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Studies on 1-Azabicyclo Compounds. X.[1] Syntheses of Ten-membered Ring Amine Derivatives and 1-Azabicyclo[4.4.1]undecane from 3,4,6,7,8,9-Hexahydro-2*H*-quinolizine[2]

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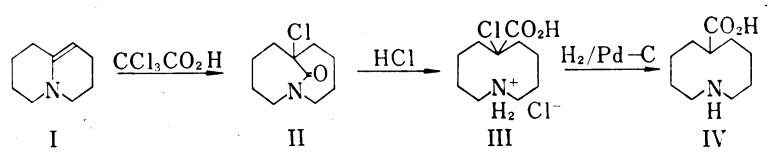
Reaction of $\Delta^{1,10}$-hexahydroquinolizine(I) with trichloroacetic acid in benzene afforded 6-chloro-1-azabicyclo[4.4.1]undecan-11-one (II). Acid hydrolysis of II followed by hydrogenation on palladium-charcoal yielded 6-carboxydecahydroazecine (IV), and alkali hydrolysis of II followed by lithium aluminum hydride reduction gave 10-hydroxymethyl-octahydroquinolizine(IX), which was also obtained by lithium aluminum hydride reduction of II. Reaction of II with sodium in liquid ammonia gave both 1-azabicyclo[4.4.1]undecan-11-ol(XIII) and 6-carbamoyldecahydroazecine(XIV). The action of *p*-toluenesulfonyl chloride on the latter compound, followed by reduction with lithium aluminum hydride afforded 1-azabicyclo[4.4.1]undecane(XVI).

It is known that cyclic enamines such as morpholine enamines reacted with trichloroacetic acid producing β,β,β-trichloroalkylamines, which in a solvating medium underwent rearrangement to α-chloroacyl amines.[4,5] Its application has led us to develop syntheses of ten-membered ring amines and 1-azabicyclo[4.4.1]undecane (XVI) from $\Delta^{1,10}$-hexahydroquinolizine (I), as reported previously in a preminary note.[2] The details of the syntheses are described here.

Reaction of the enamine[6] (I) obtained by mercuric acetate oxidation of octahydroquinolizine, with trichloroacetic acid in benzene afforded in 15% yield a crystalline product, mp 92—92.5°. The reaction product was considered to be 6-chloro-1-azabicyclo[4.4.1]undecan-11-one (II) from its elemental analytical values, and infrared spectrum, IR ν_{max}^{Nujol} cm^{-1}: 1665 (-CON). The mechanism for the reaction of I with trichloroacetic acid producing II may be visualized as shown in Chart 2. Attempts to obtain the expected trichloro compound (VIII) were unsuccessful affording only II, but VIII might be an intermediate which further underwent the rearrangement to II during the reaction. Hydrolysis of the lactam(II) in dilute hydrochloric acid gave an amino acid hydrochloride (III), mp>300°, which, when hydrogenated catalytically, gave a dechlorinated product (IV), mp 250° (decomp.). The product (IV) was subjected to methylation by formaldehyde and hydrogen in the presence of platinum oxide, followed by esterification with diazomethane, to give an N-methyl methylester (V) which formed a picrate, mp 145—146°. The picrate of V thus obtained did not show any melting point depression by the admixture with that (mp 145—146°) of 6-methoxycarbonyl-1-methyldecahydroazecine,[7] derived from the known compound, 6-carbamoyl-1-methyldecahydroazecine (VII) by acid hydrolysis followed by esterification with diazomethane, and the infrared spectra of both amines (V) were coincident.

1) Part IX: Y. Arata, S. Yoshifuji and T. Shioda, *Yakugaku Zasshi*, **92**, 69 (1972).
2) A preliminary communication has been published: Y. Arata and T. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **18**, 2361 (1970).
3) Location: *Takara-machi 13, Kanazawa.*
4) A. Łukasiewicz and J. Lesinka, *Tetrahedron*, **24**, 7 (1968).
5) A. Łukasiewicz, *Tetrahedron*, **24**, 513 (1968).
6) N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).
7) Y. Arata, S. Yoshifuji and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969).



