[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Trifluoromethylated Quinolines

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In connection with the study of the antimalarial activity of 7-halo-4-aminoquinolines it seemed of interest to prepare a number of 7-trifluoromethyl-4-dialkylaminoalkylaminoquinolines to determine the effect of replacing the 7-halogen with a trifluoromethyl group. Similar work is described in the patent literature[1] and in a more recent paper[2] wherein 4-(4-diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline and its intermediates are prepared. The present communication describes the preparation and proof of structure for a group of 3-methylquinolines having the trifluoromethyl substituent in the 5- or 7-position and in addition the preparation of 4-(3-diethylamino-2-hydroxypropylamino) - 7 - trifluoromethylquinoline. Furthermore it was confirmed by oxidation of the 4-hydroxy-3-carboxy intermediate to 2-amino-4-trifluoromethylbenzoic acid which was then deaminated to 4-trifluoromethylbenzoic acid, that the trifluoromethyl group is in the 7-position in the compound previously described (I).[1,2] This end-product is a new compound; but since it must be either the 2- or 4-trifluoromethylbenzoic acid, it has been assigned the latter structure, not being similar to the ortho derivative, a previously well characterized compound.[3] Finally the 3-methyl substituted derivatives were prepared by condensing *m*-trifluoromethylaniline with diethyl oxalpropionate and cyclizing the anil to a mixture of 5 and 7-trifluoromethyl-3-methyl substituted quinolines. The compound formed predominantly was the 7-trifluoroquinoline; this was proved by permanganate oxidation to give the 2-amino-4-trifluoromethylbenzoic acid also obtained by oxidation of (I). The structure of the 5-trifluoromethyl derivatives were inferred.

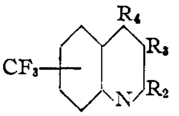
Experimental

4-(4-Diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline (I).—The intermediates used were prepared essentially as described by Snyder.[1] Our poorer yield in the cyclization reaction may be ascribed to the use of mineral oil as a cyclization medium. A mixture of 22.5 g. (1.0 mol) of 4-chloro-7-trifluoromethylquinoline and 31 g. (2.0 mols) of 1-diethylamino-4-aminopentane was heated with stirring for sixteen hours at 150–160°. The reaction mixture was then diluted with four times the theoretically necessary amount of 50% acetic acid. Finally 35% sodium hydroxide solution was added with cooling till the reaction mixture was basic to litmus. The product was extracted thoroughly with a large amount of ether. The ether was evaporated and the residue distilled under high vacuum. Yield was 27.9 g., b. p. 148–154° at 0.01 micron. This sirup soon crystallized to give a nonhygroscopic solid, m. p. 81–83° after trituration with cold Skellysolve A (b. p. 28–38°).

4-(3-Diethylamino-2-hydroxypropylamino)-7-trifluoromethylquinoline (II).—A mixture of 27.4 g. (2 mols) of 3-diethylamino-2-hydroxypropylamine and 21.7 g. (1 mol) of 4-chloro-7-trifluoromethylquinoline was heated on an oil-bath to 140°. At this point heating was stopped but the temperature rose rapidly to 175°. After the temperature had dropped back to 150°, the reaction mixture was kept here for one hour more. The work up was similar to that described with (I). The product distilled at 150° under a pressure of 0.05 micron. The distillate crystallized. It was triturated under Skellysolve A and dried; yield 28.2 g., m. p. 128–129°.

