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Studies on Organic Fluorine Compounds. XIV.[1] Syntheses and Reactions of (Trifluoromethyl)indoles[2]

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To compare the reactivity of (trifluoromethyl)indoles with that of (trifluoromethyl)quinolines, 2- and 3-(trifluoromethyl)indoles (**12** and **13**) were synthesized from 3- and 4-(trifluoromethyl)quinoline in four steps: N-oxidation, oxidative cyanation using potassium cyanide and potassium ferricyanide, photomigration reaction to benzoxazepine derivatives, and recyclization with hydrogen chloride to indoles. Reactions of **12** and **13** with nucleophiles (sodium ethoxide, lithium aluminum hydride, sodium borohydride, and sodium amide) were examined, and **12** and **13** were found to undergo SN1-type reaction and the trifluoromethyl group in **13** was more reactive than that in **12**. These results were discussed.

A trifluoromethyl group on an aromatic ring is generally a very stable substituent,[3] and there has been little study of the reactions of the trifluoromethyl group on the heterocyclic ring. In previous papers[4] we have reported a study of the reactivity of the trifluoromethyl group on the quinoline ring with nucleophilic reagents and found three types of reactions: SN2 substitution of fluoride, elimination of fluoride, and displacement of the trifluoromethyl carbanion. Typical examples are shown in Scheme I.

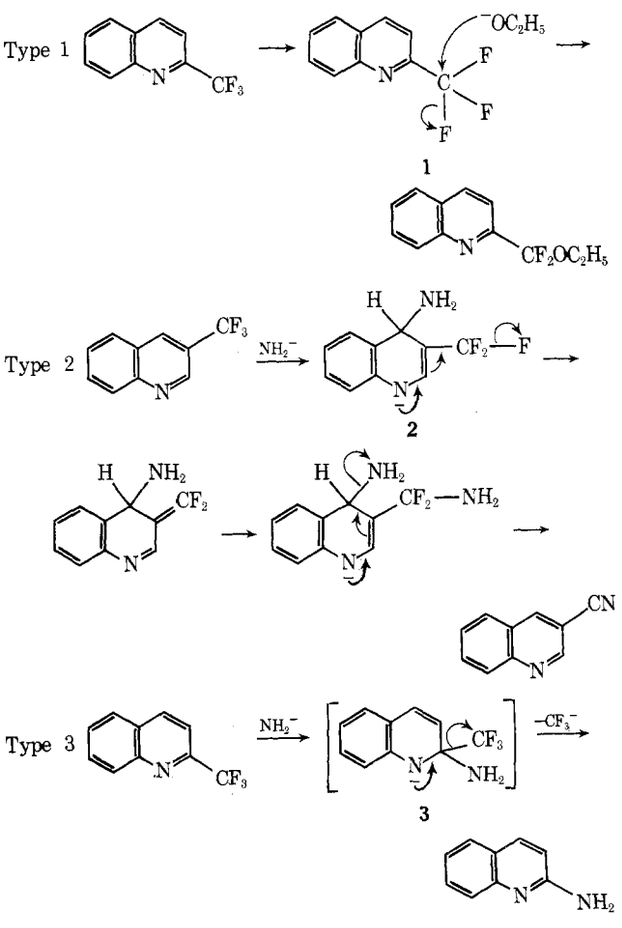
Since the trifluoromethyl group on the π-deficient quinoline ring shows unusual reactivity to nucleophilic reagents, it was of interest to examine the reactivity of this group on the π-electron excess indole ring. Indoles with a trifluoromethyl group on the pyrrole ring have not been reported to date. We have devised a synthetic route to such indoles from (trifluoromethyl)quinoline by the series of reactions shown in Scheme II.

In this method, 3- or 4-(trifluoromethyl)quinoline (**4** or **5**), obtained with sulfur tetrafluoride[5] or copper powder–trifluoromethyl iodide,[6] was converted into its *N*-oxide (**6** or **7**) by acetic acid–hydrogen peroxide.[7] A cyano group was introduced into the 2 position of **6** or **7** with retention of the *N*-oxide group by oxidative cyanation with potassium ferricyanide and potassium cyanide.[8] The resultant compound (**8** or **9**) was photoirradiated in an aprotic solvent to produce a benzoxazepine derivative (**10** or **11**), and the corresponding 2- or 3-(trifluoromethyl)indole (**12** or **13**) was successfully synthesized by ring opening and then closure with dry hydrogen chloride gas in methanol. When photoirradiation was carried out in methanol, the *N*-methoxycarbonylindole derivative (**14** or **15**) was obtained as a by-product. However, hydrolysis of **14** (or **15**) to **12** (or **13**) was unsuccessful; this may be due to the carbamate group of **14** (or **15**), which was stabilized by the electronic effect of the indole ring, and to the fact that indole itself is unstable to acids.

