tosylvinyl azide or 2-benzoylvinyl azide, forms and slowly rearranges to **T** in the presence of base (N_3^-) in aprotic solvent.[9]

In a second group of syntheses, X may or may not be lost in the reaction, but here *a redox process or some other deep-seated changes* may occur: three β-nitrostyrenes yield 4-aryltriazoles and *sym*-triarylbenzenes;[8] β-cyanostyrene yields 4-phenyltriazole and 4-cyano-5-phenyltriazole;[8] three β-aroylethylene sulfonates yield corresponding 4-aroyltriazoles and phenylacylmethionic acids [p-$XC_6C_4COCH_2CH(SO_3^-)_2$];[10] three nitrocinnamates yield 4-(nitrophenyl), 5-carboethoxytriazole (eq 2). In his work, Zefirov, *et al.*, has pointed out that neither alkynes nor vinyl azides are necessary intermediates in these reactions; they suggest **4**, **5**, or the carbene **6** as possible precursors of the triazole.[8] However, even superficial consideration of these four examples discloses probable differences in the stoichiometry of the processes, in the nature of the coproducts, and in their detailed mechanisms. The formation of 4-cyano-5-phenyltriazole and the nitrophenyl-5-carboethoxytriazoles clearly require a hydride transfer; in the remaining reactions the cyano and sulfonate groups appear to be exchanged in "disproportionations." What does appear to connect all of the examples of this group and what does not seem to have been identified and emphasized previously is that redox processes are occurring. Admittedly, critical mechanistic information about them is still lacking. Since there would be obvious advantages in going to triazole directly from an alkene rather than from an alkyne made from the same alkene, there are practical and theoretical incentives for unravelling the mechanism(s) of these syntheses.

Experimental Section

Syntheses of Nitrophenyl-5-carboethoxy-1,2,3-triazoles from Nitrocinnamates.—The following preparative method was general, but the details of separation of components apply specifically to the para ester rather than to the ortho and meta compounds, for which the coproducts of the derived triazole were not identified. A summary of this work is given in Table I.

To a stirred suspension of sodium azide in an aprotic solvent,[11] blanketed by a stream of dry N_2, was added dropwise a solution of ethyl 4-nitrocinnamate in the same solvent at 75–150° over 30 min. The solution was kept at this temperature for 2–14 hr, when it turned green-brown, and then evaporated to dryness at *ca.* 60° under reduced pressure (2–3 mm). The residue was taken up in 50% aqueous methanol. Materials insoluble in the aqueous methanol were filtered off, washed with water, redissolved, and reprecipitated from acetone–water; these may consist of ethyl nitrocinnamate, ethyl azocinnamate, and possibly ethyl azoxycinnamate. Further separation was attempted by column chromatography on alumina with chloroform and chloroform–acetone as eluting solvents. Unreacted ethyl nitrocinnamate appeared in the first eluates. When present, the azo compound appeared next (trace amounts of azoxy compound mixed in with the azo compound were sometimes detected by mass spectroscopy, parent peak m/e 394). The aqueous solution, from which the mixture of the azo compound and the unchanged reactant were separated, was neutralized with 10% hydrochloric acid. An orange solid gradually precipitated. This was filtered off, washed with water, dried under reduced pressure, and reprecipitated from ethanol–water. The light orange solid was further purified by chromatography on silica gel with benzene, ether, and methanol as eluents, and identified as 4-nitrophenyl-5-carboethoxytriazole.

Ethyl p,p'-Azocinnamate (p-3).—This compound had mp 150–153° dec; nmr ($CDCl_3$) τ 8.65 (t, J = 7.3 Hz, 6 H), 5.69 (q, J = 7.3 Hz, 4 H), 3.51 (d, J = 16.2 Hz, 2 H), 2.27 (d, J = 16.2 Hz, 2 H), 2.32 (d, J = 8.7 Hz, 4 H), 2.05 (d, J = 8.7 Hz, 4 H); ir (Nujol) 1704, 1630 cm^{-1}; uv (ethanol) λ_{max} 366 nm (ε 52,300); mass spectrum m/e 378 (P^+), 333, 203, 181, 175, 147.

