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Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. I. Trifluoromethyl Quinolines (1)

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The condensation of ethyl trifluoroacetoacetate with various aromatic amines, in polyphosphoric acid at 150°, gave substituted 2-trifluoromethyl-4-quinolinols. The structure of these compounds was established from a study of their infrared and ultraviolet spectra and, in some cases, by independent synthesis and cyclization of the intermediate 3-arylaminocrotonates. The 2-trifluoromethyl-4-quinolinols were converted to 2-trifluoromethyl-4-chloroquinolines which were subjected to hydrogenolysis with Raney nickel to yield 2-trifluoromethylquinolines and to treatment with an excess of hydrazine to give the corresponding hydrazino derivatives. The diazotization of 2-trifluoromethyl-4-hydrazinoquinolines yielded azides which were unusually stable. The infrared and ultraviolet spectra of some of the compounds prepared are discussed.

Ethyl trifluoroacetoacetate has not been widely used for the synthesis of heterocyclic compounds other than various trifluoromethyl pyrimidines and purines (2-4). Since trifluoromethyl groups have been known to introduce physiological activity into molecules (5,6,7) we decided to study the condensation of ethyl trifluoroacetoacetate with aromatic amines to prepare some substituted quinolines containing the trifluoromethyl group.

Ethyl acetoacetate can react with an aromatic amine in either of two ways. Reaction of the amine at the ester group leads to the formation of an acetoacetanilide while the reaction of the amine at the β-keto group leads to the formation of a β-aminocrotonate (8,9). The β-aminocrotonate can be cyclized to give a 4-quinolinol (10,11). The acetoacetanilide can be cyclized to yield a 2-quinolinol (12,13). The 2- or 4-quinolinols can be prepared without isolating the intermediates.

In the present investigation, it was expected that the electron-withdrawing power of the trifluoromethyl group might lead to the formation of only one intermediate so that subsequent cyclization would yield only one product. This expectation proved to be correct and 4-quinolinols were formed almost exclusively.

The condensation of ethyl trifluoroacetoacetate with various aromatic amines was carried out in polyphosphoric acid at 140-150° by a method similar to that of Staskun and Israelstam (14). Although these authors isolate their products as their corresponding hydrochlorides, in our case, no sparingly soluble hydrochlorides could be obtained even in the presence of a large excess of hydrochloric acid. It is possible that hydrochlorides do not form under these conditions because the basicity of the nitrogen atom in 2-trifluoromethyl-4-quinolinols is greatly decreased by the electron-withdrawing trifluoromethyl group in the 2-position. In the condensation of *o*-toluidine with ethyl trifluoroacetoacetate a by-product was identified as 8-methyl-4-trifluoromethyl carbostyryl.

In order to definitely establish the structures as 2-trifluoromethyl-4-quinolinols, several of them were synthesized by the usual Conrad-Limpach method which involves the isolation and subsequent cyclization of the intermediate 3-aminocrotonates or anils (15,16) (see equation 1).

None of the corresponding arylacetoacetanilide was isolated but in two cases a by-product which appears to be a 3-arylaminoarylcrotonamide was obtained. A similar product has been reported from the reactions of ethyl acetoacetate (17) and ethyl benzoylacetate (18) with amines. It was believed to arise by initial formation of some arylacetoacetanilide which reacts further with free amine, since the reaction of the 3-arylaminocrotonate with more amine yields little if any of this product (15,19).

The 3-arylaminocrotonates were cyclized in refluxing diphenyl ether to give good yields of 2-trifluoromethylquinolinols (I). Mixtures of these products and the compounds prepared by cyclization in polyphosphoric acid showed no depression in melting point and their infrared spectra were identical. Cyclization of 3-(*p*-toluidino)-N-(*p*-tolyl)-4,4,4-trifluorocrotonamide (II, R = *p*-CH_3) in concentrated sulfuric acid gave a quantitative yield of the corresponding carbostyryl (III).

Infrared data has been used as a means of distinguishing between 2- and 4-quinolones (20,21,22). These data show that 2-quinolones absorb in the range 1641-1667 cm^{-1} while 4-quinolones absorb

