Indian Journal of Chemistry
Vol. 10, April 1972, pp. 344-350

Condensed Heterotricycles: Pyrrolo[1,2-*a*]quinoxaline Derivatives*

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Manuscript received 16 *August* 1971; *accepted for publication* 8 *October* 1971

Treatment of 1-(*o*-aminophenyl)pyrrole (II) with phosgene gives lactam (IV), from which 4-chloro- (V) and 1,4-dichloro- (VI) derivatives become available. Acid hydrolysis of VI affords chlorolactam (IX). Treatment of IV and IX with appropriate halides leads to N-aminoalkyl derivatives (X) and (XI) respectively. V and VI react with amines to yield aminoquinoxalines VII and VIII respectively while V and aminoalkoxide give XII. The action of CNBr on II results in the formation of aminoquinoxaline VII ($R_1 = NH_2$), while $POCl_3$ cyclization of the phenyl urea of II affords the anilino compound VII (R_1= NHPh). The mercapto derivative XIII is obtained from II using CS_2, and is utilized to form S-aminoalkyl derivatives. Oxidative treatment of II with benzaldehyde produces the phenylquinoxaline (XVII), while the chloroacetyl derivative cyclizes under mild conditions to the chloromethyl compound XIX. The acetylene dicarboxylic ester adducts XXI and XXII of II, upon treatment with PPA, undergo cyclization to XXIII and XXIV, with elimination of alkyl acetate. A mechanism is suggested for this novel cyclization. Bromination and nitration products of the parent pyrrolo[1,2-*a*]quinoxaline (III) are described.

As part of a continuing project for the synthesis of condensed tricyclic systems[1-4] with one or more nitrogen atoms and their biological evaluation, we were interested in examining the pyrroloquinoxaline ring. Among the several possible variants of this tricycle, the known ones are pyrrolo-[1,2-*a*][5], [2,3-*b*][6], [2,3-*g*][7], [3,4-*b*][8], [3,4-*g*][9] and [1,2,3-*de*][10]quinoxalines. Out of these our attention was attracted in 1966 to the pyrrolo[1,2-*a*]-quinoxaline system[1-4] (III), because of a report on the facile formation of this ring from 1-(*o*-aminophenyl)pyrrole (II) which was itself readily available from *o*-phenylenediamine and 2,5-diethoxytetrahydrofuran (I) in viable yields[11]. Initially our objectives were two-fold: (i) study of electrophilic substitution on III, and (ii) synthesis of diverse derivatives for biological screening. However, we concentrated our efforts on the latter, because of successive elaborate publications from the Cheeseman group on the former.

Treatment of II with phosgene in boiling toluene gave the lactam IV in quantitative yield. A synthesis of IV from II in two steps by cyclization of the corresponding urethane was reported subsequently[12]. Reaction of IV with hot $POCl_3$ alone afforded the chloro derivative V, whereas in the presence of PCl_5, the dichloroderivative VI was formed in high yield. The placement of the second chlorine atom at position-1 was suggested by the appearance of the signal due to the C-9 proton as a complex multiplet at extremely low field in the NMR spectrum of VI in $CDCl_3$ (8·85 ppm) as the A part of an *ABCD* system, due to long range deshielding by the halogen atom[13,14] and the absence of a similar signal below 8 ppm in the spectrum of V. V was converted into VI under similar conditions, but only in moderate yield. Since III itself yielded no characterizable chlorinated product with $POCl_3$-PCl_5 mixture, it is felt that in the formation of VI from IV, the chlorolactam (IX) was more likely to be the intermediate. Palladium-catalysed hydrogenation of VI, rather surprisingly, gave V.

