Some 5,6-Dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines

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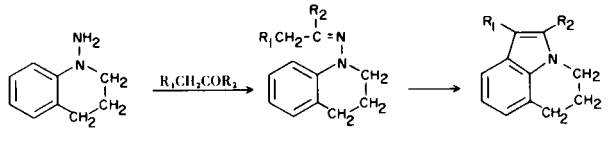
On the basis of structural features which relate 5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines to indoles, several representative groups of derivatives were synthesized.

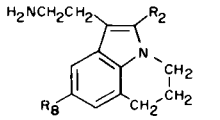
Numerous heterocyclic types have become the subject of detailed investigations because features thereof appear in certain alkaloids. This has not been obtained appreciably with pyrrolo[3,2,1-*i,j*]quinolines even though such a moiety (in varying states of hydrogenation) occurs in numerous alkaloids, inclusive of strychnine, aspidospermine, galanthine, lycorine, pluvine, crinine, and pyrifoline (*cf.* 2,3). Additionally, one may note that 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline has long been known by a trivial name, lilolidine (4,5). 5,6-Dihydro-4*H*-pyrrolo-[3,2,1-*i,j*]quinolines have been relatively little studied (*cf.* 5,24), and work was deemed justified in such series. Until recently, very few other than oxo compounds have been synthesized as representatives of this structure.

The various 5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines (III) were fundamentally produced as 1,7-trimethylene indoles through application of the Fischer indole synthesis to a 1-amino-1,2,3,4-tetrahydroquinoline (I). This procedure (with or without isolation of the intermediate hydrazone type (II), has become recognized recently (12-15, 20, 22, 24) as a flexible route to this series since it was first reported by Barger and Dyer (9). The greater share of compounds listed (*inter alia*, Tables I and II) was prepared from a 1-amino-1,2,3,4-tetrahydroquinoline and a ketonic intermediate to form the requisite 5,6-dihydro-4*H*-pyrrolo[3,2,-1-*i,j*]quinolines.



I II III

In general, selection of functional groupings for target compounds of the 5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline series was based upon those indicated to confer interesting or valuable biological effects upon indoles. Examples of this are the 1-(2-aminoethyl)-5,6-dihydro -4*H*-pyrrolo[3,2,1-*i,j*]quinolines (*e.g.*, IV - VI) which may be related to tryptamine. In fact, this aspect has become apparent in recent Russian work (22,24), and hence we have felt constrained to report our findings (11). Here, attention has been especially directed to the synthesis of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines having diverse substituents at positions 1 or/and 2, which are equivalent to positions 3 and 2 on the indole moiety. The Experimental serves to detail the preparation of the various compounds in the series chosen.



IV $R_1 = R_8 = H$
V $R_1 = CH_3$; $R_8 = H$
VI $R_1 = CH_3$; $R_8 = Cl$

EXPERIMENTAL (25)

A. Intermediates.

1-Amino-1,2,3,4-tetrahydroquinoline.

This compound was isolated and stored as the hemisulfate. It was made from 1,2,3,4-tetrahydroquinoline (26) by the procedure of Holliman and Mann (27, also *cf.* 12, 13, 15, 22). The base (m.p. 53-55°) was unstable, and was liberated from the salt only as required.

1-Amino-6-chloro-1,2,3,4-tetrahydroquinoline.

This compound was synthesized after the manner of the parent compound. 6-Chloroquinoline (28) was reduced (29), and nitrosated (*cf.* 27) to give a 82-95% yield of crude, light yellow product, m.p. 69-70°. The crude 6-chloro-1-nitroso-1,2,3,4-tetrahydroquinoline was reduced (*cf.* 27) with zinc dust in aqueous acetic acid-ethanol, and the base taken into ether and dried. The hydrochloride was precipitated in 84-89.5% yield, m.p. 203-205° dec. It was crystallized from absolute ethanol to afford *ca.* 75% yield of pure product, m.p. 208-209° dec.

Anal. Calcd. for $C_9H_{11}ClN_2.HCl$: Cl (total), 32.36; Cl (42) 16.18. Found: Cl (total) 32.06; Cl (42), 16.18.

4-Methoxyphenylpyruvic acid was obtained from 2-thiono-4-oxazolidinone (30) by the method of Gorizdra and Baranov (31).

