[Chem. Pharm. Bull. 17(12)2405—2410(1969)] UDC 547.455.04 : 547.787.07

Studies on Ketene and Its Derivatives. XXXI.[1] 2-Acetonyloxazolines

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(Received September 11, 1968)

N-Allylacetoacetamide (III) was heated in conc. H_2SO_4 to give 2-acetonyl-5-methyl-2-oxazoline (IVb). Acidic hydrolysis of IVb afforded isopropanolamine, acetone and carbon dioxide.

N-(β-Hydroxyalkyl)acetoacetamide (X) was heated under reflux with thionyl chloride in chloroform to give N-(β-chloroalkyl)acetoacetamide (XI). Treatment of XI with methanolic KOH gave 2-acetonyl-2-oxazoline (IV).

When the reaction of X with thionyl chloride was carried out at room temperature, 2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XII) was obtained.

There are considerable literatures dealing with the syntheses of the oxazolines. The usual patterns for the formation of the oxazolines are the cyclization of N-acylderivatives of β-hydroxy, β-halo, and β,γ-unsaturated amines.[3] However, none of references are available concerning the preparation of the oxazolines using N-acetoacetate of amines as starting materials.

During the course of an investigation on the reaction of amines with diketene, attention in our laboratory was focussed upon the syntheses of the acetonyloxazolines from acetoacetamides which are easily prepared from diketene and appropriate primary amines.

The work described herein involves the reaction of the acetoacetate of amines to give the expected the acetonyloxazolines. In addition, we wish to report the reaction of the N-acetoacetate of β-hydroxyamine to afford the seven membered ring compounds such as XIIa or XIIb, besides the oxazoline derivatives.

Cyclization of N-Allylacetoacetamide

In 1893, Kay[4] reported that N-allylbenzamide (I) was heated in conc. sulfuric acid to give 2-phenyl-5-methyloxazoline (II). Modifying this method, we tried the ring closure reaction of N-allylacetoacetamide[5] (III). Thus, III was heated with conc. sulfuric acid to give colorless crystals (IVb) in 30% yield. Elemental analysis and molecular weight determination established its empirical formula as $C_7H_9O_2N$, the isomer of the starting material (III). The infrared spectrum of IVb was apparently different form that of III, and exhibited C=N absorption at 1629 cm^{-1} ($CHCl_3$). In the nuclear magnetic resonance (NMR) spectrum of IVb none of allylic protons were appeared, which were observed in III, and doublet methyl protons appeared, which could not be observed in the spectrum of III. Hydrolysis of IVb with 10% hydrochloric acid gave isopropanolamine, acetone and carbon dioxide. IVb formed a stable complex with copper sulfate. On the basis of these data described above, 2-acetonyl-5-methyl-2-oxazoline (IVb) will be given as the most resonable structure for this isomer. Attempts to prepare 2-acetonyl-5-benzyl-2-oxazoline (VI) from N-cinnamylacetoacetamide (V) were unsuccessful.

1) Part XXX: T. Kato and Y. Kubota, *Yakugaku Zasshi*, **89**, 1477 (1969).
2) Location: *Aobayama, Sendai.*
3) R.H. Wiley and L.L. Bennett, *Chem. Rev.*, **44**, 447 (1949).
4) P. Kay, *Chem. Ber.*, **26**, 2848 (1893).
5) G.D. Jones, U.S. Patent 2561205 (1951) [*C.A.*, **46**, 1032 (1952)].

Although none of the details of the experimental were described, Seeliger, *et al.*[6] reported the reaction of 2-methyl-2-oxazoline (VII) with ketene to give 2-acetonyl-2-oxazoline (IVa), mp 115—116°. According to this procedure, attempts were made to prepare IVb from 2,5-dimethyl-2-oxazoline[7] (VIII) by acetylation, but failed.

