Imine–Enamine Tautomers from Hydrazine and Aryl Hydrazine Additions to Acetylenedicarboxylate

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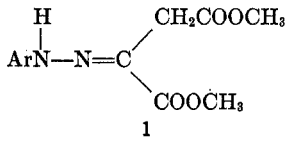
Aryl hydrazine and hydrazine react with dimethyl acetylenedicarboxylate to yield 1:1 adducts which exist as imine–enamine tautomers. Both isomers appear to arise directly from the condensation of the coreactants, since in most cases the more stable imine isomer predominates in the product mixture; but postreaction isomerization, while easily demonstrable, is not sufficiently rapid to explain the isomer balance observed in the direct reaction. These adducts serve as intermediates in the condensation of hydrazines and dimethyl acetylenedicarboxylate to yield 3-carbomethoxy-5-pyrazolinones.

Although hydrazones and aryl hydrazones are theoretically capable of existing in tautomeric equilibria with an enehydrazine (enamine) isomer, no valid evidence for the latter has been reported in simple systems.[1] Indeed, thorough efforts to detect the



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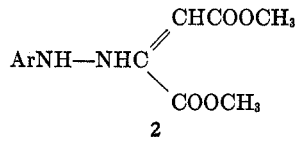
hydrazone or imine



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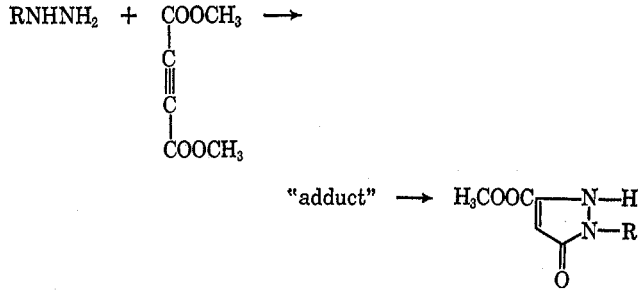
enehydrazine or enamine

enehydrazine species by Raman[2] and nmr spectroscopy[3] have been unsuccessful, and so have labeling experiments.[4] Molecular orbital–linear combinations of atomic orbitals calculations have indicated that the normal aryl hydrazone tautomer possesses π–p–π conjugation, which should provide extensive stabilization relative to the enehydrazine species.[2,5]

Previous studies in our laboratories[6-8] and at the hands of others[9-11] have established that the addition of primary amines to acetylene esters constitutes a facile synthesis of enamines, which nmr spectra have shown to be free of imine tautomer. It would therefore appear that the analogous addition of hydrazines to dimethyl acetylenedicarboxylate might afford the hitherto unreported enehydrazines.

This reaction of hydrazines and acetylenedicarboxylate is a well-established synthesis of 3-carbomethoxy-5-pyrazolinones;[12] and, especially in the case of hydrazine itself, no noncyclized 1:1 adducts have been characterized. Stable, open-chain isomers, of undefined structure, have been isolated from the addition of phenylhydrazine to dimethyl[13] and diethyl acetylenedicarboxylate,[14] and, upon heating, these do experience ring closure to 1-phenyl-3-carboalkoxypyrazolin-5-ones.[14]



We have examined the products of the addition of phenylhydrazine, *p*-tolylhydrazine, *p*-chlorophenylhydrazine, 2,4-dinitrophenylhydrazine, 1-methyl-1-phenylhydrazine, and hydrazine to dimethyl acetylenedicarboxylate (**3**). Somewhat surprisingly, the major product of most of the additions was clearly the imine tautomer (*i.e.*, the normal hydrazone), although enamine isomers were detected in several cases (see Table I).

