Benzocycloheptapyridines. Analogs of Azatadine

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Certain 3-substituted derivatives of cyproheptadine (**1a**) have been shown to possess potent pharmacological properties. The structural analogy between cyproheptadine and azatadine (**2**) prompted the preparation of 9-substituted derivatives of **2** and its 5,6-dehydro analog for pharmacological comparison. The 9-cyano and 9-trifluoromethylthio derivatives were prepared by direct displacement of the corresponding 9-bromo compounds. Acid hydrolysis of the nitriles generated the carboxylic acids. Oxidation of the trifluoromethylthio compounds **15a** and **18a** gave the epoxy sulfones **19a** and **19b**, which could not be deoxygenated. Therefore, the trifluoromethylsulfonyl moiety was introduced prior to the formation of the exocyclic olefin.

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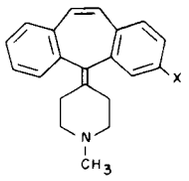
Cyproheptadine, 1-methyl-4-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine, **1a**, has been shown to be a useful therapeutic agent [1]. The introduction of nuclear substituents into the 3-position not only determines the biological profile of each derivative, but also introduces atropisomerism into the series [5]. For example, the 3-cyano derivative exhibits neuroleptic properties, and this activity has been established to residue predominantly in the (−)-enantiomer [2]. Hydrolysis of the nitrile to the carboxylic acid in conjunction with reduction of the 10,11-double bond abolishes the anti-psychotic activity while producing a substance with enhanced appetite stimulant properties [3,4]. Synthesis of the 3-trifluoromethylthio (**1e**) and the 3-trifluoromethylsulfonyl (**1f**) derivatives produced potent antipsychotics, in which the predominant neuroleptic activity resided in one isomer [5,6].



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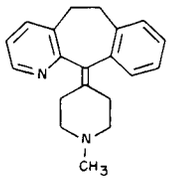
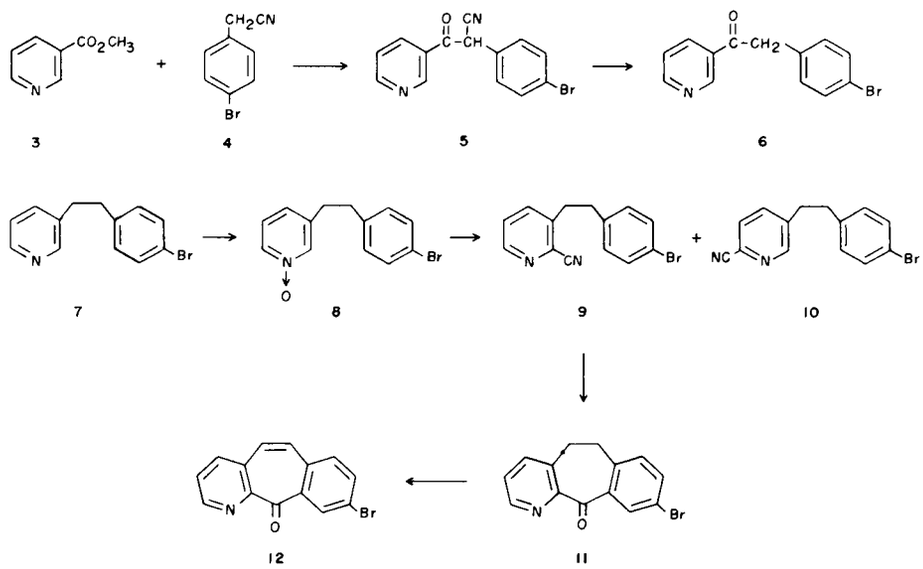


2

a, X = H
b, X = Br
c, X = CN
d, X = COOH
e, X = SCF_3
f, X = SO_2CF_3

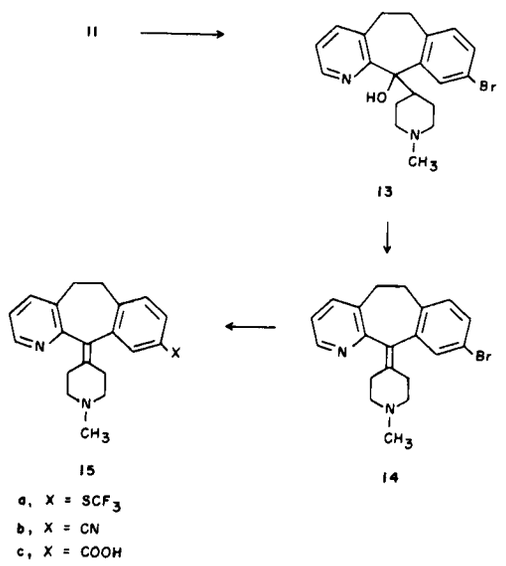
Azatadine (**2**) also possesses antihistaminic properties [7] and bears a structural resemblance to cyproheptadine. Azatadine differs from **1a** by the replacement of the 4-carbon by nitrogen and saturation of the 10,11-olefinic linkage. It was of interest, therefore, to prepare azatadine and 5,6-dehydroazatadine with the aforementioned substituents in the 9-position for comparative pharmacological testing.