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86. Found: C, 69.89; H, 5.82.

4-(p-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This material had mp 170–171°; nmr (CD_3COCD_3) τ 8.66 (t, J = 7.1 Hz, 3 H), 5.60 (q, J = 7.1 Hz, 2 H), 1.72 (s and m, 4 H); ir (KBr) 3120, 1720, 1605, 1525 cm^{-1}; uv (ethanol) λ_{max} 290 nm (ε 12,400).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.52; H, 4.09.

4-(m-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This compound had mp 105–106°; nmr (acetone) τ 8.57 (t, J = 7.2 Hz, 3 H), 5.48 (q, J = 7.2 Hz, 2 H), 2.34 (m, 1 H), 1.71 (m, 2 H), 1.10 (t, J = 1.8 Hz, 1 H); ir (KBr) 3100, 1725, 1540 cm^{-1}; uv (ethanol) λ 249 nm (ε 16,700).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 49.83; H, 3.90. In this reaction, the azo compound was presumed to be a coproduct.

4-(o-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This light red triazole had mp 27–41°; nmr ($CDCl_3$) τ 8.82 (t, J = 7.1 Hz, 3 H), 5.72 (q, J = 7.1 Hz, 2 H), 2.33 (m, 3 H), 1.90 (m, 1 H); ir (liquid) 3160, 1715, 1520, 1440 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.14; H, 3.78.

Registry No.—p-2, 35307-27-8; m-2, 35378-21-3; o-2, 35307-28-9; p-3, 35340-31-9.

(9) (a) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 985 (1968); (b) S. Maiorana, *Ann. Chim. (Rome)*, **56**, 1531 (1960); (c) G. L'abbé and A. Hassner, *Angew. Chem., Int. Ed. Engl.*, **10**, 98 (1971).

(10) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **166**, 1362 (1966).

(11) *E.g.*, DMF, DMAC, or DMSO.

Nuclear Magnetic Resonance and Infrared Studies on the Tautomerism of 1-Ethyl-3-(3′-dimethylaminopropyl)-carbodiimide[1a]

TOM TENFORDE,*[1b] RASHID A. FAWWAZ, AND NORMAN K. FREEMAN

Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720

NEAL CASTAGNOLI, JR.

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122

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Chemotherapy trials performed during the past year have demonstrated that 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (**1**), when administered as a saline solution of its hydrochloride salt, exerts a carcinostatic effect on transplanted tumors in mice.[2] Sheehan, *et al.*,[3] have suggested from ir studies that protonation of the tertiary amine of the carbodiimide **1** may lead to the formation of the tautomeric, reduced pyrimidines 2-ethylamino-3,3-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (**4**) and/or 2-ethylimino-3,3-dimethylper-

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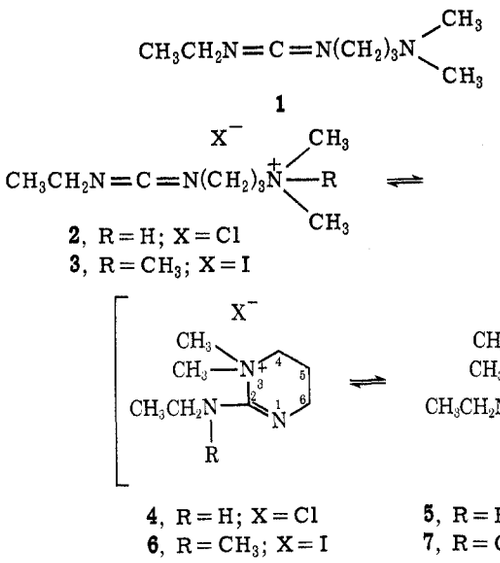
(2) R. Fawwaz and T. Tenforde, *Proc. Amer. Ass. Cancer Res.*, **13**, 36 (1972).

(3) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).

hydropyrimidine chloride (**5**). Titration data have established that the pK_a of compound **1** is ~10.75.



