Antimalarials. 6. Some New α-Alkylaminomethyl-4-quinolinemethanols[1]

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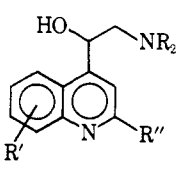
Received August 10, 1970

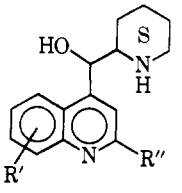
Nine new 4-quinoline amino alcohols were synthesized for antimalarial tests. Successful approaches for introducing the α-pyridyl group were addition of the 4-quinolyllithium to 2-pyridyl nitrile and to 2-pyridaldehyde. Selective hydrogenation of 8-trifluoromethyl-4-quinolyl 2-pyridyl ketone gave low yields of the quinoline α-pyridylmethanol and large yields of the tetrahydroquinoline. 7-Trifluoromethylcinchoninic acid added 2-pyridyllithium giving low yields of both the ketone and the α,2-dipyridyl ketone; the ester gave the pyridyl ketone in good yield but subsequent selective hydrogenation was unsuccessful.

A large number of 2-aryl-4-quinoline amino alcohols of types **1** and **2** (R″ = aryl)[4,5] have proved to be active or curative against *Plasmodium berghei* in mice,[6] but they were highly phototoxic, due possibly, it has been postulated,[7] to enhancement of nuclear conjugation by the coplanar 2-aryl group. Substitution of CF_3 for the 2-aryl group produced only moderately active antimalarials and these were moderately phototoxic.[8] This paper deals with syntheses and testing of 9 new analogs and investigation of some potentially useful procedures.



1

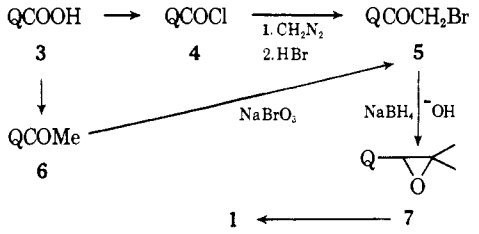
	R	R′	R″
a	Et	6,8-Me_2	*p*-tolyl
b	Bu	6,8-Me_2	*p*-tolyl
c	Et	7-Cl	H
d	Bu	7-CF_3	H



2

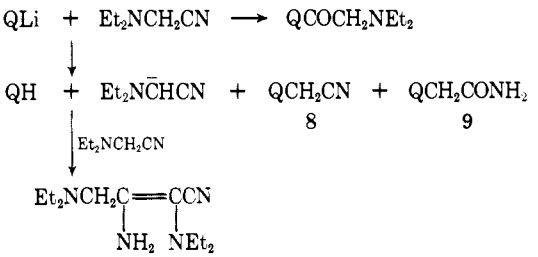
	R′	R″
a	6-F	*p*-tolyl
b	6-F	CF_3
c	8-H	CF_3
d	8-CF_3	H

α-Dialkylaminomethyl-4-quinolinemethanols (1).—The recent and useful modification of the classical synthetic procedures[4] involves the facile and high yield reaction of a dialkylamine with the ethylene oxide **7** which is made either from the appropriate aldehyde, if available,[9] or from the bromo ketone **5** by $NaBH_4$ reduction and added base.[5c,10] An alternative route to the bromo ketone **5**, avoiding the use of CH_2N_2,[4] was through the Me ketone **6** which was prepared by addition of MeLi to the acid **3**. Bromination of **6** with $NaBrO_3$ in HBr[11] gave **5** in high yield, *e.g.*, 2-*p*-tolyl-6,8-dimethyl-4-acetylquinoline (**6a**, 72% from **3**) gave **5a** in 88% yield (66% from **3** which is a better yield than *via* **42**).[3] The bromination of **6a** directly in AcOH or by ammonium perbromide involved formation of considerable amounts of the dibromomethyl ketone as by-product.



