The Mitomycin Antibiotics. Synthetic Studies. XIV.[1] The Nenitzescu Indole Synthesis. Formation of Isomeric Indoles and Reaction Mechanism.

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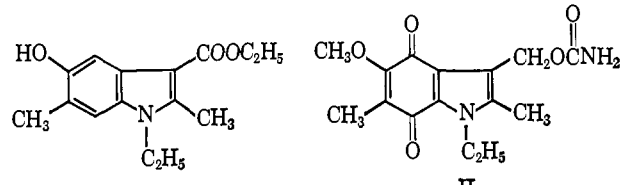
Abstract: The condensation of 2-alkyl-1,4-benzoquinones with 3-amino- and 3-alkylaminocrotonates (Nenitzescu synthesis) is shown to give 7-alkyl- (IV) as well as the hitherto reported 6-alkyl-2-methyl-3-carbethoxy-5-hydroxyindoles (III). The isomer ratio III/IV appears to be directly dependent on the bulk of the substituents on the quinone ring and the crotonate nitrogen. Several products resulting from Michael-type condensation of the quinone with the C terminal of the aminocrotonate enamine system were isolated. Appropriate experiments demonstrated that these substances can be converted into the observed indoles, thus establishing a mechanistic pathway for the Nenitzescu synthesis.

The condensation of 1,4-benzoquinones with 3-aminocrotonates, first described by Nenitzescu,[2] constitutes an indole synthesis of some consequence.[3] We have previously reported[5] the utility of this procedure for the preparation of the mitomycin-related quinone II *via* indole ester I. In view of our interest in congeners of II, we have found it necessary to prepare by the Nenitzescu procedure a variety of indole esters related to I, and as a result of this effort have noted certain previously unobserved facets concerning this synthetic method.

With a 2-substituted 1,4-benzoquinone the formation of three isomeric 5-hydroxyindole-3-carboxylates (*bz* substituent at 4, 6, or 7) is theoretically possible, and although such quinones have been used somewhat



I II

extensively in this condensation,[4a-c,e] only the formation of 6-substituted 5-hydroxyindole-3-carboxylic esters, *e.g.*, III, has been recorded. In fact, we have found that when the quinone substituent is an alkyl group such condensations do not proceed exclusively in this manner, but are *usually accompanied by formation of the isomeric 7-alkyl-5-hydroxyindole-3-carboxylic ester IV.* This latter isomer is normally formed in lesser amounts, but in at least one instance it is as prevalent as the previously observed III. Thus, the condensation of toluquinone with ethyl 3-aminocrotonate[6,7] gave IIIa and IVa in essentially equivalent yield after partition chromatography.

The results obtained from our study of the Nenitzescu condensation of various 2-substituted benzoquinones and 3-aminocrotonates are listed in Table I. The following observations concerning these results seem pertinent. (1) Low yields (11–32% for purified material) were always obtained with 2-alkylbenzoquinones.[8] (2) From seven of nine condensations involving 2-alkylbenzoquinones both 6- and 7-substituted isomers were obtained, although in most instances the latter were formed in little more than trace amounts. (3) In contrast to our observations with the 2-alkylquinones, 2-methoxybenzoquinone afforded in one (IIIk) of two instances a good (63%) yield of indole derivative. In neither instance was the formation of the 7-substituted isomer observed, in spite of the fact that one of these condensations (j) was carried out under the most favorable circumstances for such formation, namely with the N-unsubstituted ethyl 3-aminocrotonate. (4) In no instance were we able to

(1) Paper XIII: R. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, **31**, 1012 (1965). (b) A preliminary report of this work has appeared in *Chem. Ind.* (London), 2096 (1965); 117 (1966).

(2) C. D. Nenitzescu, *Bul. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, 24, 110 (1930).

(3) The versatility of this procedure is exemplified in the literature by the preparation of 5-hydroxyindole-3-carboxylates having at the 6 position hydrogen,[2] alkyl,[4a] hydroxy,[4a] alkoxy,[4a] or benzylthio[4b] substituents. 2-Chloro-1,4-benzoquinone is reported to react with ethyl β-ethylaminocrotonate to give a benzylchloro isomer of undetermined structure.[4c] The preparation of 4,7-[4d] and 6,7-dichloro,[4d] as well as 4,7-[4a] and 6,7-dialkyl,[4e] derivatives has also been noted. The 2 substituent is represented variously by methyl,[2] propyl,[4f] heptadecyl,[4f] ethoxy,[4g] and phenyl.[4h] It is also possible to vary the nitrogen substituent, examples with hydrogen,[2] alkyl,[4c] cyclohexyl,[4d] aryl,[2,4d] aralkyl[4i,j] or substituted alkyl[4b,k,l] at this site having been reported. Finally, it may be noted that 1,4-naphthoquinone reacts with aminocrotonates to give 2-alkyl-5-hydroxy-1H-benz[g]indole-3-carboxylates.[4c,d]

(4) (a) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951); (b) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Org. Chem.*, **24**, 1750 (1959); (c) A. N. Grinev, N. K. Kul'bovskaya, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **25**, 1355 (1955); *Chem. Abstr.*, **50**, 4903 (1956); (d) A. N. Grinev, I. A. Zaitsev, V. I. Shvedov, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **28**, 447 (1958); *Chem. Abstr.*, **52**, 14585 (1958); (e) H. J. Teuber and G. Thaler, *Ber.*, **91**, 2264 (1958); (f) A. N. Grinev, V. N. Ermakova, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **31**, 490 (1961); *Chem. Abstr.*, **55**, 22286 (1961); (g) R. J. S. Beer, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 1262 (1953); (h) D. Raileanu and C. D. Nenitzescu, *Rev. Roumaine Chim.*, 10, 339 (1965); *Chem. Abstr.*, **63**, 9903 (1965); (i) A. N. Grinev, V. N. Ermakova, and A. P. Terent'ev, *Dokl. Akad. Nauk SSSR*, **121**, 862 (1958); *Chem. Abstr.*, **53**, 1167 (1959); (j) G. Domschke and H. Furst, *Ber.*, **92**, 3244 (1959); (k) A. N. Grinev, N. E. Rodzevich, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **27**, 1960 (1957); *Chem. Abstr.*, **52**, 3762 (1958); (l) A. N. Grinev, V. N. Ermakova, E. Vrotek, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **29**, 2777 (1959).

(5) (a) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3878 (1964); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Org. Chem.*, in press.

(6) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(7) This condensation was first recorded in ref 4a.

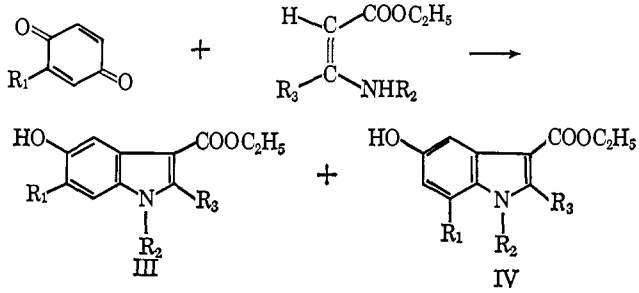
(8) These low yields are in harmony with the results generally recorded in the literature.[4] However, the condensation of benzoquinone with ethyl 3-aminocrotonate is reported to proceed in 49–55% yield.[4j]

Table I. Indole Esters Formed from the Condensation of 1,4-Benzoquinones with Ethyl 3-Amino- and 3-Alkylaminocrotonates

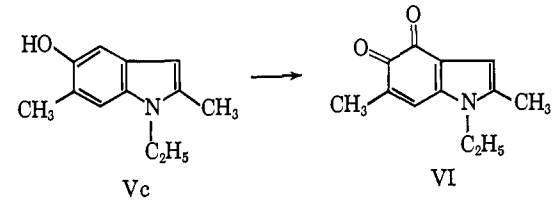
Pair	R_1	R_2	R_3	Yield, %[a] 6 isomer (III)	7 isomer (IV)	Ratio[a] of III/IV
a	CH_3	H	CH_3	9 (12)	8 (14)	1.1 (0.9)
b	CH_3	CH_3	CH_3	22[b]	10[b]	2.2
c	CH_3	C_2H_5	CH_3	21 (24)	2 (4.6)	10.5 (5)
d	CH_3	C_3H_7	CH_3	21[b]	1[b]	21
e	CH_3	C_4H_9	CH_3	18	2	9.0
f	CH_3	i-C_3H_7	CH_3	18	...	...
g	C_2H_5	H	CH_3	30	...	...
h	C_2H_5	C_2H_5	CH_3	14	0.2	70
i	CH_3	C_2H_5	C_2H_5	20	1.5	13
j	CH_3O	H	CH_3	19	...	...
k	CH_3O	C_2H_5	CH_3	63	...	...

