# Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. VII. The Condensation of *m*-Anisidine and Ethyl Trifluoroacetoacetate.

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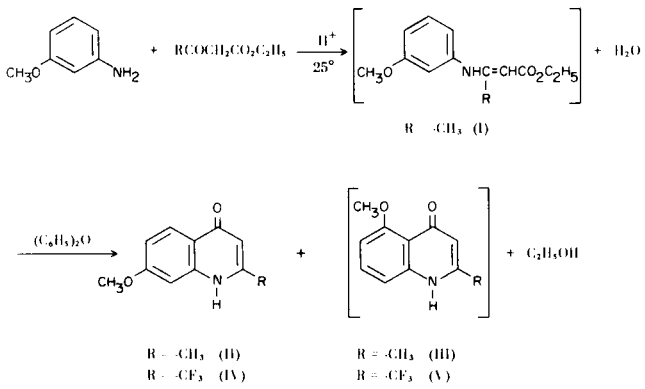
*m*-Anisidine has previously been condensed (1-3) with ethyl acetoacetate, under acidic conditions, to give ethyl β-*m*-methoxyanilinocrotonate (I). When I was cyclized thermally, it yielded only 7-methoxy-2-methyl-4-quinolone (II). The other possible isomer, 5-methoxy-2-methyl-4-quinolone (III) could not be isolated from the reaction mixture (Scheme I).

SCHEME I

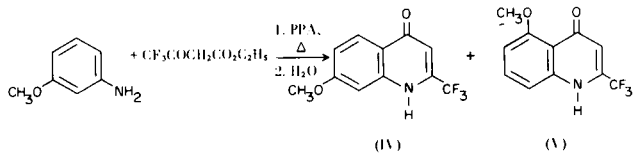


Similar results were obtained when *m*-anisidine was condensed with glycerol in the presence of sulfuric acid and sodium *m*-nitrobenzenesulfonate (4). Only 7-methoxyquinoline was formed. The other possible isomer, 5-methoxyquinoline, could not be detected. From this experimental data, it was concluded (4,5) that aromatic rings containing *o*- and *p*-directing substituents such as the methoxyl group will always yield 7-substituted quinolines (4,5).

Because of our previous interest in the reaction of ethyl trifluoroacetoacetate with aromatic amines (6), we investigated the condensation of this ester with *m*-anisidine under the conditions described in the literature for ethyl acetoacetate (1-3). Only 7-methoxy-2-(trifluoromethyl)-4-quinolone (IV) was obtained. The other isomer, 5-methoxy-2-(trifluoromethyl)-4-quinolone (V) could not be isolated (Scheme I).

However, when *m*-anisidine was condensed with ethyl trifluoroacetoacetate in the presence of polyphosphoric acid, both of the expected isomers (IV) and (V), were obtained in approximately equal amounts (Scheme II). The formation of (V) is an example of a condensation occurring *ortho* to a methoxyl group.

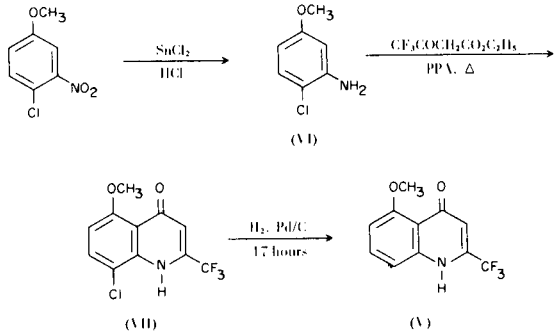
SCHEME II



In each of the foregoing schemes, 2-quinolone products could also be formed, although they have never been detected under the cited reaction conditions (6). That products IV and V are indeed 4-quinolones is substantiated by their infrared spectra. Infrared spectroscopy has been used successfully in a number of other systems to distinguish between 2- and 4-quinolones (6-10). 2-Quinolones are reported to absorb in the range 1641-1667 $cm^{-1}$ while 4-quinolones absorb between 1620-1647 $cm^{-1}$ (8-10). 2-(Trifluoromethyl)-4-quinolones absorb between 1600-1628 $cm^{-1}$ while 4-(trifluoromethyl)-2-quinolones absorb between 1660-1670 $cm^{-1}$ (6). The infrared spectra of compounds (IV) and (V) showed strong absorptions at 1620 $cm^{-1}$ and 1610 $cm^{-1}$, respectively, well within the range established for 4-quinolones.