Q = substituted 4-quinolyl

Attempts toward a more direct introduction of the amino alcohol group into the quinoline through reaction of 2-trifluoromethyl-4-quinolyllithium[8] with MeCN or with diethylaminoacetonitrile were unsuccessful (not surprisingly[12]). Neither the Me nor the diethylaminomethyl 4-quinolyl ketones were isolated. Evidently extensive ionization and dimerization of both nitriles had occurred, and in the case of diethylaminoacetonitrile, there occurred considerable displacement of the NEt_2 group by the 4-quinolyl anion, presumably giving **8** and **9**. The structure of the one dimer characterized, namely **10**, is based on anal. and ir and nmr spectra.



Q = substituted 4-quinolyl

α-(2-Piperidyl)-4-quinolinemethanols (2).—Of particular interest as potentially useful methods are the following. The addition of 6-chloro- and 6-methyl-2-trifluoromethyl-4-quinolyllithiums at −70° to 2-cyanopyridine gave the known α-(2-pyridyl)-4-quinolyl ketones **11**.[8] The addition of 2-PyLi to 6,8-dimethyl-4-cyano-2-trifluoromethylquinoline also gave **11**. Additions to-2-pyridaldehyde of 2-trifluoromethyl-4-

(1) This work, largely done prior to summer 1968, was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-49-193-MD-2955. Contribution No. 838 of the Army Program on Malaria, R. E. Lutz, Responsible Investigator.

(2) Postdoctoral Research Associates.

(3) A. L. Crosby, M.S. Thesis, University of Virginia, Charlottesville, Va., 1950.

(4) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

(5) (a) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967); (b) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968); (c) *cf.* C. J. Ohnmacht, F. Davis, and R. E. Lutz, *ibid.*, **14**, 17 (1971).

(6) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967). Tests were performed by Dr. Leo Rane, and results were provided through the Walter Reed Army Institute of Research.

(7) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(8) A. Burger and R. M. Pinder, *ibid.*, **11**, 267 (1968).

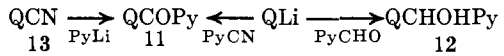
(9) W. C. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *ibid.*, **11**, 1222 (1968).

(10) E. R. Atkinson and A. J. Puttick, *ibid.*, **11**, 1223 (1968).

(11) J. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1831 (1946).

(12) E. L. Eliel and N. J. Murphy, *ibid.*, **75**, 3589 (1953).

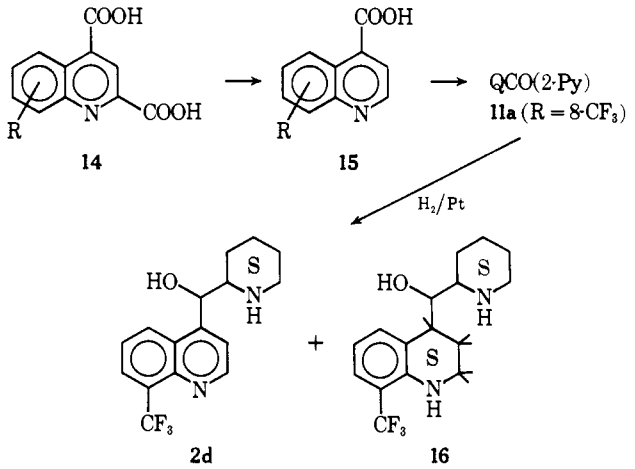
quinolyllithium or its 6-Me derivative gave the corresponding known α-(2-pyridyl)-4-quinolinemethanols **12**.[8]



Py = 2-pyridyl

4-Quinoline Amino Alcohols without a 2 Substituent (1c,d, 2d).—Three examples of these compounds were made to test the effectiveness of Cl and CF_3 groups in the 7 position and of the CF_3 in the 8 position. These, without the 2-aryl group, were not expected to be seriously phototoxic.

Syntheses started from the corresponding isatins which were prepared following published procedures.[13] Pfitzinger condensations of these with pyruvic acid to the quinoline-2,4-dicarboxylic acids **14**[14] and selective thermal decarboxylations in $PhNO_2$ or Ph_2O gave the cinchoninic acids **15**.

