Preparation and Stereochemistry of Methyl 3-(and 4)-*p*-Chlorothiophenoxy-1-methylpiperidine-4-(and 3)-carboxylates, and Cyclization to Benzothiopyranopyridinones

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Received June 29, 1987

The title piperidines were prepared by (a) methanolysis of the corresponding nitriles and (b) addition of *p*-chlorothiophenol to the appropriate tetrahydropyridines. Three esters were obtained with stereochemistry assigned by nmr analysis: **2** [3(a) SAr, 4(e) CO_2Me], **5** [4(e) SAr, 3(e) CO_2Me], **6** [4(a) SAr, 3(e) CO_2Me]. Compounds **2** and **6** cyclized in 70% sulfuric acid. The product structures were established by X-ray crystallography and, surprisingly, both had trans-fused rings. Compound **5**, however, did not cyclize but gave 4-(methylthio)chlorobenzene as the sole isolated product.

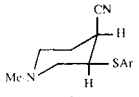
J. Heterocyclic Chem., **25**, 321 (1988).

We previously reported results on the addition of thiophenols to various di and tetrahydropyridinecarbonitriles, where the stereochemistry of the products was determined [1]. Attempts to cyclize these adducts to various tricyclic systems were unsuccessful and we therefore switched attention to the corresponding esters. The patent literature contains a report of pharmacologically active benzothiopyranopyridinones being prepared from ethyl 1-methyl-1,2,5,6-tetrahydropyridine-4-carboxylate [2]. Isomeric mixtures were reported and the stereochemistry of the isolated products was not known.

The required intermediates were available by (a) alcoholysis of the nitriles and (b) by thiophenol addition to the alkyl tetrahydropyridinecarboxylates. Due to nitrogen inversion and the flexibility of the ring system, the stereochemical results of such reactions were not predictable. This paper is therefore particularly concerned with the stereochemistry of the intermediates [3] and with unexpected results from attempts to form the appropriate tricyclic compounds.

4-Series.

One isomer was obtained in the previous work [1], with the stereochemistry shown (**1**). On treatment with methanol/sulfuric acid, one ester was formed with structure



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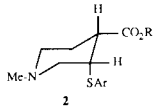


2

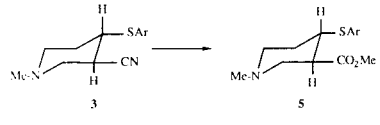
assigned as **2** (R = Me), *i.e.*, where the substituents have the opposite configuration to those in the nitrile. This and other structures were assigned by a combination of ^1H and ^{13}C nmr, utilising knowledge gained in the nitrile analyses. In all compounds, the N-Me is equatorial (^{13}C nmr: $\delta \sim 45$ ppm) and a combination of ring flipping, where necessary, to provide the more stable substituent conformation, and nitrogen inversion, can accommodate the observed stereochemical changes.

The complex ^1H nmr spectrum in deuteriochloroform (at 200 MHz) did reveal four ring proton signals below the N-Me signal (δ = 2.27). The lowest field signal, a poorly resolved quartet (3.68, J ~ 4 Hz) was assigned as H-3 and the lack of substantial coupling means H-3(e). The next two signals, apart from the methoxy one (3.45, s), at 3.0 (dd, J = 11, 4 Hz) and 2.85 (br d, J = 8.5 Hz) were assigned as H-2(e) and H-6(e) respectively. The remaining distinguishable signal at 2.63 (dt - 4 spin system) was due to H-4 and the coupling (J = 11, 4 Hz) is only compatible with an axial proton.

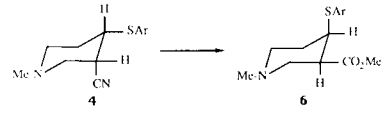
Thus, whereas in the nitrile the sulfur function has stereochemical priority and occupies the equatorial position, the ester group takes this role in the ester derivative.

3-Series.

Two nitriles were isolated and identified in previous work and each was converted to the methyl ester, with the results indicated.



3 **5**



4 **6**

Three ring proton signals in the ^1H nmr spectrum of **5** were well resolved. The lowest field signal at 3.15 was assigned to H-4 and the splitting required that this be axial (td, J = 10.5, 4 Hz). The other td signal at 2.68 was then assigned to H-3(a) (J = 10.5, 4 Hz), while the intermediate signal (2.9, dd, J = 10.5, 6 Hz) was assigned as H-2(e).

