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Several amide oximes underwent condensation reactions with dimethyl acetylene dicarboxylate to afford 1:1 adducts. Under basic conditions, these adducts underwent ring closure to afford several methyl [3-(substituted)-4,5-dihydro-5-oxo-6*H*-1,2,4-oxadiazin-6-ylidene]acetates. The reactions of these compounds with a variety of amines resulted in addition-rearrangement reactions with the formation of the corresponding methyl 2-substituted-5-substituted amino-1,6-dihydro-6-oxo-4-pyrimidine carboxylates.

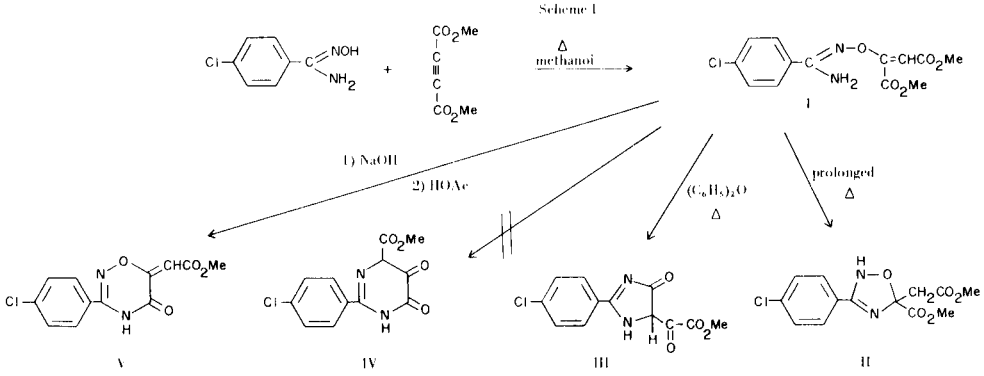
J. Heterocyclic Chem., 16, 213 (1979).

Heindel and Chun (1) have reported that aryl amides oximes undergo reaction with dimethyl acetylenedicarboxylate (DMAD) to form 1:1 adducts typified by I (Scheme I) when heated under reflux in methanol for 3 hours. Prolonged heating in the same solvent produced II by internal cyclo-addition. These investigators further showed that I underwent a Claisen type rearrangement with loss of methanol when heated in refluxing diphenyl ether to afford the imidazolinone III (m.p. 256-257°) rather than the isomeric pyrimidinone IV. This conclusion was supported by the fact that their rearrangement product, when treated with *o*-phenylenediamine, gave a derivative having a mass spectral fragmentation pattern in accord with the one expected from III but not from IV.

During the course of an investigation relating to the synthesis of various heterocyclic derivatives involving condensation reactions of DMAD with difunctional nucleophiles, we also had occasion to examine the reaction of several amide oximes with DMAD, including *p*-chlorobenzamide oxime. The 1:1 adduct I was obtained as previously described (1). When the adduct was treated with sodium hydroxide followed by acidification, a new compound, V (m.p. 232-235°), was obtained which is isomeric with III. Spectral comparison with a sample of III prepared by the Heindel procedure confirmed that the products are not the same. The product gave a negative ferric chloride test which substantiated the absence of a highly enolic system. Apart from the aromatic protons, the nmr spectrum indicated a vinylic proton singlet at 5.95 ppm which remained after deuteration and a methyl ester group singlet at 3.70 ppm. The NH resonance is not clearly defined. The 1,2,4-oxadiazine is apparently formed without rearrangement by displacement of an ester group in the adduct I by the amino group of the amide oxime. The base catalyzed cyclization of other 1:1 adducts obtained from the reactions of DMAD with several amide oximes afforded the corresponding 1,2,4-oxadiazines shown in Table II.

