Synthesis in the Diazasteroid Group. V. (1). Synthesis of the 9,14-Diazasteroid System

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By the condensation reaction of 2-chloroquinoline (X) and ethyl 2-pyrrolidineacetate (II), 2-[1′-(2′-carboethoxymethyl)pyrrolidyl]quinoline (XI) was prepared. Compound XI was converted to the quarternary base (XIII) having a 9,14-diazasteroid skeleton by the reduction of the ester to the corresponding alcohol followed by the quaternarization *via* tosylation. Compound XIII was reduced with sodium borohydride to 9,14-diazagona-1,3,5(10)-triene (III), which is suggested to have the *trans-anti-trans* conformation.

Previously, syntheses of various diazasteroids having an isoquinoline moiety as the parent nucleus have been reported (2). In this paper, the synthesis of a 9,14-diazasteroid, a quinoline derivative, is reported. Initially, the following synthetic approach was considered and studied.

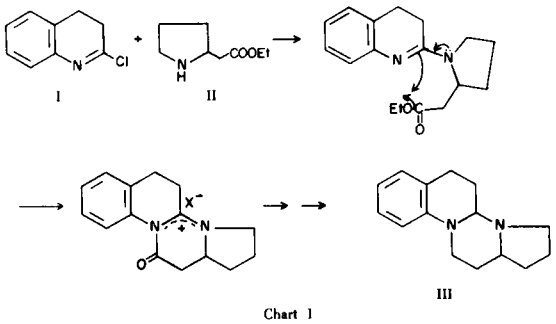

Chart 1

2-Chloro-3,4-dihydroquinoline (I) obtained from 3,4-dihydrocarbostyril should condense with ethyl 2-pyrrolidineacetate (II) to give the corresponding adduct, which should cyclize followed by reduction to the 9,14-diazagona-1,3,5(10)triene (III).

To determine the feasability of this approach, a model reaction of I and cyclohexylamine was studied. Since I prepared from 3,4-dihydrocarbostyril was not easily purified, the unpurified product was treated with an excess of cyclohexylamine to establish that I had been prepared. From the reaction mixture cyclohexylamine salts were carefully eliminated leaving two adducts. The main adduct, purified to a crystalline substance through a silica gel column, exhibited an absorption due to the amidine group at 1540 cm^{-1} in the ir spectrum and the nmr spectrum suggested it to be the 1:1-adduct of carbostyril and cyclohexylamine. From the above data and the elementary analysis, this adduct was shown to be 3,4-dihydro-2-(*N*′-cyclohexyl)aminoquinoline (IV). Thus it was established that I had been formed. The second adduct, the minor one, was also a crystalline compound, which exhibited signals in the nmr spectrum due to two secondary amine protons at 4.40 δ and 10.45 δ, and a signal at 2.95 δ due to benzyl type protons. This compound was shown to be 1,4-dihydro-3-(2′-quinolyl)-2-(*N*′-cyclohexyl)aminoquinoline (V) from the above data, the elementary analysis and the mass fragmentation pattern.

When I was treated with a molar equivalent or a small molar excess of cyclohexylamine in pyridine, triethylamine or sodium ethoxide in ethanol, the formation of IV and V were detected in minute amounts by tlc. The products isolated, however, were the following three dimers; 3,4-dihydro-3-[2′-(3′,4′-dihydro)quinolyl]carbostyril (VI), 2-hydroxy-3-(2′-quinolyl)quinoline (VII), and 2-chloro-3-(2′-quinolyl)quinoline (VIII).

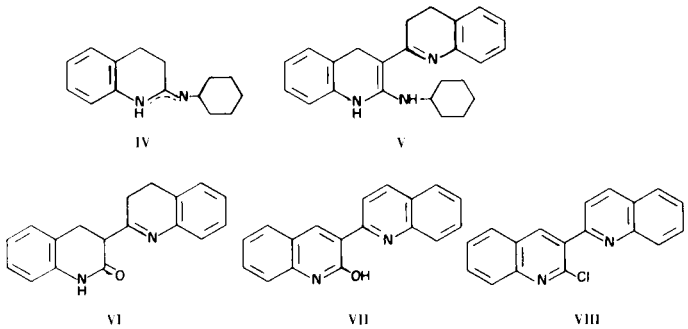

Chart 2

The ratio of VI, VII and VIII was about 7:1.5:1.5. The amount of VII increased with increasing reaction temperature. Compound VI was readily produced when I in ethanol was heated on a water bath. Compound VI was oxidized to VII by heating at its melting point, and moreover, VII was chlorinated by treatment with phosphorus oxychloride. Compounds VII and VIII are known compounds (3). For these dimers, satisfactory elementary analyses and mass spectra were obtained. A suggested mechanism for the formation of these products is shown in Chart 3.