Deoxybenzoin was made by reduction of benzil (32). The requisite 4-hydroxy deoxybenzoin, and also the 4-methoxy- and 4,4'-

TABLE I

2-Carboxy 5,6-Dihydro 4*H*-Pyrrolo[3,2,1-*i*,*j*]quinoline Derivatives

Compound	2-Substituent	Form (a)	Appearance	Solvent (b)	M.p., °C.	Yield, %	Formula	Analyses Calcd., % C	H	N	Found C	H	N
1	$-CO_2CH_3$	B	Col. oil	(c)	(d)	81.5-86	$C_{13}H_{13}NO_2$	72.54	6.09	6.51	72.28	6.30	6.36
2	$-CO_2CH_2CH_2N(CH_3)_2$	C	Prisms	A-E	186-187	85.5	$C_{16}H_{20}N_2O_2.HCl$	11.48 (e)		9.07	11.35 (e)		8.93
3	$-CONH_2$	B	Microcrysts	aA;B	196.5-197.5	81.5	$C_{12}H_{12}N_2O$	71.97	6.04	13.99	71.99	5.87	13.80
4	$-CON(C_2H_5)_2$	B	Prisms	aA	80.5-81.5	64	$C_{16}H_{20}N_2O$	74.96	7.87	10.93	74.80	7.50	11.02
5	$-CONCH_2CH_2N(C_2H_5)_2$	C	Platelets	Pr-E	175-177	73.5	$C_{18}H_{25}N_3O.HCl$	10.56 (e)		12.51	10.38 (e)		12.76
6	$-CSNHCH_2CH_2N(C_2H_5)_2$	C	Microcryst	A-E	248.5-249.5	82	$C_{18}H_{25}N_3S.HCl$	10.05 (e)		9.08 (f)	9.84 (e)		9.35 (f)
7	$-CSNHC(CH_3)CH_2OH$	B	Microcryst	B-H	136.5-137	78.5	$C_{15}H_{18}N_2O_2$	69.76	7.02	10.85	69.96	6.80	11.07

(a) B, base; C, hydrochloride. (b) Legend: A, ethanol; a, aqueous; B, benzene; E, ether; H, hexane; Hp, heptane; iPr, 2-propanol; Pr, propanol. (c) n_D^{25}=1.6198. (d) b.p. 116-117° (0.03 mm.). (e) Chlorine. (f) Sulfur.

TABLE II

1,2-Diaryl 5,6-Dihydro 4*H*-Pyrrolo[3,2,1-*i*,*j*]quinolines

Compound	R_1	R_2	Appearance	Solvent (a)	M.P., °C.	Yield, %	Formula	Analyses Calcd., % C	H	N	Found, % C	H	N
8	C_6H_5	C_6H_5	Creamy needles	iPr	176.5-177.5	80.5	$C_{23}H_{19}N$	89.28	6.19	4.53	88.90	6.17	4.49
9	C_6H_5	$4\text{-}C_6H_4OH$	Creamy microcryst	A	210.5-211.5	91	$C_{23}H_{19}NO$	84.88	5.88	4.30	84.94	5.99	4.29
10	C_6H_5	$4\text{-}C_6H_4OCH_3$	Glistening needles	Hp	178-179	90	$C_{24}H_{21}NO$	84.93	6.24	4.13	84.73	5.88	4.10
11	$4\text{-}C_6H_4OCH_3$	$4\text{-}C_6H_4OCH_3$	Pale tan microcryst	A	167.5-168.5	78.5	$C_{25}H_{23}NO_2$	81.27	6.28	8.66 (b)	81.51	6.56	9.00 (b)
12	$4\text{-}C_6H_4OCH_3$ (c)	$4\text{-}C_6H_4OCH_3$ (c)	Needles	A	173.5-174.5	65.5	$C_{25}H_{22}ClNO_2$	74.38	5.49	8.78 (d)	74.08	5.16	8.78 (d)

(a) Legend, as in Table I. (b) Oxygen. (c) 8-Chloro compound. (d) Chlorine.

dimethoxydeoxy benzoins were prepared by the elegant procedure of Nakazawa, *et al.* (33). In this, the phenylacetic acid type and a substituted benzene were mixed in polyphosphoric acid, heated on the steam bath, and the product separated after quenching the reaction mixture.