Scheme I



Preparation of these products required significant quantities of the bromoketones **11** and **12** (Scheme 1). These intermediates were generated by incorporating slight variations of Villani's general methods to the chloro derivatives [8]. Condensation between methyl nicotinate (**3**) and *p*-bromophenylacetonitrile (**4**) using sodium methoxide in toluene gave **5**. Hydrolysis of the cyano function and decarboxylation of the newly formed carboxylate was accomplished with boiling 48% hydrobromic acid. The Huang-Minlon modification of the Wolff-Kishner reduction reduced the ketone **6** to the saturated derivative **7**. Although Villani [8] reports *N*-oxidation of derivatives of this type using 30% hydrogen peroxide in glacial acetic acid, we found this procedure unreproducible. Oxidation of **7** to **8** was accomplished using *m*-chloroperbenzoic acid in methylene chloride. The cyanation of **8** to a mixture of **9** (the desired isomer) and **10** was performed as described by Villani for related products [8]. After several unsuccessful attempts to separate the mixture cleanly by distillation, we found that the desired isomer (**9**) could be isolated in 40-50% yield using a simple solvent wash of the crude reaction mixture (see Experimental). The higher melting isomer exhibited a broad singlet (1H) at 8.48 δ in its pmr spectrum, whereas, the lower melting isomer displayed a four-line multiplet at 8.55 δ. These absorptions are assigned to the protons α- to the pyridine nitrogen and thus establish the substitution pattern as being 2,5 in the former case (**10**) and 2,3 in the latter (**9**).

Scheme 2



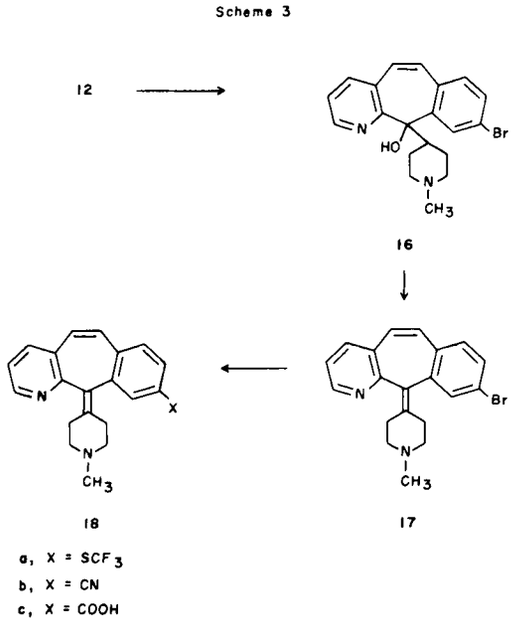
Cyclization of the nitrile **9** to **11** occurred in hot polyphosphoric acid (180°, 18 hours) in approximately 40% yield. Although considerable effort was spent toward trying to increase this conversion, changes in quantity of PPA, temperature, or time seemed to be detrimental. In addition, the crude reaction product appeared to contain more than one bromoketone isomer (tlc, glc, ms). Either the bromine is scrambled during the cyclization or, more likely, the intermediate in the reaction is the spiro derivative (**24**), which could migrate the alkyl function rather than the acyl moiety to generate other isomers. Treatment of **11** with selenium dioxide in pyridine generated the unsaturated ketone **12**.

At this stage it was decided to add the piperidylidene function prior to dispacement of the bromine. Although the trifluoromethylthio and trifluoromethylsulfonyl groups are compatible with Grignard reactions, the nitrile and carboxyl groups would not be. In addition, this strategy allows the use of the expensive metal reagent needed for the displacement to be deferred as late as possible in the sequence.

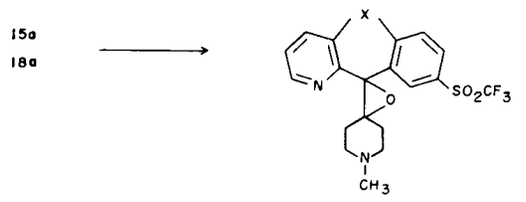
The Grignard reagent derived from 1-methyl-4-chloropiperidine [9] was added to each ketone producing the two tertiary carbinols **13** and **16**. Dehydration of the carbinols to the exocyclic piperidylidene derivatives **14** and **17** was accomplished in warm 85% sulfuric acid. The dehydration of the olefinic carbinol **16** required a much longer reaction time, an observation which probably reflects differing energy requirements in the formation of the intermediary carbonium ions.

Displacement of the bromine from the two derivatives **14** and **17** with cuprous cyanide exhibited little difference in reactivity. Both substrates required approximately 30 hours at 165-170° for complete reaction (tlc). The nitriles **15b** and **18b** were, in turn, hydrolyzed to the corresponding carboxylic acids **15c** and **18c** respectively, in boiling 6*N* hydrochloric acid and were charactarized as hydrochloride salts.

Scheme 3



Scheme 4



19

a, X = CH_2CH_2

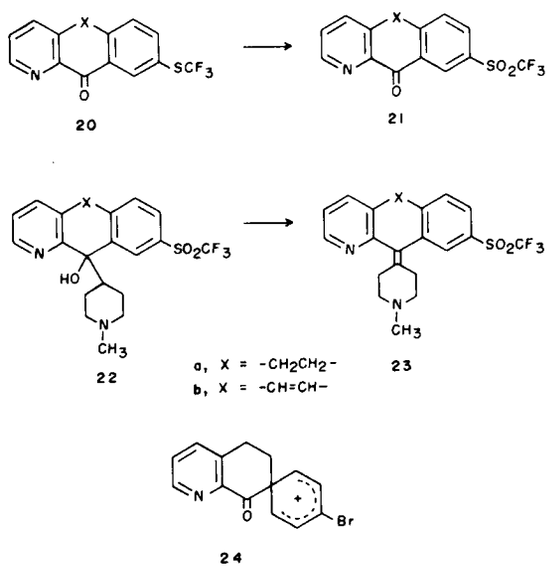
b, X = CH=CH

Preparation of the trifluoromethylthio derivatives similarly followed standard procedures. Remy [10] and Yagupulski [11] have demonstrated the displacement of aromatic halides by bis(trifluoromethylthio)mercury in the presence of copper powder or trifluoromethylthiocopper. The ready availability of bis(trifluoromethylthio)mercury [12] led us to try this reagent first. The displacements from the piperidylidene derivatives **14, 17** required elevated temperatures (140-150°) and fairly long reaction times (12-20 hours) in hexamethylphosphoric triamide. Both of these displacements, however, occurred more readily than did those with cuprous cyanide. The F-nmr spectra displayed a sharp singlet for each product (41.9 ppm for **15a** and 42.2 ppm for **18a**). These signals are in the appropriate chemical shift region for aryl-SCF_3 substituents as described by Remy *et al.* [6]. We subsequently generated trifluoromethylthiocopper [11], but it showed no increase in reactivity over the mercury procedure.