By contrast, the low field ring proton signal in the spectrum of **6** at 3.6 had the appearance of a narrow but broad

Table 1

^{13}C NMR Chemical Shifts

Compound	Carbon 1	2	3	4	4a	5	6	10a	NMe	C=O	OMe
2		60.6	48.7	44.2		23.8	54.0		45.9	171.9	50.9
5		57.3	45.8	47.9		31.4	54.7		45.8	172.5	51.9
6		53.1	46.2	47.3		31.2	51.2		46.0	171.4	51.5
10	59.2		55.2	25.6	49.5			42.7	45.9	193.9	
11	55.1		54.5	31.0	42.2			50.2	46.4	193.3	

quartet. The absence of large coupling indicated H-4(e). The downfield shift in comparison to **5** agrees with expectation for the axial to equatorial change. Irradiation of this signal in a decoupling experiment caused a change in a dt at 2.9 (J = 10.5, 4 Hz), but the large coupling was maintained. This latter signal was then assigned as H-3(a), and the stereochemistry was therefore defined.

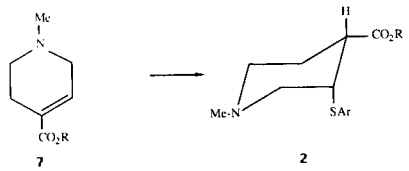
The chief distinguishing feature of the ^{13}C nmr spectra was the downfield shift of the C-2 and C-6 signals from **6** to **5** (Table 1). This substantial effect (4 ppm) on a β-C signal with change from axial to equatorial sulfur substituent is noted in 4-methylthio-5-*t*-butylcyclohexanes [4].

The results fit the pattern suggested by the 4-series, *i.e.*, the ester has stereochemical priority. The change from **3** to **5** does not involve a stereochemical change but in order to obtain the equatorial ester in **6**, the reaction requires accompanying ring flipping and nitrogen inversion.

p-Chlorothiophenol Addition to Alkyl Tetrahydropyridinecarboxylates.

4-Series.

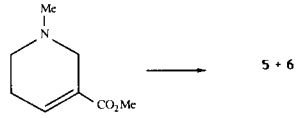
The reaction of **7** (R = Me) with *p*-chlorothiophenol in ethanol in the presence of a small amount of sodium ethoxide gave a 36% isolated yield of **2**, with the rest being largely a mixture of *p*-chlorophenyldisulfide and unreacted **7**. The same reaction of the ethyl ester gave the reported [2] compound **2** (R = Et) in much the same yield.



7 2

3-Series.

Addition of *p*-chlorothiophenol to **9** under basic conditions (sodium ethoxide/ethanol) gave a mixture of isomers **5** and **6** in a time dependent ratio; the proportion of the diequatorial isomer, **5**, increased slowly with an increase in reflux time.



9

Cyclization.

The esters **2**, **5**, and **6** were therefore available for cyclization attempts and the results were quite unexpected. The ester **2** (R = Et) was reportedly cyclized with polyphosphoric acid [2]. We found that this and 70% sulfuric acid were equally and only moderately successful and the latter was preferred.

The first surprise was that **5**, with the two substituents equatorial and in good proximity for ring closure, failed to

Table 2

Crystal Data for **10** and the 1-Butanol Solvate of **11**

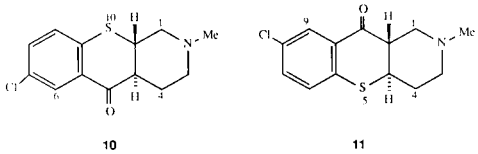
	10	**11** C_4H_9OH
Formula	$C_{13}H_{14}ClNOS$	$C_{13}H_{14}ClNOS.C_4H_{10}O$
Formula weight	267.8	341.9
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$
a(Å)	8.114(1)	7.907(1)
b(Å)	15.899(2)	14.892(2)
c(Å)	9.764(1)	7.977(1)
α(deg)	90	108.00(1)
β(deg)	98.99(1)	91.85(1)
γ(deg)	90	94.69(1)
V(Å^3)	1244.1(2)	888.7(2)
Z	4	2
D_m(g cm^{-3})	1.42(1)	[a]
D_c(g cm^{-3})	1.430	1.278
F(000)	560	364
λ(Å)	1.5418	1.5418
μ(Cu Kα) (cm^{-1})	39.8	29.2
Crystal size (mm)	0.07 x 0.19 x 0.35	1.20 x 0.86 x 0.15
T(K)	289	289

[a] Not determined due to crystal instability.

give any of the expected product under various conditions. The base insoluble fraction isolated was shown to be almost entirely 4-(methylthio)chlorobenzene. From the ethyl ester analog, 4-(ethylthio)chlorobenzene was likewise identified.

