Research on Heterocyclic Compounds. XX. Synthesis of Trifluoromethyl Derivatives of Fused Imidazole Systems

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A series of heterocyclic compounds having an imidazole ring fused with another ring with a bridgehead nitrogen atom and bearing a trifluoromethyl moiety was synthesized by reaction of 3-bromo-1,1,1-trifluoroacetone with various heteroarylamines. In some cases, an intermediate compound obtained together with the required product was isolated and its structure was elucidated: *e.g.*, starting from 2-aminopyridine we have obtained 2-trifluoromethylimidazo[1,2-a]pyridine and 2-hydroxy-2-trifluoromethyl-2,3-dihydro-1*H*-imidazo [1,2-*a*]pyridinium bromide. Such results confirmed the mechanism previously proposed for this reaction.

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Nonsteroidal antiinflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds which usually share the feature of containing an acidic moiety. Another common property is to exert their characteristic antiinflammatory, analgesic and antipyretic activities inhibiting the biosynthesis and release of prostaglandins. NSAIDs share also the tendency to produce gastric ulceration.

Some nonacidic NSAIDs containing different heterocyclic rings were more or less recently discovered, particularly trifluoromethyl derivatives, *e.g.*, flumizole [1], NC 1140 [2], BW 755C [3], and tiflamizole [4] (**1-4**, Chart 1).

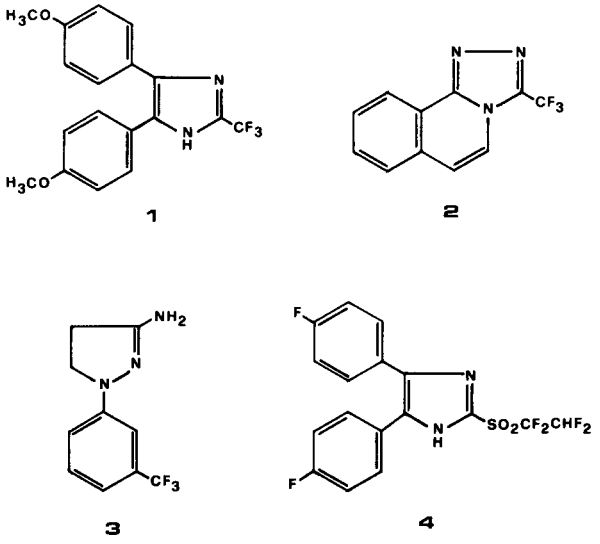
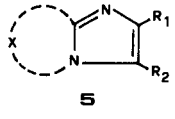


CHART 1

These and other compounds represent a second NSAIDs class with lower tendency to produce gastric mucosal damage, to all appearance in consequence of their lack of acidic character.

Such considerations prompted us to study the possibility to prepare some nonacidic analogs of the antiinflammatory heteroaryl-carboxylic and -acetic acids which were the subject of our previous researches [5]. These acidic compounds were all related to the structural model **5**, in which X represents a heterocyclic ring (pyridine, pyrazine, thiazole *etc.*) fused with the imidazole ring bearing an acidic moiety (R_1 or R_2). A number of such compounds showed remarkable antiinflammatory activity; studies on their structure-activity relationships are in progress [6].

In this context we have considered interesting to prepare some compounds related to the same structural model, but bearing a $-CF_3$ group instead of an acidic function, in order to study the pharmacological action of such compounds and then to compare their activity with that of their acidic analogs.



A series of trifluoromethyl derivatives related to the above mentioned structure **5** was prepared by a general synthetic method (Chart 2): the proper heteroarylamine

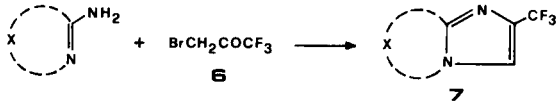


CHART 2

was reacted in anhydrous ethanol with 3-bromo-1,1,1-trifluoroacetone **6** [7] to afford the corresponding product **7** bearing a trifluoromethyl moiety on to the imidazole ring. Compounds **7a-j** (see Chart 3) were prepared by this method, except compound **7h** which was obtained from **7g** *via* reductive dehalogenation. Compounds **7a-d** were previously reported by Rackham [8] with no data about preparation.