4-Chlorobenzohydryl isothiocyanate was prepared in 88% yield from the corresponding chloride and potassium thiocyanate (34); b.p. 147-150° (0.6 mm), n_D^{25} 1.6308.

α-Ketoglutaric acid was made according to Organic Synthesis (35).

γ-Aminobutyraldehyde diethylacetal was prepared from acrolein (36).

5-Phthalimido-2-pentanone was obtained in 81% yield by reaction of 5-chloro-2-pentanone with potassium phthalimide in DMF (37). It separated from hexane as creamy prisms, m.p. 74-75°. 6-Phthalimido-2-hexanone was synthesized by use of the acetoacetic ester procedure of Baker, *et al.* (38).

5-(4-Methyl-1-piperazinyl)-2-pentanone was made by interaction of 5-chloro-2-pentanone with two equivalents of 1-methyl piperazine at 130-135°. The compound was isolated by way of the hydrochloride, and an over-all yield of 77% of the base resulted. The yellowish oil boiled at 82-85° (1.1-1.3 mm) n_D^{25} 1.4676.

Anal. Calcd. for $C_{10}H_{20}N_2O$: N, 15.28. Found: N, 14.92.

2-Carboxy-5,6-dihydro 4*H*-pyrrolo[3,2,1-*i,j*]quinoline was prepared by the method of Barger and Dyer (9). The use of acids (or Lewis acids) other than hydrochloric acid was not satisfactory in this case, therefore this form of the Fischer synthesis was retained throughout this work. Only in few cases was it unsatisfactory.

B. 2-Carboxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline Derivatives.

Table I lists various simple derivatives prepared from 2-carboxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline. Of those, all but compound **7** were obtained from the acid chloride, made in benzene. That hydroxypropylamide was produced by interaction of the methyl ester **1** with 2-amino-1-propanol after a procedure used for other *N*-hydroxyalkyl amides (39). In several instances (as, **5**), it was expedient to pre-purify the compounds by chromatography on alumina (benzene-hexane mixtures were used as solvent) before crystallization.

2-Carboxy-8-chloro-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

Conversion of 1-amino-8-chloro-1,2,3,4-tetrahydroquinoline hydrochloride to the desired pyrroloquinoline was accomplished by a variant on that used (9) for the parent compound. To a suspension of 21.9 g. (0.1 mole) of the stated hydrochloride in aqueous sodium acetate solution (13.6 g., 0.1 mole, of the trihydrate of 20 ml. water) there was added 20 ml. of glacial acetic acid, followed by 10.5 g. (0.12 mole) of pyruvic acid in 15 ml. 50% acetic acid. The temperature rose rapidly from 25° to 37°, and very gentle warming sufficed to keep the reaction mixture at 40° for one hour. After chilling, the yellow product was collected and dried (24.5 g., 97% yield, m.p. 119-120° dec.), then crystallized from cyclohexane. The pure 1-[(carboxymethyl)-methylene]amino-6-chloro-1,2,3,4-tetrahydroquinoline was obtained as yellow needles, m.p. 121.5-122° dec.

Anal. Calcd. for $C_{12}H_{13}ClNO_2O_2$: C, 57.03; H, 5.18; Cl, 14.03; O, 12.67. Found: C, 57.02; H, 5.37; Cl, 13.77; O, 12.70.

The above-described hydrazone type (13.0 g., 0.05 mole) was cyclized to the desired pyrroloquinoline by heating a suspension of it in 20% hydrochloric acid (170 ml.) at 70° for 4 hours. At the end of heating, the crude product was collected after cooling, and dried, m.p. 227-230° dec. It was crystallized twice from benzene to give 9.7 g. (82% yield) of creamy microneedles, m.p. 233.5-235° dec.

Anal. Calcd. for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; Cl, 15.05. Found: C, 61.15; H, 4.14; Cl, 15.10.