Although the enehydrazines (enamines) were exceedingly labile isomers, undergoing thermal cyclization to pyrazolinones and, in several cases, spontaneous transformation in solution or solid state to the hydrazones, they nevertheless were capable of isolation and spectral characterization. Nmr spectroscopy was the most applicable tool in distinguishing the tautomeric possibilities. The normal hydrazones possessed a characteristic methylene resonance at δ 3.72 ± 0.24 and the enehydrazines displayed a single vinyl absorption at δ 5.40 ± 0.54 (in DMSO-d_6). It is interesting that Huisgen has reported the vinyl resonance in anilinofumarates (arising from the addition of anilines to dimethyl acetylenedicarboxylate) at δ 5.40, and, by analogy to the results with aryl amines, these enehydrazines probably exist as the fumarate isomer.[10]

The reaction of an alcoholic solution of hydrazine hydrate with dimethyl acetylenedicarboxylate at ambient temperatures is exothermic and produces a mixture of 40% dimethyl oxalacetate hydrazone and 60% 3-carbomethoxy-5-pyrazolinone by nmr product assay after 5 min of contact. If the mixture is allowed to

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TABLE I

$$RNHN{=}C(COOMe)CH_2COOMe \rightleftarrows RNHNHC^{-}(COOMe){-}CHCOOMe$$

Registry no.	Hydrazine	Concn[a]	Temp, °C	Im/En[b]	Adduct yield, %	Mp, °C	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
	$PhNHNH_2$	0.01 (EtOH)	−40	4:1	64	118–119 (Im)	57.59	5.64	11.19	57.83	5.70	11.41
						149–150 (En)	57.59	5.64	11.19	57.56	5.93	11.18
	$PhNHNH_2$	0.01 (Et_2O)	0	Imine	84							
	$PhNHNH_2$	0.02	25	3.8:1	95[c]							
22158-24-3	N_2H_4	0.02	−40	Imine	54	98–99	41.38	5.79		41.67	5.69	
	N_2H_4	0.02	25	Imine	40[c]							
22158-25-4	4-$ClPhNHNH_2$	0.01	−40	Imine	39	121–122	50.63	4.60	9.84	50.54	4.25	9.79
22158-26-5	4-$MePhNHNH_2$	0.01	25	Enamine	37[c]	144–145	59.08	6.10	10.60	59.19	6.18	10.89
22158-27-6 (imine)	$Ph(Me)NNH_2$	0.01	25	1:3	100[c]							
22158-28-7 (enamine)	$Ph(Me)NNH_2$	0.01	−40	Enamine	22	67–68.5	59.08	6.10	10.60	59.33	6.11	10.42
6745-50-2	2,4-DNPH	0.004 (1:1 DMSO–MeOH)	25	Imine	53	157–158.5	42.36	3.55	16.47	42.60	3.78	16.22

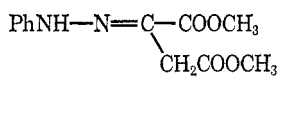
[a] Concentration in moles of hydrazine and dimethyl acetylenedicarboxylate combined in 20 ml of methanol at indicated temperature. Exceptions to use of methanol as solvent are indicated. Product isolated after 15–30 min, with the exception of 2,4-DNPH which was allowed a 1.5-hr reaction time. [b] Imine/enamine ratio determined by nmr on isolated product. [c] Nmr assay of the crude reaction material was performed to obtain isomer balance, and differences between adduct yield reported and 100% were observed to be pyrazolinone.

stand in methanol at room temperature for 2 hr, a quantitative conversion into the pyrazolinone occurs. If the same reaction is carried out at −40° in a Dry Ice–acetone bath, the intermediate hydrazone precipitates directly in 54% yield and can be isolated in analytical purity. Even the crystalline solid stored in a sealed vial ring closed completely in 3 months.