1

2, R = H; X = Cl
3, R = CH_3; X = I

4, R = H; X = Cl
6, R = CH_3; X = I

5, R = H; X = Cl
7, R = CH_3; X = I

Consequently, **1** exists largely as the protonated species in aqueous solution at physiological pH. We therefore have undertaken spectroscopic studies to confirm the existence of structures **4** and/or **5**, and to quantitate the relative percentages of isomeric species **2**, **4**, and **5** present in water at neutral pH. Information of this nature may prove to be of value both in understanding the mechanism of drug action against tumors and in the synthesis of new potentially tautomeric carbodiimides.

When examined in aqueous solution or as a crystalline dispersion in Nujol, the hydrochloride salt of **1** exhibits a weak absorption at 2128 cm^{-1} corresponding to the fundamental antisymmetric -N=C=N- stretching mode.[4] A strong band occurs at 1702 cm^{-1}, characteristic of the -N=C stretching mode present in structures **4** and **5**.[5] Ir spectra of the methiodide derivative of **1** in water and Nujol show a strong carbodiimide band at 2128 cm^{-1}, with no absorption at 1702 cm^{-1}. These observations are consistent with the anticipated N-methylation structure **3**, and indicate that reaction of **1** with methyl iodide does not produce isomeric structures **6** and/or **7**. Ir spectra of the free carbodiimide base, either in neat phase or in chloroform or unbuffered aqueous solution, are consistent with the open-chain structure **1**.

Since the methiodide derivative of **1** must exist exclusively in the carbodiimide form **3**, the extinction coefficient for the -N=C=N- band at 2128 cm^{-1} could be measured and was found to be 1.67×10^6 cm^2/mol in water. Assuming the same extinction coefficient for the 2128-cm^{-1} band observed in the aqueous solution ir spectrum of the hydrochloride salt of **1**, it was calculated that 7.4% of this compound exists as the open-chain carbodiimide hydrochloride **2**. Spectra were recorded in solutions buffered over the pH range of 6 to 9, and no significant variation was noted in the strength of the carbodiimide absorbance. Outside this pH range, carbodiimide hydrolysis prevented accurate measurements.

(4) G. D. Meakins and R. W. Moss, *J. Chem. Soc.* (*London*), 993 (1957).
(5) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, pp 265–267.

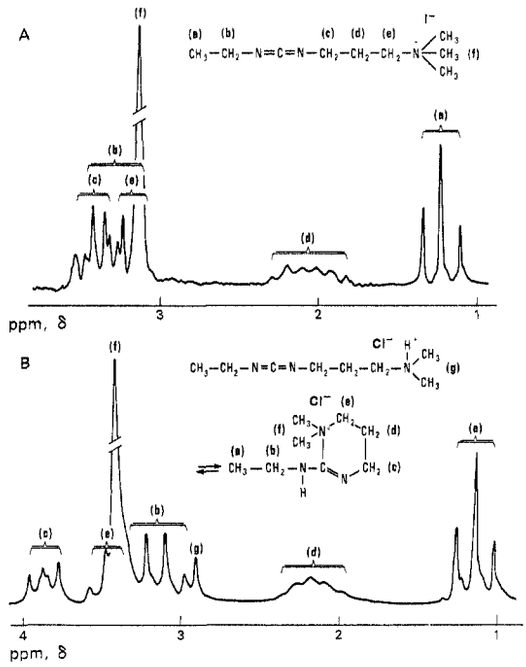


Figure 1.—Nmr spectra at 60 MHz in deuterium oxide of (A) 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide methiodide and (B) the hydrochloride salt of 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide. Both spectra were recorded with sodium 4,4-dimethyl-4-silapentanesulfonate (SDSS) as an internal reference standard (SDSS, 0.0 ppm).

