sion of the nitro form to aci-nitro anion rather than the ester hydrolysis. Only ethyl nitroacetate developed a wave for the aci-nitro anion. The coulometric n values and the products obtained, combined with the polarographic results, suggest the scheme (1) as the most probable reduction mechanism. The production of amine is only possible through C=N double bond formation, but not through hydroxyamino derivatives as usually suggested.

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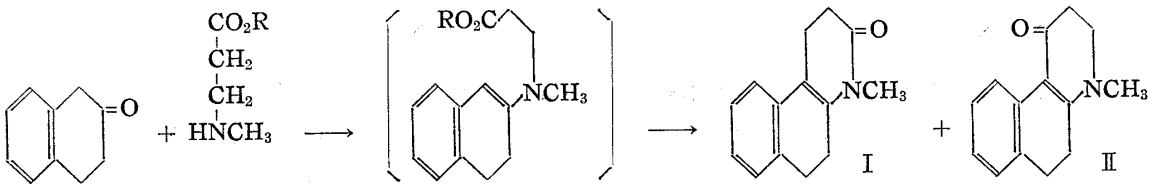
191. Zen-ichi Horii, Chuzo Iwata, Ichiya Ninomiya, Nobuhiko Imamura, Masayoshi Ito, and Yasumitsu Tamura : Studies on Ergot Alkaloids and Its Related Compounds. X.*1 Condensation of Cyclic Ketones and 3-Methylaminopropionates.

(*Faculty of Pharmaceutical Sciences, Osaka University**2)

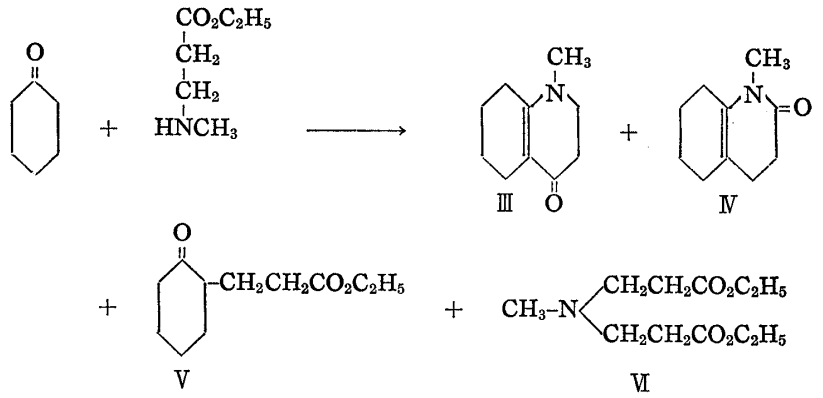
In 1958, Nelson and his coworkers[1] carried out the condensation of 2-tetralone and methyl 3-methylaminopropionate and assigned the structure of the sole product as 4-methyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2*H*)-one (II). Later in 1962,[2] we applied their procedure to the reactions between a variety of cyclic ketones and the 3-methylaminopropionates and formulated the structures of the major products as III, IX, X, XVIII′~XXI′ and XXIII~XXV on the basis of the Nelson's conclusion. However, it has recently been found by the joint work[3] of Nelson's and our groups that the structure of the major product from 2-tetralone and methyl 3-methylaminopropionate should be 4-methyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (I) instead of II and, further, that compound (II) is also formed, although a very small amount, in the reaction.*1 These results prompted us to reinvestigate our previous work[2] in order to make necessary corrections on the structures of the reaction products and, at the same time, to elucidate the course of this type of the reaction.



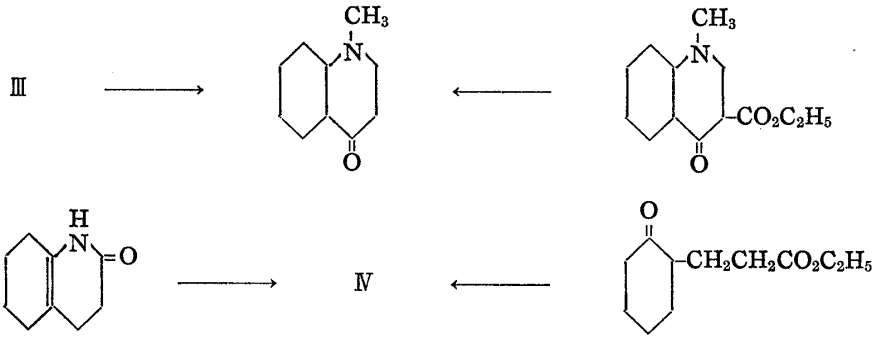
Reaction of Cyclohexanone and Ethyl 3-Methylaminopropionate

A mixture of equimolar amounts of cyclohexanone and ethyl 3-methylaminopropionate was heated under reflux for 50 hours as in the previous paper.[2] The products were purified by fractional distillation, followed by column chromatography on alumina, giving 1-methyl-2,3,5,6,7,8-hexahydro-4(1*H*)-quinolone (III) in 53% yield, along with small

*1 Part IX : Yakugaku Zasshi, **85**, 1220 (1964).
*2 Toneyama, Toyonaka, Osaka-fu (堀井善一, 岩田宙造, 二宮一弥, 今村信彦, 伊藤允好, 田村恭光).
1) N. A. Nelson, J. E. Ladbury, R. S. P. Hsi : J. Am. Chem. Soc., **80**, 6633 (1958).
2) Z. Horii, C. Iwata, Y. Tamura : This Bulletin, **10**, 940 (1962).
3) Z. Horii, C. Iwata, Y. Tamura, N. A. Nelson, G. H. Rasmusson : J. Org. Chem., **29**, 2768 (1964).



