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Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. II. Trifluoromethyl Benzo[h]quinolines, Benzo[h]-1,6-napthyridines, 1,7- and 1,10-Phenanthrolines (1)

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Four heterocyclic rings containing the trifluoromethyl group have been prepared by the reductive dehalogenation of the corresponding chloro compounds. These were obtained from the hydroxy derivatives which, in turn, were formed in the condensation of ethyl trifluoroacetoacetate with 1-naphthylamine and some substituted aminoquinolines. Spectral data were used to ascertain the position of the hydroxyl group in the hydroxy derivatives. In one case, the position of this group was established by an independent synthesis.

Previous work in this laboratory has dealt with the condensation of ethyl trifluoroacetoacetate with *o*-phenylenediamine (2). Recently (3) we studied the condensation of ethyl trifluoroacetoacetate with various aromatic amines, in polyphosphoric acid at 150°, to prepare 2-trifluoromethyl-4-quinolinols which were used in the synthesis of substituted trifluoromethylquinolines. To test the general scope of this reaction it was extended to 1-naphthylamine and some heterocyclic amines. The condensation of ethyl trifluoroacetoacetate with these amines enabled us to prepare new heterocyclic compounds containing the trifluoromethyl group. Since preliminary tests on the previously prepared trifluoromethylquinolines indicated that these compounds might have physiological activity, it was thought that the introduction of trifluoromethyl groups in other heterocyclic rings might produce compounds of desirable properties.

The condensation of ethyl trifluoroacetoacetate with 1-naphthylamine and some of its heterocyclic analogs was carried out by a previously described method (3). The reaction of the ester and 1-naphthylamine in shown in equation 1.

The condensation of 4-aminoquinaldine with the ester, equation 2, gave a rather low yield of product (II). The yield of naphthyridinol was low either because the 3-position of the quinoline ring of the amine is sterically hindered by the methyl group or because the amino group is deactivated by the presence of the ring nitrogen. 4-Aminoquinaldine gave low yields of product in the Skraup and Doebner-Miller reactions (4) and failed to under go the Conrad-Limpach reaction (5), although it reacted with ethyl acetoacetate, at 160°, to give an amide which was cyclized to 4,5-dimethylbenzo[h]-1,6-naphthyridin-2-ol in concentrated sulfuric acid.

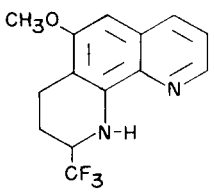
The reaction of ethyl trifluoroacetoacetate and 5-aminoquinoline yielded 2-trifluoromethyl-1,7-phenanthrolin-4-ol (III) in good yields, equation 3.

The condensation of ethyl trifluoroacetoacetate with 8-amino-6-methoxyquinoline, equation 4, proceeded in rather low yield. Steric effects must be involved in this case since the methoxy group should in fact activate the 7-position where ring closure must occur. 5-Methoxy-2-trifluoromethyl-1,10-phenanthrolin-4-ol (IV) is insoluble in 10% sodium hydroxide unlike the previously prepared trifluoromethyl 4-quinolinols or quinolones (3).

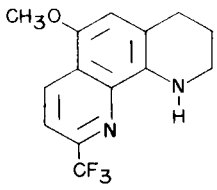
In order to establish the structure of at least one of the compounds prepared by an independent synthesis, it was decided to isolate the intermediates formed in the reaction of ethyl trifluoroacetoacetate and 1-naphthylamine, in benzene using glacial acetic acid as a catalyst. This reaction did not yield the expected 3-arylaminocrotonate but N-(1-naphthyl)-4,4,4-trifluoroacetoacetamide (VI) and N-(1-naphthylamino)-4,4,4-trifluorocrotonamide (VII) as shown in equation 5.

1-Naphthylamine reacted in a similar manner with ethyl acetoacetate under Conrad-Limpach conditions to yield N-(1-naphthyl)-acetoacetamide (6). Compound VI cyclized spontaneously above its melting point to give V.