1-Dimethylaminomethyl-2-methoxycarbonyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

Thirty millimoles (6.45 g.) of **1** (Table I) was added to a stirred mixture comprised of 60 ml. of glacial acetic acid, 16 ml. of 30% (w/w) aqueous dimethylamine solution, and 8 ml. of 37% formalin. It was heated on the steam bath for 5 hours, then quenched in 300 ml. ice water, basified strongly, and the oil extracted with ether. The extracts were washed, dried, and freed of solvent to produce 6.3 g. (77% yield) of pale yellow, oily Mannich base. The methobromide was formed in methanol, and precipitated with ether. It was crystallized from 2-propanol and ether to give an 86% yield of methobromide as white microcrystals; m.p. 182-183° dec.

Anal. Calcd. for $C_{17}H_{23}BrN_2O_2$: Br, 21.76; N(40), 3.81; O, 8.71. Found: Br, 21.63; N(40, 41), 3.89; O, 8.60.

2-Carboxy-1-(4-methoxyphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]-quinoline.

This compound was formed directly when 1-amino-1,2,3,4-tetrahydroquinoline and 4-methoxyphenylpyruvic acid interacted in acetic acid. The yield was 76.5%. It separated from ethanol as pale yellow blades; m.p. 208.5-209.5°, with intumescence.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.57; O, 15.62. Found: C, 74.56; H, 5.77; O, 15.50.

2-Carbamyl-1-(4-methoxyphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

This compound was prepared in 98% yield from the foregoing acid *via* the acid chloride with use of aqueous ammonia. The amide crystallized from benzene as feathery needles which melted at 219-220°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.47; H, 5.92; N, 9.15. Found: C, 74.17; H, 5.98; N, 9.08.

C. 2-Methyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines.

Application of the Fischer indole synthesis to 1-amino-1,2,3,4-tetrahydroquinoline (or, its 8-chloro analogue) and diverse ketonic types required such varied procedures that tabulation would not be helpful.

1-Carbethoxy-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

A mixture of 18.8 g. (0.126 mole) 1-amino-1,2,3,4-tetrahydroquinoline base with 16.5 g. (0.126 mole) ethyl acetoacetate, 25 ml. concentrated hydrochloric acid, and 125 ml. ethanol was stirred and refluxed 3 hours. The solvents were removed, and the residue mixed with 100 ml. water, filtered, leached well with water, and dried. The dark solid was extracted (Soxhlett) with pentane, and the extracts evaporated to give 5.35 g. (17.4% yield) of orange crystals, m.p. 115-116°. The pure compound was obtained as microcrystals by chromatography on alumina (hexane), followed by low-temperature crystallization from pentane; m.p. 116.5-117.5°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.75. Found: C, 74.47; H, 6.89; N, 5.88.

2-Methyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolin-1-yl acetic Acid.

A solution of 18.8 g. (0.126 mole) 1-amino-1,2,3,4-tetrahydroquinoline base in 250 ml. of hot ethanol was treated with 15.5 g.

(0.13 mole) of levulinic acid in 50 ml. of ethanol, then 30 ml. of concentrated hydrochloric acid added to the stirred mixture and the entire refluxed 3 hours. The brownish solid was collected, combined with the residue left from stripping solvents from the liquors, and triturated with hexane-ethanol (4:1). There resulted 18.0 g. (64.5%) of a creamy solid which melted at 78-80°. This acid was too soluble in water for effective crystallization, but separated from methanol as prisms, m.p. 79-80°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.36; H, 6.86; N, 6.21.

8-Chloro-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinolin-1-yl acetic acid.

A solution of 5.47 g. (0.025 mole) 1-amino-6-chloro-1,2,3,4-tetrahydroquinoline hydrochloride in 110 ml. ethanol containing 5 ml. concentrated hydrochloric acid was refluxed (stirring) for 2 hours with 3.20 g. (0.028 mole) of levulinic acid. The solvents were removed, and the residue dried by azeotropic distillation (benzene-ethanol). It was then leached with hexane-ethanol (10:1) to give a creamy solid, m.p. *ca.* 100°. A similar product was obtained from the liquors to give a combined yield of 5.55 g. (84%). It separated from methanol as fine needles, m.p. 107-108°.

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: Cl, 13.44; N, 5.32. Found: Cl, 13.21; N, 4.98.

1-(2-Aminoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]-quinoline.

