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89. Akira Takamizawa and Kentaro Hirai : Studies on the Pyrimidine and Related Compounds. XXXVI.*1 Infrared Spectra of 1-(and 3)-Substituted 3,4-dihydro-2(1*H*)-pyrimidinone Derivatives and Some Reactions of These Compounds.*2

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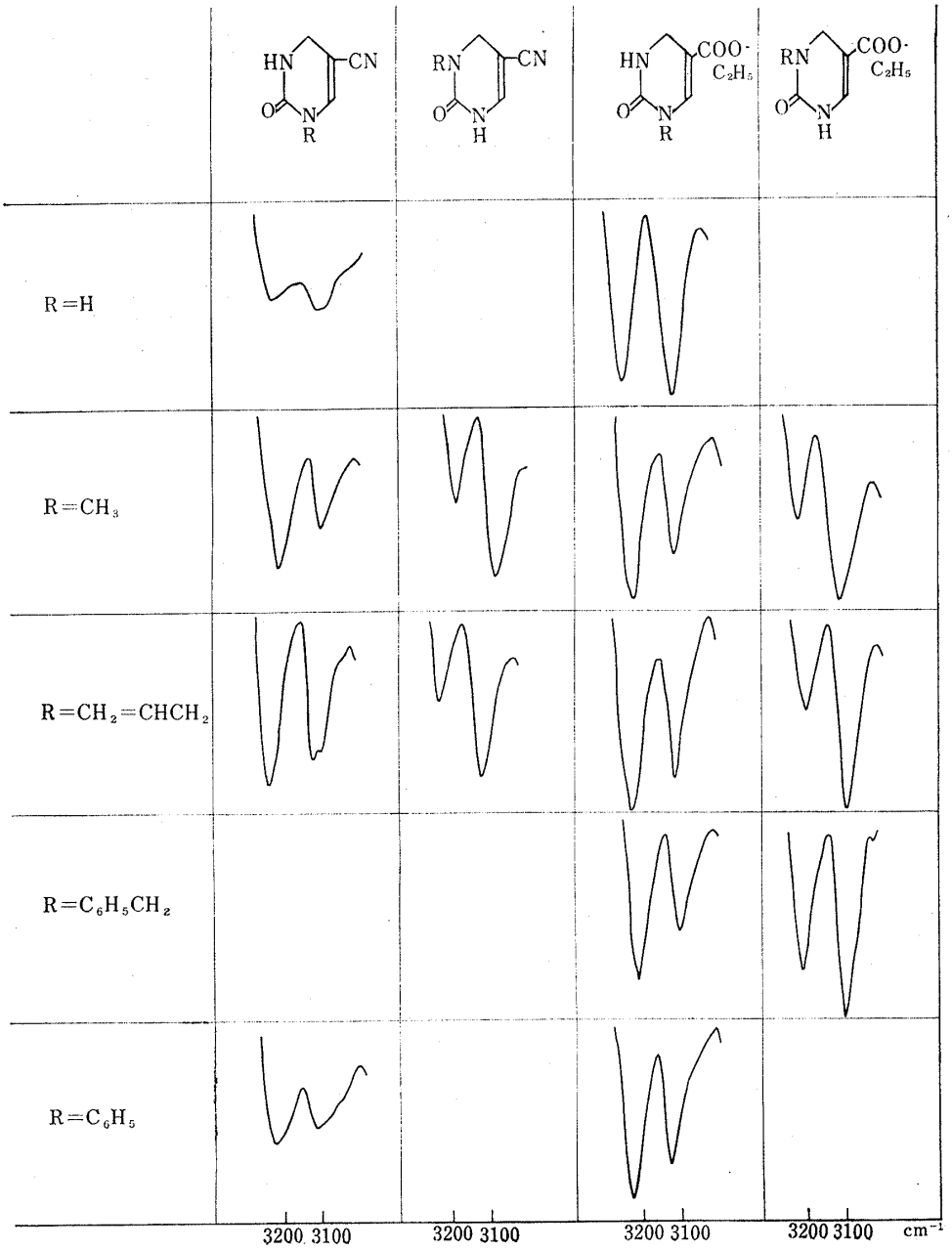

Fig. 1. NH Streching Patterns in Infrared Spectra of 2-Oxotetrahydropyrimidine Derivatives (in Nujol)

*1 Part XXXV : Tetrahedron Letters, 2803, 3599 (1964).

