Imine–Enamine Adducts From Hydrazine Addition to Dimethyl Acetylenedicarboxylate

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Summary Hydrazines, in contrast to amines, yield mainly imine tautomers on addition to dimethyl acetylenedicarboxylate.

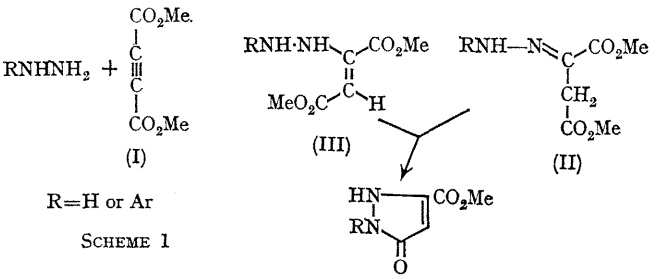
AMINE additions to dimethyl acetylenedicarboxylate have been the object of intensive synthetic[1] and mechanistic[2] investigation. In all cases, the adducts of primary amines to dimethyl acetylenedicarboxylate (I) have been characterised as the fumarate enamines, and no evidence has been reported for the other theoretically possible tautomer, the imine.

We report that imine isomers (II) can be obtained from hydrazine and arylhydrazines treated with (I) and that these tautomers are of greater stability than the corresponding enamines (III). The reaction of hydrazine and acetylene esters constitutes a ready synthesis of 3-substituted pyrazolin-5-ones.[3] No non-cyclized 1:1 intermediates from the combination of N_2H_4 and acetylene esters have been reported, although mechanistic expectations would be that N*H* to alkyne addition precedes the cycle-forming alkoxide displacement step (Scheme 1).

Below −30° we have obtained crystalline imine (hydrazone) products from the condensation of hydrazine and dimethyl or diethyl acetylenedicarboxylate. In solution or in solid state, these hydrazones undergo ring-closure to the pyrazolinones. No fumarate enamine from hydrazine is generated in the direct addition process, but this isomer can be obtained in 46% yield by cautious treatment of the imine with NaOMe in dioxan. The enamine was a highly labile isomer and could not be recrystallised or melted without cyclisation to 3-methoxycarbonylpyrazolin-5-one. An n.m.r. spectrum [$(CD_3)_2SO$] revealed a vinyl resonance at δ 5·97 p.p.m., two ester methoxy-groups at δ 3·59 and 3·81, and a broad, exchangeable N*H*–NH_2 signal at δ 9·6 p.p.m.

Since both imine and enamine derived from hydrazine itself were unstable, more detailed studies were carried out on the phenylhydrazine adducts of (I). Both enamine and imine were isolated from arylhydrazines (see Table) and, could be characterised by the distinctive methylene resonance at δ 3·72 ± 0·24 p.p.m. in imines and the vinyl absorption at 5·40 ± 0·54 p.p.m. for enamines [$(CD_3)_2SO$].

A non-cyclic adduct of undefined structure has been reported from the reaction of phenylhydrazine and diethyl acetylenedicarboxylate which yields 3-ethoxycarbonyl-1-phenylpyrazolin-5-one on thermal treatment.[4] In MeOH at room temperature, reaction of phenylhydrazine with (I) produces an imine–enamine mixture in 3·8:1 ratio. Both species could be obtained by fractional crystallisation (enamine is less soluble in MeOH and imine is less soluble isomer in benzene), but on prolonged standing in MeOH, Me_2SO, or Et_2O the enamine is converted slowly into the more stable imine. Although enamine–imine isomerisation is spontaneous, it is not sufficiently rapid to explain the extensive, and in some cases exclusive, production of the imine isomer in the direct combination experiments. Thus, while it is tempting to rationalise imine formation as a post-reaction isomerisation of an initially formed enamine, this interpretation is not in accord with the facts.

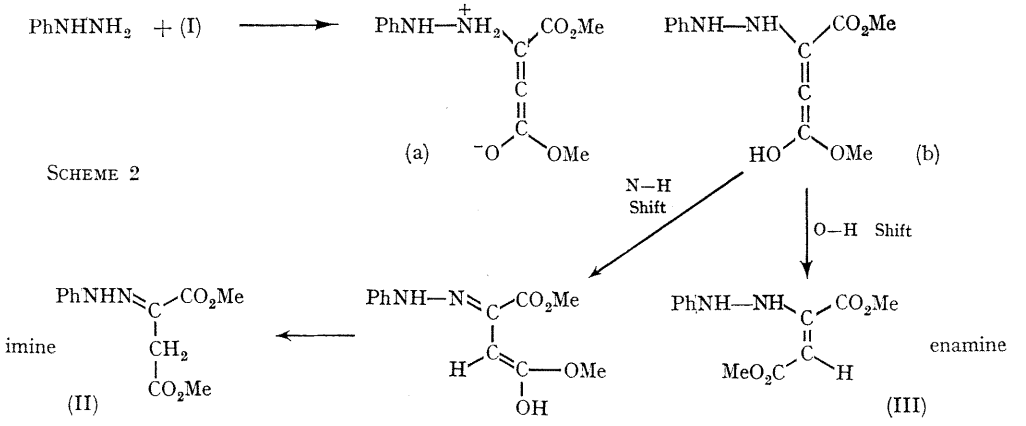


SCHEME 1

TABLE

Reactants	Conditions[a]	Imine : enamine	% Yield imine + enamine	Adduct m.p.[b]
N_2H_4 + (I)	25° in EtOH	All imine	40	98—99° (imine)
N_2H_4 + (I)	−40° in MeOH	All imine	54	
N_2H_4 + DEADC[c]	−40° in MeOH	All imine	52	93—94° (imine)
$PhNHNH_2$ + (I)	25° in MeOH	3·8 : 1	95	118—119° (imine) 149—150° (enamine)
$PhNHNH_2$ + I)	0° in ether	All imine	84	
$PhNHNH_2$ + (I)	−40° in MeOH	4 : 1	63	
$PhMeNNH_2$ + (I)	25° in MeOH	0·54 : 1[d]	100	67—68·5° (imine)
$PhMeNNH_2$ + (I)	−40° in MeOH	All imine	22	
2,4-DNPH + (I)	25° in 1 : 1, MeOH : Me_2SO	All imine	53	157—158·5° (imine)

[a] Satisfactory analyses were obtained for all new compounds.
[b] Reactions were carried out by combination of equimolar quantities (0·02 mole) of reactants in 75—100 ml. of the indicated solvent. Product was isolated after 5 min. with the exception of 2,4-DNPH (*i.e.*, 2,4-dinitrophenylhydrazine) which reacted more slowly with (I) and was allowed 1·5 hr. In addition to the stated yields of "adducts," remaining material was either the corresponding pyrazolinone or unreacted components.
[c] Diethyl acetylenedicarboxylate.
[d] Enamine could be detected by n.m.r. assay of the crude reaction product but could not be isolated in analytically pure form.



SCHEME 2

An alternative explanation is shown in Scheme 2. The zwitterionic intermediate (a) suggested[2,5] for amine–acetylene additions would collapse to (b), either by intramolecular prototropic shift [or intermolecular shift from another molecule of (a)] in aprotic solvents, or by intermolecular transfer in alcoholic solvents. The relative proportions of enamine and imine would then depend on the relative rates of proton tautomerism from OH and NH, respectively. Such a kinetic effect would be highly dependent on temperature, solvent, and reactant structure.

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