Synthesis in the Diazasteroid Group VIII. Synthetic Studies of the 14,17-Diazasteroid System (1)

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Two synthetic routes leading to the 14,17-diazasteroid system have been developed. One of these gives 14,17-diazagona-1,3,5(10),6,8,9,11,13(17)heptaene (V), prepared from benzo[*f*]quinolin-3(4*H*)one (I) and ethanolamine. The other route gives 14,17-diazagona-1,3,5(10),8,12-heptaen-11-one (XVIa) *via* the reaction of 2-tetralone with ethyl 2-imidazolidinylidenacetate (IXa).

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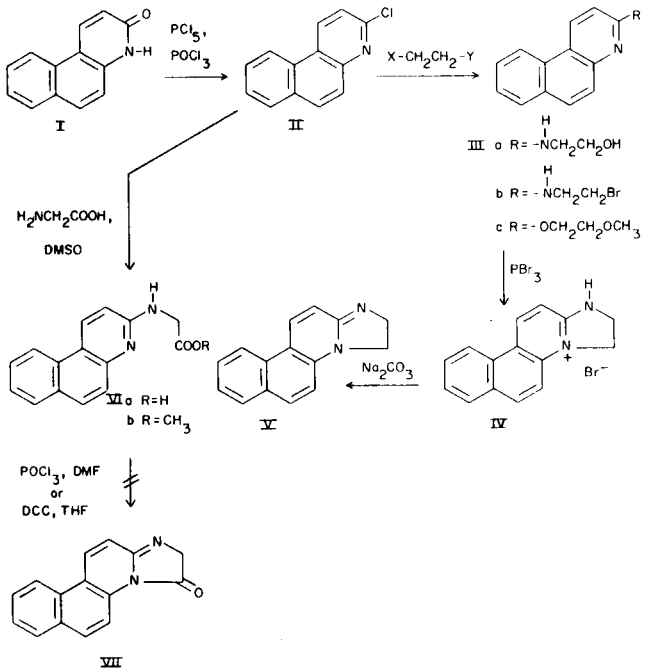
As a continuation of our studies on diazasteroids (1), we now report the synthesis of the 14,17-diazasteroid system. Two routes leading to the synthesis of this system were developed. The first of these, which yields 14,17-diazagona-1,3,5(10),6,8,11,13(17)heptaene (V) is outlined in Scheme 1. The synthesis of this title compound was achieved in a similar manner to that reported by Koyama, *et al.*, (2). The starting material for this synthetic sequence, benzo[*f*]quinolin-3(4*H*)one (I), was synthesized *via* two methods reported in the literature (3,4). Compound I was chlorinated with phosphorus pentachloride in phosphorus oxychloride giving 3-chlorobenzo[*f*]quinoline (II) in 75% yield. Compound II was successfully treated with an excess of ethanolamine. The product exhibited two broad signals due to two methylene protons at δ 3.70 and 3.80 ppm in the nmr spectrum. From this spectral data and the elemental analysis of its hydrochloride, the product was shown to be 3-(2-hydroxyethylamino)benzo[*f*]-quinoline (IIIa). Treatment of IIIa with phosphorus tribromide yielded pale yellow crystals, which melted at a high temperature and exhibited a parent peak at m/e 220 in the mass spectrum and an N-H band at 3270 cm^{-1} in the ir spectrum. From these data, the product was suggested to be 14,17-diazagona-1,3,5(10),6,8,11,13-heptaenium bromide (IV) rather than 3-(2-bromoethylamino)benzo-[*f*]quinoline (IIIb). The structure of IV was further substantiated upon neutralization with 10% sodium carbonate yielding the corresponding free base, 14,17-diazagona-1,3,5(10),6,8,9,11,13(17)heptaene (V). Compound V melted at 202-204° and exhibited an imine band at 1640 cm^{-1} in the ir spectrum and a broad singlet at δ 3.86 ppm due to two methylene protons in the nmr spectrum. The elemental analysis of V was also consistent with its proposed structure.

Scheme I



Our interests were next turned to the synthesis of VII, the 15-oxo analog of V (Scheme 1). The key intermediate in this synthesis, *N*-(benzo[*f*]quinolin-3-yl)glycine (VIa) was prepared according to the general method of Koyama, *et al.*, (5), with one variation in experimental conditions. Under the reported conditions, IIIc and not VIa was the only product which could be isolated from the reaction mixture. Compound IIIc exhibited two triplets at δ 3.66 and 4.70 due to two methylene protons in the nmr spectrum. Using aqueous DMSO as the solvent, however, VIa was obtained in 58% yield. Compound VIa exhibited N-H and carbonyl bands at 3300 and 1685 cm^{-1}, respectively, in the ir spectrum, and appropriate signals due to the methylene protons of the glycine moiety in the nmr spectrum. Several attempts to cyclize VIa to obtain the desired product VII, failed. Cyclization was attempted with