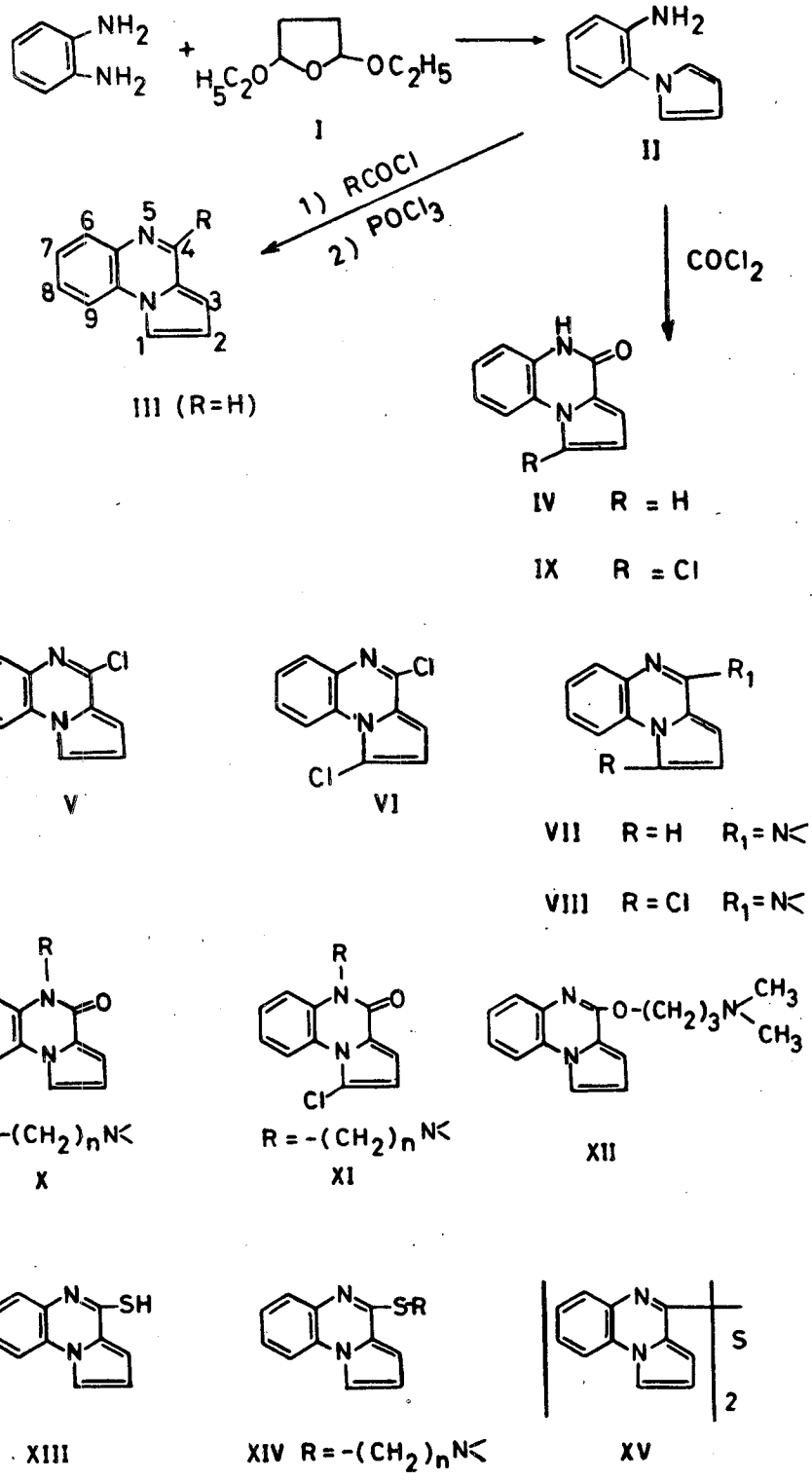
Reaction of V with several bases afforded chlorine-displaced products VII; similarly, VI and amines gave rise to VIII, still containing the chlorine atom at C-1. The NMR spectrum of a representative example, VIII (R_1=N<=N'-methylpiperazino) in DMSO had the C-9 proton signal at low field, at 8·80 ppm, indicating that C_4-Cl and not C_1-Cl had been displaced. In corresponding VII, the C-9 proton signal was probably present at about 8·00 ppm, and there was no signal below 8·33 ppm. For a study of long range shielding effects, it would have been of interest to displace the chlorine at C-1 also, but this was not achieved even under vigorous conditions†.

Two other syntheses of VII were achieved. The action of cyanogen bromide on II directly gave VII ($R_1 = NH_2$) but in poor yield. The previously reported synthesis of this amine is from V and KNH_2 in xylene or NH_3 in MeOH[12]. $POCl_3$ cyclization of the phenyl urea of II gave VII (R_1= NHPh) in good yield.

Treatment of VI with hot aqueous acid resulted in hydrolysis of the C_4-Cl atom, to afford chlorolactam (IX), exhibiting a low field multiplet for C_9-H at 8·75 ppm in its NMR spectrum in DMSO. Lactams IV and IX were aminoalkylated on the nitrogen atom by using NaH and appropriate dialkylaminealkyl chlorides to give respectively products X and XI. The dimethylaminopropyl derivative thus obtained was stable to treatment with hot acid and was different from XII obtained

*Contribution No. 230 from CIBA Research Centre.

†However, this study has been now made using 4-chloro-2-methylbenzo(f)quinoline. Nagarajan, K. & Shah, R. K., presented before Convention of Chemists, Madras, 30 Nov., 4 Dec. 1970.



by treating V with sodium dimethylaminopropyl oxide.

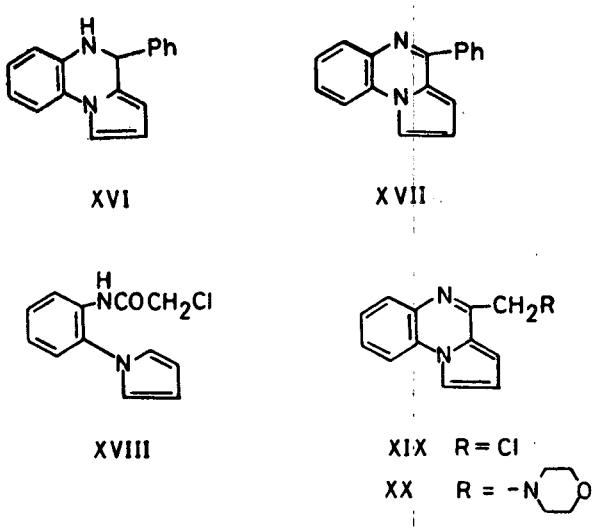
Treatment of II with thiophosgene in hot toluene did not afford the expected XIII; instead a high melting product was obtained which appeared to be sulphide XV from analytical data. However, XIII could be obtained in excellent yield by treatment of II with CS_2 in alcoholic alkali. A different synthesis[12] of XIII utilizes the action of NaSH on chloro compound V. Reaction of XIII with aminoalkyl halides gave the S-alkylated products XIV with UV spectra similar to the O-alkylated product XII. Condensation of II with benzaldehyde alone was attempted in the hope of forming the dihydropyrroloquinoxaline (XVI), but this was not realized. However, in the presence of cupric acetate, the known 4-phenyl derivative XVII was formed in good yield. The reaction is reminiscent of the formation of benzimidazoles from *o*-phenylenediamines and aldehydes in the presence of oxidizing agents[15]. Presumably XVI, formed as an intermediate, was irreversibly oxidized to XVII, thus providing a novel synthesis of this ring system.