The 4-hydroxyl group in all the compounds prepared was replaced by chlorine in excellent yields. Reductive dehalogenation of these compounds with Raney nickel yielded the corresponding trifluoromethyl substituted heterocyclic rings except in the case of 4-chloro-5-methoxy-2-trifluoromethyl-1,10-phenanthroline. The treatment of this compound with Raney nickel resulted both in the removal of chlorine and in the reduction of one ring as indicated by the analytical data. Although the structure of this reduced compound was not definitely established its infrared spectrum shows the presence of a sharp band at 3435 cm^{-1}, which could be attributed to the N-H stretching of a secondary amine. This suggests that one of the heterocyclic rings was reduced to give either A or B. Of the two, B appears to be the most probable since the unsubstituted ring should

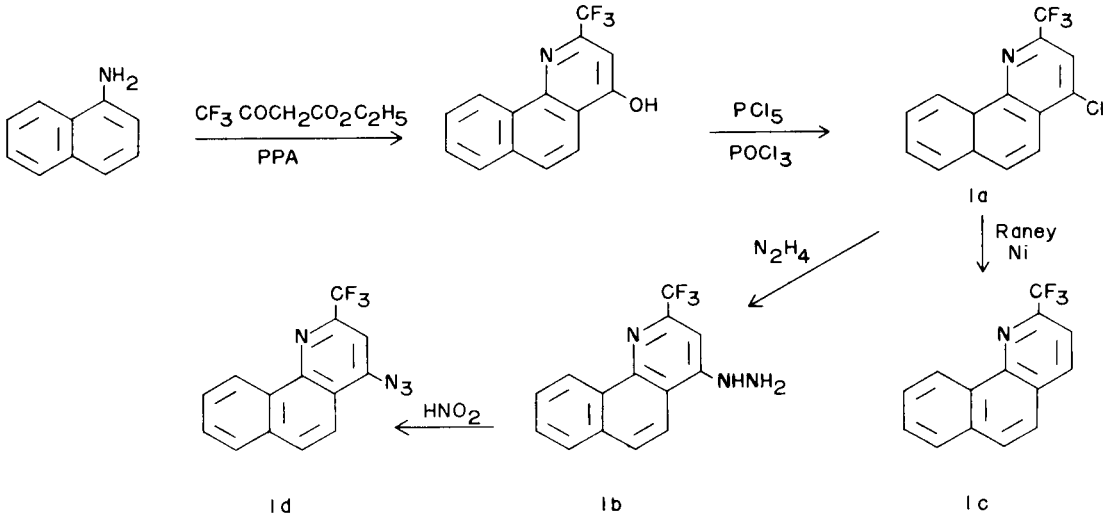


A



B

(1)



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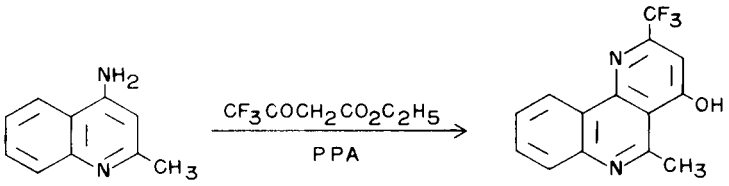

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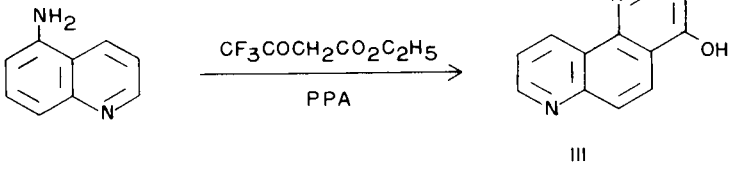

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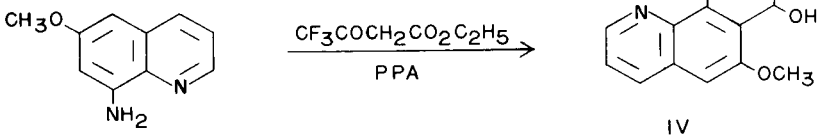

