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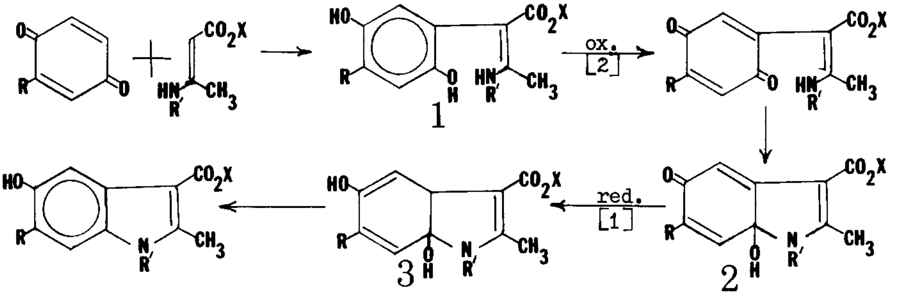
STUDIES ON THE NENITZESCU SYNTHESIS OF 5-HYDROXYINDOLES

James B. Patrick* and Elizabeth K. Saunders[1]
John Baker Daffin Laboratory of Chemistry,
Mary Baldwin College,
Staunton, Virginia 24401

Summary: The efficiency and convenience of the title synthesis are significantly enhanced by using methyl β-aminocrotonates in nitromethane as a reaction medium. A bimolecular face-to-face electron transfer complex is a key intermediate in the mechanism of this reaction.

Since its discovery 50 years ago[2] the Nenitzescu synthesis of 5-hydroxyindoles has come to be generally recognized as an interesting and complex example of Michael addition of an enamine, followed by several steps, including an internal oxidation-reduction[3] (Eq. 1).



Eq. 1

The ease with which rather complicated 5-hydroxyindoles, often having physiological importance, can be made from simple, accessible starting materials has made the reaction an attractive one, but yields are often poor, as could be expected from such an elaborate mechanism with its numerous possibilities for side reactions.

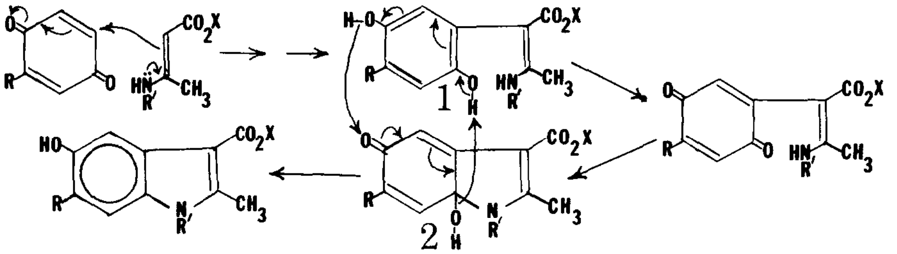
We now report two alterations in the procedure for the Nenitzescu reaction which together enable it to be carried out with much greater ease and convenience and give substantially higher yields. We further propose a modification of the accepted mechanism which accounts for these improvements.

If nitromethane is used as the reaction medium, the Nenitzescu reaction proceeds spontaneously at room temperature, and in almost all cases the product crystallizes directly from the reaction mixture. Table I (column 3) shows that yields by this method are often less than the best previously reported, but become relatively better as the number and size of substituents increases. The time saved and the convenience of conducting the reaction this way can sometimes compensate for the lower yields, however.

If methyl esters of β-amino- or alkylaminocrotonic acid are used instead of the more usual ethyl esters, a remarkable increase in yield generally results (Table I, column 5). To our knowledge, this simple expedient has not previously been tried in the half-century that the Nenitzescu reaction has been known.

The following is a representative procedure: Toluquinone (1.22 g; 10 mmol) in nitromethane (10 ml) was added all at once to methyl 3-isopropylaminocrotonate[4] (1.69 g; 10 mmol) in nitromethane (10 ml) at room temperature. The solution immediately turned dark red and became warm. After standing 24 hours at room temperature the mixture was filtered and the crystals washed with fresh nitromethane and dried, yielding 2.15 g (82 %) of methyl 2,6-dimethyl-5-hydroxy-1-isopropylindole-3-carboxylate as tan crystals, m.p. 198-199°.A single recrystallization from ethyl acetate gave white crystals, m.p. 201-202°.By way of contrast, the corresponding ethyl ester has been prepared in only 18% yield by refluxing the reactants in acetone for 2.5 hours under nitrogen[4].

