The Chemistry of 2*H*-1,3-Benzoxazine-2,4-(1*H*)dione (Isatoic Anhydride). 8. A One Step Synthesis of the Quinindoline Ring System and Related Compounds

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The reaction between *N*-substituted isatoic anhydrides and the carbanion generated from 3-methylthiooxindole to produce the quinindoline ring skeleton is discussed. Analogous reactions of azaisatoic anhydride **6** and tricyclic anhydride **8** produces the 4-aza analog **7** and pentacycle **9**. Some spectral data is also described.

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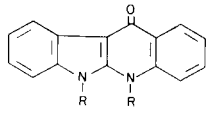
The quinindoline ring system (**1**) had been shown to exhibit antibiotic, cytostatic and central nervous system activities (1).



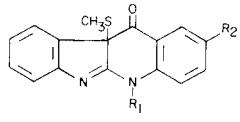
Two synthetic routes leading to this type of ring system have been reported. The first involves a reaction of an oxindole with *o*-nitrobenzoyl chloride in the presence of base followed by reduction then cyclization (2). The second route proceeds by a condensation of an oxindole with an anthranilic ester followed by a dehydrative cyclization (3).

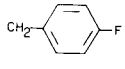
A variety of heterocyclic ring systems have been obtained by the reaction of an isatoic anhydride (**2**) with carbanions (4-6). It would therefore be logical to assume that the interaction between an isatoic anhydride and a carbanion derived from an oxindole would directly produce a quinindoline or an intermediate capable of being converted to a quinindoline. Reactions with oxindoles possessing a substituent in the 3-position would result in a quinindoline with that substituent residing in the 10b-position.

It was decided that a quinindoline with a sulfur containing functionality at the 10b-position would present interesting possibilities in the search for biological activity. The required oxindoles possessing this type of substituent (*e.g.*, 3-methylthiooxindole (**3**)) have been conveniently prepared from aniline derivatives and α-carboalkoxy sulfides (7). The second reactant necessary in the synthetic scheme, an isatoic anhydride (**2**), can readily be prepared with a wide variety of substituents on the nitrogen (8).

The anion of **3**, generated with sodium hydide in DMF at 0°, reacted smoothly with the *N*-substituted isatoic anhydride and directly afforded the 10b-methylthioquinindolin-11-one (**5**) in low yield with none of the intermediate **4** being isolated. A search of the reaction mixture revealed the presence of unreacted 3-methylthiooxindole and a large quantity of *N*-substituted anthranilic acid. The formation of the anthranilic acid can be explained by the

Table 1



R_1	R_2	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	S	Cl
CH_3	H	168-170	48	$C_{17}H_{14}N_2OS$	69.4	4.8	9.5	10.9	
					(69.4	4.9	9.4	10.5)	
CH_3	Cl	202-204	43	$C_{17}H_{13}ClN_2OS$	62.1	4.0	8.5	9.8	10.8
					(62.5	4.3	8.5	10.2	10.9)
CH_3	OCH_3	227-229	17	$C_{18}H_{16}N_2O_2S$	66.6	5.0	8.6		
					(66.3	5.3	8.7)		
$CH_2CH=CH_2$	H	160-162	73	$C_{19}H_{16}N_2OS$	71.2	5.0	8.7	10.0	
					(71.3	5.1	8.8	10.2)	
	H	194-196	53	$C_{23}H_{17}FN_2OS$	71.1	4.4	7.2	8.3	
					(71.3	4.2	7.3	8.4)	

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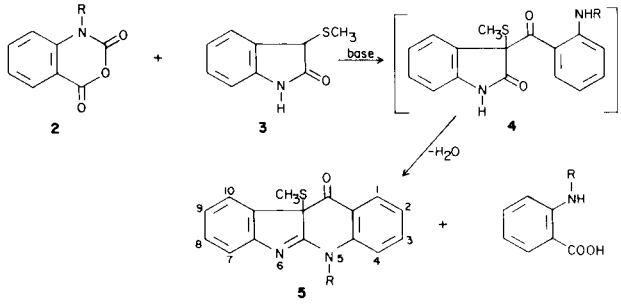
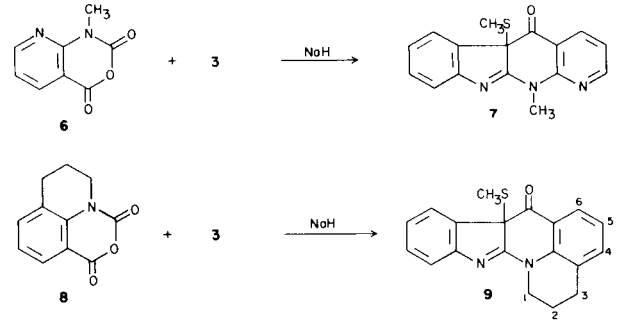
ring opening of the isatoic anhydride by water in the presence of base. Even in scrupulously dried DMF, the anthranilic acid is produced and unreacted **3** is isolated with no appreciable increase in the yield of **5**. This suggests that the water produced in the reaction, resulting from the dehydration of **4**, is responsible. To circumvent this situation, the reaction was performed using two equivalents of **2**, and this resulted in doubling the isolated yield of **5** with only the corresponding anthranilic acid as a by-product.



