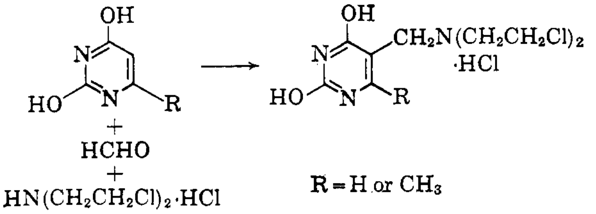
derivatives of uracil in which the alkylating function has been separated by one or more aliphatic carbon atoms from the pseudoaromatic pyrimidine ring.[2]

We now wish to report the successful application of the Mannich reaction to uracil and 6-methyluracil with formaldehyde and β,β′-dichlorodiethylamine with formation of the desired type of compound. Previous reports of success of the Mannich reaction with β,β′-dichlorodiethylamine may be found in the literature.[3]



Uracil (5.6 g.), paraformaldehyde (95%) (1.58 g.), and β,β′-dichlorodiethylamine hydrochloride (8.93 g.) in 90 ml. of glacial acetic acid were heated rapidly to 110° with stirring and held at that temperature for 2 hr. After rapid cooling to room temperature the mixture was stirred for an additional 2 hr. The precipitate was collected (6.9 g., 46%) and recrystallized twice from methanol-ether to give crystalline material, m.p. 210–211° dec. *Anal.* Calcd. for $C_9H_{13}Cl_2N_2O_3 \cdot HCl$: C, 35.72; H, 4.66; N, 13.89. Found: C, 35.82; H, 4.55; N, 13.80. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ C_2H_5OH}$ 263 mμ, ϵ 6.8 × 10^3.

The analogous derivative of 6-methyluracil was prepared in dimethylformamide rather than acetic acid. The yield of crude material was 58%. Recrystallization from methanol and then from methanol-ether gave analytically pure material, m.p. 204–205° dec. *Anal.* Calcd. for $C_{10}H_{15}Cl_2N_3O_2 \cdot HCl$: C, 37.93; H, 5.09; N, 13.27. Found: C, 38.11; H, 5.14; N, 13.28. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ C_2H_5OH}$ 266 mμ, ϵ 6.9 × 10^3.

The infrared spectra of these compounds present several points of interest. These will be discussed more fully in a later communication.

ADDED IN PROOF: Since the submission of this note, we have received a paper by Farkaš and Šorm[5] describing the synthesis of the above uracil mustard by another route.

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(2) *Cf.* W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960); J. A. Carbon, *J. Org. Chem.*, **25**, 1731 (1960); J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).

(3) R. F. Phillips, C. H. Shunk, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 1661 (1948); M. Izumi, *Pharm. Bull.* (*Japan*), **2**, 275 (1954); U. Novitski, Y. K. Yuryev, U. A. Afanaseva, I. G. Bolesov, and A. F. Oleinik, *Zhur. Obshchei. Khim.*, **30**, 2199 (1960); M. Ishidate, Y. Sakurai, and I. Aiko, *Pharm. Bull.* (*Japan*), **8**, 732 (1960).

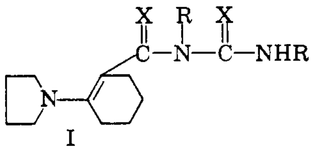
(4) U. S. Public Health Service Predoctoral Fellow.

(5) J. Farkaš and F. Šorm, *Collection, Czechoslov. Chem. Communs.*, **26**, 893 (1961).

The Reaction of Enamines of Cyclic Ketones with Isocyanates

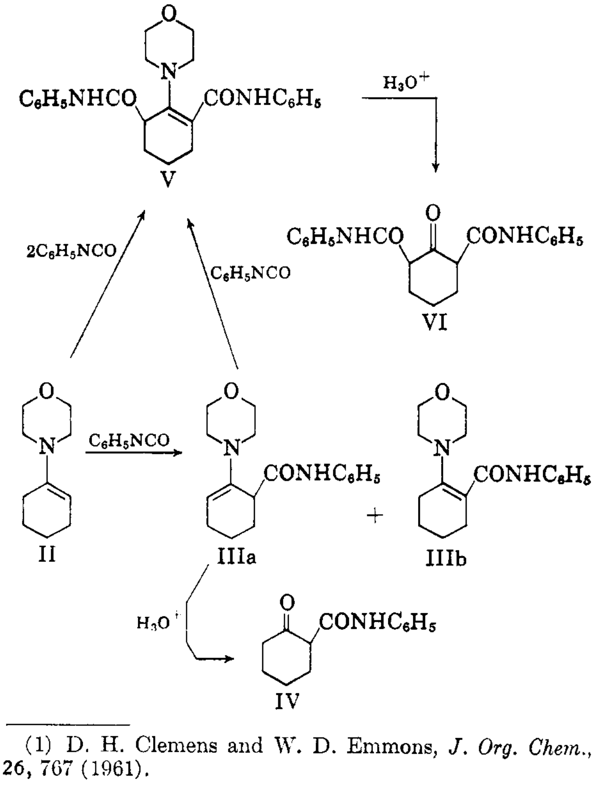
Sir:

The reactions of 1-(*N*-pyrrolidino)cyclohexene with ethyl isocyanate, *n*-butyl isocyanate and ethyl isothiocyanate were recently reported to yield products possessing structure I (X = O, R = $-C_2H_5$, *n*-C_4H_9; X = S, R = $-C_2H_5$).[1] A similar structure was reported for the product from the reaction of 1-(*N*-pyrrolidino)cyclopentene with *n*-butyl isocyanate. Structure proof of these products was based on analysis, neutral equivalent, spectra, and vigorous hydrolysis.