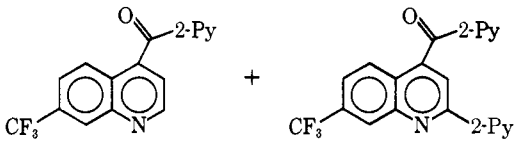


The 8-CF_3 acid **15** added 2-PyLi giving the pyridyl ketone **11a** (76%). This, using Pt/H_2 under a variety of conditions, gave at best only 4% of the target α-(2-piperidyl)methanol **2d**; the principal other product was the tetrahydroquinolyl analog **16** (46%). The unusually poor yield of **2d** might be attributed to decreased selectivity of protonation of **11a** at the pyridyl N because of the absence of the 2 substituent and/or the absence of the deterrent steric effects by 2 substituents on hydrogenation of the quinoline N ring.

An attempted preparation of **2d** by the 6-step Ainly and King synthesis[15] failed in the last stages.

Treatment of 7-trifluoromethylcinchoninic acid (**15b**) with 2-PyLi at −70° in 30% THF–Et_2O gave the desired 2-pyridyl ketone **11b** but in only 16% yield. Also isolated in 12% yield was the diaddition product, α-pyridyl 2-(2-pyridyl)-7-trifluoromethyl-4-quinolyl ketone **17** which must have involved both addition of 2-PyLi at position 2 and oxidative aromatization of the resulting dihydroquinoline. These two compounds were characterized by anal. and nmr spectra.

Addition of 2-PyLi to the 7-trifluoromethylcinchoninic ester in Et_2O, unlike the addition to the acid **15b** where THF was required for solubilizing the substrate, yielded the ketone **11b** in 67% yield; and formation of **17** was not observed. Unfortunately in the several attempts to reduce the pyridyl ketone **11b** by Pt/H_2, no pure piperidyl alcohol was isolated from the complex mixture of products.



Since the α-(2-piperidyl)-7-trifluoromethyl-4-quinolinemethanol corresponding to **17** was not obtained, the α-dibutylaminomethyl analog **1d** was synthesized through the diazomethylation of the corresponding cinchoninic acid by standard procedures.[4,5c,10]

7-Chlorocinchoninic acid (**15**, R = 7-Cl) did not give the desired ketones upon treatment with MeLi or 2-PyLi. The α-diethylaminomethyl-7-chloro-4-quinolinemethanol was therefore synthesized by the classical procedure employed earlier for the dihexyl analog.[16]

2-Substituted-α-(2-piperidyl)-4-quinolinemethanols (2).—Three of these, the 6-fluoro-2-*p*-tolyl and 6-fluoro-2-trifluoromethyl derivatives **2a** and **2b,** and the 8-fluoro-2-trifluoromethyl compound **2c**, were synthesized by known procedures.[5,8] In each case, as in the many analogous syntheses in this series, only one of the two possible diastereoisomeric racemates was isolated, presumably formed predominantly by stereospecific hydrogenation.[5c]

Biological Data.[6]—The antimalarial activities of compounds **1** and **2,** listed in Table I, were not outstanding. The most active, **1a** and **1b,** were partially curative at 640 mg/kg and active at 160 mg/kg. Only **1a** effected low but significant increase in survival time at 40 mg/kg. The one tetrahydroquinoline, **16,** was inactive.

TABLE I

ACTIVITIES[a] AGAINST *P. berghei* IN MICE[b]

Compd	640 mg/kg	160 mg/kg	40 mg/kg
1a	2C/29.1[c]	6.8	0.8
1b	2C/27.2[c]	16.7	2.9
1c	0.8	0.6	0.4
1d	8.5	0.1	0.1
2a	1.3	1.1	0.9
2b	9.1	3.5	0.7
2c	10.5	5.1	0.3
2d		5.9	0.5
16	0.5	0.3	0.3

[a] Figures are average increases in survival time (days) of infected mice (5 per test group) beyond that of untreated controls. [b] See ref 6. [c] Two cures and an average increase in survival time of 3 mice.

Experimental Section[17]

2-Aryl-4-acetylquinolines (6).—In a typical example, 9.5 g (0.034 mole) of powdered 2-*p*-tolyl-6-methylcinchoninic acid followed by 200 ml of dry Et_2O was rapidly added to a vigorously

(13) (a) S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.*, **148**, 481 (1958); (b) L. Simet, *J. Org. Chem.*, **28**, 3580 (1963); **21**, 169 (1956).