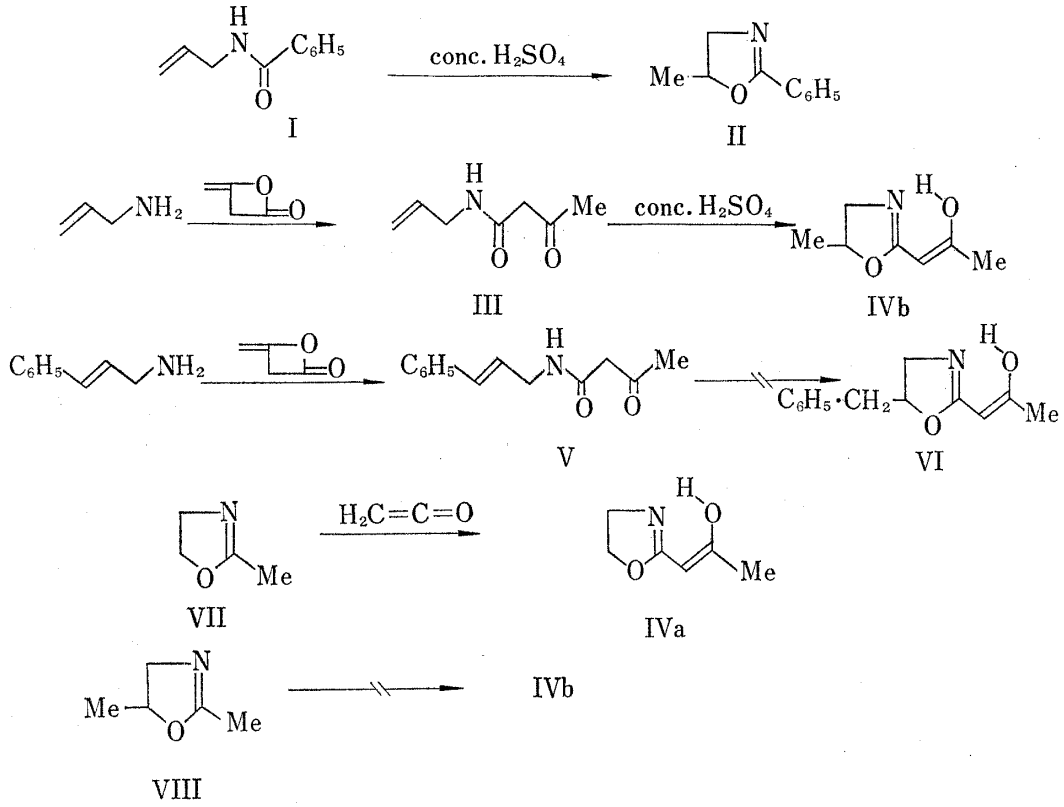

Chart 1

Cyclization of N-(2-Hydroxyalkyl)acetoacetamide

As described in the biginning of this paper, one of the most usual methods of the oxazoline synthesis is the ring-closure of N-(2-hydroxyalkyl)acetoacetamide such as Xb or Xa. Isopropanolamine (IXb) reacted easily with diketene to give N-(2-hydroxypropyl)acetoacetamide (Xb), which, on heating with thionyl chloride and then with methanolic potassium hydroxide, was transformed into IVb in 50% yield. Similarly, N-(2-hydroxyethyl)acetoacetamide (Xa), prepared from ethanolamine and diketene, cyclized to 2-acetonyl-2-oxazoline (IVa) in 65% yield. When Xa was treated with thionyl chloride, N-(2-chloroethyl)acetoacetamide (XIa) was obtained in 40% yield, besides a small amount of IVa hydrochloride and colorless crystals, which, as described subsequently, was characterized as 7-methyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIIa).

In this reaction the first stage seems to be the formation of the oxazoline hydrochloride (IVa–HCl), since the yield of XIa increased, on the contrary the yield of IVa–HCl decreased with the lapse of the reaction time. Moreover, allowing to stand in chloroform IVa–HCl was easily converted into XIa. Treatment of XIa with methanolic potassium hydroxide solution at 50—60° gave 2-acetonyl-2-oxazoline (IVa) in good yield. When the reaction of Xa with thionyl chloride was carried out at room tepmerature, the oxazepine derivative (XIIa) was obtained in good yield (60—70%). The reaciton of N-(2-hydroxypropyl)acetoacetamide (Xb) proceeded similarly as above giving the oxazepine derivative (XIIb) in 60% yield.

6) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, *Angew. Chem.*, **78**, 913 (1966).
7) A. Uedinck, *Chem. Ber.*, **32**, 967 (1899).

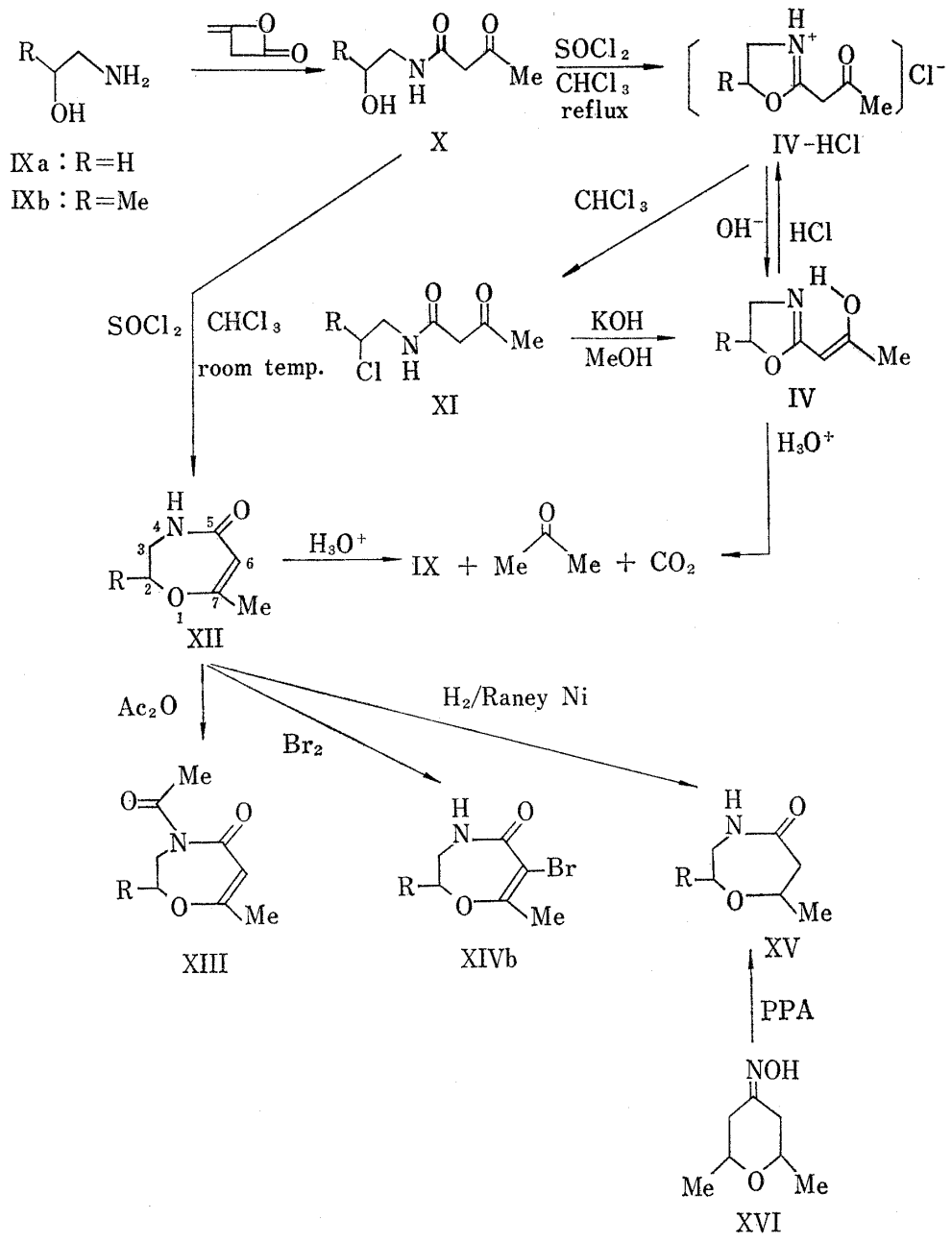

Chart 2

Structural assignment of XII was made as follows: that is, elemental analysis and molecular weight determination provided its empirical formula as the dehydrated product of the starting material (X), the isomer of IV. Infrared spectra of XIIa and XIIb indicated the secondary amide absorption bands at 3200 cm^{-1} and 1640 cm^{-1}. Both of the NMR spectra of XIIa and XIIb showed the signals of the 7-methyl protons at 1.95 ppm, an olefinic proton at 5.0 ppm and the broad signal of the NH proton at 7.85 ppm. In the case of XIIb, the signal of 2-methyl protons was observed at 1.35 ppm as a doublet. Heating of XII with acetic anhydride gave N-acetyl derivatives (XIII), and bromination of XIIb in chloroform afforded the monobromo derivative, which was identified as the 6-bromo compound (XIVb) by the NMR spectral studies.

Catalytic reduction of XII with Raney Ni as a catalyst afforded the dihydro derivatives (XV). The structural assignments of both XVa and XVb were made on the basis of the infrared and NMR spectral studies, which are shown in Table I. Moreover, XVb is already

Table I. Infrared and Nuclear Magnetic Resonance Spectra of Oxazepine Derivatives

Compound No.	Solvent	NMR (δ ppm) 2-H	3-H	6-H	7-H	4-H	2-CH_3	7-CH_3	IR (cm^{-1} $CHCl_3$) NH	C=O
XIIa	$CDCl_3$	4.27 2H(m)	3.40 2H(m)	4.97 1H		7.80 1H(b)		1.90 3H(s)	3165—3401	1639
XIIb	$CDCl_3$	4.32 1H(m)	3.27 2H(q)	4.90 1H		8.0 1H(b)	1.35 3H(d)	1.94 3H(s)	3195—3436	1642
