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114. Akira Takamizawa and Kentaro Hirai : Studies on the Pyrimidine Derivatives. XXXI.*1 Reactions of Ethyl 2-Methoxymethylene-3-ethoxypropionate with Ureas.

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In a previous paper[1] of this series, the reaction of 2-methoxymethylene-3-ethoxypropionitrile (I) and 2-ethoxymethyl-3-ethoxy-3-methoxypropionitrile (II) with urea derivatives were reported. This paper deals with the reactions of ethyl 3-ethoxy-2-methoxymethylenepropionate (III) with urea and N-substituted ureas.

2-Oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (IV) has already been obtained by the reaction of I (or II) with urea. Therefore, in the case of III instead of I, similar condensation would be expected.

Reaction of III with urea has carried out in ethanol solution in the presence of hydrochloric acid and a product (V), $C_7H_{10}O_3N_2$, was obtained in 72% yield. The infrared spectrum of V showed NH bands and C=O bands. Acetylation of V afforded the diacetate (VI). The nuclear magnetic resonance (NMR) spectrum*3 of VI (Table I) showed the proton signals of ethyl of ester, two N-acetyl, C_4-methylene, and C_6-methylidyne groups, respectively. From these results, V can be formulated as ethyl 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate. Dehydrogenation of V by the action of bromine in acetic acid gave ethyl 2-oxo-1,2-dihydro-5-pyrimidinecarboxylate (VII), which was converted into ethyl 2-chloro-5-pyrimidinecarboxylate (VIII) on treatment with phosphoryl chloride and N,N-dimethylaniline. Amination of VIII gave the 2-amino derivative (IX), which was saponified to afford 2-amino-5-pyrimidinecarboxylic acid (X). 2-Amino-5-pyrimidinecarbonitrile (XI), obtained in the previous work,[1] was hydrolyzed to give the 5-carboxy derivative and the identity of these compounds was confirmed by comparison of their infrared spectra.

Formerly, Ballard and Johnson[2] reported the synthesis of X from diethyl malonate and ethyl pseudothiourea *via* VIII through longer steps than our route. Our method gave a more satisfactory yield in obtaining VIII.

Reaction of III with 1,3-dimethylurea in ethanol solution in the presence of hydrochloric acid afforded a product (XII), $C_9H_{14}O_3N_2$, in 85% yield. Infrared spectrum of XII showed C=O bands, but no NH band. NMR spectrum of XII exhibited the proton signals of ethyl of ester, two N-methyl, C_4-methylene, and C_6-methylidyne groups, respectively (Table I). Thus, XII was formulated as ethyl 2-oxo-1,3-dimethyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

Reaction of III with N-methylurea in ethanol solution in the presence of hydrochloric acid gave a product of m.p. 95~97°, $C_8H_{12}O_3N_2$. However, this product showed two spots on a thin-layer chromatogram (TLC).*4 NMR spectrum of this product exhibited two pairs of signals of N-methyl and NH protons whose respective relative integrated intensities are about 5:4. These facts suggest that this product is a mixture of

*1 Part XXX. A. Takamizawa, K. Hirai, Y. Hamashima, M. Hata : This Bulletin, 12, 558 (1964).