*2 A part of this paper was presented at the 14th General Meeting of Kinki Branch of the Pharmaceutical Society of Japan, Kyoto, November, 1964.

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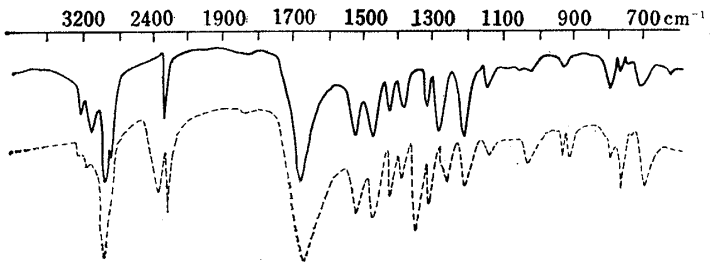


Fig. 2. Infrared Spectra (in Nuiol)

—— 2-Oxo-3-methyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile

------ deuterated compound $\frac{\nu_{NH}}{\nu_{ND}}=\frac{3086}{2277}=1.36$

The syntheses of 1-(and 3)-substituted 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (and 5-ethyl carboxylate) were reported in previous papers.[1~3] During the course of infrared spectral studies of these compounds, a correlation was seen between the spectral patterns and the structures of these compounds. The infrared spectra in Nujol mull showed two absorption bands due to NH stretching at about 3200 and 3100 cm^{-1}. The patterns of these bands of 1-substituted compounds differs apparently from those of 3-substituted compounds (Fig. 1). In the case of 1-substituted compounds, the intensities of the bands at about 3200 cm^{-1} are stronger than those of the bands at lower frequencies. In contrast, 3-substituted compounds showed bands at about 3100 cm^{-1} with weaker bands at higher frequencies. On exchange of the NH hydrogen atom for D by deuterium oxide treatment, two bands at about 3200 and 3100 cm^{-1} of these compounds shifted to about 2300 cm^{-1} due to ND vibration.[4] (Figs. 2, and 3).

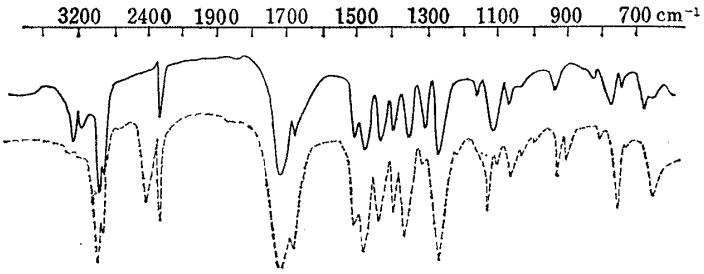


Fig. 3. Infrared Spectra (in Nuiol)

—— 1-Methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile

------ deuterated compound $\frac{\nu_{NH}}{\nu_{ND}}=\frac{3238}{2360}=1.37$

Difference of the patterns of the NH bands of 1-substituted compounds and 3-substituted compounds was considered to be due to the differences between the strengths of the intermolecular hydrogen bondings of these compounds. It should be noted that the infrared spectra are also useful*4 to assign the position of the NH group in these compounds.

In chloroform solution, however, both 1-NH and 3-NH absorption bands appeared at 3440 cm^{-1} as a single band and no differences between them were seen.

Attempts to test the reactivities of 1-NH and 3-NH groups were made. Hydrolysis of ethyl 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (I) with ethanolic potassium hydroxide gave 5-carboxylic acid (II), and the action of hydrazine hydrate on I afforded 5-hydrazide (III). Dihydropyran reacted with I in the presence of hydrochloric acid to give the product (IV) which was found to be substituted by one tetrahydropyranyl group. The infrared spectrum of IV showed a characteristic 1-NH band as described above. The proton magnetic resonance (NMR)*5 spectrum of IV showed a broad doublet at 1.60 τ due to 1-NH group and a C_6-methylidyne proton signal at 2.83 τ as the doublet

*4 NMR spectra of these compounds showed the signal of 1-NH proton at lower field than that of 3-NH proton and the NMR spectral measurement was used to assign the position of the NH group.[1~3]

*5 All NMR spectra were taken with a Varian A-60 spectrometer on about 10% solution in deuteriochloroform containing about 1% tetramethylsilane (TMS) as an internal reference.