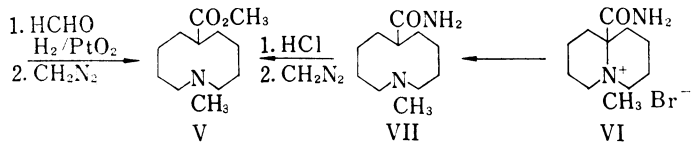
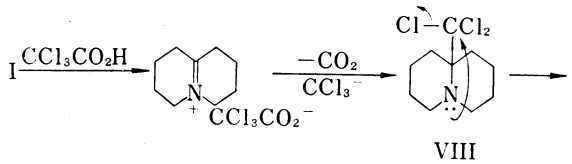


Chart 1



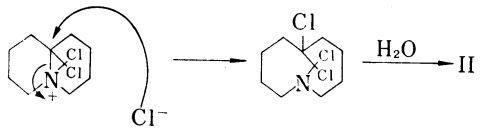


Chart 2

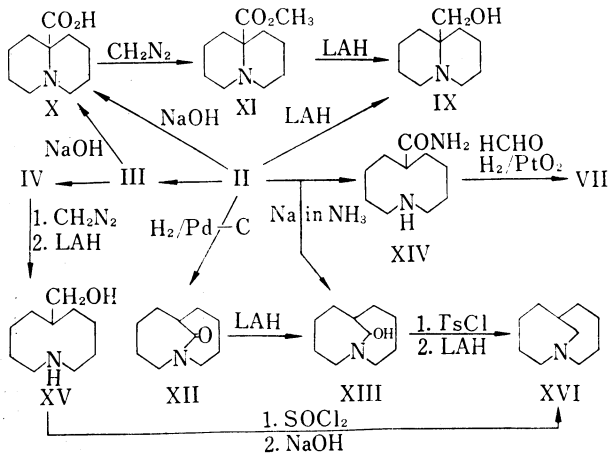


Chart 3

Furthermore, reduction of the lactam (II) by lithium aluminum hydride produced an amino alcohol (IX), mp 137—137.5°. The nuclear magnetic resonance spectrum of IX exhibited a hydroxyl signal at τ 6.93 (1H, singlet) and >C-C$\underline{H}_2$-O- signal at τ 6.44 (2H, singlet). The infrared spectrum of IX in a dilute carbon tetrachloride solution showed bands, at 3400 (broad) and 3660 (sharp) cm^{-1}. The former was attributed to the OH···N type bonded hydroxyl group, and the latter to the free hydroxyl. This fact indicated that IX existed as the conformational equilibrium mixture IXa⇌IXb, as shown in Chart 4. The mechanism for the reaction of II with lithium aluminum hydride to IX may be realized as illustrated in Chart 5. IX was also prepared by an alternative route. Hydrolysis of II with aqueous sodium hydroxide gave an amino acid (X), hydrochloride: mp>300°, which was further esterified by diazomethane to yield a methylester (XI), picrate: mp 131—132°. Heating of III with aqueous sodium hydroxide followed by esterification with diazomethane also gave XI. Reduction of XI with lithium aluminum hydride afforded the alcohol (IX), mp 137—137.5°, mentioned above in 80% yield. No depression of melting point by admixture and no difference of the infrared spectra indicated that the alcohol thus obtained was in accordance with IX directly derived from II.

Hereupon, hydrogenation of II on palladium-charcoal gave in 74% yield a lactam (XII), IR $\nu_{max}^{liq.}$ cm^{-1}: 1675 (lactam), which, on reduction of lithium aluminum hydride, afforded an azabicyclo undecane derivative (XIII), mp 89—90°, in 77% yield. Its infrared spectrum exhibited a band at 3160 cm^{-1} owing to a hydroxyl group and its nuclear magnetic resonance