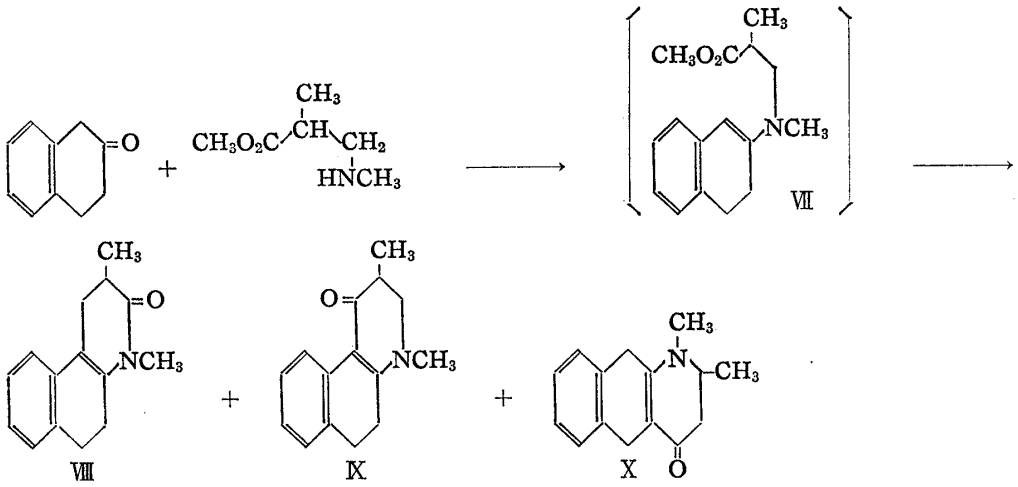
amounts of three early eluted fractions. The structure of the vinylogous lactam (Ⅲ) was confirmed by the lithium aluminum hydride reduction[2] to *trans*-1-methyloctahydro-4(1*H*)-quinolone, which was identified with the authentic specimen prepared[4] by hydrolysis and simultaneous decarboxylation of ethyl *trans*-1-methyl-4-oxodecahydro-3-quinolinecarboxylate. Although no pure samples could be isolated from the three early eluted fractions because of their small quantities, vapor phase chromatography and thin-layer chromatography showed that these fractions were consisted of 1-methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone (Ⅳ), ethyl 2-oxocyclohexanepropionate (Ⅴ) and diethyl methyliminodipropionate (Ⅵ), respectively. An authentic specimen of the enamine-lactam (Ⅳ) for vapor phase and thin-layer chromatographies was prepared by two routes, that is, by methylation of 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone[5] with methyl iodide in 69% yield and by keeping the ketoester (Ⅴ) with 30% benzene solution of methylamine in a sealed flask for 40 hours in 21% yield. Specimens of compounds (Ⅴ) and (Ⅵ) were prepared by the methods of Stork, *et al.*[6] and Mozingo, *et al.*,[7] respectively.



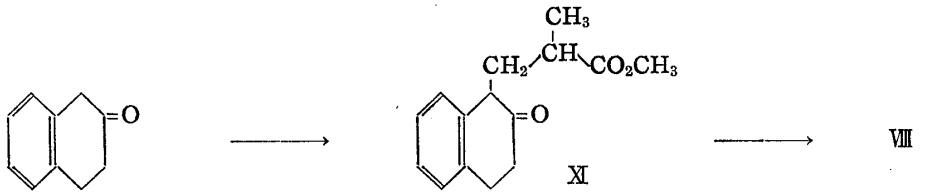
Reaction of 2-Tetralone and Methyl 2-Methyl-3-methylaminopropionate

The reaction was carried out, as reported in the previous paper,[2] by refluxing a mixture of equimolar amounts of 2-tetralone and methyl 2-methyl-3-methylaminopropionate in toluene for 10 hours, followed by heating an intermediate enamine-ester (Ⅶ) in ethylene glycol for further 10 hours. Distillation of the crude product, followed by recrystallization gave 2,4-dimethyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (Ⅷ), along with small amounts of 2,4-dimethyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2*H*)-one (Ⅸ) and 1,3-dimethyl-1,2,5,10-tetrahydrobenzo[*g*]quinolin-4(3*H*)-one (Ⅹ). The structure of

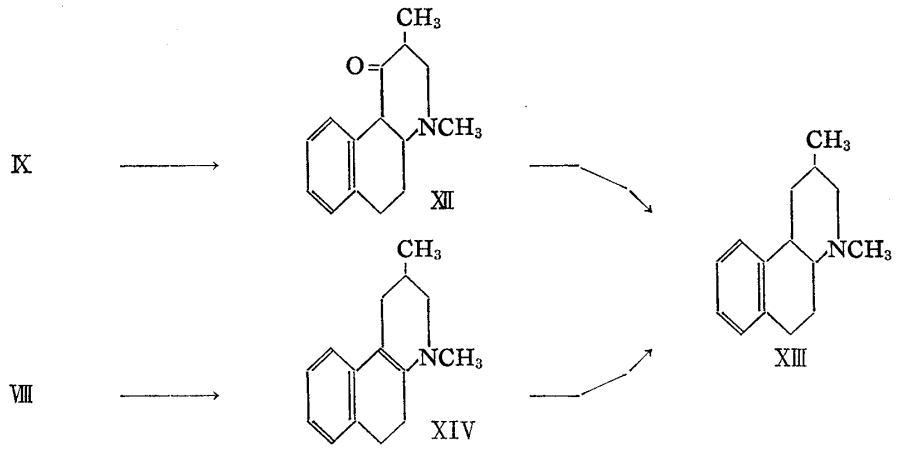
4) Z. Horii, T. Watanabe, M. Ikeda, Y. Tamura: Yakugaku Zasshi, **83**, 930 (1963).
5) A. D. Campbell, I. R. R. Stevens: J. Chem. Soc., **1956**, 959; W. A. Ayer, J. A. Berezowsky, G. G. Iverack: Tetrahedron, 8, 567 (1962).
6) G. Stork, A. Brizzolora, H. Landesman, J. Szmuszkovicz, R. Terrell: J. Am. Chem. Soc., 85, 207 (1963).
7) R. Mozingo, J. H. McCracken: Org. Syntheses, Coll. Vol. Ⅲ, p. 258 (1955).



the major product (Ⅷ), which had been assigned structure Ⅸ previously,[2] was proved by the following synthetic evidence. Michael condensation[8] of 2-tetralone and methacrylate in the presence of sodium methoxide gave a 78% yield of methyl α-methyl-2-oxo-1,2,3,4-tetrahydro-1-naphthalenepropionate (Ⅺ), which was kept in a sealed flask with 30% benzene solution of methylamine at room temperature for 50 hours to give the enamine-lactam (Ⅷ) in 39% yield. No depression in melting point was observed on admixture of both specimens of the enamine-lactam (Ⅷ) prepared above.



