Substituted Uracils from Ethoxycarbonyl Isocyanate and Primary or Secondary Enamines

Robert W. Lamon

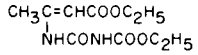
Research Laboratories, Eastman Kodak Company

The preparation of compounds of the pyrimidine series from acyl isothiocyanates and primary or secondary enamines has been investigated recently (1-4). In particular, 4-thiouracils have been prepared by the reaction of phenoxycarbonyl isothiocyanate with ethyl 3-aminocrotonates or 4-amino-3-penten-2-ones, among other similarly constituted enamines (2-4). The adducts initially formed, cyclized with the loss of phenol spontaneously or upon treatment with base.

Brief studies of the preparation of uracils by the analogous use of the more reactive ethoxycarbonyl isocyanate are reported in the present paper (5).

Ethoxycarbonyl isocyanate was obtained by Cohen (6) in 53% yield, using procedures similar to those described by Speziale (7).

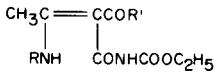
Addition of the isocyanate to cold ether solutions of the appropriate enamine produced adducts which were mainly, if not entirely, products of attack on carbon (I-VI, Table I). The nmr spectra of recrystallized material showed no vinyl proton signals. However, the crude product obtained from ethyl 3-aminocrotonate was only partly soluble in 25% trimethylamine, the cyclizing agent. The insoluble material was shown to be the product of reaction at the enamine nitrogen (VII) by its nmr spectrum.



VII

Treatment of the adducts II-VI with aqueous trimethylamine gave the expected 5-acetyl- or 5-carbethoxy-6-methyluracils IX-XIII (Table II) in yields of 71-99%. Crude material was used as obtained from the addition

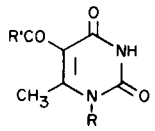
TABLE I



Compound	R	R′	Yield %(a)	M.P., °C (c)	Recrystallization Solvent (d)	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	H	OC_2H_5	54 (b)	152-153	Ether	$C_{10}H_{16}N_2O_5$	49.2	6.6	11.5	48.9	6.2	11.4
II	H	CH_3	69	139-140	Ethyl acetate	$C_9H_{14}N_2O_4$	50.5	6.6	13.1	50.7	6.4	13.0
III	CH_3	OC_2H_5	57	66-68	Ethyl-ligroin	$C_{11}H_{18}N_2O_5$	51.2	7.0	10.9	51.5	7.0	10.7
IV	CH_3	CH_3	94	105-106	Methylene chloride-ether-ligroin	$C_{10}H_{16}N_2O_4$	52.6	7.1	12.3	52.8	7.2	12.3
V	C_6H_5	OC_2H_5	76	87-88	Ether	$C_{16}H_{20}N_2O_5$	60.0	6.3	8.7	60.3	6.3	8.8
VI	C_6H_5	CH_3	89	123-124	Ether	$C_{15}H_{18}N_2O_4$	62.1	6.3	9.7	61.8	6.0	9.8

(a) Based on crude material. (b) Corrected for amount of product of *N*-attack isolated. (c) Uncorrected. (d) The ligroin used throughout was a hydrocarbon solvent of b.p. 35-60°.

