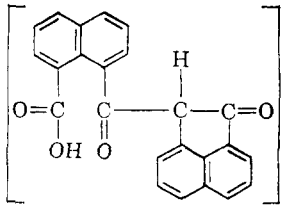
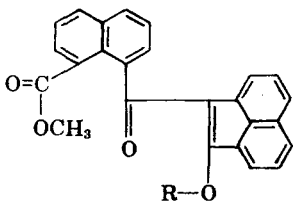
nitrogen. The initial suspension became a clear, yellow solution within 15–20 min. After 1 hr., the solvent was removed *in vacuo* at temperatures below 20°. The tan crystalline residue was shown to be a *2:1 adduct* (III) derived from the "quinone" and the phosphite. Methanol (150 ml.) was added, the mixture was heated to reflux (20–30 min.) and the insoluble enol lactone VI (16.5 g., 95%; m.p. *ca.* 255°) was collected and recrystallized from toluene. The yield of VI of m.p. 275–276° was about 90%. Pure VI was colorless and had bands at 5.78, 6.33, and a somewhat stronger doublet at 5.90 and 6.00 μ (methylene chloride); $\lambda_{max}^{CH_3CN}$ 335 mμ (ϵ 26,500); *Anal.* Calcd. for $C_{24}H_{12}O_3$: C, 82.8; H, 3.5. Found: C, 83.0; H, 3.6. Trimethyl phosphate (VII) was obtained from the methanol solution. Similar results were observed when an excess of trimethyl phosphite was employed.

The enol lactone VI was cleaved into 1,8-naphthalic acid (1 mole) and acenaphthenone (1 mole) by 3 equivalents of degassed *N* aqueous sodium hydroxide (12–24 hr. at room temperature, under nitrogen.) This is consistent with a β-diketonecarboxylic acid intermediate VIII. The enol lactone VI was converted into an orange salt (bands at 5.90, 6.13, and 6.3 μ, in Nujol mull) by 1 equivalent of sodium methoxide in methanol (15 hr. at room temperature, under nitrogen) The orange salt reverted to VI on treatment with boiling acetic acid; cold acetic acid, however, gave a yellow substance, m.p. 204–205° (from benzene) which had bands at 3.26, 5.81, 6.06, and 6.18 μ (carbon tetrachloride) and gave a green color with ferric chloride. This is probably the enol tautomer IX (*Anal.* Calcd. for $C_{25}H_{16}O_4$: C, 79.0; H, 4.2. Found: C, 78.9; H, 4.4.) IX reverted to the enol lactone VI on heating with acetic anhydride and gave a yellow substance, m.p. 220–221° (from ethyl acetate) when treated with diazomethane in ether. This is presumably the enol ether X with bands at 5.81 and 5.92 μ (methylene chloride) (Calcd. for $C_{26}H_{18}O_4$: *Anal.* C, 79.3; H, 4.6. Found: C, 79.0; H, 4.7.)

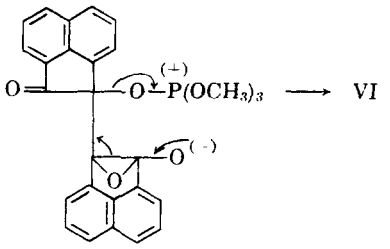


VIII



IX. R = H
X. R = CH_3

A possible mechanism for the molecular rearrangement leading to the enol lactone VI is indicated in formula XI. The ejection of a phosphate ester from a molecular complex appears to provide a strong driving force for reactions[3] The conversion of phthalic anhydride into biphthalyl by triethyl phosphite at *elevated temperatures* is another manifestation of this driving force.[4]



XI

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(3) F. Ramirez, N. B. Desai, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 492 and ref. therein.

(4) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Am. Chem. Soc.*, **83**, 173 (1961).

Application of the Mannich Reaction with β,β-Dichlorodiethylamine to Derivatives of Uracil

Sir:

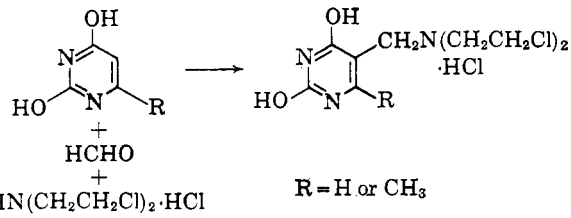
The concept of incorporating an alkylating function, *e.g.* the β,β'-dichlorodiethylamine group, into a molecule known to play an important role in biogenesis of nucleic acids has received increasing attention in recent years from those interested in chemotherapeutic control of neoplastic disease.[1] Among such molecules uracil occupies an important position inasmuch as it is a primary component of the nucleic acid moiety. Hitherto alkylating agents of the type referred to have involved incorporation of the β,β'-dichlorodiethylamine function into the uracil molecule with the amine nitrogen directly attached to the pyrimidine ring in the 5-position.[1d,e]

It has been recognized for some time that the so-called "nitrogen mustard" function varies in its alkylating properties depending on whether it is directly attached to an aromatic or pseudo-aromatic ring system or to an aliphatic system.[1c] As far as we are aware no reports have appeared in the literature concerning nitrogen mustard

(1) (a) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 4585 (1960); (b) R. C. Elderfield and R. N. Prasad, *J. Org. Chem., in press;* (c) H. H. Liu and C. C. Price, *J. Org. Chem.*, **26**, 264 (1961); (d) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, **80**, 6459 (1958); (e) L. F. Larianov, *Brit. J. Cancer*, 10, 26 (1956) *inter alia.*

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 × 10³.

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 × 10³.

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).

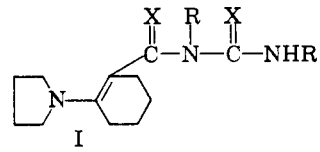
(4) U. S. Public Health Service Predoctoral Fellow.

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

The Reaction of Enamines of Cyclic Ketones with Isocyanates

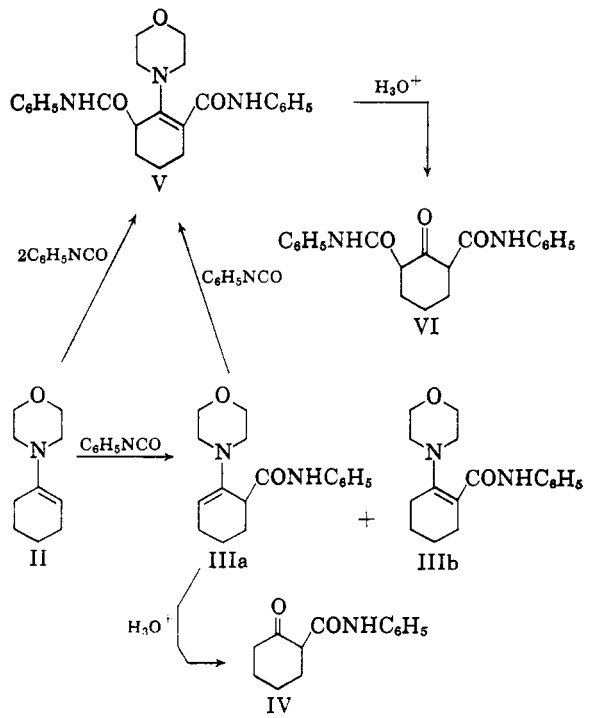
Sir:

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



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