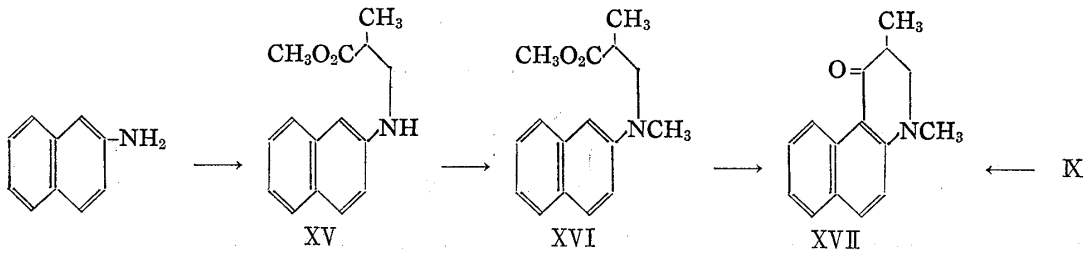
That the vinylogous lactam (Ⅸ) had the same benzo[*f*]quinoline skeleton as the enamine-lactam (Ⅷ) was proved by reactions as described below. The vinylogous lactam (Ⅸ) was reduced with lithium in liquid ammonia to 2,4-dimethyl-3,4,4*a*,5,6,10*b*-hexahydrobenzo[*f*]quinolin-1(2*H*)-one (Ⅻ) in 70% yield, which was further reduced by refluxing with amalgamated zinc in conc. hydrochloric acid for 36 hours[9] to 2,4-dimethyl-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline (XIII) in 20% yield. On the other hand, the enamine-lactam (Ⅷ) was reduced with lithium aluminum hydride in ether, quantitatively, to 2,4-



8) E. D. Bergmann, D. Ginsburg, R. Pappo : Org. Reactions, **10**, 179 (1959).
9) G. R. Clemo, J. G. Cook, R. Raper : J. Chem. Soc., **1938**, 1103.

dimethyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (XIV), which was further reduced[10] with lithium in liquid ammonia to compound (XIII) in 40% yield. Both specimens of compound (XIII) obtained above were shown to be identical by comparison of the melting points and infrared spectra of their methiodides as well as the infrared spectra of the free bases. The configuration of compound (XIII) will be discussed in later paper.

The evidence for the location[11] of the carbonyl function, therefore, the complete structure of the vinylogous lactam (IX) was provided by its conversion to 2,4-dimethyl-3,4-dihydrobenzo[*f*]quinolin-1(2*H*)-one (XVII), which was synthesized by an independent route. The conversion from IX to XVII was effected by refluxing a benzene solution of IX in the presence of chloranil[12] for 3 hours in 25% yield. Compound (XVII) was also prepared as followed.[13] 2-Naphthylamine was condensed with 2-methyl-3-bromopropionic acid in butanol in the presence of sodium butoxide, followed by esterification with methanol and hydrogen chloride, gave methyl 2-methyl-3-(2-naphthylamino)propionate (XV) in 15% yield. The naphthylamine (XV) was methylated to methyl 2-methyl-3-(N-methyl-2-naphthylamino)propionate (XVI) with methyl bromide in a sealed tube in 30% yield, or with dimethyl sulfate in aqueous sodium bicarbonate solution in 78% yield. Hydrolysis of the aminoester (XVI) with 10% sodium hydroxide solution, followed by heating under reflux in a mixture of equal amounts of acetic anhydride and pyridine for 3 hours, gave compound (XVII) in 10% yield. Both specimens of compound (XVII) obtained above were shown to be identical by their mixed melting point determination as well as by comparison of their infrared spectra.

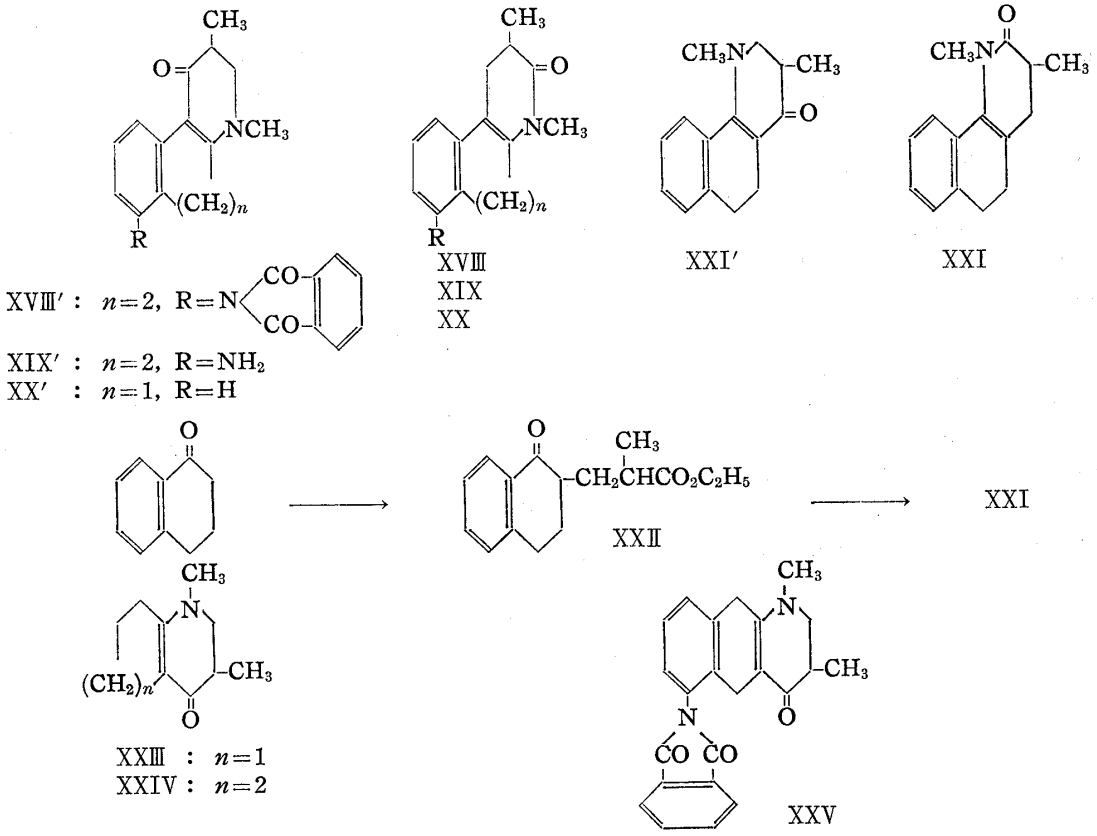


The assignment of the structure of the other vinylogous lactam (X) will be discussed in next chapter of this paper.

