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CONDENSED PYRROLE COMPOUNDS—I

3H-PYRROLO(2,3,-c)QUINOLINES

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Abstract—The synthesis of a number of 3H-pyrrolo(2,3-c)quinolines by the Fischer method is reported.

ECHITAMYRINE obtained by the selenium dehydrogenation of echitinolide was shown to be 3-methyl-3H-pyrrolo(2,3-c)quinoline (Ia).[1] This compound, also obtained by oxidation of calycanthine with silver acetate[2] has been synthesized by Eiter and Nagy[3] using a Madelung type ring closure on N-formyl-3-amino-lepidine, followed by N-methylation. It was considered of interest to study the application of the Fischer indole method for the synthesis of this type of compound, since the only 3-quinolylhydrazone cyclized is that of cyclohexanone.[4] In general, it appears from reports in the literature that cyclization on a pyridine ring proceeds with great difficulty, if at all. Negative results have been reported in the cyclization of acetone 2-quinolylhydrazone[5] and with a number of 2-pyridylhydrazones.[6] Clemo and Holt[7] succeeded in cyclizing cyclohexanone 2-methyl-3-pyridylhydrazone, but failed with the pyruvic acid derivative. Okuda and Robison[8] have reported the cyclization of cyclohexanone 2-pyridylhydrazone in 53 per cent using polyphosphoric acid. They could similarly cyclize desoxybenzoin 2-pyridylhydrazone, but failed with the 2-pyridylhydrazones of acetaldehyde, acetone and pyruvic acid. Ficken and Kendall[9] have cyclized isopropyl methyl ketone 2-pyridylhydrazone to give 2,3,3-trimethyl-3H-1,7-diazaindene using catalytic amounts of zinc chloride. 4-Pyridyl and 4-quinolylhydrazones of cyclohexanone have been cyclized to 6,7,8,9-tetrahydro-γ-carboline and its 3,4-benzo derivative respectively.[10]

In the present study ethyl pyruvate 3-quinolylhydrazone has been cyclized using a large excess of anhydrous zinc chloride at 260° to 3H-pyrrolo(2,3-c)quinoline, agreeing well in melting point and U.V. spectrum with the data reported by Eiter and Nagy.[3] 3-Quinolylhydrazones of acetone, methyl ethyl ketone, diethyl ketone, acetophenone, propiophenone, desoxybenzoin and α-tetralone have been cyclized to the corresponding pyrroloquinolines by heating with anhydrous zinc chloride in *p*-cymene solution. In the last case, the product (II) was subsequently dehydrogenated with Pd/C to give the dibenzo-β-carboline (III).

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[1] T. R. Govindarhari and S. Rajappa, *Chem. & Ind.* 1154 (1959).
[2] E. Späth, W. Stroh, E. Lederer and K. Eiter, *Monatsh.* **79**, 11 (1948).
[3] K. Eiter and M. Nagy, *Monatsh.* **80**, 607 (1949).
[4] G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.* 671 (1951).
[5] W. H. Perkin and R. Robinson, *J. Chem. Soc.* 1973 (1913).
[6] R. G. Fargher and R. Furness, *J. Chem. Soc.* 688 (1915).
[7] G. R. Clemo and R. J. W. Holt, *J. Chem. Soc.* 1313 (1953).
[8] S. Okuda and M. M. Robison, *J. Amer. Chem. Soc.* **81**, 740 (1959).
[9] G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* 3202 (1959).
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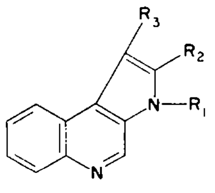

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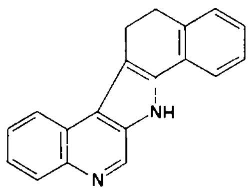
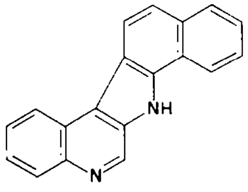


II



III

Ia $R_1 = CH_3$; $R_2 = R_3 = H$

Ib $R_1 = R_2 = R_3 = H$

Ic $R_1 = H$; $R_2 = CH_3$; $R_3 = H$

Id $R_1 = H$; $R_2 = R_3 = CH_3$

Ie $R_1 = H$; $R_2 = C_2H_5$; $R_3 = CH_3$

If $R_1 = H$; $R_2 = C_6H_5$; $R_3 = H$

Ig $R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$

Ih $R_1 = H$; $R_2 = R_3 = C_6H_5$

The U.V. absorption characteristics of the pyrroloquinolines have been recorded in Table 1. The simple pyrroloquinolines exhibit a characteristic violet fluorescence in acid solution. In the U.V. spectra, there is as expected a bathochromic shift of about 20–35 mμ of the longest wavelength band.[11] If there is a phenyl ring attached to the 2-position of the pyrroloquinoline, the compound exhibits a blue fluorescence even in neutral solution.