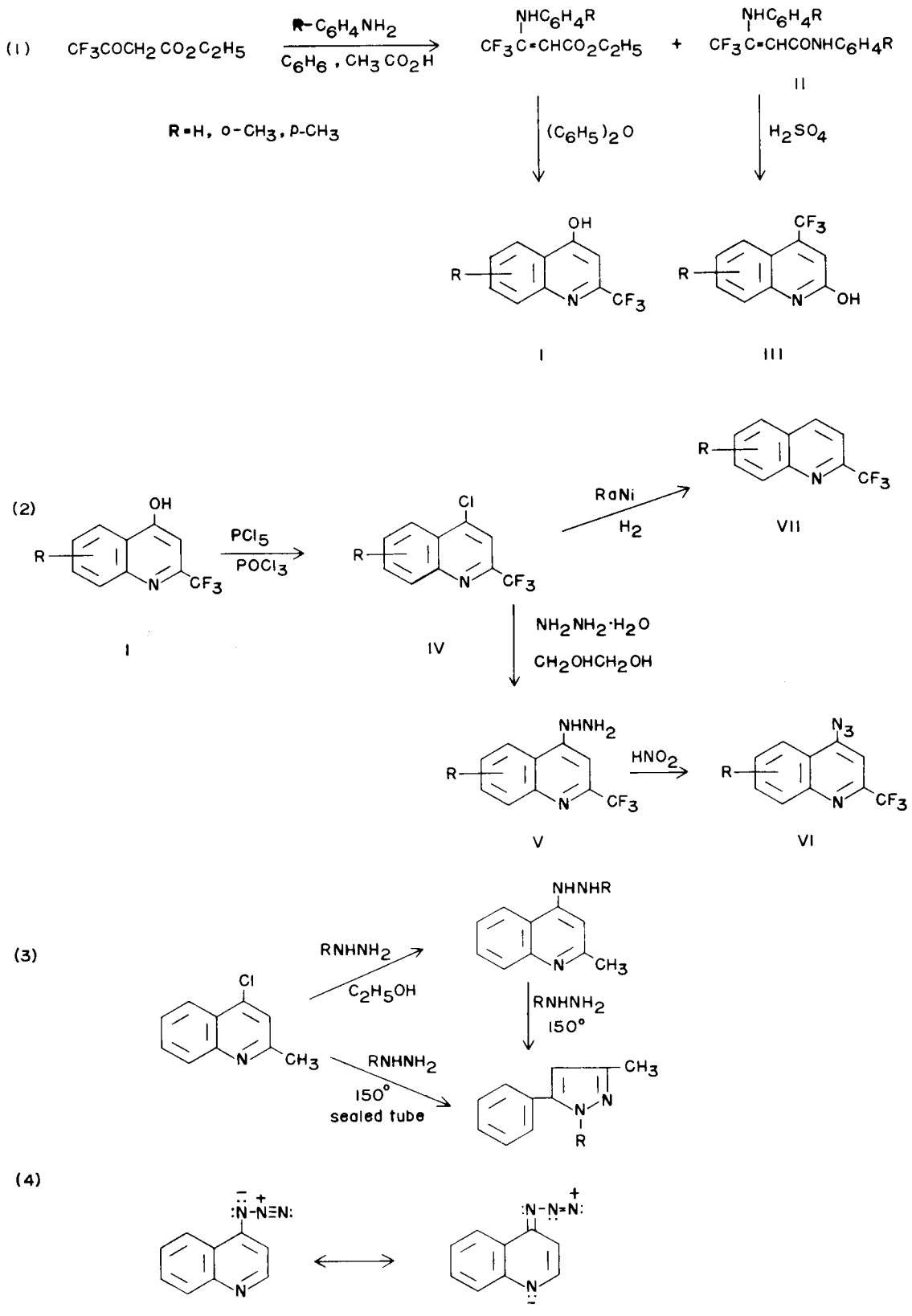
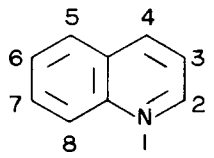

(1)
CF3COCH2CO2C2H5
R-C6H4NH2
C6H6, CH3CO2H
NHC6H4R
CF3C=CHCO2C2H5
+
NHC6H4R
CF3C=CHCONHC6H4R
II
R=H, o-CH3, p-CH3
(C6H5)2O
H2SO4
OH
CF3
R
N
CF3
OH
I
III
(2)
PCl5
POCl3
Cl
RaNi
H2
VII
IV
NH2NH2·H2O
CH2OHCH2OH
NHNH2
HNO2
N3
V
VI
(3)
RNHNH2
C2H5OH
NHNHR
CH3
RNHNH2
150°
150°
sealed tube
(4)