Characteristic Properties of the Vinylogous Lactam and the Enamine-lactam, and Re-examination of the Structures reported in the Previous Paper

From the close resemblances of their infrared, ultraviolet spectra and their attitudes towards the ferric chloride test, with those of the enamine-lactams (I)[3] and (VIII), and not with those of the vinylogous lactams (II)*[1] and (IX) (Table I), the structures of the condensation products of 5-phthalimido-2-tetralone, 2-indanone and 1-tetralone with methyl 2-methyl-3-methylaminopropionate should be revised to 7-phthalimido-2,4-dimethyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (XVIII), its 7-amino derivative (XIX), 1,3-dimethyl-1,3,4,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-2-one (XX) and 1,3-dimethyl-3,4,5,6-tetrahydrobenzo[*h*]quinolin-2(1*H*)-one (XXI) from structures XVIII′~XXI′ previously assigned.[2] Among them, compound (XXI), however, possesses a little different chromophore from those of the other enamine-lactams. Therefore, the following synthetic proof was given for its structure. Michael condensation of 1-tetralone with ethyl methacrylate in the presence of sodium methoxide, followed by treatment of the resulting ketoester (XXII)

10) A. J. Birch, H. Smith : Quart. Rev., **12**, 17 (1958).
11) cf. L.P. Walls in "Heterocyclic Compounds" Ed. by R.C. Elderfield, John Wiley & Sons, Inc., New York, Vol. 14, p. 625 (1952).
12) J. M. Osbond : J. Chem. Soc., **1961**, 4711.
13) A. Stoll, J. Rutschmann : Helv. Chim. Acta, **34**, 382 (1951).



with 30% benzene solution of methylamine in a sealed tube, gave the enamine-lactam (XXI), which was shown to be identical with the product obtained by the condensation of 1-tetralone and methyl 2-methyl-3-methylaminopropionate by the mixed melting point determination.

The confirmation of the structure of the vinylogous lactam (III), which was presented in the first chapter of this paper, proved the structures of the major product (XXIII) from cyclopentanone and methyl 2-methyl-3-methylaminopropionate, the major product (XXIV) from cyclohexanone and methyl 2-methyl-3-methylaminopropionate, the minor product

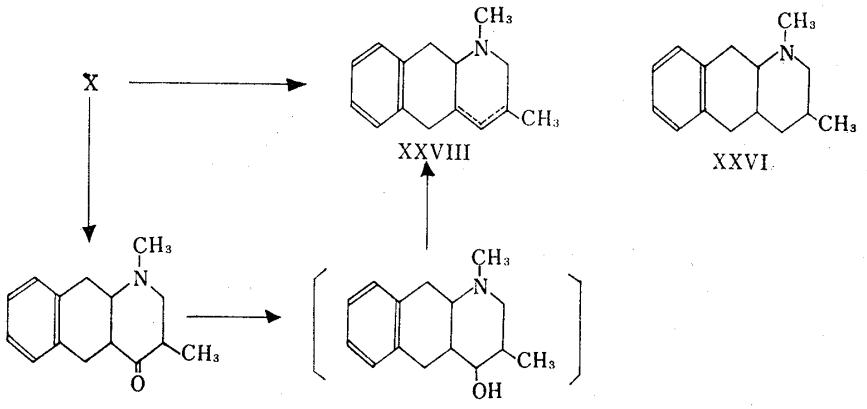
Table I. Characteristic Properties of the Vinylogous Lactam and Enamine-lactam

	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	UV λ_{max} mμ ($\varepsilon \times 10^3$) EtOH	UV λ_{max} mμ ($\varepsilon \times 10^3$) EtOH+HCl	$FeCl_3$
III	1613(s), 1548(v s)[a]	337 (10.1)[a]	330 (7.4)	+
X	1620(s), 1600(v s),[a] 1553~1563(v s)	269 (10.7),[a] 331.2 (12.2)	268 (10.0), 322 (8.7)	+
XXIII	1623(s), 1567(v s)[a]	331 (15.0)[a]	—	+
XXIV	1608(s), 1550(v s)[a]	335 (12.8)[a]	329 (8.7)	+
XXV	1618(s), 1600(s),[a,b] 1563(v s)	335 (12.0)[a]	330 (9.3)	—
II	1613(s), 1543(v s)[c]	280 (15.3),[c] 356 (10.5)	252.5 (18.4),[c] 353 (6.3)	+[c]
IX	1618(s), 1540(v s)	278 (15.2), 353 (10.8)	251 (18.5), 352 (7.5)	+
VIII	1654(s)[a]	229.7 (10.8),[a] 308.5 (16.8)	—	—
XVIII	1664(s)[a,b]	308 (10.7)[a]	—	—
XIX	1650(s)[a,b]	231 (16.0),[a] 311 (16.3)	—	—
XX	1653(s)[a]	228.5 (7.7),[a] 304 (12.1)	—	—
XXI	1653(s)[a]	226.8 (17.2),[a] 285 (6.6)	—	—

a) Z. Horii, *et al.*: This Buletin, **10**, 940 (1962). *b*) Nujol. *c*) Z. Horii, *et al.*: Yakugaku Zasshi, **84**, 1220 (1964).
s: strong v s: very strong

(XXV) from 5-phthalimido-2-tetralone and methyl 2-methyl-3-methylaminopropionate, and compound (X) to be correct as assigned in the previous paper.[2] Because the structural assignments of (XXIII~XXV) and X have come from the similarities in the behaviors of these compounds towards the lithium aluminum hydride reduction and ferric chloride test, and in the ultraviolet and infrared spectra with those of the vinylogous lactam (III) (Table I). Characteristic properties of the vinylogous lactams and enamine-lactams mentioned in this paper were summarized in Table I.

We have reported in the previous paper[2] that the reduction of the vinylogous lactam (X) with lithium aluminum hydride gives the saturated amine (XXVI). We found that structure XXVI should be revised to structure XXVIII from the following evidence. When the reduction was carried out at room temperature, the major product was a 34% yield of the aminoketone (XXVII). This aminoketone was reduced with lithium aluminum hydride in boiling ether, followed by dehydration with a mixture of phosphorus oxychloride, phosphoric acid and pyridine[14] at room temperature to give compound (XXVIII), which was identical with the product obtained by the lithium aluminum hydride reduction of the vinylogous lactam (X) in boiling ether.