The failure to cyclize becomes even more difficult to understand when it was found that the other two esters did cyclize to products where the sulfur and carbonyl functions are diequatorial.

Both **2** and **6**, containing axial SAr and equatorial ester groups, cyclized similarly and the products were isolated in 35 and 40% yield respectively. The product from **2** had a melting point in agreement with that of the literature compound. Analysis of the ^{1}H nmr spectrum of this compound indicated an unexpected isomerism to give a trans ring junction and an X-ray structure determination of each was carried out to confirm **10** (from **2**) and **11** (from **6**). A suitable crystal of **11** was obtained only with difficulty, from a butanol-propanol-methanol solvent mixture. The crystals went opaque very rapidly on removal from the solvent.



10 11

The conformations of the tricyclic system in **10** and **11** are similar (Figure 1). The piperidine ring is in a fairly regular chair form (see torsion angles given in Table 5),

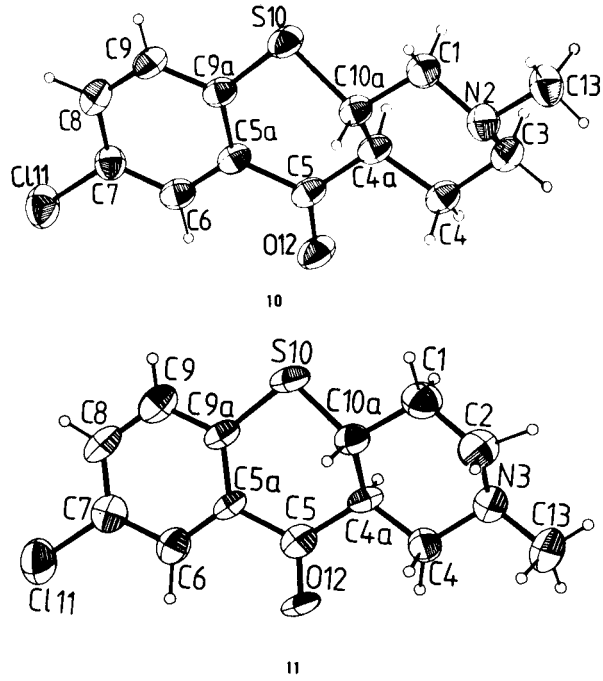


Figure 1. ORTEP drawing of the molecules (a) **10** and (b) **11**. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms are spheres of arbitrary radii.

Table 3

Atom Coordinates with Isotropic Temperature Factors for $C_{13}H_{14}ClNOS$ (**10**) and $C_{17}H_{24}ClNO_2S$ (**11**.C_4H_9OH). The Estimated Standard Deviations are Given in Parentheses (See Figure 1 for atom numbering)

10

ATOM	10^4x	10^4y	10^4z	B_{eq} [a]	ATOM	10^3x	10^3y	10^3z	B_{iso}
C1	7401(4)	6216(2)	5462(3)	3.92(7)	H1α	723(4)	672(2)	603(3)	4.8(7)
N2	8963(3)	6294(1)	4915(2)	4.45(6)	H1β	649(4)	617(2)	471(4)	6.0(8)
C3	10357(4)	6373(2)	6060(3)	4.00(7)	H3α	1018(4)	687(2)	666(4)	5.8(8)
C4	10487(3)	5600(2)	6969(3)	3.68(7)	H3β	1134(4)	644(2)	566(3)	4.2(6)
C4a	8865(3)	5427(2)	7532(3)	3.29(6)	H4α	1077(3)	512(2)	643(3)	3.6(6)
C5	8941(3)	4620(2)	8362(3)	3.30(6)	H4β	1137(4)	567(2)	773(3)	4.3(6)
C5a	7356(3)	4261(2)	8707(2)	3.19(7)	H4a	865(3)	589(2)	821(3)	4.1(6)
C6	7479(4)	3601(2)	9654(3)	3.66(6)	H6	854(3)	340(2)	996(3)	2.9(5)
C7	6084(3)	3284(2)	10103(3)	3.84(7)	H8	360(4)	337(2)	997(3)	4.5(7)
C8	4514(4)	3602(2)	9598(3)	4.16(7)	H9	331(4)	443(2)	832(3)	4.4(7)
C9	4374(3)	4238(2)	8640(3)	3.91(7)	H10a	745(3)	496(2)	577(3)	5.7(8)
C9a	5767(3)	4578(2)	8175(3)	3.37(6)	H13α	994(4)	701(2)	359(3)	4.5(7)
S10	5413(1)	5397(1)	6966(1)	4.15(2)	H13β	894(4)	756(2)	447(4)	5.7(8)
10a	7402(3)	5432(2)	6337(3)	3.31(6)	H13γ	796(5)	697(2)	325(4)	7.3(10)
Cl11	6275(1)	2479(1)	11328(8)	5.63(2)					
O12	10273(2)	4288(1)	8801(2)	4.52(5)					
C13	8901(4)	7002(2)	3961(4)	5.00(10)					