TABLE I

Substituted Quinolines



Compd.	Position of Substituents							Analysis, %							
								Carbon		Hydrogen		Fluorine		Nitrogen	
No.	2	4	6	8	Formula	M.p., °C	Yield, %	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Ia	CF_3	OH	H	H (a)	$C_{10}H_6F_3NO$	210.5-211.5	58.8	56.35	56.59	2.84	2.71	26.74	26.66	6.57	6.41
Ib	CF_3	OH	H	CH_3	$C_{11}H_8F_3NO$	130-132	60.5	58.15	57.98	3.55	3.63	25.09	24.84	6.17	6.28
Ic	CF_3	OH	CH_3	H	$C_{11}H_8F_3NO$	251-252	87	58.15	57.93	3.55	3.29	25.09	24.98	6.17	6.23
Id	CF_3	OH	OCH_3	H	$C_{11}H_8F_3NO_2$	275-277	79	54.33	54.20	3.32	3.34	23.44	23.65	5.76	5.69
Ie	CF_3	OH	Br	H (b)	$C_{10}H_5BrF_3NO$	240-260	84	41.12	41.04	1.72	1.77	19.52	19.73	4.79	4.61
IIIa	OH	CF_3	H	CH_3	$C_{11}H_8F_3NO$	240-242	--	58.15	57.88	3.55	3.56	25.09	25.45	6.17	5.96
IIIb	OH	CF_3	CH_3	H	$C_{11}H_8F_3NO$	243-245	100	58.15	58.33	3.55	3.53	25.09	25.02	6.17	6.31
IVa	CF_3	Cl	H	H (c)	$C_{10}H_5ClF_3N$	38-40	95	51.86	51.62	2.18	2.15	---	---	6.05	5.90
IVb	CF_3	Cl	H	CH_3 (d)	$C_{11}H_7ClF_3N$	---	73	53.78	53.87	2.87	3.09	---	---	5.70	5.58
IVc	CF_3	Cl	CH_3	H	$C_{11}H_7ClF_3N$	66-68	96	53.78	53.84	2.87	2.79	---	---	5.70	5.65
IVd	CF_3	Cl	OCH_3	H	$C_{11}H_7ClF_3NO$	105-107	97.2	50.49	50.63	2.70	2.92	---	---	5.34	5.00
IVe	CF_3	Cl	Br	H	$C_{10}H_4BrClF_3N$	97-98	99.3	38.68	38.73	1.30	1.38	---	---	4.51	4.32
Va	CF_3	$NHNH_2$	H	H	$C_{10}H_8F_3N_3$	215-217	93	52.86	52.79	3.55	3.71	25.09	25.20	18.50	18.61
Vb	CF_3	$NHNH_2$	H	CH_3	$C_{11}H_{10}F_3N_3$	146-148	55	54.76	54.70	4.18	4.29	23.63	23.76	17.42	17.55
Vc	CF_3	$NHNH_2$	CH_3	H	$C_{11}H_{10}F_3N_3$	200-200.5	87	54.76	54.67	4.18	4.34	23.63	23.72	17.42	17.27
Vd	CF_3	$NHNH_2$	OCH_3	H	$C_{11}H_{10}F_3N_3O$	226-228	85	51.36	51.48	3.92	4.08	22.16	22.05	16.34	16.37
Ve	CF_3	$NHNH_2$	Br	H (e)	$C_{10}H_7BrF_3N_3$	203.5-205.5	95.5	39.24	39.17	2.30	2.21	18.62	18.56	13.73	13.66
VIa	CF_3	N_3	H	H	$C_{10}H_5F_3N_4$	120-122	81.5	50.43	50.21	2.12	1.99	23.93	24.10	23.53	23.45
VIb	CF_3	N_3	H	CH_3	$C_{11}H_7F_3N_4$	75-78	91.5	52.38	52.19	2.80	2.93	22.60	22.47	22.22	22.39
VIc	CF_3	N_3	CH_3	H	$C_{11}H_7F_3N_4$	126-128	76.3	52.38	52.33	2.80	2.85	22.60	22.61	22.22	22.40
VId	CF_3	N_3	OCH_3	H	$C_{11}H_7F_3N_4O$	172.5-173	83.2	49.26	49.34	2.63	2.82	21.25	21.11	20.89	20.77
VIe	CF_3	N_3	Br	H	$C_{10}H_4BrF_3N_4$	128-129.5	88	37.87	37.80	1.27	1.30	17.97	18.11	17.67	17.58
VIIa	CF_3	H	H	H (f)	$C_{10}H_7ClF_3N$	145	43.7	51.41	51.16	3.02	3.29	---	---	5.99	6.01
VIIb	CF_3	H	H	CH_3 (g)	$C_{11}H_8F_3N$	---	39	62.56	62.66	3.82	3.91	26.99	26.99	6.63	6.70
VIIc	CF_3	H	CH_3	H	$C_{11}H_8F_3N$	92-93	8.8	62.56	62.73	3.82	3.95	26.99	27.09	6.63	6.48
VIId	CF_3	H	OCH_3	H (h)	$C_{11}H_8F_3NO$	54.5-57	89	58.15	58.05	3.55	3.48	25.09	25.13	6.17	6.18

(a) Previously prepared but no m.p. reported. (b) Sublimes without melting. (c) Lit. (19) m.p. 33.5-34°. (d) Light yellow oil, b.p. 60° (0.2 mm.). (e) Calculated bromine: 26.10%. Found: 26.05%. (f) Isolated as its hydrochloride. (g) Colorless oil, b.p. 50° (0.35 mm.). (h) Recrystallized from cyclohexane.