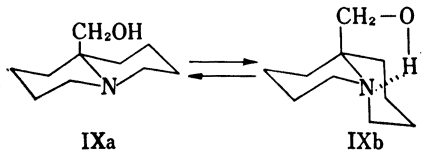


Chart 4

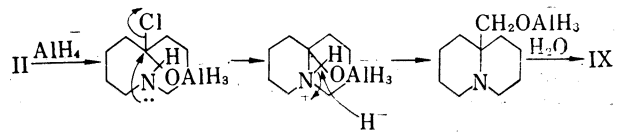


Chart 5

spectrum showed the hydroxyl signal at τ 4.47 (1H, broad) and N–CH–O– signal at τ 5.07 (1H, –CH– doublet, J=5.5 cps). The compound XIII easily reduced Fehling's solution. Reaction of II with sodium in liquid ammonia gave both the compound XIII, mp 89—90°, and carbamoyldecahydroazecine (XIV), mp 173—174°, in 74% and 3% yield, respectively. The former compound was found to be identical with XIII derived from XII by mixed melting point determination and infrared spectral comparison. Methylation of the latter by formaldehyde and hydrogen in the presence of platinum oxide gave the compound, mp 177—179°, IR ν_{max}^{KBr} cm^{-1}: 3400, 3230, 1655 ($CONH_2$), 2800(N–CH_3), which did not show any melting point depression by the admixture with 6-carbamoyl-1-methyldecahydroazacine[7] (VII) derived from 10-carbamoyl-1-methyloctahydroquinolizinium bromide (VI). The action of *p*-toluenesulfonyl chloride on XIII, followed by reduction with lithium aluminum hydride, afforded, as expected, 1-azabicyclo[4.4.1]undecane (XVI) which gave a picrate, mp 220—223° (decomp.).

On the other hand, esterification of IV with diazomethane, and lithium aluminum hydride reduction of the resulting product, yielded an amino alcohol (XV), picrate: mp 180—183°. Reaction of XV with thionyl chloride, followed by treatment with an alkaline solution, afforded the same product (XVI) which gave a picrate, mp 220—223° (decomp.), as mentioned above. The picrate did not show any melting point depression by the admixture with that of XVI derived from XIII, and the infrared spectra of both amines (XVI) were completely coincident.

Experimental[8]

6-Chloro-1-azabicyclo[4.4.1]undecan-11-one(II)——To a solution of 30 g of 3,4,6,7,8,9-hexahydro-2*H*-quinolizine[6] (I) in benzene (100 ml), a solution of trichloroacetic acid (35.7 g) in benzene was added in drops and the mixture was stirred for 24 hr at room temperature under nitrogen atomosphere. Hexahydroquinolizinium chloride deposited was separated from the mother liquor, which was evaporated *in vacuo*. The residue was dissolved in ether (100 ml), to this was added a solution of saturated hydrogen chloride in ether to deposite the precipitate. To the precipitate obtained by the decantation water (50 ml) was added and the mixture was extracted with benzene. The benzene solution was desiccated and then evaporated under the reduced pressure. The residue was recrystallized from isopropyl ether to give colorless prisms, mp 92—92.5°. Yield: 4.7 g. Possitive Beilstein's test was observed. The compound was soluble in neither aqueous sodium hydroxide nor dilute hydrochloric acid. IR ν_{max}^{Nujol} cm^{-1}: 1665 (lactam). *Anal.* Calcd. for $C_{10}H_{16}ONCl$: C, 59.55; H, 8.00; N, 6.94. Found: C, 59.58; H, 7.91; N, 7.27.

6-Carboxy-6-chlorodecahydroazecine Hydrochloride(III)——A mixture of the lactam (II) (1.0g) and 10% hydrochloric acid (30 ml) was refluxed for 3 hr. The reaction solution was evaporated to dryness *in vacuo* and the residue was recrystallized from 70% ethanol giving colorless plates. mp>300°. Yield: 1.1 g. IR ν_{max}^{KBr} cm^{-1}: 1735 (^{1}COOH). *Anal.* Calcd. for $C_{10}H_{19}O_2NCl_2$: C, 46.88; H, 7.48; N, 5.47. Found: C, 47.05; H, 7.44; N, 5.79.

6-Carboxydecahydroazecine (IV)——A solution of the hydrochloride (III) dissolved in ethanol (40 ml) and added with palladium on charcoal was shaken in hydrogen stream at 50°, absorbing 46 ml of hydrogen. After the separation of the catalyzer, the filtrate was evaporated to dryness. The residue was dissolved in water, an excess of silver carbonate was added, and the mixture was stirred for 2 hr and filtered. Hydro-

8) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were determined with a H-60-C of Japan Electron Optics Co., Ltd. using tetramethylsilane as internal standard, and infrared spectra were measured with a Spectrophotometer S and DS-402G, Japan Spectroscopic Co., Ltd.

gen sulfide was passed through the filtrate, precipitated silver sulfide was filtered off, and the filtrate was evaporated to dryness in a reduced pressure. The residue was recrystallized from methanol to give colorless prisms, mp 250° (decomp.). Yield: 180 mg. IR ν_{max}^{KBr} cm^{-1}: 1640 (-COOH).