Table 3 (continued)

11.C_4H_9OH

ATOM	10^4x	10^4y	10^4z	B_{eq}	ATOM	10^3x	10^3y	10^3z	B_{iso}
C1	3676(9)	2917(5)	6887(10)	4.6(1)	O14 [b]	−30	196	396	5.6(1)
C2	4195(9)	2579(5)	4999(10)	4.6(1)	C15	−38	98	342	9.8(2)
N3	2961(6)	2799(3)	3808(6)	4.2(1)	C16a	−230(10)	74(6)	323(10)	9.2(4)
C4	2820(8)	3825(4)	4275(8)	3.8(1)	C16b	−178(10)	35(4)	388(10)	14.1(6)
C4a	2267(6)	4220(4)	6163(8)	3.1(1)	C17a	−296	−30	240	11.7(5)
C5	2111(6)	5269(4)	6633(9)	3.7(1)	C17b	−307	35	232	12.9(6)
C5a	1979(6)	5841(4)	8529(8)	2.9(1)	C18	−473	−43	232	11.4(3)
C6	1578(6)	6767(4)	8834(8)	3.8(1)	H1α	265(10)	264(6)	705(10)	10(3)
C7	1379(6)	7316(4)	10594(10)	4.1(1)	H1β	481(9)	278(5)	787(10)	10(2)
C8	1568(6)	6944(5)	11960(11)	4.0(1)	H2α	521(7)	275(4)	471(8)	5(2)
C9	1991(6)	6023(4)	11654(8)	4.0(1)	H2β	443(7)	182(4)	437(8)	5(1)
C9a	2188(6)	5471(4)	9930(8)	3.0(1)	H4α	393(7)	418(4)	410(8)	6(2)
S10	2726(2)	4317(1)	9669(2)	3.76(3)	H4β	160(9)	417(5)	358(9)	9(2)
C10a	3466(6)	3983(4)	7471(8)	3.5(1)	H4a	113(5)	395(3)	629(6)	2(1)
Cl11	829(2)	8466(1)	11042(2)	5.88(4)	H6 [c]	140	715	796	8
O12	2028(6)	5653(3)	5477(6)	4.9(1)	H8	143(7)	724(4)	1307(8)	5(2)
C13	3455(11)	2433(6)	1957(11)	5.5(1)	H9 [c]	213	579	1256	8
					H10a	448(6)	442(4)	754(6)	4(1)
					H13α	343(7)	179(4)	167(8)	5(2)
					H13β	253(8)	252(5)	105(10)	7(2)
					H13γ	493(8)	291(5)	194(9)	8(2)

[a] $B_{eq} = (8\pi^2/3)\Sigma\Sigma U_{ij} a_i^* a_j^* \mathbf{a_i}\cdot\mathbf{a_j}$. [b] Atom numbering for butanol is O14–C15–C16–C17–C18. [c] Parameters not refined.

the *N*-methyl substituent is equatorial, and the two heterocyclic rings are trans-fused. The bridgehead atoms of the heterocyclic rings in both molecules lie 0.24(1) Å (C adjacent to C=O) and 0.55(1) Å (C adjacent to S) from the plane of the other four atoms of the central ring and on opposite sides of it. The oxo group is twisted by 14° from the phenyl ring plane. The comparable bond lengths and angles in the two molecules are in good agreement (Table 4).

The ^{1}H 200 MHz nmr spectra could then be partially analysed in terms of these structures. That for **10** was quite unequivocal. The low field saturated ring proton signal (3.50-3.65) was assigned as H-10a. This qd (4 spin system) (J = 13, 11, 4 Hz) is in accord with an axial configuration with coupling to two other axial protons. The proton H-4a, which is also axial, was assigned to the signal at 2.4-2.53, which had an almost identical splitting pattern. The intermediate narrow 2H multiplet 2.95-3.05 was assigned to the equatorial H-1 and H-3 protons. Unique among all spectra in these compounds, the most upfield signal at 1.55-1.75 was distinguishable, as a 16-line 1H multiplet (J = 13, 12, 11, 4 Hz). This was assigned to the axial H-4.