TABLE II

Infrared Spectra of Some Substituted Quinolines (a)

Ia	Ib	Ic	Id	Ie	IIIa	IIIb	VIa	VIb	VIc	VId	VIe
3240w	3255w	3250w	3250w	3250w							
3085w	3190w	3150m	3170w	3160w	3175w	3160w					
2975w	3120w	3080s	3090m	3075m	3065w			2170w	2164w	2180w	
2920w		2975s	2980m	2960m		3020w				2160m	
2815w		2920s				2920w	2135s	2110s	2118s	2125s	2122s
		2815m	2825w	2800w		2850w					
1615s	1622m	1605s	1610s	1620m	1670s	1660s					
	1605m			1600s	1615s	1600m	1615w	1606w	1615w	1610s	
							1590m	1585m	1580m	1570m	1572w
1565s	1577s	1560s	1560s	1550s		1560w	1565m	1570m	1563m		1550m
1525s	1530m	1510s	1520s	1505s			1510m	1505m	1498m	1492s	1480m
1473m	1460m	1485s	1490s	1460s	1465w		1470w	1468w	1480w	1472s	
1448m	1450w	1450w	1440w		1450w		1430w		1442w	1428w	1450s
	1400m	1410w	1425w	1400w	1400w	1420m	1420w	1412w		1410w	
							1380s	1380s	1375s	1372s	
1350w	1370w	1355w	1385m	1345w	1380w		1365s	1356s	1360s	1353s	1355s
1318s	1300m	1300s	1300m	1285s	1317m	1310w	1342w	1320w	1325w	1315w	1308m
1278s	1270s	1270s	1275m	1270s	1275s	1280m	1280s	1272s	1272s	1275s	1268s
1233m	1245m	1240w			1260m	1260s	1255s	1250s	1250s	1253s	1242m
					1240m		1248m		1240s	1240s	1230m
		1225m	1220s	1215m	1200s	1210w			1213w	1225s	1190s
							1170s	1178s	1170s	1178m	1170s
1190s	1185s	1190s	1190s	1180s	1175s	1160s		1163s		1167s	1153s
	1175s	1180s					1135s	1135s	1145s	1123s	1135s
	1155m					1130s	1105s	1108m	1100s	1090s	1093m
1133s	1140s	1135s	1135s	1135s	1125s	1120s				1015m	1050w
1100w	1095m	1090m	1100m	1095w	1070s		920s	915m	913s	915m	904m
	1060w		1075w	1075w		985w	850s	843s	850s	903m	865w
	995w		1025w			950w	785w	808w	820w	840s	840m
	955w		945w		960w	870w	772s	765s	750w	825m	
940w	937w	935m	915w	930w	895s	810w	735m	730m	710m	700m	725w

(a) Bands are in cm^{-1}, w = weak, m = medium, s = strong.

TABLE III

Ultraviolet Spectra of Some Substituted Quinolines

	λ max (C_2H_5OH), mμ (log ε)	λ max (0.2 M HCl in C_2H_5OH), mμ (log ε)
Ia	225(4.45); 319(3.84); 335(3.85)	229(4.57); 321(3.95); 335(3.89)
Ib	228(4.72); 293(3.78); 319(3.63)	219(3.88); 292(3.90); 319(3.60)
Ic	231(4.55); 293(3.69); 327(3.79); 341(3.76)	236(4.50); 326(3.76)
Id	241(4.45); 326(3.83)	242(4.46); 296(3.51)
Ie	239(4.55); 330(3.83); 342(3.81)	239(4.62); 294(3.76); 340(3.64)
IIIa	224(4.23); 274(3.74); 346(3.65)	233(4.12); 255(3.90); 284(3.56); 344(3.44)
IIIb	233(4.59); 257(3.90); 276(3.76); 351(3.75)	235(4.33); 254(3.73); 274 shoulder
VIa	233(4.61); 305(3.91)	
VIb	237(4.55); 314(3.85)	
VIc	238(4.63); 308(3.88)	
VId	246(4.45); 306(3.70)	
VIe	239(4.72); 306(4.02)	
VIIc	231(4.66); 235(4.68); 293(3.51); 306(3.51); 320(3.47)	
VIId	241(4.56); 284(3.42); 330(3.60)	

between 1647 cm^{-1} and 1620 cm^{-1}. All of the compounds prepared by the polyphosphoric acid procedure absorbed between 1600 cm^{-1} and 1628 cm^{-1}, close to the range established for 4-quinolones. The 2-quinolones which were prepared (IIIa and b) showed strong carbonyl peaks in the 1660-1670 cm^{-1} region, characteristic of true amides.

Ultraviolet spectra can also be used to differentiate between the 2- and 4-isomers. The 2-quinolones have maxima at 263-298 mμ (log ε ~ 3.9) while the 4-quinolones have a minimum at 270 mμ. The 2-quinolones, like true amides show no shift in acid in the ultraviolet but the 4-quinolones give curves identical to those of their quaternary analogs in 0.2 M methanolic hydrogen chloride (20). Compounds Ia-e showed no maxima between 254 mμ and 287 mμ, in agreement with the assignment of the 4-quinolone structure to these compounds. However, the compounds containing the 2-trifluoromethyl-4-quinolone structure are too weakly basic for their spectra to show appreciable shifts in acid. This is in agreement with the previous observation that they could not be isolated as their hydrochlorides from solution. Compounds IIIa and b had maxima at 274 mμ (log ε = 3.74) and 276 mμ (log ε = 3.76), in ethanol, thus supporting the carbostyril structure.