6-Methoxycarbonyl-1-methyldecahydroazecine (V)——1) A solution of the amino acid (IV) (200 mg), 35% formaline (1 ml) and 0.1N ferrous chloride (0.5 ml) dissolved in water (20 ml) and added with platinum oxide (50 mg) was shaken in hydrogen stream for 2 hr, absorbing 24 ml of hydrogen. The mixture was filtered and evaporated to dryness in a reduced pressure. The residue was dissolved in methanol, to this was added a solution of diazomethane in ether and kept standing for 3 hr. The reaction solution was evaporated *in vacuo*. The residue was made alkaline with aqueous sodium hydroxide and the precipitates deposited were extracted with ether, which was washed with water, desiccated and then evaporated. The residue was distilled at 135—140° (bath temperature)/18 mmHg to give a colorless liquid. Yield: 130 mg. IR ν_{max}^{liq} cm^{-1}: 1730 (ester), 2800 (N-methyl). The infrared spectra of this amine and 6-methoxycarbonyl-1-methyldecahydroazecine[7] derived from 6-carbamoyl-1-methyldecahydroazecine (VII) were completely coincident. Picrate: Recrystallized from ethanol. Yellow needles, mp 145—146°. No depression of melting point was observed by the admixture of the picrate with that of 6-methoxycarbonyl-1-methyldecahydroazecine.[7] *Anal.* Calcd. for $C_{18}H_{26}O_9N_4$: C, 48.86; H, 5.92; N, 12.66. Found: C, 48.96; H, 6.01; N, 12.63.

2) A solution of 500 mg of 6-carbamoyl-1-methyldecahydroazecine[7] in 10% hydrochloric acid (5 ml) was refluxed for 8 hr. The reaction solution was evaporated to dryness *in vacuo*. The residue was dissolved in methanol, to this was added a solution of diazomethane in ether and the solution was kept standing for 1 hr. The residue evaporated from the reaction solution was made alkaline with aqueous sodium hydroxide and shaken with ether. The ether solution was washed with water, desiccated and then evaporated. The residue was distilled at 130—150° (bath temperature)/18 mmHg to give a colorless liquid. Yield: 32 mg. IR ν_{max}^{liq} cm^{-1}: 1730 (ester), 2800 (N-methyl). Picrate: Recrystallized from ethanol to afford yellow needles, mp 146—147°.

Lithium Aluminum Hydride Reduction of II (Formation of 10-Hydroxymethyl-octahydroquinolizine (IX))——A solution of 500 mg of II in ether (30 ml) was added dropwise into a suspension of lithium aluminum hydride (200 mg) in ether (10 ml) and the mixture was stirred for 4 hr at room temperature. To this water was added and the mixture was extracted with ether. The ether layer was washed with water and desiccated, followed by the evaporation of the solvent. The residue was recrystallized from isopropyl ether to yield colorless prisms, mp 137—137.5°. Yield: 370 mg. IR ν_{max}^{KBr} cm^{-1}: 3150, 1065 (hydroxyl). NMR (10% solution in $CDCl_3$) τ: 6.93 (1H, singlet, OH), 6.44 (2H, singlet, >C-CH_2-O-). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.87; H, 11.30; N, 7.99. The infrared spectrum of IX in a dilute carbon tetrachloride solution (3 mg/5 ml; 1 mg/5 ml) showed bands, at 3660 (sharp), 3400 (broad) (OH), 2775 and 2750 cm^{-1} (*trans*-quinolizidine)

10-Carboxyoctahydroquinolizine (X)——1) Alkali Hydrolysis of II. Hydrochloride: A mixture of II (200 mg) and 10% sodium hydroxide solution was refluxed for 5 hr. The reaction solution was acidified with hydrochloric acid and evaporated to dryness. The residue was extracted with ethanol. The ethanol solution was evaporated to dryness and the residue was recrystallized from ethanol to give colorless prisms, mp >300°. Yield: 190 mg. IR ν_{max}^{KBr} cm^{-1}: 1720 (-COOH). *Anal.* Calcd. for $C_{10}H_{18}O_2NCl$: C, 54.66; H, 8.26; N, 6.38. Found: C, 54.94; H, 8.21; N, 6.46.