The hydrazone is sufficiently stable in aprotic solvents such as dioxane, chloroform, and dimethyl sulfoxide for spectral examination, but even here it does undergo slow ring closure over a 3-day period. The nmr spectrum in $CDCl_3$ displays a characteristic methylene singlet at δ 3.50 and no vinyl absorptions. If, however, a dioxane solution of this imine tautomer is treated with a catalytic amount, less than 1×10^{-3} g of NaOMe / 0.1 g of imine, and allowed to react at 0° for 3 days, a 46% isomerization to dimethyl hydrazinofumarate ensues. This enehydrazine isomer is the less soluble form in dioxane and can be isolated in analytical purity by filtration. It too is very labile toward pyrazolinone formation and cannot be warmed or melted without cycle generation. An nmr spectrum can be obtained (DMSO-d_6) which reveals a vinyl resonance at δ 5.97 and the complete absence of the initial methylene signal.

The direct formation of imine isomer by condensation of hydrazine and **3** constitutes a unique observation in light of the expectation that NH to alkyne addition should initially yield enehydrazine tautomers. Moreover, since the enehydrazine itself could not be clearly demonstrated to be an intermediate in imine formation, being converted instead into 3-carbomethoxy-5-pyrazolinone, a second mechanistic hypothesis was tested. It might be reasoned that the water present in the hydrazine hydrate converted **3** into oxalacetic acid ester and the latter underwent normal hydrazone formation. However, it could be established that authentic oxalacetic ester did not undergo hydrazone formation at −40°, nor did dimethyl acetylenedicarboxylate undergo hydration under these conditions.

A tautomeric system more amenable to investigation arises from the aryl hydrazine condensation with **3**. The adducts resulting in this case are considerably more stable toward cycle formation and can be isolated in discrete tautomeric forms directly from the reaction mixture. The enamine is the less soluble isomer in methanol and the imine is the less soluble form in benzene.



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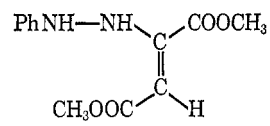

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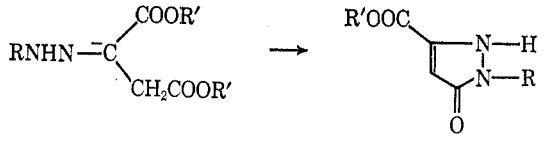
Both infrared and nmr spectra provide a clear distinction between the isomers. In particular, the methylene resonance of **5** appears as a sharp singlet at δ 3.72 while the vinyl proton in **6** occurs at δ 4.84. In the infrared, **5** shows carbonyl absorptions at 1745 and 1735 cm^{-1}, presumably due to the nonbonded and bonded species of the nonconjugated ester carbonyl, and at 1710 cm^{-1} for the conjugated C=O. The enamine tautomer, **6**, shows only two carbonyls at 1735 and 1675 cm^{-1}.

The results in Table I summarize the product distributions obtained from phenylhydrazine additions to **3**. The adducts, either imine or enamine, precipitated from the reaction mixture in the concentration ranges employed; and in those instances in which the mother liquors were assayed by nmr, the corresponding pyrazolinone was invariably detected. The enamine isomer was considerably less stable than the imine in both protonic and aprotic solvents. However, the spontaneous, uncatalyzed isomerization of enamine to imine was slow even in methanol. To effect complete transformation of enamine to imine, 45 min of reflux in methanol was required.

Catalytic quantities of acid accelerated the isomerization rate, but equimolar quantities brought about cyclization. Furthermore, neither excess phenylhydrazine alone, nor dimethyl acetylenedicarboxylate alone, nor mixtures of phenylhydrazine and dimethyl acetylenedicarboxylate caused the rate of enamine–imine interconversion to accelerate. Since substantial or exclusive amounts of imine tautomer were present even after the shortest possible contact times for phenylhydrazine and **3**, and since the enamine–imine