[a] Data in parentheses (pairs a and c) were determined from experiments wherein the total crude product without work-up other than solvent evaporation was chromatographed. [b] These data are based on the separation of the corresponding 3-hydrogen indoles.

detect a 4-substituted isomer. We also call attention to the role of partition chromatography for the resolution of the condensation products. With pairs b and d we were unable to achieve a separation of the two isomers. However, after decarbethoxylation (essentially quantitative yield with hydrochloric acid), a separation proved possible. For definition of R_1, R_2, and R_3 see Table I.



Although we intuitively assumed, as had previous workers in this field, that the major product from the 2-alkylbenzoquinones was the 6-substituted isomer III, definitive proof was in fact required. (In this connection we would note that the structure of ethyl 5-hydroxy-6-methoxy-2-methylindole-3-carboxylate (IIIj) has been established unequivocally by Beer and co-workers.[4a]) The structure for the 6-methyl isomer IIIc was demonstrated by decarbethoxylation to Vc, which on potassium nitrosodisulfonate (Fremy's salt)[4e] oxidation gave the *o*-quinone VI, identical with material prepared by an alternate unequivocal pathway.[9,10]



Vc VI

Moreover, the structures of all the 6-substituted isomers III followed from their pmr spectra (Table II), inasmuch as the two aromatic proton signals did not show either *meta* or *ortho* coupling as would be expected for the 7- or 4-substituted isomers, respectively. Instead low order secondary coupling[11] was noted between one of these protons and the *bz*-alkyl protons. Additionally, isomers IIIc and IIIj, the structures of which were established independent of pmr data, were correlated with the other 6 isomers (III) by the consistent pattern observed for the chemical shifts of their common structural features (see Table II).

Table II. Proton Resonance Data for Ethyl 6-Substituted 5-Hydroxyindole-3-carboxylates (cps)[a]

Compd	1 substituent (J)	2 substituent (J)	3 ester[b]	4 proton	5 hydroxy	6 substituent (J)	7 proton
IIIa	680	158.5	82, 257	447	c	135	425
b	214	157	82, 257	447	c	136	427
c	73, 245 (7.5)	158	80, 253	441	528	134	425
d	53, 243 (7.5)[d]	158.5	82, 257	447.5	533	136	429
e	54, 241 (7.5)[d]	159	83, 258	451	c	138	429
f	91,[e] 282[f]	163	83, 258	454	535	139	440
g	680	159	81, 257	448	529	72.5, 159 (7.5)	425
h	74, 248 (7.5)	160	82, 259	450	530.5	74, 162 (7.5)	430
i	73, 249 (7.5)	77, 187 (7.5)	83, 259	452	c	138.5	434
j	679	158.5	81, 256	445	506	229	414
k	74, 255 (7.5)	159	81, 255	446	508	230	422

[a] All spectra were determined in dimethyl sulfoxide-d_6. [b] The 80–83-cps resonance is a triplet and that at 253–259 cps is a quartet; J = 7.5 cps. [c] Not located. [d] Only those resonances for the NCH_2 and terminal CH_3 are given. [e] Doublet, J = 7.5 cps. [f] Multiplet.

The various coproducts were indicated to be 5-hydroxyindole-3-carboxylates on the basis of spectral and analytical data. A definitive structural assignment as the 7-alkyl isomers IV was made from a consideration of the following pmr spectral observations (Table III). (1) The aromatic protons were in a *meta* relationship as indicated by characteristic[12] spin–spin coupling constants of 2.5–3.0 cps. (2) Relative to the N-H derivative IVa and to the 1,6-dialkyl isomers III, the N-alkyl derivatives IVc, e, h, and i revealed a mutual paramagnetic shift for the 7-methyl (9–12 cps) and the NCH_2 resonances (5–10 cps), respectively. This effect presumably arises from the proximity of the two groups.[13,14] (3) Decarbethoxylation of the 7

(9) See paper XIII of this series (ref 1a).

(10) The previous[5] transformation of ester IIIc into substances having the 4,7-indoloquinone chromophore provided additional evidence for its formulation as the 6 isomer.

(11) For other examples of secondary coupling between aryl methyl protons and adjacent ring protons see (a) H. Rottendorf and S. Sternhell, *Tetrahedron Letters*, No. 20, 1289 (1963); (b) P. M. Nair and G. Gopakumar, *ibid.*, No. 13, 709 (1964), and references cited therein.

(12) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 85.

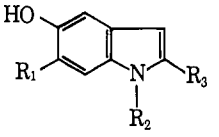
(13) Similar paramagnetic shifts have been recorded for the 6- and 19-methyl proton resonances for a series of 6β-methylpregnanes and

Table III. Proton Resonance Data for Ethyl 7-Substituted 5-Hydroxyindole-3-carboxylates (cps)[a]

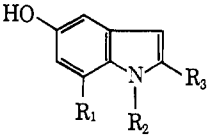
Compd	1 substituent (J)	2 substituent (J)	3 ester[b]	4 proton[c]	5 hydroxy	6 proton[c]	7 substituent (J)
IVa[d]	675	160	82, 258	436	*e*	391	145
c	74, 253 (7.5)	158.5	80, 254	434	521	382	154
e	56, 246 (7.5)[f]	159	81, 255	440	*e*	387	154.5
h	75, 257 (7.5)	162	81, 257	442	528	382	76, 176 (7.5)
i	73, 259 (7.5)	77, 187 (7.5)	81, 258	442	*e*	390	157

[a] All spectra determined in dimethyl sulfoxide-d_6. [b] The high-field resonance is a triplet and the low-field resonance is a quartet; J = 7.5 cps. [c] J = 2.5–3.0 cps. [d] Determined at 60°. [e] Not located. [f] Only those resonances for the NCH_2 and terminal CH_3 are recorded.

Table IV. Proton Resonance Data for 1,2,6-Trisubstituted 5-Hydroxyindoles (V) and 1,2,7-Trisubstituted 5-Hydroxyindoles (VII) (cps)[a]



V

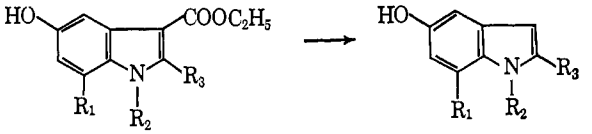


VII

	Compound										
	Va[b]	VIIa[b]	Vb	VIIb	Vc	Vd	VIId	Ve	VIIe	Vi[c]	VIIi[c]
1 substituent	609	622	209	222	76, 242	52, 232	54, 241.5	55, 234	53, 243	77, 236	?, 247
2 substituent	134	144[d]	137	137	142	138	138.5	139	137.5	73, 157	?
3 proton	355	360	358	358	363.5	361	362	360.5	362	362	362
4 proton[e]	410	402	412	400	412	406	402	406	402	408	401
5 hydroxy		504	475	485	281	286	296	289	323	296	304
6 proton[e,f]		387		383			382		382		380
6 substituent[f]	137		139		142	140		140		140	
7 proton[f]	419		415		421	416		416		417	
7 substituent[f]		145.5[d]		155			153		152		153

[a] For definition of R_1, R_2, and R_3 see Table I or VII; all spectra are for deuteriochloroform solution unless noted otherwise. [b] Determined in dimethyl sulfoxide-d_6. [c] Determined on unresolved mixture which on the basis of integrals appeared to consist of 75–80% Vi and 20–25% VIIi. [d] Assignments not definitive and may be reversed. [e] For series VII, $J_{4,6}$ = 2.5–3.0 cps. [f] These assignments resulted from the low order secondary coupling manifest in these resonances (see ref 11).

isomers (IV) gave products (VII), the spectra of which showed no significant shift in the *bz*-methyl resonance. Furthermore, the position of the 3-proton resonance in these products was essentially identical with that of the 3-proton signal in the decarbethoxylated 6-substituted isomers (V) (Table IV). Of particular significance was the diamagnetic shift (34–51 cps) of one of the aryl proton resonances, which is thus assigned to the 4 position.[15] These observations dictate the formulation of the Nenitzescu coproducts as the 7-substituted isomers.[16]



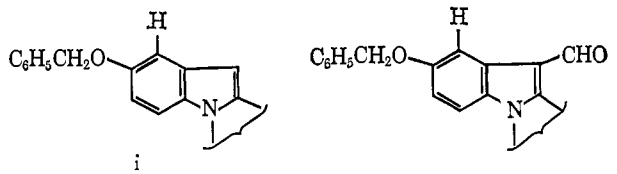
IV VII

Inspection of the results summarized in Table I indicates that the ratio of 6-substituted isomer to 7-substituted isomer (III/IV) is dependent upon the bulk of R_1 ($CH_3 < C_2H_5$) (pairs a and g) and R_2 ($H < CH_3 < C_2H_5 \simeq C_3H_7 \simeq C_4H_9 < i\text{-}C_3H_7$) (pairs a–f, g, and h) and is probably independent of R_3 (pairs c and i).[17] This apparent steric dependence directed our attention to a consideration of the mechanism of the Nenitzescu indole synthesis. Of the two most reasonable mechanisms that can be proposed for this reaction, that[4b] presented in Scheme I is more obviously susceptible to steric factors. Although the C terminal of the enamine triad is the initial reaction site predicted from a consideration of the chemistry of this system,[18–20] prece-

-pregnenes: G. Slomp, Jr., and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959).