1) A. Takamizawa, K. Hirai, Y. Sato, K. Tori: J. Org. Chem., **29**, 1740 (1964).
2) A. Takamizawa, K. Hirai: This Bulletin, **12**, 804 (1964).
3) *Idem*: *Ibid.*, **12**, 1418 (1964).
4) L. J. Bellamy: "The Infra-red Spectra of Complex Molecules," 207 (1958). John Wiley & Sons, Inc., New York.

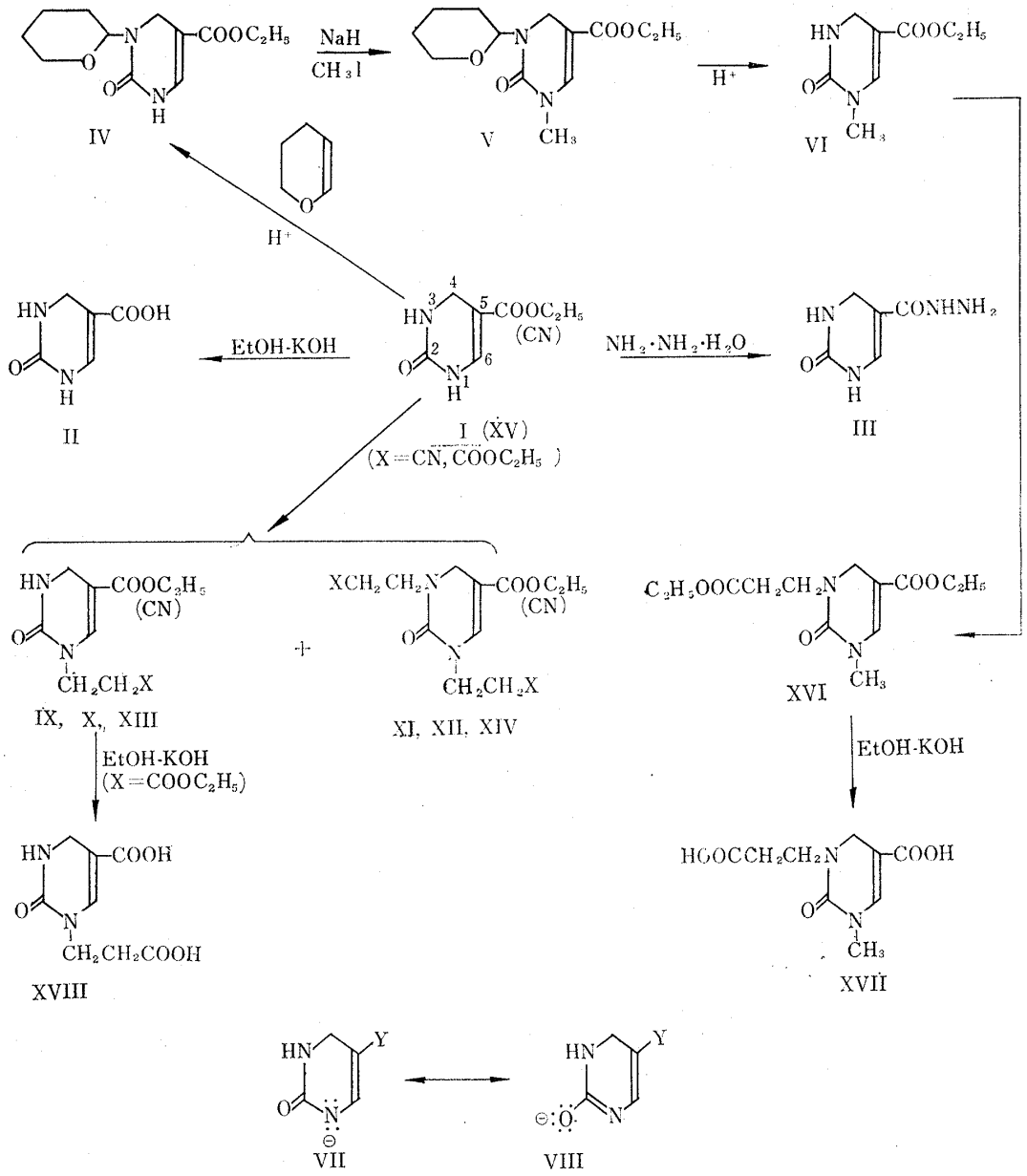


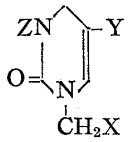
Chart 1.