(14) A. E. Senear, H. Sargent, J. F. Mead, and J. B. Koepfli, *J. Amer. Chem. Soc.*, **68**, 2695 (1946).

(15) A. D. Ainly and H. King, *Proc. Roy. Soc. Ser. B*, **125**, 60 (1938).

(16) (a) N. H. Leake, Ph.D. Dissertation, University of Virginia, Charlottesville, Va., 1946, p 162; (b) R. E. Lutz, J. F. Codington, and N. H. Leake, *J. Amer. Chem. Soc.*, **69**, 1260 (1947).

(17) Instruments used were: Thomas-Hoover apparatus for mp, uncorr. Anal. were correct (±0.4%); Gailbraith Lab, Inc., and Swartzkopf Microanalytical Lab. Vacuum sublimation of analytical samples was at 10–50° the respective mp. Satisfactory spectra were obtained, for structural determination where required, and randomly in other cases: ir, Perkin-Elmer 337; nmr, Hitachi, P. E. R20; mass spectrograph, Hitachi, P-E, RMU 6E.

stirred soln of 0.087 mole of MeLi (from 1.2 g of Li and 14 g of MeI) in 120 ml of anhyd Et_2O under N_2. After stirring for 2 addl hr and hydrolysis and evapn of the ether layer, the residue was recrystd from abs EtOH; 8.1 g of **6b** (86%).

α-Bromomethyl 2-Aryl-4-quinolyl Ketones (5a–d). A.—To a stirred refluxing soln of 2.75 g (0.01 mole) of **6b** in 25 ml of glacial AcOH, was added over 15 min, a soln of 1.60 g (0.01 mole) of Br_2 in 15 ml of glacial AcOH, with continued refluxing for 10 min. Upon cooling and pouring onto ice, the resulting ppt was washed with $NaHCO_3$ soln, and recrystd from abs EtOH; 2.0 g (56%).

B.—To a stirred slurry of 5.79 g (0.02 mole) of **6a** and 50 ml of glacial AcOH was added 1.01 g (0.0066 mole) of $NaBrO_3$ followed under heating at 100° by dropwise addition of 14 g of 48% HBr. The mixture was then poured onto ice-H_2O and the resulting ppt was recrystd from EtOH; 6.48 g (88%). The yield of **5b** by this method was 75%.

α-(Di-*n*-butylaminomethyl)-2-*p*-tolyl-6,8-dimethyl-4-quinolinemethanol·HCl (1b).—A mixture of crude bromohydrin (11.1 g, 0.03 mole, obtained in 81% yield by $Al(O\text{-}i\text{-}Pr)_3$ reduction of the bromo ketone **5a**[4,11]) and 19.5 g (0.015 mole) of *n*-Bu_2NH at 80–85° was stirred for 60 hr, cooled, and dild with dry Et_2O. After removing the pptd salt by filtration the soln was concd under reduced pressure and the unused *n*-Bu_2NH was then removed by vac distn. A soln of the residual viscous oil in a small amount of abs EtOH was cooled in ice and treated with ethereal HCl. The resulting ppt was recrystd from EtOH-Et_2O; 12.68 g (93%); **1a** was made similarly. Compd **1c** was prepared from the corresponding bromohydrin by the action of refluxing Et_2NH-benzene mixture (15 hr). An Et_2O soln of the base (obtained as above for **1b**) was treated with ethereal HCl, giving a hygroscopic brown dihydrochloride, which upon rapid recrystn from *i*-PrOH-Et_2O yielded 42% of analytically pure, hygroscopic monohydrochloride (**1c**), mp 135–138° dec.

Isatins.—The 6-Cl, 6-Br, 6-F, 6-CF_3, and 7-CF_3 isatins were prepd according to published procedures.[13] Mixtures of 4- and 6-substituted isatins were sepd by the method of Sadler.[18]

Quinoline-2,4-dicarboxylic acids (**14**) were prepared from the corresponding isatins by the method of Senear, *et al.*[14]

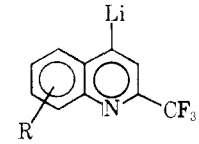
Cinchoninic acids (**15**) were obtained from the corresponding quinoline-2,4-dicarboxylic acids **14** by decarboxylation, in refluxing $PhNO_2$ for 1 hr, or in Ph_2O at 215° for 15 min.