With these six derivatives at hand, the only remaining analogs to be prepared were the two trifluoromethylsulfonyl derivatives **23a** and **23b**. The unsaturated product **23b** was selected as the initial product for synthesis since any method to this structure should be amenable to the saturated derivative. A number of attempts to prepare the sulfone by oxidation of **18a** with hydrogen peroxide (30%) in acetic acid were extraordinarily slow and complex. Utilization of trifluoroperacetic acid (generated from trifluoroacetic anhydride and 90% hydrogen peroxide) completely converted the sulfide to the sulfone after 24 hours in methylene chloride (25°). Removal of any accompanying *N*-oxides with phosphorus trichloride generated a product that still contained three oxygen atoms. The F-nmr exhibited a peak at 77.4 ppm characteristic of aryl trifluoromethylsulfones [6] and the ^{1}H-nmr displayed olefinic proton absorption (δ 7.23), thus indicating the presence of the 5,6-double bond. There was no evidience suggestive of remaining *N*-oxides; hence, the extraneous oxygen was assigned to the exocyclic position in an epoxide function, **19b**. Confirmation of this assignment was obtained from the mass spectrum that displayed an M^+-112 peak in addition to the M^+-96 fragment. These fragments arise from decompositions in which both the tricyclic system and the piperidine ring retain the oxygen atom from the epoxide.

The discovery that the exocyclic olefin was more readily attacked by oxidizing agents than was the 5,6-bond, made it necessary to introduce the trifluoromethylsulfonyl moiety prior to the piperidine function. Therefore, the ketones **11** and **12** were treated with bis(trifluoromethylthio)mercury to give the sulfides **20a** and **20b**. Oxidation to **21a** could be accomplished, albeit slowly, with 30% hydrogen peroxide in acetic acid, whereas, preparation of **21b** required trifluoroperacetic acid. Addition of the piperidyl Girgnard reagent gave the carbinols **22a** and **22b**, which were dehydrated with 85% sulfuric acid to the desired products **23a** and **23b**.

Scheme 5



20 21 22 23

a, X = $-CH_2CH_2-$

b, X = -CH=CH-

24

The comparative evaluation of these compounds, relative to the corresponding cyproheptadine structure, indicated much lower levels of activity in all the assays investigated [13].

EXPERIMENTAL

Melting points were taken on a Thomas Hoover melting point apparatus in open capillaries and are uncorrected values. The ^{1}H-nmr and ^{19}F-nmr were recorded on a Varian T-60 spectrometer by Mr. Riley McGaughran and all shifts are relative to tetramethylsilane and fluorotrichloromethane respectively as internal standards. Mass spectra were run on an AEI MS 902 by Mr. R. E. Rhodes. Microanalyses were performed under the direction of Mr. Kermit Streeter.

3-[2-(4-Bromophenyl)-2-cyanoacetyl]pyridine (**5**).

A solution of 4-bromophenylacetonitrile (98.03 g, 0.50 mole) in toluene (150 ml) was added over 0.5 hour to a stirred mixture of methyl nicotinate (68.57 g, 0.50 mole), sodium methoxide (54.03 g, 1.0 mole) and toluene (600 ml) at 90°. The mixture was refluxed overnight, the condenser was replaced by a distilling head, and distillate was collected until the head temperature was essentially the same as the pot temperature (>110°). The reaction mixture was cooled and filtered. THe yellow brown solid was dissolved in water (2500 ml), the aqueous solution was extracted with ether then acidified by the addition of glacial acetic acid

(40 ml). The resulting orange solid was filtered, washed well with water and dried under a stream of warm air to give 130.5 g, mp 180-187°. Recrystalization from acetonitrile raised the mp to 200-201.5°; ir (potassium bromide): 2200 cm^{-1} (-CN).

Anal. Calcd. for $C_{14}H_9BrN_2O$ (301.15): C, 55.83; H, 3.01; N, 9.30. Found: C, 55.56; H, 2.94; N, 9.49.

3-[2-(4-Bromophenyl)acetyl]pyridine (**6**).

A mixture of **5** (15 g) and 48% hydrobromic acid (150 ml) was heated to reflux for 24 hours. The solution was cooled to 25° and poured onto ice (500 g) with stirring. The resulting mixture was made alkaline by the addition of concentrated ammonium hydroxide, and the precipitated solid was collected, washed with water and dried, yield 11.9 g. Recrystallization from hexane produced straw-colored needles, 9.1 g, mp 104-106°.

Anal. Calcd. for $C_{13}H_{10}BrNO$ (276.14): C, 56.54; H, 3.65; N, 5.07. Found: C, 56.61; H, 3.59; N, 5.16.

3-[2-(4-Bromophenyl)ethyl]pyridine (**7**).

A mixture of **6** (114 g, 0.41 mole), sodium hydroxide (45 g), hydrazine hydrate (45 ml) and diethylene glycol (550 ml) was stirred and heated to reflux (105-115°). After one hour at this temperature, a Dean-Stark head was added to the apparatus, and excess hydrazine and water were distilled out until the temperature of the reaction medium reached 200°. The Dean-Stark trap was removed and the mixture was heated an additional three hours (*ca.*200°). The cooled reaction mixture was poured into cold water (5-10°, 1500 ml) and extracted with ether (3 × 500 ml). The combined extracts were washed with water (2 × 500 ml), saturated sodium chloride solution (2 × 300 ml) and dried (sodium sulfate). Filtration and removal of the solvent gave 97.5 g of red-orange oil. Vacuum distillation (0.3 mm) gave 87.2 g of a clear, pale yellow oil, bp 149.5-150.5°; nmr (deuteriochloroform): δ 2.80 (s, $-CH_2CH_2-$, 4H), 6.83-7.53 (m, bromophenyl, H-4, H-5, 6H), 8.36-8.46 (m, H-2, H-6, 2H).