The nmr spectra of (IV) and (V) are also consistent with the proposed structures (Figures 1 and 2).

SCHEME III



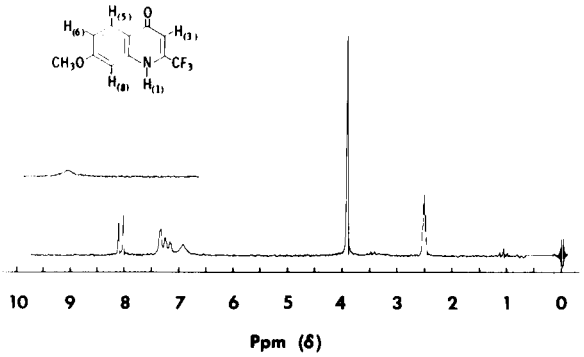



Figure 1. The 100 MHz nmr spectrum of 7-methoxy-2-(trifluoromethyl)-4-quinolone (IV) in DMSO-$d_6$ at a sweep width of 1000 Hz. The insert is offset 300 Hz.

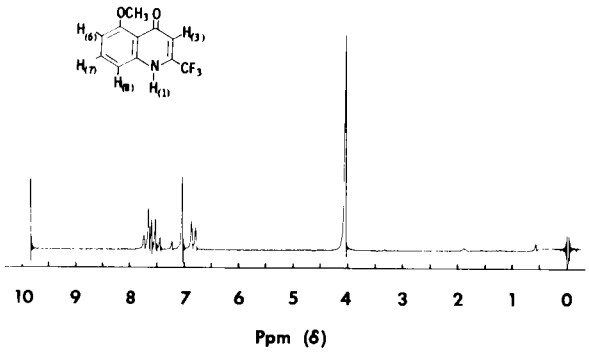



Figure 2. The 100 MHz nmr spectrum of 5-methoxy-2-(trifluoromethyl)-4-quinolone (V) in deuteriochloroform at a sweep width of 1000 Hz.

The structure of compound V was further supported by an independent synthesis (Scheme III).

4-Chloro-3-nitroanisole was reduced with stannous chloride and hydrochloric acid to afford 4-chloro-3-aminoanisole (VI). This compound was condensed with ethyl trifluoroacetoacetate to give 8-chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (VII). The reductive dehalogenation of (VII) afforded a product that was identical in every respect to the 5-methoxy-2-(trifluoromethyl)-4-quinolone (V) obtained from the condensation of *m*-anisidine with ethyl trifluoroacetoacetate (Scheme II).

## EXPERIMENTAL

Solids were recrystallized to constant melting points and dried *in vacuo* in an Abderhalden pistol containing sodium hydroxide. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were carried out by Midwest Microlab. Ltd., Indianapolis, Indiana. Infrared spectra were obtained with a Perkin-Elmer 521 spectrophotometer. The abbreviations s, m, and w are used to designate strong, medium, and weak peaks. Nuclear magnetic resonance spectra were obtained with a Varian HA-100 spectrometer. Tetramethylsilane was used as the internal standard. Chemical shifts are expressed in δ values.

Condensation of *m*-Anisidine with Ethyl Trifluoroacetoacetate under Acidic Conditions, Followed by Thermolysis in Diphenyl Ether (Scheme I).

This reaction was carried out according to directions given for the condensation of *m*-anisidine with ethyl acetoacetate (1-3).