Three g. (0.02 mole) of 1-amino-1,2,3,4-tetrahydroquinoline base was dissolved in (3 ml. of concentrated hydrochloric acid in 25 ml. ethanol) and to it was added 4.66 g. (0.021 mole) 5-phthalimido-2-pentanone in 15 ml. hot ethanol. The stirred mixture was refluxed for 2 hours, then chilled to obtain crude 5,6-dihydro-2-methyl-1-[2-(*N*-phthalimido)ethyl]-4*H*-pyrrolo[3,2,1-*i,j*]quinoline, m.p. 151-152°. Evaporation of the liquors gave intractable gum. Crystallization of the crude compound from ethanol afforded 4.20 g. (62% yield) of bright yellow, fine, felted needles; m.p. 153.5-154.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.14. Found: C, 76.36; H, 5.85; N, 7.97.

The foregoing phthalimide intermediate (9.47 g., 0.0265 mole) was refluxed for 24 hours in ethanol (420 ml.) containing 85% hydrazine hydrate (1.85 g., 0.031 mole), and then the solvents were removed *in vacuo*. The yellowish residue was heated on the steam bath for 1½ hours with 75 ml. 4 *N* hydrochloric acid, and the phthalhydrazide collected after cooling. The solid was leached well with hot water, and all filtrates united and concentrated to yield the hydrochloride of the tryptamine analogue; m.p. 259-260.5° dec. The crude product was crystallized from 2-propanol and ether to give 5.85 g. (87.5%) of creamy prisms which melted at 263.5-266° dec.

Anal. Calcd. for $C_{14}H_{18}N_2 \cdot HCl$: N, 11.17; Cl, 14.14. Found: N, 11.12; Cl, 14.25.

5,6-Dihydro-1-[2-(2-isoindolinyl)ethyl]-2-methyl-4*H*-pyrrolo-[3,2,1-*i,j*]quinoline.

A Soxhlett thimble was charged with 6.94 g. (0.02 mole) of 5,6-dihydro-2-methyl-1-[2-(*N*-phthalimido)ethyl]-4*H*-pyrrolo-[3,2,1-*i,j*]quinoline, and in the flask below there was placed 1.7 g. (0.45 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. The ether solution was refluxed 20 hours, then excess of reducing agent destroyed with ethyl acetate, and 35% sodium hydroxide solution added to dissolve salts. The layers were separated, and the aqueous phase extracted exhaustively with ether, then the combined extracts washed with brine, dried, and stripped of solvent. A quantitative yield of oily base resulted, and it could be induced to crystallize. The yield of once-crystallized (hexane) pinkish base was 89%; it melted 89-91°. It was readily converted into the hydrochloride, which crystallized well from 2-propanol and ether as plates, m.p. 257-258° dec.

Anal. Calcd. for $C_{22}H_{24}N_2 \cdot HCl$: N, 7.94; Cl, 10.04. Found: N, 7.89; Cl (42), 9.98.

5,6-Dihydro-2-methyl-1-[2-(4-methylphenylsulfonamido)ethyl]-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

This compound was produced in quantitative yield by the action of *p*-toluenesulfonyl chloride on 1-(2-aminoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinoline base in ethylene dichloride solution in the presence of sodium hydroxide. It separated from cyclohexane-heptane as microcrystals which melted at 152.5-153.5°.

Anal. Calcd. for $C_{21}H_{23}N_2O_2S$: N, 7.62; S, 8.73. Found: N, 7.56; S, 8.43.

1-(2-Ureidoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]-quinoline.

A solution of 5.01 g. (0.02 mole) of 1-(2-aminoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinoline in 100 ml. of water was treated with 1.62 g. (0.02 mole) of potassium cyanate, 3 drops of concentrated hydrochloric acid added, and set aside at ambient temperature overnight. The mixture was basified with ammonium hydroxide, chilled, and the urea derivative collected. It was obtained in 86% yield (4.44 g.); it separated from toluene in the form of blades which melted at 190-191°.

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.02; H, 7.44; N, 16.63. Found: C, 70.21; H, 7.69; N, 16.03.

1-[2-(4-Chlorobenzohydrylthiocarbamyl)ethyl]-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

This compound resulted when the 1-(2-aminoethyl) base and 4-chlorobenzohydryl isothiocyanate were refluxed in benzene. An 81.5% yield of white microcrystalline solid was obtained after two crystallizations from acetone-pentane mixture. It melted at 167.5-168.5°.