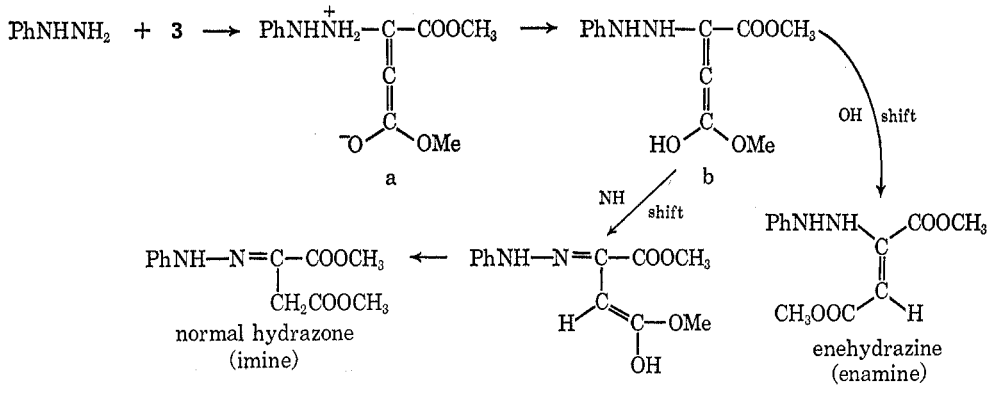
TABLE II



Registry no.	R	R′	Method[a]	Yield, %	Mp, °C	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
	H	CH_3	i	100	225–226[b]						
	H	CH_3CH_2	i	100	184–185[c]						
	Ph	CH_3	ii	69	203–205[d]						
22158-29-8	*p*-ClPh	CH_3	ii	79	219–220	52.29	3.59	11.09	52.21	3.59	10.98
22158-30-1	*p*-MePh	CH_3	iii	75	257–258	62.06	5.21	12.06	61.82	5.14	12.30

[a] Methods: (i) allow the 1:1 adduct of hydrazine and acetylene diester to stand for 3 hr in MeOH; (ii) dissolve the adduct in methanol containing *p*-toluenesulfonic acid; (iii) melt the 1:1 adduct and sublime the pyrazolinone from the melt. [b] Literature mp 226.5–227.5°: V. Rothenburg, *Chem. Ber.*, **26**, 2055 (1893). [c] Literature mp 179°: V. Rothenburg, *ibid.*, **25**, 3442 (1892). [d] Literature mp 197°: W. Wislicenus and A. Grossmann, *Ann.*, **277**, 375 (1893).

isomerization is slow, it does not seem likely that the imine arises as a postreaction tautomerization of the initially produced enamine. One possible mechanism which rationalizes these results is shown below.



The zwitterionic species a has been invoked by numerous workers to explain the results of amine to acetylene additions.[9–11,15–17] The zwitterion could collapse to the allenic enol b either by intramolecular prototropic shift [or intermolecular from a like (a) species] in aprotic solvents or by intermolecular transfer in alcoholic solvent. The relative proportions of enamine to imine would then depend on the relative rates of proton tautomerism from oxygen (OH) *vs.* nitrogen (NH). Such a kinetic effect would be expected to be highly dependent on temperature, solvent, and reactant structure and would explain the predominance of the nonthermodynamic product.

Adducts were also obtained from the reaction of *o*-chlorophenylhydrazine and *p*-tolylhydrazine with **3**, and the results are summarized in Table I. Since these hydrazines were freed from their corresponding hydrochloride salts by pretreatment with sodium methoxide and since the absence of either excess acid or base could not be certified, no correlation is suggested for the isomer balances obtained. Similarly, solubility difficulties prevented the investigation of 2,4-dinitrophenylhydrazine addition under the same solvent and temperature conditions. This hydrazine reacted only sluggishly with dimethyl acetylenedicarboxylate, a presumed reflection of diminished nucleophilicity.

All of the adducts except those derived from 1-phenyl-1-methylhydrazine and 2,4-dinitrophenylhydrazine underwent facile ring closure to yield 1-(*R*)-3-carbomethoxypyrazolin-5-ones under a variety of conditions (see Table II). Refluxing in glacial acetic acid, treatment with acid in methanol or benzene, long standing (1 week) in polar solvent, or simply heating above the melting point effected conversion into the pyrazolinone.