Analogous reactions using azaisatoic anhydride **6** (9) and tricyclic anhydride **8** (10) afforded the 4-aza analog **7** and pentacycle **9** in low yields.



Compounds **5**, **7** and **9** exhibit an infrared carbonyl absorption between 1690-1670 cm^{-1}, a C=N stretching frequency between 1560 and 1545 cm^{-1}, and a band at 750 cm^{-1} which may be attributed to C-S stretching. In the nmr, the angular methylthio group signal is observed generally between δ 2.3-2.1.

In compounds where the substituent at the 5-position is a methyl, the N-CH_3 signal appears at δ 4.3-4.1.

Attempts to desulfurize **5** using Raney Nickel resulted only in the reisolation of starting material.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60 and EM 360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. Dimethylformamide was freshly distilled over calcium hydride prior to every reaction.

General Procedure for the Preparation of 5-Substituted 5,10b-dihydro-10b-methylthio-11*H*-quinindolin-11-ones (**5**) (Table 1).

To a solution of 0.012 mole of **3** (7) in 40 ml. of dimethylformamide (cooled in an ice bath), under a blanket of nitrogen, was added 0.013 mole of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at 0-5° for 15 minutes; then a solution of 0.022 mole of the appropriate isatoic anhydride in 40 ml. of dimethylformamide was added dropwise. The resulting mixture was stirred at 0-5° for 15 minutes and then at room temperature for 18 hours. The solvent was removed under reduced pressure, water was added to the residue, and the mixture was extracted into methylene chloride. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product. Analytical samples were crystallized from ethyl acetate.

5a,11-Dihydro-4-methyl-5a-methylthio-5*H*-indolo[2,3-*b*][1,8]naphthyridin-5-one (**7**).

To a solution of 2.75 g. of **3** in 75 ml. of dimethylformamide (cooled in an ice bath), under a blanket of nitrogen, was added 0.75 g. of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at 0-5° for 15 minutes. Then a solution of 5.5 g. of **6** in 60 ml. of dimethylformamide was added dropwise and the mixture was stirred at 0-5° an additional 30 minutes and then at room temperature for 5 days. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride. The organic solution was washed with water, dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was chromatographed on a column of silica gel using chloroform to elute the product, 0.7 g. (6.5%) of **7**. An analytical sample was crystallized from methylene chloride/ether, m.p. 165-168°; ir (potassium bromide): 1690, 1560, 750 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (m, 3), 7.9-7.0 (m, 4), 4.4 (s, 3), 2.3 (s, 3); ms: (70 eV) m/e 295 (M+).

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.1; H, 4.4; N, 14.2; S, 10.9. Found: C, 65.6; H, 4.9; N, 14.3; S, 10.9.

Reanalysis of carbon and hydrogen did not improve the values.

2,3-Dihyro-7a-methylthio-1H-benz[*i,j*]indolo[3,2-*b*]quinolizin-7(7aH)one (**9**).

To a cooled solution of 4.4 g. of **3** in 100 ml. of dimethylformamide (under a blanket of nitrogen) was added 1.2 g. of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at 0-5° for 15 minutes. Then a solution of 10.0 g. of **8** (10) in 125 ml. of dimethylformamide was added dropwise and the mixture was stirred at 0-5° for 15 minutes and then at room temperature for 5 days. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. The resulting solution was washed with dilute sodium bicarbonate and was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from methylene chloride/ethyl acetate to give 1.4 g. (9%) of **9**; m.p. 231-232°; ir (potassium bromide): 1675, 1545, 750 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 8.65 (m, 1), 8.05 (m, 1), 7.7-7.0 (m, 5), 4.85 (t, 2), 2.9 (m, 2), 2.25 (s, 3), 2.15 (t, 2); ms: (70 eV) m/e 320 (M+).

Anal. Calcd. for $C_{19}H_{16}N_2OS$: C, 71.2; H, 5.0; N, 8.7; S, 10.0. Found: C, 71.3; H, 5.5; N, 8.6; S, 9.7.

Reanalysis of hydrogen did not improve the value.

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