Treatment of II with chloracetyl chloride in benzene mainly yielded the expected neutral derivative XVIII, but a base was also obtained in about 10% yield, which was identified as the pyrroloquinoxaline (XIX). XIX was formed in 50% yield when the chloracetylation reaction was conducted in dioxane. The product was identical with the one obtained from XVIII under Friedel-Crafts conditions or by treatment with PPA. The formation of XIX from II under the mild acidic conditions of chloracetylation is indicative of the great facility with which the pyrrole nucleus in II undergoes electrophilic substitution[11]. XIX and morpholine afforded the morpholino derivative XX, characterized as a dihydrochloride.

Interesting results were obtained from PPA cyclizations of the adducts XXI and XXII of II with acetylenedicarboxylic esters. The dimethyl ester adduct XXI was shown by elemental analysis to arise by a 1:1 addition. Its NMR spectrum in $CDCl_3$ showed two 3-proton singlets for CO_2Me at 3·65 and 3·68 ppm, a 2-proton triplet for the pyrrole β-protons at 6·35 ppm and another 2-proton triplet for the pyrrole α-protons at 6·90 ppm, besides multiplets for 4 aromatic protons and a broad singlet for NH at 9·25 ppm.

cis-Stereochemistry for the CO_2Me groups was indicated by the location of the olefin singlet at 5·47 ppm[16]. PPA cyclization of XXI resulted in the loss of elements of methyl acetate. The product showed in its NMR spectrum in $CDCl_3$, a 3-proton singlet for CO_2CH_3 at 4·1 ppm and one β-pyrrole proton quartet at 6·9 ppm. A complex multiplet of 4 aromatic and 2-pyrrole protons were spread from 7·3 to 8·3 ppm. Structure XXIII was consequently deduced for the product. Likewise XXIV was obtained from the diethylester adduct XXII. Further confirmation was provided by identifying XXIV with a sample unambiguously synthesized from the oxamidate XXV of II using $POCl_3$. A likely mechanism for the formation of XXIII from XXI is indicated on the chart. This reaction has been extended to the acetylene-dicarboxylic ester adduct of *o*-aminodiphenyl. Details of our interesting observations will be reported in a future communication (Nagarajan, K., Nair, M. D. & Shah, R. K., unpublished work).

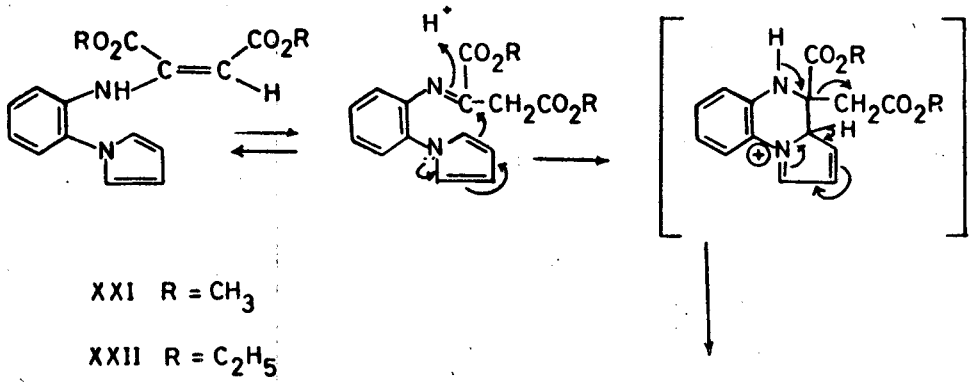
Treatment of III with bromine (1 mole) in cold acetic acid gave the 1-bromo derivative (XXVI), which had a multiplet for the C-9 proton in its NMR spectrum in $CDCl_3$ at 9·17 ppm. With 2 moles of bromine in acetic acid at room temperature, the 1,3-dibromo derivative (XXVII) was obtained. XXVI and XXVII have been reported to be formed from III by the action of NBS, while bromine in boiling HBr was reported to yield the 2,3-dibromo derivative (XXIX)[17]. Treatment of XXVI with boiling acid is again known to isomerize it to XXVIII. Presumably acetic acid, alone or in the presence of HBr generated during bromination at room temperature or below, is unable to bring about the formation of XXVIII and XXIX. Treatment of III with HNO_3 in acetic acid gave no