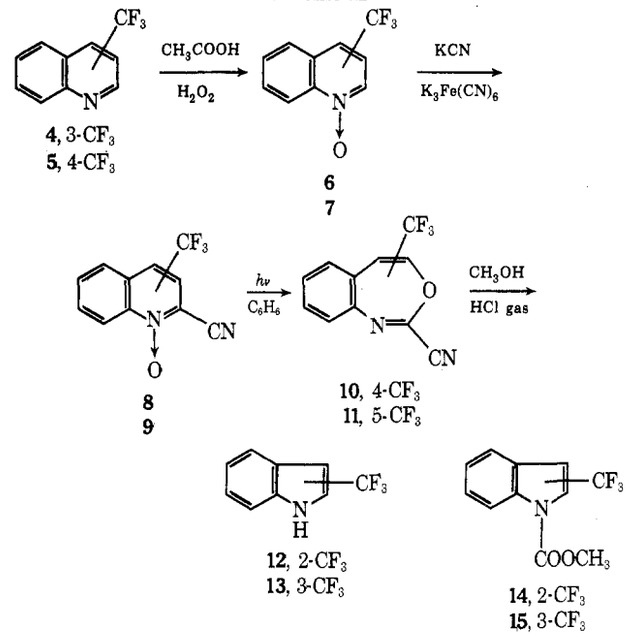
Next, we examined the reaction of **12** or **13** with nucleophilic reagents. We used sodium ethoxide and sodium amide; we also used metal hydrides to examine the reduction, since they attack as the hydride anion. These results are shown in Scheme III.

The fact that benzotrifluoride was recovered in these reaction conditions shows that susceptibility of the trifluoromethyl group to nucleophilic attack is increased by the electronic effect of the indole ring. This suggests that the carbon–fluorine bond in the trifluoromethyl group is cleaved in SN1-like manner. Further investigation of the results from **12** and **13** shows a considerable difference in their reactivity. Both compounds undergo alcoholysis when refluxed with sodium ethoxide in ethanol. With the