The reaction of V with various primary amines resulted in a rearrangement process producing enamines having structures consistent with those which would be formed from the 5-oxo-pyrimidine IV and these amines. For example, the reaction of V with *N,N*-diethylaminoethylamine afforded methyl 2-(4-chlorophenyl)-5-[2-(diethylamino)-ethylamino]-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate (VI) (Scheme II). Confirmatory evidence that rearrangement to the pyrimidine had taken place and that the structure of the enamine is indeed correct is shown by the fact that hydrolytic cleavage of the enamine gave the 5-oxopyrimidine IV (m.p. 147-150°), which is isomeric with III and V. The nmr spectrum of IV indicates that in solution it exists partially as the 5-hydroxy tautomer (IV′). This is evidenced by the fact that there are two separate methyl resonance singlets at 3.72 and 3.82 ppm, in-

Scheme I



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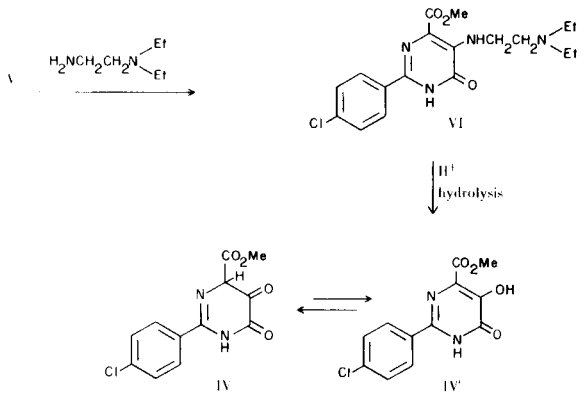
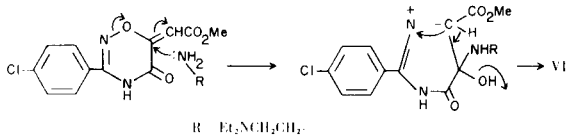
tegrating for a total of 3 protons, and that the 4-methinyl resonance at 6.20 ppm integrated for approximately 0.6 of a single proton which disappeared on deuteration.

Scheme II



Mechanistically, this rearrangement may be depicted as proceeding through an initial attack of the amine at the 6-position of the oxadiazine ring, generating an open-chain fusion intermediate. This can undergo cyclization and elimination of water, the entire process occurring in either a stepwise or concerted fashion (Figure 1). Other reports have appeared which show that oxime:DMAD adducts can undergo rearrangements involving cleavage of the N-O bond with subsequent formation of a new N-C bond (1,3,4).