Anal. Calcd. for $C_{28}H_{28}ClN_3S$: Cl, 7.48; S, 6.76. Found: Cl, 7.22; S, 6.72.

1-(2-Aminoethyl)-8-chloro-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*i,j*]quinoline.

This compound was synthesized by the same procedure as the parent (non halogenated) tryptamine analogue. In this case, the intermediate 1-[2-(*N*-phthalimido)ethyl] compound separated from the reaction mixture in nearly quantitative yield after only 20 minutes of refluxing. It melted at 167.5-168.5° as obtained, and it separated from ethanol (charcoal) as bright yellow prisms, m.p. 169-169.5°.

Anal. Calcd. for $C_{22}H_{19}ClN_2O_2$: Cl, 9.31; N, 7.36. Found: Cl, 9.44; N, 7.31.

Cleavage of the foregoing intermediate with hydrazine in ethanol gave an 85.5% crude yield of 1-(2-aminoethyl)-8-chloro-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i,j*]quinoline hydrochloride. Attempts to purify the salt (m.p. *ca.* 220°) were hampered by problems of solubility, hence it was converted into the base, and the monohydrogen citrate formed in ether. That salt separated from methanol-ether as a cryptocrystalline, pale tan solid of m.p. 196-197° (intumescence).

Anal. Calcd. for $2\,C_{14}H_{17}ClN_2 \cdot C_6H_8O_7$: Cl, 10.28; N, 8.12. Found: Cl, 10.15; N, 7.96.

8-Chloro-5,6-dihydro-1-[2-(2-isoindolinyl)ethyl]-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline.

This compound resulted in 87% yield when the above phthalimido compound was reduced with lithium aluminum hydride in the manner described for the parent type, however employing a 48 hour reaction time. The base separated from benzene as a cryptocrystalline solid, m.p. 131-133°.

Anal. Calcd. for $C_{22}H_{23}ClN_2$: N (40), 3.99. Found: N (40), 4.01.

The hydrochloride was analytically pure when made in acetone-ether, and separated as glistening plates; m.p. 269-270°.

Anal. Calcd. for $C_{22}H_{23}ClN_2 \cdot HCl$: Cl, 18.31; N, 7.23. Found: Cl, 18.15; N, 7.03.

8-Chloro-1-(2-diethylaminoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline.

A solution of 4.38 g. (0.02 mole) 1-amino-6-chloro-1,2,3,4-tetrahydroquinoline hydrochloride in 20 ml. hot ethanol was treated with 3.30 g. (0.021 mole) 5-diethylamino-2-pentanone and 3 ml. concentrated hydrochloric acid, and then the golden solution was refluxed 2 hours. The resulting garnet solution deposited a creamy solid upon chilling. Further amounts of product were obtained by concentrating the liquors and leaching the residues with pentane-ethanol. The combined fractions of hydrochloride was crystallized from 2-propanol and ether to give 5.3 g. (78% yield) of creamy prisms; m.p. 169-170°.

Anal. Calcd. for $C_{18}H_{25}ClN_2 \cdot HCl$: N, 8.26; Cl (42), 10.39. Found: N, 8.14; Cl (42), 10.41.

5,6-Dihydro-2-methyl-1-[2-(4-methyl-1-piperazinyl)ethyl]-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline.

This compound was prepared by refluxing 1-amino-1,2,3,4-tetrahydroquinoline base with 5-(4-methyl-1-piperazinyl)-2-pentanone in aqueous alcoholic hydrochloric acid during 4 hours. This was done in a manner closely similar to the above reaction of 5-diethylamino-2-pentanone. The yield of dihydrochloride was 51%. It was obtained as a microcrystalline solid from methanol-ether, and decomposed with intumescence at 297°.

Anal. Calcd. for $C_{19}H_{27}N_3 \cdot 2HCl$: Cl (42), 19.15; N, 11.35. Found: Cl (42), 19.02; N, 11.48.

5,6-Dihydro-1-(2-mercaptoethyl)-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]-quinoline.