Anal. Calcd. for $C_{13}H_{12}BrN$ (262.16): C, 59.56; H, 4.61; N, 5.34. Found: C, 59.85; H, 4.89; N, 5.31.

3-[2-(4-Bromophenyl)ethyl]pyridine-1-oxide (**8**).

A solution of **7** (13.11 g, 0.05 mole) and *m*-chloroperoxybenzoic acid (85%, 10.5 g, *ca.* 0.05 mole) in methylene chloride was stirred at 25° for two hours. The solution was cooled and 7.5*M* ammonium hydroxide (150 ml) was added. The layers were separated and the organic layer was washed with dilute ammonium hydroxide (150 ml), water (4 × 150 ml), saturated sodium chloride solution (2 × 150 ml) and dried (sodium sulfate). Removal of the drying agent and evaporation of the solvent gave 11.2 g of a beige powder, mp 96-106°. Recrystallization from 1-chlorobutane and cyclohexane produced 8.6 g, mp 107-109°; nmr (deuteriochloroform): δ 2.87 (s, $-CH_2CH_2-$, 4H), 6.93-7.57 (m, bromophenyl, H-4, H-5, 6H), 8.03-8.17 (m, H-2, H-6, 2H).

Anal. Calcd. for $C_{13}H_{12}BrNO$ (278.16): C, 56.13; H, 4.35; N, 5.04. Found: C, 55.84; H, 4.69; N, 4.93.

2-Cyano-3-[2-(4-bromophenyl)ethyl]pyridine (**9**) and 2-Cyano-5-[2-(4-bromophenyl)ethyl]pyridine (**10**).

Dimethyl sulfate (42.6 ml, 56.8 g, 0.45 mole) was added to **8** (125.2 g, 0.45 mole) over 0.25 hour. The resulting mixture was heated on the steam bath for three hours, cooled to 25° and dissolved in water (250 ml). This solution was added slowly to a cold (0-3°) solution of sodium cyanide (29.42 g, 0.6 mole) in water (250 ml). When addition was complete (1-3 hours), the reaction mixture was stirred overnight as the ice melted and the temperature gradually increased. The reaction mixture was extracted with chloroform (5 × 200 ml), and the combined organic extracts were washed with water (2 × 500 ml), saturated sodium chloride solution (2 × 500 ml) and dried (sodium sulfate). The drying agent was removed and the solvent was evaporated *in vacuo*. Chlorobutane (125 ml) was added to the residue and the mixture was stirred for two hours. Filtration gave 15.0 g, mp 120-132°. Tlc examination, fluorescent silica, benzene-ethyl acetate (1:1, v/v), indicated one major component (rf = 0.79). Analysis of the nmr spectrum indicated this product to be **10**. Recrystallization from chlorobutane raised the mp to 133-135°; nmr (deuteriochloroform): δ 2.97 (s, $-CH_2CH_2-$, 4H), 7.00-7.73 (m, bromophenyl, H-3, H-4, 6H), 8.48 (br s, H-6, 1H).

Anal. Calcd. for $C_{14}H_{11}BrN_2$ (287.17): C, 58.55; H, 3.86; N, 9.76. Found: C, 58.26; H, 4.00; N, 9.51.

The filtrate from **10** was evaporated and the resulting amber oil was stirred with isopropanol (150 ml). This mixture was chilled and filtered to give 60.44 g, mp 75-83°. Tlc indicated one major component (rf = 0.73) and the nmr spectrum confirmed the structure as **9**. Recrystallization from cyclohexane gave material with mp 83.5-85.5°; nmr (deuteriochloroform): δ 2.90-3.30 (m, $-CH_2CH_2-$, 4H), 6.93-7.77 (m, bromophenyl, H-4, H-5, 6H), 8.53-8.73 (m, H-6, 1H).

Anal. Calcd. for $C_{14}H_{11}BrN_2$ (287.17): C, 58.55, H, 3.86; N, 9.76. Found: C, 58.36; H, 4.10, N, 9.49.

9-Bromo-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**11**).

A mixture of **9** (50 g) and polyphosphoric acid (500 g) was stirred and heated at 180° for 24 hours. The reaction mixture was cooled to 100° and poured into water (3 ℓ) with stirring. After one hour, the mixture was made alkaline by the addition of 40% sodium hydroxide solution. The resulting tan solid was filtered, washed with water, and air-dried, yield 27.2 g. This material was stirred with chloroform (800 ml) for two hours and refiltered. Evaporation of the chloroform filtrate gave 22.6 g of solid that was triturated with benzene. The white solid that resulted was filtered, washed with a little fresh benzene and dried to give 19.8 g, mp 148-151°.

Anal. Calcd. for $C_{14}H_{10}BrNO$ (288.15): C, 58.35; H, 3.50; N, 4.86. Found: C, 58.29; H, 3.66; N, 4.95.

1-Methyl-4-hydroxy-4(9-bromo-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]-pyridin-11-yl)piperidine (**13**).

From the addition of **11** (28.2 g, 0.098 mole) in THF (400 ml) to a solution of 1-methyl-4-piperidylmagnesium chloride in THF (800 ml, 0.18*M*, 0.14 mole) there was obtained 18.2 g of crude product after work-up with saturated ammonium chloride. Recrystallization from aqueous acetonitrile gave 11.8 g, mp 171-175.5° (mp 172-174° [7]).