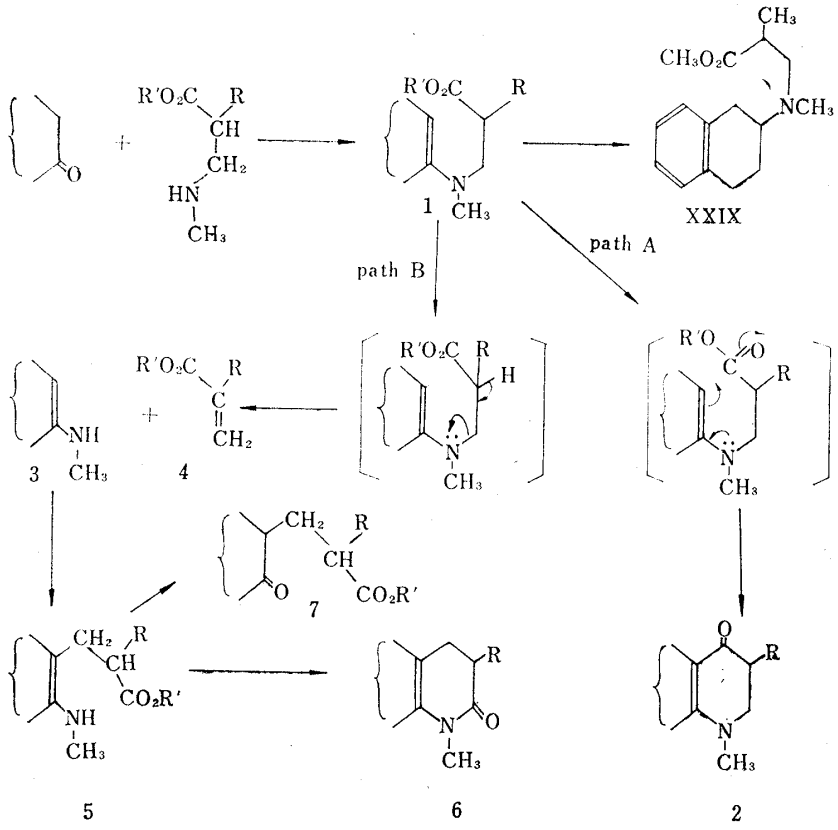
Discussion on the Course of Reaction

From the results obtained above, one can readily depict the course of the condensation of the cyclic ketone and β-methylaminopropionate to the vinylogous lactam or enamine-lactam as follows;

At the first stage of the reaction, the enamine-ester (1) is formed from the ketone and the aminoester with loss of a molecule of water, and this is obvious from the fact that the intermediate produced by heating 2-tetralone and methyl 2-methyl-3-methylaminopropionate in toluene showed an infrared absorption band at 1600~1595 cm^{-1}, characteristic to an enamine and, further, it gave methyl 2-methyl-3-(N-methyl-1,2,3,4-tetrahydro-2-naphthylamino)propionate (XXIX)[15] on hydrogenation with one mole of hydrogen over 10% palladium on carbon.

At successive stages, the enamine-ester (1) would give, *via* either path A or path B, the vinyllogous lactam (2) or the enamine-lactam (6). Path A would involve an intramolecular acylation[16] of the enamine-ester (1) to the vinylogous lactam (2). In path B, the intermediate (1) would be decomposed thermally into the enamine (3) and the α,β-

14) J. Elks : J. Chem. Soc., **1958**, 4001.
15) Z. Horii, T. Watanabe : Yakugaku Zasshi, **81**, 1786 (1961).
16) J. Szmuszkovicz in "Advances in Organic Chemistry" Ed. by R. A. Raphael E. C. Taylor, H. Wynberg, Interscience Publishers Inc., Vol. 4, p. 1 (1963).



unsaturated ester (4), which would be recombined by Michael condensation to the amino-ester (5). Isolation of the ketoester (V) by hydrolysis of the crude condensation product between cyclohexanone and ethyl 3-methylaminopropionate would give a strong support for the intermediate (5). The enamine-ester (5) would, then, undergo cyclization to the enamine-lactam (6).

Experimental*3

Reaction[2] of Cyclohexanone with Ethyl 3-Methylaminopropionate——A solution of 7.8 g. of cyclohexanone and 10.4 g. of ethyl 3-methylaminopropionate in 100 ml. of toluene was heated under reflux for 50 hr. in a stream of N_2. A Dean-Stark apparatus was used to remove H_2O as it formed during the course of the reaction. Toluene was removed from the reaction mixture under reduced pressure and the residual oil was distilled, giving two fractions, b.p_3 105~128° (2 g.) and b.p_3 145~151° (8 g.). Chromatography of the higher boiling fraction on Al_2O_3 using benzene as eluent gave 7 g. (53%) of an oily 1-methyl-2,3,5,6,7,8-hexahydro-4(1*H*)-quinolone (III).[2] The picrate of III was recrystallized from EtOH as yellow crystals, m.p. 155~156°.[2] Reduction[2] of III with $LiAlH_4$ gave *trans*-1-methyloctahydro-4-(1*H*)-quinolone which was identified with the authentic specimen as reported previously.[4]

Chromatography of the lower boiling fraction on Al_2O_3 using benzene as eluent gave 0.7 g. of an oil (IR: $\nu_{max}^{CHCl_3}$ 1725 cm^{-1}) as the first fraction, which was identified with diethyl methyliminodipropionate (VI)[7] from comparison of the behaviors on vapor phase and thin-layer chromatographies. The second oily fraction (30 mg.) (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1710) was identified with ethyl 2-oxocyclohexanepropionate (V)[6] from comparison of the IR spectrum and the behaviors on vapor phase and thin-layer chromatographies. The third oily fraction was identified with 1-methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone (IV), prepared as described below, from comparison of the behaviors on vapor phase and thin-layer chromatographies.

1-Methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone (IV)——a) To a stirred solution of 2.75 g. of 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone[5] in 100 ml. of anhyd. toluene was added 0.27 g. of NaH, and the reaction

*3 All melting points are uncorrected. Aluminum oxide standardized (E. Merk) was used for the column chromatographies. The vapor phase chromatographies were carried out with a Shimadzu Seisakusyo Model GC-IB instrument equipped with HFD-1 and SE-30 (1.5% on Chromosorb W) column.

mixture was heated under reflux for 2.5 hr. in a stream of N_2. After cooling, 20 ml. of methyl iodide was added, and the mixture was warmed on a water bath for 6 hr. The precipitate was filtered off and washed with toluene. The filtrate and washing were combined and evaporated. Distillation of the residual oil gave 2.08 g. (69%) of IV as a colorless oil, b.p_4 124°. IR : $\nu_{max}^{CHCl_3}$ 1639 cm^{-1}(CO), *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.92; H, 9.37. Found : C, 72.69; H, 9.15.

b) Prepared by keeping a solution of ethyl 2-oxocyclohexanepropionate and a large excess of 30% CH_3NH_2-benzene at room temperature for 40 hr. in 21% yield.

Reaction[2] of 2-Tetralone with Methyl 2-Methyl-3-methylaminopropionate——Was carried out in the same manner as reported in the previous paper.[2] The compound of m.p. 99~100° (colorless crystals) was identified with an authentic specimen of 2,4-dimethyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (VIII), prepared by the method described below, by mixed melting point determination and comparison of their IR spectra. The compounds of m.p. 116~117° (colorless crystals), and m.p. 120~121° (orange crystals) were assigned as 2,4-dimethyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2*H*)-one (IX) and 1,3-dimethyl-2,3,5,10-tetrahydrobenzo[*g*]quinolin-4(1*H*)-one (X), respectively, from the bases described in the main text.