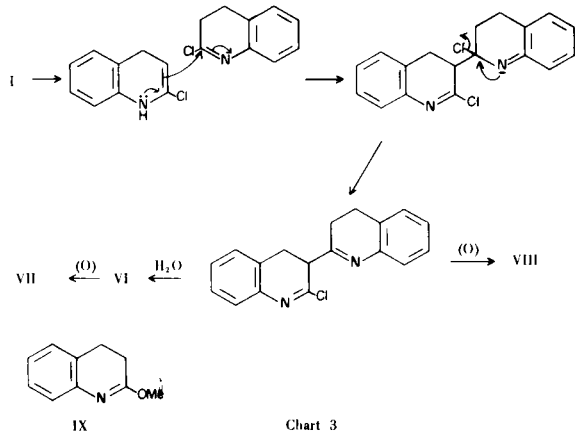

Chart 3

Thus the synthetic path starting with I was abandoned. In a similar fashion, the reactivity of the methoxy compound (IX) derived from I was examined. Crude IX, obtained by the treatment of I with sodium methoxide in methanol, dimerized to VI and VII more readily than I.

Next the synthetic approach from 2-chloroquinoline (X) was examined as shown in Chart 4.

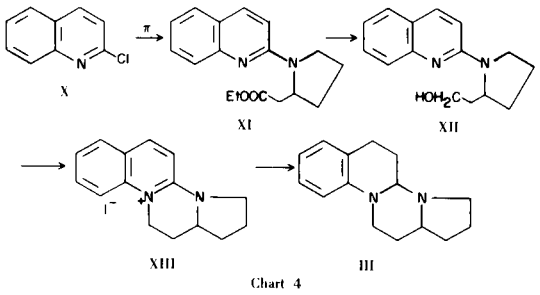

Chart 4

For this purpose, a model compound of amino alcohol (XII), 2-pyrrolidylquinoline (XIV) which was prepared (4) from X and pyrrolidine, was treated with methyl iodide to afford *N*-methyl-2-pyrrolidylquinolinium iodide (XV), a model compound of iodide (XIII). As shown in Chart 5, the structure of XV was assumed from the stabilization based on the resonance and afirmed by reductive cleavage. Compound XV was reduced by catalytic reduction in the presence of Adams' catalyst, sodium borohydride, and lithium aluminum hydride. In all cases, the reduction products were 1-methyl-1,2,3,4-tetrahydroquinoline (kairoline) and pyrrolidine. They were identified by conversion to the corresponding picrate and the *p*-nitrobenzoate, respectively.

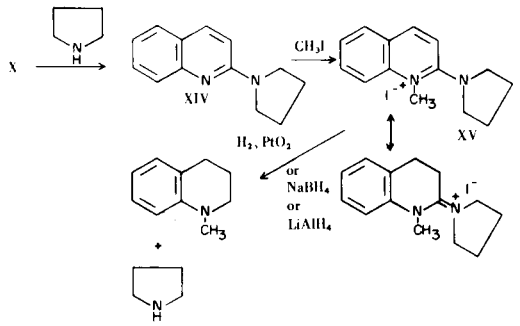

Chart 5

From the cleavage of the N-C-N bond (cleavage of steroid ring C) during the reduction of XV, we were apprehensive about the survival of the intact ring system during the reduction of XIII. Nevertheless, we attempted the synthesis of XIII as indicated later.

First we describe the synthesis of II. Compound II was prepared by Horii, *et al.*, (5) in four steps from benzyl cyanoacetate and butyrolactim methyl ether (XVI). On the other hand, Oishi *et al.*, (6) succeeded in preparing ethyl 2-piperidylideneacetate from ethyl 2-piperidylideneacetoacetate by treatment with trifluoroacetic acid. With these data available, II was synthesized in three steps in a satisfactory yield from ethyl acetoacetate and XVI as shown in Chart 6.

Table I

No.	II/X	Solvent	Catalyst	Temperature	Time	Result: Recovery of X	Result: Yield of Adduct
1	1.3	-	-	60°	2 days	*Ca.* 60%	*Ca.* 20%
2	1.3	-	-	130°	5 hours	40-50%	30-35%
3	1.3	Benzene	NaOEt (1 eq.)	reflux	5 hours	quantitative	-