Methyl Ester (XI): To a solution of the hydrochloride (100 mg) dissolved in methanol (30 ml), a solution of diazomethane in ether was added and kept standing for 1 hr. The residue evaporated from the reaction solution was made alkaline with aqueous sodium hydroxide and shaken with ether. The ether solution was washed with water, desiccated, and then evaporated. The residue was distilled at 120—125° (bath temperature)/18 mmHg to give a colorless liquid. Yield: 50 mg. IR ν_{max}^{liq} cm^{-1}: 1730 (ester). The picrate was recrystallized from ethanol to afford yellow needles, mp 131—132°. *Anal.* Calcd. for $C_{17}H_{22}O_9N_4$: C, 47.88; H, 5.20; N, 13.14. Found: C, 47.85; H, 5.22; N, 13.11.

2) Heating of III in an Alkaline Solution. Hydrochloride: A solution of the amino acid (III) (200 mg) in 10% aqueous sodium hydroxide was heated for 2 hr. The solution was acidified with hydrochloric acid and evaporated to dryness. The residue was extracted with methanol. The methanol solution was evaporated to dryness and the residue was recrystallized from ethanol to afford colorless prisms, mp >300°. IR ν_{max}^{KBr} cm^{-1}: 1720 (-COOH). The infrared spectra of this compound and the hydrochloride derived from II were coincident.

Methyl Ester (XI): prepared from the hydrochloride in the same manner as described above. IR ν_{max}^{liq} cm^{-1}: 1730 (ester). A colorless liquid. The picrate was recrystallized from ethanol to give yellow needles, mp 131—132°. No melting point depression was observed by the admixture of this picrate with that of XI mentioned above.

Lithium Aluminum Hydride Reduction of XI (Formation of 10-Hydroxymethyl-octahydroquinolizine (IX))——To a solution of the ester (XI) (50 mg) in ether (10 ml), lithium aluminum hydride (20 mg) was added and the mixture was stirred for 4 hr. To this water was added and the mixture was extracted with ether. The ether layer was washed with water and desiccated, followed by the evaporation of the solvent. The residue was recrystallized with isopropyl ether to give colorless prisms, mp 137—137.5°. No depres-

sion of melting point was observed by the admixture of the alcohol with IX derived from II, and the infrared spectra of both compounds were completely coincident.

1-Azabicyclo[4.4.1]undecan-11-one (XII)——A solution of 2.0 g of II and triethylamine (1.0 g) in dioxane (40 ml) was hydrogenated with palladium on charcoal for 7 hr at 50°, absorbing 220 ml of hydrogen. After the separation of the catalyst, the filtrate was evaporated to dryness. The residue was shaken with ether. The ether solution was desiccated and evaporated to give a colorless liquid which was distilled at 120° (bath temperature)/3 mmHg. Yield: 1.25 g. IR ν_{max}^{liq} cm^{-1}: 1675 (lactam). *Anal.* Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25; N, 8.38. Found: C, 70.84; H, 10.08; N, 8.71.

Lithium Aluminum Hydride Reduction of XII (Formation of 1-Azabicyclo[4.4.1]undecan-11-ol (XIII))——To a solution of 200 mg of the lactam (XII) in tetrahydrofuran was added lithium aluminum hydride (70 mg) and the mixture was refluxed for 5 hr. To this water was added and the mixture was extracted with ether. The ether layer was desiccated, followed by the evaporation of the solvent. The residue was recrystallized from petroleum ether to give colorless sandy crystals, mp 89—90°. Yield: 155 mg. IR ν_{max}^{KBr} cm^{-1}: 3160 (OH). NMR (12% solution in $CDCl_3$) τ: 4.47 (1H, broad, OH), 5.07 (1H, doublet, $J=5.5$ cps, >N-CH-O-). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.78; H, 11.36; N, 8.19.