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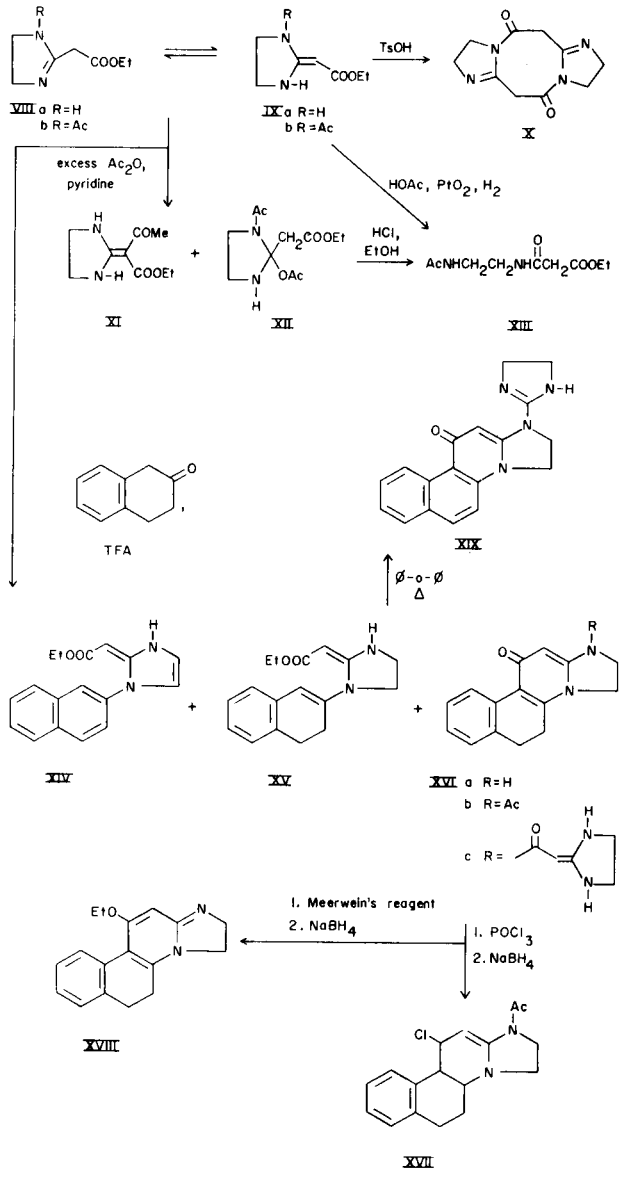
Scheme 2



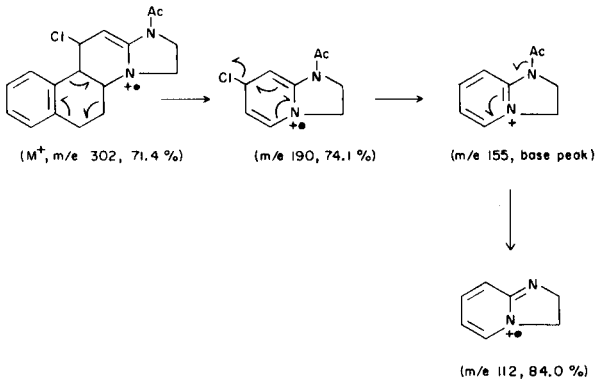
phosphorus oxychloride in DMF and with *N,N*-dicyclohexylcarbodiimide (DCC) in THF. Attempts to cyclize the methyl ester of VIa, VIb, were also unsuccessful under catalytic reduction conditions.

The second successful route to the 14,17-diazasteroid system which was developed yielded 14,17-diazagona-1,3,5(10),8,12-pentaen-11-one (XVIa), and is outlined in Scheme 2. The starting compound in this synthetic sequence, VIIIa, is known, but it could not be prepared in satisfactory yields according to procedures reported in the literature (6,7). Thus, following a similar procedure used to prepare 2-imidazolinemethanol (8), VIIIa was readily prepared from ethyl β-imino-β-ethoxypropionate hydrochloride and ethylenediamine. The ir and nmr spectral data for this compound suggest that it exists in the urethane form as ethyl 2-imidazolidinylidenacetate (IXa), rather than as VIIIa (6). Compound IXa dimerized readily to the dilactam X under reflux in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid and resisted catalytic reduction under both normal and medium pressures in acetic acid.

The following reactions were carried out starting with IXa, with the intent of synthesizing XVIa. Ethyl *N*-acetyl-2-imidazolinacetate (VIIIb) was obtained by treating IXa with a small excess of acetic anhydride in pyridine. The nmr and ir spectral data of VIIIb suggest that it exists in equilibrium with ethyl *N*-acetyl-2-imidazolidinylidenacetate (IXb) in a 1:1 ratio. However, using a large excess of acetic anhydride, IXa could be reacted to give ethyl 2-acetoxy-*N*-acetyl-2-imidazolidinacetate (XII) as the major product together with a small amount of ethyl 2-imidazolidinylidinacetate (XI). Compound XII was hydrolyzed to *N*-acetyl-*N'*-ethyl malonylethylenediamine (XIII) and decomposed on heating to *N,N'*-diacetylethylenediamine. Compound IXb was hydrolyzed to XIII by treatment with 2-tetralone in the presence of one molar equivalent of TFA or by catalytic reduction in acetic acid. Thus, the title compound XVIa could not be obtained *via* this synthetic sequence.

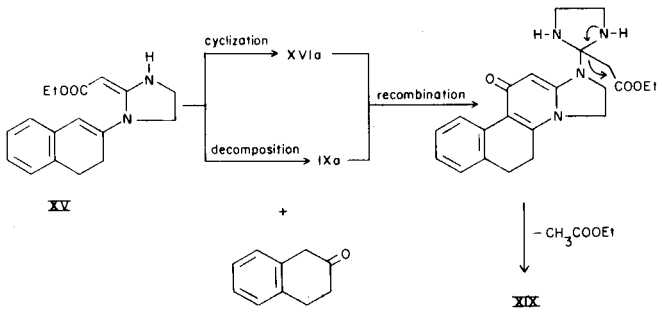
Fianlly, 14,17-diazagona-1,3,5(10),8,12-pentaen-11-one (XVIa) was obtained along with three other minor products, by condensing IXa with 2-tetralone in the presence of a one molar equivalent of TFA. Compound XVIa was probably obtained as its TFA salt, but was identified both as its hydrochloride and hydroiodide salts. Compound XVIa hydroiodide exhibited a carbonyl band at 1650 cm^{-1} in the ir spectrum and absorption maxima at 268, 250 and 224 nm in the uv spectrum. Compound XVIa was acetylated with acetic anhydride to give XVIb, which exhibited a carbonyl band at an unusually high frequency (1695 cm^{-1}) in the ir spectrum and also an unusually low field peak at δ 8.2 ppm (due to the C(12)-vinylic proton) in the nmr spectrum owing to the anistropy of the C(17)-acetyl group. Only XVIa hydroiodide could be isolated in several attempts to methylate XVIa with methyl iodide in ethanol (9). Attempts to reduce XVIa or XVIb directly, *via* either metal hydrides or catalytic hydrogenation, also proved fruitless. However, sodium borohydride reduction (10,11) of the corresponding iminochloride or iminoether analogs gave 17-acetyl-11-chloro-14,17-diazagona-1,3,5(10),12-hexaene (XVII) and 11-ethoxy-14,17-diazagona-1,3,5(10),8,11,13(17)hexaene (XVIII), respectively. The mass spectrum for XVII exhibited four intense peaks which are explained in Scheme 3. Compound XVIII was identified as its hydroiodide salt (m.p. 253-255°) and exhibited absorption maxima at 285 and 218 nm in the uv spectrum.