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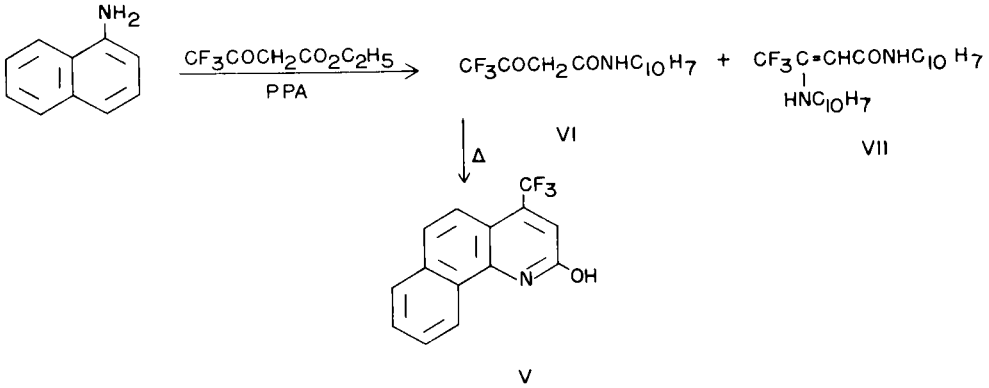


TABLE I

Trifluoromethyl Substituted Heterocyclic Compounds

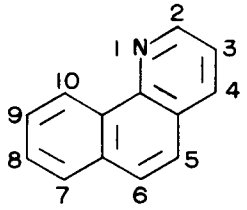
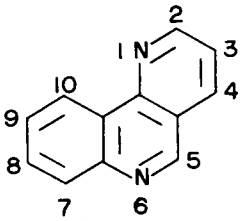
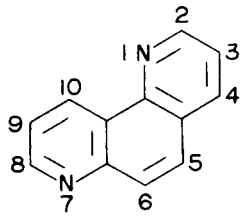
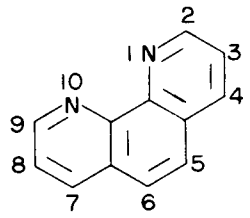
Compd. No.	Position of Substituents			Formula	M.p., °C	Yield, %	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Nitrogen Calcd.	Nitrogen Found
														
	2	4												
I	CF_3	OH		$C_{14}H_8F_3NO$ (a)	152-154	83	63.88	64.14	3.06	3.11	21.66	21.92	5.32	5.53
V	OH	CF_3		$C_{14}H_8F_3NO$ (b)	304-305	92	63.88	64.05	3.06	3.19	21.66	21.67	5.32	5.50
Ia	CF_3	Cl		$C_{14}H_7ClF_3N$	105-107	69	59.69	59.52	2.50	2.64	---	---	4.97	4.82
Ib	CF_3	$NHNH_2$		$C_{14}H_{10}F_3N_3$	232-235	86.5	60.65	60.68	3.64	3.74	20.56	20.45	15.16	15.18
Id	CF_3	N_3		$C_{14}H_7F_3N_4$ (c)	149-152	100	58.34	58.50	2.45	2.45	19.78	19.68	19.44	19.42
Ic	CF_3	H		$C_{14}H_8F_3N$	91-93	90.5	68.02	68.19	3.26	3.33	23.05	22.97	5.67	5.79
														
	2	4	5											
II	CF_3	OH	CH_3	$C_{14}H_9F_3N_2O$ (d)	335 d.	39	60.43	60.33	3.26	3.31	20.49	20.38	10.07	9.96
IIa	CF_3	Cl	CH_3	$C_{14}H_8ClF_3N_2$	112.5-115	61.5	56.67	56.55	2.72	2.68	---	---	9.44	9.47
IIb	CF_3	$NHNH_2$	CH_3	$C_{14}H_{11}F_3N_4$	167-169	59.2	57.53	57.55	3.79	3.80	19.50	19.66	9.17	9.17
IIc	CF_3	H	CH_3	$C_{14}H_9F_3N_2$	96-100	76.5	64.12	64.02	3.46	3.58	21.74	21.69	10.68	10.56