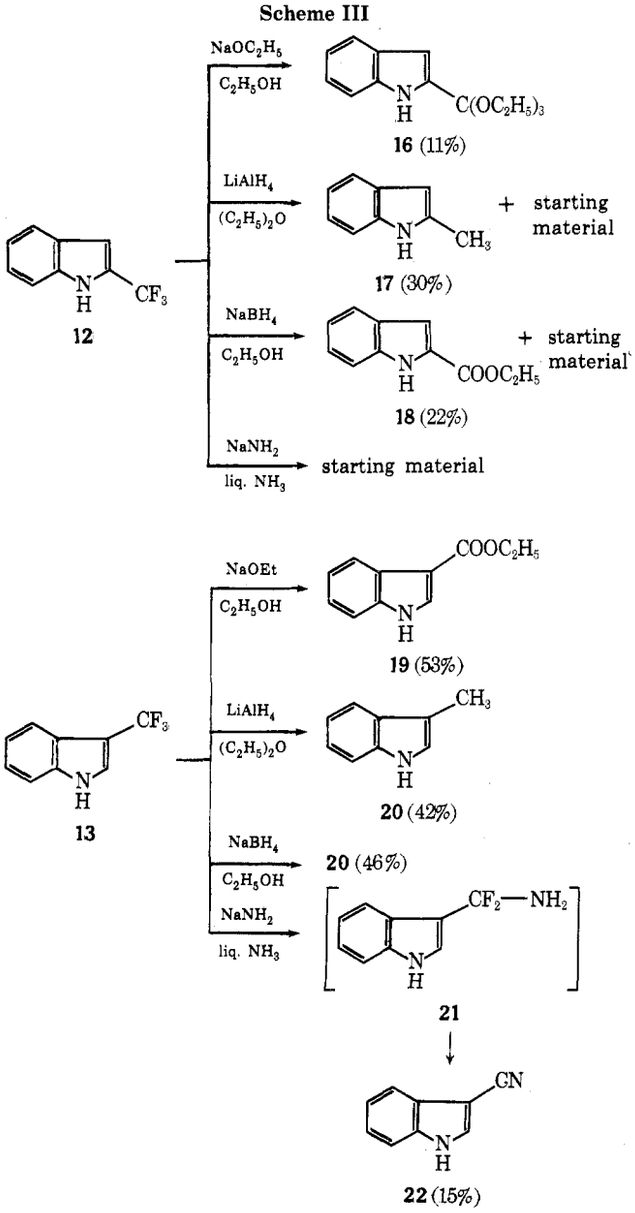
Scheme I



Scheme II



Scheme III



β-trifluoromethyl compound (13), the ortho ester, which should have been produced in the first step, was partially hydrolyzed to an ester (19). This may have been due to the higher electron density at the β position than at the α position in the indole ring. When refluxed with lithium aluminum hydride in ether, 13 easily gave skatole (20), while 12 required a much longer reaction time than 13 and a considerable amount of the starting material was recovered even then. The greater reactivity of 13 became more apparent in the reaction with sodium borohydride. When refluxed with sodium borohydride in ethanol, 13 gave 20, while most of 12 was recovered with an ester (18) as a by-product in 22% yield.

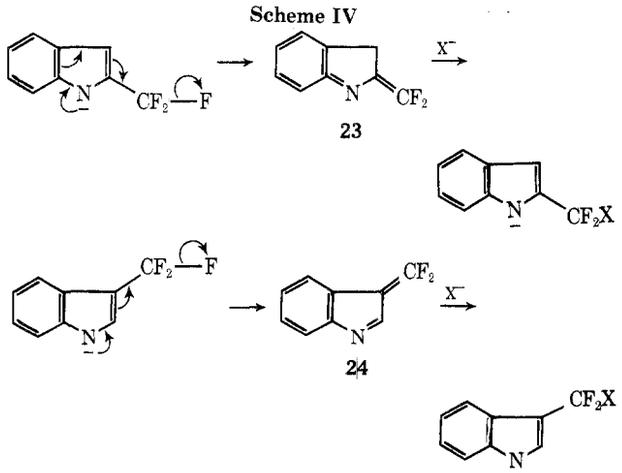
This may be explained as follows. The rate of reduction is much greater for 13 than for 12 and the rate of decomposition of sodium borohydride is significantly greater for the latter. Accordingly, sodium ethoxide produced by the decomposition of sodium borohydride attacks the trifluoromethyl group and gives the ester 18. Therefore, this reaction also shows that the β-trifluoromethyl compound has a greater reactivity than the α compound.

The difference in reactivity between 12 and 13 was also observed with sodium amide. Although 12 was recovered unchanged, 13 gave a cyano derivative (22), which was produced by the substitution of one fluorine atom with an amino group followed by dehydrofluorination.

In these reactions the excess π-electron density of the indole ring appears to promote the SN1-like cleavage of the carbon–fluorine bond. The concept that the difference between reactivities of 12 and 13 is explained by the difference between stabilities of 23 and 24 (Scheme IV) has been recognized with methylene analogs.[9] The fact that the β position has a higher electron density than the α position from MO calculation of the indole ring in the literature[10] also supports the assumption that SN1-like cleavage of the carbon–fluorine bond is promoted more strongly in the β-trifluoromethyl compound than in the α-trifluoromethyl compound.

In contrast to the SN2-like reactions of 2- and 4-(trifluoromethyl)quinolines, which showed the electron-withdrawing effect of the ring, SN1-like reactions occurred in the present case with a π-electron excess system. The interesting point is that the results of 3-(trifluoromethyl)indole correspond with those of 3-(trifluoromethyl)quinoline, which we reported in the preceding paper.[4] Moreover, the intermediate proposed for 3-(trifluoromethyl)indole is quite similar to that proposed for this quinoline, namely, both have the same enamine conjugation.

Scheme IV



Experimental Section

Photoreaction of 2-Cyano-3-(trifluoromethyl)quinoline 1-Oxide[8] (8). A. A solution of 300 mg (1.25 mmol) of 8 dissolved in

300 ml of benzene was irradiated with a high-pressure mercury lamp (Ushio UM-102, 100 W) under a stream of nitrogen in a Pyrex vessel for 30 min. After evaporation of benzene, the residue was purified by silica gel column chromatography and **10** was obtained from the hexane eluate. Recrystallization from hexane gave yellow prisms: mp 88°; yield 273 mg (91%); ir (KBr) 2280 (C≡N), 1193 and 1150 cm^{-1} (broad, CF_3); nmr ($CDCl_3$) δ 6.42 (1 H, s, 5-H); mass spectrum m/e 238 (M^+). *Anal.* Calcd for $C_{11}H_5F_3N_2O$: C, 55.47; H, 2.12; F, 23.93; N, 11.76. Found: C, 55.41; H, 2.26; F, 23.31; N, 11.52.