Scheme 3



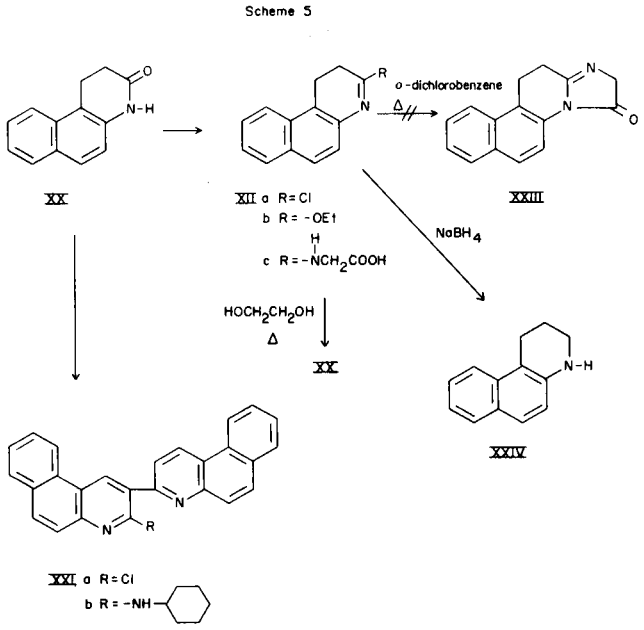
The three minor components obtained along with XVIa in the condensation of IXa with 2-tetralone were identified as XV (uncyclized intermediate to XVIa), XIV (dehydrogenated product of XV) and XVIc. Compound XV exhibited a carbonyl band at 1645 cm^{-1} in the ir spectrum and a signal due to the enamine proton at δ 6.33 ppm in the nmr spectrum. Further, XV was converted to XIX under reflux in phenyl ether. A proposed mechanism for this transformation is shown in Scheme 4. The structure of XIX was proved by its physical data and elemental analysis. The second minor component, XIV, melted at 194-196° and exhibited peaks at δ 1.3 and 4.4 ppm and in the aromatic region of the nmr spectrum. The third minor component, XVIc, melted at 288-290°. The structure of this component was proved on the basis of its physical data, and the physical data and elemental analysis of its acetate derivative (m.p. 240-242°).

Scheme 4



An unsuccessful attempt to synthesize the 14,17-diazasteroid system is outlined in Scheme 5. 1,2-Dihydrobenzo[*f*]quinolin-3(4*H*)one (XX) was chlorinated with either phosphorus oxychloride or phosphorus pentachloride in chloroform to give a red compound which was insoluble in most organic solvents and yielded yellow crystals on treatment with cyclohexylamine. This cyclohexylamine derivative was shown to have the structure XXIb from its

Scheme 5



spectral data and elemental analysis. This result suggests that the originally obtained product was 3-chloro-2-(3-benzo[*f*]quinolyl)benzo[*f*]quinoline (XXIa) rather than the expected 1,2-dihydro-3-chlorobenzo[*f*]-quinoline (XXIIa). This finding corresponds with results previously obtained in our laboratory (12). Consequently, the iminoetheration of XX was attempted next. The product obtained by treating XX with Meerwein's reagent exhibited signal due to the ethoxy and two methylene group protons in the nmr spectrum and is suggested to be 1,2-dihydro-3-ethoxybenzo[*f*]quinoline (XXIIb). Being unstable, the crude product was treated with glycine yielding colorless crystals, which exhibited a carbonyl band at 1695 cm^{-1} in the ir spectrum and signals due to the methylene protons of the glycine and dihydroquinoline moieties at δ 4.66 and 3.1-3.7 ppm, respectively in the nmr spectrum. These data together with the elemental analysis supported the structure of the product as the expected *N*-(1,2-dihydrobenzo[*f*]quinolin-3-yl)glycine (XXIIc). Attempts to cyclize XXIIc both in refluxing *o*-dichlorobenzene as described in the literature (13) and in refluxing ethylene glycol were unsuccessful, resulting in the recovery of starting material and the hydrolysis product XX, respectively. On treatment with sodium borohydride, XXIIc yielded the over-reduced product, 1,2,3,4-tetrahydrobenzo[*f*]quinoline (XXIV) in moderate yield. The catalytic reduction of XXIIc was not attempted (12).

EXPERIMENTAL

All melting points and boiling points are uncorrected. Ir spectra were determined using a Hitachi Grating ir spectrophotometer with absorptions given in cm^{-1}. Nmr spectra were recorded on a JEOL C-60H Spectrometer using TMS as the internal standard. The chemical shifts and

coupling constants (J) are described in δ and Hz, respectively. Mass spectra were measured with a JEOL TMS-01SG (75 eV, direct inlet system) Spectrometer. Uv spectra were obtained in ethanol or methanol using a Hitachi EPS-2T Spectrometer. All solvents were evaporated under reduced pressure.