TABLE I

(Continued)

Compd. No.	Position of Substituents			Formula	M.p., °C	Yield, %	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Nitrogen Calcd.	Nitrogen Found
														
	2	4												
II	CF_3	OH		$C_{13}H_7F_3N_2O$ (e)	303-304	73	59.09	59.26	2.67	2.77	21.57	21.46	10.60	10.46
IIIa	CF_3	Cl		$C_{13}H_6ClF_3N_2$	136-137.5	95.6	55.24	55.12	2.14	1.98	---	---	9.91	9.89
IIIb	CF_3	H		$C_{13}H_7F_3N_2$	95.5-97.5	89	62.90	62.88	2.84	2.66	22.96	23.07	11.29	11.15
														
	2	4	5											
IV	CF_3	OH	OCH_3	$C_{14}H_9F_3N_2O_2$ (f)	280 d.	49.5	57.15	57.22	3.08	3.10	19.37	19.15	9.52	9.38
IVa	CF_3	Cl	OCH_3	$C_{14}H_8ClF_3N_2O$	244-245	95.5	53.77	53.96	2.60	2.87	---	---	8.96	8.88

(a) ν C=O (KBr) 1623 cm^{-1}. (b) ν C=O (KBr) 1660 cm^{-1}. (c) ν N=N=N 2110 cm^{-1}. (d) ν C=O (KBr) 1610, 1635 cm^{-1}. (e) ν C=O (KBr) 1600 cm^{-1}. (f) 1628 cm^{-1}.

TABLE II

Ultraviolet Spectra

Compound No.	λ max (C_2H_5OH) mμ (log ϵ)	λ max (0.2 M HCl in C_2H_5OH) mμ (log ϵ)
I	240(4.60); 287(3.83); 298(3.96)	253(4.62); 296(3.99); 308(3.99)
V	230(4.44); 275(4.18); 287(4.17); 304(3.73)	229(4.45); 275(4.15); 303(3.68)
II	246(4.47); 320(2.79)	222(4.28); 248(4.40)
III	244(4.38); 325(2.74)	230(4.70); 236(4.69); 269(4.48)
IV	231(4.81); 254(4.69); 303(4.13); 345(3.90)	223(4.39); 237(4.48); 279(4.47); 324(3.62)
Id	258(4.47); 317(3.98)	

be more reactive both from electronic and steric considerations.

4-Chloro-2-trifluoromethylbenzo[h]quinoline and 4-chloro-5-methyl-2-trifluoromethylbenzo[h]-1,6-naphthyridine, prepared from the corresponding 4-hydroxy compounds by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride, (eq. 1) were treated with an excess of hydrazine in refluxing ethylene glycol. These conditions have been reported to cause cleavage of 4-chloroquinolines to substituted pyrazoles (7) but with our compounds only the corresponding hydrazino compounds were isolated. 2-Trifluoromethyl-4-chloroquinolines also give only the hydrazines under similar conditions (3). 4-Hydrazino-2-trifluoromethylbenzo[h]quinoline (Ib) was diazotized to yield 4-azido-2-trifluoromethylbenzo[h]quinoline (Id).