XIIIa	CCl_4	4.19 4H(m)		5.12 1H(s)		2.48[a] 3H(s)		1.96 3H(s)		1690 1654
XIIIb	CCl_4	3.30—4.57 3H(m)		5.00 1H(s)		2.42[a] 3H(s)	1.33 3H(d)	1.95 3H(s)		1690 1654
XIVb	$CDCl_3$	4.35 1H(m)	3.30 2H(m)			8.2 1H(b)	1.35 3H(d)	2.30 3H(s)	3155	1642
XVa	$CDCl_3$		2.4—4.1 7H(m)			7.30 1H(b)		1.25 3H(d)	3226—3413	1661
XVb	$CDCl_3$		2.2—4.0 6H(m)			7.30 1H(b)	1.25 (1.15) 3H(d)	1.15 (1.25) 3H(d)	3226—3425	1664

NMR spectrum was determined on a Hitachi H-60 and TMS was used as an internal reference, and multiplicities of signals are represented as d(doublet), s(singlet), t(triplet), q(quartet), m(multiplet)t, b(broad).
a) N-acetyl protons

known, and the product was identified unequivocally by the comparison of IR spectra and a mixed melting point with an authentic specimen prepared from XVI according to the literature.[8]

Experimental

N-Allylacetoacetamide (III)——This was prepared in 86% yield according to the procedure reported by G. Jones,[5] bp 115—117° (2.5 mmHg), pale yellow crystalline solids, mp 27—28° (lit.[5] mp 28°). Recrystallization from ether afforded colorless leaves of mp 30—30.5°.

N-Cinnamylacetoacetamide (V)——To an ice-cooled solution of cinnamylamine (1.2 g, 0.009 mole) in ether (30 ml), was added a solution of diketene (0.84 g, 0.01 mole) in ether (10 ml) dropwise with stirring. Stirring was continued for an additional 20 min and crystals separated were collected, washed with ether to give colorless needles of mp 85—87°. Recrystallization from benzene gave colorless prisms, mp 88—89°. Yield, 1.6 g (82%). *Anal.* Calcd. for $C_{13}H_{15}O_2N$ (V): C, 71.86; H, 6.96; N, 6.54. Found: C, 72.17; H, 7.08; N, 6.48.