It has been reported that 2-quinolinol gives a brownish color with ferric chloride while 4-quinolinol gives a red color more typical of a phenol. When this test was applied to our compounds, the 2-quinolones showed no color change while the 4-quinolinols gave darker orange or brownish color. This test was not found suitable to differentiate between the isomers.

The 4-hydroxyl groups in compounds Ia-e were easily substituted by chlorine by treating these compounds with phosphorus pentachloride and phosphorus oxychloride. Compounds containing the 4-chloroquinoline structure are versatile intermediates since the halogen atom is located on a carbon atom which has a low electron density and consequently it is reactive towards various nucleophilic reagents. The halogen atom can also be removed by catalytic reduction (24).

The 2-trifluoromethyl-4-chloroquinolines were very reactive intermediates and were utilized for the preparation of various quinoline derivatives according to the scheme shown in equation 2.

Koenings and Freund (25) showed that the reaction between 4-chloroquinaldine and hydrazine or phenylhydrazine may be represented as shown in equation 3. Alberti (26) reported that cleavage to the substituted pyrazole ring also occurred when the reagents were refluxed in ethylene glycol for three hours. The 4-chloro compounds (IVa-e) were treated with a large excess of hydrazine in refluxing ethylene glycol according to the procedure of Alberti (26), in the hope of effecting the cleavage to substituted pyrazoles. The 4-hydrazino compounds were obtained as the sole products.

The 4-hydrazino structure was supported by the infrared spectra of these compounds and the reactions of a hydrazino group. Hydrazino groups in the 2- or 4-positions of a quinoline ring can be removed by treatment with alkali or a salt such as cupric sulfate or ferric chloride (27). Treatment of compound Vc (R = 6-Me) with ferric chloride gave 6-methyl-2-trifluoromethylquinoline which proved to be identical to compound VIIc prepared by the reduction of compound IVc with Raney nickel and hydrogen. The synthesis via reaction of the hydrazine with ferric chloride is not as convenient as the catalytic reduction procedure to prepare unsubstituted quinolines, since it is difficult to remove the products from the large amount of inorganic precipitate at the end of the reaction.

Further evidence for the presence of a hydrazino group was obtained by the fact that on diazotization

the hydrazino compounds Va-e did not yield pyrazolotriazines but rather 4-azidoquinolines (VIa-e) (30). Compounds VIa-e were quite stable and did not decompose even on melting. They showed strong infrared absorption bands in the triple bond region near 2120 cm^{-1}. The azide group is reported to absorb in the infrared at 2080-2169 cm^{-1} and 1177-1343 cm^{-1}, the first band being more useful in diagnosis (28). Another infrared study of many aliphatic and aromatic azides has shown the strong asymmetric vibration of the azido group occurs at 2083-2114 cm^{-1} and is practially independent of environment (29).

Kamiya (31) reported that 4-azidoquinoline-1-oxide on treatment with alkoxides gave the corresponding 4-alkoxyquinoline-1-oxides, and that when the compound was treated with a variety of anions of active methylene compounds very low yields of triazole were obtained along with 4-aminoquinoline-1-oxide. 4-Azidoquinoline itself did not react with sodium alkoxide but with the sodium salt of ethyl acetoacetate it gave a substituted triazole (31). The azido group could also be reduced to an amino group by treatment with hydrogen over palladium on charcoal.

The 4-azido-2-trifluoromethylquinolines behave differently. When compound VIe was treated with ethyl cyanoacetate and sodium ethoxide in ethanol, at room temperature, 4-amino-6-bromo-2-trifluoromethylquinoline was isolated in good yield. Compound VId yielded an even better yield of 4-amino-6-methyl-2-trifluoromethylquinoline, under the same conditions; it did not react with sodium ethoxide in ethanol, at room temperature. Reduction of compound VIa with Raney nickel in refluxing ethanol gave a quantitative yield of 4-amino-2-trifluoromethylquinoline. Attempts to react compound VId with naphthoquinone failed and unreacted starting material was recovered after refluxing the mixture in ethanol for three hours. When the mixture was refluxed in diphenyl ether extensive decomposition resulted.

The stability and low reactivity of the 4-azidoquinolines can probably be explained by the fact that the 4-azidopyridine system can include the ring nitrogen in resonance with the azido group giving it increased stabilization over compounds similar to phenyl azide. This resonance is pictured in equation 4.

Some of the compounds prepared (Ib, Id and Vd) were submitted to microbiological tests. Only compound Ib was found to inhibit the growth of some microorganisms.

The physical properties and analytical data for the compounds synthesized are shown in Table I. Data concerning the infrared and ultraviolet absorption of some of the new compounds prepared are shown in Table II and III respectively.

EXPERIMENTAL (32)

Ethyl 3-Anilino-4,4,4-trifluorocrotonate.