XVI XVII

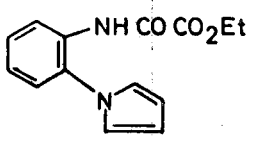
XVIII XIX R = Cl

XX R = -N O

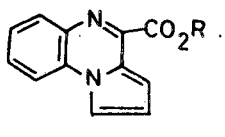


XXI R = CH_3

XXII R = C_2H_5

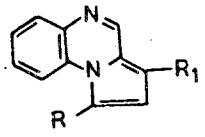


XXV



XXIII R = CH_3

XXIV R = C_2H_5

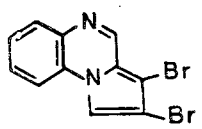


XXVI R = Br ; R_1 = H

XXVII R = R_1 = Br

XXVIII R = H ; R_1 = Br

XXX R = H ; R_1 = NO_2



XXIX

characterizable nitro derivative. A mono-nitro derivative, m.p. 233-5° (d), was obtained from III by using KNO_3 in H_2SO_4. The m.p. corresponded to that of the product, prepared by Cheeseman and Tuck[18], and assigned the 3-nitro structure XXX for cogent chemical reasons. The NMR spectrum of the nitro compound could not be run in $CDCl_3$ or DMSO-d_6. In CF_3CO_2H, it showed a broadened singlet at 10 ppm (C_4-H) and a doublet at 8·87 ppm (C-1 pyrrole H ?). The characteristic multiplet due to the C_9-H was not seen in the region between these new signals, thus ruling out position-1 for the NO_2 group. In the NMR spectrum of III in CF_3CO_2H, the C-1 proton was seen as a doublet at 8·28 ppm and the C-4 proton at 8·67 ppm. Its marked downfield shift to 10 ppm in the nitro derivative would be in keeping with the assignment of NO_2 group to the 3 position.

The new compounds reported in this paper were examined extensively for a wide spectrum of biological activities and were found uninteresting.

Experimental Procedure

All melting points are uncorrected. IR spectra were taken as nujol mulls, unless otherwise stated. UV spectra were taken in 95% ethanol. NMR spectra were run on a Varian A-60 spectrometer. Chemical shifts are in ppm downfield from TMS internal standard.

4,5-*Dihydro*-4-*oxopyrrolo*[1,2-*a*]*quinoxaline* (IV)— A solution of N-(2-aminophenyl)pyrrole (II)[11] (4·7 g) in 65 ml toluene and phosgene in toluene (20%, 35 ml) was heated under reflux for ½ hr. Nitrogen was bubbled in to drive off excess phosgene. The solution was then allowed to come to room temperature and set aside for 18 hr. The heavy crystalline precipitate was filtered off and washed with light petrol to give IV (5·0 g), which was recrystallized from DMF-methanol; m.p. 276-8°; $\nu_{C=O}$ 1650 cm^{-1} (Found: C, 72·16; H, 4·57; N, 14·82. $C_{11}H_{18}N_2O$ requires C, 71·72; H, 4·38; N, 15·21%).

4-*Chloropyrrolo*[1,2-*a*]*quinoxaline* (V)— A suspension of the above lactam (15 g) in phosphorus oxychloride (75 ml) was heated at 95° for 1 hr and then at 120-30° for 5 hr. Crushed ice was added to the resultant solution and the chloro compound extracted with methylene chloride. Evaporation of the dried extract gave a product (15·1 g), which crystallized from CH_2Cl_2-cyclohexane, m.p. 170-71° (Found: C, 65·36; H, 3·20; N, 13·81. $C_{11}H_7ClN_2$ requires C, 65·20; H, 3·48; N, 13·83%).

1,4-*Dichloropyrrolo*[1,2-*a*]*quinoxaline* (VI)— A mixture of (IV) (10 g) and phosphorus pentachloride (21 g) in phosphorus oxychloride (45 ml) was heated under reflux for 2½ hr. The resultant solution was poured into crushed ice and the product extracted with methylene chloride. Evaporation of the dried extract afforded the dichloro derivative VI (12·9 g), which was crystallized from hexane; 9·9 g, m.p. 110-11° (Found: C, 55·38; H, 2·84; N, 12·10; Cl, 29·83. $C_{11}H_6Cl_2N_2$ requires C, 55·72; H, 2·55; N, 11·82; Cl, 29·82%).

The 1,4-dichloro compound was also obtained in a slightly impure state, when 4-chloropyrrolo-[1,2-*a*]quinoxaline (V) (2 g), phosphorus pentachloride (3·2 g) and phosphorus oxychloride (10 ml) were heated together for 2 hr.

1-*Chloro*-4,5-*dihydro*-4-*oxopyrrolo*[1,2-*a*]*quinoxaline* (IX)— The 1,4-dichloro derivative (VI) (14·5 g) was suspended in water (100 ml) containing conc. HCl (3 ml) and the mixture heated under reflux for 10 hr. The product was filtered, and washed with (9 g) and recrystallized from THF, m.p. 304-5° (Found: C, 59·80; H, 3·37; N, 13·18. $C_{11}H_7ClN_2O$ requires C, 60·38; H, 3·23; N, 12·81%).

Catalytic reduction of (VI)—The dichloro derivative (VI) (0·95 g) in methanol (50 ml) containing sodium acetate (0·6 g) was hydrogenated at atmospheric pressure and room temperature, using Pd/C (0·15 g). One mole equivalent of hydrogen was taken up in 1 hr. The mixture was filtered and the filtrate evaporated. The residue was triturated with aqueous ammonia and washed with water; 0·5 g, m.p. 138-50°. Two crystallizations from hexane gave 4-chloropyrrolo[1,2-*a*]quinoxaline, m.p. 167-9°; undepressed by admixture with authentic sample.