The infrared spectrum of compound IV shows a strong absorption at 1628 cm^{-1} in the range which is typical of the 4-quinolone structure. Compound II has a weak absorption at 1635 cm^{-1} but a strong one at 1610 cm^{-1}, both of these are still within the range for 4-quinolones (3). The only 2-quinolone prepared, 4-trifluoromethylbenzo[h]quinolin-2-ol, (V) shows a strong infrared absorption band at 1660-1670 cm^{-1} which is typical of true amides. Compound V had an ultraviolet absorption band at 275 mμ (4.15) which is also typical of the 2-quinolone structure. The ultraviolet spectra of the quinolones prepared were determined both in absolute ethanol and 0.2 M ethanolic hydrogen chloride to further establish their structures. The absorption bands of 2-quinolones should show no shifts in acid while those of 4-quinolones should give absorption curves identical to those of their quaternary analogs in 0.2 M methanolic hydrogen chloride. Although simple 2-trifluoromethyl-4-quinolones are too weakly basic for their spectra to show appreciable shifts in acid (3), the compounds synthesized in this investigation showed the behavior expected of a 4-quinolone structure. For instance, the ultraviolet spectrum of compound IV can be compared with the spectrum of 5-methoxy-2-methyl-1,10-phenanthrolin-4-ol which shows maxima at 241, 272 and 319 mμ in 0.1 N sodium hydroxide but is shifted to 207, 233 and 266 mμ in 0.1 N hydrochloric acid (8). 2-Methyl-1,10-phenanthrolin-4-ol shows a similar behavior in these two solvents while 1,10-phenanthrolin-2-ol has maxima at 222 and 286 mμ in base, and at 218 and 284 mμ in acid, therefore remaining essentially unchanged.

The compounds prepared in this investigation are shown in Table I. The ultraviolet data are listed in Table II.

EXPERIMENTAL (9)

Preparation of the Quinolines, Naphthyridines and Phenanthrolines.

These reactions were carried out according to a previously described method (3) and are illustrated with the preparation of 2-trifluoromethylbenzo[h]quinolin-4-ol. A mixture of 1-naphthylamine (7.1 g., 0.05 mole), which had been previously recrystallized from aqueous ethanol, and 30 ml. of polyphosphoric acid was stirred and heated to 100-110°. Ethyl trifluoroacetoacetate (9.2 g., 0.05 mole) was added to it, in small portions. The mixture was heated at 140-150° for 1.5 hours and allowed to stand at room temperature overnight. The dark purple solution was cooled in an ice bath and diluted with 150 ml. of water and 60 ml. of 10% sodium hydroxide, with stirring, to *p*H 1. The pink solid which formed was removed by filtration and dissolved in 50 ml. of ice-cold 10% sodium hydroxide. A small amount of black tar was removed from the basic solution and the filtrate acidified to *p*H 5 with glacial acetic acid, to yield a pink solid which was recrystallized from aqueous ethanol to give 2-trifluoromethylbenzo[h]quinolin-4-ol (I) as a beige powder. Compound I may also be sublimed at 135-140° at 0.1 mm. but this process does not remove the colored impurities.

N-(1-Naphthyl)-4,4,4-trifluoroacetamide (VI).

This condensation was carried out by a method similar to the one described in Organic Syntheses (10) for the preparation of ethyl 3-anilinocrotonate. Ethyl trifluoroacetoacetate (18.6 g., 0.1 mole), 1-naphthylamine (14.3 g., 0.1 mole), five drops of glacial acetic acid and 50 ml. of benzene were placed in a 250 ml. round-bottomed flask fitted with an addition funnel and a Dean-Stark tube surmounted by a reflux condenser. The mixture was refluxed for 3 hours and a yellow color developed. Benzene was added occasionally to the reaction mixture and water was removed from the trap. At the end of the refluxing period, the reaction was cooled and a yellow powder deposited, 4.68 g. (17.2% yield) of N-(1-naphthyl)-4,4,4-trifluoroacetoacetamide (VI).

Anal. Calcd. for $C_{14}H_{10}F_3NO_2$: C 59.79; H 3.58; F 20.27; N, 4.98. Found: C, 59.77; H, 3.69; F, 20.43; N, 5.08.

This compound melted from 209-210° with vigorous bubbling and the formation of long needles which in turn melted at 305°.

When compound VI (2.03 g., 0.007 mole) was placed in a test tube and heated with a free flame until the product melted and resolidified, a yellow product was obtained which was recrystallized from acetone to yield 4-trifluoromethylbenzo[h]quinolin-2-ol (V).