The ^{1}H nmr spectrum of **11** was not as easy to interpret. In this case, the signal assigned to the proton α to sulfur (H-4a) was not the lowest field ring proton signal, but did have a similar chemical shift to H-4 in ester **5**, nor did it have the distinct appearance of the analogous signal in **10**. The lowest field signal in this case (3.45-3.65 J = 12, 4, 2 Hz) is therefore due to the equatorial H-1. The rigid structure of **11** holds this proton and the carbonyl group almost coplanar and H-1 therefore experiences a deshielding effect from the carbonyl. The other distinguishable signals were for the axial H-10a (qd, J = 13, 11, 4 Hz) at 2.78-2.9 merging into a narrow multiplet (H-3e) centred at 2.95. Decoupling experiments supported these assignments and indicate that the 2 Hz coupling in H-1(e) is due to H-3(e).

Selective proton decoupling aided the assignment of the ^{13}C spectra, and shifts are included in Table 1. The 4-5 ppm differences in C-1 and C-4 in the two structures are in agreement with the additive effects of α and β equatorial sulfur and carbonyl functions obtained from cyclohexane data [4] [5].

None of the current results give any information on the mechanism of the cyclization reaction. Though the cyclized products have the sulfur and carbonyl functions in equatorial positions, the starting esters each have an axial, equatorial arrangement and so the cyclization involves

Table 4

Bond Lengths (Å) and Angles (deg) for **10** and **11**. Atoms are Denoted by Numerals Only (see Figure 1)

	10	**11**		**10**	**11**
1-2	1.456(4)	1.515(11)	5-12	1.219(3)	1.229(9)
1-10a	1.511(4)	1.535(9)	5a-6	1.392(4)	1.389(8)
2-3	1.466(3)	1.465(10)	6-7	1.372(4)	1.411(9)
2-13	1.457(4)		5a-9a	1.406(3)	1.401(10)
3-13		1.485(10)	7-8	1.388(4)	1.376(13)
3-4	1.510(4)	1.471(7)	7-11	1.742(3)	1.733(6)
4-4a	1.528(4)	1.531(8)	8-9	1.370(4)	1.388(10)
4a-5	1.514(4)	1.506(8)	9a-10	1.751(3)	1.756(6)
4a-10a	1.529(3)	1.527(9)	10-10a	1.815(3)	1.800(6)
5-5a	1.493(4)	1.501(8)			
2-1-10a	110.7(2)	110.0(5)	5-5a-6	117.6(2)	116.1(4)
1-2-3	109.9(2)	110.7(5)	5-5a-9a	123.5(2)	123.0(4)
1-2-13	110.8(2)		6-5a-9a	118.8(2)	120.8(4)
3-2-13	111.5(2)		6-7-8	120.7(2)	121.0(5)
2-3-4	110.7(2)	111.8(4)	6-7-11	120.0(2)	119.7(4)
2-3-13		110.0(5)	8-7-11	119.3(2)	119.3(5)
4-3-13		109.5(4)	7-8-9	119.0(2)	121.1(5)
3-4-4a	111.9(2)	110.8(4)	8-9-9a	121.6(2)	118.7(5)
4-4a-5	112.3(2)	110.7(4)	5a-9a-9	119.0(2)	120.5(4)
4-4a-10a	109.5(2)	110.9(4)	5a-9a-10	124.1(2)	123.9(4)
5-4a-10a	112.0(2)	112.3(4)	9-9a-10	116.9(2)	115.6(4)
4a-5-5a	118.7(2)	119.4(5)	9a-10-10a	101.0(2)	101.6(3)
4a-5-12	121.0(2)	120.7(4)	1-10a-4a	111.6(2)	110.7(5)
5a-5-12	120.2(2)	119.8(4)	1-10a-10	107.1(2)	108.4(4)
5a-6-7	120.8(2)	117.8(4)	4a-10a-10	111.5(2)	112.3(4)