*m*-Anisidine (10 g., 0.081 mole) and ethyl trifluoroacetoacetate (15 g., 0.081 mole) were mixed in a 250 ml. round-bottomed flask equipped with an air condenser. Concentrated hydrochloric acid (2-3 drops) was added to this mixture and the contents of the flask were allowed to stand at room temperature for two days. Diphenyl ether (100 ml.) was then added to the reaction mixture. The resulting solution was heated under reflux for 40 minutes and cooled to room temperature. After six hours, a white solid deposited (13 g., m.p. 200-230°). This product was recrystallized several times from absolute ethanol to give 9 g. (45.5% yield) of 7-methoxy-2-(trifluoromethyl)-4-quinolone (IV), m.p. 254-255°. The ir spectrum (potassium bromide) of (IV) showed major absorptions at 3360(w), 3215(w), 3050(m), 1620(s), 1550(m), 1500(m), 1475(m), 1440(m), 1300(s), 1275(s), 1250(s), 1190(s), 1140(s), 1090(m), 1020(m), 940(m), 830(s), 720(m), and 705(m) $cm^{-1}$; nmr signals (DMSO-$d_6$) were present at δ 3.91 (3H, singlet, $OCH_3$), 6.93 (1H, broad singlet, $H_{(3)}$), 7.14-7.38 (2H, multiplet $H_{(6)}$ and $H_{(8)}$), 8.02-8.11 (1H, multiplet, $H_{(5)}$), and 12.04 (1H, broad singlet, $H_{(1)}$). Since quinolones presumably exist in equilibrium with their hydroxyquinoline tautomers, the resonance signal at δ 12.04 cannot be assigned unequivocally to an O-H or N-H proton. The addition of deuterium oxide to the nmr sample caused the disappearance of this resonance signal as well as the sharpening of the resonance signals of $H_{(3)}$, $H_{(6)}$, and $H_{(8)}$.

*Anal.* Calcd. for $C_{11}H_8NO_2F_3$: C, 54.32; H, 3.29; N, 5.76. Found: C, 54.57; H, 3.42; N, 5.76.

The crude product and the filtrate from the reaction mixture were examined for the presence of the other isomer, 5-methoxy-2-(trifluoromethyl)-4-quinolone. Thin-layer chromatography experiments on these fractions (silica gel, 3:1 benzene/chloroform) failed to show any compounds with an $R_f$ value similar to that of the known 5-methoxy-2-(trifluoromethyl)-4-quinolone. Furthermore, neither the nmr spectrum of the crude solid nor that of the filtrate gave any evidence of the presence of 5-methoxy-2-(trifluoromethyl)-4-quinolone in the reaction mixture.

Condensation of *m*-Anisidine with Ethyl Trifluoroacetoacetate in Polyphosphoric Acid (Scheme II).

This condensation was carried out according to a modification of the method of Staskun and Israelstam (11,6). Polyphosphoric acid (150 ml.) was placed in a 500 ml. three-necked, round-bottomed flask fitted with a mechanical stirrer, water condenser, and addition funnel. *m*-Anisidine (20 g., 0.16 mole) was added slowly to the acid. The mixture was heated to 80°. Ethyl trifluoroacetoacetate (31.9 g., 0.17 mole) was then added to the mixture, in small portions, with vigorous stirring, over a period of 20 minutes. After two and one half hours at 100°, the flask was cooled and its contents were poured into 2500 ml. of an ice-water mixture. The resulting solution was stirred overnight. The precipitate that formed was isolated by filtration, dried, and recrystallized from absolute ethanol to yield 27 g. of an isomeric mixture, m.p. 200-213°. The components of the mixture were separated by "dry-column" chromatography using a 2″ x 24″ column filled with 250 g. of Woelm silica gel. The column was eluted with chloroform. The first fractions (3 x 500 ml.) were

collected and evaporated *in vacuo* to afford a pure, crystalline compound, m.p. 131-132° (12.3 g., 31% yield). The ir and nmr spectra of this compound were identical to those of an authentic sample of 5-methoxy-2-(trifluoromethyl)-4-quinolone obtained by the reductive dehalogenation of 8-chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (VII). Mixtures of these two compounds showed no depression in melting point.

The column was next eluted with a 50:50 mixture of chloroform and absolute ethanol (4 x 400 ml.). After the removal of the solvent, these fractions afforded 17.2 g. (43.5% yield) of 7-methoxy-2-(trifluoromethyl)-4-quinolone (IV), m.p. 255-256°. Recrystallization of this solid from absolute ethanol did not raise its melting point. This product had the same ir and nmr spectra as the product obtained from the condensation of *m*-anisidine with ethyl trifluoroacetoacetate under acidic conditions and subsequent thermolysis in diphenyl ether (Scheme I). Mixtures of the two compounds showed no depression in melting point.

4-Chloro-3-aminoanisole (VI).