of triplets (J=6.0, 1.0 c.p.s.), which changed into a tripet (J=1.0 c.p.s.) by the addition of a small amount of deuterium oxide to the solution examined. The action of sodium hydride on Ⅳ in absolute dioxane solution and subsequent methylation with methyl iodide gave the methyl derivative (Ⅴ). On treatment of Ⅴ with hydrochloric acid, tetrahydropyranyl group was removed to give the product (Ⅵ) which was identical with ethyl 1-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate previously obtained.[2,3] Accordingly, the product (Ⅳ) should be ethyl 2-oxo-3-(tetrahydro-2-pyranyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate. It was considered that the tetrahydropyranyl-C_2-cation which resulted from proton attack on dihydropyran[5] was attacked by more nucleophilic nitrogen on 3-NH of Ⅰ to yield the 3-substituted compound preferentially.

5) L. F. Fieser, M. Fieser: "Advanced Organic Chemistry," 311 (1962). Reinhold Publishing Coorp., Maruzen Co., Ltd.

Next, the addition of I, presumably as anion, to acrylonitrile and to ethyl acrylate was made. When this addition[6] was carried out in refluxing ethanol with a catalytic amount of sodium ethoxide using 1.2 moles of acrylic reagents to each mole of I, respective mono-addition products were obtained and some amount of the unchanged material was recovered. Thin-layer chromatography (TLC)*[6] of the reaction mixture failed to detect any di-addition products. The mono-addition products obtained here showed characteristic a 3-NH band as described above, and NMR spectra of these compounds showed a 3-NH signal at about 4.0 τ (Table I). The mono-adducts, therefore, were assigned to be N-1-adducts (IX, X). However, with three reactant molar

TABLE I. Addition Compounds and Derivatives



Compound	X	Y	Z	m.p. (°C)	Appearance
IX	CH_2CN	$COOC_2H_5$	H	135	colorless needles[a]
X	$CH_2COOC_2H_5$	〃	〃	94～95	colorless prisms[b]
XI	CH_2CN	〃	CH_2CH_2CN	136	colorless needles[a]
XII	$CH_2COOC_2H_5$	〃	$CH_2CH_2COOC_2H_5$	—	colorless oil
XIII	〃	CN	H	98～100	colorless prisms[b]
XIV	〃	〃	$CH_2CH_2COOC_2H_5$	—	colorless oil
XVI	H	$COOC_2H_5$	〃	—	〃
XVII	〃	COOH	CH_2CH_2COOH	181～182[c]	colorless needles
XVIII	CH_2COOH	〃	H	174～175[c]	colorless prisms

Recryst. from *a*) H_2O, *b*) AcOEt-petr. ether, *c*) decomp.

TABLE II. Physicochemical Data of the Compounds shown in Table I

	TLC (Rf)	IR ν_{max}^{Nujol} cm^{-1}	NMR (τ, NH)	UU λ_{max}^{EtOH} (log ε)
IX	0.24	3200>3100	4.07	214, 290 (3.93, 3.98)
X	0.37	3280>3140	3.88	214, 293 (3.98, 4.02)
XI	0.54	—	—	
XII	0.69	—	—	
XIII	0.46	3238>3118	3.88	284 (4.04)
XIV	0.67	—	—	
XVI	0.64	—	—	

TABLE III. Analytical Data of the Compounds shown in Table I

Compound	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
IX	$C_{10}H_{13}O_3N_3$	53.80	5.87	18.83	53.89	6.02	18.70
X	$C_{12}H_{18}O_5N_2$	53.32	6.71	10.37	53.84	6.84	10.38
XI	$C_{13}H_{16}O_3N_4$	56.51	5.84	20.28	56.08	5.97	20.05
XIII	$C_{10}H_{13}O_3N_3$	53.80	5.87	18.83	53.62	5.91	18.41
XVII	$C_9H_{12}O_5N_2$	47.37	5.30	12.28	47.31	5.57	12.12
XVIII	$C_8H_{10}O_5N_2$	44.86	4.71	13.08	44.71	4.86	13.07

*6 TLC: Alumina plate, AcOEt solvent, detected by I_2 vapor.