3-(2-Hydroxyethylamino)benzo[*f*]quinoline (IIIa).

Method A.

3-Chlorobenzo[*f*]quinoline (II, 0.5 g., 2.3 mmoles) (3) was heated with monoethanolamine (10 ml.) at 130-140° for 4 hours. Upon cooling, the reaction mixture was poured into ice water giving white crystals, which were collected by filtration and washed thoroughly with water. The part of the product which was soluble in benzene was dried and the solvent was removed. Recrystallization from chloroform afforded IIIa (0.4 g., 70%), m.p. 150-152°; ir (nujol): ν NH 3350 (br) C=C 1610 (br), C=C 1060, 820, 750; nmr (deuteriochloroform): δ 3.70 (2H, br, >N-CH_2-), 3.80 (2H, br, -CH_2-O-), 5.16 (1H, br, -OH or >NH), 6.66 (1H, d, J = 9, aromatic H), 7.30-8.66 (7H, m, aromatic H). To prepare the hydrochloride, 10% hydrochloric acid was added dropwise to an ethanolic solution of IIIa. The crystals were collected by filtration and recrystallized from aqueous ethanol, m.p. 230-232°.

Anal. Calcd. for $C_{15}H_{14}N_2O$•HCl: C, 65.57; H, 5.46; N, 10.20. Found: C, 65.84; H, 5.46; N, 10.38.

Method B.

To a suspension of lithium aluminum hydride (0.5 g., 13 mmoles) in dry THF (30 ml.), VIa (0.2 g., 0.8 mmole) was added to give a yellow solution. After refluxing for 2 hours, the reaction mixture was cooled and a solution of ammonium chloride (3.5 g., 65 mmoles) was added to decompose the complex. The solution was then filtered and the precipitate was washed with chloroform. The filtrate and washings were combined and the solvents evaporated, yielding a crystalline product which was recrystallized from aqueous ethanol, m.p. 148-151° (0.1 g., 53.4%). This sample was identified along with IIIa prepared *via* Method A by its ir and mixed melting point.

14,17-Diazagona-1,3,4(10),6,8,11,13-heptaene Bromide (IV).

A benzene solution of IIIa (0.6 g., 2.5 mmoles) and phosphorus tribromide (17.1 g., 63 mmoles) was refluxed for 4 hours. The reaction mixture was then concentrated *in vacuo* at 110°, and the resulting residue was triturated with water. The resulting solid mass was filtered, washed with water and recrystallized from ethanol giving IV (0.57 g., 76%), m.p. 290°; ir (nujol): ν NH 3270, C=N 1640; uv (ethanol): λ max nm (ε) 246 (19,200), 212 (7,000); uv (alkaline ethanol): 266 (19,100), 258 (sh), 207 (39,700); ms: m/e 221 (M + 1, 75.8%), 220 (M^+, base peak), 219 (M-1, 25.8%).

Anal. Calcd. for $C_{15}H_{13}BrN_2$•1.25 H_2O: C, 55.64; H, 4.79; N, 8.65. Found: C, 55.40; H, 4.51; N, 8.51.

14,17-Diazagona-1,3,5(10),6,8,11,13(17)heptaene (V).

A solution of IV (0.15 g., 0.5 mmole) in 10% sodium carbonate was stirred for 2 hours, precipitating a yellow green solid. The solid was filtered, washed well with water and recrystallized from benzene or ethanol (0.043 g., 39%), m.p. 202-204°; ir (nujol): ν C=N 1640; uv (ethanol): λ max nm (ε): 269 (9,100), 246 (37,100), 212 (10,000); nmr (deuteriochloroform): δ 3.86 (br s, 4H, 2 X CH_2<), 6.20, 6.83 and 7.0-8.0 (8H, m, aromatic H).

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.81; H, 5.45; N, 12.72. Found: C, 81.58; H, 5.21; N, 12.71.

3-(2-Methoxyethoxy)benzo[*f*]quinoline (IIIc).

To a mixture of glycine (56 mg., 0.7 mmole) and potassium carbonate (1.03 g., 7 mmoles) in water (1 ml.), II (0.16 g., 0.7 mmole) in ethylene glycol monomethyl ether (20 ml.) was added. The reaction mixture was heated with stirring at 120-130° for 20 hours. After removal of the solvent, the insoluble part in ethanol was removed. The resulting filtrate was concentrated and the residue recrystallized from ethanol giving IIIc (0.11 g., 59%), m.p. 81-84°; nmr (deuteriochloroform): δ 3.43 (3H, s, -OCH_3), 3.66 and 4.70 (each 2H, t, J = 4, >N-CH_2-CH_2-), 7.00 (1H, d, J = 8, aromatic H), 8.70 (1H, d, J = 8, aromatic H).

N-(Benzo[*f*]quinolin-3-yl)glycine (VIa).

To a solution of glycine (1.41 g., 18.8 mmoles) and potassium carbonate (1.3 g., 94 mmoles) in water, II (1 g., 4.7 mmoles) in DMSO (40 ml.) was added. The solution was warmed at 150° for 21 hours. The mixture was then cooled, poured onto ice and the insoluble substance (0.15 g., recovered starting material) was filtered off. The filtrate was acidified to *p*H 4 with 30% acetic acid giving white woolly crystals which were filtered and recrystallized (57.6%), m.p. 260° dec.; ir (nujol): ν NH 3250, C=O 1680, C=C 840, 790, 765, 660; nmr (trifluoroacetic acid): δ 4.63 (2H, s, >CH_2), 7.20-8.70 (7H, m, aromatic H), 9.18-9.33 (1H, d, J = 9, aromatic H); uv (ethanol): λ max nm (ε): 295.5 (17,200), 255 (61,400), 247.5 (sh), 204 (20,100); ms: m/e 252 (M^+, 41.3%), 234 (M - H_2O, 32.7%), 208 (M - ·CO_2, base peak), 179 (m/e 208 - CH_2=NH, 94.8%).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.20; H, 5.02; N, 10.92.