The reaction of 2-aminopyridine with **6** was carried out at room temperature in anhydrous ethanol and gave an abundant precipitate; the required 2-trifluoromethylimid-

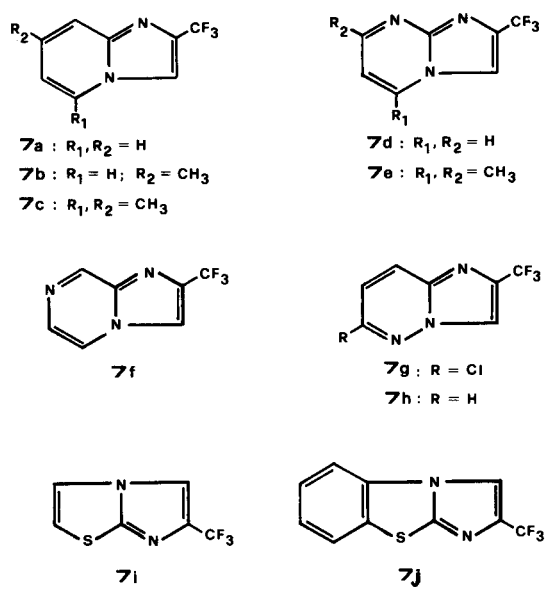


CHART 3

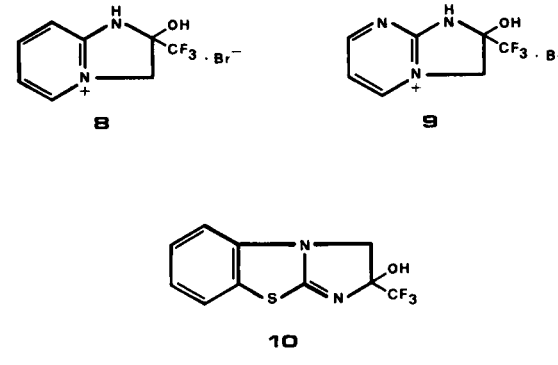


CHART 4

azo[1,2-*a*]pyridine **7a** was obtained in low yield from the filtrate. The structure **8** (see Chart 4) was assigned to the product obtained as a precipitate, which resulted very soluble in water. Such structure is closely similar to that of a not isolable intermediate in the reaction mechanism proposed by Hand and Paudler [9] for similar reactions of 2-aminopyridine with α-haloacetophenones.

In the case of the reaction with 3-bromo-1,1,1-trifluoroacetone **6**, the low solubility in ethanol caused the precipitation of the most part of the intermediate, whereas the small amount which remained in solution was transformed into the final product **7a**. The structure assigned to **7a** was essentially supported by the nmr spectrum which was consistent with literature nmr data for imidazo[1,2-*a*] pyridines [9,10], whereas the structural assignment of compound **8** was based on (a) elemental analytical data, (b) the ir spectrum which showed no bands in the 1660-1800 cm^{-1} region (lack of C = O group), and (c) the nmr spectrum which showed a couple of doublets with a coupling constant J = 16 Hz in the 5 δ region (two geminal protons in position 3) and two broad singlets at 8.72 and 9.58 δ (OH and NH) which disappeared after treatment with deuterium oxide. The location of the NH group in position 1 is based on the work of Paudler and Blewitt [11] which showed that protonation of imidazo[1,2-*a*]pyridines occurs at this position. Furthermore, a small amount of compound **8**

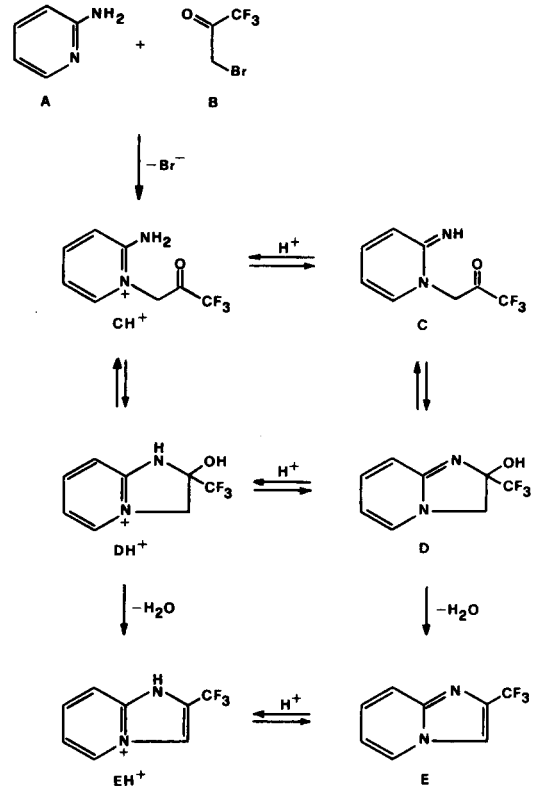


CHART 5

dissolved in the necessary large volume of ethanol and refluxed for five hours was completely converted into **7a**. It has to be pointed out that a 2,3-dihydroimidazo[1,2-*a*] pyridinium bromide, similar to our compound **8**, was also isolated by Bradsher *et al.* [12] as an intermediate of an analogous reaction.