B. A solution of 300 mg of **8** dissolved in 300 ml of MeOH was irradiated in the same manner as in A. MeOH was evaporated and the residue was recrystallized from benzene to give yellow crystals (**14**): mp 204°; yield 104.1 mg (34%); ir (KBr) 1676 (C=O) and 1126 cm^{-1} (broad, CF_3); nmr ($CDCl_3$) δ 3.86 (3 H, s, OCH_3); mass spectrum m/e 243 (M^+), 228 ($M^+ - CH_3$); high mass on m/e 228 ($M^+ - CH_3$), 228.025 (calcd, 228.027).

Recrystallization of the residue from mother liquor and hexane gave **10**, yield 96 mg (32%).

Photoreaction of 2-Cyano-4-(trifluoromethyl)quinoline 1-Oxide[8] (9). A. A solution of 300 mg of **9** dissolved in 300 ml of benzene was treated as in the case of **8**. After evaporation of benzene, the residue was purified by being passed through a silica gel column in hexane solution. The effluent was recrystallized from hexane to give yellow crystals (**11**): mp 59–60°; yield 291 mg (97%); ir (KBr) 2240 (C≡N), 1305, 1140 cm^{-1} (broad, CF_3); nmr (CCl_4) δ 6.93 (1 H, s, 4-H); mass spectrum m/e 238 (M^+). *Anal.* Calcd for $C_{11}H_5F_3N_2O$: C, 55.47; H, 2.12; F, 23.93; N, 11.76. Found: C, 55.22; H, 2.38; F, 23.07; N, 11.48.

B. A solution of 300 mg of **9** dissolved in 300 ml of MeOH was treated as in the case of **8**. The residue obtained after evaporation of MeOH was recrystallized from benzene to give yellow crystals (**15**): mp 238.5°; yield 24.5 mg (8%); ir (KBr) 1670 (C=O) 1156, 1120 cm^{-1} (CF_3); nmr (DMSO-d_6) δ 3.91 (3 H, s, OCH_3); mass spectrum m/e 243 (M^+), 228 ($M^+ - CH_3$); high mass on m/e 228 ($M^+ - CH_3$) 228.026 (calcd, 228.027).

The residue obtained by evaporation of the mother liquor was purified by silica gel column chromatography in hexane solution to give 144 mg (48%) of **11**.

2-(Trifluoromethyl)indole (12). HCl gas was passed through a solution of 300 mg of **10** dissolved in 15 ml of MeOH with stirring for 10 min and the reaction mixture was poured into ice water. This mixture was neutralized with Na_2CO_3 and extracted with Et_2O. The Et_2O solution was washed with H_2O and dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was passed through a column of silica gel in hexane solution. The effluent was recrystallized from hexane and gave colorless plates (**12**): mp 102°; yield 144.5 mg (62%); ir (KBr) 3410 (NH), 1165, 1100 cm^{-1} (CF_3); nmr ($CDCl_3$) δ 6.94 (1 H, s, 3-H), 8.32 (1 H, broad, NH); mass spectrum m/e 185 (M^+). *Anal.* Calcd for $C_9H_6F_3N$: C, 58.42; H, 3.27; F, 30.80; N, 7.57. Found: C, 58.70; H, 3.33; F, 30.16; N, 7.24.

3-(Trifluoromethyl)indole (13). The same treatment of 300 mg of **11** as in the case of **10** gave colorless plates (**13**): mp 110°; yield 149 mg (64%); ir (KBr) 3440 (NH), 1183, 1120, 1087 cm^{-1} (CF_3); nmr ($CDCl_3$) δ 8.37 (1 H, broad, NH); mass spectrum m/e 185 (M^+). *Anal.* Calcd for $C_9H_6F_3N$: C, 58.42; H, 3.27; F, 30.80; N, 7.57. Found: C, 58.48; H, 3.50; F, 30.42; N, 7.73.