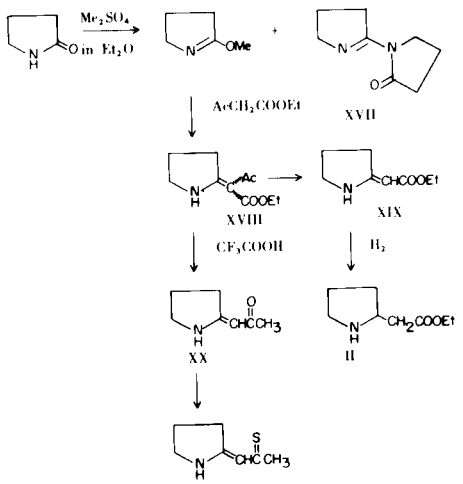

Chart 6

In this case the following important points were found: (a) The byproduct in the preparation of XVI was shown to be the pyrrolidone dimer (XVII) by elementary analysis, ir and nmr spectra. (b) Ethyl 2-pyrrolidylideneacetoacetate (XVIII), prepared from XVI and ethyl acetoacetate, was converted to ethyl 2-pyrrolidylideneacetate (XIX) by treating with trifluoroacetic acid-ethanol (1:1) or with sodium ethoxide in ethanol in 60-65% or 75-80% yield, respectively. (c) Compound XVIII was treated with only trifluoroacetic acid, in a similar fashion to that reported by Oishi, *et al.*, (6); the sole product was 2-pyrrolidylideneacetone (XX), which was unstable and was converted to the thione derivative. (d) Compounds XIX and XX were clearly different from each other by glc.

The condensation of II with X was carried out under the following three sets of conditions and the results are shown in Table I.

The separation of X and the adduct were easily performed on a silica gel column. Compound X and the adduct were eluted with benzene and ether, respectively. This adduct exhibited absorptions in the ir spectrum at 900-700 cm^{-1} due to the bending vibration of the aromatic ring and at 1730 cm^{-1} due to the ester carbonyl group. On the other hand in the nmr spectrum, six protons of the aromatic ring at 6.5-8.3 δ and five protons of the ester were observed. These data suggested that the adduct was 2-[1′-(2′-carboethoxymethyl)pyrrolidyl]quinoline (XI) and was converted to the picrate, which was identified by elementary analysis (Chart 4). Compound XI obtained in this manner was reduced with lithium aluminum hydride in ether to give the reduction product in good yield, which exhibited an hydroxyl band at 3280 cm^{-1} in the ir spectrum. This reduction product was proposed as XII, which was subjected to cyclization to form the steroid C-ring without further purification. Crude XII was treated with *p*-toluenesulfonyl chloride in pyridine followed by cyclization to give the quarternary iodide, XIII, in 41% yield, m.p. 228-230°. The structure of XIII was established by elementary analysis and mass spectrum.

The reduction of XIII was carried out under the same conditions as those used in the reduction of XV (Chart 5). Initially, sodium borohydride was used to reduce XIII. The reduction product was purified through an alumina column to give a substance which had a low melting point. This compound exhibited Bohlmann bands at 2800-2600 cm^{-1} in the ir spectrum and in nmr spectrum signals composed of a doublet of triplet and a triplet due to the two angular methine protons at 4.05 δ and 3.59 δ, respectively. From these data, the compound was not a cleavage product, XXI, (chart 7), but the expected reduction product, III. The structure of III was proven from the elementary analysis and the mass spectrum as shown in Chart 7.