The reaction of 2-aminopyrimidine with **6** gave similar results: a water-soluble product precipitated abundantly during the reaction and the required product **7d** was obtained in low yield from the alcoholic filtrate. On the basis of experimental data very similar to those found in the case of 2-aminopyridine, structure **9** was assigned to the precipitate (see the experimental section for details). This product was completely converted into **7d** by refluxing for five hours in ethanol solution.

When 2-aminobenzothiazole was reacted with **6**, no precipitate was formed, but a product with a structure similar to compounds **8** and **9** was isolated from the reacted solution after the usual treatment with sodium bicarbonate, namely the free base **10**, together with the required product **7j**. Compound **10** showed the same spectral features of compounds **8** and **9**, namely the absence of the C = O band in the ir spectrum and a couple of doublets with a large J in the δ 4 region, but only one broad singlet (δ 7.66, -OH). It is evident that **10** was both soluble enough in ethanol in form of hydrobromide to remain in solution and stable enough as free base to be isolated, even if in low yield, after six hours at reflux and the subsequent working up.

It has to be pointed out that all other heteroarylamines selected for reaction with **6** (*i.e.*, 2-amino-4-methyl- and 2-amino-4,6-dimethylpyridine, 2-amino-4,6-dimethylpyrimidine, 2-aminopyrazine, 3-amino-6-chloropyridazine, and 2-aminothiazole) gave only the required products, namely **7b** and **7c**, **7e**, **7f**, **7g**, and **7i**, respectively. In all these cases it was never possible to isolate any different product in appreciable amount.

All new compounds showed nmr and ir spectra coherent with the structures assigned and in good accordance with available literature spectral data for imidazo[1,2-*a*] pyridines [10], imidazo[1,2-*a*]pyrimidines [13], imidazo [1,2-*a*]pyrazines [13b,14], imidazo[1,2-*b*]pyridazines [15], imidazo[2,1-*b*]thiazoles [16], and imidazo[2,1-*b*]benzothiazoles [17], respectively.

The isolation of intermediate compounds **8-10** confirmed the reaction mechanism proposed by Hand and Paudler [9]: such mechanism applied to the case of 2-aminopyridine is illustrated in Chart 5. The mechanism involves the formation of two intermediates, **C** and **D**, which are in equilibrium with each other, and then the slower formation of the required product **E**. Since hydrogen bromide is generated during the reaction, the various bases (**A**, **C**, **D**, and **E**) are in equilibrium with the protonated forms, which can precipitate as hydrobromides in case of low solubility in ethanol.

EXPERIMENTAL

All compounds were designated as pure when they showed a single spot on thin-layer chromatograpy on precoated silica gel 60 F254 plates from Merck with chloroform alone or chloroform-methanol mixtures as solvent, when detected by either uv light or treatment with iodine vapors. Column chromatography was done on silica gel 60 Merck (70-230 mesh). Melting points were determined with a Kofler hot stage microscope and are uncorrected. The elemental analyses were performed by a Perkin-Elmer Elemental Analyzer mod. 240. Infrared spectra were run as potassium bromide disks on a Perkin-Elmer 177 spectrophotometer. The ^{1}H nmr spectra were recorded with a Bruker WM250 spectrometer with chemical shift values reported in δ (parts per million) relative to an internal standard (tetramethylsilane).

2-Trifluoromethylimidazo[1,2-*a*]pyridine (**7a**).