A solution of 7.6 g. (0.1 mole) thiourea in 100 ml. absolute ethanol was refluxed with 12.1 g. (0.11 mole) of 5-chloro-2-pentanone for 4 hours. To that hot mixture there was added 14.82 g. (0.1 mole) 1-amino-1,2,3,4-tetrahydroquinoline base in 100 ml. ethanol, followed by 20 ml. concentrated hydrochloric acid, and the entire was refluxed for 2 hours. The reddish-brown solution was concentrated to *ca.* 100 ml. and dried by azeotropic distillation with benzene and ethanol. Cooling gave 13.2 g. yellowish solid (m.p. 217-219°), and the liquors afforded an additional 9.9 g. (m.p. 215-218°) when concentrated and the residues leached with 2-propanol. The combined isothiuronium salt (75% crude yield) failed to undergo appreciable improvement when crystallized (as, from 2-propanol ether or from ethanol-ether); hence it was hydrolyzed by refluxing it in excess of 10% sodium hydroxide solution for 2 hours. A creamy, granular solid precipitated by adding a slight excess of hydrochloric acid. The yield of crude product (m.p. 73-75°) was 91%. Careful crystallization from 60% ethanol gave fine prismatic needles which melted at 74.5-75.5°.

Anal. Calcd. for $C_{14}H_{17}NS$: N, 6.06; S, 13.86. Found: N, 5.95; S, 13.55.

8-Chloro-5,6-dihydro-1-(2-mercaptoethyl)-2-methyl-4*H*-pyrrolo-[3,2,1-*i*,*j*]quinoline and bis-[2-(8-chloro-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolin-1-yl)ethyl]sulfide.

Preparation of 8-chloro-1-(2-chloroethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline was effected essentially after the procedure used for the 1-(2-diethylaminoethyl) compound here with use of 5-chloro-2-pentanone. The base was isolated in 66% yield after crystallization from methanol as prisms which melted at 89-91°.

Anal. Calcd. for $C_{14}H_{15}Cl_2N$: Cl, 26.44; N, 5.22. Found: Cl, 26.05; N, 5.17.

To a solution of 11.1 g. (0.041 mole) of the above chloroethyl compound in 100 ml. ethanol there was added 3.5 g. (0.045 mole) thiourea dissolved in 50 ml. ethanol, and the light amber mixture refluxed 3 hours. The solvent was then removed *in vacuo* and the white residue leached with cold ethanol to give 12.09 g. (85.5% yield) of crude isothiuronium salt: m.p. *ca.* 215° dec. It separated from ethanol-ether as a microcrystalline solid of m.p. 226.5-228.5° dec.

Anal. Calcd. for $C_{15}H_{19}Cl_2N_3S$: Cl (42), 10.30; N, 12.21. Found: Cl (42), 10.22; N, 11.98.

A solution of 2.85 g. (0.07 mole) of 97% sodium hydroxide in 30 ml. of water and 11.90 g. (0.034 mole) of the above isothiuronium salt was refluxed under nitrogen for 3 hours. The aqueous portion was decanted, extracted well with warm benzene, and the residual gum dissolved in the extracts by heating. The benzene solution (*ca.* 175 ml.) was shaken with anhydrous sodium sulfate, decanted, and heated to 60° prior to adding 175 ml. boiling pentane. After slow cooling, the mixture was kept at 0° for several days prior to collecting a white solid (A) and retaining the filtrates (B). Fraction A (2.35 g., m.p. 154.5-157°) was crystallized from *ca.* 800 ml. ethanol to give a microcrystalline compound, m.p. 164-165°. This was bis-[2-(8-chloro-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolin-1-yl)ethyl]sulfide.

Anal. Calcd. for $C_{28}H_{30}Cl_2N_2S$: Cl, 14.26; S, 6.45. Found: Cl, 14.22; S, 6.54.

The filtrates (B) were evaporated, and the oily residue taken up in 1:10 mixture of ether and pentane. Evaporative removal of the solvents left 4.2 g. fluffy white solid, m.p. 70-71°. Low temperature crystallization from pentane raised the melting point to 70.5-71.5°; it was the mercaptoethyl compound.

Anal. Calcd. for $C_{14}H_{16}ClNS$: C, 63.26; H, 6.07; Cl, 13.34. Found: C, 63.10; H, 6.23; Cl, 13.44.