Methyl α-Methyl 2-oxo-1,2,3,4-tetrahydro-1-naphthalenepropionate (XI)——To a stirred solution of 1.8 g. of Na in 80 ml. of anhyd. MeOH was added dropwise a mixture of 11.5 g. of 2-tetralone and 9.0 g. of ethyl methacrylate, the temperature being maintained at 20° during the addition. The mixture was then heated under reflux for 2 hr. The resulted brown solution was cooled, poured into ice, acidified with 10% H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. After the unreacted 2-tetralone (2 g.), b.p_4 110~120°, was removed, the residual oil was hydrolyzed by boiling with 20% KOH for 2 hr. The cooled reaction mixture was washed with Et_2O, acidified with 10% H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporated. The resulted viscous oil was esterified by boiling with CH_3OH in the presence of conc. H_2SO_4, giving 11.9 g. (61%) of XI, b.$p_{0.1}$ 140~150°. An analytical specimen of XI, a yellow viscous oil, has b.$p_{0.1}$ 145°. IR : $\nu_{max}^{CHCl_3}$ 1728 cm^{-1}(-$COOCH_3$ and CO), *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.39. Found : C, 73.36; H, 6.99.

2,4-Dimethyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (VIII)——A mixture of 1 g. of the ketoester (XI) and 15 ml. of 30% CH_3NH_2-benzene was kept at room temperature in a sealed flask for 75 hr. Removal of the solvent from the reaction mixture, trituration of the residue with Et_2O and filtration gave 220 mg. (22%) of VIII, m.p. 98~99°. The filtrate was condensed and chromatographed on Al_2O_3 using benzene as eluent gave an additional 170 mg. (17%) of VIII, m.p. 97~99°. An analytical specimen was obtained by recrystallization from EtOH-H_2O as colorless crystals, m.p. 99~100°. *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found : C, 79.26; H, 7.44; N, 6.37.

2,4-Dimethyl-3,4,4*a*,5,6,10*b*-hexahydrobenzo[*f*]quinolin-1(2*H*)-one (XII)——A suspension of 500 mg. of the vinylogous lactam (IX) in 30 ml. of anhyd. Et_2O was added to a stirred solution of 500 mg. of Li in 300 ml. of liq. NH_3. The blue solution was stirred for 7 min. and 2 g. of NH_4Cl was added. After NH_3 was allowed to evaporate, H_2O and Et_2O were added to the residue. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The Et_2O layer and Et_2O extract were combined, washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. Chromatography of the residue on Al_2O_3 using benzene as eluent gave 350 mg. (70%) of XII, b.$p_{0.06}$ 130~140° (bath temperature). IR : $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}(CO). The picrate of XII was recrystallized from EtOH as yellow crystals, m.p. 181~182° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}ON \cdot C_6H_3O_7N_3$: C, 55.02; H, 4.84; N, 12.22. Found : C, 54.79; H, 5.03; N, 12.06.

2,4-Dimethyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (XIV)——To a stirred solution of 1.5 g. of the enamine-lactam (VIII) in 60 ml. of anhyd. Et_2O was added portionwise 600 mg. of $LiAlH_4$. The mixture was then heated under reflux for 4 hr. before decomposing the excess hydride by adding AcOEt and then 50% KOH. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The Et_2O layer and Et_2O extract were combined, washed with H_2O, dried over anhyd. K_2CO_3 and evaporated. Distillation of the residual oil gave 1.4 g. (quantitative yield) of XIV, b.$p_{0.05}$ 130~135°. An analytical specimen of XIV, a pale yellow oil, has b.$p_{0.05}$ 135°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1616, 1597, 1566 (Ph-C=C-N), *Anal.* Calcd. for $C_{15}H_{19}N$: C, 84.63; H, 8.61. Found : C, 84.45; H, 8.98.

2,4-Dimethyl-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline (XIII)——a) From the enamine (XIV) : A solution of 540 mg. of the enamine (XIV) in 20 ml. of anhyd. Et_2O was added dropwise to a stirred solution of 100 mg. of Li in 200 ml. of liq. NH_3. The blue solution was stirred for 3 hr. and then 3 g. of NH_4Cl was added. After NH_3 was allowed to evaporate, H_2O and Et_2O were added to the residue. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The Et_2O layer and Et_2O extract were combined, washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residual oil gave 426 mg. of the crude XIII, b.p_1 125~130° (bath temperature). Chromatography on Al_2O_3 using benzene as eluent gave 215 mg. (40%) of XIII. The methiodide of XIII was recrystallized from EtOH as colorless crystals, m.p. 263~264° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}N \cdot CH_3I$: C, 53.79; H, 6.77; N, 3.93. Found : C, 53.97; H, 6.65; N, 4.17.

b) From the aminoketone (XII) : Two hundred and seventy milligrams of the aminoketone (XII) was heated under reflux with 30 ml. of conc. HCl and Zn-Hg for 16 hr. Further 12 g. of Zn-Hg and 30 ml.

of conc. HCl were added, and the mixture was heated under reflux for an additional 20 hr. The liquid was decanted from the excess of metal, which was washed with H_2O. The HCl solution and washing were combined, washed with Et_2O, basified with 50% NaOH and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Chromatography of the residue (100 mg.) on Al_2O_3 using benzene as eluent gave 50 mg. (20%) of XIII. This compound was identified with XIII prepared in a) by comparison of the IR spectrum and the behavior on vapor phase chromatography of the free base and the melting point of the methiodide.

Methyl 2-Methyl-3-(2-naphthylamino)propionate (XV)——A solution of 7.6 g. of Na in 350 ml. of BuOH was added dropwise to a boiling solution of 43 g. of 2-naphthylamine and 50 g. of 2-methyl-3-bromopropionic acid in 600 ml. of anhyd. BuOH under stirring over a period of 3 hr. The reaction mixture was heated under reflux for an additional 3 hr., and then 750 ml. of 2*N* NaOH was added. The whole mixture was condensed to its half volume and filtered. The filtrate was washed with Et_2O. The alkaline solution was roughly neutralized with conc. HCl under ice-cooling. After adding a few drops of 30% aq. AcOH to the solution, the resulted turbid solution was extracted with Et_2O, and this procedure was repeated until no more turbidity was observed on addition of 30% aq. AcOH. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (30 g.) was dissolved in 100 ml. of anhyd. MeOH, saturated with dry HCl and allowed to stand at room temperature for 20 hr. After the solvent was removed under reduced pressure, 500 ml. of H_2O was added to the residue. The aqueous layer was washed with Et_2O, basified with Na_2CO_3 and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 11.5 g. (15%) of XV as a slightly pink-colored oil, $b.p_{0.05}$ 140°, m.p. 61°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (NH), 1719 ($COOCH_3$). The hydrochloride of XV was recrystallized from MeOH as colorless crystals, m.p. 101° (decomp.). *Anal.* Calcd. for $C_{15}H_{17}O_2N \cdot HCl$: C, 64.29; H, 6.48; N, 5.01. Found: C, 64.25; H, 6.57; N, 5.18.