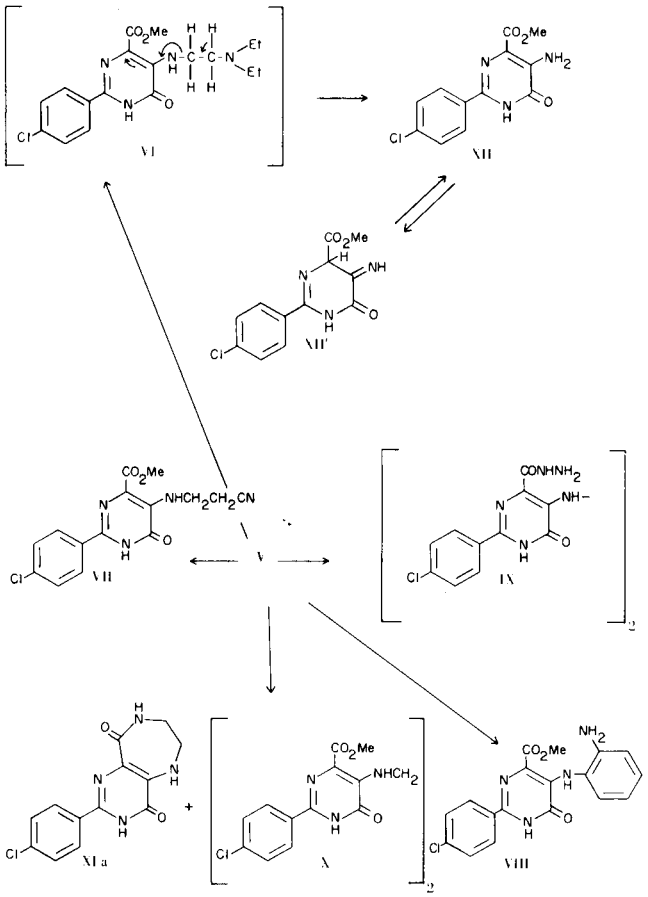
Figure 1



In Figure 2 are depicted the reactions of V with several other nucleophiles. In each example, rearrangement to the pyrimidine occurred, with the resulting formation of the enamine at position 5 of the pyrimidine ring. For example, treatment of V with 3-aminopropionitrile afforded the pyrimidine VII. Reaction of V with *o*-phenylenediamine gave VIII. When V was allowed to react with hydrazine, formation of the bis-enamine-hydrazide IX resulted. Similarly, the reaction of V with ethylenediamine afforded the bis-enamine derivative X. A second product isolated from the reaction is the pyrimido[5,4-*e*][1,4]diazepine XIa. Other pyrimido[5,4-*e*][1,4]diazepines XIb and XIc (Table III) were similarly prepared *via* the reactions of ethylenediamine with the 1,2,4-oxadiazines Vc and Vd, respectively. The reaction of V with *N,N*-diethylaminoethylamine, described earlier in this report, gave a different product when the amine was used as the solvent and under refluxing conditions. The product obtained was XII, possibly being generated from VI *via* elimination of diethyl vinyl amine as depicted. The ir spectrum (potassium bromide) indicated that the product is in the conjugated 5-amino-4-carbomethoxy form XII. In solution, however, it is apparent from nmr that the unconjugated ester XII′ is the predominant tautomer. This is evidenced by the presence of an α-methinyl resonance singlet found at 5.75 ppm which integrates for a full proton. Several of the enamines in this report which are depicted in the conjugated form also exhibit this tautomeric behavior.

In summary, the 1:1 adducts formed from the reactions of amide oximes with DMAD can undergo cyclization in a number of different ways, leading to several different products. Prolonged heating in refluxing ethanol under neutral conditions leads to 1,2,4-oxadiazole formation while heating in relfuxing diphenyl ether for a short time produces imidazolinones (1). The present investigation has shown that under alkaline conditions, 1,2,4-oxadiazines are formed which can undergo addition-rearrangement reactions with amines to form the corresponding 5-enamines of the 4-carbomethoxypyrimidines.

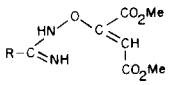
Figure 2



EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained

Table I



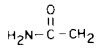
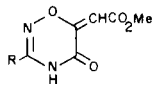
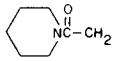
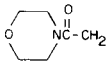
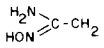
Compound	R	M.p.°C	Recrystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
Ia	4-ClC$_6$H$_4$	58-60	Methanol	$C_{13}H_{13}ClN_2O_5$	49.93	4.19	8.96	49.82	4.15	9.21
Ie		113-114	Ethanol	$C_9H_{13}N_3O_6$	41.70	5.06	16.21	41.62	5.19	16.28
If		128-132	Water	$C_8H_{12}N_4O_6$	36.93	4.65	21.53	36.92	4.49	21.62

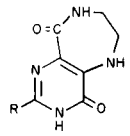
Table II

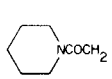
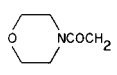