1-Methyl-4-(9-bromo-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**14**).

A mixture of the carbinol **13** and 85% sulfuric acid (60 ml) was warmed on the steam bath with stirring for 24 hours. The cooled reaction mixture was worked-up as described by Villani to give 9.1 g, mp 121-124.5° (mp 120-122° [7]).

Essentially no dehydration was detected (tlc) when the reaction mixture was allowed to stir at room temperature for up to 24 hours.

9-Bromobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**12**).

A mixture of **11** (20 g), selenium dioxide (13 g) and pyridine (50 ml) was heated under reflux for 18 hours. The reaction mixture was filtered while hot (Supercell) and the filter was washed with warm ethanol (300 ml). The combined filtrates were evaporated to dryness and the residue was stirred with 3*N* hydrochloric acid (600 ml). The resulting solid was collected and stirred with a mixture of water (300 ml) and concentrated ammonium hydroxide (100 ml). After an additional hour the beige solid was filtered, washed with water and dried, yield 17.5 g, mp 165-168.5°. Recrystallization from acetonitrile or butyl chloride gave material of mp 168-171°.

Anal. Calcd. for $C_{14}H_8BrNO$ (286.13): C, 58.76; H, 2.82; N, 4.90. Found: C, 58.21; H, 2.83; N, 4.96.

1-Methyl-4-hydroxy-4-(9-bromobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-piperidine (**16**).

A solution of **12** (22 g) in THF (450 ml) was added to a stirred solution of 1-methyl-4-piperidyl magnesium chloride in THF (500 ml, 0.3*M*, 0.15 mole). When addition was complete the mixture was heated to reflux for four hours. Ammonium chloride solution (300 ml, 10%) was added and the layers separated. The aqueous phase was extracted with THF (3 × 150 ml), and the combined organic extracts were washed with saturated

sodium chloride solution (2 × 500 ml) and dried (sodium sulfate). After removal of the filtered solvent by evaporation, the residual oil (28.7 g) was triturated with acetonitrile to give 20.1 g of yellow-brown solid, mp 175-185°.

1-Methyl-4-(9-bromobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)piperidine (**17**).

A mixture of the crude carbinol **16** (11.8 g) and 85% sulfuric acid (55 ml) was heated on the steam bath for 24 hours. The cooled reaction mixture was mixed with ice (300 g), and the resulting solution was made alkaline by the addition of 40% sodium hydroxide solution. The aqueous mixture was extracted with ether (5 × 20 ml) and the combined extracts were washed (water, saturated sodium chloride solution) and dried (sodium sulfate). Removal of the solvent *in vacuo* gave a yellow solid, 5.3 g, mp 159-161.5°. Recrystallization from hexane produced no change in mp.

Anal. Calcd. for $C_{20}H_{19}BrN_2$ (367.29): C, 65.40; H, 5.21; N, 7.63. Found: C, 65.52; H, 5.37; N, 7.62.

1-Methyl-4-(5,6-dihydro-9-trifluoromethylthiobenzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-ylidene)piperidine (**15a**).

A mixture of **14** (9.1 g, 0.025 mole), bis(trifluoromethylthio)mercury (39 g, 0.097 mole), copper dust (18 g, electrolytic) and hexamethylphosphoric triamide (150 ml) was heated to 145-150° (internal temperature) for 20 hours. The resulting mixture was cooled slightly and added to concentrated ammonium hydroxide (1500 ml), followed by the addition of ether (1500 ml). After stirring for three hours, the layers were separated, and the aqueous layer was extracted with ether (4 × 300 ml). The combined extracts were washed with water until the washings were neutral, followed by saturated sodium chloride solution and dried (sodium sulfate). Removal of the ether *in vacuo* gave 8.1 g of reddish-orange solid. Recrystallization from petroleum ether (30-60°) gave 4.5 g, off-white needles, mp 122-124°. An additional 1.3 g, mp 119-122° was recovered from the filtrate.

Anal. Calcd. for $C_{21}H_{21}F_3N_2S$ (390.47): C, 64.59; H, 5.42; N, 7.18. Found: C, 64.64; H, 5.52; N, 7.08.

A small sample of **15a** was converted to a fumarate salt, mp 200-201° (acetone); F-nmr (DMSO-d_6): δ 41.9 (s, -SCF_3).

1-Methyl-4-(9-cyano-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**15b**).

A mixture of **14** (7.39 g, 0.02 mole), cuprous cyanide (10.75 g, 0.12 mole) and DMF (50 ml) was stirred and heated to 165-170° for 30 hours. The cooled reaction mixture was diluted with a combination of saturated ammonium hydroxide (200 ml) and benzene (200 ml). The layers were separated and the aqueous phase was extracted with benzene (4 × 200 ml). The combined organic extracts were washed with dilute ammonium hydroxide (500 ml), water (500 ml), saturated sodium chloride solution (3 × 500 ml) and dried (sodium sulfate). After removal of the solvent, the residual oil (5.1 g) was chromatographed over alumina (100 g, acid-washed) using chloroform as the eluant. The fractions containing the desired material were evaporated and the residual oil was triturated with acetonitrile to give 2.85 g, mp 155-157°. An additional 0.25 g, mp 148-153° was recovered from the filtrate. Recrystallization from acetonitrile raised the mp to 157-159°.

Anal. Calcd. for $C_{21}H_{21}N_3$ (315.40): C, 79.97; H, 6.71; N, 13.32. Found: C, 80.08; H, 6.62; N, 13.54.

1-Methyl-4-(9-carboxy-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**15c**).