(14) Interestingly, the position of the 2-methyl resonance is not appreciably affected by the presence or absence of *n*-alkyl groups on the ring nitrogen (see Tables II and III). However, a 1-isopropyl group (IIIf, Table II) results in an apparent deshielding of the 2-methyl group; this bulky 1-substituent also deshields the adjacent 7 proton, which is largely unaffected by the presence of *n*-alkyl groups on the ring nitrogen (Table II). Decarbethoxylation in both the 7-alkyl and the 6-alkyl series results in a significant diamagnetic shift of the 2-methyl resonance (*ca.* 22–26 cps).

(15) A prior example of deshielding by a 3-carbonyl substituent on the *peri* 4 hydrogen was noted in the pyrroloindole series: W. A. Remers, *J. Am. Chem. Soc.*, **86**, 4608 (1964). The doublet of the 4 proton (indole numbering) in part-structure i is shifted from τ 2.80 to 1.95 on formylation at the 3 position. With the 6 isomers III, decarbethoxylation to V results in a diamagnetic shift (average *ca.* 40 cps) of the 4-proton resonance.



i

(16) We would note the possible diagnostic value of ultraviolet spectra in distinguishing between 6-alkyl and 7-alkyl isomers of 1-hydrogen-2-alkyl- or 1,2-dialkyl-5-hydroxyindoles. In the 1-hydrogen series the low wavelength maximum is found at 207 and 218 mμ for the 6- and 7-alkyl isomers, respectively, whereas in the 1,2-dialkyl series this maximum is at 209–210 and 222–225 mμ for the 6- and 7-alkyl isomers, respectively.

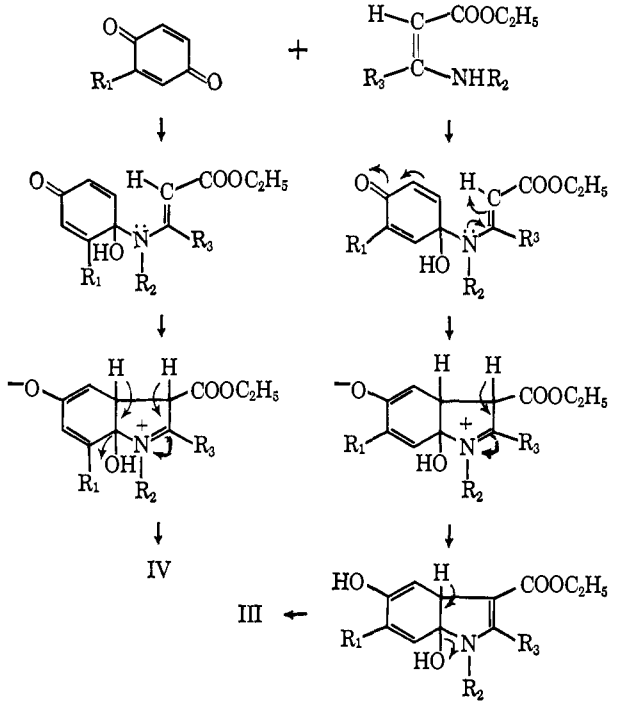
(17) The significance of these observations is supported by two experiments wherein the total crude product, without work-up other than solvent evaporation, was directly submitted to partition chromatography, and the ratio of isolated indoles was found not to have been appreciably altered.

(18) E. D. Bergmann, D. Ginsburg, and R. Pappo in "Organic Reactions," Vol. 10, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p 226.

(19) Reaction of ethyl 3-aminocrotonate with ethyl iodide gives, after

dent for the initial 1,2 addition of the aminocrotonate to the carbonyl group is to be found in the reversible nucleophilic 1,2 addition of bisulfite and hydroxide ions,[21] and the irreversible 1,2 addition of an unsaturated oxyphosphorane to the carbonyl group of *p*-quinones.[22]

Scheme I



The alternate mechanism, which has been more generally suggested[4g,j,18] and is more consistent with the chemistry of the enamine system, is given in detail in Scheme II for formation of the 6 isomer; an analogous scheme, wherein initial condensation occurs at C-6 of the benzoquinone, may be written for the formation of the 7 isomer. Despite the apparent freedom of the initial carbon–carbon condensation from steric influences (but not electronic effects[23]) such a mechanism could account for the effect of these forces in the subsequent carbon-to-nitrogen cyclization step. In sterically unfavorable environments, cyclization of the intermediate 1,4 adduct might be impeded (for an extreme example, XI, see below) and the uncyclized intermediate might revert to the reactants or could be responsible for the amorphous by-products and low yields usually noted in this reaction.

Relevant to this question is the isolation of hydroquinones VII (5%) and VIII (0.3%) from those condensations giving indolic pairs a and h, respectively. The structure of these substances was indicated by their ultraviolet spectra, which were essentially identical with those of the ethyl 3-alkylaminocrotonates, and

hydrolysis, ethyl α-ethylacetoacetate: Collie, *Ann.*, **226**, 316 (1884); see also footnote 9, ref 22.

(20) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

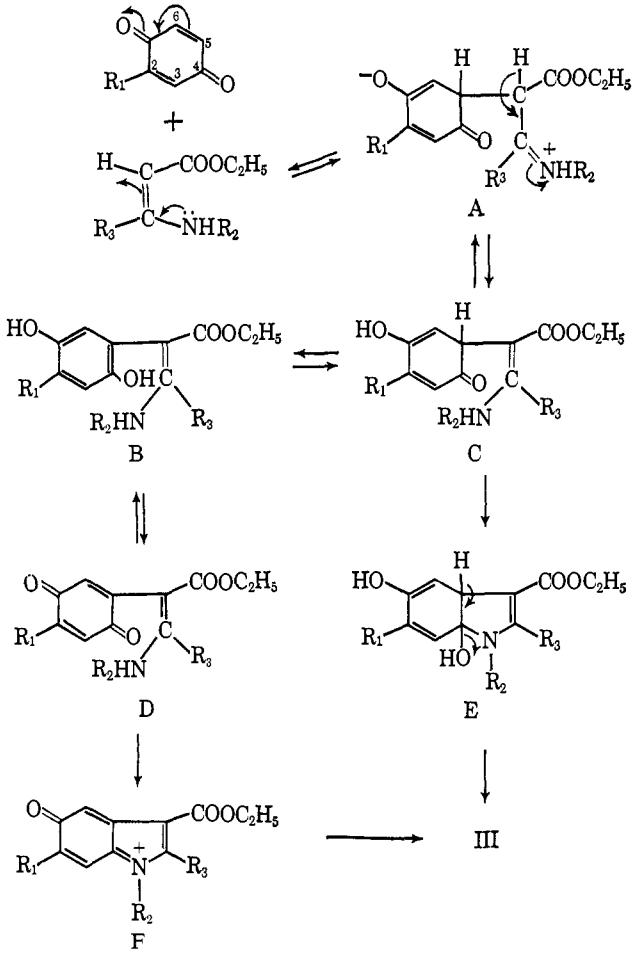
(21) (a) C. A. Bishop, R. F. Porter, and L. K. J. Tong, *ibid.*, **85**, 3991 (1963); (b) C. A. Bishop and L. K. J. Tong, *Tetrahedron Letters*, **No. 41**, 3043 (1964).

(22) F. Ramirez, H. J. Kugler, and C. P. Smith, *ibid.*, **No. 4**, 261 (1965).

(23) In fact, these effects probably play a predominant and in certain instances, *e.g.*, with alkoxyquinones, an overriding role. See ref 24 for a recent study and pertinent references.