Ethyl 2-Imidazolidinylidenacetate (IXa).

To an ethanolic solution of ethylenediamine (8 g., 0.13 mole), powdered ethyl β-imino-β-ethoxypropionate hydrochloride (26 g., 0.13 mole) was added under cooling in an ice-salt water bath. A solution of hydrogen chloride (4.7 g., 0.13 mole) in ethanol (65 ml.) was added to the reaction mixture over a period of 1 hour, while stirring at 0°. After standing for several hours at 0°, the mixture was warmed to 40° for 1 hour. The warm solution was filtered (to remove ammonium chloride) and the solvent was evaporated. The resulting oily residue was dissolved in water and the aqueous solution was made basic with 10% sodium hydroxide, yielding a white precipitate which was recrystallized from ethanol (11 g., 54.2%), m.p. 111-113° (lit. (7) m.p. 111-113°); ir (nujol): ν 1560-1660 (br); nmr (deuteriochloroform): δ 1.23 (3H, t, J = 6.5, -CH_3), 3.54 (4H, s, -CH_2CH_2-), 3.7-4.3 (3H, m, -CH_2-O- and vinylic H), 5.2 and 7.3 (each 1H, br s, 2 X NH).

Dilactam (X).

A solution of IXa (6.4 g., 41 mmoles) and 2-tetralone (6 g., 41 mmoles) in toluene was refluxed overnight in the presence of 0.2 g. of *p*-toluenesulfonic acid. The resulting insoluble material was recrystallized from water giving X (3 g., 33%); ir (nujol): ν C=O 1663, C=N 1583; nmr (trifluoroacetic acid): δ 3.7-4.6 (m).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.76; H, 5.74; N, 25.56.

Ethyl *N*-Acetyl-2-imidazolinacetate (VIIIb) or Ethyl *N*-Acetyl-2-imidazolidinylidenacetate (IXb).

Compound IXa was treated with acetic anhydride (1.3 molar equivalent) in pyridine at room temperature for 3 days. After water was added to decompose the excess anhydride, the solvent was evaporated. The resulting residue was washed with water and recrystallized from ethanol yielding VIIIb (or IXb) (91%), m.p. 139-141°; ir (nujol): ν C=O 1700, 1658, C=N 1600; nmr (deuteriochloroform): δ 2.14 and 2.30 (3H, each s, -$COCH_3$), 5.46 (0.5H, s, vinylic H), 8.06 (0.5H, s, >NH).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.41; H, 7.33; N, 14.32.

Ethyl 2-Acetoxy-*N*-acetyl-2-imidazolidinacetate (XII) and Ethyl 2-Imidazolidinylidenacetoacetate (XI).

Compound IXa (2 g., 0.013 mole) was treated with a large excess of acetic anhydride at room temperature overnight and the reaction mixture was worked up as described above. Separation of the products on a column packed with silica gel and eluted with benzene, gave XI and XII in the first and second fractions, respectively. Compound XII was isolated as a viscous oil (2 g., 60.5%); ms: m/e 258 (M^+); ir (film): ν 1650-1760; nmr (deuteriochloroform): δ 6.7 (1H, br s, >NH), 1.98 and 2.32 (each 3H, s, -$COCH_3$). Compound XI had m.p. 128-130° (0.2 g., 7.9%); ir (nujol): ν 1645, 1580; nmr (deuteriochloroform): δ 2.36 (3H, s, -$COCH_3$), 3.70 (4H, s, -CH_2-CH_2-).

Anal. Calcd. for $C_9H_{14}N_2O_3$ (XI): C, 54.53; H, 7.12; N, 14.13. Found: C, 54.26; H, 7.01; N, 14.26.

N-Acetyl-*N'*-ethylmalonylethylenediamine (XIII).

Method A.

A solution of XII dissolved in ethanolic hydrogen chloride was refluxed for 2 hours. After the ethanol was evaporated, the residue was dissolved in water and made basic with 10% sodium carbonate solution. The aqueous solution was extracted with chloroform and the chloroform solution was evaporated to dryness yielding a precipitate which was recrystallized from benzene (quantitative yield), m.p. 119-121°; ir (nujol): ν 1745, 1638, 1570; nmr (deuteriochloroform): δ 1.98 (3H, s, $-COCH_3$), 3.4 (6H, m, 3 X $CH_2<$), 6.9 and 7.7 (each 1H, br s, >NH).

Anal. Calcd. for $C_9H_{16}N_2O_4$: C, 50.00; H, 7.41; N, 12.96. Found: C, 50.22; H, 7.23; N, 12.71.

Method B.

A mixture of VIIIb (or IXb) and platinum oxide in acetic acid was shaken overnight at room temperature under 4 atmospheres of hydrogen gas. After the catalyst was filtered, the acetic acid was evaporated giving a viscous oil, which was basified with a 10% sodium carboante solution. The resulting precipitate was recrystallized from benzene and identified as XIII (quantitative yield).

N,N'-Diacetylethylenediamine.

Compound XII was microdistilled to give *N,N'*-diacetylethenediamine in quantitative yield, m.p. 176-178° (lit. (14) m.p. 175°); ir (nujol): ν 1643, 1580; nmr (deuteriochloroform): δ 2.41 (6H, s, $-COCH_3$), 3.80 (4H, br s, 2 X $CH_2<$), 8.40 (2H, br s, 2 X NH). This compound was identical with an authentic sample prepared from ethylenediamine and acetic anhydride.