Reduction of II with Sodium in Liquid Ammonia (Formation of XIII and 6-Carbamoyldecahydroazecine (XIV))——To a solution of the chloro lactam (II) (1.0 g) in liquid ammonia (300 ml), 300 mg of sodium was added. The solution was stirred for 10 min, and to this was added 500 mg of ammonium chloride. After the evaporation of ammonia, to the residue water and ether were added with stirring. The ether layer was desiccated and evaporated. The residue was recrystallized from isopropyl ether giving colorless needles (XIV), mp 173—174°. Yield: 45 mg. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200, 1650 ($CONH_2$). *Anal.* Calcd. for $C_{10}H_{20}ON_2$: C, 65.17; H, 10.94; N, 15.21. Found: C, 65.13; H, 10.85; N, 15.06. The recrystallization mother liquor was evaporated and the residue was recrystallized from petroleum ether to yield colorless sandy crystals (XIII), mp 89—90°. Yield: 630 mg. IR ν_{max}^{KBr} cm^{-1}: 3160 (OH). No melting point depression was observed by the admixture of this compound with XIII derived from XII, and the infrared spectra of both compounds were coincident.

6-Carbamoyl-1-methyldecahydroazecine (VII)——According to the preparation of V from IV, methylation of XIV to VII was carried out. Colorless needles, mp 177—179° was obtained from isopropyl ether. IR ν_{max}^{KBr} cm^{-1}: 3400, 3230, 1655 ($CONH_2$), 2800 ($N\text{-}CH_3$). No melting point depression was observed by the admixture of this compound with 6-carbamoyl-1-methyldecahydroazecine[7] (VII) derived from VI and the infrared spectra of both compounds did not show any difference.

6-Hydroxymethyl-decahydroazecine (XV)——To a solution of 200 mg of the amino acid (IV) in methanol (30 ml), an excess of diazomethane in ether was added and the solution was kept standing for 1 hr. After the evaporation of the solvent, to the residue ether and aqueous sodium hydroxide were added with stirring. The ether layer was desiccated and evaporated to give a colorless liquid (methyl ester) which was distilled at 140—150° (bath temperature)/20 mmHg. Yield: 190 mg. IR ν_{max}^{liq} cm^{-1}: 3360 (OH), 1735 (ester). To a solution of 180 mg of the ester in ether (30 ml) was added lithium aluminum hydride (100 mg) and the mixture was stirred for 5 hr. To this water was added and the mixture was extracted with ether. The ether solution was washed with water and desiccated, followed by the evaporation of the solvent. The residue was distilled at 105° (bath temperature)/3 mmHg giving a colorless liquid (XV). Yield: 140 mg. IR ν_{max}^{liq} cm^{-1}: 3360, 1060 (OH). Picrate: Recrystallized from ethanol affording yellow needles, mp 180—183°. *Anal.* Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.99; H, 5.98; N, 13.97.

1-Azabicyclo[4.4.1]undecane (XVI)——1) To a solution of 200 mg of XIII dissolved in ether and added with triethylamine (0.5 ml), *p*-toluenesulfonyl chloride (260 mg) was added under cooling in a small portion. The solution was kept standing for 4 hr and then filtered. To the filtrate was added lithium aluminum hydride (250 mg) and the mixture was stirred for 5 hr. To this water was added, and the mixture was extracted with ether. The ether solution was desiccated followed by the evaporation of the solvent. The residue was distilled at 110° (bath temperature)/18 mmHg to yield a colorless liquid. Yield: 70 mg. Picrate: Recrystallized from acetone to give yellow needles, mp 220—223° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_7N_4$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.50; H, 5.93; N, 14.41.

2) A solution of 50 mg of XV in thionyl chloride was refluxed for 2 hr and then evaporated *in vacuo*. The residue was made alkaline with aqueous sodium hydroxide and the mixture was warmed at 60° for 1 hr. The reaction mixture was shaken with ether and the ether solution was desiccated followed by the evaporation of the solvent. The residue was distilled at 110° (bath temperature)/18 mmHg to give a colorless liquid. Yield: 18 mg. Its infrared spectrum was completely in accordance with that of XVI derived from XIII. Picrate: Recrystallized from acetone giving yellow needles, mp 220—222° (decomp.).

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