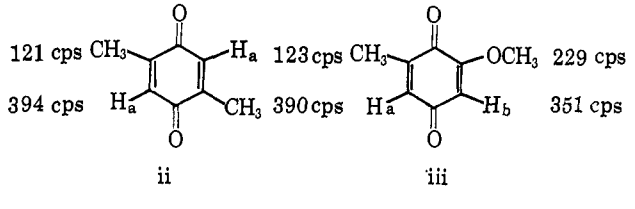
(24) H. S. Wilgus, III, E. Frauenglass, E. T. Jones, R. F. Porter, and J. W. Gates, Jr., *J. Org. Chem.*, **29**, 594 (1964).

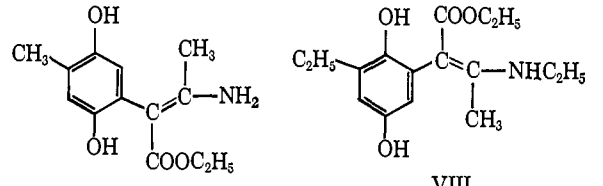
Scheme II



microanalyses. The gross features and the pattern of aryl substitution were defined by their pmr spectra—that of VII having two unsplit single-proton resonances and that of VIII having two single-proton resonances each existing as doublets with a typical *meta* coupling constant of 3 cps. In addition to these hydroquinones, the quinone–crotonate adduct IX was isolated (10%) from the condensation giving IIIj; this adduct apparently had been isolated previously by Beer and coworkers,[4a] but its constitution was not recognized at that time. Structure IX (or the geometrical isomer) was established for this product by microanalytical and spectral data (λ_{max} 210, 273, 345, and 465 mμ; 2.92, 3.02, 6.04, 6.15, and 6.27 μ; unsplit single proton resonances[25] at 365 and 388.5 cps).

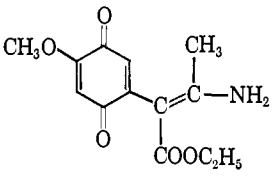
(25) It has recently been shown that proton spin–spin coupling constants for certain substituted benzoquinones are of the same magnitude as those observed for benzene derivatives.[24] In order to define the nuclear substitution in quinone IX, we examined the pmr spectra of 2,5-xyloquinone (ii) and 6-methoxytoluquinone (iii): F. Henrich and G. Nachtigall, *Ber.*, **36**, 894 (1903). The spectrum of ii is characterized by two distinct resonances having the anticipated $J_{Ha-CH_3} = 1.7$ cps[12] in addition to $J_{Ha-Ha} \simeq 0.5$ cps. In the spectrum of iii H_a is coupled with the allylic methyl protons ($J = 1.7$ cps) and with H_b ($J_{Ha-Hb} = 2.3$ cps). In this connection it may be noted that a value for J_{Ha-Hb} of similar magnitude (2.5–3.0 cps) has been recorded for 2-methyl-6-N-methylanilinobenzoquinone and 2-chloro-6-methylbenzoquinone: M. F. Ansell, B. W. Nash, and D. A. Wilson, *J. Chem. Soc.*, 3012 (1963).



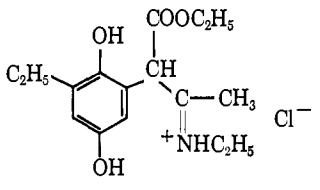


VII

VIII



IX



X

Inasmuch as the hydroquinone and quinone adducts represented possible intermediates for the mechanism illustrated in Scheme II, we attempted to demonstrate their ability to serve as indole precursors under Nenitzescu conditions. However, when either hydroquinone VII or quinone IX was placed in boiling acetone for 22 hr, no indole formation could be detected. Moreover, when hydroquinone VII (potential precursor to indole IIIa) was similarly treated in the presence of toluquinone and ethyl 3-ethylaminocrotonate (those reactants giving IIIc and IVc), no indole ester IIIa was found (71% recovery of VII), even though IIIc and IVc were formed. Similarly, exposure of quinone IX (potential precursor to indole IIIj) to a reaction of methoxybenzoquinone with ethyl 3-ethylaminocrotonate (those reactants giving IIIk) gave no indole ester IIIj (46% recovery of IX), although the 1-ethyl analog IIIk was formed.

It appeared probable that the failure of hydroquinone VII and quinone IX to cyclize was due to unfavorable stereochemistry about the exocyclic double bond—namely, a *trans* relationship between the amino function and the ring, as depicted in structures VII–IX. That these substances in fact were characterized by *trans* stereochemistry was indicated later by comparison of their pmr spectra with those reported for the isomeric ethyl 3-benzylaminocrotonates,[26] in which the resonance for protons of the vinyl methyl group *trans* to the carbethoxy group is found at 107 and at 157 cps for the *cis*-methyl group. For compounds VII–IX the vinyl methyl resonance occurs at 97–113 cps affording strong support for the assigned stereochemistry. Since protonation of the enamine system in 3-aminocrotonates occurs on the terminal carbon,[27] equilibration of these adducts to isomers with favorable stereochemistry appeared feasible. Thus, hydroquinone VIII (potential precursor for indole IVh) and a catalytic amount of the conjugate acid X were subjected to the Nenitzescu conditions in the presence of toluquinone and ethyl 3-ethylaminocrotonate (those reactants giving indoles IIIc and IVc). In addition to indole ester IIIc, there indeed was formed indole ester IVh (12–26%), *the origin of which must be hydroquinone VIII.*

That the transformation of VIII and conjugate acid X into indole ester IVh had not occurred *via* a Bucherer-type reaction (B → C → E) was shown by the failure of VIII and X to cyclize in boiling acetone in the absence of toluquinone (and ethyl 3-ethylaminocrotonate). It would appear then that for *cis*-VIII (see B) to proceed to the indole product it first must undergo oxidation to the quinone state (D). In the usual course of events this oxidation is presumably effected by starting quinone or, after initiation of the reaction, by a more advanced intermediate, such as the quinoniminonium derivative F.[28] Moreover, the necessary reduction of F (see below) is effected by the hydroquinone adduct B or the hydroquinone derived from starting quinone.

In accordance with this concept of the Nenitzescu mechanism, when the quinone adduct IX (see D) and its conjugate acid (IX failed to cyclize under Nenitzescu conditions, see above) were dissolved in acetone at room temperature and subsequently treated with sodium hydrosulfite, indole IIIj was isolated in 22% yield. In the absence of hydrosulfite this product could not be detected, the reaction presumably having stopped at the quinonimine stage corresponding to F.

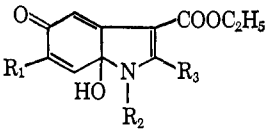
A remaining unresolved question is which species, hydroquinone adduct B or hydroquinone derived from starting benzoquinone, serves as reductant in this final step of a usual Nenitzescu reaction. The identity of this species was determined for the 1-hydrogen series in the following manner. Treatment of *cis*-VII (generated *in situ* by equilibration, see B) with 1 equiv of toluquinone resulted in immediate loss of reactants but no formation of indole IIIa (tlc), even after a prolonged reaction time. However, addition of sodium hydrosulfite gave IIIa (51%). Use of 0.1 equiv of toluquinone afforded IIIa (55%) *without the intervention of an external reductant.* Thus, it would appear that the hydroquinone adduct B, rather than toluhydroquinone, serves as the reductant for the conversion of the latter-stage quinonimine intermediate (corresponding to F)[28] into indole III, and that toluquinone only initiates the conversion of B to quinone adduct D. However, these experiments do not necessarily bear upon the situation in the N-alkyl series, since it is possible that the structure of the F intermediate in this series is of sufficiently higher potential (charged quinoniminonium derivative F *vs.* neutral quinonimine) so as to permit reduction by toluhydroquinone. In light of these experiments the pathway *via* B, D, and F[28] as originally postulated by Beer, Davenport, and Robertson,[4g] is established for the Nenitzescu synthesis, although other pathways are not excluded.[29]

We have observed above that the initial carbon–carbon condensation to give B apparently should be independent of steric influences and that the isomer ratios reported in Table I are presumably the result of the manifestation of these forces on the subsequent requisite cyclization (D → F). In this connection we would note the isolation of XI (18%) after re-

(26) G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963).

(27) B. Witkop, *ibid.*, 78, 2873 (1956).

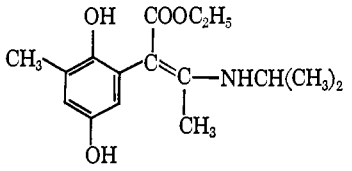
(28) Species iv represents a reasonable alternative for the F intermediate.



iv

(29) A similar conclusion has been reached independently by Raileanu and Nenitzescu.[4h]

duction of the mother liquor from condensation f with sodium hydrosulfite. In principle, *cis*-XI is a progenitor of the unobserved 7-alkylindole IVf. Yet, treatment of *cis*-XI (assumed to have been generated *in situ* by equilibration) with an equivalent of toluquinone and then sodium hydrosulfite as described above for the preparation of IIIa failed to give the 7-alkylindole IVf, presumably as a result of the adverse steric effects on the required cyclization.