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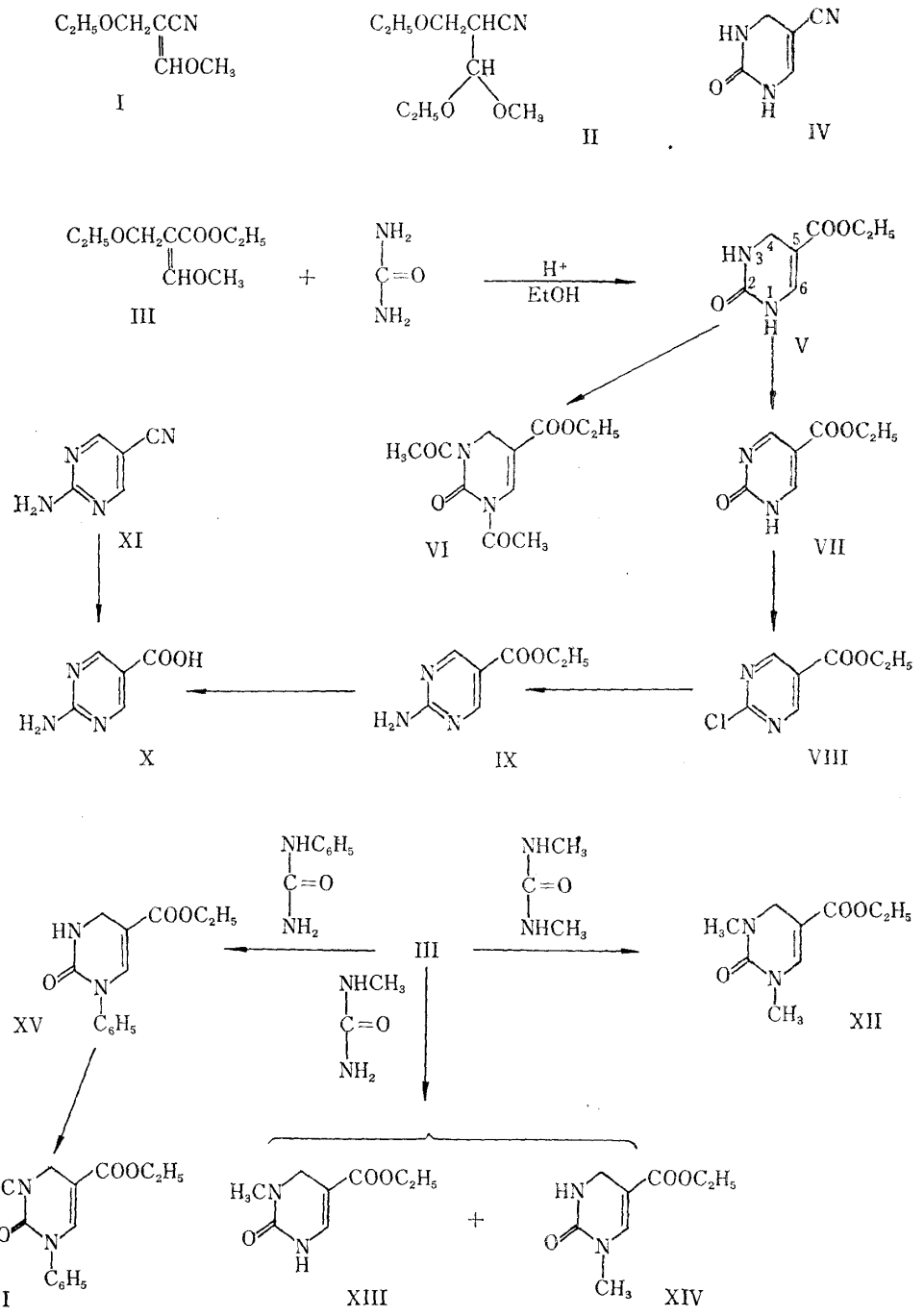
*3 All NMR spectra were taken with a Varian A-60 spectrometer on about 10% solution in $CDCl_3$ containing about 1% tetramethylsilane (TMS) as an internal reference. Chemical shiftes are expressed in τ-values and coupling constants are in c.p.s.

*4 TLC : alumina plate, ethyl acetate solvent, detected by I_2 vapor.

1) A. Takamizawa, K. Hirai, Y. Sato, K. Tori : J. Org. Chem. to be published in July, 1964.

2) E. Ballard, T. B. Johnson : J. Am. Chem. Soc., **64**, 794 (1942).



ethyl 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XIII) and the 1-methyl isomer (XIV) in a ratio of 5:4. This mixture was subjected to columnar chromatography on alumina and two crystalline products, m.p. 126~127° (XIII) and m.p. 117~118° (XIV), were obtained separately. The assignment of these compounds was made as follows. NMR spectrum of XIII exhibited the signal of N-methyl protons at higher field (7.07 τ) than that of XIV (6.88 τ). This fact suggests*5 that the N-methyl group in XIII should be situated at the position 3. The spectrum of XIII also exhibited a doublet (J=5.7 c.p.s.) at 1.08 τ due to the NH group and the C_6-methylidyne proton signal as a doubling

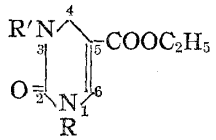
*5 NMR spectra of 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile and 1-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile[1] exhibit the signals of N-methyl groups at 7.08 and 6.88 τ, respectively.

triplet (J=5.7, 1.0 c.p.s.) at 2.78 τ, which changed into a triplet by the addition of a small amount of deuterium oxide to the solution examined. This decoupling results from the proton exchange of the NH group. These facts indicate that the NH group is situated at a position adjacent to the C_6-methylidyne group.*6 Therefore, XIII can be formulated as ethyl 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

XIV, which exhibited the signal of NH proton at 4.33 τ and a triplet due to C_6-methylidyne proton at 2.82 τ, can be formulated as the 1-methyl isomer.