The nitrile **15b** (1.5 g) in 6*N* hydrochloric acid (30 ml) was heated to reflux for 20 hours. The solvent was removed *in vacuo* and the residue was taken up in isopropyl alcohol (50 ml). A small amount of insoluble material was filtered and the filtrate was evaporated to dryness. The residue was dried under high vacuum to remove the last traces of water, then dissolved in isopropyl alcohol (25 ml). Pyridine (0.5 ml) was added and the solution was stirred overnight. The pink-tinged solid was filtered, washed well with acetone and air-dried to give 1.2 g, mp 300-303° dec. Recrystallization from ethanol-ether provided material with mp 307-309° dec, when the sample was inserted at 270°. The mp was dependent upon the insertion temperature and the rate of heating.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$·HCl (370.87): C, 68.00; H, 6.25; N, 7.56; Cl, 9.56. Found: C, 67.65; H, 6.49; N, 7.38; Cl, 9.72.

1-Methyl-4-(9-trifluoromethylthiobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**18a**).

A mixture of **17** (1.85 g), bis(trifluoromethylthio)mercury (6.9 g), copper dust (3.5 g, electrolytic) and hexamethylphosphoric triamide (25 ml) was heated to 140° (bath temperature) for 12 hours. The resulting mixture was cooled slightly and diluted with concentrated ammonium hydroxide (250 ml). Ether (300 ml) was added and the mixture was stirred for a few hours. The layers were separated and the aqueous phase was extracted with 3 × 100 ml portions of ether. The combined organic extracts were washed with water until the washings were neutral, followed by saturated sodium chloride solution, and dried (sodium sulfate). The solvent was removed *in vacuo* and the residual solid (1.90 g) was recrystallized from 1-chlorobutane to give 1.2 g, pale yellow powder, mp 140-143.5°. Further recrystallization from 1-chlorobutane gave the analytical sample, mp 143-144°; F-nmr (deuteriochloroform): δ 42.2 (-SCF_3).

Anal. Calcd. for $C_{21}H_{19}F_3N_2S$ (388.45): C, 64.93; H, 4.93; N, 7.21. Found: C, 64.97; H, 5.13; N, 7.36.

1-Methyl-4-(9-cyanobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**18b**).

A mixture of **17** (5.5 g, 0.015 mole), cuprous cyanide (8.07 g, 0.09 mole) and DMF (75 ml) was heated at 165° (bath temperature) for 28 hours. The mixture was cooled to room temperature and diluted with a mixture of saturated sodium cyanide solution (200 ml) and benzene (200 ml). After stirring for an hour the layers were separated and the aqueous layer was extracted with benzene (5 × 150 ml). The combined organic extracts were washed with water (2 × 500 ml), saturated sodium chloride solution (2 × 400 ml) and dried (sodium sulfate). After filtration of the drying agent, the solvent was removed under reduced pressure to give 5.6 g brown solid, mp 160-180°. Several recrystallizations from acetonitrile provided material with mp 187-189°.

Anal. Calcd. for $C_{21}H_{19}N_3$ (313.38): C, 80.48; H, 6.11; N, 13.41. Found: C, 80.36; H, 6.31; N, 13.50.

1-Methyl-4-(9-carboxybenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**18c**).

A mixture of **18b** (1 g) and 6*N* hydrochloric acid (20 ml) was heated to reflux for 20 hours. The mixture was evaporated to dryness under reduced pressure and the residue stirred with isopropyl alcohol (30 ml). After filtration of a small amount of insoluble material, the solvent was evaporated *in vacuo* and the hygroscopic residue was dried under high vacuum. The resulting hygroscopic solid was dissolved in isopropyl alcohol (25 ml) and pyridine (0.5 ml) was added. The solid that precipitated on standing was filtered, washed with fresh isopropyl alcohol and dried, 0.80 g, mp 280.5-283°.

Anal. Calcd. for $C_{21}H_{20}N_2O_2$·HCl (368.86): C, 68.38; H, 5.74; N, 7.60; Cl, 9.61. Found: C, 68.18; H, 5.87; N, 7.42; Cl, 9.50.

Oxidation of **18b** (**19b**).

Trifluoroacetic anhydride (11.9 ml, 0.084 mole) in methylene chloride (25 ml) was added dropwise to a cold (0-5°) solution of 90% hydrogen peroxide (1.9 ml) in methylene chloride (50 ml). The reaction mixture was allowed to warm to room temperature and after 0.5 hour, a solution of **18** (4.5 g, 0.0116 mole) in methylene chloride (25 ml) was added over 0.25 hour. After stirring for 24 hours, saturated sodium bicarbonate solution (100 ml) was added dropwise and the layers separated. The aqueous layer was extracted with methylene chloride (4 × 100 ml) and the combined organic extracts were washed with sodium bicarbonate solution, saturated sodium chloride solution and dried (sodium sulfate). The drying agent was filtered and the solvent was evaporated *in vacuo* to give a tan foam.

The foam was heated to reflux with phosphorus trichloride (32 ml) in chloroform (150 ml) for 3 hours. The cooled reaction mixture was poured into a stirred mixture of ice (30 g) and water (300 ml), followed by addition of solid sodium bicarbonate until the solution was basic. The layers were separated, the aqueous layer re-extracted with chloroform and the combined organic extracts were washed (water, saturated sodium chloride solution) and dried (sodium sulfate). The residual viscous oil (4.3 g) was chromatographed over alumina (E. Merck, Activity 1), eluting with benzene-ethyl acetate mixtures, but no separation was obtained. The collected material (2.5 g) was rechromatographed over acid-washed alumina (200 g) eluting with benzene-ethyl acetate (1:1). Combined fractions containing the major component were stripped to a viscous oil (0.80 g). Trituration with petroleum ether (30-60°) produced an off-white solid (**19b**), 0.70 g, mp 180.5-182.5°. Recrystallization from 1-chlorobutane-hexane did not change the mp; F-nmr (deuteriochloroform): δ 77.4 (-SO_2CF_3); ms: (M^+/e) 436 (M^+), 340 (M-96), 324 (M-112), 303 (M-133), 96 (base peak).