D. 1,2-Diaryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolines.

1,2-Diaryl types derived from the 1,7-trimethylene indole structure were prepared from a 1-amino-1,2,3,4-tetrahydroquinoline and a deoxybenzoin by refluxing in alcoholic hydrochloric acid (usually 10-15%). Products usually separated after one or two hours of reaction, and the solids were readily purifiable by crystallization. Table II summarizes data on simple 1,2-diaryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolines thus synthesized.

4-(1-Phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolin-2-yl)phenyl Hydrogen Succinate.

This compound was prepared as an approach to enhancing the solubility of this group. 2-(4-Hydroxyphenyl)-1-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline (compound **9** in Table II; 10.3 g., 0.032 mole) and succinic anhydride (6.4 g., 0.064 mole) were ground together and fused at 130-135° for 4 hours. The

resulting vitreous solid was triturated with water, and a tan solid collected. After drying superficially, it was taken up in 150 ml. of boiling benzene, shaken with anhydrous sodium sulfate, decanted and filtered, then 50 ml. of pentane added in the hot, and cooled very slowly. The product (10.3 g., 76% yield) separated as greyish prismatic crystals, m.p. *ca.* 145°, with intumescence. Several additional crystallizations from benzene-pentane were required to give pure compound in the form of prisms which melted without intumescence at 159-161° (immersed at 155°).

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.21; H, 5.45; O, 15.04. Found: C, 76.36; H, 5.45; O, 15.10.

E. Other 5,6-Dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolines.

5,6-Dihydro-1-(4-methoxyphenyl)-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

2-Carboxy-5,6-dihydro-1-(4-methoxyphenyl)-4*H*-pyrrolo[3,2,1-*i,j*]quinoline (9.95 g., 0.032 mole) was placed in a small flask equipped with a mercury manometer and provided with a stopcock by-pass which permitted venting. It was immersed in an oil bath at 200° and then stirred at 215-220° until evolution of carbon dioxide ceased (*ca.* 5 minutes). The off-white product obtained on cooling (8.5 g., quantitative yield) melted at 127-128°. It separated from ethanol as iridescent plates, m.p. 129.5-130.5°.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.92; H, 6.44; N, 5.31.

2-Carboxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinolin-1-yl Acetic Acid.

1-Amino-1,2,3,4-tetrahydroquinoline base (9.85 g., 0.066 mole) in diluted acetic acid (40 ml. of glacial acetic acid and 10 ml. of water) was stirred and 10.6 g. (0.068 mole) α-ketoglutaric acid was added. After 1 hour heating on the steam bath, dilution of the mixture with 30 ml. of water led to separation of a gum. The liquors were decanted, and the gum taken up in 60 ml. of 10% sodium hydroxide solution. Following removal of some colored material by ether extraction, the caustic solution was treated with charcoal, heated to boiling, filtered, then cooled and the diacid precipitated. The crude product (10.5 g., 61.5% yield) was a rust-colored solid which melted with intumescence at 204-206°. It was extracted well with hot ethyl acetate, insolubles removed, and the filtrates concentrated. To the hot liquors (*ca.* 50 ml.) there was added half their volume of boiling pentane and the mixture cooled slowly. Light tan microcrystals resulted, m.p. 233-234°, with intumescence.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.85; H, 5.05; N, 5.40. Found: C, 64.70; H, 4.87; N, 5.26.

1-(2-Aminoethyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*i,j*]quinoline.

Three and six-tenths g. (0.024 mole) of 1-amino-1,2,3,4-tetrahydroquinoline base was suspended in 100 ml. of dry toluene, then 4.05 g. (0.025 mole) of γ-aminobutyraldehyde diethyl acetal and 3.27 g. (0.024 mole) of finely pulverised, anhydrous zinc chloride was added. The well-stirred mixture was refluxed 3 hours, decanted from gum, and the toluene extracted well with concentrated hydrochloric acid. The extracts were concentrated *in vacuo*, leaving an amber solid which decomposed *ca.* 160°, with intumescence. It afforded the hydrochloride as a creamy, cryptocrystalline solid (2.1 g., 36.5% yield) of m.p. 178-180°, with intumescence. The picrate of the base has been reported recently (24).

Anal. Calcd. for $C_{13}H_{16}N_2 \cdot HCl$: N, 11.83; Cl (42), 14.97. Found: N, 11.71; Cl (42), 14.83.

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