6) R. West: J. Org. Chem., 28, 1991 (1963).

ratios, di-addition products were obtained, accompanied with mono-adducts. The di-adducts (XI, XII) showed no NH band in their infrared spectra. The addition reaction of the 5-cyano compound (XV) with three moles of ethyl acrylate using Triton B as catalyst also proceeded to yield mono- and di-addition products (XIII and XIV). Ethyl 1-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (VI) yielded N-3-addition product (XVI) as oily product, which was hydrolyzed to dicarboxylic acid (XVII) to confirm the structure. Compound (X) was also hydrolyzed to give dicarboxylic acid (XVIII). These reactions presumably proceeded as follows. The more acidic 1-NH proton was preferentially abstracted by basic catalyzer and the addition of the resulted tetrahydropyrimidine anion (VII) to the electron-deficient β-carbon of the α,β-unsaturated acceptor molecule yielded N-1-adduct, which followed by subsequent addition on the 3-NH group, yielded di-addutc.[7]

By resonance considerations, tetrahydropyrimidine anion hybrid should receive contributions from O-anion structure (VIII) through which O-addition might occur. Ultraviolet spectra of these addition products, however, were very similar to those of N-1-alkyl compounds (Fig. 4), therefore, it was proved that such O-addition did not occur. Thus, the differences of the reactivities between 1-NH and 3-NH groups were recognized. These addition compounds obtained here would be valuable synthetic intermediates for the preparation of the biologically active compounds.

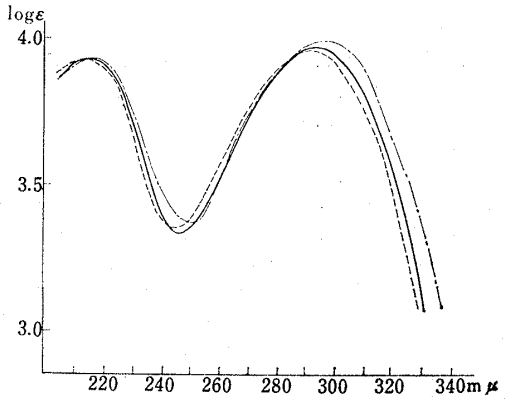


Fig. 4. Ultraviolet Spectra (in EtOH)

——— Ethyl 1-(2-Ethoxycarbonylethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (X)

- - - - - - - Ethyl 1-(2-Cyanoethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IX)

——— Ethyl 1-Allyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Experimental*7

2-Oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic Acid (II)——To the solution of 0.17 g. of I in 5.0 ml. of 70% EtOH, 0.3 g. of KOH was added and rafluxed for 0.5 hr. The reaction mixture was evaporated *in vacuo* and dil. HCl was added to the residue. Separated colorless prisms were collected, yield 0.093 g., m.p. 218~219°(decomp.). UV λ_{max}^{EtOH} mμ (log ε) : 288 (4.02). *Anal.* Calcd. for $C_5H_6O_3N_2$: C, 42.25; H, 4.26; N, 19.71. Found : C, 42.05; H, 4.48; N, 19.38.

2-Oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic Acid Hydrazide (III)——To the solution of 0.34 g. of I in 8.0 ml. of EtOH, 0.25 g. of $NH_2NH_2 \cdot H_2O$ (ca. 80%) was added and refluxed for 8 hr. After cooling, separated colorless needles were collected, yield 0.062 g., m.p. 188~189°(decomp.). To the filtrate, 0.25 g. of $NH_2NH_2 \cdot H_2O$ (ca. 80%) was added and refluxed for 7 hr. Separated crystals were collected after cooling, yield 0.10 g., which was identical with the crystals obtained above. On addition of ammoniac $AgNO_3$ to these crystals, silver mirror was formed. *Anal.* Calcd. for $C_5H_8O_2N_4$: C, 38.46; H, 5.16; N, 35.88. Found : C, 38.60; H, 5.52; N, 35.57.

Ethyl 2-Oxo-3-(tetrahydro-2-pyranyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (IV)——To the suspension of 0.558 g. of I in 20 ml. of $CHCl_3$, 1.0 ml. of 2,3-dihydro-4*H*-pyran was added and 1 drop of conc. HCl was added with stirring. On slightly warming, the suspension became clear. The reaction mixture was washed with dil. $NaHCO_3$, dried over anhyd. $MgSO_4$, and evaporated the solvent. The residue was treated with petr. ether to give 0.51 g. of crystals. Recrystallization from AcOEt-petr. ether gave colorless needles, m.p. 150°. UV λ_{max}^{EtOH} mμ (log ε) : 287 (3.99). *Anal.* Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.14; N, 11.02. Found : C, 56.81; H, 7.23; N, 11.10.

Ethyl 1-Methyl-2-oxo-3-(tetrahydro-2-pyranyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (V)——To the solution of 0.228 g. of IV in 4.0 ml. of abs. dioxane, 0.043 g. of NaH (50% oil suspension) and 0.2

*7 All melting points were uncorrected.