In an effort to confirm and to extend the structural information obtained from ir data, nmr spectra of **1**, its hydrochloride salt, and its methiodide derivative **3** were recorded in deuterium oxide. In the spectrum of the methiodide derivative **3** (Figure 1A, Table I),

TABLE I
60-MHz CHEMICAL SHIFT AND COUPLING CONSTANT DATA[a]

Protons[b]	δ in ppm (J in Hz)		
	1	3	HCl salt of 1
a	1.21 (t, 7)	1.22 (t, 7)	1.16 (t, 7)
b	3.26 (q, 7)	3.31 (q, 7)	3.17 (q, 7)
c	3.27 (t, 6.5)	3.44 (t, 6.5)	3.86 (t, 7)
d	1.7 (m)	2.1 (m)	2.2 (m)
e	2.28 (t, 7)	3.20 (t, 7)	3.48 (t, 6.5)
f	2.21 (s)	3.16 (s)	3.41 (s)
g			2.92 (s)

[a] Spectra were recorded in deuterium oxide with sodium 4,4-dimethyl-4-silapentanesulfonate (SDSS) as an internal reference standard (SDSS, 0.0 ppm). [b] Proton designations are the same as in Figure 1.

the two partially resolved triplets centered at δ 3.20 and 3.44 ppm can be assigned to the c and e methylene proton resonances since all other signals can be unambiguously assigned. The difference in δ values for the f proton signals of the free base **1** and the methiodide derivative **3** ($\Delta_{1\rightarrow 3}\delta_f$, Table I) is 0.95 ppm. Assuming a similar downfield shift of the e proton resonance for species **3** relative to **1**, the triplet at δ 3.20 ppm ($\Delta_{1\rightarrow 3}\delta_e$ = 0.92 ppm) must be assigned to the signal for protons e. Consequently, the δ 3.44 ppm signal is associated with the c methylene protons.

The nmr spectrum of the hydrochloride salt of **1** in deuterium oxide (Figure 1B, Table I) indicates the presence of one major and one minor species. The

weak singlet appearing at δ 2.92 ppm has been assigned to the resonance of the *N,N*-dimethyl protons of the open-chain hydrochloride salt, structure **2**. The intensity of this signal is ~8% as great as that of the major *gem*-dimethyl proton signal at δ 3.41 ppm and is consistent with the percentage of **2** calculated from ir spectral data. The upfield shift of this signal relative to the NCH_3 signals for the quaternary compounds considered here can be explained by localization of the positive charge predominantly on the proton bonded to the tertiary nitrogen.[6] As a result of this charge distribution, the deshielding of the NCH_3 protons is less for species **2** than for the quaternary compounds.

Identification of the major component present in the hydrochloride salt of **1** can be made by comparison of chemical shift data for this compound and the free carbodiimide base **1** (Figure 1B, Table I). In the spectrum of the hydrochloride salt of **1**, the partially obscured triplet centered at δ 3.48 ppm can be assigned to the signal for the e protons since $\Delta_{1\rightarrow 1HCl}\delta_f = \Delta_{1\rightarrow 1HCl}\delta_e = 1.20$ ppm. The low field triplet at δ 3.86 ppm can then be assigned to the c proton signal. A comparison of the spectra of **1** and the hydrochloride salt of **1** also shows that $\Delta_{1\rightarrow 1HCl}\delta_b = -0.09$ ppm and $\Delta_{1\rightarrow 1HCl}\delta_c = 0.59$ ppm. Using these relative chemical shift data, we have assigned **4** as the predominant species present in the hydrochloride salt of **1** for the following reasons. First, the deshielding effect of N-1 in structure **4** is expected to be greater than that of the carbodiimino nitrogen of **1**, resulting in a downfield shift for the c proton signal.[7] Second, the deshielding effect of the amino nitrogen of **4** is expected to be less than that of the carbodiimino nitrogen of **1**, resulting in an upfield shift for the b proton signal. In the case of structure **5**, one would predict the signal for the b protons to occur downfield, and the c proton signal upfield, relative to the corresponding signals for compound **1**.

Nmr spectra were also recorded for the free carbodiimide base **1** in neat phase and as a solution in chloroform. In both cases, the observed chemical shifts and coupling constants were consistent with an open chain carbodiimide structure.

In summary, the ir and nmr studies presented here demonstrate that the hydrochloride salt of **1** in water at neutral pH exists as a mixture of two isomeric forms: 7.4% as **2** and 92.6% as **4**. The methiodide derivative **3** and the free base **1** exist only as open-chain carbodiimide structures.