α-(Bromomethyl) 7-Trifluoromethyl-4-quinolyl Ketone·HBr, (5e).—A stirred soln of 12.1 g (0.05 mole) of **15b** in 60 ml of $SOCl_2$ was refluxed for 1.5 hr. The $SOCl_2$ was distd at 1 atm pressure and 100 ml of dry C_6H_6 was added and distd. A soln of the residue in 125 ml of dry Et_2O was filtered through glass wool, stored in a dropping funnel under a $CaCl_2$ drying tube, and added dropwise over 0.5 hr to a cooled, stirred soln of 6 g (0.14 mole) of CH_2N_2 in 415 ml of Et_2O, a yellow ppt appearing toward the end. The mixture was stirred for 4 hr and then treated dropwise with 40 ml of 48% HBr. After 1 hr of additional stirring the tan solid **5e** was collected, washed with 30% ACOH-Et_2O, and oven-dried; 12.54 g (63%), yellow, mp 187–193° dec.

7-Trifluoromethyl-4-quinolylethylene Oxide (7a).—A soln of 9.36 g (0.024 mole) of **5e** in 75 ml of MeOH was treated with aq 5% $NaHCO_3$ until pH 7 was reached; it was then treated dropwise over 15 min with a soln of 1.5 g of $NaBH_4$ in 15 ml of H_2O to which had been added 4 ml of 2 *N* NaOH. After stirring for 1 hr, diluting with 125 ml of H_2O, and extg with petr ether (30–60°), the ext was dried (K_2CO_3) and evapd, giving 4.62 g (82%), wax product, mp 53–59°, recrystd from isooctane, 4.01 g (72%), mp 58–60°.

α-(Di-*n*-butylaminomethyl)-7-trifluoromethyl-4-quinolinemethanol Succinate (1d).—A stirred soln of **7a** (4.0 g, 0.0168 mole) and 20 ml of *n*-Bu_2NH was heated at 120° for 1.5 hr. After evapg excess *n*-Bu_2NH *in vacuo*, the residual oil was taken up in Et_2O; and the hydrochlorides were fractionally pptd by ethereal HCl. The first crop was crystn (*n*-Bu_2NH·HCl), but subsequent crops were gums from which Et_2O was decanted. Treatment of these with NaOH soln and extn with Et_2O, drying ($MgSO_4$), and retreating with ethereal HCl gave a tan oil which solidified upon cooling with Dry Ice–acetone; white, hygroscopic. Treatment of the salt with base and extn with Et_2O gave 3.51 g of tan oil (57%). A 125-ml Et_2O soln of this was treated with an equimolar amount (1.13 g) of succinic acid in 450 ml of Et_2O. Evapn to 400 ml and standing at 0° for several days gave 3.61 g (44%) of 1d succinate, mp 96–97.5°; a second crop of 0.60 g (7%) was obtained on concn of the Et_2O soln to 100 ml (total yield 51%).

TABLE II



R	Reactant[a]	Products[a]
6-Cl	PyCN	QCOPy (43%)
6-Me	PyCN	QCOPy (76%)
H	PyCHO	QCHOHPy (43%)
6-Me	PyCHO	QCHOHPy (39%)
6-Me	PipCOOH	QH (**23**, 55%)
6,8-Me_2, 6-Cl	PipCOOH	None isolated
6-Me	MeCN[b]	QH (**23**, 61%)
6-OMe, 6,8-Cl_2	MeCN[b]	None isolated
6-Me	Et_2NCH_2CN[b,c]	QH (**23**, 30%); QCH_2CN (**8a**, 30%, mp 104°);[d] QCH_2CONH_2 (**9a**, 20%, mp 200°);[e] **10** (25%)[f]
6-Cl	Et_2NCH_2CN[b]	QCH_2CONH_2 (**9b**, 50%)[g]