The 2,4-dinitrophenylhydrazine adduct, however, could not be cyclized by fusion, sublimation, refluxing in acetic acid, or heating in benzene containing *p*-toluenesulfonic acid. An isomerization of the adduct did occur, producing an isomeric material with a different melting point (174–175°), different carbonyl infrared frequencies (1730 and 1695 cm^{-1}), and different nmr resonances [δ 3.71 and 3.73 (5 H) and 3.90 (3 H)]. Since no vinyl absorptions were present and a methylene resonance, superimposed on methyl, still was evident, it was apparent that geometric isomerization about the imine bond had resulted in preference to ring closure. Treatment with base (NaOMe in acetonitrile) gave a similar result. Such *syn–anti* isomers of 2,4-dinitrophenylhydrazones are well established.[18]

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(16) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).
(17) W. E. Truce, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, Organic Division, paper no. 98.
(18) J. Buckingham, *Quart. Rev.* (London), **23**, 44 (1969).

Experimental Section[19]

General Procedure for Adduct Formation (See Table I).—Phenylhydrazine (5.40 g, 0.05 mol) was dissolved in ethanol (50 ml) and cooled to −40 ° in a Dry Ice–acetone bath. This solution was added dropwise to a second solution of dimethyl acetylenedicarboxylate (7.10 g, 0.05 mol) in ethanol (50 ml) also being maintained at −40°. After addition had been completed (*ca.* 20 min), the mixture, now containing a precipitated solid, was stirred at −40° for 30 min and filtered rapidly through a chilled filter funnel. A mixture of isomeric adducts (7.95 g, 64%) was obtained which nmr spectroscopy revealed to be 80% normal hydrazone and 20% enehydrazine by integration of the respective methylene and vinyl resonances. Two recrystallizations from methanol provided pure enehydrazine: mp 149–150°; nmr (DMSO-d_6) δ 3.50 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 4.84 (s, 1, =CH), 5.56 (broad s, 2, NHNH), and 7.3–7.5 (m, 5 ArH). If the initial adduct precipitate was recrystallized from benzene, pure normal hydrazone (imine) could be isolated: mp 118–119°; nmr (DMSO-d_6) δ 3.66 (s, 3, OCH_3), 3.73 (s, 2, CH_2), 3.76 (s, 3, OCH_3), 7.3–7.5 (m, 5, ArH), and 10.3 (broad s, 1, NH).

General Procedure for Adduct Cyclization (See Table II).—Dimethyl oxalacetate phenylhydrazone (1, 1.0 g, Ar = C_6H_5) was dissolved in methanol (10 ml) containing *p*-toluenesulfonic acid (0.1 g) and allowed to stand at room temperature for 0.5 hr. The solution was concentrated to half-volume and the precipitated material was removed by filtration. 1-Phenyl-3-carbomethoxypyrazolin-5-one (0.60 g, 69%) was obtained: mp 203–205° (lit.[20] mp 197°).

Preparation of Dimethyl Oxalacetate 2,4-Dinitrophenylhydrazone.—An equimolar (0.01 mol) mixture of dimethyl acetylenedicarboxylate and 2,4-dinitrophenylhydrazine in 1:1 DMSO–MeOH (50 ml) was allowed to stand at room temperature for 1.5 hr. The yellow needles which had precipitated were filtered off and recrystallized from MeOH to yield dimethyl oxalacetate 2,4-dinitrophenylhydrazone (1.80 g, 53%): mp 157–158.5°; ir (Nujol) 3250 (NH), 1730, and 1715 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 3.75 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.95 (s, 2, CH_2), 7.93–8.82 (m, 3, ArH), and 11.23 (s, 1, NH). Analytical data are reported in Table I.