N-(2-Hydroxypropyl)acetoacetamide (Xb)——Fifty milliliters of $CHCl_3$ was placed in a reaction flask and cooled with stirring, to which were added a solution of diketene (16.8 g, 0.2 mole) in $CHCl_3$ (total volume, 50 ml) and a solution of isopropanolamine (15.0 g, 0.2 mole) in $CHCl_3$ (total volume, 50 ml) simultaneously at a same rate. The reaction temperature was kept below 5°, and the stirring was continued for an additional 30 min. The reaction mixture was evaporated *in vacuo* to give crude Xb as a colorless viscous oil, which solidified after allowing to stand overnight at 5°. 2,4-Dinitro phenylhydrazone, yellow needles of mp 170° (from MeOH). *Anal.* Calcd. for $C_{13}H_{17}O_6N_5$: C, 46.01; H, 5.05; N, 20.64. Found: C, 46.12; H, 4.89; N, 20.76.

N-(2-Hydroxyethyl)acetoacetamide (Xa)——Employing the similar manner described in the above run, the reaction of diketene (16.8 g) with ethanolamine (12.28 g) afforded hygroscopic semi-solid, mp 60—62°. Recrystallization from AcOEt gave colorless leaves of mp 67—68°. Yield, 22.6 g (78%). *Anal.* Calcd. for $C_6H_{11}O_3N$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.25; H, 7.84; N, 9.57.

2,5-Dimethyl-2-oxazoline[7] (VIII)——Employing the similar fashion reported by Wagner, *et al.*[9] the mixture of isopropanolamine (6 g) and AcOH (7.5 g) was heated at 150° for 5 hr and distillated at 250° in a

8) C. Barkenbus, J.F. Diehl, and G.R. Vogel, *J. Org. Chem.*, **20**, 871 (1955).
9) T. Wanger-Jauregg and M. Roth, *Chem. Ber.*, **93**, 3036 (1960).

stream of N_2. The distillate was dried over KOH pillets, extracted with ether. The ether fraction was purified by distillation to give a colorless oil of bp 116—117°. Yield, 7.9 g (80%). Picrate, mp 118—120° (lit.[7] mp 114—115°). *Anal.* Calcd. for $C_{11}H_{12}O_8N_4$: C, 40.25; H, 3.69; N, 17.07. Found: C, 40.52; H, 3.86; N, 17.11.

Reaction of III with conc. H_2SO_4 to give 2-Acetonyl-5-methyl-2-oxazoline (IVb)——A mixture of III (7.05 g, 0.05 mole) and conc. H_2SO_4 (8 ml) was heated at *ca.* 120° for 2 hr. After cooling, the reaction mixture was poured into ice-water, made alkaline with Na_2CO_3 and extracted with ether. The organic layer was dried over anhydrous K_2CO_3, evaporated to give a brown residue, which was purified by distillation giving an oil, bp 91—92° (2 mmHg), which solidified, mp 45—46°. Yield, 2.1 g (30%). Recrystallization from ether gave colorless prisms of mp 48—49°. *Anal.* Calcd. for $C_7H_{11}O_2N$ (IVb): C, 59.55; H, 7.85; N, 9.92; mol. wt., 141.2. Found: C, 59.64; H, 8.13; N, 10.03; mol. wt. (Rast), 144. Cu-complex, green needles (recrystallized from MeOH), mp 139—140°. *Anal.* Calcd. for $(C_7H_{10}O_2N)_2Cu$: C, 48.90; H, 5.86; N, 8.15. Found: C, 49.18; H, 5.93; N, 8.15.

Reaction of Xa with $SOCl_2$ to give N-(2-Chlorethyl)acetoacetamide (XIa)——To a solution of Xa (14.5 g, 0.1 mole) in $CHCl_3$ (50 ml), a solution of $SOCl_2$ (12.0 g, 0.1 mole) in $CHCl_3$ (10 ml) was added slowly with ice-cooling and stirring. The mixture was warmed gently on a water bath with stirring, and refluxed for 3—4 hr.

Initial coloration of the reaction mixture was yellow, but turned to reddish brown, and finally to yellow again. After evaporation of the solvent *in vacuo*, the residue was extracted with ether, and the ether layer was washed with a small amount of water, dried over anhyd. Na_2SO_4, evaporated to give a residue, which was purified by crystallization from ether–petr. ether (bp 35—40°) giving 6.5 g of crude XIa as light yellow needles. Recrystallization from ether afforded colorless needles of mp 60—61°. *Anal.* Calcd. for $C_6H_{10}O_2NCl$ (XIa): C, 44.04; H, 6.17; N, 8.56. Found: C, 44.33; H, 6.45; N, 8.72.