XI

Finally, we can now offer several reasons for the low yields usually associated with the Nenitzescu indole synthesis: (1) the formation of 7-substituted indole isomers; (2) the formation of quinone- or hydroquinone–crotonate adducts having the wrong stereochemistry for the required cyclization, the usual reaction conditions being nonequilibrating. (3) When starting benzoquinone is utilized for oxidation of hydroquinone adduct B and the derived hydroquinone is unable to reduce the F-type intermediate, then the desired reaction is adversely affected in two ways: (a) since the hydroquinone derived from starting quinone can not reduce F (and be converted into benzoquinone), it is unavailable for reaction with the aminocrotonate; (b) to the extent that hydroquinone adduct B is oxidized by benzoquinone, the former is unavailable for the necessary reduction of F, causing an accumulation of this intermediate. The significance of this last contribution will depend on the relative reaction rates of the several steps and the relative oxidation–reduction potential of the F intermediate *vs.* that of the starting quinone.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer in the indicated solvent using tetramethylsilane as an internal standard. In describing these last spectra, the signals are expressed as *x*s (singlet), *x*d (doublet), *x*t (triplet), *x*q (quartet), or *x*m (multiplet), where *x* refers to the number of protons indicated by integration. The petroleum ether used was that fraction boiling at 30–60°. Unless otherwise noted, evaporations were carried out at reduced pressure.

Ethyl-1,4-benzoquinone. To a solution of 5.11 g (37 mmoles) of ethylhydroquinone[30] in 100 ml of methanol was added a solution of 20.0 g (74 mmoles) of ferric chloride hexahydrate in 120 ml of 1 *N* hydrochloric acid solution. The resulting solution was kept at room temperature for 45 min, whereafter it was distributed between methylene chloride and water. The organic solution was evaporated to give 4.90 g (96%) of crude solid of sufficient purity for the Nenitzescu reaction. It could be recrystallized from ether with much loss to give yellow plates, mp 37–39° (lit.[30,31] mp 37 and 38.2°).

Methoxy-1,4-benzoquinone. This quinone was prepared by the procedure of Erdtman.[32]

Preparation of Ethyl 3-Alkylaminocrotonates. The following preparation is illustrative. With magnetic stirring 54.8 g (0.75 mole, 74.2 ml) of butylamine was added to 98.5 g (0.846 mole, 100 ml) of ethyl acetoacetate at such a rate that the temperature remained at 40–45°; the addition required about 1 hr. A second phase appeared during this reaction. A warm water bath was placed under the reaction mixture, and stirring was continued for 2 hr at 40–45°. A small portion of ether was added to facilitate the separation of the aqueous phase. Distillation of the dried organic solution under reduced pressure gave 111.1 g (80%) of **ethyl 3-butylaminocrotonate** as a colorless liquid: bp 129.5–131.0° (14 mm); λ_{max} 285 mμ (ε 21,300); 3.05 5.92 (sh), 6.06, 6.23, 7.85, 8.55, 8.75, and 12.77 μ; pmr 56 (ill-defined, $CH_3CH_2CH_2CH_2$), 69 (t, J = 7.5 cps, CH_3CH_2O), 111 (3s, CH_3—C=), 190 (2m, $NHCH_2$), 239 (2q, J = 7.5 cps, CH_3CH_2O), 263 (1s, C=C—H), 518 cps (1, broad, NH).

Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.96; H, 10.27; N, 7.51.

Ethyl 3-ethylaminocrotonate was obtained in 93% yield: bp 108–112° (14 mm); λ_{max} 282 mμ (ε 21,000); 3.05, 5.92 (sh), 6.06, 6.23, 7.92, 8.52, 8.70, and 12.76 μ; pmr 69 (3t, J = 7.5 cps, CH_3CH_2O), 70 (3t, J = 7.5 cps, CH_3CH_2N), 113 (3s, CH_3—C=), 193.5 (2m, $NHCH_2CH_3$), 241 (2q, J = 7.5 cps, OCH_2CH_3), 263 (1s, H—C=), 513 cps (1 broad, NH).

Anal. Calcd for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.62; N, 8.91. Found: C, 61.32; H, 9.21; N, 8.99.

Ethyl 3-propylaminocrotonate (78%) had bp 119.0–119.5° (14 mm); λ_{max} 285 mμ (ε 20,100); 3.05, 5.92 (sh), 6.05, 6.21, 7.86, 8.52, 8.70, and 12.75 μ; pmr 57, 69.5 (overlapping triplets, $CH_3CH_2CH_2$, CH_3CH_2O), 89 (m, $CH_3CH_2CH_2$), 112 (3s, CH_3—C=), 188 (apparent quartet, $NHCH_2$), 240 (2q, J = 7.5 cps, OCH_2CH_3), 263 cps (1s, H—C=), 519 (1, NH, ill-defined triplet, eight times greater amplitude).

Anal. Calcd for $C_9H_{17}NO_2$ (171.23): C, 63.13; H, 10.00; N, 8.18. Found: C, 63.29; H, 10.06; N, 8.43.

Ethyl 3-isopropylaminocrotonate (73%) had bp 106.0–106.5° (11 mm); λ_{max} 285 mμ (ε 19,700); 3.05, 5.92 (sh), 6.06, 6.23, 7.85, 8.55; 8.72, and 12.77 μ; pmr 69 (d, J = 6 cps, $(CH_3)_2CH$), 70 (t, J = 7.5 cps, CH_3CH_2O), 114 (3s, CH_3C=), 218 (m, $(CH_3)_2CH$), 241 (2q, J = 7.5 cps, CH_3CH_2O), 262 (1s, H—C=), 514 cps (1d, broad, apparent J = 8.5 cps, NH).

Anal. Calcd for $C_9H_{17}NO_2$ (171.23): C, 63.13; H, 10.00; N, 8.18. Found: C, 62.97; H, 10.11; N, 8.28.

Ethyl 3-ethylamino-2-pentenoate (59%) had bp 113° (12 mm); λ_{max} 283 mμ (ε 18,900); pmr 65, 72 (overlapping triplets, CH_3CH_2O, CH_3CH_2NH, CH_3CH_2C=), 135 (2q, J = 7.5 cps, CH_3CH_2C=), 196 (2m, CH_3CH_2NH), 242 (2q, J = 7 cps, CH_3CH_2O), 264 (1s, H—C=), 510 cps (1 broad, NH).

Anal. Calcd for $C_9H_{17}NO_2$ (171.23): C, 63.13; H, 10.00; N, 8.18 Found: C, 62.82; H, 10.16; N, 8.15.

Nenitzescu Condensations. In a typical experiment a solution of 98.0 g (0.80 mole) of toluquinone and 100 g of ethyl 3-aminocrotonate[6] in 450 ml of acetone was heated at reflux temperature under nitrogen with magnetic stirring for 2.5 hr. The deep red solution was concentrated by distillation at ambient pressure, 175 ml of distillate being collected. The concentrate was stored in the refrigerator overnight, and the solid was collected by filtration and washed with ice-chilled ethanol to give 66.2 g of solid, mp 135–>165°. A 1.000-g sample of this material was subjected to partition chromatography on Celite[33,34] diatomaceous silica using a heptane–ethyl acetate–methanol–water (70:30:15:6) system. The fraction with peak hold-back volume (hbv) 3.1 (Vm/Vs 2.86) was evaporated, and the residue was recrystallized from acetone–hexane to give 254 mg of white crystals of **ethyl 5-hydroxy-2,6-dimethylindole-3-carboxylate** (IIIa). The fraction with peak hold-back volume 5.4 was treated in the same manner to give 220 mg of **ethyl 5-hydroxy-2,7-dimethylindole-3-carboxylate** (IVa). The characterization of these substances is given in Tables V and VI.

The fraction having peak hold-back volume 9.8 was evaporated, and the residue was recrystallized from acetone–hexane to give 134 mg (5%) of ethyl 3-amino-2-(2,5-dihydroxy-*p*-tolyl)crotonate (VII) as crystals, mp 186–188°; λ_{max} 285 mμ (ε 15,000); 2.98, 6.08, 6.24, 6.64, 7.88, and 8.35 μ; pmr 62 (3t, J = 7.5 cps, OCH_2CH_3), 97 (3s, vinyl CH_3), 122 (3s, low order coupling with adjacent ring

(30) Prepared by the Clemmensen reduction of 2,5-dihydroxyacetophenone: E. Clemmensen, *Ber.*, **47**, 56 (1914).

