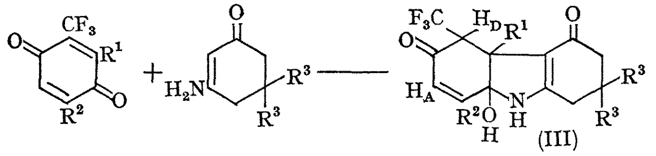
Observations on the Mechanism of the Nenitzescu Indole Synthesis

By R. LITTELL, G. O. MORTON, and G. R. ALLEN, JUN.*

(*Process and Preparations Research Section* and Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York,* 10965)

Summary Compounds derived from initial nitrogen–carbon condensation of an enamine and a 1,4-benzoquinone are not true intermediates in the Nenitzescu indole synthesis; such substances are converted into indoles only after transformation into intermediates arising from carbon–carbon condensation.

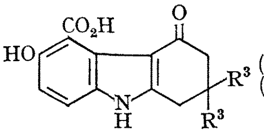
Two mechanisms, differing in the order of the required nitrogen–carbon and carbon–carbon condensations have been proposed for the Nenitzescu indole synthesis, a procedure wherein an alkyl 3-aminocrotonate condenses with a 1,4-benzoquinone.[1] The validity of that mechanism involving initial carbon–carbon condensation was demonstrated independently by two groups,[2,3] but the available evidence did not permit a conclusion with respect to the alternative mechanism.[4] Evidence precluding the latter mechanism is presented here.



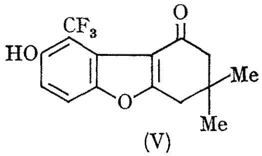
(Ia) $R^1=R^2=H$
(Ib) $R^1=R^2=D$
(Ic) $R^1=H$, $R^2=Cl$

(IIa) $R^3=Me$
(IIb) $R^3=H$

	R^1	R^2	R^3
a;	H_c	H_b	Me
b;	D	D	Me
c;	H_c	Cl	Me
d;	H_c	H_B	H

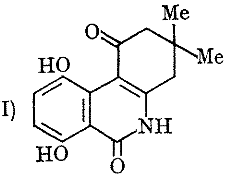


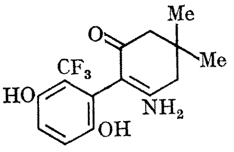
(IVa) $R^3=Me$
(IVb) $R^3=H$



(V)

(VI)





(VII)

Trifluoromethyl-1,4-benzoquinones (Ia—c) reacted with enamine (IIa) in acetic acid at 40—45° (15—45 min.) to give 35—43% of carbinolamines (IIIa—c)† (m.p. 237—240° decomp., 243—245° decomp., 232—234° decomp., respectively). Similarly, quinone (Ia) reacted with enamine (IIb) in boiling ethanol (4 hr.) to furnish 55% of carbinolamine (IIId),† m.p. 215° decomp., rather than the 5-hydroxyindole derivative which is usually formed in this medium. The structures of (IIIa—d) are predicted on their n.m.r. spectra and appropriate decoupling experiments, from which the following coupling constants were deduced: $J_{H_D\text{-}CF_3} = 9{\cdot}2$ Hz; $J_{H_AH_B} = 10{\cdot}0$ Hz; $J_{H_CH_D} = 3{\cdot}0$ Hz; $J_{H_AH_D} = 2{\cdot}0$ Hz; $J_{H_BH_C} = 1{\cdot}0$ Hz. Carbinolamines (III) formally represent intermediates arising from initial nitrogen–carbon condensation of (II) onto (I), and their isolation made possible an examination of the validity of the second mechanism.[4]

Interaction of quinone (Ia) with (II) in boiling acetic acid (4—16 hr.) gave 23—25% of the carbazolecarboxylic acids (IVa),† m.p. 262—264° decomp. and (IVb), m.p. 260° decomp. The intermediacy of (III) in these preparations was suggested by the conversion of (IIIa) and (IIId) into (IV) on treatment with 0·1 equiv. of (Ia) under similar conditions.

Three possible routes for the latter conversions are apparent: (1) acid-catalysed dehydration of (III) to (IV); (2) dehydrogenation of (III) by quinone (Ia) to afford the dieneone precursor of a quinonimine, reduction of which yields an indole derivative;[2,3] and (3) fragmentation of (III) into quinone (Ia) and enamine (II), the alternative combination of which gives (IV). However, treatment of (IIIa) with boiling acetic acid [16 hr., no (Ia)] gave 23% of (V), m.p. 194—197°, and 37% of (VI),† m.p. 295—300° decomp., as the only products. Attempted dehydrogenation of (IIIa) with one equiv. of (Ia) was ineffective. Finally, reaction of (IIIb) with 0·18 equiv. of (Ia) in acetic acid (16 hr.) gave (^{2}H-IVa), the n.m.r. spectrum of which indicated the absence of (IVa). The presence of this last substance would be expected had route (3) intervened, for in this circumstance quinones (Ia) and (Ib) would be available for reaction with enamine (IIa).

These results eliminate the above delineated processes from consideration and suggest the dominant reaction of (IIIa) in acid to be protonation of the C-terminal of the enamine triad.[5] In accord with this concept, brief (5 min.) treatment of (IIIa) with acetic acid gave 85% of hydroquinone (VII),† m.p. 264—266° decomp., the intermediate formally derived from initial carbon–carbon condensation of enamine (IIa) onto quinone (Ia). Reaction of (VII) with a limited quantity of (Ia) in boiling acetic acid then afforded carbazolecarboxylic acid (IVa).

In view of these results we conclude that compounds derived from initial nitrogen–carbon condensation of an enamine and a quinone are not true intermediates in the Nenitzescu procedure, and that such substances are converted into indole derivatives only after their transformation into intermediates arising from carbon–carbon condensation.

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† Satisfactory analytical and spectral data were obtained for all new compounds.

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