Compound	R	M.p.°C	Recrystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
Va	4-ClC$_6$H$_4$	232-235	Methanol	$C_{12}H_9ClN_2O_4$	51.36	3.23	9.98	51.11	3.18	9.89
Vb (a)	3,4,5-(CH$_3$O)$_3$C$_6$H$_2$	223-224	Methanol	$C_{15}H_{16}N_2O_7$	53.57	4.80	8.33	53.68	4.92	8.44
Vc (a)		173-175	Ethanol	$C_{13}H_{19}N_3O_5 \cdot H_2O$	49.84	6.11	13.41	50.14	5.94	13.44
Vd (a)		181-183	Ethanol	$C_{12}H_{15}N_3O_6 \cdot H_2O$	45.71	5.44	13.33	45.42	5.44	13.28
Ve		215-216 dec.	Ethanol	$C_8H_9N_3O_5$	42.29	3.99	18.50	42.09	3.98	18.38
Vf		253 dec.	Water	$C_7H_8N_4O_5$	36.85	3.53	24.56	36.89	3.51	24.27

(a) Prepared from unpurified 1:1 amide oximes-DMAD adducts.

Table III



Compound	R	M.p.°C	Recrystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
XIa	4-ClC$_6$H$_4$	264-266	Ethanol	$C_{13}H_{11}ClN_4O_2$	53.71	3.81	19.27	54.08	3.84	19.35
XIb		234-236	Ethanol	$C_{14}H_{19}N_5O_3$	55.07	6.27	22.94	55.32	6.42	22.77
XIc		234-236	Ethanol	$C_{13}H_{17}N_5O_4$	50.81	5.58	22.29	50.45	5.66	22.40

in potassium bromide disks using a Perkin-Elmer (Model 21) spectrophotometer. Nmr spectra were obtained with either a Varian A-60 spectrometer or (JEOL C60-HL) spectrometer using deuteriochloroform or DMSO-d_6 as indicated. Chemical shifts were measured in ppm (δ) with respect to tetramethylsilane.

Dimethyl 2-[[[Amino(4-chlorophenyl)methylene]amino]oxy]-2-butenedioate (I).

A stirred mixture of 4.1 g. (0.02 mole) of *p*-chlorobenzamidoxime and 2.84 g. (0.02 mole) of dimethyl acetylenedicarboxylate in 50 ml. of methanol was heated under reflux for 1 hour. The solvent was stripped in a rotary evaporator and the residue passed through a neutral aluminum oxide column using ethyl acetate as the eluent. The ethyl acetate was removed in a rotary evaporator and the residue was dissolved in a minimum amount of ethanol. This solution was cooled in a dry ice-acetone bath giving the product, m.p. 58-60°; ir (potassium bromide): 3436, 3205 (NH), 1724 (C=O), 1236 (C-O) cm^{-1}; nmr (DMSO-d_6): δ 3.62 (s, 3, CO_2Me), 3.80 (s, 3, CO_2Me), 5.86 (s, 1, $CHCO_2Me$), 6.77 (s, 2, NH_2).

Methyl 2-(4-Chlorophenyl)-4,5-dihydro-α,4-dioxo-1*H*-imidazole-5-acetate (III).

A stirred mixture of 1 g. of I in 25 ml. of diphenyl ether was heated under reflux for 1 hour. The solution was cooled and the insoluble material was collected and recrystallized from 2-ethoxyethanol, giving the analytical sample, m.p. 271-274° dec. (lit. 256-257°); ir (potassium bromide): 3077 (NH, OH), 1715 (lactam C=O), 1678 (ester C=O), 1212 (C-O) cm^{-1}; nmr (DMSO-d_6): δ 3.88 (s, 3, CO_2Me), 7.52 8.07 (A, B quartet, 4 aromatic H's, J = 7.5 Hz).

Anal. Calcd. for $C_{12}H_9ClN_2O_4$: C, 51.36; H, 3.23; N, 9.98. Found: C, 51.49; H, 3.16; N, 9.89.

Methyl 2-(4-Chlorophenyl)-1,4,5,6-tetrahydro-5,6-dioxo-4-pyrimidinecarboxylate (IV).