Reaction of III with N-phenylurea in ethanol solution in the presence of hydrochloric acid afforded ethyl 1-phenyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XV) in 81% yield as the sole product and 3-phenyl isomer was not obtained. The structure of XV was confirmed by NMR spectrum. Namely, XV showed N_3-H proton signal at 3.91 τ and the signal of C_4-methylene protons of its acetate (XVI) shifted to lower field by adjacent N_3-acetyl group (see Table I).

Table I. Nuclear Magnetic Resonance Spectral Data in Deuterochloroform (10%)[a]

Compd.		$COOC_2H_5$[b]	N_1-$COCH_3$	N_3-$COCH_3$	N_1-CH_3	N_3-CH_3	N_1-H	N_3-H	C_4-CH_2[c]	C_6-H[c]
										
R=R'=$COCH_3$	VI	8.67^t 5.70^q	7.33	7.42	—	—	—	—	5.50^d	1.80^t
R=R'=CH_3	XII	8.73^t 5.83^q	—	—	6.87	7.07	—	—	5.90^d	2.83^t
R=H, R'=CH_3	XIII	8.75^t 5.81^q	—	—	—	7.07	1.08^d	—	5.87^d	2.78^{d-t}
R=CH_3, R'=H	XIV	8.72^t 5.83^q	—	—	6.88	—	—	4.33	5.84^t	2.82^t
R=C_6H_5, R'=H	XV	8.75^t 5.81^q	—	—	—	—	—	3.91	5.78^t	about 2.6[d]
R=C_6H_5, R'=$COCH_3$	XVI	8.73^t 5.80^q	—	7.47	—	—	—	—	5.38^d	about 2.7[d]

a) Peak multiplicities are presented by d (doublet), t (triplet), q (quartet) and d-t (doubling triplet).
b) J=7.0 c.p.s.
c) $J_{4,6}$=1.0 c.p.s.
d) Overlap with the signal of phenyl protons.

Experimental*7

Ethyl 2-Oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (V)——Urea (3.0 g.) and 9.4 g. of ethyl 2-methoxymethylene-3-ethoxypropionate (III) were added to the solution of 250 ml. of EtOH and 5 ml. of conc. HCl. The mixture was refluxed for 8 hr. and concentrated *in vacuo* to dryness. Residual crystals were recrystallized from EtOH to give 6.1 g. (72%) of colorless prisms, m.p. 178~180°. IR ν^{Nujol} cm^{-1}: 3258, 3118, 1719, 1704, 1271, 1075. UV λ_{max}^{EtOH} mμ (log ε): 214 (3.92), 288 (3.98). *Anal.* Calcd. for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.55; H, 6.03; N, 16.42.

Ethyl 2-Oxo-1,3-diacetyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (VI)——A mixture of 0.5 g. of V and 5 ml. of Ac_2O was refluxed for 4 hr. The excess reagent was removed *in vacuo* and the residue was distilled under reduced pressure. Colorless oil of $b.p_{0.6}$ 143~145° (0.3 g.) was obtained. *Anal.* Calcd. for $C_{11}H_{14}O_5N_2$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.24, H, 5.81; N, 11.03.

Ethyl 2-Oxo-1,2-dihydro-5-pyrimidinecarboxylate (VII) Hydrobromide——To a mixture of 0.5 g. of V in 10 ml. of AcOH, a solution of 0.47 g. of Br_2 in 2 ml. of AcOH was added and refluxed for 1 hr. Reaction mixture was concentrated *in vacuo* to dryness and the residual crystals (0.53 g., 62%) was recrystallized from EtOH-AcOH to give 0.48 g. (56%) of pale orange prisms, m.p. 184~186 (decomp.). UV λ_{max}^{EtOH}: 257 mμ (log ε 4.19), 265, 305 mμ (shoulder). *Anal.* Calcd. for $C_7H_8O_3N_2 \cdot HBr$: C, 33.75; H, 3.64; N, 11.25. Found: C, 33.81; H, 3.78; N, 11.66.

*6 Spin coupling between =CH proton and -CONH- proton in 2-oxo-2,3-dihydro-6*H*-1,3-thiazine-5-carbonitrile has been reported in a previous paper.[1]
*7 All melting points were taken on a Köfler hot plate and are uncorrected.