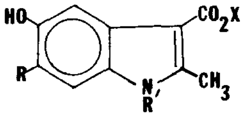
Although the Table shows a few exceptions, there seems to be a general trend whereby the yield is depressed as the size of either the 6-substituent or the alkyl moiety of the ester increases. Equation 1 does not show any obvious way by which the alkyl group of the ester can interact with 6-substituent, yet the data strongly suggest such an interaction. We propose a modification of the mechanism in which the oxidation-reduction step is mediated by a bimolecular face-to-face electron transfer complex analogous to a quinhydrone (Eq. 2).



The formation of such face-to-face "sandwich" complexes is known to be highly sensitive to the steric requirements of the two components. The intense blood-red color that invariably characterizes Nenitzescu reaction mixtures also accords well with the formation of an electron transfer complex. Furthermore, the readiness with which the reaction takes place in nitromethane is easily explicable in view of the greater electron density of the bimolecular intermediate compared to the electron densities of the starting materials. Solvents of high dielectric constant tend to promote reactions which involve relatively electron-dense intermediates, and nitromethane has an exceptionally high dielectric constant compared to the more usual solvents in which the Nenitzescu reaction has been carried out.

However, studies of the Nenitzescu reaction in nitroethane, 2-nitropropane, and in various mixtures of formamide and acetic acid indicate that the role of the solvent is more complex than the dielectric constant alone would suggest. None of these latter solvents gave results as good as those obtained with nitromethane, although all are comparable

TABLE I



R	R'	% Yield X = C_2H_5 (CH_3NO_2)	% Yield (Best Previous Lit.)[3] X = C_2H_5	% Yield X = CH_3 (CH_3NO_2)	% Yield X = t-Bu (CH_3NO_2)
H	H	23	22-59	82	--
H	methyl	25	32-60	73	38
H	ethyl	49	75	63	--
H	n-propyl	50	--	85	--
H	i-propyl	5	27-30	95	--
H	n-butyl	33	27-30	93	--
H	benzyl	57	22-58	72	--
H	phenyl	28	27-53	80	--
methyl	H	0	9-12[a]; 6-14[b]	38[c]	--
methyl	methyl	24[c]	22[a]; 10[b]	99[c]	1.0
methyl	ethyl	20[c]	24[a]; 5[b]	50[c]	--
methyl	n-propyl	24	21	75	--
methyl	i-propyl	0	18	82	--
methyl	n-butyl	22	18-23	13	--
methyl	benzyl	38	25	20	--
methyl	phenyl	14	--	0	--
prenyl[d]	H	0	--	39	--
prenyl	methyl	60	--	70	0
prenyl	ethyl	45	--	53	--

a. 6-substituted isomer

b. 7-substituted isomer

c. combined 6- and 7-substituted isomers

d. 3'-methylbut-2'-enyl

dielectrics. Likewise, the acidity of the solvent (nitromethane has a pK_a of 10.2, close to that of phenol) does not correlate in any obvious fashion with the rate or yield of the Nenitzescu reaction. We also considered the possibility that the readiness of the product indoles to crystallize from the reaction mixture might be a key factor in the usefulness of nitromethane. If that were the case, seeding of the reaction mixtures in advance should probably have produced improvements in yield[5], but no effect could be observed.

In retrospect one can see that the oxidation-reduction step in Equation 1 must, in fact, imply the existance of an electron transfer intermediate, although such an intermediate has not been explicitly postulated before. Not only does our modified formulation now clarify some of the steric effects in the Nenitzescu reaction, but it also leads to the conclusion that intermediate 3 in Equation 1 is unnecessary and presumably has no independent existance.

Further research on solvent effects in the Nenitzescu reaction and studies to establish the nature and orientation of the bimolecular intermediate more precisely are in progress.

References

1. This communication is taken in part from the baccalaureate thesis of E.K.S., Mary Baldwin College, 1979. Presented at the 30th Southeastern Regional Meeting, American Chemical Society in Savannah, Georgia, November 8-10, 1978.
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