To a stirred solution of 9.4 g (0.1 mole) of 2-aminopyridine in 125 ml of anhydrous ethanol, 19.1 g (0.1 mole) of 3-bromo-1,1,1-trifluoroacetone were added at room temperature, obtaining a precipitate. The mixture was gently heated on a water bath for 30 minutes and then the precipitate was separated by filtration. The filtrate was evaporated to dryness in vacuo; the residue was crystallized from *n*-hexane to afford 1.5 g (8%) of colorless crystals, mp 93-95°; nmr (hexadeuterodimethyl sulfoxide): δ 7.80 (split t, H-6, 1H), 8.17 (split t, H-7, 1H), 8.41 (split d, H-8, 1H), 9.26 (s, H-3, 1H), 9.33 (split d, H-5, 1H); $J_{5,6}$ = 6 Hz, $J_{6,7}$ = 6.5 Hz, $J_{6,8}$ = 2 Hz, $J_{7,8}$ = 9 Hz.

Anal. Calcd. for $C_8H_5F_3N_2$: C, 51.6; H, 2.7; F, 30.6; N, 15.0. Found: C, 51.3; H, 2.8; F, 30.2; N, 15.2.

2-Hydroxy-2-trifluoromethyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-4-ium Bromide (**8**).

The precipitate obtained as described in the above procedure was crystallized from ethanol to obtain 17 g (60%) of colorless crystals, mp >270° dec; nmr (hexadeuterodimethyl sulfoxide): δ 4.86 and 5.14 (2 doublets, 2H in position 3, J = 16 Hz), 7.22 (m, H-6 and H-8, 2H), 8.17 (split t, H-7, 1H), 8.39 (split d, H-5, 1H), 8.72 and 9.58 (2 broad singlets, 2-OH and 1-NH, 1H each).

Anal. Calcd. for $C_8H_8BrF_3N_2O$: C, 33.7; H, 2.8; F, 20.0; N, 9.8. Found: C, 34.0; H, 2.9; F, 19.7; N, 9.5.

7-Methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (**7b**).

To a stirred solution of 10.8 g (0.1 mole) of 2-amino-4-methylpyridine in 130 ml of anhydrous ethanol, 19.1 g (0.1 mole) of **6** were added at room temperature. No precipitate was formed. The solution was refluxed for 5 hours and then evaporated to dryness *in vacuo*. The residue was stirred with hot *n*-hexane and filtered. Colorless crystals crystallized out from the filtrate (1.5 g, 7.5%), mp 144-146°; nmr (deuterochloroform): δ 2.37 (s, CH_3, 3H), 6.73 (double d, H-6, 1H), 7.40 (d, H-8, 1H), 7.83 (s, H-3, 1H), 8.06 (d, H-5, 1H); $J_{5,6}$ = 6.5 Hz, $J_{6,8}$ = 1.5 Hz.

Anal. Calcd. for $C_9H_7F_3N_2$: C, 54.0; H, 3.5; F, 28.5; N, 14.0. Found: C, 54.2; H, 3.5; F, 28.2; N, 13.9.

5,7-Dimethyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (**7c**).

A solution of 4.9 g (0.04 mole) of 2-amino-4,6-dimethylpyridine and 7.6 g (0.04 mole) of **6** in 80 ml of anhydrous ethanol was refluxed for 2 hours and then evaporated to dryness *in vacuo*. The residue was stirred with sodium bicarbonate saturated solution and extracted with chloroform. The organic layer was washed with water, dried on anhydrous sodium sulfate and evaporated *in vacuo* to provide a solid which was crystallyzed from *n*-hexane to yield 1.3 g (15%) of colorless crystals, mp 110-112°; nmr (deuterochloroform): δ 2.28 and 2.45 (2 singlets, 5- and 7-CH_3, 3H each), 6.46 (s, H-6, 1H), 7.18 (s, H-8, 1H), 7.58 (s, H-3, 1H).

Anal. Calcd. for $C_{10}H_9F_3N_2$: C, 56.1; H, 4.2; F, 26.6; N, 13.1. Found: C, 55.9; H, 4.3; F, 26.4; N, 13.0.

2-Trifluoromethylimidazo[1,2-*a*]pyrimidine (**7d**).

A solution of 5.7 g (0.06 mole) of 2-aminopyrimidine and 11.4 g (0.06 mole) of **6** in 90 ml of anhydrous ethanol was refluxed for 4 hours. A solid product precipitated during the reaction: this product was collected by filtration and washed with ethanol. The combined filtrate was evaporated to dryness *in vacuo*; the residue was treated with sodium bicarbonate saturated solution and extracted with chloroform. The organic layer was washed with water, dried on anhydrous sodium sulfate and concentrated *in vacuo* to a small volume and then chromatographed on a silica gel column eluting with chloroform. The product obtained was crystallized from *n*-hexane to afford 0.55 g (4.9%) of colorless crystals, mp 183-185°; nmr (hexadeuterodimethyl sulfoxide): δ 8.00 (double d, H-6, 1H), 9.27 (s, H-3, 1H), 9.51 (double d, H-7, 1H), 9.81 (double d, H-5, 1H); $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz, $J_{6,7}$ = 4 Hz.