4-*Aminopyrrolo*[1,2-*a*]*quinoxalines* (VII)— A mixture of V (3 g) and morpholine (10 ml) was heated at 140° for 6 hr. After trituration with water, the product was extracted with ether and the ether layer dried and evaporated. Treatment of the residual basic product with HCl gas in isopropanol afforded 4-morpholinopyrrolo[1,2-*a*]quinoxaline hydrochloride, which was crystallized from MeOH-ether; 3·5 g, m.p. 278-80° (d) (Found: C, 62·32; H, 5·43; N, 14·40. $C_{15}H_{16}ClN_3O$ requires C, 62·17; H, 5·57; N, 14·50%). Similarly were prepared the following derivatives: 4-hydrazino, m.p. 169-71° (d) (from ethanol) (Found: C, 66·75; H, 5·30; N, 28·65. $C_{11}H_{10}N_4$ requires C, 66·65; H, 5·09; N, 28·27%); 4-N-(N′-methyl)-piperazino, dihydrochloride, m.p. 281-3° (from methanol) (Found: C, 52·76; H, 6·48; N, 14·88. $C_{16}H_{18}N_4.2HCl.1\frac{1}{2}H_2O$ requires C, 52·40; H, 6·25; N, 15·30%); dipicrate, m.p. 216-17° (from methanol) (Found: C, 46·31; H, 3·42; N, 19·44. $C_{16}H_{18}N_4.2C_6H_3N_3O_7$ requires C, 46·40; H, 3·35; N, 19·33%); 4-(γ-dimethylaminopropylamino) dihydrochloride, m.p. 238-40° (loss of H_2O at 163-5°) (from ethanol) (Found: C, 53·81; H, 7·00; N, 15·46. $C_{16}H_{20}N_4.2HCl.H_2O$ requires C, 53·50; H, 6·70; N, 15·60%); and 4-N-(N′-*o*-tolyl)-piperazino dihydrochloride, m.p. 275-8° (d) (from methanol) (Found: C, 62·22; H, 6·38; N, 13·29. $C_{22}H_{22}N_4.2HCl.\frac{1}{2}H_2O$ requires C, 62·26; H, 5·89; N, 13·21%).

1-*Chloro*-4-*aminopyrrolo*[1,2-*a*]*quinoxalines* (VIII) — Treatment of 1,4-dichloro compound (VI) (3 g) with morpholine [10 ml] as above gave 1-chloro-4-morpholinopyrrolo[1,2-*a*]quinoxaline, characterized as the HCl salt (3·1 g), m.p. 249-50° (from ethanol) (Found: C, 55·14; H, 4·99; N, 12·59; Cl, 21·38. $C_{15}H_{14}ClN_3O.HCl$ requires C 55·57; H, 4·66; N,,

12·96; Cl, 21·91%); similarly were prepared the following derivatives: 1-chloro-4-N(N'-methyl)piperazino, m.p. 44-46° (from hexane) (Found: C, 67·68; H, 6·07; N, 13·57. $C_{17}H_{18}ClN_3$ requires C, 68·10; H, 6·05; N, 14·02%); 1-chloro-4-hydrazino hydrochloride, m.p. 214-16° (from ethanol) (Found: C, 46·47; H, 4·08; N, 19·71. $C_{11}H_9ClN_4.HCl.H_2O$ requires C, 46·01; H, 4·21; N, 19·51%), forming a *p*-anisylidene derivative, m.p. 179-80° (from benzene) (Found: C, 64·83; H, 4·04; N, 16·23. $C_{19}H_{15}ClN_4O$ requires C, 65·05; H, 4·31; N, 15·97%); and 1-chloro-4-N(N'-*o*-tolyl)piperazino, m.p. 110-12° (from dil. ethanol) (Found: C, 70·30; H, 5·72; N, 14·50. $C_{22}H_{21}ClN_4$ requires C, 70·11; H, 5·62; N, 14·87%); hydrochloride, m.p. 242-5° (d) (from ethanol) (Found: C, 63·86; H, 5·54; N, 13·73. $C_{22}H_{21}ClN_4.HCl$ requires C, 63·93; H, 5·36; N, 13·56%).

4-Aminopyrrolo[1,2-a]quinoxaline. (VII) (R=NH_2) — A solution of N-(2-aminophenyl)pyrrole (II) (4 g) and cyanogen bromide (2·8 g) in methanol (100 ml) containing sodium bicarbonate (3·5 g) was kept at room temperature for 3 days and then refluxed for 1½ hr. The solvent was removed *in vacuo* and the residue dissolved in dil. HCl and filtered. The filtrate was basified with ammonia. The precipitated base (0·7 g) was crystallized from dil. ethanol and then from benzene; m.p. 221-2° (Found: C, 71·89; H, 4·82; N, 22·68. $C_{11}H_9N_3$ requires C, 72·11; H, 4·95; N, 22·94%).