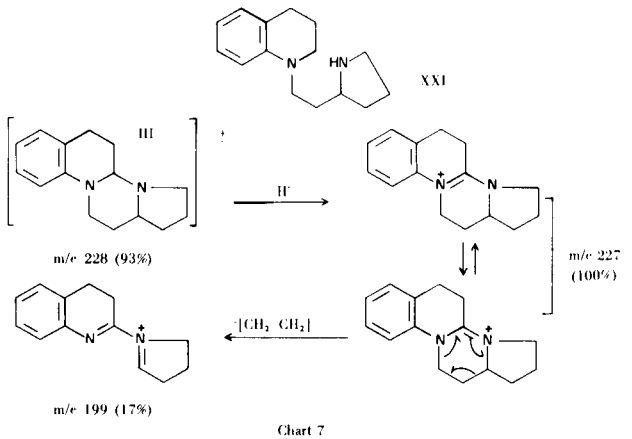

Chart 7

Next the reduction of XIII was carried out using Adams' catalyst in ethanol. Under both atmospheric and medium pressures, the reduction product was obtained in about 50% yield and was different from III. The starting material was recovered in 35-40% yield. The catalytic reduction product, m.p. 184-186°, was shown to have the composition of $C_{15}H_{19}IN_2$ from the elementary analysis and the mass spectrum. It exhibited an absorption band in the ir spectrum at 1710 cm^{-1} due to the immonium salt and signals in the nmr spectrum of A_2B_2 type at 2.90 δ and 3.20 δ. Furthermore, from the fact that this salt could not be converted into the corresponding free base by treatment with 10% sodium hydroxide solution at room temperature, it was suggested that this product was the dihydroiodide (XXII) (Chart 8). Thus, XXII was converted into III with sodium borohydride quantitatively. When XXII was treated with 10% sodium carbonate solution on a water bath for 5 minutes or with sodium ethoxide in ethanol at room temperature for about 10 minutes, XXII was converted into the iodine compound. The structure was shown to be the cleavage product, amide (XXIII), not the free base of XXII, based upon the following data: (a) The absorption band due to the NH group at 3340 cm^{-1} and that due to amide carbonyl at 1660 cm^{-1} in the ir spectrum were evident. (b) In the mass spectrum, the fragmentation pattern was different from that of XXII as shown in Chart 8.

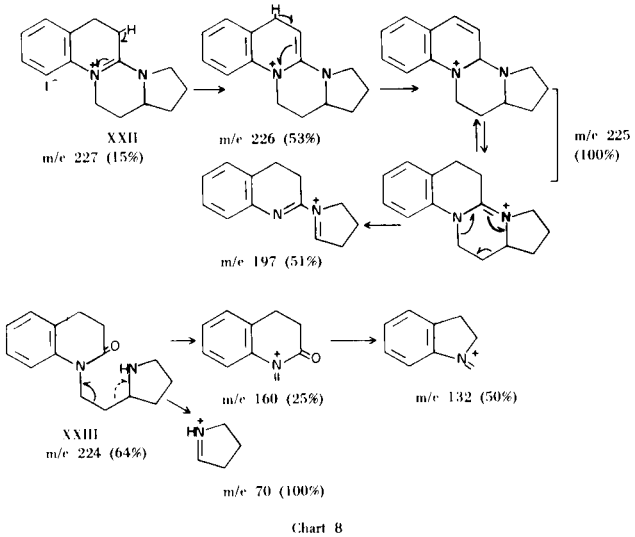

Chart 8

The stereochemistry of the diazasteroid (III) is suggested to be *trans-anti-trans* from the spectral data of the reduction products of the two iodides, XIII and XXII, with sodium borodeuteride. Compound XXII was reduced to 8-monodeuterioIII (XXIV), whose structure is supported by the fact that in the nmr spectrum, the triplet signal at 3.59 δ in III disappeared. In the spectrum of XXIV, only weak Bohlmann bands of the *trans*-azaindolizidine moiety was shown at 2790 cm^{-1}.

In a similar fashion, XIII was reduced to 6,8-dideuterio-III (XXV) with sodium borodeuteride, whose structure was suggested by the fact that in the nmr spectrum of XXV the triplet signal at 3.59 δ and the signal at 2.70 δ in III corresponding to one proton were diminished. In the ir spectrum of XXV, only weak Bohlmann bands were exhibited at 2810 cm^{-1}.

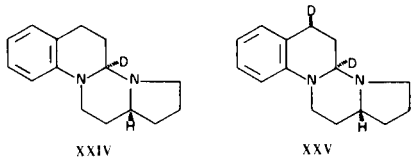

Chart 9

EXPERIMENTAL

The melting points were taken on a Kofler block. The boiling points are uncorrected. The following equipment was used: ir spectra, Hitachi Grating Infrared 215 spectrophotometer; nmr spectra, JEOL C-60H spectrometer with TMS as an internal standard; glc, Shimazu gas chromatograph Model GC-3AF (5% SE-30 column, nitrogen gas 40 ml./minute); mass spectra, JEOL TMS-01SG (75 eV, direct inlet system). The tlc values were obtained with Kiesel gel G nach Stahl (Merck) as the adsorbent. The spots were detected by spraying with 1% ceric sulfate-10% sulfuric acid followed by heating. For silica gel and alumina column chromatography, Wakogel C-200 and Aluminiumoxid standardiert nach Brockmann (Merck) were used, respectively. The chemical shifts and coupling constants (J) in the nmr spectra were described in δ and Hz, respectively. The abbreviations used to demonstrate coupling patterns are as follows; singlet-s, doublet-d, triplet-t, quartet-q, multiplet-m, broad-br. Unless otherwise stated, all the solvents were evaporated under reduced pressure.

2-Chloro-3,4-dihydroquinoline (I) (Crude).

3,4-Dihydrocarbostyril (2 g., 13.6 mmoles) prepared by the catalytic reduction of *o*-nitrocinnamic acid over Raney-Ni under high pressure was stirred and refluxed with phosphorus oxychloride (6.2 g., 40.8 mmoles) in chloroform for about 2 hours. The excess phosphorus oxychloride and chloroform were evaporated and the residue was poured onto about 100 g. of ice to separate the yellow-brown precipitate. After filtration, it was dried *in vacuo*.