7) E. D. Bergmann, D. Ginsburg, R. Pappo : "Organic Reactions," Vol. X, 229 (1959). John Wiley & Sons, Inc., New York.

ml. of CH_3I were added and refluxed for 1 hr. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from AcOEt-petr. ether to give 0.20 g. of colorless prisms, m.p. 101~103°. NMR : 6.85 τ (NCH_3), 2.85 τ (=CH). *Anal.* Calcd. for $C_{13}H_{20}O_4N_2$: C, 58.19; H, 7.51; N, 10.44. Found : C, 58.15; H, 7.70; N, 10.32.

Ethyl 1-Methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (VI)——To the solution of 0.153 g. of V in 5.0 ml. of EtOH, 1 drop of 15% HCl was added and refluxed for 5 min. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from H_2O to give 0.043 g. of colorless needles, which was identical with the sample obtained previously.[2,3]

Preparation of the Adducts (Table I, II, III)——a) A small piece of sodium metal (ca. 20 mg.) was allowed to react with 10 ml. of abs. EtOH. To this were added 0.003 mole of I and 0.0036 mole of ethyl acrylate. After 3 hr. at reflux under anhydrous conditions, the solvent was removed and the residue was dissolved in $CHCl_3$ The $CHCl_3$ solution was washed with H_2O, dried over anhyd. $MgSO_4$, and the solvent was removed. The residue was recrystallized from AcOEt-EtOH to give starting material (I) (24%) and from the filtrate X was obtained, yield 36%.

b) Addition of I (0.34 g.) to acrylonitrile was carried out under the same condition as above a) and 0.30 g. of crystals were obtained. TLC of these crystals showed two spots arising from I and IX.

c) Reaction of 0.003 mole of I with 0.009 mole of acrylonitrile was carried out as described above. The reaction mixture showed two spots on TLC. By Al_2O_3 chromatography of the crude product, IX (28%) and XI (24%) were obtained separately.

d) Reaction of 0.005 mole of I with 0.015 mole of ethyl acrylate was carried out as described above. The reaction mixture showed two spots on TLC. By Al_2O_3 chromatography of the crude product, X (52%) and XII (28%) were obtained separately.

e) To the solution of 0.005 mole of powdered 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (XV) in 150 ml. of EtOH, 2.0 ml. of ethyl acrylate and 0.1 ml. of Triton B were added and refluxed for 5 hr. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$ and subjected to Al_2O_3 chromatography. The fractions showed the spot at Rf 0.67 on TLC were collected. Removal of the solvent left XIV as oil.

The fractions showed the spot at Rf 0.46 were collected and the solvent was removed to give 0.42 g. (48%) of XIII.

1-Methyl-2-oxo-5-carboxy-1,2,3,4-tetrahydro-3-pyrimidinepropionic Acid (XVII)——To the solution of 0.61 g. of I in 10 ml. of abs. EtOH, NaOEt solution and 1.0 g. of ethyl acrylate were added and refluxed as described above. The reaction mixture was concentrated *in vacuo* to leave XVI as oil which showed a single spot on TLC.

This was dissolved in 20 ml. of EtOH and 1.0 g. of KOH was added and refluxed for 0.5 hr.

The reaction mixture was concentrated *in vacuo* and the residue was added dil. HCl. Separated crystals were collected, yield 0.45 g. Recrystallization from MeOH gave XVII (Table I, III).

2-Oxo-5-carboxy-1,2,3,4-tetrahydro-1-pyrimidinepropionicAcid (XVIII)——To the solution of 0.224 g. of X in 10 ml. of 70% EtOH, 0.3 g. of KOH was added and refluxed for 0.5 hr. On treatment as above, 0.13 g. of XVIII (Table I, III) was obtained. UV λ_{max}^{EtOH} mμ (log ε) : 293 (4.07).

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Summary

The correlation was seen between the positions of NH groups and the NH stretching pattern in infrared spectra of 1-substituted tetrahydropyrimidine derivatives and 3-substituted compounds. The measurement of the infrared spectra of these compounds in Nujol mull is useful to assign their structures.

Differences in the reactivities between 1-NH and 3-NH groups were recognized by several reactions. Addition of dihydropyran to I occurred at 3-NH and the Michael-type addition reaction proceeded giving N-1-adducts and N-1,3-di-adducts.

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