4-Anilinopyrrolo[1,2-a]quinoxaline (VII) (R=NHPh)— N-(2-Aminophenyl)pyrrole (II) (1·6 g) and phenyl isocyanate (1·2 g) refluxed together in benzene (10 ml) for 1 hr gave the phenyl urea (2 g), m.p. 182-3·5° (from ethanol) (Found: C, 73·49; H, 5·24; N, 14·70. $C_{17}H_{15}N_3O$ requires C, 73·63; H, 5·48; N, 15·15%). A mixture of the urea (0·3 g) and phosphorus oxychloride (1 ml) was heated at 90-100° for 5½ hr. The solution was poured into ice and treated with excess ammonia. The product was extracted into ether and crystallized twice from ether-hexane; 200 mg, m.p. 114-16° (Found: C, 78·52; H, 5·03; N, 16·05. $C_{17}H_{13}N_3$ requires C, 78·74; H, 5·05; N, 16·21%).

5-Aminoalkyl-4,5-dihydro-4-oxopyrrolo[1,2-a]quinoxalines (X) — A solution of the 4-oxopyrroloquinoxaline (IV) (3·7 g) in dimethylformamide (50 ml) was added to a suspension of sodium hydride (50% suspension in kerosene; 2 g) in 10 ml of the same solvent. The mixture was stirred at room temperature for 2 hr and then treated with γ-dimethylaminopropyl chloride (3·6 g) in dimethylformamide (10 ml); the temperature was raised to 60° and the mixture kept stirred for 18 hr. The solvent was then removed *in vacuo*, the residue treated with excess 2*N* HCl and filtered. The filtrate was extracted with ether and the aqueous phase made basic with ammonia to yield the aminoalkylated product. This was recovered with ether and converted to hydrochloride of 4,5-dihydro-5-(γ-dimethylaminopropyl)-4-oxopyrrolo[1,2-*a*]quinoxaline, 2·9 g, m.p. 209-10° (from ethanol); $\gamma_{C=O}$ 1630 cm^{-1} (Found: C, 60·06; H, 6·90; N, 13·27. $C_{16}H_{19}N_3O.HCl.H_2O$ requires C, 59·47; H, 6·81; N, 13·03%); picrate, m.p. 204-5° (from ethanol) (Found: C, 53·19; H, 4·74; N, 16·93. $C_{16}H_{19}N_3O.C_6H_3N_3O_7$ requires C, 53·01; H, 4·45; N, 16·86%); similarly were prepared the following derivatives: 5-β-N-morpholinoethyl hydrochloride, m.p. 269-71° (d) (from methanol-ether) (Found: C, 58·51; H, 6·27; N, 11·88. $C_{17}H_{19}N_3O_2.HCl.H_2O$ requires C, 58·04; H, 6·25; N, 11·93%); picrate, m.p. 275-6° (d) (from aq. DMF) (Found: C, 52·93; H, 4·65; N, 15·69. $C_{17}H_{19}N_3O_2.C_6H_3N_3O_7$ requires C, 52·47; H, 4·18; N, 15·97%); β-N-pyrrolidinoethyl hydrochloride, m.p. 235-8° (from ethanol) (Found: C, 63·66; H, 6·07; N, 13·15. $C_{17}H_{19}N_3O.HCl$ requires C, 64·24; H, 6·34; N, 13·22%); and from 1-chloro-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline (VI), 1-chloro-4,5-dihydro-5-(β-N-morpholinoethyl)-4-oxopyrrolo[1,2-*a*]quinoxaline hydrochloride (XI), m.p. 309-10° (d) (from water) (Found: C, 55·43; H, 5·42; N, 11·79. $C_{17}H_{18}ClN_3O_2.HCl$ requires C, 55·44; H, 5·20; N, 11·41%) and 1-chloro-4,5-dihydro-5-(β-dimethylaminoethyl)-4-oxopyrrolo[1,2-*a*]quinoxaline hydrochloride (XI), m.p. 301-2° (from water) (Found: C, 55·55; H, 5·40; N, 12·99. $C_{15}H_{16}ClN_3O.HCl$ requires C, 55·22; H, 5·25; N, 12·88%).

4-(γ-Dimethylaminopropyloxy)-pyrrolo[1,2-a]quinoxaline (XII)— To the sodium salt of γ-dimethylaminopropanol prepared from the alcohol (0·62 g) and sodium hydride (0·6 g of 50% suspension in kerosene) in dioxane (35 ml) in 1 hr was added 4-chloropyrrolo[1,2-*a*]quinoxaline (V) (0·8 g). The mixture was stirred at 25° for 2 hr and then at 60° overnight. Dioxane was evaporated *in vacuo* and ether added to the residue and filtered. Addition of dry HCl gas to the filtrate precipitated the hydrochloride (0·6 g) which was obtained crystalline from ethanol-ether; however, it was very hygroscopic, losing water at 112-14°, solidifying and remelting at 230°; $\gamma_{C=C}$ 1620 cm^{-1}. The picrate was crystyllized from acetone-ethanol, m.p. 210-11° (Found: C, 52·74; H, 4·70; N, 17·22. $C_{22}H_{22}N_6O_8$ requires C, 53·01; H, 4·45; N, 16·86%).

4-Mercaptopyrrolo[1,2-a]quinoxaline (XIII) — A mixture of N-(2-aminophenyl)pyrrole (II) (24 g) in ethanol (750 ml) and CS_2 (40 g) and sodium hydroxide (12 g) in water (25 ml) was heated under reflux for 50 hr. The product obtained on removal of ethanol was purified by dissolving in hot 5% sodium hydroxide, filtering and acidifying the filtrate with acetic acid. Repeated washing with ethanol gave a product (23·5 g), m.p. 275°. A sample was recrystallized from DMF for analysis; m.p. 278° (Found: C, 66·08; H, 4·18; N, 14·21. $C_{11}H_8N_2S$ requires C, 65·99; H, 4·03; N, 13·99%).