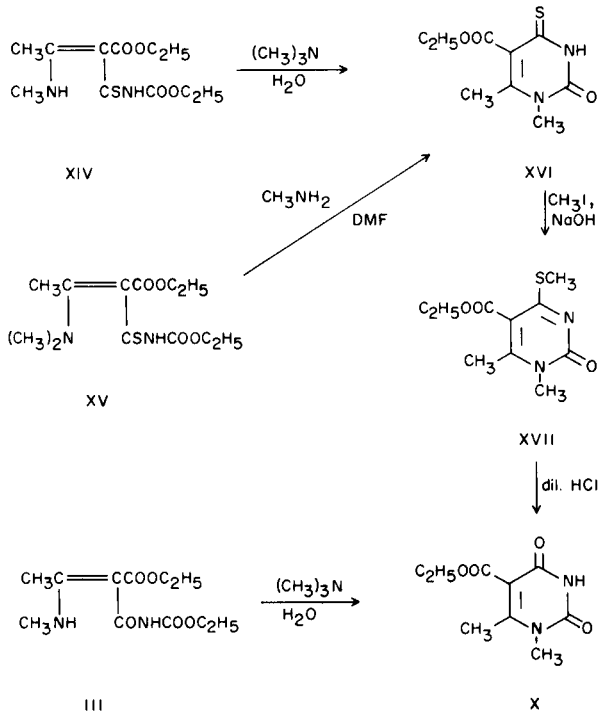
TABLE II



Compound	R	R′	Yield %(a)	M.p., °C (c)	Recryst'n Solvent	Formula	Calcd. C	H	N	Found C	H	N	λ max (d)	x 10^{-3}
VIII	H	OC_2H_5	62 (b)	233-234	Ethanol	$C_8H_{10}N_2O_4$	48.5	5.1	14.1	48.2	4.9	14.2	268	11.9
IX	H	CH_3	71	226-227	Ethanol	$C_7H_8N_2O_3$	50.0	4.8	16.7	49.9	4.8	16.7	230 278	7.6 10.4
X	CH_3	OC_2H_5	91	200-201	Ethanol	$C_9H_{12}N_2O_4$	50.9	5.7	13.2	51.1	5.7	13.3	273	11.9
XI	CH_3	CH_3	88	211-212	Ethanol	$C_8H_{10}N_2O_3$	52.7	5.5	15.4	52.9	5.6	15.3	236 282	6.3 10.4
XII	C_6H_5	OC_2H_5	99	273-274 dec.	Chloroform-ethanol	$C_{14}H_{14}N_2O_4$	61.3	5.1	10.2	61.0	4.9	10.3	270	10.0
XIII	C_6H_5	CH_3	89	196-197	Ethyl acetate	$C_{13}H_{12}N_2O_3$	63.9	5.0	1.5	63.6	4.8	11.3	233 278	6.4 13.0

(a) Based on crude material. (b) Calculated from unrecovered starting material. (c) Uncorrected. (d) Solvent, ethanol.

SCHEME I



step. After isolation of VII, the filtrate yielded 5-carbethoxy-6-methyluracil (VIII) in 62% yield, based on unrecovered starting material.

The structures could be inferred from previous work just quoted and also from the earlier Shaw synthesis, the latter proceeding through similar intermediates (8). Furthermore, the nmr spectra of VIII, XI, and XIII were in accord with assigned structures. As shown in Scheme 1, the previously described 4-thiouracil (XVI) could be prepared from either XIV or XV (9). Desulfurization by the usual techniques afforded material identical with that obtained by using the methods described here.

EXPERIMENTAL (10)

Ethoxycarbonyl Isocyanate (6,7).

Oxalyl chloride (250 g., 2.0 moles) was added rapidly to a suspension of ethyl carbamate (123 g., 1.4 moles) in 750 ml. of chloroform. After cessation of gas evolution, the mixture was refluxed overnight under nitrogen. The mixture was cooled, filtered, and the filtrate distilled under reduced pressure. A fraction boiling at 40-65° (80 mm.) was redistilled at the same pressure to give 85 g. (53%) of desired product, b.p. 54-60°.

3-(*N*-Carbethoxycarbamoyl)-4-methylamino-3-penten-2-one (IV).

A stirred solution of 11.3 g. (0.10 mole) of 4-methylamino-3-

penten-2-one (11) in 60 ml. of anhydrous ether was chilled in an ice-brine bath. The mixture was treated dropwise with 11.5 g. (0.10 mole) of ethoxycarbonyl isocyanate, diluted (1:1) with dry ether. The resulting suspension was stirred in the cold for several hours, filtered, and the product was washed with ether and air-dried, yield, 21.4 g., m.p. 91-92°. A small sample was recrystallized twice from methylene chloride-ether-ligroin to give white needles, m.p. 105-106°. The nmr spectrum (deuteriochloroform) showed no vinyl proton peak but did contain methyl signals at δ 2.13, 2.18 (allylic and acetyl methyl) and δ 3.30 (methylamino, doublet replaced by singlet on deuteration). The characteristic ethyl peaks were observed at δ 1.30 (triplet) and 4.19 (quartet) as were NH signals at δ 9.5 and 12.1.