Anal. Calcd. for $C_7H_4F_3N_3$: C, 44.9; H, 2.1; F, 30.4; N, 22.4. Found: C, 45.0; H, 2.2; F, 30.1; N, 22.4.

2-Hydroxy-2-trifluoromethyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium Bromide (**9**).

The side product obtained as a precipitate in the preparation of compound **7d** (see the above procedure) was recrystallized from ethanol to yield 8 g (46%) of colorless crystals, mp >270° dec; nmr (hexadeuterodimethyl sulfoxide): δ 4.94 and 5.10 (2 doublets, 2H in position 3, J = 14.5 Hz), 7.41 (double d, H-6, 1H), 8.97 (double d, H-5, 1H), 9.03 (double d, H-7, 1H), 8.68 and 11.75 (2 broad singlets, 2-OH and 1-NH, 1H each); $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 2 Hz, $J_{6,7}$ = 4.2 Hz.

Anal. Calcd. for $C_7H_7BrF_3N_3O$: C, 29.4; H, 2.5; F, 19.9; N, 14.7. Found: C, 29.6; H, 2.6; F, 19.7; N, 14.6.

5,7-Dimethyl-2-trifluoromethylimidazo[1,2-*a*]pyrimidine (**7e**).

A solution of 7.4 g (0.06 mole) of 2-amino-4,6-dimethylpyrimidine and 11.4 g (0.06 mole) of **6** in 100 ml of anhydrous ethanol was refluxed for 5 hours and then evaporated to dryness *in vacuo*. The residue was treated with sodium bicarbonate saturated solution and extracted with chloroform. After washing with water and drying on anhydrous sodium sulfate, the organic layer was concentrated to a small volume and then chromatographed on a silica gel column eluting first with *n*-hexane and then with *n*-hexane-chloroform mixtures containing increasing amounts of chloroform. The required product obtained by this procedure was crystallized from *n*-hexane to give 0.7 g (5.4 %) of colorless crystals, mp 232-235°; nmr (hexadeuterodimethyl sulfoxide): δ 2.67 and 2.81 (2 singlets, 5- and 7-CH_3, 3H each), 7.15 (s, H-6, 1H), 8.55 (s, H-3, 1H).

Anal. Calcd. for $C_9H_8F_3N_3$: C, 50.2; H, 3.7; F, 26.5; N, 19.5. Found: C, 50.0; H, 3.9; F, 26.2; N, 19.3.

2-Trifluoromethylimidazo[1,2-*a*]pyrazine (**7f**).

A solution of 4.8 g (0.05 mole) of 2-aminopyrazine and 9.5 g (0.05 mole) of **6** in 80 ml of anhydrous ethanol was refluxed for 5 hours and then worked up in a manner identical to that described for **7e** to afford the required compound in form of colorless crystals (0.8 g, 8.8%), mp 165-166°; nmr (deuterotrifluoroacetic acid): δ 8.26 (d, H-6, 1H), 8.78 (s, H-3, 1H), 9.10 (double d, H-5, 1H), 10.02 (d, H-8, 1H); $J_{5,6}$ = 4.5 Hz, $J_{5,8}$ = 1 Hz.

Anal. Calcd. for $C_7H_4F_3N_3$: C, 44.9; H, 2.1; F, 30.4; N, 22.4. Found: C, 44.7; H, 2.1; F, 30.3; N, 22.5.

6-Chloro-2-trifluoromethylimidazo[1,2-*b*]pyridazine (**7g**).

A solution of 6.5 g (0.05 mole) of 3-amino-6-chloropyridazine and 9.5 g (0.05 mole) of **6** in 100 ml of anhydrous ethanol was refluxed for 5 hours and then worked up as described for **7c**, with the only difference that the crude product was crystallized from carbon tetrachloride to yield 1.8 g (16%) of colorless crystals, mp 129-131°; nmr (hexadeuterodimethyl sulfoxide): δ 7.68 (d, H-7, 1H), 8.48 (d, H-8, 1H), 9.15 (s, H-3, 1H); $J_{7,8}$ = 9.8 Hz.