S-Aminoalkyl-4-mercaptopyrrolo[1,2-a]quinoxalines (XIV) — Treatment of the foregoing mercapto compound XIII with the appropriate aminoalkyl chloride as before gave the following derivatives: S-β-dimethylaminoethyl hydrochloride, m.p. 226-8° (d) (from ethanol) (Found: C, 58·60; H, 6·10; N, 13·97. $C_{15}H_{17}N_3S.HCl$ requires C, 58·53; H, 5·89; N, 13·66%); S-β-pyrrolidinoethyl hydrochloride, m.p. 190-93° (too hygroscopic for analysis); and S20-γ-dimethylaminopropyl hydrochloride, m.p. 200-204° (from ethanol) (too hygroscopic for analysis); dipicrate, m.p. 176-7° (from ethanol) (Found: C, 45·48; H, 3·61; N, 17·63. $C_{16}H_{19}N_3S.2C_6H_3N_3O_7$ requires C, 45·22; H, 3·30, N, 16·96%).

Action of thiophosgene on N-(2-aminophenyl)pyrrole (II) — A solution of II (5·2 g) in toluene (80 ml) was treated with thiophosgene (4 g) in toluene (20 ml) with cooling during ½ hr. The mixture was then heated under reflux for 2 hr, and then cooled. The product was filtered and washed with benzene (4 g) and crystallized from DMF-

ethanol in yellow crystals of XV, m.p. 314-17° (d) (Found: C, 71·08; H, 4·43; N, 15·08; S, 9·88. $C_{22}H_{14}N_4S$ requires C, 72·12; H, 3·85; N, 15·29; S, 8·73%).

N-(o-Chloracetylaminophenyl)pyrrole (XVIII)— To a solution of N-(*o*-aminophenyl)pyrrole (II) (9·6 g) in dry benzene (150 ml) was added chloracetyl chloride (7 g) in dry benzene (20 ml) during 20 min with stirring and at room temperature. After being set aside overnight, the mixture was heated under reflux for 2 hr and the solvent then removed *in vacuo*. The residue was triturated with water and filtered (9·9 g) and crystallized from aq. ethanol, m.p. 150-51° (Found: C, 61·16; H, 4·94; N, 12·23. $C_{12}H_{11}ClN_2O$ requires C, 61·41; H, 4·72; N, 11·94%). The aqueous filtrate upon neutralization with ammonia afforded 1·2 g of a basic product. This was obtained in greater yield (4·9 g, m.p. 143-4° from ethanol), when the chloracetylation was conducted as before, but in dioxane; this was identified as 4-chloromethylpyrrolo[1,2-*a*]quinoxaline (XIX) (see below) (Found: C, 66·39; H, 4·53; N, 12·89. $C_{12}H_9ClN_2$ requires C, 66·52; H, 4·19; N, 12·93%).

4-*Chloromethylpyrrolo*[1,2-*a*]*quinoxaline* (XIX) — The chloracetyl derivative (9·3 g) and anhydrous aluminium chloride (5·6 g) in benzene (100 ml) were heated under reflux for 3 hr. The solvent was removed and the residue dissolved in 2*N* HCl and filtered. The filtrate was made ammoniacal to yield the product, 7·5 g, m.p. 143°, identical with the previous preparation. PPA cyclization gave lesser yield in the cyclization.

4-(*Morpholinomethyl*)*pyrrolo*[1,2-*a*]*quinoxaline* (XX) — A mixture of XIX (3 g) and morpholine (5 ml) was heated for 1 hr, after the initial exothermic reaction subsided. After trituration with water, the product was extracted into ether and precipitated as the dihydrochloride. Crystallization from methanol-ether gave 4·4 g, m.p. 232-4° (Found: C, 56·62; H, 6·01; N, 12·51. $C_{16}H_{19}Cl_2N_3O$ requires C, 56·48; H, 5·63; N, 12·35%).

4-*Phenylpyrrolo*[1,2-*a*]*quinoxaline* (XVII)— A mixture of II (3·2 g) in methanol (50 ml) and water (100 ml), containing cupric acetate (8 g) was heated on a water-bath and treated slowly with benzaldehyde (2·1 g) in methanol (50 ml). The mixture was then heated under reflux for 6 hr and filtered. The filtrate was stripped of methanol *in vacuo* and the concentrate extracted with ether. Evaporation of the dried ether extract gave 4-phenylpyrrolo[1,2-*a*]-quinoxaline (2·4 g), m.p. 92-93°, after one crystallization from hexane. The m.p. rose to 97° after a few more crystallizations (lit. m.p. 97·5-99°) (Found: C, 83·63; H, 5·08; N, 11·31. $C_{17}H_{12}N_2$ requires C, 83·58; H, 4·95; N, 11·47%).