TABLE I

5/7 SUBSTITUTED TRIFLUOROMETHYLQUINOLINE DERIVATIVES



R_2	R_3	R_4	Position of CF_3	Yield, %	M. p., °C.	Molecular formula	Analyses, %					
							Calcd.			Found		
							C	H	N	C	H	N
H	$COOC_2H_5$	OH	7	54	>300	$C_{13}H_{10}F_3NO_3$			4.91			4.69
H	COOH	OH	7	100	250–251	$C_{11}H_6F_3NO_3$			5.45			5.27
H	H	OH	7	88	266–268	$C_{10}H_6F_3NO$			6.57			6.46
H	H	Cl	7	93	70–71	$C_{10}H_5ClF_3N$			6.05			5.89
H	H	[a]	7	86	128–129	$C_{17}H_{22}F_3N_3O$	59.81	6.48	12.31	59.79	6.41	12.13
H	H	[b]	7	91	81–83	$C_{19}H_{26}F_3N_3$	64.57	7.43	11.89	64.90	7.31	11.82
$COOC_2H_5$	CH_3	OH	7	46	216–217	$C_{14}H_{12}F_3NO_3$			4.70			4.67
COOF	CH_3	OH	7	100	238–240	$C_{12}H_8F_3NO_3$			5.17			4.95
H	CH_3	OH	7	98	>300	$C_{11}H_8F_3NO$			6.16			6.17
H	CH_3	Cl	7	92	64.5–66.5	$C_{11}H_7ClF_3N$			5.70			5.54
H	CH_3	[a]	7	62	103.5–105.5	$C_{18}H_{24}F_3N_3O$	60.83	6.81	11.82	60.83	6.67	11.78
H	CH_3	[b]	7	24	Oil[c]	$C_{20}H_{28}F_3N_3$	65.36	7.70	11.43	65.10	7.65	11.23
$COOC_2H_5$	CH_3	OH	5	11	207–209	$C_{14}H_{12}F_3NO_3$			4.70			4.63
COOH	CH	OH	5	100	>300	$C_{12}H_8F_3NO_3$			5.17			5.26
H	CH_3	OH	5	97	>300	$C_{11}H_8F_3NO$			6.16			6.08
H	CH_3	Cl	5	92	102–102.5	$C_{11}H_7ClF_3N$	Cl 14.45		5.70	Cl 14.05		6.00
H	CH_3	[a]	5	42	Oil[d]	$C_{18}H_{24}F_3N_3O$	60.83	6.81	11.82	60.45	6.34	11.72

[a] 3-Diethylamino-2-hydroxypropylamino. [b] 4-Diethylamino-1-methylbutylamino. [c] n^{25}_D 1.5328. [d] n^{25}_D 1.5522.

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(1) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(2) Snyder, Freier, Kovacic and Van Heyningen, THIS JOURNAL, **69**, 371 (1947).

(3) de Brouwer, *Bull. soc. chim. Belg.*, **39**, 298 (1930).

Ethyl 7- and 5-Trifluoromethyl-4-hydroxy-3-methyl-2-quinoline Carboxylates.—To 100 g. (1 mol) of *m*-aminobenzotrifluoride was added 138 g. (1 mol) of diethyloxalpropionate at room temperature. Some heat was evolved. The reaction mixture was kept three days at 40°. It was then washed with 0.5 *N* hydrochloric acid, 0.5 *N* sodium hydroxide solution and finally with water. A yield of 160 g. of red oil which showed some signs of crystallizing resulted. This oil was added over a period of about twenty minutes to 550 cc. of diphenyl ether kept at 260–265° and heating was continued with stirring till no more alcohol was evolved. The reaction mixture was then allowed to cool and the product was filtered off, washed with Skellysolve A and dried; yield 109.5 g., m. p. 172–184°.

The mixture was dissolved in 600 cc. of hot 95% ethanol and cooled. From the alcohol there resulted 87 g., m. p. 199–206°, which upon recrystallization gave 63 g., m. p. 216–217°. Another crystallization did not affect this melting point. This was pure ethyl 4-hydroxy-3-methyl-7-trifluoromethyl-2-quinoline carboxylate.

The alcoholic liquors were diluted with water and the precipitated product filtered and dried. The product was dissolved in 200 cc. of glacial acetic acid and the solution saturated with hydrogen chloride and cooled. This precipitated 16.5 g. of impure 7-isomer. The acetic acid solution was diluted with water and the precipitate filtered and dried to give 23.1 g. of material, melting point 197–201°. After repeated crystallization from toluene 13.3 g. of ethyl 4-hydroxy-3-methyl-5-trifluoromethyl-2-quinoline carboxylate, m. p. 207–209° resulted. A mixed melting point with the 7-isomer gave a 30° depression.

