620[n]	Nujol
XIIb	[c]	252 (4.37)	283 (4.15)	291[d] (4.12)	—	3300	1688	1620	Nujol
IIe	225 (4.84)	—	283 (4.09)	291 (4.04)	—	3350	1715	1657	Nujol
						3410[o]			
IIf	225 (4.90)	274 (4.25)	278[d] (4.25)	290[d] (4.17)	—	3290	1688	1625	Nujol
						3360[o]			
IIg	225 (4.85)	—	284 (4.19)	291 (4.17)	—	3320	1704	1602[p]	KBr
						3320	1703	1600[p]	Nujol
IIg K salt	226 (4.81)	—	285 (4.15)	291[d] (4.12)	—	[a]	[a]	[a]	
XXI	222[d,q] (4.36)	253 (4.19)	280[d] (3.86)	291[d] (3.79)	—	none	—1688[r]—		Nujol
2,3,3-Trimethylindolenine[s]	216[t] (4.27)	255 (3.78)	—	—	—	none	none	1579[u]	liquid

[a] Not determined. [b] Preparation described in ref. 32. [c] Rising end absorption. [d] Inflection. [e] Also weaker band at 1651 cm.$^{-1}$. [f] The m.p., 162–163.5° dec. with carbon dioxide evolution, of our sample recrystallized from acetonitrile was higher than that reported, 157°.[16] [g] The m.p., 162–163° dec. with carbon dioxide evolution, of our sample recrystallized from acetonitrile was lower than that reported, 169–170°.[16] [h] Sulfur dioxide bands. [i] Also weaker band at 1634 and very strong band at 1586 cm.$^{-1}$. [j] Also weaker bands at 1682 and 1647 cm.$^{-1}$. [k] Also weaker bands at 1680 and 1647 cm.$^{-1}$. [l] Also strong band at 1644 cm.$^{-1}$. [m] Also strong band at 1650 cm.$^{-1}$. [n] Also strong band at 1590 cm.$^{-1}$. [o] Weaker band. [p] Also strong band at 1580 cm.$^{-1}$. [q] Also inflection at 228 mμ (log ε 4.25). [r] Single very strong carbonyl band; weaker bands at 1602 and 1583 cm.$^{-1}$. [s] Prepared by the method of G. Plancher, *Ber.*, **31**, 1496 (1898). Very unstable; it was redistilled just prior to analysis: colorless, n^{27}_{D} 1.5406, b.p. 105.5–106° (9 mm.); reported b.p. 227–229°. The picrate, prepared in ether, yellow needles from benzene, melted at 161–163°; reported m.p. 158°. *Anal.* Calcd. for $C_{17}H_{16}N_4O_7$ (388.33): C, 52.78; H, 4.15; N, 14.43. Found: C, 53.00; H, 4.08; N, 14.65. [t] Also inflection at 222 mμ (log ε 4.08). [u] Strong C=N band.

methylpyrrole has acted as an A component, either at its 2- or 3-positions, as well as structures in which it has acted as a B component at its 2-position, are invalid. Structure XIIa is left as the probable structure for indole:2,5-dimethylpyrrole dimer. It is completely analogous to other dimers in which indole has acted as an A component.

Indole:di-2,5-dimethylpyrrole trimer is assumed to have the analogous structure XIII.[13a] The ultraviolet spectrum (see Table I) has a single maximum at 283 mμ (log ε 3.36), characteristic of the *o*-toluidine system resulting from opening of the single indole nucleus. *o*-Toluidine has maxima in alcohol at 284 mμ (log ε 3.23) and 234 (3.88).[30] In indole:di-2,5-dimethylpyrrole trimer (XIII), the lower wave-length *o*-toluidine band is overshadowed by rising end absorption, because of the two intact pyrrole nuclei, which, by analogy with those in tripyrrole (XI, 219, log ε 4.24[27]), should have their maximum below 220 mμ. The strong and dominant ultraviolet absorption maxima at about 225, 283, and 290 mμ, characteristic of intact indole nuclei, such as those in indole trimers (II), are absent.