The ether insoluble residue was dissolved in $CHCl_3$, and the $CHCl_3$ fraction was washed with 10% Na_2CO_3, dried, and condensed to give a semi-solid, which was extracted with benzene. The benzene solution was condensed to give pale yellow prisms of mp 114—116°, undepressed on admixture with a sample of IVa, obtained in the next run. Yield, 0.9 g (7%). The mother-liquor was distilled to give a crystalline solid, bp 120° (1 mmHg), mp 63—64°, undepressed on admixture with a specimen of XIIa obtained in the run described later. Yield, 0.7 g (6%).

Reaction of Xa with $SOCl_2$ to give 2-Acetonyl-2-oxazoline (IVa)——A solution of Xa (14.5 g) and $SOCl_2$ (12 g) in $CHCl_3$ (50 ml) was refluxed for 4 hr. The solvent was removed *in vacuo* and then a solution of KOH (11.7 g) in MeOH (50 ml) was added slowly under cooling. After heating for an additional 30 min on a water bath the mixture was condensed. The residue was dissolved in H_2O, and extracted with $CHCl_3$. The $CHCl_3$ fraction was dried, condensed and extracted with benzene. From the benzene extract, pale yellow needles of mp 112—114° were obtained. Recrystallization from benzene gave colorless prisms of mp 118—119° (lit.[6] mp 115—116°). Yield, 8.2 g (65%). *Anal.* Calcd. for $C_6H_9O_2N$ (IVa); C, 56.68; H, 7.14; N, 11.02. Found: C, 56.85; H, 7.04; N, 10.95.

Reaction of Xa with $SOCl_2$ at Room Temp. to give 7-Methyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIIa)——A solution of Xa (14.5 g) and $SOCl_2$ (12 g) in $CHCl_3$ (50 ml) was allowed to stand at room temperature for 1—2 days. After washing with 10% Na_2CO_3, the reaction mixture was condensed. The residue was purified by distillation under diminished pressure to give 7.5—9 g (60—70%) of a colorless solid (XIIa), bp 120—123° (1 mmHg), mp 65—66°. *Anal.* Calcd. for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02; mol. wt. 127.1. Found: C, 56.08; H, 7.39; N, 10.93. mol. wt. (Rast), 130.

Reaction of Xb with $SOCl_2$ to give IVb——Following the procedure given for N-(2-hydroxyethyl)acetoacetamide (Xa), the reaction of N-(2-hydroxypropyl)acetoacetamide (Xb) (16 g) with $SOCl_2$ (12 g) afforded an oily product, which, however, could not be obtained in analytically pure form. This was dissolved in abs. MeOH (20 ml), to which was added slowly a solution of KOH (17 g) in abs. MeOH (30 ml) with cooling and stirring. After the addition being completed, the mixture was warmed at 60—70° for 30 min, condensed *in vacuo*, extracted with ether. From the ether soluble layer, 7.0 g (50%) of IVb (bp 92°/2.5 mmHg, mp 44—46°) were obtained.

Reaction of Xb with $SOCl_2$ to give 2,7-Dimethyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIIb)——Employing the procedure given for XIIa, Xb (16 g) was treated with $SOCl_2$ (12 g) in $CHCl_3$ (50 ml). The residual product was extracted with ether. The ether layer was decolorized with Norit (*ca.* 2 g). From the ether extract pale yellow crystals were obtained. Yield, 8.4 g (60%). Recrystallization from ether–petr. benzine (bp 60—75°) gave colorless needles of mp 89—90°. *Anal.* Calcd. for $C_7H_{11}O_2N$ (XIIb): C, 59.55; H, 7.85; N, 9.92. Found: C, 59.81; H, 8.12; N, 9.95.