Methyl 2-Methyl-3-(N-methyl-2-naphthylamino)propionate (XVI)——a) With $(CH_3)_2SO_4$: One and half grams of $(CH_3)_2SO_4$ was added at once to a suspension of 2.3 g. of the powdered aminoester (XV), 1.2 g. of $NaHCO_3$ and 10 ml. of H_2O under stirring. The mixture was stirred for an additional 14 hr. and then warmed at 50~60° for 1 hr. After cooling, the reaction mixture was extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residual oil gave 1.9 g. (78%) of XVI as a colorless oil, $b.p_1$ 163~167°. IR: $\nu_{max}^{CHCl_3}$ 1723 cm^{-1} ($COOCH_3$). The picrate of XVI was recrystallized from CH_3OH as yellow crystals, m.p. 138° (decomp.). *Anal.* Calcd. for $C_{16}H_{19}O_2N \cdot C_6H_3O_7N_3$: C, 54.32; H, 4.56; N, 11.52. Found: C, 54.16; H, 4.73; N, 11.62.

b) With methyl bromide: A solution of 2.0 g. of the aminoester (XV) and 2.5 ml. of methyl bromide in 9 ml. of MeOH was placed in a sealed tube and heated at 120~170° for 30 min. After cooling, the reaction mixture was concentrated under reduced pressure. Saturated aq. Na_2CO_3 was added to the residue and the mixture was extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 0.7 g. (30%) of XVI, $b.p_1$ 185~190° (bath temperature). This compound was identified with XVI prepared in a) by comparison of the IR spectrum of the free base and melting point of the picrate.

2,4-Dimethyl-3,4-dihydrobenzo[*f*]quinolin-1(2*H*)-one (XVII)——a) From methyl 2-methyl-3-(N-methyl-2-naphthylamino)propionate (XVI): A mixture of 4.1 g. of the aminoester (XVI) and 15 ml. of 10% NaOH was heated under reflux for 1.5 hr. After cooling, the reaction mixture was roughly neutralized with 10% HCl. After adding a few drops of 30% aq. AcOH to the solution, a resulted turbid solution was extracted with Et_2O, and this procedure was repeated until no more turbidity was observed on addition of 30% AcOH. The Et_2O extract was dried over anhyd. $MgSO_4$ and evaporated. To the residue (2.5 g., m.p. 107~108°) was added 25 ml. of pyridine and 25 ml. of Ac_2O, and the mixture was heated under reflux for 3 hr. in a stream of N_2. The reaction mixture was concentrated under reduced pressure, trituration of the residue with Et_2O and filtration gave 350 mg. (10%) of XVII, m.p. 95~97°. Recrystallization from Et_2O gave an analytical specimen as yellowish green crystals, m.p. 98~99°. IR: $\nu_{max}^{CHCl_3}$ 1616 cm^{-1} (CO). *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.03; H, 6.80; N, 6.17.

b) From 2,4-dimethyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2*H*)-one (IX): A solution of 80 mg. of the vinylogous lactam (IX) in 50 ml. of anhyd. benzene was heated under reflux with 80 mg. of chloranil for 3 hr. After cooling the reaction mixture was washed with 10% NaOH, H_2O, dried over anhyd. Na_2SO_4, and evaporated. Chromatography of the residue on Al_2O_3 using benzene as eluent gave 20 mg. (25%) of XVII, m.p. 97~98°. This compound did not depress the melting point of XVII prepared in a) on admixture, and the IR spectra of both specimens were identical.

Ethyl α-Methyl-1-oxo-1,2,3,4-tetrahydro-2-naphthalenepropionate (XXII)——To a stirred solution of 4.6 g. of Na in 100 ml. of anhyd. MeOH was added dropwise a mixture of 29.2 g. of 1-tetralone and 23 g. of ethyl methacrylate, the temperature being maintained at 20° during the addition. The mixture was then heated under reflux for 2 hr. The resulted brown solution was cooled, poured into ice, acidified with 10% H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd.

Na_2SO_4 and evaporated. The unreacted 1-tetralone (10 g.), $b.p_4$ 110~120°, was removed. The residual oil was hydrolyzed by boiling with 20% KOH for 2 hr. The cooled reaction mixture was washed with Et_2O, acidified with 10% H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporated. The resulted viscous oil was esterified by boiling with EtOH in the presence of conc. H_2SO_4, giving 18 g. (35%) of XXII, $b.p_{0.4}$ 150~155°. An analytical specimen of XXII, a slightly yellow viscous oil, has $b.p_{0.4}$ 151°. IR: $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (COOEt). *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.84; H, 7.96.

1,3-Dimethyl-3,4,5,6-tetrahydrobenzo[*h*]quinolin-2(1*H*)-one (XXI)——A mixture of 1.2 g. of the keto-ester (XXII) and 30 ml. of 30% CH_3NH_2–benzene was placed in a sealed tube and heated on an oil bath at 180~200° for 30 hr. Removal of the solvent from the reaction mixture, trituration of the residue with Et_2O and filtration gave 0.8 g. (73%) of XXI, m.p. 96~97°. An analytical specimen was obtained by recrystallization from petr. ether as colorless crystals, m.p. 97~98°. This compound did not depress the melting point of XXI, prepared from 1-tetralone and methyl 2-methyl-3-methylaminopropionate in the previous paper,[2] on admixture, and the IR spectra of both specimens were identical. *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.97; H, 7.57; N, 6.28.

1,3-Dimethyl-1,2,4*a*,5,10,10*a*-hexahydrobenzo[*g*]quinolin-4(3*H*)-one (XXVII)——Two hundred milligrams of $LiAlH_4$ was added to a stirred suspension of 130 mg. of the vinylogous lactam (X) in 50 ml. of anhyd. Et_2O at room temperature. The reaction mixture was stirred for an additional 3 hr. at room temperature before decomposing the excess hydride by adding AcOEt and then 50% KOH. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The Et_2O layer and Et_2O extract were combined, washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Chromatography of the residue on Al_2O_3 using benzene as eluent gave 45 mg. (35%) of XXVII as a pale yellow oil. IR: $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (CO). The picrate of XXVII was recrystallized from EtOH as yellow crystals, m.p. 195~196° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}ON \cdot C_6H_3O_7N_3$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.13; H, 4.90; N, 12.26.