The ultraviolet spectra of indole dimers (Table I) represent a composite of the spectra of the indole and indoline nuclei which they contain, but the indole absorption maxima, being more intense, dominate the spectra. The maximum at 240 or 241 mμ, present in the spectra of indoline and 2-methylindoline (see Table I), does appear, however, as a weak inflection at 244–248 mμ in the spectra of many indole dimers (Ia, di-2-methylindole, Ic, VIa) and their salts (Ia, Ib, VIa). With the dimer of 1,3-dimethylindole (VIb), and its hydrochloride, the indoline inflection at 249 mμ is of sufficient intensity to become an important part of the spectrum. The infrared spectra of acyl derivatives of all indole dimers (Ia, Ib, Id, IIIa, VIa) not derived from 1-methylindoles, as well as the maleyl derivative of indole:2,5-dimethylpyrrole dimer (XIIa), contain an NH band (see Table II). Thus, in agreement with the structures assigned, the original dimers must have contained *two* NH groups and could not have contained an indole nucleus in the indolenine form.

Indole:di-2,5-dimethylpyrrole trimer (XIII) differs from the mixed indole trimers in that only one indole molecule has gone into its formation. Here arises an interesting question as to the mechanism of formation of mixed indole trimers. The formation of trindole is assumed to proceed through nucleophilic attack at the 2-position of the indoline portion of protonated diindole by a third indole molecule acting as a B component.[6] That the corresponding reaction does not go at an unactivated (though much less sterically hindered) 2-position of an indoline nucleus is illustrated by the failure of indoline to undergo ring opening with 2-methylindole or 1,2-dimethylindole. After eighteen hours in homogeneous ethanolic hydrochloric acid solution at room temperature, no evidence was found for ring opening products; indoline was recovered (as 1-succinylindoline) in 97% and 74% yields, respectively, along with 72% 1,2-dimethylindole in the latter case. With indole dimers, the ease of the displacement reaction must depend upon the presence of the highly reactive gramine-type system; the reaction probably involves a prior ring opening to a 3H-pseudoindole intermediate[31] (XIV), which then undergoes Michael-type addition by the B-component. Either a mixed indole dimer (Ib or Ic) or diindole (Ia) might serve as the intermediate dimer, but the relative ease of formation of mixed dimers relative to diindole makes it most probable that the mixed dimers are the intermediates. If this is true, then the final B component must be indole and not the more nucleophilic 2-methylindole or 1,2-dimethylindole. This can only be because indole would offer the minimum steric hindrance to attack at a sterically hindered reaction site. 2,5-Dimethylpyrrole, however, is little more sterically hindered at the 3-position than indole. Being more nucleophilic than indole, it becomes the successful B component in the attack on indole:2,5-dimethylpyrrole dimer (XIIa), thus accounting for the two 2,5-dimethylpyrrole nuclei in indole:di-2,5-dimethylpyrrole trimer (XIII).

The physical properties and elemental analyses of the mixed indole dimers and trimers and their salts are reported in Table III.

Acyl derivatives. Two of the free dimers were oils (Ib, XIIa) and four others were difficult to isolate in pure crystalline form (Ia, Ic, Id, IIIa), probably because of a tendency to dissociate into the monomers. These dimers were commonly isolated as their amide derivatives, which had the dual advantage of being highly crystalline derivatives and of being stable with respect to dissociation into the monomers, because acylation ties up the electrons on the indoline nitrogen. A convenient derivatization procedure, commonly employed throughout this work, involved neutralization of the dimer and trimer hydrochlorides with aqueous ammonia in the presence of a water-immiscible organic solvent such as methylene chloride or benzene. The solution of the dimer and trimer in the organic solvent was then separated, dried over magnesium carbonate, and acylated, without necessity for isolation of the free dimer. Maleic anhydride, or one of its derivatives, was usually chosen as the acylating agent because the α,β-unsaturated derivatives of the dimers were desired for study in the novel rearrangement described in the following paper.[32]