I

We wish to report evidence that such 2:1 adducts are dicarboxanilides rather than urea



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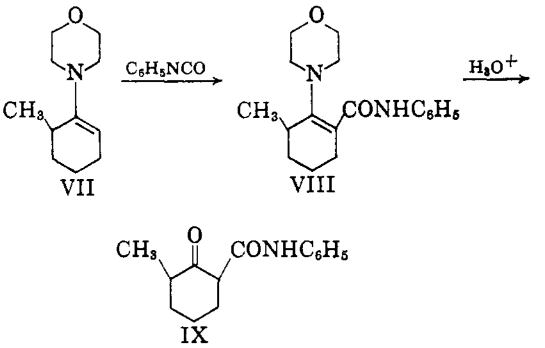
(1) D. H. Clemens and W. D. Emmons, *J. Org. Chem.*, **26**, 767 (1961).

derivatives. Treatment of II with one molar equivalent of phenyl isocyanate in benzene yielded a crystalline, broad-melting product (93%) which may be a mixture of IIIa and IIIb. Purification by recrystallization from acetonitrile yielded IIIa (60%), m.p. 130.2–134.7° (C, 71.53; H, 7.89; N, 9.91), $\lambda_{\max}^{\text{cyclohexane}}$ 244 mμ (ε 14,600). The NMR spectrum of IIIa as a 20% solution in deuterochloroform showed a triplet at 5.04 p.p.m. from tetramethylsilane,[2] thereby establishing the presence of the vinyl proton. Mild acid hydrolysis of IIIa produced IV which was identical to cyclohexanone-2-carboxanilide prepared from the reaction of 2-carbethoxycyclohexanone and aniline.[3] The reaction of enamines of cyclic ketones with phenyl isocyanate has also been reported by Hünig and Hübner.[4]

When IIIa was treated with one molar equivalent of phenyl isocyanate in benzene or when II was treated with two molar equivalents of phenyl isocyanate in benene, V was produced (87%), m.p. 191.4–192.8° (C, 70.71; H, 6.57; N, 10.34). The structure of V was established by mild acid hydrolysis to VI, m.p. 254.9–256.6° (C, 71.47; H, 5.97; N, 8.48). Compound VI was identical to the sample prepared by the reaction of 2,6-dicarbomethoxycyclohexanone with aniline.[5]

A similar sequence of reactions has been completed starting with 1-(*N*-morpholino)cyclopentene and 1-(*N*-morpholino)cycloheptene.

Further evidence that the 2:1 adduct possesses structure V rather than structure I is indicated by the following observations. The reaction of equimolar quantities of 6-methyl-1-(*N*-morpholino)-cyclohexene (VII) and phenyl isocyanate in benzene produced VIII (82%), m.p. 114.2–119.4° (C, 71.91; H, 8.01; N, 9.47); the position of the double bond in VIII has not been firmly established.



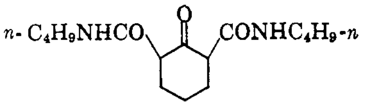
VII

VIII

IX

Mild acid hydrolysis of VIII produced IX, m.p. 130.9–131.7° (C, 72.85; H, 7.50; N, 6.04) which was identical to the product from the reaction of 2-carbethoxy-6-methylcyclohexanone and aniline. Attempts to prepare a 2:1 adduct from VII yielded only VIII.

Repetition of the reaction of 1-(*N*-pyrrolidino)-cyclohexene and *n*-butyl isocyanate and hydrolysis of the reaction mixture as described by Clemens and Emmons[1] afforded a product possessing the same physical properties reported by these workers. The product is identical to the one obtained from the reaction of 2,6-dicarbomethoxycyclohexanone and *n*-butylamine and therefore must be X. It is suggested that all of the 2:1 adducts obtained



X

from the reactions of isocyanates with enamines of cyclic ketones may be the β,β′-diadducts.

Further studies on the isomerization of the carbon-carbon double bond in enamines is in progress.

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[2] Recorded with a 60-mc. oscillator frequency and calibrated by the use of audio sidebands.

[3] B. K. Blount, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 1975 (1929); H. K. Sen and U. Basu, *J. Indian Chem. Soc.*, 6, 309 (1929).

[4] S. Hünig, *Angew. Chem.*, 71, 312 (1959); S. Hünig, private communication; K. Hübner, dissertation, Univ. Marburg, 1960.

[5] This compound has previously been prepared by the reaction of 2,6-dicarbethoxycyclohexanone with aniline: P. C. Guha and N. K. Seshadriengar, *Ber.*, 69, 1212 (1936).