Experimental Section[8]

The hydrochloride salt of 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide (**1**) with uncorrected mp 109–110° (lit.[3] mp 114–115°) was purchased from the Ott Chemical Co. (Muskegon, Mich.). The derivative 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide methiodide (**3**) with uncorrected mp 90–93° (lit.[3] mp 106.5–107.5°) was prepared from freshly distilled carbodiimide base **1** and methyl iodide.[3] Structure **3** and the hydrochloride salt of **1** in 50% methanol–50% acetone move on silica gel as single bands with R_f values of 0.65 and 0.71, respectively. Only trace amounts of impurities are present. The spectra of these compounds in water and as Nujol mulls demonstrate the absence of urea bands in the 1530–1680-cm^{-1} range. As determined from the absorbance at 2128 cm^{-1}, the hydrolysis of these compounds in water at neutral pH follows first-order kinetics. At 37°, the $t_{1/2}$ for hydrolysis of the hydrochloride salt of **1** is 60 hr, and for hydrolysis of **3** it is 26 hr.

Registry No.—**1**, 1892-57-5; **2**, 25952-53-8; **3**, 22572-40-3.

(6) J. M. George, L. B. Kier, and J. R. Hoyland, *Mol. Pharmacol.*, **7**, 328 (1971).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon, Oxford, England, 1969, pp 80, 81.

(8) Melting points were measured on a Thomas-Hoover apparatus. Ir spectra were recorded on a Perkin-Elmer Model 421 spectrometer. Spectra of solutions were obtained using matched 0.018-mm CaF_2 cells. Because of the weak absorbance of the hydrochloride salt of **1** at 2128 cm^{-1}, measurements at this frequency in aqueous solution were made by recording the transmittance at 5× scale expansion. Nmr spectra were recorded at ambient temperature on a Varian A-60A spectrometer.

A Facile Synthesis of 4-Substituted 3a,4,5,9b-Tetrahydrobenz[*e*]isoindolines

KENNETH D. PAULL AND C. C. CHENG*

Midwest Research Institute, Kansas City, Missouri 64110

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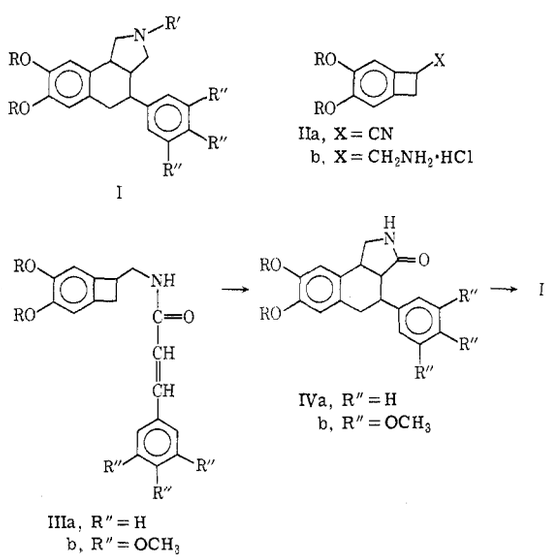
As part of our general structure–activity study of biologically active compounds,[1] synthesis of a series of 4-aryl-substituted 7,8-dialkoxy-3a,4,5,9b-tetrahydrobenz[*e*]isoindolines (I) was needed. Compounds of this type may be prepared by an Oppolzer reaction.[2] Although this route has been studied, certain required unsaturated amines may not be readily accessible and thus preclude its becoming a practical route. An alternate route has therefore been proposed. This involves direct reduction of the nitrile IIa to the amine IIb, treatment of the latter with the acid chloride of an appropriate α,β-unsaturated acid, and thermal cyclization of the resulting amide III to the α-lactam IV. The desired product I can be obtained from IV.



Since α,β-unsaturated acids are readily available and each of the aforementioned steps are convenient, high yield conversions, our method provides a useful route to compounds of this type. As an example, synthesis of 7,8-dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline (I, R = CH_3; R′ = C_2H_5; R″ =

(1) K. Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci.*, **59**, 1630 (1970).

(2) W. Oppolzer, *J. Amer. Chem. Soc.*, **93**, 3833 (1971).