Maleyldiindole[16] (XVa) was prepared in 90% yield from diindole hydrochloride by the acylation procedure described above. Succinyldiindole[16] (XVIIa) was obtained in 93% yield by succinylation of diindole. Itaconyldiindole was obtained in 93% yield from diindole hydrochloride by acylation of the neutralized base with itaconic anhydride. Itaconyldiindole underwent alkaline hydrolysis to diindole (isolated in 67% yield as succinyldiindole) and mesaconic acid (in 81% yield), an isomeriza-

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[30] P. Grammaticakis, *Bull. soc. chim.*, 139 (1949).

[31] J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.*, 81, 2239 (1959).

[32] W. E. Noland and C. F. Hammer, *J. Org. Chem.*, 25, 1536 (1960).

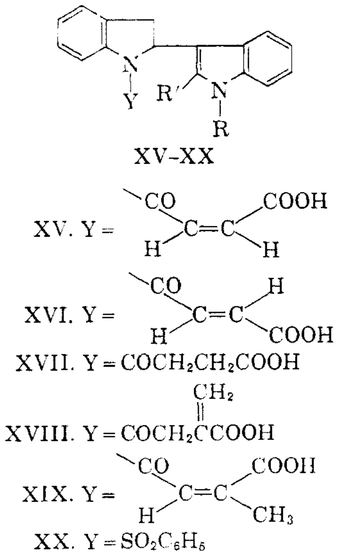
TABLE III

MIXED INDOLE DIMERS AND TRIMERS, AND THEIR SALTS

Compound		Best Yield, %	M.P., ° Color	Recrystallization Solvent	Molecular Formula and Weight	Analyses, % Found Calcd.		
Number	Name					C	H	N
Ib·HCl	2-Methyl-3-(2-indolinyl)indole hydrochloride	100[a]	133–135 light yellow	none	$C_{17}H_{17}NCl$ 284.78	72.00 71.70	6.14 6.02	9.94 9.84
Ic	1,2-Dimethyl-3-(2-indolinyl)-indole	98[b]	134–135 white platelets	methanol	$C_{18}H_{18}N_2$ 262.34	82.13 82.40	6.87 6.92	10.78 10.68
Ic·HCl	Hydrochloride of the above	82[c]	149–151 white	none	$C_{18}H_{19}N_2Cl$ 298.81	71.96 72.35	6.63 6.41	8.98 9.38
	Bisdiskatole oxalate	98[d]	184–185[e] white fine needles	ethanol	$C_{38}H_{38}N_4O_4$ 614.72	74.22 74.24	6.19 6.23	9.32[e] 9.12
VIb	1,3-Dimethyl-2-(1,3-dimethyl-2-indolinyl)indole	94·	124–125.5 white	90% ethanol	$C_{20}H_{22}N_2$ 290.39	82.98 82.72	7.65 7.64	9.68 9.65
VIb·HCl	Hydrochloride of the above	98[c]	113–117 white	none	$C_{20}H_{23}N_2Cl$ 326.86	73.19 73.49	7.23 7.09	8.55 8.57
XIIa·HCl	2,5-Dimethyl-3-(2-indolinyl)-pyrrole hydrochloride	90[c]	134–136 white[g]	none	$C_{14}H_{17}N_2Cl$ 248.75	68.00 67.59	6.86 6.89	10.89 11.26
IId	Diindole:1,2-dimethylindole trimer	14	165–166 white	methanol	$C_{26}H_{25}N_3$ 379.48	82.50 82.29	6.77 6.64	11.00 11.07
XIII	Indole:di-2,5-dimethylpyrrole trimer	41[f]	197–199 white platelets	ethanol	$C_{20}H_{25}N_3$ 307.43	78.41 78.13	8.54 8.20	13.76 13.67