EXPERIMENTAL

Pyruvic acid 3-quinolylhydrazone. 3-Quinolylhydrazine[4] (4 g) was refluxed in alcohol for 15 min with pyruvic acid (2 ml) and a few drops of acetic acid. Crystallization from methanol gave the *hydrazone* (5 g), m.p. 179–180°. (Found: C, 62·7; H, 4·8. $C_{12}H_{11}O_2N_3$ requires: C, 62·9; H, 4·8%).

Ethyl pyruvate 3-quinolylhydrazone. The above hydrazone (2·5 g) was refluxed with alcohol (30 ml) and conc sulphuric acid (2 ml) for 4 hr. The solution was then neutralized with ammonia and the precipitate filtered, washed with water and crystallized from dil alcohol to yield the *ester* (2 g), m.p. 175–176°. (Found: C, 65·6; H, 5·4. $C_{14}H_{15}O_2N_3$ requires: C, 65·4; H, 5·8%).

3H-*pyrrolo*(2,3-c)*quinoline.* The above hydrazone (1 g) was mixed with freshly fused zinc chloride (5 g) and heated on a metal-bath at 260° for 45 min, the mixture being stirred frequently. After cooling, the zinc chloride complex was decomposed with 10% hydrochloric acid, and the solution poured into sodium hydroxide solution (25%; 50 ml). The base was extracted in ether, dried and the solvent evaporated. Material from three such batches was combined and sublimed at 110–170°/10^{-4}mm. Crystallization of the sublimate from methanol–benzene yielded 3H-*pyrrolo*(2,3-c)*quinoline* (100 mg), m.p. 228–230°. (Found: C, 78·8; H, 4·8. $C_{11}H_8N_2$ requires: C, 78·6; H, 4·8%). (Eiter and Nagy[3] report m.p. 233°).

Acetone 3-quinolylhydrazone. 3-Quinolylhydrazine (1 g), acetone (0·5 ml) and acetic acid (a few

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[11] *Cf.* C. T. K. Adler and A. Albert, *J. Chem. Soc.* 1794 (1960).

TABLE 1

Compound	Neutral solution		Acid solution	
	λ max	log ε	λ max	log ε
Ib	240	4·47	230	4·37
	305	4·03	342	4·03
	320*	3·91		
Ic	230	4·54	262*	3·66
	245	4·56	275	3·46
	312	4·21	345	4·25
	325	4·18		
Id	230	4·38		
	240	4·39		
	325	4·09		
Ie	230	4·49		
	240*	4·48		
	325	4·18		
If	235	4·52		
	260	4·36		
	335	4·52		
Ig	235	4·39		
	255	4·35		
	335	4·29		
Ih	240*	4·43		
	260	4·43		
	335	4·44		
II	240	4·45	235	4·46
	265	4·25	260	4·29
	350	4·46	350	4·03
	368	4·38	395	4·42
III	245	4·31		
	275	4·66		
	300	4·31		
	355	4·29		
	380*	3·75		
	405*	3·40		

* Inflexion.

drops) were refluxed in alcohol for 15 min, to yield the *hydrazone* (1 g), m.p. 194–195°, (from methanol). (Found: C, 72·7; H, 6·9. $C_{12}H_{13}N_3$ requires: C, 72·4; H, 6·5%).

2-*Methyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I b). The following modified method was adopted for the cyclization of this and subsequent hydrazones. The hydrazone (1·1 g) was refluxed with fused zinc chloride (4 g) in *p*-cymene (15 ml) for 3 hr. After decanting the *p*-cymene, the solid was washed with a little ether, then digested with 10% hydrochloric acid and the acid solution poured into a well-cooled sodium hydroxide solution (25%; 75 ml). The base was extracted in chloroform, dried and the solvent evaporated. The residue was chromatographed in benzene solution over alumina. Elution with benzene removed the impurities. Subsequent elution with 0.5% alcoholic benzene and crystallization from methanol-benzene yielded the *pyrroloquinoline* (I b; 100 mg), m.p. 218–219°. (Found: C, 78·9; H, 5·6. $C_{12}H_{10}N_2$ requires: C, 79·1; H, 5·5%). The base yielded a *picrate*, m.p. 261–263° (decomp) (Found: C, 52·8; H, 3·2. $C_{18}H_{13}O_7N_5$ requires: C, 52·6; H, 3·2%).