Lithium Aluminum Hydride Reduction of the Aminoketone (XXVII) and Subsequent Dehydration——To a stirred solution of 50 mg. of the aminoketone (XXVII) in 30 ml. of anhyd. Et_2O was added 100 mg. of $LiAlH_4$ at room temperature. The mixture was then heated under reflux for 3 hr. before decomposing the excess hydride by adding AcOEt and then 20% KOH. After cooling, the Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The Et_2O layer and Et_2O extract were combined, washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. A mixture of the resulted crude aminoalcohol (40 mg.), 2 ml. of pyridine, 0.02 ml. of H_3PO_4 and 0.3 ml. of $POCl_3$ was placed in a sealed flask, and allowed to stand at room temperature for 30 hr. The reaction mixture was condensed under reduced pressure on a water bath. To the residue were added 10% HCl and Et_2O. The aqueous layer was basified with $NaHCO_3$ and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Chromatography of the residue on Al_2O_3 using benzene as eluent gave 26 mg. (55%) of XXVIII. This compound was identical with XXVIII prepared by $LiAlH_4$ reduction[2] of the vinylogous lactam (X) by comparison of the IR spectrum and melting point of the picrate.

Catalytic Reduction of Methyl 2-Methyl-3-(N-methyl-3,4-dihydro-2-naphthylamino)propionate (VII)——A solution of 3 g. of the crude enamine (VII) in 20 ml. of anhyd. MeOH was hydrogenated over 1 g. of 10% Pd-C at room temperature and atmospheric pressure. One mole of hydrogen was consumed (15 hr.). The catalyst was filtered off and the solvent was evaporated. To the residue were added Et_2O and 10% AcOH. The aqueous layer was washed with Et_2O, basified with K_2CO_3 and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 1.6 g. of methyl 2-methyl-3-(N-methyl-1,2,3,4-tetrahydro-2-naphthylamino) propionate[16] (XXIX) as a colorless oil, $b.p_1$ 145~147°. The oxalate of XXIX was recrystallized from MeOH, as colorless crystals, m.p. 172~173°. *Anal.* Calcd. for $C_{16}H_{23}O_2N \cdot C_2O_4H_2$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.95; H, 7.02; N, 3.99.

Hydrolysis of the Enamine (VII)——One and six-tenths grams of the crude enamine (VII) was dissolved in 10 ml. of 2*N* HCl and heated on a water bath for 3 min. After cooling, the mixture was extracted with Et_2O. The Et_2O extract was washed with saturated aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 550 mg. of 2-tetralone, $b.p_3$ 130~140° (bath temperature).

The authors are indebted to Dr. Masami Makita for vapor phase chromatographic analyses.

Summary

The previous work on the condensation of the several cyclic ketones and the 3-methylaminopropionates [This Bulletin, **10**, 940 (1962)] was re-investigated. As a result, it was shown that the condensation of cyclohexanone and ethyl 3-methylaminopropionate

gave 1-methyl-2,3,5,6,7,8-hexahydro-4(1*H*)-quinolone (Ⅲ) accompanied with a small amount of 1-methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolone (Ⅳ), while the same condensation of 2-tetralone and methyl 2-methyl-3-methylaminopropionate gave 2,4-dimethyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (Ⅷ) as a major product, and 2,4-dimethyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2*H*)-one (Ⅸ) and 1,3-dimethyl-1,2,5,10-tetrahydrobenzo[*g*]-quinolin-4(3*H*)-one (Ⅹ) as minor products. Unequivocal synthetic proofs were given to these reaction products. The results enabled us to develop some discussion on the course of this type of the reaction. Revisions on the structures of the products in the previous paper were also described.

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192. Tsutomu Momose, Yo Ueda, Mitsuyoshi Kageura, Toshiko Masumura, and Kiyoko Ohta : Color Reaction Mechanism of Cholesterol with Perchloric Acid, Phosphoric Acid and Ferric Chloride Reagent. I. (Organic Analysis. LVIII.*1)

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In a previous paper of this series, a new method of determination of cholesterol in blood serum was presented with a mixture of perchloric acid, phosphoric acid and ferric chloride as the coloring reagent.[1] The developed color was so stable that fitted for measuring absorption intensities of a large number of samples in a clinical laboratory. A cholesterol solution in acetic acid was mixed with the color reagent and 0.2% ferric chloride solution in acetic acid, and the mixture was heated in a boiling water-bath for 20 minutes. During this period the color changed with the time of heating from

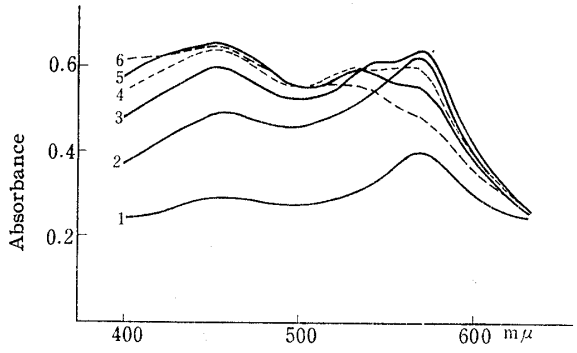

Fig. 1. Change of Absorption Spectrum of the Reaction Mixture of Cholesterol, Ferric Chloride, and the Color Reagent with the Time of Heating

1 : 3 min., 2 : 5 min., 3 : 10 min.,
4 : 15 min., 5 : 20 min., 6 : 30 min.,

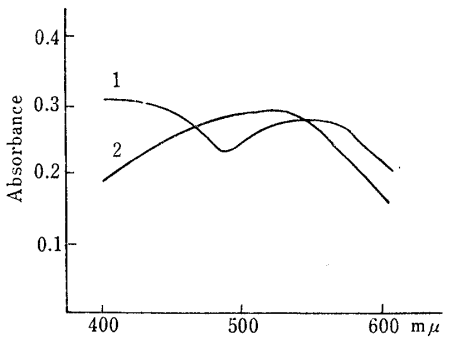

Fig. 2. Absorption Spectra of (1) Chloroform, and (2) Acid Layer of the Reaction Mixture of Cholesterol, Ferric Chloride, and the Color Reagent

*1 Part LVII. This Bulletin, **12**, 1500 (1964).
*2 Katakasu, Fukuoka (百瀬 勉, 上田 陽, 影浦光義, 益邑紀子, 太田紀代子).
1) T. Momose, Y. Ueda, K. Yamamoto, T. Masumura, K. Ohta : Anal. Chem., **35**, 1751 (1963).