[a] Prepared from the monomers by George J. Meisters. [b] From alkaline hydrolysis of the maleyl derivative. [c] Prepared in ether solution from the free base. [d] Prepared essentially by the method of ref. 8. [e] Reported m.p. 180°, % N, 9.58.[8] [f] From neutralization of the crude hydrochloride in warm ethanol with aqueous 2*N* sodium hydroxide solution. [g] Unstable; turns orange and then brown at room temperature after a few days.

tion product of itaconic acid. The fact that itaconyldiindole does not undergo the rearrangement described in the following paper[32] leads in part to the assumption that the double bond is not conjugated with the carboxamide group and that acylation has occurred, as would be expected, at the less sterically hindered and less resonance-stabilized, saturated carbonyl group. Consequently, itaconyldiindole is tentatively assigned structure XVIIIa. Benzenesulfonyldiindole (XXa) was obtained in quantitative yield from the Hinsberg reaction of diindole and benzenesulfonyl chloride. When indole was substituted for diindole in the Hinsberg procedure, benzenesulfonyldiindole was again obtained. The diindole may have been formed by action of hydrochloric acid (from prior hydrolysis of benzenesulfonyl chloride in the organic layer) on indole—or benzenesulfonyldiindole may be formed by the direct action of benzenesulfonyl chloride on indole (in a manner similar to the direct action of maleic anhydride on indole, forming maleyldiindole[16,34]).



XV-XX

XV. Y =

XVI. Y =

XVII. Y = $COCH_2CH_2COOH$

XVIII. Y = $COCH_2\overset{\overset{CH_2}{\|}}{C}COOH$

XIX. Y =

XX. Y = $SO_2C_6H_5$

XVa, XVIIa, XVIIIa, XXa. R = R′ = H
XVb-XIXb. R = H, R′ = CH_3
XVc-XVIIc. R = R′ = CH_3
XVd. R = H, R′ = C_6H_5

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(33) Fred B. Stocker, M.S. thesis, University of Minnesota, August 1955.

(34) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, 23, 320 (1958).

From indole:2-methylindole dimer hydrochloride, after neutralization and acylation with maleic anhydride, a stereoisomeric pair of maleyl (XVb) and fumaryl (XVIb) derivatives was obtained in yields of up to 54% and 19%, respectively. A novel rearrangement involving these derivatives is described in the following paper.[32] Both stereoisomers were hydrogenated over Raney nickel in yields of 95% and 88% to the succinyl derivative (XVIIb), which was prepared independently by substituting succinic anhydride for maleic anhydride in the acylation procedure. Similarly obtained were the itaconyl derivative (XVIIIb), in 33% yield by acylation with itaconic anhydride, and the citraconyl derivative (XIXb), in 25% yield by acylation with citraconic anhydride. The structures of these derivatives (XVIIIb, XIXb) are tentatively assigned on the basis of their behavior in the novel rearrangement and the considerations described in the following paper.[32]

From indole:1,2-dimethylindole dimer hydrochloride another stereoisomeric pair of maleyl (XVc) and furmaryl (XVIc) derivatives was obtained in yields of 47% and 7%, respectively, by acylation with maleic anhydride. Both stereoisomers were hydrogenated over Raney nickel to the succinyl derivative (XVIIc), which was prepared independently in 93% yield by succinylation of the pure dimer. The dimer (Ic) was obtained in yields of 98% and 39%, along with fumaric acid, from alkaline hydrolysis of the maleyl and fumaryl derivatives, respectively.

From indole:2-phenylindole dimer hydrochloride only a maleyl derivative (XVd) was obtained, in 23% yield. A novel rearrangement involving this derivative is described in the following paper.[32] From indole:2,5-dimethylpyrrole dimer hydrochloride again only a maleyl derivative (XIIb) was obtained, in 67% yield. Alkaline hydrolysis of this derivative gave, along with a quantitative yield of fumaric acid, the free dimer as an oil in 85% yield. This oil was reconverted into the maleyl derivative in 64% yield.