Anal. Calcd. for $C_{21}H_{19}F_3N_2O_3S$ (436.45): C, 57.79; H, 4.39; N, 6.42; S, 7.35; F, 13.06. Found: C, 57.77; H, 4.46; N, 6.27; S, 7.30; F, 12.93.

Oxidation of **18a** (**19a**).

A mixture of -SCF_3 compound (4.0 g), 30% hydrogen peroxide (40 ml) and glacial acetic acid (160 ml) was stirred at room temperature for 5 days. The reaction mixture was poured into water (1.5 ℓ) and sodium carbonate (100 g) was added portionwise. The resulting mixture was saturated with sodium chloride and extracted with chloroform (1 ℓ), which was washed (saturated sodium chloride) and dried (sodium sulfate). The residue, after removal of the drying agent and solvent, was dissolved in dioxane (75 ml) and sulfur dioxide (g) was added beneath the surface of the liquid for 0.5 hour. After a further 4 hours the solvent was removed *in vacuo* and the residue was dissolved in chloroform (200 ml), washed (saturated sodium carbonate, saturated sodium chloride) and dried (sodium sulfate). Removal of the solvent *in vacuo* left 1.6 g of a reddish-orange viscous oil (**19a**); F-nmr (deuteriochloroform): δ 77.5 (-SO_2CF_3); ms: (M^+/e) 438 (M^+).

5,6-Dihydro-9-trifluoromethylthiobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**20a**).

A mixture of **11** (14.4 g, 0.05 mole), bis(trifluoromethylthio)mercury (40.2 g, 0.10 mole), copper dust (28.80 g, electrolytic) and hexamethylphosphoric triamide (125 ml) was heated in an oil bath to 145° (bath temperature). A tlc probe (fluorescent silica, benzene-ethyl acetate, 1:1, v/v) indicated the reaction was complete after 2 hours. The reaction mixture was cooled to room temperature and cautiously mixed with concentrated ammonium hydroxide (1200 ml). Ether (600 ml) was slowly added and the resulting mixture was stirred for 0.5 hour. The layers were separated and the aqueous layer was extracted with ether (3 × 500 ml). The combined organic extracts were washed (water, saturated sodium chloride) and dried (sodium sulfate). The residue (8.29 g) after removal of the drying agent and solvent was chromatographed over silica gel (200 g) using 15% ethyl acetate in benzene as the eluant. The product fractions were combined and after removal of the solvent *in vacuo* the residual oil (7.4 g) was triturated with petroleum ether to give a beige powder, 6.2 g, mp 76-81°. Recrystallization from hexane raised the mp to 82-86°; F-nmr (deuteriochloroform): δ 41.9 (-SCF_3); ms: (M^+/e), 309 (M^+), 281 (M^+-CO), 240 (M^+-CF_3), 212 (M^+-CO-CF_3), 208 (M^+-SCF_3), 180 (M^+-CO-SCF_3).

5,6-Dihydro-9-trifluoromethylsulfonylbenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**21a**).

To a solution of **20a** (5.1 g) in acetic acid (100 ml) was added 30% hydrogen peroxide (75 ml) over 0.5 hour. The oxidation was followed by F-nmr. The -SCF_3 (41.9 ppm) was converted to a 2:1 mixture of trifluoromethylsulfinyl (74.0 ppm) and trifluoromethylsulfonyl (78.3 ppm) within 2 days. After 8 days the trifluoromethylsulfinyl was barely detectable. The reaction mixture was diluted with water (1 ℓ) and made alkaline by the gradual addition of sodium bicarbonate. Extraction with chloroform (3 × 300 ml) produced a yellow waxy solid which was probably the *N*-oxide of the desired material. This solid was heated to reflux for 2 hours with phosphorus trichloride (2 ml) in chloroform (25 ml). The cooled reaction mixture was diluted with water, made alkaline by the addition of saturated sodium carbonate solution and extracted with chloroform (2 × 100 ml). The combined extracts were washed with saturated sodium chloride solution and dried (sodium sulfate). The residual oil after filtration of the drying agent and removal of the solvent was chromatographed over silica gel eluting with 20% ethyl acetate in benzene. The fractions containing the product were combined and evaporated *in vacuo* to give 1.65 g, mp 117-121°. The analytical sample was obtained from 1-chlorobutane-hexane, pale yellow needles, mp 125-126.5°.

Anal. Calcd. for $C_{15}H_{10}F_3NO_3S$ (341.31): C, 52.78; H, 2.95; N, 4.10. Found: C, 52.92; H, 3.03; N, 3.99.

1-Methyl-4-hydroxy-4(5,6-dihydro-9-trifluoromethylsulfonylbenzo[5,6]-cyclohepta[1,2-*b*]pyridine-11-yl)piperidine (**22a**).

A solution of **21a** (1.5 g, 4.4 mmoles) in THF (10 ml) was added dropwise to a 0.4*M* solution (20 ml, 8 mmoles) of 1-methyl-4-piperidylmagnesium chloride in THF. The resulting dark mixture was heated to reflux for 4 hours. The reaction mixture was cooled to room temperature, a 10% ammonium chloride solution (30 ml) was added and the layers were separated. The aqueous phase was extracted with THF (4 × 50 ml) and the extracts were combined, washed with saturated sodium chloride solution (2 × 150 ml) and dried (sodium sulfate). The viscous oily residue (1.6 g) after removal of the dried solvent was chromatographed over alumina (30 g) eluting with chloroform and the major band collected and rechromatographed over alumina (50 g) eluting with 80% benzene-20% chloroform. The fractions containing the product were combined and evaporated *in vacuo* to give 0.77 g of a viscous dark amber oil; ms: (M^+/e) 440 (M^+).

Anal. Calcd. for $C_{21}H_{23}F_3N_2O_3S$ (440.48).