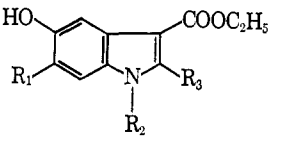
(31) H. P. Bayrac, *Bull. Soc. Chim. France*, **11**, 1130 (1894).

(32) H. G. H. Erdtman, *Proc. Roy. Soc.* (London), **A143**, 177 (1933).

(33) Celite is the trademark of Johns-Manville Co. for diatomaceous silica products.

(34) For a complete description of this technique (developed by C. Pidacks) see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, 20, 357 (1964).

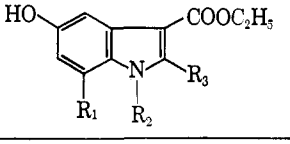
Table V. Ethyl 1,2,6-Trisubstituted 5-Hydroxyindole-3-carboxylates (III)



Compd	R_1	R_2	R_3	Chromatography: Solvent system[a]	Hbv	Vm/Vs	Mp, °C[b]	Formula	Analysis: Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Nitrogen Calcd	Nitrogen Found
a	CH_3	H	CH_3	HEMW (70:30:15:6)	3.1	2.86	228–229[c,d]	$C_{13}H_{15}NO_3$	66.93	66.50	6.48	6.73	6.01	6.16
b	CH_3	CH_3	CH_3				222–225[e]	$C_{14}H_{17}NO_3$	67.99	67.90	6.93	7.06	5.66	5.91
c	CH_3	C_2H_5	CH_3	HEMW (90:10:17:4)	3.2	2.62	200–201	$C_{15}H_{19}NO_3$	68.94	68.97	7.33	7.40	5.36	5.48
d	CH_3	C_3H_7	CH_3	HEDW (140:60:40:5)	2.5	3.07	193.5–195.0	$C_{16}H_{21}NO_3$	69.79	69.45	7.69	7.77	5.09	5.00
e	CH_3	C_4H_9	CH_3	HEM_1W (85:15:17:4)	2.5	2.71	174.0–176.5	$C_{17}H_{23}NO_3$	70.56	70.73	8.01	7.79	4.84	4.85
f	CH_3	*i*-C_3H_7	CH_3	HEM_1W (80:20:17:4)	1.4	3.08	201.5–203.0	$C_{16}H_{21}NO_3$	69.79	69.93	7.69	8.11	5.09	5.21
g	C_2H_5	H	CH_3	HEMW (70:30:17:4)	3.2	2.68	200–202	$C_{14}H_{17}NO_3$	67.99	68.18	6.93	6.98	5.66	5.34
h	C_2H_5	C_2H_5	CH_3	HM (1:1)	4.5	2.80	207–208	$C_{16}H_{21}NO_3$	69.79	69.37	7.69	7.66	5.09	5.00
i	CH_3	C_2H_5	C_2H_5	HEM_1W (80:20:17:4)	1.3	3.06	169.0–170.5	$C_{16}H_{21}NO_3$	69.79	69.54	7.69	7.61	5.09	5.34
j	CH_3O	H	CH_3	HEMW (70:30:15:6)	6.5	2.78	223.0–224.5[f,g]	$C_{13}H_{15}NO_4$						
k	CH_3O	C_2H_5	CH_3	HEMW (70:30:17:4)	3.0	2.72	141.5–142.0[h]	$C_{15}H_{19}NO_4$	64.96	64.63	6.91	6.82	5.05	4.96

[a] Solvents: H = heptane, E = ethyl acetate, M = methanol, W = water, M_1 = 2-methoxyethanol, D = dimethylformamide. [b] Except where noted otherwise, all compounds were recrystallized from acetone–hexane. [c] Reported in ref 4a: 220–221°. [d] Compounds IIIa–i had λ_{max} 214–219 mμ (ε 32,700–38,600), 242–246 (14,500–16,950), 295–296 (10,250–13,750); in addition to these maxima IIIa and IIIi had λ_{max} 263–265 mμ (ε 9150–10,500). Compounds IIIa–k had λ_{max} 3.00–3.10, 6.02–6.10, 8.30–8.46, 8.62–8.88, and 8.97–9.15 μ. [e] Separated from the 7 isomer by repeated crystallizations from alcohol and then acetone. [f] Reported in ref 4a: 220°. [g] Ultraviolet spectrum: 219 mμ (ε 30,500), 240 (sh, 12,100), 282 (10,700), 308 (sh, 8250), 321 (sh, 7000). [h] Ultraviolet spectrum: 218 mμ (ε 32,700), 238 (13,800), 288 (13,000), 300 (12,600).

Table VI. Ethyl 1,2,7-Trisubstituted 5-Hydroxyindole-3-carboxylates (IV)



Compd	R_1	R_2	R_3	Chromatography: Solvent system[a]	Hbv	Vm/Vs	Mp, °C[b]	Formula	Analysis: Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Nitrogen Calcd	Nitrogen Found
a	CH_3	H	CH_3	HEMW (70:30:15:6)	5.4	2.86	200–202[c]	$C_{13}H_{15}NO_3$	66.93	66.39	6.48	6.65	6.01	5.59
c	CH_3	C_2H_5	CH_3	HEMW (90:10:17:4)	6.3	2.62	192–193[d]	$C_{15}H_{19}NO_3$	68.94	69.38	7.33	7.56	5.36	5.21
e	CH_3	C_4H_9	CH_3	HEM_1W (85:15:17:4)	4.3	2.71	157–159	$C_{17}H_{23}NO_3$	70.56	70.76	8.01	7.81	4.84	5.01
h	C_2H_5	C_2H_5	CH_3	HEMW (80:20:17:4)	4.8	2.12	148–150	$C_{16}H_{21}NO_3$	69.79	69.72	7.69	7.81		
i	CH_3	C_2H_5	C_2H_5	HEM_1W (80:20:17:4)	2.1	3.06	172–174	$C_{16}H_{21}NO_3$	69.79	69.63	7.69	7.80	5.09	5.10

[a] Solvents: H = heptane, E = ethyl acetate, M = methanol, W = water, M_1 = 2-methoxyethanol. [b] All compounds were recrystallized from acetone–hexane; λ_{max} 3.04–3.05, 6.02–6.06, 6.20–6.23, 8.50–8.53, 8.69–8.72, and 8.90–9.00 μ. [c] Ultraviolet spectrum: 214 mμ (ε 29,800), 242 (19,300), 291 (10,200). [d] Compounds IVc–i had λ_{max} 219–220 mμ (ε 30,000–35,200), 243–245 (15,400–17,300), 292–294 (10,800–13,500).

proton, aryl CH_3), 235 (2q, J = 7.5 cps), 381 (1s), 388 (1s, low order coupling with ring methyl protons) (aryl protons), 468.5, 492 cps (1s each, O*H*, erased on exchange with methanol-d_4).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.27): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.18; H, 6.85; N, 5.30.

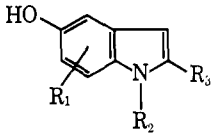
The above isolation procedure was that utilized in those condensations for which the results are recorded in Table I. In order to verify the isomer ratios III/IV obtained in this manner, condensations a and c were repeated using 10 mmoles of reactants, and the total reaction products were subjected to partition chromatography. From these experiments IIIa and IVa were obtained in 12 and 14% yield, respectively; whereas IIIc and IVc were isolated in 24 and 4.6% yield, respectively.

Decarbethoxylation of the Indole-3-carboxylic Esters. In a typical experiment 13.9 g (56.4 mmoles) of the mixture of 1,2,6- and 1,2,7-trimethylindole esters (IIIb and IVb) was suspended in 1 l. of 20% hydrochloric acid solution. This suspension was heated at reflux temperature under nitrogen and with mechanical stirring for 2.5 hr; all solid dissolved. The pH of the solution was adjusted to 5.5–6.5 by addition of a concentrated sodium hydroxide solution. The cooled mixture was extracted with methylene chloride, and the dried (magnesium sulfate) extracts were evaporated to give a residue that crystallized from methylene chloride–petroleum ether to furnish 9.8 g (100%) of crystals. A 5.00-g sample of this material was subjected to partition chromatography on Celite diatomaceous silica using a heptane–ethyl acetate–methanol–water (80:20:17:4) system. The fraction with peak hold-back volume 2.4 (Vm/Vs 3.12) was recrystallized from methylene chloride–petroleum ether to give in two crops, 3.233 g (65%), of **5-hydroxy-1,2,6-trimethylindole** (Vb) as white crystals. The fraction with peak hold-back volume 4.3 was evaporated, and the residue was recrystallized from acetone–hexane to give 1.429 g (29%) of **5-hydroxy-1,2,7-trimethylindole** (VIIb) as white needles.