The reason for the concurrent formation of fumaryl as well as maleyl derivatives from maleic anhydride and dimers containing an indole with a 2-methyl group, but not from diindole, is unknown. An analogous pair of maleyl (VIc) and fumaryl (VId) derivatives of diskatole has been described[16]: the maleyl (white, m.p. 194°) being obtained from diskatole and maleic anhydride, and the fumaryl (yellow, m.p. 246°) from acid-catalyzed dimerization of skatole in the presence of maleic anhydride. On catalytic hydrogenation both stereoisomers gave succinyldiskatole, which was also prepared independently from succinic anhydride and diskatole. In our hands, all attempts to prepare fumaryldiskatole, according to the limited experimental details of the procedure[16] for the reaction of skatole with maleic anhydride catalyzed by sulfuric acid, were unsuccessful. Likewise, attempts to isomerize maleyldiskatole to fumaryldiskatole in ethanolic solutions containing sulfuric acid or iodine resulted in recovery of unchanged maleyldiskatole.

The assignment of configuration to the maleyl and fumaryl derivatives of indole dimers is based on the greater conjugation shown in the ultraviolet spectra (Table II) of the fumaryl derivatives (XVIb–c). Also, in the two cases where stereoisomeric pairs were obtained, the member to which we have assigned the fumaryl configuration has the higher melting point (Table IV). The two fumaryl derivatives have an absorption band at 318–323 mμ, not present in the maleyl derivatives or any of the other acyl derivatives. In contrast, except for the 2-phenyl-substituted case (XVd), the maleyl (IIIb, VIc, XIIb, XVa–c), as well as the succinyl (XVIIa–c), itaconyl (XVIIIa–b), and citraconyl (XIXb) derivatives, but not the fumaryl derivatives, have an absorption maximum in the 252–269 mμ region, which is also characteristic of the maleyl and succinyl indolines (250–255 mμ). The corresponding maximum in benzenesulfonyldiindole (XXa) occurs at 271 mμ. These maxima are completely lacking in the corresponding derivatives (IIe–g) of indole trimers (IIc–d). The trimers and their derivatives lack the indoline structure and, except for a band at 274 mμ in the citraconyl derivative (IIf), have only normal indole absorption. Besides the absorption bands mentioned above, all of the indole dimers, trimers, and their derivatives have the absorption bands associated with the indole nucleus, which occur at about 218–229 and 280–294 mμ. In the 2-phenylindole-substituted case (XVd) these bands have undergone the usual bathochromic shifts of about 10 mμ characteristic of 2-phenylindole and its derivatives.

All of the acyl derivatives containing unsaturation conjugated with the carboxamide group (maleyl, fumaryl, and citraconyl), except maleyldiskatole, are yellow in color (Table IV) because of a broad tailing out of ultraviolet absorption maxima into the visible region. The yellow color is instantly discharged when the free carboxyl group of the derivatives is neutralized by conversion to a salt. This fact is illustrated by conversion of yellow maleyldiindole:1,2-dimethylindole trimer (IIg) to its colorless potassium salt (Table IV). In contrast to the yellow unsaturated acid derivatives, all of the unconjugated acyl derivatives (such as the succinyl and itaconyl) are colorless.

Maleic anhydride acylation of the neutralization products of the viscous, oily mixture of hydrochlorides from the skatole:2-methylindole reaction gave a variety of products. Included among these were maleyldiskatole (VIc) and the 1:1 and 2:1 adducts of 2-methylindole with maleic anhydride.[16] When benzene was used as a solvent for acylation, the maleyl derivative (IIIb) of skatole:2-methylindole dimer began to precipitate after two minutes