4-(3-Diethylamino-2-hydroxypropylamino)-3-methyl-7-trifluoromethylquinoline (III).—Using the standard procedures of hydrolysis, decarboxylation and chlorination, 4-chloro-3-methyl-7-trifluoromethylquinoline was prepared, and heated with two moles of 3-diethylamino-2-hydroxypropylamine at 150–170° for five hours. The reaction mixture was taken up in 40% acetic acid and brought to a *p*H of 8 with sodium hydroxide. Extraction of this solution with ether gave 28 g. of a solid, m. p. 98–150° after evaporation of the ether. This solid was distilled under a high vacuum and then crystallized from dilute dioxane giving 22.2 g. of product, m. p. 103.5–105.5°.

4-(4-Diethylamino-1-methylbutylamino)-3-methyl-7-trifluoromethylquinoline.—A mixture of 24.5 g. (1 mol) of 4-chloro-3-methyl-7-trifluoromethylquinoline and 31.6 g. (2 mols) of 4-diethylamino-1-methylbutylamine was heated to 160–170° and kept at this temperature for forty-five hours. The reaction mixture was then made alkaline with sodium hydroxide and extracted with ether. Distillation of the ether extract gave 11.0 g. of unreacted chloride and 8.7 g. of product, b. p. 135–140° at two microns, $n^{25}\text{D}$ 1.5328.

4-(3-Diethylamino-2-hydroxypropylamino)-3-methyl-5-trifluoromethylquinoline.—The 5-isomer was worked through in a similar manner and the 5-analog of III was prepared. This time the chloride and the base had to be heated together for twenty hours. From 18.3 g. of 4-chloro-3-methyl-5-trifluoromethylquinoline, 11.3 g. of 4-(3-diethylamino-2-hydroxypropylamino)-3-methyl-5-trifluoromethylquinoline resulted as an oil, b. p. 130–135° at 0.1 micron, $n^{25}\text{D}$ 1.5522.

2-Amino-4-trifluoromethylbenzoic Acid.—Eleven and four-tenths grams (1 mol) of 4-hydroxy-3-methyl-7-trifluoromethylquinoline was dissolved in 600 cc. of water containing 5 g. of potassium hydroxide at 80°. To this was added a solution of 31.6 g. (4 mols) of potassium permanganate in 800 cc. of water at 65°. The solution was stirred for thirty minutes and then decolorizing charcoal was added and stirring continued for five minutes more. The reaction mixture was filtered through filter-cel and evaporated to 200 cc. This was then made acid to congo with hydrochloric acid to give a product which was filtered off. This product was refluxed with 20 cc. of concentrated hydrochloric acid and 60 cc. of water for three hours and again filtered. The filtrate was acidified with acetic acid and the precipitated product filtered and dried in a desiccator. Recrystallization from benzene gave a product, m. p. 172–174°.

Anal. Calcd. for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.83; H, 3.40; N, 6.78.

Similarly in the series where the 3-methyl group was lacking 3-carboxy-2-hydroxy-7-trifluoromethylquinoline was oxidized to an acid, m. p. 172–174°, mixed m. p. 172–174°.

4-Trifluoromethylbenzoic Acid.—To a solution of 0.35 g. (1 mol) of sodium nitrite and 0.6 cc. of 35% sodium hydroxide in 10 cc. of water was added 1.06 g. (1 mol) of 2-amino-4-trifluoromethylbenzoic acid. The resulting solution was then added to 2.5 cc. of concentrated hydrochloric acid and 5 g. of ice. This diazo solution was allowed to stand ten minutes and then poured slowly into 7.5 cc. of 95% alcohol containing a small amount of copper sulfate. Soon the reaction mixture became cloudy and crystals were deposited. These were filtered off, dissolved in sodium hydroxide solution, treated with charcoal, and the filtered solution acidified, to precipitate the product which was filtered and dried in vacuum desiccator, m. p. 219–220°.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.84; H, 2.65. Found: C, 50.63; H, 2.68.

Summary

A series of 5- and 7-trifluoromethylquinolines have been prepared and their structures proved.

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