Similarly 37.6 g (0.137 mole) of the mixed 1-propyl esters IIId and IVd gave a crude product which was dissolved in methylene chloride and passed through a Florisil[35] magnesia silica column. Crystallization of the material in the eluate from methylene chloride–petroleum ether gave 19.64 g of crystals, mp 125–128°, which was homogeneous. Concentration of the filtrate gave 4.42 g of solid, mp 108–120°, and then 1.78 g (93% total) of oil. Each of the last two fractions was subjected to partition chromatography, using a heptane–ethyl acetate–methanol–water system. For the solid fraction a 95:5:17:4 solvent ratio was used and the material in the fraction with peak hold-back volume 1.7 (Vm/Vs 2.78) was crystallized from methylene chloride–petroleum ether to give 2.932 g of **5-hydroxy-1-propyl-2,6-dimethylindole** (Vd) as white

(35) Florisil is the trademark of the Floridin Co. for a magnesia silica adsorbent.

Table VII. 5-Hydroxy-1,2,6(or 7)-trisubstituted Indoles



Compd	R_1	R_2	R_3	Yield, %	Mp, °C[a]	Formula	Analysis: Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Nitrogen Calcd	Nitrogen Found
Va	6-CH_3	H	CH_3	71	183–184[b,c]	$C_{10}H_{11}NO$	74.51	74.33	6.88	7.03	8.69	8.91
VIIa	7-CH_3	H	CH_3	62	145–147[d]	$C_{10}H_{11}NO$	74.51	74.95	6.88	6.97	8.69	8.80
Vb	6-CH_3	CH_3	CH_3	65[e]	130–132	$C_{11}H_{13}NO$	75.40	75.34	7.48	7.54	7.99	8.07
VIIb	7-CH_3	CH_3	CH_3	29[e]	133–135[b]	$C_{11}H_{13}NO$	75.40	75.77	7.48	7.41	7.99	7.99
Vd	6-CH_3	C_3H_7	CH_3	83[e]	127–128	$C_{13}H_{17}NO$	76.81	76.73	8.43	8.64	6.89	7.06
VIId	7-CH_3	C_3H_7	CH_3	4[e]	120–122	$C_{13}H_{17}NO$	76.81	76.59	8.43	8.31	6.89	6.74
Ve	6-CH_3	C_4H_9	CH_3	78[e]	74–75	$C_{14}H_{19}NO$	77.38	77.73	8.81	8.88	6.45	6.41
VIIe	7-CH_3	C_4H_9	CH_3	1.8[e]	112–113	$C_{14}H_{19}NO$	77.38	77.40	8.81	8.61	6.45	6.32
Vf	6-CH_3	i-C_3H_7	CH_3	84	94–95	$C_{13}H_{17}NO$	76.81	76.41	8.43	8.52	6.89	7.27
Vh	6-C_2H_5	C_2H_5	CH_3	97	81–82	$C_{13}H_{17}NO$	76.81	76.88	8.43	8.47	6.89	7.18
Vi	6-CH_3	C_2H_5	C_2H_5	58	88–90	$C_{13}H_{17}NO$	76.81	76.52	8.43	8.32	6.89	7.19

[a] Except where noted otherwise, all compounds were recrystallized from methylene chloride–petroleum ether (bp 30–60°); they had λ_{max} 3.00–3.15 μ and no significant absorption in the carbonyl region. [b] Recrystallized from acetone–hexane. [c] Ultraviolet spectra for series V: λ_{max} 209–210 mμ (ϵ 26,800–29,400), 278–280 (8460–9350), 295–298 (6910–7520), 308 (4470–5490); however, for Va: λ_{max} 207 mμ (ϵ 30,100), 275 (9180), 297 (7870), 308 (6180). [d] Ultraviolet spectra for series VII, except VIIa: λ_{max} 222–225 mμ (ϵ 24,700–24,900), 275–277 (8350–8400), 290–295 (5200–5700), 308 (3650–3850); for VIIa: λ_{max} 218 mμ (ϵ 37,400), 272 (8700), 290 (5480), 302 (3870). [e] Material obtained from decarbethoxylation of mixed isomeric esters; details of chromatographic separations are given in the Experimental Section.

crystals. The fraction with peak hold-back volume 3.3 was treated in the same manner to give 860 mg of **5-hydroxy-1-propyl-2,7-dimethylindole** (VIId). For the oily fraction a 90:10:17:4 solvent ratio was used; from the fraction with peak hold-back volume 2.3 (Vm/Vs 3.08) was isolated 510 mg of Vd, mp 123–127°, and from that fraction with peak hold-back volume 4.3 was isolated 150 mg of VIId, mp 120.0–121.5°.

The decarbethoxylation of the 1-butyl esters IIIe and IVe (40.7 g) gave 21.88 g of **1-butyl-5-hydroxy-2,6-dimethylindole** (Ve) by direct crystallization. Chromatography of the oil (4.11 g) in the mother liquor using a heptane–ethyl acetate–2-methoxyethanol–water (95:5:17:4) system gave in peak hold-back volume 3.4 (Vm/Vs 2.64) an additional 2.04 g of this isomer. The material in the fraction with peak hold-back volume 6.1 gave 496 mg of **1-butyl-5-hydroxy-2,7-dimethylindole** (VIIe).

The characterization of these substances is given in Table VII.

1-Ethyl-2,6-dimethyl-4,5-dioxoindole (VI).[36] A solution of 330 mg (1.74 mmoles) of 1-ethyl-5-hydroxy-2,6-dimethylindole[6] in 100 ml of acetone was added to a solution of 935 mg (3.48 mmoles) of potassium nitrosodisulfonate in 60 ml of 1/6 *M* potassium dihydrogen phosphate solution and 120 ml of water. The solution was stirred at room temperature for 45 min whereafter the product was isolated with methylene chloride and recrystallized from methylene chloride–petroleum ether to give 215 mg (61%) of black crystals, mp 145–150°; λ_{max} 242 mμ (ϵ 29,100), 355 (4060), and 475 (1420); 6.10, 6.22, and 6.64 μ.

Anal. Calcd for $C_{12}H_{13}NO_2$ (203.23): C, 70.91; H, 6.45; N, 6.89. Found: C, 70.98; H, 6.54; N, 6.72.

Ethyl 3-Ethylamino-2-(3-ethyl-2,5-dihydroxyphenyl)crotonate (VIII). The Nenitzescu condensation between ethylbenzoquinone (14.5 g, 0.11 mole) and ethyl 3-ethylaminocrotonate (17.3 g, 0.11 mole) was carried out in 60 ml of acetone as described above. After collection of the crude indoles IIIh and IVh, the filtrate was concentrated to about one-half volume and cooled at 0° for 6 days. Filtration gave 2.004 g of solid which was chromatographed on Celite diatomaceous silica using a heptane–ethyl acetate–methanol–water (80:20:17:4) system. The material in the fraction with peak hold-back volume 4.7 (Vm/Vs 2.12) was recrystallized from acetone–hexane to give 88 mg (0.3%) of crystals, mp 129.5–130.0°; λ_{max} 295 mμ (ϵ 22,300); 2.91, 2.94, 6.17, 6.40, 8.60, 9.50 μ; pmr 66, 71, 75 (overlapping triplets, 3 CH_2CH_3), 105 (3s, vinyl CH_3), 157 (2q, J = 7.5 cps, aryl CH_2CH_3), 198 (2m, $NHCH_2CH_3$), 244 (2q, J = 7.0 cps OCH_2CH_3), 311 (2, broad, O*H*, erased by methanol-d_4), 382, 396 (1d each, J = 3.0 cps aryl *H*), 575 cps (broad, N*H*, erased by methanol-d_4).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293.35): C, 65.51; H, 7.90; N, 4.78. Found: C, 65.87; H, 8.16; N, 4.98.

(36) Experiment by Mr. J. F. Poletto.

Ethyl *trans*-3-Amino-2-(5-methoxybenzoquinonyl)crotonate (IX). The Nenitzescu condensation between methoxybenzoquinone (2.712 g, 19.6 mmoles) and ethyl 3-aminocrotonate (2.712 g, 21.0 mmoles) was carried out in 75 ml of acetone to give 2.442 g of crude material that was chromatographed using a heptane–ethyl acetate–methanol–water (70:30:15:6) system. The material eluted at peak hold-back volume 4.0 (Vm/Vs = 2.78) was recrystallized from acetone–hexane to give 546 mg (10%) of red needles, mp 147–148°; λ_{max} 210 mμ (ϵ 11,100), 273 (16,400), 345 (1620), and 465 (1450); 2.92, 3.02, 6.04, 6.15, 6.27, 8.05, 8.40, 8.55, and 9.10 μ; pmr 63 (3t, J = 7.2 cps, CH_3CH_2), 113 (3s, vinyl CH_3), 227 (3s, CH_3O), 235 (2q, J = 7.2 cps, CH_3CH_2), 365, 388.5 (1s each, aryl *H*), 475 cps (2 broad, NH_2).