TABLE IV

ACYL DERIVATIVES OF MIXED INDOLE DIMERS AND TRIMERS, AND RELATED COMPOUNDS

Compound		Best Yield, %	M.P., ° Color	Recrystallization Solvent[j]	Molecular Formula and Weight	Analyses, % Found Calcd.		
Number	Name					C	H	N
XVIIIa	3-(1-Itaconyl-2-indolinyl)-indole	93	164–165 dec.[a] White	E[j]	$C_{21}H_{18}N_2O_3$ 346.37	72.71 72.82	5.39 5.24	8.23 8.09
XXa	3-(1-Benzenesulfonyl-2-indolinyl)-indole	100	170–172 White	E-60[j]	$C_{22}H_{18}N_2O_2S$ 374.45	70.42 70.56	4.84 4.85	7.29 7.48
XVb	2-Methyl-3-(1-maleyl-2-indolinyl)-indole	54	156–157 dec.[a] Yellow	A[j]	$C_{21}H_{18}N_2O_3$ 346.37	72.69 72.82	5.38 5.24	8.09 8.09
XVIb	2-Methyl-3-(1-fumaryl-2-indolinyl)-indole	19	215–217 dec.[a] Yellow	A or C[j]	$C_{21}H_{18}N_2O_3$ 346.37	73.10 72.82	5.43 5.24	7.91 8.09
XVIIb	2-Methyl-3-(1-succinyl-2-indolinyl)-indole	39	135–137[b] White	A	$C_{21}H_{20}N_2O_3$ 348.39	72.35 72.39	5.67 5.79	8.27 8.04
XVIIIb	2-Methyl-3-(1-itaconyl-2-indolinyl)-indole	33	171–172 dec.[a] White	A	$C_{22}H_{20}N_2O_3$[k1] 360.40	73.14 73.31	5.86 5.59	7.88 7.77
XIXb	2-Methyl-3-(1-citraconyl-2-indolinyl)-indole	25	146–147 dec.[a] Yellow	A	$C_{22}H_{20}N_2O_3$ 360.40	73.07 73.31	5.82 5.59	7.90 7.77
XVc	1,2-Dimethyl-3-(1-maleyl-2-indolinyl)-indole	47[c]	164–165 dec.[a] Yellow fine needles	A	$C_{22}H_{20}N_2O_3$ 360.40	73.07 73.31	5.66 5.59	7.82 7.77
XVIc	1,2-Dimethyl-3-(1-fumaryl-2-indolinyl)-indole	7	211–212.5 dec.[a] Yellow platelets	A	$C_{22}H_{20}N_2O_3$ 360.40	73.37 73.31	5.72 5.59	7.85 7.77
XVIIc	1,2-Dimethyl-3-(1-succinyl-2-indolinyl)indole	93[d]	181–182 dec.[a] White	A	$C_{22}H_{22}N_2O_3$ 362.42	73.04 72.91	6.30 6.12	7.84 7.73
XVd	2-Phenyl-3-(1-maleyl-2-indolinyl)-indole	23	189.5–191 dec.[a] Yellow	A	$C_{26}H_{20}N_2O_3$ 408.44	76.64 76.45	5.17 4.94	6.97 6.86
IIIb	2-Methyl-3-(1-maleyl-3-methyl-2-indolinyl)-indole	37[e]	154–155 dec.[a] Yellow, hygroscopic	A	$C_{22}H_{20}N_2O_3$ 360.40	73.27 73.31	5.94 5.59	8.09 7.77
XIIb	2,5-Dimethyl-3-(1-maleyl-2-indolinyl)-pyrrole	67	156–157.5 dec.[a] Yellow[f] needles	A	$C_{18}H_{18}N_2O_3$ 310.34	69.89 69.66	5.93 5.85	9.24 9.03
IIe	Succinyldiindole: 2-methylindole trimer	15	224–225[g] White	A or E-W[j] A	$C_{29}H_{27}N_3O_3$[k2] 465.53	74.71 74.82	6.00 5.85	9.06 9.03
IIf	Citraconyldiindole: 2-methylindole trimer	62	196–197 dec.[a] Yellow	A	$C_{30}H_{27}N_3O_3$ 477.54	75.36 75.45	5.83 5.70	9.04 8.80
IIg	Maleyldiindole: 1,2-dimethylindole trimer	11[l]	183–183.5 dec.[a] Yellow fine needles	A	$C_{30}H_{27}N_3O_3$[k3] 477.54	75.53 75.45	5.89 5.70	8.85 8.80
IIg K salt	Monopotassium salt of the above	87	283–285 dec.[a] White	M[j]	$C_{30}H_{26}N_3O_3K$ 515.63	68.47 68.71[i]	5.17 5.08	8.21 8.15
XXI	Spiro[(8-carboxy-10-methyl-6,7,8,-9,9a,10-hexahydrobenzo[b]-pyrrocol-6-one)-9,3′-(2′-methyl[3]pseudoindole)]	10[h]	257–258 dec.[a] White	A	$C_{22}H_{20}N_2O_3$[k4] 360.40	73.17 73.31	5.54 5.59	7.93 7.77