Alcoholysis of 12. A solution of 150 mg of **12** dissolved in 20 ml of absolute EtOH was added dropwise into a solution of 150 mg of Na dissolved in 20 ml of absolute EtOH, with stirring, and the mixture was refluxed for 5 hr. The cooled reaction mixture was poured into ice water and extracted with Et_2O, and the extract was dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was purified by being passed through a silica gel column in CH_2Cl_2 solution. Recrystallization of the effluent from hexane gave crystals (**16**): mp 163°; yield 23.5 mg (11%); mass spectrum m/e 263 (M^+); high mass m/e 263.152 (calcd for $C_{15}H_{21}NO_3$, 263.152). **16** was partially hydrolyzed to **18** and was identified.

Alcoholysis of 13. The same treatment of 150 mg of **13** as in the case of **12** and recrystallization of the residue from the Et_2O extract from CCl_4 gave **19**, mp 124–126°, yield 81.2 mg (53%). It was identified with the authentic sample.[11]

Reaction of 12 with $LiAlH_4$. A solution of 200 mg of **12** dissolved in 20 ml of absolute Et_2O was added dropwise, with stirring, into 110 mg of $LiAlH_4$ suspended in 20 ml of absolute Et_2O, and the mixture was refluxed for 10 hr with stirring. Stirring was continued at room temperature for 2 days, but some **12** was still detected by tlc. Et_2O saturated with H_2O was added dropwise to decompose excess $LiAlH_4$ and the precipitate was filtered off. After being dried over Na_2SO_4, the filtrate was concentrated and the residue was purified through silica gel in hexane solution. The effluent was recrystallized from hexane to give 2-methylindole (**17**), mp 58.5°, yield 45.2 g (30%). It was identified with the authentic sample by comparison of their ir spectra.

Reaction of 13 with $LiAlH_4$. Treatment of 200 mg of **13** in the same way as **12**, except that refluxing was stopped as soon as **13** was no longer detected by tlc, and recrystallization of the residue obtained by evaporation of Et_2O from hexane gave skatole (**20**), mp 90–92°, yield 59.5 mg (42%).

Reaction of 12 with $NaBH_4$. A solution of 150 mg of **12** dissolved in 20 ml of EtOH was added dropwise with stirring into a solution of 200 mg of $NaBH_4$ dissolved in 20 ml of EtOH, and the mixture was refluxed for 30 hr. The cooled reaction mixture was poured into ice water and extracted with Et_2O, and the extract, after being dried over Na_2SO_4, was evaporated. The residue was chromatographed over silica gel.

From the first effluent with hexane 69 mg (46%) of the starting material (**12**) was recovered. The second effluent was recrystallized to give **18**, mp 123–125° (hexane), yield 33.7 mg (22%). **18** was identified with the authentic sample[12] by comparison of ir spectra and by a mixture melting point determination.

Reaction of 13 with $NaBH_4$. 13 (150 mg) was treated as in the case of **12**, but refluxing was continued for only 5 hr. The residue obtained by the evaporation of Et_2O was purified by silica gel chromatography in CH_2Cl_2 solution. The effluent was recrystallized from hexane to give **20**, mp 91–93°, yield 48.9 mg (46%). It was identified with the authentic skatole.

Reaction with Sodium Amide. Into about 30 ml of liquid NH_3, 0.1 g of $Fe(NO_3)_3$ crystals was added, and then 1.2 g of Na. When Na dissolved completely, 500 mg of **13** dissolved in 10 ml of absolute Et_2O was added dropwise with stirring. After 3 hr of stirring, NH_3 was evaporated and $NaNH_2$ was decomposed by a slow addition of hydrated Et_2O. The precipitate was collected by filtration and washed with Et_2O. The Et_2O layer was washed with H_2O and dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was purified through a silica gel column in CH_2Cl_2 solution. The effluent was recrystallized from benzene to give 3-cyanoindole (**22**), mp 182–183°, yield 57.6 mg (15%). It was identified with the authentic sample.[13]

12 was recovered (75%) in this reaction and no product was isolated.

Registry No.—**8**, 35666-36-5; **9**, 35666-38-7; **10**, 51310-52-2; **11**, 51310-53-3; **12**, 51310-54-4; **13**, 51310-55-5; **14**, 51310-56-6; **15**, 51310-57-7; **16**, 51310-58-8; **17**, 95-20-5; **18**, 3770-50-1; **19**, 776-41-0; **20**, 83-34-1; **22**, 5457-28-3.

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