This compound was prepared from ethyl trifluoroacetoacetate and aniline by a procedure similar to the one described for the preparation of ethyl-3-anilinocrotonate (16). The product was purified by fractional distillation and was obtained as an almost colorless liquid, yield 47.2%, b.p. 77° (0.28 mm.), n_D^{20} 1.5020.

Anal. Calcd. for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; F, 22.00; N, 5.40. Found: C, 55.79; H, 4.66; F, 21.85; N, 5.56.

The residue which remained in the distilling flask solidified on cooling. This solid was recrystallized from aqueous ethanol and shown to be identical to previously prepared 2-trifluoromethyl-4-quinolinol.

Ethyl 3-(*o*-Toluidino)-4,4,4-trifluorocrotonate.

This compound was prepared by the method described above (16), yield 30.8%, b.p. 82-84° (0.3-0.4 mm.), n_D^{20} 1.5034.

Anal. Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; F, 20.86; N, 5.13. Found: C, 57.00; H, 4.98; F, 20.69; N, 5.31.

In this case, a thick gummy residue was left in the distilling flask. It was dissolved in acetone and on evaporation a solid was obtained which was recrystallized from ethanol to yield white needles, 2.18 g., m.p. 149-150.5°. The analytical results seemed to indicate that this solid was impure 3-(*o*-toluidino)-N-(*o*-tolyl)-4,4,4-trifluorocrotonamide.

Anal. Calcd. for $C_{18}H_{17}F_3N_2$: C, 64.66; H, 5.12; F, 17.05; N, 8.38. Found: C, 65.24; H, 5.15; F, 18.35; N, 8.25.

The infrared spectrum of this compound also supports this structure since it shows absorption bands at 3275 cm^{-1}, 1643 cm^{-1}, 1535 cm^{-1} and 1285 cm^{-1} characteristic of secondary amides.

Ethyl 3-(*p*-Toluidino)-4,4,4-trifluorocrotonate.

This compound was prepared by the previously described procedure, yield 46.9%, b.p. 92° (0.25 mm.), n_D^{21} 1.5059.

Anal. Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; F, 20.86; N, 5.13. Found: C, 56.99; H, 5.06; F, 20.77; N, 5.30.

A thick residue was left in the distilling flask. It was dissolved in acetone and treated with water to yield a solid which was recrystallized from aqueous ethanol to give 3.1 g. (19.5%) of 3-(*p*-toluidino)-N-(*p*-tolyl)-4,4,4-trifluorocrotonamide, m.p. 124-126°.

Anal. Calcd. for $C_{18}H_{17}F_3N_2O$: C, 64.66; H, 5.12; F, 17.05; N, 8.38. Found: C, 64.89; H, 5.22; F, 17.33; N, 8.40.

2-Trifluoromethyl-4-quinolinols.

a. Direct Condensation of Aromatic Amines with Ethyl Trifluoroacetoacetate.

These preparations were carried out according to a modification of the method of Staskun and Israelstan (14). The general procedure is illustrated with the condensation of *o*-toluidine and ethyl trifluoroacetoacetate, the only example in which both isomeric 4- and 2-quinolinols could be isolated. Ethyl trifluoroacetoacetate (9.2 g., 0.05 mole) and 50 ml. of polyphosphoric acid were placed in a 250 ml. three-necked, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, reflux condenser and a calcium chloride drying tube. The mixture was stirred, heated to 100° in a wax bath, and redistilled *o*-toluidine (5.4 g., 0.05 mole) was added to it gradually. The reaction was heated at 140-150° for 1.5 hours. After standing at room temperature overnight, the mixture was cooled in an ice bath, and diluted with water and 10% sodium hydroxide to a total volume of 600 ml. (*p*H 1). The beige solid which formed was collected by filtration and dissolved in 40 ml. of ice-cold 10% sodium hydroxide. A small amount of insoluble material was removed by filtration and the filtrate acidified to *p*H 5 with glacial acetic acid. This solid which formed was recrystallized from aqueous ethanol to yield a white powder, 8-methyl-2-trifluoromethyl-4-quinolinol (Ib).

The material which was insoluble in sodium hydroxide was also recrystallized from aqueous ethanol to yield a white solid, 8-methyl-4-trifluoromethyl-2-quinolinol (IIIa).

b. By Cyclization of the 3-Arylaminocrotonates.

The previously prepared 3-arylaminocrotonates were cyclized in diphenyl ether according to previously described directions used to cyclize ethyl-3-anilinocrotonate (16). All three compounds yielded the corresponding 2-trifluoromethyl-4-quinolinols.
6-Methyl-4-trifluoromethyl-2-quinolinol (IIIb).

3-(*p*-Toluidino)-N-(*p*-tolyl)-4,4,4-trifluorocrotonamide was cyclized in concentrated sulfuric acid by a procedure similar to the one described for the preparation of 4-methylcarbostyryl (33). A quantitative yield of 6-methyl-4-trifluoromethyl-2-quinolinol was obtained.