Anal. Calcd. for $C_7H_3ClF_3N_3$: C, 37.9; H, 1.4; F, 25.7; N, 19.0. Found: C, 38.1; H, 1.5; F, 25.4; N, 19.0.

2-Trifluoromethylimidazo[1,2-*b*]pyridazine (**7h**).

A solution of 2.2 g (0.01 mole) of **7g** and sodium hydroxide (0.4 g) in 30 ml of ethanol was added with 0.5 g of 5% palladium on activated charcoal and stirred with hydrogen (2.5 atm) at room temperature. After cessation of hydrogen uptake, the catalyst was removed by filtration and the solvent was evaporated. The residual solid was extracted with carbon tetrachloride; the extract was concentrated *in vacuo* to a small volume and chromatographed on a silica gel column using first *n*-hexane and then *n*-hexane-diethyl ether mixtures with increasing percentages of the latter solvent. The purified product was crystallized from *n*-hexane to afford 0.8 g (43%) of colorless crystals, mp 102-104°; nmr (hexadeuterodimethyl sulfoxide): δ 7.53 (double d, H-7, 1H), 8.38 (double d, H-8, 1H), 8.80 (double d, H-6, 1H), 9.08 (s, H-3, 1H); $J_{6,7}$ = 4.5 Hz, $J_{6,8}$ = 1.3 Hz, $J_{7,8}$ = 9.6 Hz.

Anal. Calcd. for $C_7H_4F_3N_3$: C, 44.9; H, 2.1; F, 30.4; N, 22.4. Found: C, 45.1; H, 2.2; F, 30.3; N, 22.2.

6-Trifluoromethylimidazo[2,1-*b*]thiazole (**7i**).

This product was prepared in the same manner described for **7e**, starting from 7 g (0.07 mole) of 2-aminothiazole and 13.4 g (0.07 mole) of **6** in 110 ml of anhydrous ethanol. Crystallization from *n*-hexane gave 1.2 g (8.9%) of colorless crystals, mp 68-70°; nmr (deuterochloroform): δ 6.91 (d, H-2, 1H), 7.42 (d, H-3, 1H), 7.72 (s, H-5, 1H); $J_{2,3}$ = 4.5 Hz.

Anal. Calcd. for $C_6H_3F_3N_2S$: C, 37.5; H, 1.6; F, 29.6; N, 14.6. Found: C, 37.2; H, 1.5; F, 29.4; N, 14.7.

2-Trifluoromethylimidazo[2,1-*b*]benzothiazole (**7j**).

A solution of 7.5 g (0.05 mole) of 2-aminobenzothiazole and 9.5 g (0.05 mole) of **6** in 100 ml of anhydrous ethanol was refluxed for 6 hours. After removal of the solvent, the residue was dissolved in sodium bicarbonate saturated solution and extracted with chloroform. The organic layer was washed with water, dried on anhydrous sodium sulfate, concentrated to a small volume and then chromatographed on a silica gel column eluting first with *n*-hexane and then with *n*-hexane-chloroform mixtures containing increasing amounts of chloroform: the required product **7j** was eluted first, and then another compound was obtained (**10**). Compound **7j** was crystallized from *n*-hexane to give 2.2 g (18%) of colorless crystals, mp 132-134°; nmr (deuterochloroform): δ 6.95-7.50 (series of multiplets, aromatic protons, 4H), 7.74 (s, H-3, 1H).

Anal. Calcd. $C_{10}H_5F_3N_2S$: C, 49.6; H, 2.1; F, 23.5; N, 11.5. Found: C, 49.3; H, 2.2; F, 23.3; N, 11.6.

2-Hydroxy-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]benzothiazole (**10**).

The second product eluted from the chromatographic column mentioned in the above procedure was crystallized from a *n*-hexane-carbon tetrachloride mixture to give 2.5 g (19%) of colorless crystals, mp 199-201°; nmr (hexadeuterodimethyl sulfoxide): δ 4.05 and 4.25 (2 doublets, 2H in position 3, J = 12 Hz), 7.18, 7.41, and 7.74 (3 multiplets, aromatic protons, 4H), 7.66 (broad singlet, 2-OH, 1H).

Anal. Calcd. for $C_{10}H_7F_3N_2OS$: C, 46.1; H, 2.7; F, 21.9; N, 10.8. Found: C, 46.0; H, 2.7; F, 21.6; N, 10.7.

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