Bromination of pyrrolo[1,2-*a*]*quinoxaline* (III)— (i) Bromine (1·6 g, 10 mmoles) in acetic acid (10 ml) was added to a cooled solution of III (1·7 g, 10 mmoles) in the same solvent (20 ml). After 1 hr, the precipitate was filtered off and washed with water to give 1-bromopyrrolo[1,2-*a*]quinoxaline (XXVI) hydrobromide (3·1 g), which was crystallized from ethanol, m.p. 187-8° (Found: C, 40·26; H, 2·47; N, 8·57. $C_{11}H_7BrN_2.HBr$ requires C, 40·25; H, 2·45; N, 8·54%). The free base was liberated with ammonia and crystallized from aq. alcohol, m.p. 100-101° (lit.[16] m.p. 107-8°) (Found: C, 53·37; H, 3·24; N, 11·35. $C_{11}H_7BrN_2$ requires C, 53·46; H, 2·86; N, 11·34%).

(ii) A solution of bromine (6·4 g, 40 mmoles) in acetic acid (10 ml) was added to III (3·4 g) in acetic acid (35 ml). The precipitate (perbromide ?) was filtered off, washed with ether, suspended in ethanol (50 ml) and heated under reflux for ½ hr. Excess aq. ammonia was then added and the precipitated base filtered off and washed with water; 5·6 g. This was recrystallized from ethanol to give the dibromo derivative XXVII, m.p. 161-2° (lit.[16] m.p. 162-3°) (Found: C, 40·86; H, 2·04; N, 8·79. $C_{11}H_6Br_2N_2$ requires C, 40·52; H, 1·85; N, 8·59%).

Nitration of pyrrolo[1,2-*a*]*quinoxaline* (III)— A solution of III (3·4 g) in conc. sulphuric acid (25 ml) was cooled in ice and treated slowly with potassium nitrate (2·5 g). After being set aside for 1 hr, the solution was poured into ice and the precipitate collected. This was extracted with hot ethanol (100 ml) and filtered. A product crystallized from this filtrate and was recrystallized from ethanol; m.p. 205-7° (d). These crystals and the ethanol-insoluble part were extracted with hot dioxane (50 ml) and the extract cooled to give yellow crystals, which were further recrystallized from aq. dioxane to give the 3-nitro compound (XXX), m.p. 233-5° (d) (Found: C, 61·70; H, 3·51; N, 19·66. $C_{11}H_7N_3O_2$ requires C, 61·97; H, 3·31; N, 19·71%).

Addition of acetylenedicarboxylic esters to N-(o-aminophenyl)pyrrole (II)— A solution of II (3·2 g) in methanol (25 ml) was mixed with dimethylacetylene dicarboxylate (3·2 g) to give a mild exothermic reaction. After 24 hr, the crystalline product XXI (4 g), m.p. 45°, was filtered off and recrystallized from methanol; m.p. 52-55° (Found: C, 63·45; H, 5·37; N, 9·68. $C_{16}H_{16}N_2O_4$ requires C, 63·99; H, 5·37; N, 9·33%).

The adduct XXII from the pyrrole and diethylacetylene dicarboxylate was a liquid.

PPA cyclization of the above adducts — A mixture of the dimethyl ester (XXI) (1 g) and polyphosphoric acid (25 g) was heated at 100° for 6 hr, cooled, treated with ice and excess ammonia. The yellow precipitate was collected; 0·7 g, m.p. 153-7°, and recrystallized from aq. ethanol to give methylpyrrolo[1,2-*a*]quinoxaline-4-carboxylate (XXIII), m.p. 160-61° (Found: C, 68·63; H, 4·32; N, 12·80. $C_{13}H_{10}N_2O_2$ requires C, 69·01; H, 4·46; N, 12·38%).

(XXIV) was similarly obtained from XXII by treatment with PPA and purified by crystallization from hexane and then from aq. ethanol; m.p. 98-100°, undepressed by admixture with an authentic sample obtained below (Found: C, 69·58; H, 4·92; N, 11·90. $C_{14}H_{12}N_2O_2$ requires C, 69·99; H, 5·03; N, 11·66%).

Ethyl N-(2-pyrrylphenyl)oxamidate (XXV)— N-(2-Aminophenyl)pyrrole (II) (6·3 g) and diethyl oxalate (11·8 g) were heated together at 120° for 6½ hr. The product was triturated with ether, filtered and recrystallized from ethanol to give the oxamidic ester (5 g), m.p. 112-13° (Found: C, 65·44; H, 5·64; N, 11·17. $C_{14}H_{14}N_2O_3$ requires C, 65·10; H, 5·46; N, 10·85%).

$POCl_3$ cyclization of the oxamidic ester — The above ester (4·7 g) and phosphorus oxychloride (25 ml) were heated under reflux for 20 min. Excess phosphorus oxychloride was removed *in vacuo*, the residue treated with ammonia and the liberated

base extracted into ether. The ether extract was evaporated and the gummy product crystallized twice from hexane and once from aq. ethanol to give ethyl pyrrolo[1,2-*a*]quinoxaline-4-carboxylate (XXIV), m.p. 99° (Found: C, 69·97; H, 5·16; N, 11·98. $C_{14}H_{12}N_2O_2$ requires C, 69·99; H, 5·03; N, 11·66%).

Acknowledgement

The authors are grateful to Prof. T. R. Govindachari, Director, for his interest in the work and to Dr S. Selvavinayakam and his associates for analytical and spectral data.

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