14,17-Diazagona-1,2,3(10),8,12-heptaen-11-one (XVIa).

A mixture of 2-tetralone (1.4 g., 9.6 mmoles), IXa (1.5 g., 9.6 mmoles) and TFA (1.06 g., 9.6 mmoles) in toluene (150 ml.) was refluxed for 2 days with a Dean-Stark water separator. The precipitate which formed during reflux was collected on a glass filter (2.0 g.). This crude product was difficult to recrystallize giving XVIa•TFA, m.p. 184-186° (recrystallized from chloroform-ethanol), ms: m/e 238 (M^+, base peak), 237 (M-1, 55%), 209 (M - CH_2=NH, 27%); ir (nujol): ν C=O 1660 (br); nmr (trifluoroacetic acid): δ 2.97 (4H, s, C_6- and C_7-methylene), 4.14 and 4.50 (each 2H, d, J = 9, C_{15}- and C_{16}-methylene), 4.1 (1H, br s, >NH), 6.46 (1H, s, C_{12}-vinylic H). To an ethanolic solution of XVIa•TFA salt, 10% ethanolic hydrochloric acid was added to give XVIa hydrochloride, m.p. 288-290° (recrystallized from ethanol); ir (nujol): ν C=O 1650, C=C 1588.

Anal. Calcd. for $C_{15}H_{14}N_2O$•HCl: C, 65.57; H, 5.46; N, 10.20. Found: C, 65.30; H, 5.31; N, 10.02.

To an aqueous solution of its hydrochloride, saturated aqueous sodium iodide was added giving a white precipitate of XVIa hydroiodide, m.p. 142-144°; uv (methanol): λ max nm (ϵ): 268 (19,500), 250 (23,000), 224 (33,800).

Anal. Calcd. for $C_{15}H_{14}N_2O$•HI: C, 49.18; H, 4.10; N, 7.65. Found: C, 49.12; H, 4.30; N, 7.52.

14.17-Diaza-17-acetylgona-1,3,5(10),8,12-heptaen-11-one (XVIb).

A solutionn of crude XVIa (0.15 g., 0.6 mmole) and acetic anhydride (0.1 ml., 1.1 mmoles) in pyridine was allowed to stand overnight at room temperature. An excess of acetic anhydride was decomposed by the addition of water and the mixture was concentrated *in vacuo*. The remaining residue was poured into water and the precipitate was collected by filtration giving XVIb (0.13 g., 77.4%), m.p. >300° (recrystallized from ethanol); ms: m/e 280 (M^+, base peak), 238 (M - CH_2=C=O, 71.2%), 237 (M - Ac, 66.1%), 209 (m/e 238 - CH_2=NH, 20.1%); ir (nujol): ν C=O 1695, 1620; uv (methanol): λ max nm (ϵ) 300 (15,500), 261.5 (37,700), 229 (18,800); nmr (trifluoroacetic acid): δ 2.57 (3H, s, $-COCH_3$), 3.13 (4H, s, C_6- and C_7-methylene), 4.8 (4H, br s, C_{15}- and C_{16}-methylene), 7.4 (3H, br s, C_2-, C_3- and C_4-aromatic H), 8.2 (2H, br s, C_1-aromatic H and C_{12}-vinylic H).

The Reaction of XVIa with Methyl Iodide.

An ethanolic mixture of XVIa (0.5 g., 2.1 mmoles) and methyl iodide (1.4 g., 10 mmoles) was refluxed on a water bath for 6 hours. The solvent was removed and the resulting residue was extracted with hot water, from which a crystalline mass was obtained. This product was identified as XVIa hydroiodide (0.5 g., 65%), m.p. 142-144°.

Reduction of XVIb with Sodium Borohydride.

An ethanolic mixture of XVIb (0.2 g., 0.7 mmole) and sodium borohydride (0.2 g., 5.3 mmoles) was refluxed for 2 hours. The precipitate obtained after the usual work-up was recrystallized from ethanol giving XVIa (0.15 g., 88.2%) m.p. 282-284°. The ir spectrum of this sample was identical with that of XVIa.

Reduction of XVIa Hydrochloride with Sodium Borohydride.

An ethanolic mixture of XVIa hydrochloride (0.2 g., 0.7 mmole) and sodium borohydride (0.2 g., 5.3 mmoles) was stirred for 2 hours at room temperature. A small amount of acetic acid was then added to decompose the excess hydride. The residue obtained after evaporation of the solvent was poured into water yielding white prisms, which were recrystallized from ethanol to give XVIa (0.15 g., 86.2%), m.p. 282-284°; ir (nujol): ν C=O 1657 (sharp); uv (methanol): λ max nm (ϵ): 263 (21,600), 250 (27,100), 227 (23,700).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.81; H, 5.63; N, 11.63.

17-Acetyl-11-chloro-14,17-diazagona-1,3,5(10),12-tetraene (XVII).

To a solution of XVIb (0.2 g., 0.7 mmole) in toluene, phosphorus oychloride (0.15 ml., 1.4 mmoles) was added and the mixture was refluxed for 4 hours. After removal of the solvent by decantation, sodium borohydride (0.5 g., 13 mmoles) in ethanol was added to an ethanolic solution of the residue over a period of 15 minutes under ice cooling. After stirring the resulting solution for an additional 30 minutes at room temperature, the mixture was refluxed for 30 minutes. The solvent was then evaporated and the resulting residue was extracted with ethyl acetate. The ethyl acetate solution was washed first with 10% acetic acid and then with saturated aqueous sodium chloride. After drying the organic solution, the solvent was removed giving a crystalline compound which was purified by silica gel column chromatography. From the fraction eluted with chloroform-ethanol (9:1), XVII was obtained (0.15 g., 71%), m.p. 148-150° (recrystallized from benzene); ir (nujol): ν C=O 1640; nmr (deuteriochloroform): δ 2.10 (3H, s, $-COCH_3$), 1.5-4.2 (11H, m), 7.2 (4H, m, aromatic H), 8.0 (1H, m); ms: m/e 304 (M+2, 29.6%), 302 (M^+, 71.0%), 190 (74.1%), 155 (base peak), 112 (84.0%) (see Scheme 3).