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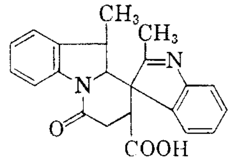
[a] With carbon dioxide evolution. [b] After being dried at 90° *in vacuo* for 3 hr., the crystals softened at 118°, with partial melting, followed by solidification and remelting at 169–170°. The Nujol infrared spectra were sensitive to the length of the drying time at 90°. A sample prepared in methylene chloride melted at 133–134°. [c] Also regenerated from the pure dimer obtained by its alkaline hydrolysis. [d] From the pure dimer. [e] Prepared in benzene solution. [f] The impure compound is particularly unstable, and it must be recrystallized quickly. [g] A mixed melting point with succinyltriindole,[33] m.p. 213–214°, was depressed and the Nujol infrared spectra were different. [h] Prepared in 1:1 (by volume) methylene chloride–acetonitrile. [i] Allowing for 0.5 C-atom left as a residue of potassium carbonate. [j] E, ethanol; E-60, 60% ethanol; A, acetonitrile; C, acetone; E-W, ethanol-water; M, methanol. [k] Neutralization equivalent: k_1, 361; k_2, 458; k_3, 461; k_4, 346. [l] Also prepared in 97% yield by acylation of the free mixed trimer in acetonitrile solution.

and was obtained in 37% yield after three hours. When acylation was carried out in a more polar solvent (methylene chloride, or methylene chloride to which an equal volume of acetonitrile has been added), from which the maleyl derivative did not precipitate, the residue from overnight evaporation of the solvent contained 2–10% yields of a colorless (or grayish white) isomer, m.p. 257–258° dec. This isomer has been assigned the spiro indolenine structure XXI on the basis of the following evidence: (1) The elemental analyses and neutralization equivalent are consistent with a monobasic



XXI

acid of the formula $C_{21}H_{19}N_2O{\cdot}COOH$. The compound is soluble in acid as well as base; (2) The infrared spectrum in Nujol contains no NH band, but does contain a single very strong carbonyl band at 1688 cm.$^{-1}$. The intensity of the carbonyl band is consistent with its being the resultant of superposition of bands due to a six-membered ring lactam carbonyl and a carboxyl carbonyl. The infrared spectrum contains a double bond band at 1583 cm.$^{-1}$, similar to that at 1579 cm.$^{-1}$ in liquid 2,3,3-trimethylindolenine (see Table II); (3) The ultraviolet absorption maximum at 253 (4.19) is very similar to that in 1-succinylindoline at 252 (4.19) and is also similar in location to that at 255 mμ (log ϵ 3.78) in 2,3,3-trimethylindolenine; (4) The compound undergoes the alkaline hydrolysis rearrangement and yields the same products as does the maleyl derivative IIIb.[32]