Anal. Calcd for $C_{13}H_{15}NO_5$ (265.26): C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 6.03; N, 5.14.

Conversion of Ethyl 3-Ethylamino-2-(2,5-dihydroxy-3-ethylphenyl)-crotonate (VIII) into Ethyl 1,7-Diethyl-5-hydroxy-2-methylindole-3-carboxylate (IVh). Crotonate VIII (2.2 mg) was dissolved in methylene chloride and a stream of hydrogen chloride was introduced briefly into the solution. The solvent was removed and the residue was treated with 48 mg (0.16 mmole) of VIII, 12 mg (0.1 mmole) of toluquinone, and 16 mg (0.1 mmole) of ethyl 3-ethylaminocrotonate in 5 ml of boiling acetone for 3 hr. The solvent was removed and the residue was subjected to partition chromatography on Celite diatomaceous silica using a heptane–ethyl acetate–methanol–water (90:10:17:4) system. The fraction eluted at peak hold-back volume 3.7 (Vm/Vs 3.3) was evaporated and the residue was recrystallized from acetone–hexane to give 3 mg of ethyl **1-ethyl-5-hydroxy-2,6-dimethylindole-3-carboxylate** (IIIc) as crystals, mp 197–199°.

The fraction eluted at peak hold-back volume 4.5 was evaporated to give 12 mg (26%) of crude indole ester IVh; this material was recrystallized from acetone–hexane to give 5 mg (12%) of IVh as crystals, mp 148–150°.

Conversion of Ethyl *trans*-3-Amino-2-(5-methoxybenzoquinonyl)-crotonate (IX) into Ethyl 5-Hydroxy-6-methoxy-2-methylindole-3-carboxylate (IIIj). A solution of 38 mg (0.2 mmole) of *p*-toluenesulfonic acid monohydrate in benzene was azeotropically distilled; additional benzene was added to the residue and removed (two times). The residue was dissolved in 5 ml of acetone and 53 mg (0.2 mmole) of ethyl *trans*-3-amino-2-(5-methoxybenzoquinonyl)-crotonate (IX) was added. The resulting solution was then treated with 0.05 ml of a solution of 7.3 mg (0.07 mmole) of triethylamine in 0.1 ml of acetone. Thin layer chromatography (tlc) of an aliquot in a benzene–acetone–water (2:1:2) system revealed a nonmobile spot, whereas adduct IX was mobile in this system. At various time intervals an aliquot (~0.3–0.5 ml) was withdrawn, treated with an aqueous sodium hydrosulfite solution, and extracted with methylene chloride. The dried extract was evaporated, and the

residue was examined *via* tlc; after 1 hr a substance with the same mobility as indole ester IIIj was observed. After a total reaction time of 5 hr, the reaction was treated in the above manner; the material thus obtained was recrystallized from acetone–hexane to give 11 mg (22%) of IIIj as white crystals, mp 225–226°. The identity of this material was established by the usual criteria.

Conversion of Ethyl *trans*-3-Amino-2-(2,5-dihydroxy-*p*-tolyl)-crotonate (VII) into Ethyl 5-Hydroxy-2,6-dimethylindole-3-carboxylate (IIIa). A solution of 100 mg of VII in methylene chloride was treated briefly with hydrogen chloride; amorphous material separated. The solvent was removed and a solution of 500 mg (2.56 mmoles total) of VII in methanol was added; this solution was heated under reflux for 5 hr. The cooled solution was treated with 312 mg (2.56 mmoles) of toluquinone; this resulted in immediate generation of a red color. Thin layer chromatography showed two major components, neither having the mobility of the starting materials. After 5 days at room temperature IIIa could not be detected by tlc. The solution was treated with a sodium hydrosulfite solution until the red color was discharged, and the resulting mixture was extracted with methylene chloride. The dried extracts were evaporated, and the residue was recrystallized from acetone–hexane to give 313 mg (52%) of IIIa, mp 222–225°.

In a subsequent experiment the equilibration solution from 600 mg (2.56 mmoles) of VII was treated with 31 mg (0.25 mmole) of toluquinone. The resulting red solution was heated under reflux for 90 min, after which the solvent was removed. The residue was recrystallized from acetone–hexane to give 102 mg (17%) of VII, mp 182–184°. The filtrate was evaporated, and the residue was chromatographed on silica gel. The material eluted with ether was recrystallized from acetone–hexane to give 252 mg (55% based on unrecovered VII) of crystals, mp 215–217°. An additional recrystallization gave 207 mg of IIIa as white crystals, mp 225–227°.

Ethyl *trans*-3-Isopropylamino-2-(2,5-dihydroxy-*m*-tolyl)crotonate (XI). The condensation between toluquinone (6.11 g, 0.05 mole) and ethyl 3-isopropylaminocrotonate (8.56 g, 0.05 mole) was effected in boiling acetone. The cherry red solution was treated with an excess of a sodium hydrosulfite solution, whereupon the red color was discharged. The resulting mixture was distributed between ethyl acetate and water. The dried organic solution was evaporated, and the residue was triturated with ether to give 2.51 g (18%) of **ethyl 5-hydroxy-1-isopropyl-2,6-dimethylindole-3-carboxylate** (IIIf) as white crystals, mp 202.0–203.5°. The ethereal filtrate was chilled in the refrigerator for 3 days to give 2.60 g (18%) of white crystals, mp 140–143° after recrystallization from acetone–hexane; λ_{max} 298 mμ (ε 22,300); 2.93, 6.16, 6.40, 7.75–7.95, 8.09, 8.24, and 12.64 μ; pmr 65 (3t, J = 7.5 cps), 73.5 (6d, J = 7 cps, $CH(CH_3)_2$), 105 (3s, $=C-CH_3$), 136 (3s, aryl CH_3), 210–258 (3m, OCH_2CH_3 and $CH(CH_3)_2$), 315 (2 broad, O*H*, erased by methanol-d_4), 380, 394 (1d each, J = 2 cps, aryl *H*), 580 cps (1d, J = 9.0 cps, N*H*, erased by methanol-d_4).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293.25): C, 65.51; H, 7.90; N, 4.78. Found: C, 65.65; H, 8.08; N, 5.01.

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Reactions of Phosphinates. The Acid-Catalyzed and Acid-Inhibited Hydrolysis of *p*-Nitrophenyl Diphenylphosphinate

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Abstract: The rates of hydrolysis of *p*-nitrophenyl diphenylphosphinate have been studied in acidic dioxane–water (40:60, v/v). Oxygen-18 studies show that hydrolysis occurs by cleavage of the P–O bond. The dependence of rate on acid concentration passes through a maximum at ~1.5 *M* $HClO_4$. The observed data give a w value (Bunnett) of 12 although ΔS^* is only −27 eu. Measurement of the basicity of dimethylphosphinic acid (pK_a = −4.0) and methyl diphenylphosphinate (pK_a = −4.8) has shown that phosphinates have very different protonation behavior compared to Hammett bases, and it is clear that very little of the substrate is protonated at the acidity giving a maximum rate of hydrolysis. The observed maximum rate at ~1.5 *M* acid then is not due to extensive protonation of substrate as is true for carboxylic amides nor is it due to solvation effects alone as the Bunnett hypothesis would suggest. Rather, it is primarily due to large changes in activity coefficients with increased acidity, although solvation of the transition state seems to be of some importance in the cause of this phenomenon.

There have been relatively few detailed studies of displacement at phosphorus under acidic conditions.[1] Hudson and Keay studied a variety of phosphonates in aqueous 1 *N* benzenesulfonic acid[2] with results indicating displacement at carbon in alkyl esters and displacement at phosphorus in aryl esters. Dibenzyl phosphate was studied in mildly acidic solution and presumably hydrolyzes by an acid-catalyzed mechanism involving cleavage of the carbon–oxygen band.[3] Oxygen-18 studies and kinetic data indicate that the acid-catalyzed hydrolysis of dimethyl phosphate[4–6] proceeds with complete[4] or nearly complete[6] attack at carbon. A similar analysis of oxygen-18 and kinetic results for monomethyl phosphate[7] is complicated by the rapid hydrolysis of the monoanion. The rates of hydrolysis of both dimethyl phosphate[6] and monomethyl phosphate[7] show linear dependence on acid concentration at constant ionic strength. The rate of

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