This compound was synthesized by a modification of a previously reported procedure for the reduction of dinitrotoluenes (12,13). Stannous chloride dihydrate (140 g., 0.62 mole) and concentrated hydrochloric acid (180 ml., specific gravity 1.19) were placed in a one liter beaker and stirred mechanically. 4-Chloro-3-nitroanisole (40 g., 0.21 mole) was added in one portion and the reaction mixture was warmed to 30-40°. A vigorous reaction ensued and the temperature rose to 80°. The reaction mixture was cooled to 30° and stirred overnight. The stannic chloride salt of 4-chloro-3-aminoanisole precipitated as a white slurry which was removed by filtration and washed with dry diethyl ether. The salt (47 g.), m.p. 198-202°, was suspended in 150 ml. of water. The suspension was then cooled in an ice-bath and a solution containing 300 g. of sodium hydroxide in 400 ml. of water was slowly added to it with stirring. During the addition, the temperature of the reaction mixture was maintained at 40°. The resulting aqueous solution was extracted with diethyl ether (2 x 400 ml.). The ethereal extract was then washed with water (2 x 50 ml.) and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo* to yield 4-chloro-3-aminoanisole (VI) as a yellow oil (19 g.). This product was used in the next step without further purification.

8-Chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (VII).

The condensation of 4-chloro-3-aminoanisole (19 g., 0.12 mole) with ethyl trifluoroacetoacetate and polyphosphoric acid was carried out under the same conditions used for the condensation of *m*-anisidine with ethyl trifluoroacetoacetate in polyphosphoric acid. The product that formed was collected and dried to give 34 g. of 8-chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (VII), m.p. 208-212°. This compound was recrystallized from absolute ethanol to give 31 g. (95% yield) of pure VII, m.p. 216-219°. Nmr signals (DMSO-$d_6$) were present at $\delta$ 3.99 (3H, singlet, $OCH_3$), 7.07 (1H, doublet, $H_{(6)}$, J = 8.5), 7.23 (1H, singlet, $H_{(3)}$), 7.89 (1H, doublet, $H_{(7)}$, J = 8.5), and 11.19 (1H, broad singlet, $H_{(1)}$). The addition of deuterium oxide caused the disappearance of the resonance signal at $\delta$ 11.19.

*Anal.* Calcd. for $C_{11}H_7ClF_3NO_2$: C, 47.56; H, 2.52; N, 5.05. Found: C, 47.85; H, 2.69; N, 5.11.

Reductive Dehalogenation of 8-Chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (VII).

Dehalogenation was accomplished by a modification of a procedure reported for the hydrogenolysis of 3-halo-6,8-dimethoxyisoquinolines (14). Potassium hydroxide (0.5 g.) was dissolved in hot absolute ethanol (100 ml.) and the resulting solution was added to a small amount of 8-chloro-5-methoxy-2-(trifluoromethyl)-4-quinolone (0.5 g.) admixed with 10% palladium-on-carbon catalyst (1 g.). The mixture was heated to 75° and then placed in a Parr hydrogenator for seventeen hours. After removal of the catalyst, the filtrate was concentrated *in vacuo* and poured into 100 ml. of water. The mixture was stirred for one hour. Solid material was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid. A precipitate formed and was collected by filtration. This solid was washed with hot water (3 x 10 ml.) and then with a 50:50 mixture (2 x 10 ml.) of ethanol and water. After drying, 0.3 g. of 5-methoxy-2-(trifluoromethyl)-4-quinolone (V) was obtained (69% yield), m.p. 132-133°. Further recrystallizations from ethanol did not raise the melting point of (V). The principal bands in the ir spectrum (chloroform) of (V) were found at 3350(m), 2970(m), 2910(m), 2870(m), 1610(s), 1565(s), 1465(m), 1395(s), 1320(m), 1225(s), 1180(m), 1125(s), 1090(s), 910(s) and 850(m) $cm^{-1}$. Nmr signals (deuteriochloroform) were present at $\delta$ 4.05 (3H, singlet, $OCH_3$), 6.80-6.88 (1H, multiplet, $H_{(6)}$), 7.04 (1H, singlet, $H_{(3)}$), 7.46-7.77 (2H, multiplet, $H_{(7)}$ and $H_{(8)}$), and 9.85 (1H, singlet, $H_{(1)}$). In DMSO-$d_6$ the resonance signal of proton $H_{(1)}$ appears as a broad singlet at $\delta$ 10.84. The addition of deuterium oxide to the nmr sample in either solvent caused the disappearance of this signal.

*Anal.* Calcd. for $C_{11}H_8F_3NO_2$: C, 54.32; H, 3.29; N, 5.76. Found: C, 54.36; H, 3.52; N, 5.79.

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