Ethyl 2-Chloro-5-pyrimidinecarboxylate (VIII)——A mixture of 0.53 g. of Ⅶ·HBr, 3 ml. of $POCl_3$, and 0.3 ml. of dimethylaniline was refluxed for 1 hr. The excess reagent was removed under reduced pressure and ice H_2O was added to the residue. After the solution was made alkaline by adding dil. NaOH, it was extracted with AcOEt. The AcOEt extract was dried over anhyd. $MgSO_4$ and AcOEt was removed. The residue was extracted with hot petr. ether, and the petr. ether extract was concentrated to dryness to afford 0.25 g. (62%) of pale green needles, which was purified with distillation (b.p_5 80°) to give colorless needles, m.p. 45°. *Anal.* Calcd. for $C_7H_7O_2N_2Cl$: C, 45.06; H, 3.78; N, 15.01; Cl, 19.00. Found: C, 44.91; H, 3.95; N, 14.46; Cl, 19.13.

Ethyl 2-Amino-5-pyrimidinecarboxylate (IX)——A solution of crude Ⅷ (0.9 g.) in 40 ml. of EtOH saturated with NH_3 was heated at 100° in a tube for 1 hr. The reaction mixture was concentrated under reduced pressure and the separated crystals were collected to give 0.5 g. (62%), m.p. 140~141°, of colorless prisms. Recrystallization from H_2O gave colorless prisms, m.p. 140~141°. *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.27; H, 5.50; N, 24.91.

2-Amino-5-pyrimidinecarboxylic Acid (X)——a) To a solution of 25 ml. of EtOH and 1.5 ml. of 10% KOH, 0.16 g. of Ⅸ was added and boiled for 1 hr. After cooling, 5 ml. of EtOH was added to the reaction mixture and the separated crystals were collected. These were dissolved in H_2O and AcOH was added to liberate 0.07 g. of colorless prisms, m.p. >290°. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.41; H, 3.78; N, 29.88.

b) A suspension of 0.28 g. of Ⅺ[1] in 5 ml. of 10% KOH was boiled for 2 hr. The reaction mixture was made acidic by adding AcOH and concentrated to one third volume. The concentrated solution was allowed to stand to afford 0.10 g. of colorless prisms, m.p. >290°, which was found to be identical with the sample obtained above a) by comparison of their IR spectra.

Ethyl 2-Oxo-1,3-dimethyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XII)——A solution of 1.9 g. of Ⅲ, 0.9 g. of 1,3-dimethylurea and 2 ml. of conc. HCl in 100 ml. of EtOH was refluxed for 16 hr. The solution was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. $MgSO_4$, and the $CHCl_3$ was removed. The residue was collected to afford 1.7 g. (85%) of colorless prisms, m.p. 73~75°. Recrystallization from AcOEt-EtOH-petr. ether gave colorless prisms, m.p. 89~91°. UV λ_{max}^{EtOH} mμ (log ε): 221 (3.82), 300 (3.84). *Anal.* Calcd. for $C_9H_{14}O_3N_2$: C, 54.54; H, 7.13; N, 14.14. Found: C, 54.71; H, 7.20; N, 14.03.

Reaction of III with N-Methylurea——A solution of 2.96 g. of N-methylurea, 7.52 g. of Ⅲ, conc. HCl 4 ml. in 200 ml. of EtOH was refluxed for 8 hr. The solution was concentrated *in vacuo*, the residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed with dil. NaOH. After drying over anhyd. $MgSO_4$, the $CHCl_3$ was removed. The residue was recrystallized from benzene-petr. ether to afford 7.3 g. (84%) of colorless needles, m.p. 95~97°. TLC, Rf 0.67, 0.62. *Anal.* Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21. Found: C, 51.88; H, 6.55; N, 15.45.

This product was chromatographed on Al_2O_3. The fractions showing the single spot at Rf 0.67 by TLC was collected and the removal of the solvent gave 2.2 g. of colorless crystals, which was recrystallized from H_2O to give 2.0 g. of colorless needles, m.p. 117~118°. UV λ_{max}^{EtOH} mμ (log ε): 214 (3.91), 296 (4.01). IR ν^{Nujol} cm^{-1}: 3232, 3127, 1703, 1682. *Anal.* Found: C, 52.49; H, 6.81; N, 15.31. The NMR spectrum shows these crystals to be ethyl 1-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XIV). The fractions, eluted by the mixture of $CHCl_3$ and EtOH showed a single spot at Rf 0.62, and the removal of the solvent gave 1.92 g. of colorless crystals. Recrystallization from H_2O afforded colorless needles, m.p. 126~127°. UV λ_{max}^{EtOH} mμ (log ε): 219 (3.93), 289 (3.94). IR ν^{Nujol} cm^{-1}: 3216, 3113, 1703, 1648. *Anal.* Found: C, 51.93; H, 6.74; N, 15.36. The NMR spectrum shows these crystals to be ethyl 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XIII).