2-Trifluoromethyl-4-chloroquinolines (IVa-e).

The quinolinols were converted to the corresponding chloro de-

rivatives by heating with a mixture of phosphorus pentachloride and phosphorus oxychloride according to the procedure described by Snyder *et al.* (34).

2-Trifluoromethyl-4-hydrazinoquinolines (Va-e).

The procedure followed was that described by Alberti (26) for the cleavage of 4-chloroquinolines to give substituted pyrazoles. In a typical experiment hydrazine hydrate (2 g., 0.04 mole) was added to 6-bromo-4-chloro-2-trifluoromethylquinoline (1.39 g., 0.004 mole) in 10 ml. of ethylene glycol. The reaction was moderately exothermic. It was refluxed for 3 hours, cooled and diluted with water to yield 6-bromo-4-hydrazino-2-trifluoromethyl quinoline. This compound was recrystallized from ethanol to yield light orange needles.

4-Azido-2-trifluoromethyl Quinolines (VIa-e).

A typical procedure is illustrated with the preparation of 4-azido-2-trifluoromethylquinoline. Concentrated hydrochloric acid (25 ml.) was added to a solution of 4-hydrazino-2-trifluoromethyl quinoline (4.0 g., 0.017 mole) in 100 ml. of 95% aqueous ethanol. A solution of sodium nitrite (2.0 g., 0.029 mole) in 10 ml. of water was added slowly to the acid solution while cooling the reaction mixture in ice. After the reaction had stood for half an hour, the yellow solid which formed was collected by filtration. Recrystallization from aqueous ethanol yielded 4-azido-2-trifluoromethylquinoline as light orange needles.

2-Trifluoromethylquinolines (VIIa-d).

a. Hydrogenolysis of the Chloro Substituted Compounds by Raney Ni.

2-Trifluoromethylquinolines were prepared by reduction of the 4-chloroquinolines using Raney nickel W-2 (35) according to the procedure of Kaemmerer, Homer and Beck (36).

b. From 4-Hydrazino-6-methyl-2-trifluoromethyl Quinoline.

The method of Thielepape (27) was used. 4-Hydrazino-6-methyl-2-trifluoromethylquinoline (0.87 g., 0.004 mole) was dissolved in a little ethanol and heated on a steam bath. A solution of ferric chloride (7.5 g., 0.027 mole) in 68 ml. of water was added portionwise to the hot solution and gas evolution occurred. Enough ethanol was added to keep the final solution clear and the reaction was heated for 1.5 hours. Addition of 25 ml. of 10% aqueous sodium hydroxide precipitated a black powder which was removed by filtration. The filtrate was acidified to *p*H 5-6 with glacial acetic acid and its volume reduced on a rotary evaporator until white flakes began to form. The solid was removed by filtration and recrystallization from aqueous ethanol. A yield of 0.18 g. (23.7%) of 6-methyl-2-trifluoromethyl quinoline was obtained, m.p. 88-91°. A mixture of this substance with 6-methyl-2-trifluoromethyl quinoline previously prepared by the reduction of the chloro derivative with Raney Ni showed no depression in melting point. The infrared spectra of the two compounds were identical.

2-Trifluoromethyl-4-aminoquinolines.

a. By reaction of 4-Azido-2-trifluoromethyl Quinolines with Ethyl Cyanoacetate and Sodium Ethoxide.

The procedure used was similar to the one described by Dimroth (37). A typical experiment is illustrated with 4-azido-6-bromo-2-trifluoromethylquinoline. A solution of sodium (0.05 g., 0.002 mole) in 15 ml. of absolute ethanol, in a round-bottomed flask provided with a condenser, calcium chloride tube, and magnetic stirrer, was cooled and ethyl cyanoacetate (0.32 g., 0.003 mole) was added to it. A slurry of 4-azido-6-bromo-2-trifluoromethylquinoline (0.69 g., 0.002 mole) in 15 ml. of absolute ethanol was added to the cold solution with stirring. The azide dissolved and a fine yellow product precipitated. The mixture was stirred one half hour longer and 15 ml. of water added to it to give a clear orange solution (*p*H 7) which was allowed to stand for 2 days. A trace of solid which deposited was removed by filtration and the volume of the filtrate reduced. Addition of water precipitated a solid which was collected and recrystallized from aqueous ethanol to yield 0.48 g. (75% yield) of 4-amino-6-bromo-2-trifluoromethyl quinoline, m.p. 200-202.5°.

Anal. Calcd. for $C_{10}H_6BrF_3N_2$: C, 41.26; H, 2.08; F, 19.58; N, 9.62. Found: C, 41.27; H, 2.14; F, 19.75; N, 9.58.

The same method was used to obtain a 97.5% yield of 4-amino-6-methyl-2-trifluoromethyl quinoline m.p. 138-140°, from 4-azido-6-methyl-2-trifluoromethylquinoline.