5-Acetyl-1,6-dimethyluracil (XI).

This adduct (15.0 g., 0.066 mole) was dissolved in 100 ml. of 25% aqueous trimethylamine. After standing for several hours, the solution was concentrated under reduced pressure to remove most of the trimethylamine. The mixture was acidified with acetic acid, chilled, and filtered, yield, 10.5 g., m.p. 209-210°. Recrystallization from ethanol gave white plates, m.p. 211-212°.

The nmr spectrum (DMSO-d_6) showed methyl singlets at δ 2.30 (C-6), 2.41 (acetyl), and 3.36 (N-1). A broad signal at δ 11.3 was due to NH (12).

The 1-phenyl analog XIII was similarly prepared. Its nmr spectrum (DMSO-d_6) contained methyl singlets at δ 1.86 (C-6, possibly shielded by the phenyl ring) and 2.47 (acetyl), and additional peaks at δ 7.48 (phenyl) and 11.7 (NH) (12).

Reaction of Ethoxycarbonyl Isocyanate and Ethyl 3-Aminocrotonate.

The reactants were combined as in the preparation of IV, just described, yield of crude product, 16.4 g. (67%), softening at 102°, liquefying at 114-115°.

The crude material (12 g.) was swirled and gently warmed with aqueous trimethylamine to give a uniform suspension. Cooling and filtering gave 2.4 g. of crude VII, m.p. 131-132°. Recrystallization from ether-ligroin gave white needles, m.p. 134-135°. The nmr spectrum (deuteriochloroform) was consistent with the assigned structure, showing in particular a vinyl proton signal at δ 5.03, apparently coupled to the allylic methyl protons (signal at δ 2.40, J = 0.5 Hz).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.2; H, 6.6; N, 11.5. Found: C, 48.9; H, 6.8; N, 11.7.

The filtrate, after standing overnight, was concentrated to a small volume under reduced pressure and acidified with acetic acid. Chilling and filtering of the mixture produced 4.6 g. of crude VIII, m.p. 231-232°. Recrystallization from ethanol gave white needles, m.p. 233-234°. The nmr spectrum (DMSO-d_6) contained the expected ethyl proton pattern (δ 1.28 and 4.21), the C-6 methyl signal (δ 2.23), and a single broad peak due to NH (δ 11.1, 1.8H) (12).

Pure I was obtained by crystallization of the crude mixture of adducts from ether.

A crude adduct mixture from a separate run (m.p. 110-120°) consisted of 25% of VII, estimated from its nmr spectrum.

Ethyl 2-(*N*-Carbethoxythiocarbamoyl)-3-methylaminocrotonate (XIV).

Dropwise addition of 0.10 mole of ethoxycarbonyl isothiocyanate (13) to an equimolecular a mount of ethyl 3-methylaminocrotonate in dry ether, with cooling, gave the desired product in 78% yield, m.p. 89-90°. Precipitation from ethyl acetate by addition of ligroin gave yellow-orange prisms of unchanged m.p.

Anal. Calcd. for $C_{11}H_{18}N_2O_4S$: C, 48.2; H, 6.6; N, 10.2; S, 11.7. Found: C, 48.2; H, 6.5; N, 9.9; S, 11.7.

5-Carbethoxy-1,6-dimethyl-4-thiouracil (XVI).

The enamine adduct XIV was cyclized with aqueous trimethylamine in a manner similar to that just described to give a nearly quantitative yield of the 4-thiouracil, m.p. 210-212° dec. Recrystallization from ethanol gave yellow prisms, m.p. 214-215° dec. (lit. (3), m.p. 215° dec.).