11-Ethoxy-14,17-diazagona-1,3,5(10),8,11,13(17)hexaene (XVIII).

To a suspension of XVIb (0.5 g., 1.8 mmoles) in methylene chloride, Meerwein's reagent (triethyloxonium tetrafluoroborate) (1 g., 5.3 mmoles) was added under ice cooling. After the mixture was stirred for 20 hours at 25°, the methylene chloride was evaporated. To a cooled ethanolic solution of the residue, sodium borohydride (3 molar equivalents) in ethanol (30 ml.) was added. The reaction mixture was then stirred for 18 hours at 25°, after which it was poured onto ice giving a white precipitate. Fractional recrystallization from ethanol yielded XVIb (0.07 g., 14%) XVIa (0.11 g., 25.9%) and XVIII (0.3 g., 62.9%) as the first, second and third lots of crystallization, respectively. The hydroiodide of XVIII was prepared in the usual manner, having m.p. 253-255°; ir (nujol): ν 1660, 1580, 1540; uv (methanol): λ max nm (ϵ): 285 (26,100), 218 (39,700); ms: m/e 267 (M^+, 38.0%), 238, (M - C_2H_4, base peak), 237 (M - C_2H_5, 60.6%), 209 (m/e 238 - CH_2=NH, 36.0%).

Anal. Calcd. for $C_{17}H_{18}N_2O$•HI: C, 51.78; H, 4.82; N, 7.11. Found: C, 51.98; H, 5.10; N, 6.86.

Minor Components Produced in the Condensation Reaction.

After removal of XVIa•TFA salt, the filtrate was washed with 10% aqueous sodium carbonate, and the organic solution was dried. After evaporation of the solvent, the resulting residue was separated by silica gel column chromatography. From the fraction eluted with benzene-ether (9:1), (0.2 g., 7.4%) XV was obtained, m.p. 136-138° (recrystallized from ethanol); ir (nujol): ν C=O 1645, C=C 1585; nmr (deuteriochloroform): δ 1.33 (3H, t, J = 7, $-CH_3$), 2.6 (4H, m, Ar-CH_2-CH_2-), 3.6

(4H, m, N-CH_2-CH_2-N), 4.1 (2H, q, J = 7, -CH_2-O-), 4.9 (1H, br s, =CH-CO-), 6.33 (1H, s, Ar-CH=), 7.9 (1H, br s, NH); ms m/e 284 (M^+, base peak), 238 (M - EtOH, 34.4%), 237 (94.8%), 210 (M - EtOH - CO, 47.4%).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.86. Found: C, 72.06; H, 7.26; N, 10.15.

From the fraction eluted with ether, XIV was obtained (0.1 g., 3.7%) m.p. 194-196° (recrystallized from ether or ethanol); ir (nujol): ν C=O 1660, C=C 1620; nmr (deuteriochloroform): δ 4.4 (3H, q, -CH_2-O- and -CO-CH<), 7.3-8.1 (9H, m, aromatic H and vinylic H); ms: m/e 280 (M^+, 57.1%), 235 (M - OEt, base peak), 207 (M - COOEt, 48.2%).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.86; H, 5.71; N, 10.00. Found: C, 72.80; H, 5.58; N, 10.13.

From the fraction eluted with chloroform, XVIc was obtained (0.15 g., 4.5%), m.p. 288-290° (recrystallized from ethanol); ir (nujol): ν C=O 1655, 1608, 1575; nmr (trifluoroacetic acid-deuteriochloroform): δ 2.45 and 2.86 (each 2H, t like, C_6- and C_7-methylene), 3.7-4.5 (9H, m, 2 X >N-CH_2-CH_2-N< and vinylic H), 6.8 (1H, s, C_{12}-vinylic H), 7.1 (4H, s, aromatic H), 8.7 (2H, br s, 2 X >NH); ms: m/e 349 (M+1, 63.9%), 348 (M^+, base peak), 305 (M - CH_2=CH-NH_2, 47.2%). Compound XVIc was acetylated in the usual manner giving acetyl-XVIc in quantitative yield, m.p. 240-242° (recrystallized from benzene); ir (nujol): ν C=O 1650, C=C 1560.

Anal. Calcd. for $C_{22}H_{22}N_4O_3$: C, 67.67; H, 5.68; N, 14.35. Found: C, 67.78; H, 5.92; N, 14.09.

Attempts to Cyclize XV.

Method A.

A solution of XV in toluene was refluxed overnight in the presence of one molar equivalent of TFA. The resulting oily substance which was formed was insoluble in toluene and was acetylated with acetic anhydride in pyridine. However, following the work-up, the expected product, XVIb, could not be isolated. Purification of the original toluene filtrate by silica gel column chromatography also only resulted in the recovery of a small amount of XV.

Method B.

A mixture of XV (0.15 g., 0.53 mmole) and ethylene glycol (5 ml.) was heated in a sealed tube at 150° overnight. The mixture was then poured into water giving a precipitate, which was recrystallized from benzene giving an unidentified product (0.1 g.), m.p. 199-200°; ms: m/e 400 (M^+, 64.9%), 170 (base peak).

Method C.