Compound XXI is of great interest because it appears to have the structure proposed for the intermediate of the alkaline hydrolysis rearrangement.[32] It is assumed to arise from the maleyl derivative (IIIb) by addition of the nucleophilic 3-position of the 2-methylindole nucleus to the electrophilic double bond of the maleyl group at a position β- to the carboxamide group, followed by a proton transfer to the anionic α-carbon. If addition at the β-carbon were reversible, then configurational instability of the intermediate anion, or loss from the α-carbon of a different proton from the one which had added, could result in isomerization of the double bond to the fumaryl configuration. If the addition compounds formed in the indole:2-methylindole and indole:1,2-dimethylindole series, analogous to XXI in the skatole:2-methylindole series, formed but were relatively unstable, then they could serve as intermediates in formation of the fumaryl derivatives XVIb–c. As no clearcut evidence has as yet been obtained for isomerization of maleyl to fumaryl derivatives during purification by recrystallization, this possibility may not be admissible. A plausible alternative, which would account for isomerization *during* acylation, would be amine catalysis by reversible addition to the double bond by not yet acylated dimer.

EXPERIMENTAL

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

The general procedure for the preparation of mixed indole dimer hydrochlorides and acyl derivatives is illustrated by the example given below. Usually the acylations were carried out in methylene chloride solution, except that mixtures of methylene chloride:acetonitrile (1:1 by volume) were used for the preparation of IIg, XVa, XVc, XVIc, and XXI; acetonitrile was used for the preparation of XVd; and benzene was used for the preparation of IIIb, VIc, XIIb, XVIIa, XVIIc, and XVIIIa. Details of the experimental procedures may be obtained from the thesis on which this paper is based.[3] Microfilm copies may be purchased from University Microfilms, Ann Arbor, Michigan.

2-Methyl-3-(2-indolinyl)indole hydrochloride (indole:2-methylindole dimer hydrochloride; Ib·*HCl).*[35] Dry hydrogen chloride was passed slowly into a stirred and ice-cooled solution of indole (8.93 g., 0.0762 mole) and 2-methylindole (10.00 g., 0.0762 mole) in dry ether (150 cc.). The hydrogen chloride was introduced very slowly for the first 10 min. and the rate was increased until saturation was achieved after about 1 hr. The light yellow precipitate was filtered and dried in a vacuum desiccator (21.92 g., 0.0770 mole, 101%), m.p. 133–135°. The sample was analyzed without attempted recrystallization. The spectral data are reported in Table I and the elemental analyses in Table III.

2-Methyl-3-(1-maleyl-2-indolinyl)indole (XVb) *and 2-methyl-3-(1-fumaryl-2-indolinyl)indole* (XVIb). Undried 2-methyl-3-(2-indolinyl)indole hydrochloride (20.0 g., 0.0702 mole) was overlaid with methylene chloride (250 cc.) and water (50 cc.) and then neutralized with aqueous concd. ammonium hydroxide (10.6 cc.). The methylene chloride layer was separated and dried over anhydrous magnesium carbonate. Maleic anhydride (7.10 g., 0.0723 mole) was added to the dried solution, with stirring to facilitate evaporation. After 1 hr. the yellow crystals (6.14 g.), m.p. 156–157° dec., were filtered. After 2 additional hr. of stirring and evaporation more yellow crystals (3.04 g.), m.p. 154–156° dec., were obtained, making the total 9.18 g., 0.0265 mole, 38%. One recrystallization from acetonitrile yielded 2-methyl-3-(1-maleyl-2-indolinyl)indole as yellow crystals, m.p. 156–157° dec. with carbon dioxide evolution.

After the methylene chloride mother liquor had been set aside for a longer time (3 days) another yellow crystalline compound (4.62 g., 0.0133 mole, 19%), m.p. 212–216° dec., was obtained. Three recrystallizations from acetone (or acetonitrile) yielded 2-methyl-3-(1-fumaryl-2-indolinyl)-indole as yellow microcrystals, m.p. 215–217° dec. with carbon dioxide evolution.

The spectral data for these maleyl and fumaryl derivatives are reported in Table II and the elemental analyses are given in Table IV.

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(35) Experiment performed by George J. Meisters.