Reaction of XIa with KOH to give IVa——The mixture of XIa (1.6 g) and KOH (1.1 g) in MeOH was warmed on a water bath at 50—60° for 20 min. After being evaporated, the reaction mixture was dissolved in water, extracted with $CHCl_3$. From the $CHCl_3$ fraction crude IVa was obtained. Recrystallization from benzene gave colorless needles, mp 118—119° (1.2 g), whose melting point was not depressed on admixture with the sample of IVa obtained in the run described before.

Reaction of IVa with HCl to give XIa——Dry HCl was passed into a solution of IVa (1.3 g) in $CHCl_3$–ether under cooling. Crystals separated were collected, washed with the same solvent, dried to give 1.3 g

of IVa–HCl as colorless prisms of mp 85—87°. IVa–HCl (0.3 g) was dissolved in $CHCl_3$ (5 ml), and was allowed to stand at room temperature for 2 days. The mixture was washed with 10% Na_2CO_3 and evaporated. The residue was purified by crystallization from ether to give 0.25 g (83%) of XIa as colorless needles (mp 60—61°), undepressed on admixture with the sample of XIa obtained before.

4-Acetyl-7-methyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIIIa)——A mixture of XIIa (0.1 g) and Ac_2O (3 ml) was refluxed for 30 min. After removal of Ac_2O *in vacuo*, the resulting colorless residue was purified by recrystallization from petr. benzine (bp 60—70°) to give 0.1 g (75%) of colorless needles (XIIIa), mp 91—91.5°. *Anal.* Calcd. for $C_8H_{11}O_3N$: C, 56.79; H, 6.55; N, 8.27. Found: C, 56.83; H, 6.59; N, 8.39.

4-Acetyl-2,7-dimethyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIIIb)——A mixture of XIIb (0.5 g) and Ac_2O (5 ml) was refluxed for 20 min. Evaporation of Ac_2O gave a residue which was purified by recrystallization from petr. ether (bp 35—40°) to give 0.45 g (69%) of colorless needles (XIIIb), mp 44—45°. *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.02; H, 7.32; N, 7.51.

6-Bromo-2,7-dimethyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one (XIVb)——To an ice-cooled solution of XIIb (1.4 g) in $CHCl_3$ (30 ml) was added dropwise a solution of Br_2 (1.6 g) in $CHCl_3$ (10 ml) with stirring. After stirring for an additional 30 min at room temperature, the reaction mixture was washed with Na_2CO_3 solution, dried over K_2CO_3. After removal of solvent, the residue was dissolved in water. Crystals separated were collected. Recrystallization from ether gave 0.9 g (40%) of colorless needles (XIVb), mp 121—122°. *Anal.* Calcd. for $C_7H_{10}O_2NBr$: C, 38.20; H, 4.58; N, 6.37. Found: C, 38.26; H, 4.73; N, 6.45.

7-Methyl-hexahydro-1,4-oxazepin-5-one (XVa)——A mixture of XIIa (1.27 g), Raney Ni (1 g) in EtOH (50 ml) was shaken under H_2 (100 atm) at 84° for 4 hr. The catalyst was filtered off and the filtrate was condensed *in vacuo*. The resulting crystalline solid was recrystallized from petr. benzine (bp 60—70°) to give 1.15 g (89%) of colorless needles, mp 111.5—112°. *Anal.* Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.85. Found: C, 56.00; H, 8.58; N, 10.84.

2,7-Dimethyl-hexahydro-1,4-oxazepin-5-one (XVb)——A mixture of XIIb (1.4 g), Raney Ni (0.5 g) in EtOH (50 ml) was shaken under H_2 (100 atm) at 100° for 4 hr. The reaction mixture was worked up similarly as in the above run. Recrystallization from petr. benzine (bp 60—70°) gave 1.24 g (87%) of colorless needles (XVb), mp 126—127°, (lit.[8] mp 126—127°), which was identified as XVb by the mixed melting point and the comparison of the IR spectrum with that of a sample prepared by the literature.[8]

Acknowledgement This work has been supported in part by a grant from the Ministry of Education. The authors are grateful to Mrs. A. Sato, Misses C. Yokoyama and Y. Tadano of the Central Analysis Room of this Institute for elemental analysis and NMR spectral data.