Anal. Calcd. for $C_{11}H_9F_3N_2$: C, 58.40; H, 4.01; F, 25.20; N, 12.38. Found: C, 58.39; H, 4.06; F, 25.03; N, 12.51.

b. By Reduction of 4-Azido-2-trifluoromethyl Quinoline with Raney Ni.

4-Azido-2-trifluoromethylquinoline (0.62 g., 0.003 mole) in 20 ml. of absolute ethanol was added to one quarter teaspoon of Raney Ni slurry (35) in 20 ml. of absolute ethanol while stirring with a magnetic stirrer. The mixture was stirred at room temperature for 1/2 hour and then refluxed for 1.5 hours. Solids were removed by filtration through a sintered-glass funnel and the volume of the filtrate reduced on a rotary evaporator. Addition of water to the residue gave a solid which was recrystallized from aqueous ethanol to give a quantitative yield of 4-amino-2-trifluoromethyl quinoline, m.p. 139-143°.

Anal. Calcd. for $C_{10}H_7F_3N_2$: C, 56.60; H, 3.32; F, 26.86; N, 13.20. Found: C, 56.68; H, 3.36; F, 26.70; N, 13.16.

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REFERENCES

(1) Abstracted in part from the Ph. D. thesis of Adrienne Steinacker Dey, University of Pennsylvania, 1964.
(2) A. Giner-Sorolla and A. Bendick, *J. Am. Chem. Soc.*, 80, 5744 (1958).
(3) E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3278 (1959).
(4) S. Inoue, A. J. Saggiomo, and E. A. Nodiff, *J. Org. Chem.*, 26, 4504 (1961).
(5) J. A Barone and H. Tieckelman, *ibid.*, 26, 598 (1961).
(6) C. Heidelberger, D. G. Parsons, and D. C. Remy, *J. Med. Chem.*, 7, 1 (1964).
(7) H. L. Yale, *ibid.*, 1, 121 (1949).
(8) R. C. Elderfield, "Heterocyclic Compounds", Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 30.
(9) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, 70, 2402 (1948).
(10) M. Conrad and L. Limpach, *Ber.*, 20, 944, 988 (1887).
(11) L. Limpach, *ibid.*, 64, 969 (1931).
(12) L. Knorr, *Ann.*, 236, 83 (1886).
(13) K. N. Campbell, R. S. Tipson, R. C. Elderfield, B. K. Campbell, M. A. Klapp, W. J. Gensler, E. Morrison, and W. J. Moran, *J. Org. Chem.*, 11, 803 (1946).
(14) B. Staskun and S. S. Israelstam, *ibid.*, 26, 3191 (1961).
(15) S. Coffey, J. K. Thomson and F. J. Wilson, *J. Chem. Soc.*, 856 (1936).
(16) G. A. Reynolds and C. R. Hauser, "Organic Synthesis", Col. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 593.
(17) J. K. Thomson and F. J. Wilson, *J. Chem. Soc.*, 111 (1935).
(18) B. Staskun, *J. Org. Chem.*, 29, 1153 (1964).
(19) M. L. Belli, S. Fatutla, M. Forghiassin, G. Illuminati, P. Linda, G. Marino, and E. Zinato, *Ric. Sci.*, 2 (4), 530 (1963).
(20) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, 82, 4395 (1960).
(21) J. R. Price and J. B. Willis, *Aust. J. Chem.*, 12, 589 (1959).
(22) M. F. Gundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957).
(23) R. C. Elderfield, "Heterocyclic Compounds", Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 151.
(24) *Ibid.*, p. 120.
(25) E. Koenigs and J. Freund, *Ber.*, 80, 143 (1947).
(26) C. Alberti, *Gazz. Chim. Ital.*, 87, 772 (1957).
(27) E. Thielepape, *Ber.*, 55, 136 (1922).
(28) J. H. Boyer and F. C. Canter, *Chem. Rev.*, 54, 1 (1954).
(29) E. Lieber, C. N. Ramachandra Rao, T. S. Chao, and C. W. Hoffman, *Anal. Chem.*, 29, 916 (1957).
(30) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), 9, 87 (1961); *Chem. Abstr.*, 55, 27338b (1961).
(31) S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), 10, 471 (1962); *Chem. Abstr.*, 58, 4545a (1964).
(32) 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. The infrared spectra were determined with a Perkin Elmer 421 recording spectrophotometer as potassium bromide discs. The ultraviolet spectra were taken in absolute ethanol and 0.2 M hydrochloric acid in absolute ethanol 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.
(33) W. M. Lauer and C. E. Kaslow, "Organic Synthesis", Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 580.
(34) H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heymingen, *J. Am. Chem. Soc.*, 69, 371 (1947).
(35) R. Mozingo, "Organic Synthesis", Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.
(36) H. Kaemmerer, L. Horner, and H. Beck, *Chem. Ber.*, 91, 1376 (1958).
(37) O. Dimroth, *Ber.*, 35, 4041 (1902).

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