3,4-Dihydro-2-(*N'*-cyclohexyl)aminoquinoline (IV) and 1,4-Dihydro-3-(2'-quinolyl)-2-(*N'*-cyclohexyl)aminoquinoline (V).

Crude I obtained above was added portionwise to cyclohexylamine (*Ca.* 15 ml.) with stirring followed by heating at 140° for about 2 hours. After an excess of cyclohexylamine was evaporated under reduced pressure, the residue was suspended in water and extracted with benzene. The benzene layer was washed with sodium chloride solution and dried over magnesium sulfate. The residue obtained from this organic layer was fractionated through a silica gel column. The yellow oil, eluted with *n*-hexane-benzene (9:1), crystallized at room temperature. Upon recrystallization from ethanol, V was obtained as yellow needles in 20%

yield (0.48 g.), m.p. 98-100°; ir (chloroform) cm^{-1}: ν NH 3210, 1620, 1610, 1600, 1560, 1540; nmr (deuteriochloroform): 10.45 (1H, br, d, J = 7, >NH), 4.40 (1H, br, s, >NH), 2.85 (2H, s, benzylic H); mass spectrum, m/e: 355 (M^+).

Anal. Calcd. for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82. Found: C, 81.19; H, 7.05; N, 11.80.

From the benzene fraction obtained through the silica gel column, IV was obtained in 43% yield accompanied with the recovered starting material, dihydrocarbostyril (about 10%). M.p. of IV, 114-116° (colorless needles from benzene-*n*-hexane); ir (nujol) cm^{-1}: ν NH 3220, 1540; nmr (deuteriochloroform): 3.95 (1H, br, s, >NH), 2.75 and 2.25 (4H, A_2B_2 type, J = 8).

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.96; H, 8.56; N, 12.24.

3,4-Dihydro-3-[2′-(3′,4′-dihydro)quinolyl]carbostyril (VI) 2-Hydroxy-3-(2′-quinolyl)quinoline (VII), and 2-Chloro-3-(2′-quinolyl)quinoline (VIII).

i) One Example of the Formation Reaction from I and Cyclohexylamine.

Crude I (2 g.) was added portionwise with stirring to a solution of cyclohexylamine (2 molar equivalents) and pyridine (1 molar equivalent) in chloroform. This reaction mixture was stirred and refluxed for 4 hours followed by cooling. The precipitate collected by filtration was recrystallized to give VI accompanied by a small amount of VII. By repeated recrystallizations of this mixture from ethanol-chloroform, VII was separated as a difficulty soluble fraction. The yield of VI was 1.31 g. (70%), m.p. 245° (in this case, it crystallized again at a higher temperature and melted finally at about 320°); ir (nujol), cm^{-1}: ν 1625, 1595, 1570, 790, 740; mass spectrum, m/e 276 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.17; H, 5.63; N, 10.39.

Compound VI was heated at 230° in silicon oil until crystals were yellow-green in color. These colored crystals were recrystallized from dimethyl sulfoxide. Compound VII had m.p. 328-330°; ir (nujol) cm^{-1}: ν 1650, 1590, 1500, 835, 755; nmr (trifluoroacetic acid): 9.50-7.50 (m, aromatic H), mass spectrum, m/e: 272 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.28; H, 4.19; N, 10.45.

The filtrate of the mixture of VI and VII was purified through a silica gel column. A yellow oil was obtained from the fraction eluted with *n*-hexane-benzene (9:1). After standing overnight, this oil crystallized. A yield of 0.2 g. (10%) of VIII was obtained, m.p. 165-167° (white needles from methanol); ir (nujol) cm^{-1}: ν 1615, 1595, 1555, 1130, 990, 820, 750, 740; nmr (deuteriochloroform): 8.50-7.30 (m, aromatic H); mass spectrum, m/e: 291 (M^+, 100%), 293 (M+2, 33%), 255 (M-Cl, 70%).

Anal. Calcd. for $C_{18}H_{11}ClN_2$: C, 74.54; H, 3.82; N, 9.66. Found: C, 74.77; H, 3.64; N, 9.52.

ii) Formation of VI from I.

Crude I (1.5 g.) in ethanol was stirred and refluxed for 2 hours until precipitation ceased. The precipitate, obtained from the cooled mixture, was heated with 10% sodium carbonate solution for 2-3 minutes on a water bath. The solid mass thus obtained was recrystallized from pyridine to give yellow-brown crystals of VI, 1.1 g., which was identified by comparison with an authentic sample by means of the ir spectrum.

VIII from VII.