The enamine adduct XV (5.00 g., 0.017 mole) (14) and 8 ml. of 40% aqueous methylamine were dissolved in 40 ml. of dimethylformamide. After standing at room temperature for 4 hours, the solvent was removed under reduced pressure. Treatment of the residue with water and acidification gave 3.38 g. (85%) of crude product, m.p. 210-212° dec. Recrystallized material was shown to be identical with that obtained from XIV by mixture m.p. and comparison of infrared spectra (9).

5-Carbethoxy-1,6-dimethyl-4-methylthio-2(1*H*)-pyrimidinone (XVII).

The 4-thiouracil (5.48 g., 0.024 mole) was dissolved in 50 ml. of water containing 1.00 g. (0.025 mole) of sodium hydroxide. Methyl iodide (3.80 g., 0.027 mole) was added and the mixture was stirred for 3 hours, then extracted continuously with ether for 48 hours. The ether extract was evaporated and residue was freed from moisture by addition of benzene and evaporation at reduced pressure. The resulting oil solidified when swirled with ligroin, yield, 4.30 g. (74%), m.p. 76-78°. Recrystallization from methylene chloride-ligroin gave off-white needles, m.p. 77-78°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.6; H, 5.8; N, 11.6; S, 13.2. Found: C, 49.3; H, 5.6; N, 11.6; S, 13.2.

5-Carbethoxy-1,6-dimethyluracil (X).

The methylation product XVII (0.75 g., 3.1 mmoles) was refluxed for 10 minutes in 2*N* hydrochloric acid and chilled. The precipitate was collected, yield, 0.40 g. (61%), m.p. 193-196°. Two recrystallizations from ethanol gave material having m.p. 198-199°, undepressed on admixture of material obtained from ethyl 3-methylaminocrotonate by the title method. The infrared spectra of the two samples were identical.

Acknowledgment.

The author wishes to express appreciation to Dr. H. L. Cohen, for providing the preparative procedure for ethoxycarbonyl isocyanate and a sample of this material. Thanks are also due to Dr. T. H. Regan, for determination of the nmr spectra and helpful discussions.

REFERENCES

(1) G. DeStevens, B. Smolinsky, and L. Dorfman, *J. Org. Chem.*, 29, 1115 (1964).

(2) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, 96, 526 (1963).

(3) J. Goerdeler and J. Gnad, *ibid.*, 98, 1531 (1965).

(4) J. Goerdeler and D. Wieland, *ibid.*, 100, 47 (1967).

(5) The adduct formed from benzoyl isocyanate and ethyl 3-anilinocrotonate has been cyclized with mercuric acetate to 5-carbethoxy-1,2-diphenyl-6-methyl-4(1*H*)-pyrimidinone (see Ref. 1). The preparation of compounds analogous to the latter has been claimed in a patent. See G. DeStevens, U. S. Patent 3,210,355 (1965).

(6) H. L. Cohen, private communication (see Acknowledgment).

(7) A. J. Speziale, L. R. Smith, and J. E. Fedder, *J. Org. Chem.*, 30, 4306 (1965).

(8) D. J. Brown, "The Pyrimidines," Interscience Publishers, New York, N. Y., 1962, pp. 87-90, and references cited.

(9) The preparation of 4-thiouracils from ethoxycarbonyl isothiocyanate-tertiary enamine adducts is discussed elsewhere (see Ref. 13).

(10) Melting points are uncorrected. The nmr spectra were obtained in a Varian A-60 instrument with tetramethylsilane as internal standard. Ultraviolet spectra were determined on a Cary Model 11 MS Spectrophotometer. The infrared spectra were obtained from potassium bromide disks on a Perkin-Elmer Model 137 Spectrophotometer.

(11) E. Knoevenagel and W. Ruschaupt, *Ber.*, 31, 1025 (1898).

(12) The relative integrated intensities of the NH signals were low with respect to those of hydrogen on carbon.

(13) R. W. Lamon, *J. Heterocyclic Chem.*, 5, 837 (1968).

Received October 23, 1968 Rochester, New York 14650