A mixture of 8 g. (0.02 mole) of VI in 300 ml. of 10% aqueous acetic acid was stirred at room temperature for 5 minutes. The reaction mixture was filtered and the filtrate was allowed to stand overnight at room temperature. The precipitate which was formed was collected and recrystallized from ethanol, giving 4.6 g. of product, m.p. 147-151°; ir (chloroform): 3077 (broad OH, NH), 1754 (ester C=O), 1727 (ketone C=O), 1672 (conj. ester and lactam) cm^{-1}; ir (potassium bromide): 1667, 1634 (ester C=O, lactam C=O), 1208 (C-O) cm^{-1}; nmr (DMSO-d_6): δ 3.72, 3.82 (3, 2s, $CHCO_2Me$ and = CCO_2Me), 6.20 (s, 0.6 - $CHCO_2Me$), 7.55, 8.07 (A, B quartet, 4 aromatic H's, [J = 7.5 Hz]).

Anal. Calcd. for $C_{12}H_9ClN_2O_4$: C, 51.36; H, 3.23; N, 9.98. Found: C, 51.33; H, 3.22; N, 10.08.

Methyl [3-(4-Chlorophenyl)-4,5-dihydro-5-oxo-6*H*-1,2,4-oxadiazin-6-yliden]acetate (V).

To a solution of 15 g. (0.48 mole) of I in 150 ml. of methanol containing 20 ml. of water was added at room temperature 10 ml. of 50% sodium hydroxide solution. An additional 250 ml. of water was added and the solution stirred for 5 minutes. The precipitate which resulted after acidification with glacial acetic acid was removed by filtration under suction and recrystallized from methanol, giving 2.3 g. of product; ir (potassium bromide): 3225 (NH), 1706 (ester and lactam C=O), 1199 (C-O) cm^{-1}; nmr (DMSO-d_6): δ 3.70 (s, 3, CO_2Me), 5.95 (s, 1, $CHCO_2Me$), 7.62, 7.88 (A, B quartet, 4 aromatic H's, J = 7.5 Hz).

Methyl 2-(4-Chlorophenyl)-5-[2-(diethylamino)ethylamino]-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate (VI).

A stirred solution of 2.89 g. (0.01 mole) of V and 1.16 g. (0.01 mole) of *N,N*-diethylethylenediamine in 50 ml. of methanol was heated under reflux for 4 hours. The solution was cooled and diluted with water to initiate precipitation. The precipitate thus formed was collected and recrystallized from pentane giving 1.1 g. of product, m.p. 75-78°; ir (potassium bromide): 3195 (NH), 1672 (ester C=O), 1618 (lactam C=O), 1193 (C-O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{23}ClN_4O_3$: C, 57.06; H, 6.12; N, 14.79. Found: C, 57.41; H, 6.23; N, 15.02.

Methyl 2-(4-Chlorophenyl)-5-[(2-cyanoethyl)amino]-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate (VII).

A stirred mixture of 2.8 g. (0.01 mole) of V and 1.4 g. (0.02 mole) of 3-aminopropionitrile in 50 ml. of methanol was heated under reflux for 18 hours. The mixture was cooled in ice and the precipitate which formed was collected and recrystallized from methanol, giving 0.6 g. of product, m.p. 130-132°; ir (potassium bromide): 3280 (NH), 2240 (C≡N), 1662 (ester C=O), 1630 (lactam C=O), 1205 (C-O) cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}ClN_4O_3$: C, 54.15; H, 3.94; N, 16.84. Found: C, 53.96; H, 3.93; N, 16.78.

Methyl 5-[(2-Aminophenyl)amino]-2-(4-chlorophenyl)-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate (VIII).

A stirred mixture of 1.4 g. (0.005 mole) of V and 0.54 g. (0.005 mole) of *o*-phenylenediamine was heated under reflux in 25 ml. of methanol for 3 hours. The solution was cooled in ice and diluted with a few milliliters of water. The precipitate which formed was collected and recrystallized from methanol, giving 0.4 g. of product, m.p. 192-194° dec.; ir (potassium bromide): 3436, 3311 (NH_2), 1742 (unconj. ester C=O), 1700 (conj. ester C=O), 1626 (lactam C=O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.12; H, 4.29; N, 15.17.