Compound VII was treated with phosphorus oxychloride for 3 hours at reflux temperature. After an excess of phosphorus oxychloride was distilled off under reduced pressure, the residue dissolved in chloroform, was washed with 10% sodium carbonate solution and dried over magnesium sulfate. The salt obtained from the organic layer was dissolved in water and made basic with 10% sodium carbonate solution. The chloroform layer was dried and evaporated to give crystals, m.p. 165° (white plates from methanol). It was identified with an authentic sample of VIII by means of the ir spectrum.

Trial to Prepare 2-Methoxy-3,4-dihydroquinoline (IX) (Crude) and its Chemical Behavior.

Crude I was treated with an excess of sodium methoxide in methanol at room temperature. An exothermic reaction took place and I melted gradually to give a yellow turbidity. The reaction mixture was filtered off. The filtrate was concentrated at as low a temperature as possible to give a pale yellow residue of crude IX. This was treated with an excess of cyclohexylamine under the conditions mentioned for the synthesis of IV. However, IV could not be obtained and only the dimers VI and VII and carbostyril were obtained.

N-Methyl-2-pyrrolidylquinolinium Iodide (XV).

Compound XIV (2 g.) synthesized from 2-chloroquinoline (X) was treated overnight with an excess of methyl iodide in a sealed tube at 90°. The precipitate was filtered and recrystallized from ethanol. Compound XV was obtained in quantitative yield, m.p. 219-220° (leaflets); ir (nujol) cm^{-1}: ν 1620, 1575, 1535; nmr (trifluoroacetic acid): 8.25 and 7.35 (each 1H, d, J = 9, aromatic H), 8.05-7.56 (4H, m, aromatic H), 4.19 (3H, s, $-\overset{+}{N}-CH_3$), 4.15-3.80, and 2.50-1.90 (each 4H, m, aliphatic H).

Anal. Calcd. for $C_{14}H_{17}IN_2$: C, 49.45; H, 5.04; N, 8.24. Found: C, 49.74; H, 4.99; N, 8.21.

Reductions of XV.

(i) With Sodium Borohydride.

To XV (1 g.) in ethanol an excess of sodium borohydride was added. The reaction mixture was stirred for 3 hours at room temperature. Water and acetic acid were added to decompose the excess sodium borohydride. Solvent was evaporated to give a solid mass, which was washed with chloroform. After the chloroform was evaporated, the residue was separated to an acetone soluble part and an insoluble part. From the soluble part 1-methyl-1,2,3,4-tetrahydroquinoline (kairoline) was obtained in nearly quantitative yield; glc (160°) t_R: 3.3 minutes; b.p. 3 <130°; ir (film) cm^{-1}: ν 1600; nmr (carbon tetrachloride): 7.10-6.25 (4H, m, aromatic H), 3.16 (2H, m, > N-CH_2-), 2.82 (3H, s, > N-CH_3), 2.69 (2H, m, benzylic H), 1.95 (2H, m, -CH_2-); mass spectrum, m/e: 147 (M^+); Kairoline picrate, m.p. 125-127° (Lit. (7) 120°).

(ii) With Hydrogen/Platinum Dioxide.

To XV (340 mg.) in ethanol, platinum dioxide (200 mg.) was added. The mixture was shaken at room temperature under atmospheric pressure in a hydrogen atmosphere. After the catalyst was filtered off, ethanol was evaporated to give a nearly quantitative yield of kairoline which was identified with an authentic sample obtained in (i) by means of ir and nmr spectra.

(iii) With Lithium Aluminum Hydride.

An excess of lithium aluminum hydride was added to a

suspension of XV (1 g.) in ether. The reaction was carried out at room temperature for 3 hours. During this reaction, XV gradually disappeared. After saturated ammonium chloride was added under ice-cooling to decompose the complex, the inorganic substance was filtered off. The ether filtrate was evaporated under atmospheric pressure to give an oil (750 mg.), which showed two peaks in glc (160°); t_R 0.3 minutes (pyrrolidine), and 3.3 minutes (kairoline). This mixture was treated overnight with an excess of *p*-nitrobenzoyl chloride in pyridine at room temperature. After an excess of the acid chloride was decomposed by the addition of water, the solvent was evaporated. The residue was extracted with ether and the organic layer was washed with 10% hydrochloric acid, 10% sodium carbonate solution and saturated sodium chloride solution. The ether layer was dried and evaporated to give pyrrolidine *p*-nitrobenzoate, m.p. 82°, which was identified with an authentic sample, m.p. 83°, by means of the ir spectrum (chloroform). From a hydrochloric acid solution, kairoline was obtained.

Pyrrolidone Dimer (XVII).