Table 5

Selected Torsional Angles (deg) for **10** and **11**

	10	**11**		**10**	**11**
1-2-3-4	-61.5(3)	-60.1(7)	5-5a-9a-10	-3.6(4)	-3.1(8)
2-3-4-4a	56.6(3)	59.3(7)	5a-9a-10-10a	-15.7(3)	-15.6(6)
3-4-4a-10a	-50.9(3)	-55.1(6)	9a-10-10a-4a	47.7(2)	46.8(5)
4-4a-10a-1	51.1(3)	52.1(7)	10-10a-4a-5	-63.8(3)	-62.1(6)
4a-10a-1-2	-57.6(3)	-53.0(7)	10a-4a-5-5a	42.5(3)	41.4(7)
10a-1-2-3	62.0(3)	56.5(8)	12-5-5a-6	6.8(4)	-6.9(9)
10a-1-2-13	-174.3(2)		5-5a-9a-10	-3.6(4)	-3.1(8)
4a-4-3-13		-178.5(5)	5-5a-6-7	-174.8(3)	-177.6(5)
4a-5-5a-9a	-7.3(4)	-7.6(9)	8-9-9a-10	179.2(2)	-179.9(5)
			6-5a-5-12	-6.8(4)	-6.9(9)

more than a conformational charge and/or nitrogen inversion. Furthermore, ester **5**, in which there is an apparently desirable diequatorial arrangement, gives the unexpected 4-(methylthio)chlorobenzene rather than **11**. Cleavage of the starting esters can evidently occur under the acidic reaction conditions. This is also indicated in the reaction of **6** where, as well as **11**, significant amounts of disulfide and the starting tetrahydropyridine **9** were formed. Such cleavage at least makes the stereochemical changes from reactants to products feasible, but "cyclization" is an oversimplification and the details of this complex reaction are unknown to us at this time.

EXPERIMENTAL

The nmr spectra were recorded on JEOL JNM FX-200 (199.5 MHz) (^{1}H) and JEOL PFT-100 FT-NMR (25 MHz) (^{13}C) spectrometers in deuteriochloroform solvent. Preparative chromatography was done on a Chromatotron, using a silica gel plate.

Ethyl (and Methyl) 1-Methyl-1,2,5,6-tetrahydropyridine-4-carboxylates **7**.

These were prepared by borohydride reduction of the corresponding quaternary pyridinium compounds, as previously for the nitrile [6], and were sufficiently pure for further use without distillation; ^{1}H nmr (methyl ester): δ 2.3-2.6 (m, 4H), 2.35 (s, NMe), 3.0-3.15 (m, 2H), 3.72 (s, OMe), 6.85 (m, H-3, 1H).

Methyl 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**9**).

This was prepared as for **7**. The crude ester (90%) was a 7:3 mixture of **9** and the 1,4-dihydropyridine [from nmr analysis of H-4 in **9** and H-2 in the dihydro compound (a singlet at 7.2 ppm)]. Distillation gave **9** (46%), bp 75-79°/2 mm; ^{1}H nmr: δ 2.25-2.55 (m, 4H), 2.42 (s, NMe), 3.05-3.2 (m, 2H), 3.7 (s, OMe), 6.95 (m, H-4, 1H).

Methanolysis of Nitriles.

The nitrile **1**, **3**, or **4** [1] (1 g) in methanol (15 ml) and concentrated sulfuric acid (5 ml) was heated under reflux for 5 hours. The alcohol was removed under reduced pressure, ice was added to the residue which was then basified with concentrated ammonium hydroxide.

Compound **2** (R = Me) was obtained as a waxy solid (70%), mp 40-42° [from light petroleum (bp 40-70°)]; ^{1}H nmr: δ 1.8-2.4 (m, 4H), 2.27 (s, NMe), 2.63 (dt, H-4(a), 1H, J = 11, 4 Hz), 2.85 (br d, H-6(e), 1H, J = 8.5 Hz), 3.0 (dd, H-2(e), 1H, J = 11, 4 H), 3.45 (s, OMe), 3.68 (br q, H-3(e), 1H, J ≈ 4 Hz), 7.15, 7.3 (d + d, ArH, 4H, J = 9 Hz). For analysis, the methiodide, mp 190-192° (from ethanol/ethyl acetate) was preferred.

Anal. Calcd. for $C_{15}H_{21}ClINO_2S$: C, 40.8; H, 4.8; N, 3.2. Found: C, 40.7; H, 5.0; N, 3.5.

For the other two reactions, the product was extracted with dichloromethane and isolated by chromatography (5% methanol/dichloromethane). The following liquids were obtained:

Compound **5**.

This compound had ^{1}H nmr: δ 1.9-2.3 (m, 5H), 2.21 (s, NMe), 2.68 (td, H-3(a), 1H, J = 10.5, 4 Hz), 2.9 (dd, H-2(e), 1H, J = 10.5, 6 Hz), 3.15 (td, H-4(a), 1H, J = 10.5, 4 Hz), 3.69 (s, OMe), 7.2, 7.35 (d + d, ArH, 4H, J = 9 Hz). Methiodide, mp 170-172° (from methanol/ethyl acetate).