1,2-*Dimethyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I c). Methyl ethyl ketone 3-quinolylhydrazone was prepared as usual. The hydrazone (0·45 g) was cyclized as before and the product sublimed at $200°/10^{-4}$mm. Crystallization of the sublimate from methanol-benzene yielded 1,2-*dimethyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I c; 25 mg), m.p. 230–232°. (Found: C, 79·9; H, 5·8. $C_{13}H_{12}N_2$ requires: C, 79·6; H, 6·1%).

2-*Ethyl*-1-*methyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I d). Diethylketone 3-quinolylhydrazone (1 g) prepared in the usual manner was subjected to Fischer indolization as above to yield the *pyrroloquinoline* (I d; 0·4 g). After crystallization it had m.p. 203–204°. (Found: C, 80·3; H, 6·3. $C_{14}H_{14}N_2$ requires: C, 80·0; H, 6·7%).

Acetophenone 3-quinolylhydrazone was prepared in the usual manner and crystallized from methanol. It had m.p. 177°. (Found: C, 77·8; H, 5·6. $C_{17}H_{15}N_3$ requires: C, 78·2 ; H, 5·7%).

2-*Phenyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I e). The hydrazone (0·9 g) was cyclized as before. The product (0·35 g) was crystallized from methanol, to give the *pyrroloquinoline* (I e), m.p. 244–245°. (Found: C, 83·7; H, 4·7. $C_{17}H_{12}N_2$ requires: C, 83·6; H, 4·9%). The base yielded a *picrate*, m.p. 230–231°. (Found: C, 58·2; H, 3·3. $C_{23}H_{15}O_7N_5$ requires: C, 58·3; H, 3·2%).

Propiophenone 3-quinolylhydrazone, m.p. 172–173°, was prepared in the usual manner and crystallized from ethyl alcohol. (Found: C, 78·2; H, 6·0. $C_{18}H_{17}N_3$ requires; C, 78·6; H, 6·2%)

1-*Methyl*-2-*phenyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I f). The hydrazone (0.9 g) was cyclized as before to give, after crystallization from benzene–petroleum ether, the *pyrroloquinoline* (I f; 0·2 g), m.p.216–217°. (Found: C, 84·1; H, 5·7. $C_{18}H_{14}N_2$ requires: C, 83·7; H, 5·4%).

Desoxybonzoin 3-quinolylhydrazone was prepared as usual by refluxing desoxybenzoin with 3-quinolylhydrazine in alcohol. Crystallization from methanol gave the *hydrazone*, m.p. 169–171°. (Found: C, 82.0; H, 6·0. $C_{23}H_{19}N_3$ requires: C, 81·9; H, 5·6%).

1,2-*Diphenyl*-3H-*pyrrolo*(2,3-c)*quinoline* (I g). Fischer indolization of the above hydrazone (1·5 g) by the usual procedure, extraction of the product in chloroform and crystallization from methanol yielded the *pyrroloquinoline* (I g; 1·1 g), m.p. 269–271°. (Found: C, 86·5; H, 5·2. $C_{23}H_{16}N_2$ requires: C, 86·3; H, 5·0%).

α-Tetralone 3-quinolylhydrazone was prepared as usual and crystallized from methanol. It had m.p. 178–180°. (Found: C, 79·5; H, 5·6. $C_{19}H_{17}N_3$ requires: C, 79·4; H, 5·9%).

12,13-*Dihydro*-7H-*dibenz*(c,i)-*β*-*carboline* (II). The above hydrazone (1 g) was cyclized as usual with zinc chloride in *p*-cymene. Crystallization from chloroform–methanol gave the *compound* (II; 0·25 g), m.p. 333–335° (decomp). (Found: C, 84·7; H, 5·0. $C_{19}H_{14}N_2$ requires: C, 84·4; H, 5·2%).

7H-*dibenz*(c,i)-*β*-*carboline* (III). The above dihydro compound (0·4 g) was intimately mixed with 30% palladized charcoal (0·4 g) and heated at 280–300°/5 mm. The sublimed yellow solid was crystallized from pyridine–toluene to give the *dibenz*-*β*-*carboline* (100 mg), m.p. 252–254° (decomp). (Found: C, 84·9; H, 4·9. $C_{19}H_{12}N_2$ requires: C, 85·1; H, 4·5%).

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