The residue obtained by distilling off butyrolactim methyl ether (XVI) under atmospheric pressure as mentioned in our previous paper (8), was further distilled under reduced pressure to give XVII, 41% yield from pyrrolidone, b.p. $_{16}$ 131°. The product gradually solidified at room temperature; m.p. 49°; ir (nujol) cm^{-1}: ν 1720, 1625; nmr (carbon tetrachloride): 3.5-4.0 (4H, m), 2.9-3.2 (2H, m), 1.8-2.6 (6H, m).

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.38; H, 8.17; N, 18.35.

Ethyl 2-Pyrrolidylideneacetoacetate (XVIII).

Compound XVI (49.2 g., 0.5 mole) was treated directly with ethyl acetoacetate (65.1 g., 0.5 mole) at 90-95° for 24 hours. The precipitate obtained after standing at room temperature was recrystallized from aqueous ethanol to give XVIII, 87.9 g. (yield, 90%); glc (at 190°) t_R: 8.6 minutes; m.p. 90-92° (Lit., (9) 92°); ir (nujol) cm^{-1}: ν NH 3180, ν C=O 1670; nmr (deuteriochloroform): 2.4 (3H, s, $-CO-CH_3$), 11.65 (br, s, NH).

Ethyl 2-Pyrrolidylideneacetate (XIX).

(i) Using Trifluoroacetic Acid-Ethanol.

To XVIII (10%) in ethanol (50 ml.), trifluoroacetic acid (50 ml.) was added dropwise with ice-cooling. The reaction mixture was refluxed for 3 hours followed by the evaporation of trifluoroacetic acid and ethanol *in vacuo*. The residue was dissolved in chloroform, and this chloroform layer was washed with 10% sodium carbonate solution and water. The residue obtained from the organic layer was fractionally distilled to give XIX, 5.0 g. yield, 63%; glc (at 190°) t_R: 3.1 minutes; b.p. $_{1\text{-}2}$ 80°. It solidified after standing for a few hours, m.p. 62-63° (Lit. (5) 63.0-63.5°); ir (nujol), cm^{-1}: ν NH 3370, ν C=O 1660; nmr (deuteriochloroform): 4.35 (1H, s, vinylic H), 7.7 (1H, br, s, >NH).

(ii) Using Sodium Ethoxide in Ethanol.

Compound XVIII (10 g.) was refluxed with sodium ethoxide (1 molar equivalent) in ethanol for 4 hours. After the evaporation of the ethanol, the residue was treated as under (i) to give XIX, 6.0 g. (yield, 76%).

2-Pyrrolidylideneacetone (XX) and its Thione Derivative.

Compound XVIII (2 g., 10.2 mmoles) was dissolved in trifluoroacetic acid (20 ml.) under cooling followed by reflux for 2 hours. The residue obtained by the evaporation of the trifluoroacetic acid was dissolved in chloroform and the organic layer was washed with 10% sodium carbonate solution. The dried chloroform layer was evaporated to give crude XX, 1 g., glc (at 190°) t_R: 2.6 minutes; nmr (deuteriochloroform): 1.85 (3H, s, $-CO-CH_3$), 4.90 (1H, vinylic H). This crude XX was treated with phosphorus pentasulfide (0.5 g.) in pyridine and the residue which was treated with activated charcoal was extracted with *n*-hexane, from which yellow needles precipitated on standing at room temperature. The XX-thione derivative amounted to 0.6 g. (yield, 42%), m.p. 92-94°; ir (nujol) cm^{-1}: ν C=S 1100.

Anal. Calcd. for $C_7H_{11}NS$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.38; H, 7.90; N, 9.75.

2-[1′-(2′-Carboethoxymethyl)pyrrolidyl]quinoline (XI) (No. 2 in Table I).

Compound X (3 g., 18.3 mmoles) was treated with II (3.14 mmoles) with stirring at 130° for 5 hours. The reaction mixture, dissolved in chloroform, was washed with 10% sodium carbonate solution and saturated sodium chloride solution and dried over potassium carbonate; the chloroform was evaporated to give a yellow viscous oil, which was fractionated through a silica gel column. Compounds X (about 1.5 g.) and XI (1.7 g.) were obtained from the benzene and the ether fraction, respectively. Compound XI was a yellow oil; ir (film) cm^{-1}: ν C=O 1730, ν C=C 1610, ν 1510, 1480, 1430, 1400, 810, 750; nmr (carbon tetrachloride): 8.3-6.4 (6H, m, aromatic H), 4.05 (2H, t, $-O-CH_2$), 1.25 (3H, t, $-CH_2-CH_3$), 3.7-1.7 (9H, m); XI-picrate, m.p. 155-156° (from ethanol).