Anal. Calcd. for $C_{15}H_{21}ClINO_2S$: C, 40.8; H, 4.8; N, 3.2. Found: C, 40.9; H, 4.7; N, 3.0.

Compound **6**.

This compound had ^{1}H nmr: δ 1.85-2.0 (m, 3H), 2.2 (s, NMe), 2.3-2.5 (m, 2H), 2.7 (br d, H-2(e), 1H, J = 11 Hz), 2.9 (dt, H-3(a), 1H, J = 10.5, 4 Hz), 3.5 (s, OMe), 3.55-3.65 (br q, H-4(e), 1H), 7.15, 7.3 (d + d, ArH, 4H, J = 9 Hz). Methiodide, mp 164-165° (from methanol/ethyl acetate).

Anal. Calcd. for $C_{15}H_{21}ClINO_2S$: C, 40.8; H, 4.8; N, 3.2. Found: C, 40.9; H, 5.1; N, 3.1.

p-Chlorothiophenol (1.2 g) and tetrahydropyridine **7** or **9** (1.0 g) were added to a solution of sodium (0.05 g) in ethanol (50 ml) and the solution was heated under reflux under nitrogen for 4 hours. The solvent was removed at reduced pressure, and the residue taken up in dichloro-

methane, washed with dilute sodium hydroxide, water, and dried. Evaporation of the solvent gave the crude product.

This, from **7** (R = Me) (1.5 g) was taken up into warm light petroleum (bp 40-70°) which, on cooling, gave **2** (R = Me) (0.7 g, 36%) as above. The filtrate was concentrated and nmr analysis indicated that the residue was a mixture of *p*-chlorophenyldisulfide and unreacted **7**. The product from **7** (R = Et) crystallized from aqueous methanol to give **2** (R = Et) (38%), mp 63-64° (lit [2] mp 61-62°).

The crude oil from **9** (1.6 g) contained **5** and **6**. Chromatography (1% methanol/dichloromethane) gave *p*-chlorophenyldisulfide (0.2 g), mp 68-70° (lit [7] mp 72-73°) followed by **5** (0.4 g) and **6** (0.8 g), which had very similar retention times.

7-Chloro-2-methyl-1,2,3,4,4a,10a-hexahydro-5*H*-[1]benzothiopyrano-[2,3-*c*]pyridin-5-one (**10**).

Compound **2** (0.5 g) in 70% by weight sulfuric acid (5 ml) was heated at 100° for 2 hours and then left overnight. The solution was carefully basified with concentrated ammonium hydroxide, extracted with dichloromethane, and the extract dried and concentrated to give a viscous oil (0.25 g). Crystallization from methanol gave **10** as yellow crystals (0.1 g), mp 151-153° (lit [2] mp 149-150°). The crystallization residue was passed down a silica column (10% ethanol/ethyl acetate) and gave a further sample (0.05 g) of **10**, for a total yield of 34%. ^{1}H nmr: δ 1.55-1.75 (16 lines, H-4(a), 1H, J = 13, 12, 11, 4 Hz), 2.0-2.3 (m, 3H), 2.31 (s, NMe), 2.4-2.53 (qd, H-4a(a), 1H, J = 13, 11, 4 Hz), 2.95-3.05 (m, H-1(e), H-3(e), 2H, J = 4 Hz), 3.50-3.65 (qd, H-10a(a), 1H, J = 13, 11, 4 Hz), 7.14 (d, H-9, 1H, J = 8 Hz), 7.31 (dd, H-8, 1H, J = 8, 2 Hz), 8.05 (d, H-6, 1H, J = 2 Hz).

8-Chloro-2-methyl-1,2,3,4,4a,10a-hexahydro-10*H*-[1]benzothiopyrano-[3,2-*c*]pyridin-10-one (**11**).

This cyclization from **6** was carried out as for **10** and 0.7 g crude oil was obtained from **6** (0.9 g). Crystallization from methanol gave **11** (0.25 g, 32%), mp 120-122°; ^{1}H nmr: δ 1.9-2.05 (m, 4H), 2.39 (s, NMe), 2.78-2.9 (qd, H-10a(a), 1H, J = 12, 11, 4 Hz), 2.95 (narrow m, H-3(e), 1H, J ≤ 7 Hz), 3.2-3.4 (m, H-4a(a), 1H, J = 13-2 Hz), 3.45-3.65 (qd, H-1(e), 1H, J = 12, 4, 2 Hz), 7.15 (d, H-6, 1H, J = 8 Hz), 7.31 (dd, H-7, 1H, J = 8, 2 Hz), 8.0 (d, H-9, 1H, J = 2 Hz).