Attempted Cyclization of Dimethyl Oxalacetate 2,4-Dinitrophenylhydrazone.—A solution of the hydrazone (300 mg) dissolved in benzene (10 ml) containing *p*-toluenesulfonic acid (50 mg) was refluxed for 2 hr. The solvent was evaporated *in vacuo* and the residue was recrystallized from methanol to yield 200 mg (66%) of crystalline solid: mp 174–175°; ir (Nujol) 3200 (NH), 1730, and 1695 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 3.71 and 3.73 (two s, 5, OCH_3 and CH_2), 3.90 (s, 3, OCH_3), and 8.1–8.9 (m, 3, ArH). Elemental analysis indicated that the material was isomeric with the starting hydrazone.

Anal. Calcd for $C_{12}H_{12}N_4O_8$: C, 42.60; H, 3.55. Found: C, 42.31; H, 3.61.

Registry No.—5, 22158-22-1; 6, 22158-23-2.

(19) Combustion analyses were provided by Dr. George I. Robertson, Microanalytical Laboratory, Florham Park, N. J. Melting points were obtained on a Fisher-Johns block and are uncorrected. Nmr spectra were run on a Varian A-60 nmr spectrometer and are reported in δ (parts per million) units standardized against TMS. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer and were calibrated against the polystyrene 1601-cm^{-1} band.

(20) W. Wislicenus and A. Grossman, *Ann.*, **277**, 375 (1893).

N-*t*-Butyl-β-acyloxycrotonamides

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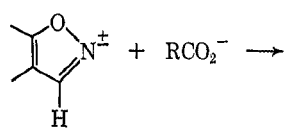
A study of the reaction of carbobenzoxyglycine and N-*t*-butyl-5-methylisoxazolium perchlorate (**7**) has brought to light a new side reaction in the reaction of carboxylic acids with 3-unsubstituted isoxazolium salts—formation of the N-*t*-butylamide of the carboxylic acid. Use of excess **7** in wet acetonitrile diminishes the extent of the side reaction and provides an efficient, generally useful method for the preparation of enol ester acylating agents. The product N-*t*-butyl esters are resistant to intramolecular rearrangement to diacylamides and are sufficiently stable to be isolated and stored.

The reaction of 3-unsubstituted isoxazolium salts (**1**) with carboxylate anions to give enol ester acylating agents (**2**) *via* intermediate acylketenimines (**3**)[1] has



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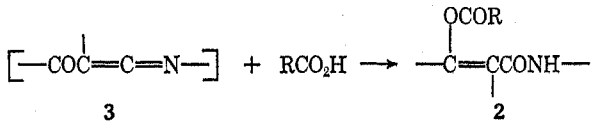
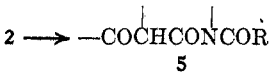


3 **2**

proven of value as a method for the conversion of N-protected amino acids into reactive intermediates for use in peptide synthesis.[2] One limitation associated with the original reagent, N-ethyl-5-phenylisoxazolium 3′-sulfonate (**4**), is instability of the derived enol esters, which is reflected in diminished yields of peptides when addition of the amine component to the ester solution is delayed.[2] A study of a model, unsulfonated N-methyl enol ester revealed spontaneous rearrangement to the diacylamide (**5**),[1] and yields in test peptide preparations with N-methylisoxazolium salts were found to be lower than with the N-ethyl compounds, suggesting that the N-ethyl esters are less susceptible to this mode of decomposition owing to the increased bulk of the ethyl group.[2] However, conversion of



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the enol esters from **4** into the less useful diacylamides still would be expected to some extent even when addition of the amine component is not postponed, and diacylamide formation thus may be a yield-limiting factor under the optimum conditions for peptide synthesis with **4**. Therefore, attempts to design isoxazolium salts which would give enol esters that are completely stable relative to this side reaction are of interest, since such reagents might provide improved yields of peptides. Moreover, stable enol esters would allow the option of isolation, purification, and storage of

(1) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

(2) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron, Suppl.*, **8**, 321 (1966).