N-(1-Naphthyl)-3-(1-naphthylamino)-4,4,4-trifluorocrotonamide (VII).

The volume of the remaining benzene solution from the above reaction was reduced and distillation of the residue was attempted, when a large amount of solid deposited in the distilling flask. The distillation was stopped and the cooled residue diluted with aqueous ethanol to give 5.97 g. of a beige solid which had a wide melting point range. This solid was insoluble in 10% sodium hydroxide. A first recrystallization from aqueous ethanol gave a small amount of compound V. Addition of water to the ethanol yielded a main fraction which after several more recrystallizations from ethanol gave pure N-(1-naphthyl)-3-(1-naphthylamino)-4,4,4-trifluorocrotonamide (VII), m.p. 188-190°.

Anal. Calcd. for $C_{24}H_{17}F_3N_2O$: C, 70.93; H, 4.22; F, 14.02; N, 6.89. Found: C, 70.88; H, 4.16; F, 14.31; N, 6.81.

The mother liquor remaining from the initial reaction gave a thick gum which could not be crystallized when further evaporation was tried.

4-Chloroquinolines, naphthyridines and phenanthrolines.

These reactions were carried out by heating the hydroxy compounds with a mixture of phosphorus pentachloride and phosphorus oxychloride at 140° for one hour (3).

4-Hydrazinoquinolines and naphthyridines.

4-Chloro-2-trifluoromethylbenzo[h]quinoline (Ia) (1.48 g., 0.005 mole) and 4-chloro-5-methyl-2-trifluoromethylbenzo[h]-1,6-naphthyridine (IIa) (1.12 g., 0.004 mole) were each refluxed with hydrazine hydrate (2 g., 0.04 mole) in 10 and 20 ml. of ethylene glycol respectively for 3 hours to yield the corresponding hydrazino derivatives as described previously (3).

4-Azido-2-trifluoromethylbenzo[h]quinoline (Id).

This compound was prepared by adding 1 ml. of concentrated hydrochloric acid to a solution of 4-hydrazino-2-trifluoromethylbenzo[h]-quinoline (Ib), (0.62 g., 0.002 mole) in 20 ml. of absolute ethanol. Sodium nitrite (0.2 g., 0.003 mole) in 5 ml. of water was added to the acid solution and the mixture diluted with water. The yellow product formed was recrystallized from aqueous ethanol to yield orange needles of Id.

1,2,3,4- or 7,8,9,10-Tetrahydro-5-methoxy-2-trifluoromethyl-1,10-phenanthroline.

A suspension of one teaspoon of Raney Nickel slurry (11) in 30 ml. of absolute methanol was saturated with hydrogen. A suspension of 4-chloro-5-methoxy-2-trifluoromethyl-1,10-phenanthroline (IVa) (1.04 g., 0.0034 mole) in 30 ml. of anhydrous methanol and 3.5 ml. of a

1 N methanolic potassium hydroxide solution was added. The mixture was stirred at room temperature for two hours while hydrogen was bubbled into the solution. The solid material was removed by filtration and the orange filtrate concentrated until a solid precipitated. Addition of water to the solution yielded more solid. Recrystallization from aqueous ethanol gave bright orange needles, m.p. 92.5-94.5°, yield 84.2%.

Anal. Calcd. for $C_{14}H_{13}F_3N_2O$: C, 59.57; H, 4.64; F, 20.19; N, 9.92. Found: C, 59.72; H, 4.70; F, 20.04; N, 9.91.

The analytical data indicates a tetrahydro derivative, either A or B.

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(9) All compounds were recrystallized from aqueous ethanol unless otherwise noted. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin Elmer 421 recording spectrophotometer and ultraviolet spectra with a Cary 14 recording spectrophotometer. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tennessee and Dr. A. Bernhardt, Max Planck Institut, 433 Mülheim (Ruhr), West Germany.

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