Anal. Calcd. for $C_{13}H_{14}ClNOS$: C, 58.3; H, 5.2; N, 5.2. Found: C, 58.1; H, 5.6; N, 5.5.

The filtrate was concentrated and residue chromatographed (10% hexane/dichloromethane → 10% methanol/dichloromethane) to give samples of *p*-chlorophenyldisulfide (0.14 g) and tetrahydropyridine **9** (0.2 g).

Reaction of **5** with Sulfuric Acid.

Compound **5** (0.8 g) when treated with 70% sulfuric acid, as above, gave 0.2 g of oil from extraction of the basified reaction mixture. Apart from minor impurities, the ^{1}H nmr spectrum consisted of two peaks, at 2.4 (s, 3H) and 7.2 (s, 4H) ppm, identical with that of authentic 4-(methylthio) chlorobenzene; ir and ^{13}C nmr spectra were also in agreement. When **5** as the ethyl ester was used, the reaction proceeded similarly and the extracted oil was largely 4-(ethylthio)chlorobenzene.

X-Ray Analyses.

Compound **10** crystallized as pale yellow needles (needle-axis along the [100] direction) from methanol, and pale yellow plate-like crystals (elongated along the [001] direction) of a 1-butanol solvate of compound **11** formed from a *n*-butanol-*n*-propanol-methanol mixture. The crystal data are given in Table 2. The setting angles for 25 reflections were used to determine the cell parameters. Intensities were measured at 298 K on a Rigaku-AFC diffractometer with CuKα radiation (graphite-crystal monochromator, λ = 1.5418 Å). The data were recorded by an ω-2θ scan with a scan range (Δω) of 1.2° + 0.5° tan θ and scan rates 2° min^{-1} (**10**) and 4° min^{-1} (**11**). Three standard reflections monitored every 50 reflection showed no significant variation in intensity during the data collections. Data to a 2θ (max) of 130° yielded 2026 (**10**) and 2223 (**11**) unique terms. The integrated intensities were corrected for Lorentz and polarization effects and for absorption. As the solvated crystals of **11** were unstable in air, a crystal was sealed in a thin-walled glass tube for the diffraction measurements.

Both structures were solved by direct methods with SHELX76 [8]. Refinement was by full-matrix least-squares with anisotropic temperature factors given to the non-hydrogen atoms of both heterocyclic molecules. During refinement of the structure of **11**, residual electron-density on difference maps indicated the presence of solvate molecules in the crystal. After considerable difficulty in obtaining a satisfactory model for the solvent, sites feasible for one 1-butanol molecule in the asymmetric unit were included. The largest peak on the difference map, which was at a distance of 2.8 Å from the ring nitrogen, was assigned to the site of the hydroxyl oxygen. Further refinement indicated that two of the butanol carbon sites, those for C16 and C17, were only partially occupied. As an approximate model to account for the disorder, the two atoms were included at alternate locations and given occupancy factors of 0.5. It is interesting to note that disordered butanol has been found to occur in a number of structures, for example see references [9] and [10]. The positional coordinates of the butanol atoms were not varied but the refined isotropic temperature factors (Table 3) support this proposed model. Apart from those of the solvent, the hydrogen positions were located on difference maps and the atoms were included in the refinement with isotropic temperature factors. Refinement with 1743 and 2142 data ($I \geq 1.5\sigma I$) for **10** and **11** respectively, converged at R = 0.047, R_w = 0.054 (**10**) and R = 0.088, R_w = 0.108 (**11**). The function minimized was $\Sigma w (|F_o| - |F_c|)^2$ with $w = (\sigma^2 |F_o| + m |F_o|^2)^{-1}$ for which m = 0.0005 (**10**) and 0.00005 (**11**). The largest peaks on the final difference maps were of heights + 0.19, − 0.31 e Å^{-3} (**10**) and + 0.50, − 0.61 e Å^{-3} (**11**). Scattering factors were taken from the International Tables for X-ray Crystallography [11].

The final atomic coordinates are given in Table 3. Bond lengths and angles for the non-hydrogen atoms are listed in Table 4, while selected torsion angles are given Table 4. Figure 1 has been prepared from the output of ORTEP-II [12]. Anisotropic thermal parameters and listings of observed and calculated structure amplitudes are available as supplementary material.

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