Ethyl 1-Phenyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XV)——A solution of 1.9 g. of Ⅲ, 1.4 g. of N-phenylurea, and 2 ml. of conc. HCl in 100 ml. of EtOH was refluxed for 3 hr. The solution was concentrated *in vacuo* to dryness, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with dil. K_2CO_3 and dried over anhyd. $MgSO_4$. Removal of the $CHCl_3$ gave 2.0 g. (81%) of colorless crystals. Recrystallization from EtOH afforded colorless needles, m.p. 159~160°. UV λ_{max}^{EtOH} mμ(log ε) : 295 (4.04,) 236 (3.96) (shoulder). IR ν^{Nujol} cm^{-1}: 3241, 3135, 1702, 1229, 1075. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.16; H, 5.93; N, 11.00.

Ethyl 1-Phenyl-2-oxo-3-acetyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XVI)——The mixture of 0.3 g. of crude XV and 3 ml. of Ac_2O was refluxed for 3 hr. The solution was concentrated *in vacuo* and the residue was distilled under reduced pressure. Colorless oil (0.4 g.), b.p_6 195°, was obtained. *Anal.* Calcd. for $C_{15}H_{16}O_4N_2$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.01; H, 5.29; N, 9.61.

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Summary

Ethyl 2-methoxymethylene-3-ethoxypropionate (Ⅲ) undergoes condensation with urea, and N-substituted urea in ethanol solution in the presence of hydrochloric acid. With urea, Ⅲ gave ethyl 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Ⅴ), with N-methylurea a mixture of ethyl 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XIII) and its isomeric 1-methyl compound (XIV), which was separated into each isomer, and with N-phenylurea the 1-phenyl compound (XV) was exclusively obtained. Conversion into pyrimidines was achieved by dehydrogenation and subsequent chlorination of Ⅴ.

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115. Terumi Aoki, Hiroko Yamamura, Kyoko Takei,*1 and Hiromu Mori*2 : Synthesis of 16-Oxygenated Androst-5-en-3β-ol Derivatives.

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Androst-5-ene-3β, 16α, 17β-triol,[1~3] androst-5-ene-3β, 16β, 17β-triol,[4] and 3β, 16α-dihydroxyandrost-5-en-17-one[5] are all steroid metabolites isolated from human urine. In our course of study on steroid metabolism, these compounds became necessary as standard samples. Androst-5-ene 3β,16α,17β-triol was first prepared by Huffman and Lott,[6] from 3β-hydroxyandrost-5-en-17-one through nine steps, but much more convenient method seems not to be reported. This paper describes much more convenient method of synthesis of androst-5-ene-3β,16α,17β-triol and related compounds.

In Huffman's method of synthesis, key steps for introduction of oxygen at C-16 contain three reactions (Ⅰ→Ⅱ→Ⅲ→Ⅳ); the condensation of 17-oxo steroid (Ⅰ) with isoamyl nitrite to 16-oximino-17-oxo compound (Ⅱ), reductive hydrolysis of Ⅱ with zinc dust in aqueous acetic acid to 17β-hydroxy-16-oxo compound (Ⅲ) and reduction of Ⅲ with sodium amalgam to 16α,17β-glycol (Ⅳ). The last step (Ⅲ→Ⅳ) is not stereospecific reaction, so that considerable amount of 16β,17β-glycol is also produced[7]. On the other hand, Gallagher and his coworkers[8] developed another method of synthesis of 16α,17β-glycol from 17-oxo steroid which is more stereospecific; Ⅰ is transformed into 17-enol acetate (Ⅴ), which on oxidation with peracid gave the oxide (Ⅵ), followed by reduction with lithium aluminum hydride to 16α,17β-glycol (Ⅳ). This elegant method could be applied for synthesis of androst-5-ene-3β,16α,17β-triol.

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1) H. Hirschman : J. Biol. Chem., **150**, 363 (1943).
2) G. F. Marrian : Nature, **154**, 19 (1944); G. F. Marrian, G. C. Butler : Biochem J., **38**, 322 (1944).
3) H. L. Mason, E. J. Kepler : J. Biol. Chem, **161**, 235 (1945).
4) K. Fotherby : Biochem. J., **67**, 259 (1957).
5) K. Fotherby, A. Colas, S. M. Atherden, G. F. Marrian : *Ibid.*, **66**, 664 (1957).
6) M. N. Huffman, M. H. Lott : J. Biol. Chem., **172**, 789 (1948).
7) *Idem* : J. Am. Chem. Soc., **71**, 719 (1949).
8) N. S. Leeds, D. K. Fukushima, T. F. Gallagher : *Ibid.*, **76**, 2943 (1954).