A mixture of XV (0.2 g.) and phenyl ether (10 ml.) was boiled for 10 minutes. *n*-Hexane was added giving a precipitate, which was recrystallized from benzene yielding XIX (75 mg., 35%); ir (nujol): ν C=O 1670, C=C 1595; nmr (trifluoroacetic acid): δ 2.7 (4H, m, C_5- and C_6-methylene), 3.9 (8H, br s, 2 X >N-CH_2-CH_2-N<), 5.6 (1H, s, >NH), 6.4 (1H, s, vinylic H), 7.1 (4H, m, aromatic H); ms: m/e 307 (M-1, 69.4%), 306 (M^+, base peak), 238 (XVIa$^+$, 4.8%), 210 (m/e 238 - C_2H_4, 3.5%).

Anal. Calcd. for $C_{18}H_{18}N_4O$: C, 70.58; H, 5.88; N, 18.30. Found: C, 70.77; H, 6.07; N, 18.40.

3-Cyclohexylamino-2-(3-benzo[*f*]quinolyl)benzo[*f*]quinoline (XXIb).

To a solution of 1,2-dihydrobenzo[*f*]quinoline (XX) (2 g., 10 mmoles) in dry chloroform (20 ml.), phosphorus pentachloride (2.06 g., 10 mmoles) was added portionwise. The mixture was stirred overnight and then refluxed an additional 2 hours. The cooled solution was then poured into ice water giving a red residue, which was filtered and washed with aqueous sodium bicarbonate and water. This crude residue was not characterized and was refluxed with cyclohexylamine for 2 hours. The cooled mixture was then poured into ice water and extracted with chloroform, washing the organic layer with aqueous saturated sodium chloride. The organic solution was then dried, the solvent was evaporated, and the resulting residue was recrystallized from chloroform giving pure XXIb (1.5 g., 67%), m.p. 254-258°; ir (nujol): ν 1610, 1600, 1580; ms: m/e 453 (M^+, 84%), 371 (M - cyclohexene, base peak).

Anal. Calcd. for $C_{32}H_{27}N_3$: C, 84.76; H, 5.96; N, 9.27. Found: C, 84.88; H, 5.93; N, 9.13.

1,2-Dihydro-3-ethoxybenzo[*f*]quinoline (XXIIb).

To a suspension of XX (4.13 g., 21 mmoles) in anhydrous methylene chloride, Meerwein's reagent (15.5 g., 80 mmoles) was added portionwise. The mixture was then refluxed for 6 hours, cooled, neutralized with 5*N* potassium carbonate and filtered through a celite mat. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The part of the residue which was soluble in ether was microdistilled (b.p. 0.5 mm, 200°), giving 1 g. (21%) of XXIIb, m.p. 70-75°; ir (nujol): ν C=N 1640; nmr (deuteriochloroform-carbon tetrachloride): δ 1.33 (3H, t, -CH_2-CH_3), 2.20-2.83 (2H, m, >CH_2), 2.85-3.40 (2H, m, >CH_2), 4.38 (2H, q, -OCH_2-), 7.06-8.70 (6H, m, aromatic H).

N-(1,2-Dihydrobenzo[*f*]quinolin-3-yl)glycine (XXIIc).

To an ethanolic solution of glycine (0.41 g., 5.8 mmoles), XXIIb (1.3 g., 5.8 mmoles) was added at room temperature. The mixture was refluxed for about 2 hours yielding white crystals, which were collected by filtration and recrystallized from aqueous ethanol (1.47 g., 68%), m.p. 270° dec.; ir (nujol): ν C=O 1695, C=N 1620; nmr (trifluoroacetic acid): δ 3.10-3.70 (4H, m, aromatic H), 9.60 (1H, s, >NH); ms: m/e 254 (M^+, 63.4%), 236 (M - H_2), 91.4%), 180 (M - NH-CH_2-COOH, base peak).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.14; H, 5.60; N, 11.21.

1,2,3,4-Tetrahydrobenzo[*f*]quinoline (XXIV).

Method A.

To a solution of XXIIc (0.6 g., 2.3 mmoles) in ethanol, sodium borohydride (0.26 g., 6.9 mmoles) was added under ice cooling with stirring. The mixture was then stirred for 1 hour at room temperature and 30% acetic acid was added to decompose the excess hydride. Following dilution with water, the precipitate (XXIIc, 0.2 g.) was filtered and the filtrate was evaporated. The resulting residue was extracted with chloroform and dried. Concentration of this solution gave an oily residue which was purified by passing it through a column packed with silica gel and eluted with benzene. Compound XXIV was thus obtained as a brown oil (0.25 g., 49%); ir (nujol): ν NH 3400; nmr (carbon tetrachloride): δ 3.48 (1H, s, >NH), 3.14 (2H, t, J = 6, >N-CH_2-), 2.88 (2H, t, Ar-CH_2-), 2.22-1.63 (2H, m, >CH_2); ms: m/e 183 (M^+). Compound XXIV hydrochloride had m.p. 240-242° (recrystallized from ethanol, lit. (14) m.p. 246-249°).

Anal. Calcd. for $C_{13}H_{14}ClN$: C, 71.07; H, 6.38; N, 6.38. Found: C, 70.93; H, 6.39; N, 6.55.

Compound XXIV picrate had m.p. 180-182° (recrystallized from ethanol).

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.59; H, 3.76; N, 13.33.

Method B.

To a suspension of lithium aluminum hydride (0.5 g., 13 mmoles) in THF (30 ml.), XX (1 g., 5 mmoles) was added portionwise at room temperature. After refluxing for 2 hours, the reaction mixture was cooled and a solution of ammonium chloride (3.5 g., 65 mmoles) was added to decompose the complex. The insoluble part of the solution was then removed by filtration and the filtrate was combined with chloroform washings of the insoluble part. The solvents were removed giving a viscous oil which was purified as described in Method A giving pure XXIV (0.8 g., 86%). This sample proved to be identical with that reported in Method A.

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