1-Methyl-4-hydroxy-4(5,6-dihydro-9-trifluoromethylsulfonylbenzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**23a**).

A mixture of **22a** (0.77 g) and 85% sulfuric acid (15 ml) was heated on the steam bath with stirring for 48 hours. The cooled reaction mixture was diluted to a volume of 200 ml with water, and neutralized by the addition of sodium bicarbonate. Extraction of the aqueous solution with ether (4 × 100 ml) followed by washing the combined extracts with water, saturated sodium chloride solution and drying (sodium sulfate) gave 0.30 g of a yellow foam. Chromatography over alumina, eluting with 90% benzene-10% ethyl acetate gave 0.15 g of a viscous yellow oil that was triturated with petroleum ether (30-60°) to give a yellow solid, 0.10 g, mp 140-142°; F-nmr (deuteriochloroform): δ 77.9 (-SO_2CF_3); ms: (M^+/e), 422 (M^+).

Anal. Calcd. for $C_{21}H_{21}N_2F_3O_2S$ (422.47): C, 59.70; H, 5.01; N, 6.63; S, 7.59; F, 13.49. Found: C, 59.56; H, 5.37; N, 6.56; S, 7.72; F, 13.30.

9-Trifluoromethylthiobenz[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**20b**).

A mixture of **12** (2.86 g, 0.01 mole), bis(trifluoromethylthio)mercury (12.06 g, 0.03 mole), copper dust (5.72 g, electrolytic dust) and hexamethylphosphorictriamide (25 ml) was heated to 145° (bath temperature) for 2.5 hours. The cooled reaction mixture was diluted with concentrated ammonium hydroxide (250 ml) and chloroform (200 ml) and stirred for 0.5 hour. The layers were separated and the aqueous phase was extracted with additional chloroform (2 × 100 ml). The extracts were filtered through Supercell and washed with water until the washings were neutral, followed by saturated sodium chloride solution and dried (sodium sulfate). The solvent was filtered and removed *in vacuo* to give a red-brown oil (HMPT present). The oil was dissolved in ether (200 ml) and washed with water (10 × 100 ml), saturated sodium chloride (2 × 100 ml) and dried (magnesium sulfate). The solvent and drying agent were removed and the residue was stirred with hexane to produce a lavender solid, 2.2 g. Recrystallization from cyclohexane (Darco) gave an off-white solid, 1.7 g, mp 94.5-96.5°; F-nmr (deuteriochloroform): δ 41.3 (-SCF_3).

Anal. Calcd. for $C_{15}H_8F_3NOS$ (307.29): C, 58.63; H, 2.62; N, 4.56. Found: C, 58.75; H, 2.86; N, 4.45.

9-Trifluoromethylsulfonylbenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**21b**).

Trifluoroacetic anhydride (23.8 ml, 0.168 mole) in methylene chloride (50 ml) was added dropwise to a cold (0-5°) solution of 90% hydrogen peroxide (2.8 ml) in methylene chloride (50 ml). The solution was allowed to warm to 25° and after 0.5 hour a solution of **20b** (8.2 g) in methylene chloride (50 ml) was added dropwise over 0.25 hour. The resulting solution was stirred for 96 hours, cooled and saturated sodium bicarbonate solution (300 ml) was added dropwise. The layers were separated and the aqueous layer was extracted with additional methylene chloride (4 × 200 ml). The combined extracts were washed with saturated sodium bicarbonate solution, saturated sodium chloride solution and dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue over silica gel (200 g) eluting with 80% benzene-20% ethyl acetate gave 2.6 g, mp 158-160°; F-nmr (deuteriochloroform): δ 77.1 ($-SO_2CF_3$).

1-Methyl-4-hydroxy-4-(9-trifluoromethylsulfonylbenzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-yl)piperidine (**22b**).

A solution of **21b** (2.6 g, 7.7 mmoles) in THF (20 ml) was added dropwise to a solution (0.43*M*, 35 ml, 15 mmoles) of 1-methyl-4-piperidyl magnesium chloride. The resulting dark mixture was heated on a steam bath for 4 hours. The reaction mixture was diluted with saturated ammonium chloride solution (75 ml) and the layers were separated. The aqueous layer was extracted with additional THF (4 × 75 ml). The combined extracts were washed (sodium chloride solution) and dried (sodium sulfate). The crude residue (2.83 g) after removal of the drying agent and solvent was used directly in the next step.

1-Methyl-4-(9-trifluoromethylsulfonylbenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (**23b**).

A mixture of crude **22b** (2.83 g) and 85% sulfuric acid was heated on the steam bath for 96 hours. A tlc probe (fluorescent silica, benzene-ethyl acetate, 1:1, v/v) indicated very little reaction had occurred. The solution was heated to 100-110° (Glascol) for an additional 96 hours, during which time the carbinol gradually disappeared (tlc). The cooled reaction mixture was mixed with ice (300 g) and neutralized by the addition of sodium bicarbonate. The solution was extracted with ether (4 × 200 ml) and the combined extracts washed (water, saturated sodium chloride) and dried (sodium sulfate). After removal of the drying agent and solvent, the viscous oily residue (1.3 g) was chromatographed over alumina (150 g) eluting with 70% benzene-30% ethyl acetate to give 0.67 g of a viscous light yellow oil. Trituration of the oil with petroleum ether (30-60°) gave 0.54 g of white solid, mp 168-170°; F-nmr (deuteriochloroform): δ ($-SO_2CF_3$); ms: (M^+/e) 420 (M^+).

Anal. Calcd. for $C_{21}H_{19}F_3N_2O_2S$ (420.45): C, 59.99; H, 4.55; N, 6.66; F, 13.56; S, 7.63. Found: C, 60.10; H, 4.54; N, 6.62; F, 13.28; S, 7.36.

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