Anal. Calcd. for $C_{23}H_{23}N_5O_9$: C, 53.80; H, 4.52; N, 13.64. Found: C, 53.93; H, 4.33; N, 13.60.

Iodide (XIII).

Compound XI (2 g., 10.4 mmoles) was reduced with an excess of lithium aluminum hydride (1 g.) in absolute ether at room temperature for 1 hour followed by reflux for 2 hours. The mixture was worked up with aqueous ammonium chloride and the precipitate was washed with chloroform several times. The ether layer and washings were combined. Crude amino alcohol (XII) was obtained after evaporation of these solvents; ir (film) cm^{-1}: ν OH 3280. Compound XII (3 g., 12.4 mmoles) was treated with tosyl chloride (3.07 g., 16.1 mmoles) in pyridine (30 ml.) overnight at room temperature. After the reaction mixture was heated for 10 minutes on a water bath, water was added to the cooled mixture to decompose an excess of tosyl chloride. The residue obtained by the evaporation of pyridine *in vacuo* was dissolved in 10% hydrochloric acid. Saturated sodium iodide solution was added to this acidic solution to give the precipitate of XIII, which was recrystallized from water, 1.8 g. (yield, 41%), m.p. 228-230° dec.; ir (nujol) cm^{-1}: ν 1635, 1580, 1560, 800, 765; mass spectrum, m/e: 225 (M^+-I, 100%).

Anal. Calcd. for $C_{15}H_{17}IN_2$: C, 51.18; H, 4.87; N, 7.96. Found: C, 51.00; H, 4.91; N, 7.71.

Sodium Borohydride Reduction of XIII.

Compound XIII (1 g., 2.8 mmoles) was added to sodium borohydride (0.6 g., 16.8 mmoles) in ethanol under ice-cooling. The mixture was stirred for 1 hour at room temperature. Water was added and ethanol was evaporated from the suspended solution. The residue was extracted with chloroform and the organic solution was dried over potassium carbonate. A pale yellow oil obtained after the removal of solvent was purified through an alumina column. From the ether fraction, 9,14-diazagona-1,3,5(10)triene (III) was obtained as a colorless oil, which

solidified after standing in a freezer overnight, m.p. 43-45°. Compound III was stable in the cold but unstable at room temperature and gradually turned red; ir (film) cm^{-1}: ν CH 2800, 2710, 2600 (Bohlmann bands), ν 1600, 1580, 1500, 980, 740; nmr (deuteriochloroform): 6.5-7.3 (4H, m, aromatic H), 4.05 (1H, d, t, J = 12, 4, C_{13}-H), 3.59 (1H, t, J = 5, C_8-H), 1.3-2.4 (14H, m); mass spectrum: see Chart 7.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 79.13; H, 9.06; N, 12.05.

Catalytic Reduction of XIII under Atmospheric Pressure.

Compound XIII (1 g., 2.8 mmoles) was shaken under a hydrogen atmosphere in the presence of platinum dioxide (300 mg.) for 20 hours. After the reaction mixture was worked up in a fashion similar to the case of XV, the residue was dissolved in chloroform to give XIII, which was removed by filtration. The filtrate was concentrated and purified through an alumina column. From the chloroform-ethanol (1:1) fraction, crude dihydroiodide (XXII) was obtained and recrystallized from acetone, 0.5 g. (yield, 50.4%); m.p. 184-186°; ir (chloroform) cm^{-1}: ν C=N 1710, ν C=C 1620, ν 1610, 1600; nmr (deuteriochloroform): 3.20, 2.90 (each 2H, A_2B_2 type, J = 12, C_6 and C_7methylene); mass spectrum: see Chart 8.

Anal. Calcd. for $C_{15}H_{19}IN_2$: C, 50.89; H, 5.41; N, 7.91. Found: C, 50.72; H, 5.52; N, 7.83.

Compound XXII was reduced quantitatively to III with sodium borohydride under the same conditions as described above.

Amide Compound (XXIII).

Compound III (0.5 g.) was stirred with sodium ethoxide (1 g.) in ethanol at room temperature for 10 minutes. After removal of the ethanol, the residue was extracted with chloroform and the organic layer was washed with water and dried over potassium carbonate. Chloroform was evaporated and the residue was purified through an alumina column. From the coloroform-ethanol (9:1) fraction, XXIII was obtained as a pale yellow oil; ir (nujol) cm^{-1}: ν NH 3340, ν C=O 1660; nmr (deuteriochloroform): 7.2 (4H, s, aromatic H); mass spectrum; see Chart 8.

Reduction with Sodium Borodeuteride.

Compounds XIII and XXII were reduced with sodium borodeuteride (6 molar equivalents) in ethanol under the same conditions as those described for the reduction of XIII with sodium borohydride.

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