5,5′-Hydrazobis[2-(4-chlorophenyl)-1,6-dihydro-6-oxo-4-pyrimidinecarboxylic Acid Hydrazide] (IX).

A stirred mixture of 2.8 g. (0.01 mole) of V and 0.64 g. (0.02 mole) of hydrazine in 50 ml. of methanol was heated under reflux for 3 hours. The resulting precipitate was collected on a filter and recrystallized from ethanol, giving 0.4 g. of product, m.p. 295-297° dec.; ir (potassium bromide): 3077 (very broad inner salt) cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}Cl_2N_{10}O_4$: C, 47.41; H, 3.25; N, 25.13. Found: C, 47.65; H, 3.29; N, 24.87.

Dimethyl 5,5′-(1,2-Ethanediyldiimino)bis[2-(4-chlorophenyl)-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate] (X).

A stirred mixture of 19.6 g. (0.07 mole) of V and 8.4 g. (0.14 mole) of ethylene diamine in 200 ml. of methanol was heated under reflux for 6 hours. The mixture was filtered and the filtrate was diluted with a few milliliters of water. The precipitate which formed was collected and the combined solids were recrystallized from 2-ethoxyethanol, giving 0.3 g. of product, m.p. 188-190°; ir (potassium bromide): 3226 (NH), 1661 (ester C=O), 1634 (lactam C=O), 1190 (C-O) cm^{-1}.

Anal. Calcd. for $C_{26}H_{22}Cl_2N_6O_6$: C, 53.34; N, 3.79; N, 14.36. Found: C, 53.40; H, 3.73; N, 14.54.

The filtrate from the above reaction was further diluted with water and left to stand at room temperature overnight. The precipitate which formed was collected and recrystallized from ethanol, giving 3.8 g. of 2-(4-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-pyrimido[5,4-*e*][1,4]diazepine-4,9(3*H*)dione (XIa); ir (potassium bromide): 3401, 3145 (NH), 1653 (lactam C=O), 1623 (C=N) cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 54.08; H, 3.84; N, 19.35.

Methyl 5-Amino-2-(4-chlorophenyl)-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate (XII).

A stirred solution of 2.0 g. (0.007 mole) of V in 20 ml. of *N,N*-diethylethylenediamine was heated under reflux for 1.5 hours. The solution was cooled in ice and diluted with water. The resulting precipitate was collected and recrystallized from ethanol, giving 0.3 g. of product, m.p. 144-146°; ir (potassium bromide): 3401, 3278 (NH_2), 1681 (ester C=O), 1642 (lactam C=O) cm^{-1}; nmr (deuteriochloroform): δ 3.77 (s, 3, CO_2Me), 5.75 (s, 1, $CHCO_2Me$), 6.70 (s, 2, NHC=O, C=N*H*), 7.48, 8.05 (A, B quartet, 4 aromatic protons, J = 7.5 Hz).

Anal. Calcd. for $C_{12}H_{10}ClN_3O_3$: C, 51.53; H, 3.60; M. 15.02. Found: C, 51.72; H, 3.69; N, 15.00.

Acknowledgment.

The authors are indebted to Mr. Bruce Hofmann and staff for the microanalyses and helpful discussions concerning interpretation of ir and nmr spectra.

REFERENCES AND NOTES

(1) N. D. Heindel and M. C. Chun, *J. Chem. Soc., D,* 644 (1971).

(2) This observation was also noted by Heindel for enolic heterocyclic compounds reference 1.

(3) T. Sheradsky, *Tetrahedron Letters,* 25 (1970).

(4) N. D. Heindel and M. C. Chun, *ibid.,* 1439 (1971).