[a] Q = Substituted 4-quinolyl; Py = 2-pyridyl; Pip = 2-piperidyl. [b] Reaction time 4 hr. [c] Worked up by column chromatography on silica gel, eluting successively with petr ether (30–60°), C_6H_6, $CHCl_3$, and Me_2CO. [d] Ir (Nujol) 2248 cm^{-1} (C≡N). [e] *Anal.* $C_{13}H_{11}F_3N_2O$, N; ir (Nujol) cm^{-1}, 3350, 3195 (NH_2), 1675 (C=O). [f] Bp 120° (3 mm); *Anal.* $C_{12}H_{22}N_4$, C, H; N, calcd 25.00, found 24.43, ir (neat) 3480, 3360 (NH_2), 3970, 3940, 3830 (CH), 2175 (C≡N) and 1630 (C=C, C=N) cm^{-1}; nmr ($CDCl_3$) δ 0.97 (m, 12, CH_3), 2.48 (m, 8, CH_2), 3.26 (s, 2, NCH_2), and 5.26 (s, 2, NH_2). [g] Ir (KBr) 3350, 3165 (amide NH_2), 1680 cm^{-1} (amide C=O).

2-Pyridyl 1-Trifluoromethyl-4-quinolyl Ketone (1b). A.—Treatment of **15b** (9.67 g, 0.04 mole) with 2-PyLi (0.189 mole) in 30% THF-Et_2O at −70° and cryst the product from EtOH yielded 5.85 g of tan solid, mp 105–165°, which was then sublimed (overnight) at 110° (0.05 mm): 1.90 g (16%); colorless; mp 117–119°.

B.—Ethyl 7-trifluoromethylcinchoninate (8.3 g, 0.031 mole), when treated in Et_2O as above with 0.137 mole of 2-PyLi, gave 6.25 g (67%) of **11b**, mp 111–114°. No **17** was found.

2-Pyridyl 2-(2-Pyridyl)-7-trifluoromethyl-4-quinolyl Ketone (17).—Recrystn from MeCN of the residue from the above sublimation of **11b** yielded 1.87 g of **17** (12%), mp 169°–171°.

α-(2-Piperidyl)-8-trifluoromethyl-4-quinolinemethanol·HCl (2d).—A mixture of 5.0 g (0.0165 mole) of **11a**, 1.2 ml of concd HCl, 0.25 g of PtO_2, and 125 ml of abs EtOH was hydrogenated at 2.8 kg/cm^2 for 1 hr; total H_2 absorbed, 0.059 mole. Filtering, evapn to 30 ml, pouring into dil NaOH, Et_2O extn, drying ($MgSO_4$), treatment with ethereal HCl, decantation from the gummy salt, dissolving in abs EtOH, and treatment with anhyd Et_2O until cloudy gave an off-white ppt, which was filtered and air-dried: 0.80 g (14%), mp 165–172° dec; recrystd from *i*-PrOH-Et_2O; 0.22 g (4%); tan; mp 204–206° dec.

α-(2-Piperidyl)-8-trifluoromethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (16).—A mixture of 9.50 g (0.0315 mole) of **11a**, 5 ml of concd HCl, 0.95 g of PtO_2, and 200 ml of abs EtOH was hydrogenated as above, absorbing 0.15 mole. The base was recrystd from a small vol of MeCN: 0.60 g; colorless; mp 179–183°.

α-(2-Piperidyl)-6- and -8-fluoro-2-trifluoromethyl-4-quinolinemethanol·HCl (2b and 2c) were prepared by the previously reported reaction sequence:[8] the 4-quinolone → QBr → QCOOH → QCOPy → **2b,c**.

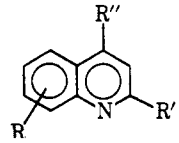
α-(2-Piperidyl)-6-fluoro-2-*p*-tolyl-4-quinolinemethanol (2a) was obtained (by published procedure[5]) from the corresponding 6-fluoro-2-*p*-tolylcinchoninic acid (prepared by the Pfitzinger reaction between 5-fluoroisatin and *p*-methylacetophenone).

Reactions of 2-Trifluoromethyl-4-quinolyllithium Derivatives (Prepared as Previously Described[8]).—The products were identified by comparison of mp and ir spectra with those of authentic samples.[8] In a typical example, a slight excess of 2-cyanopyridine was added to a soln of 6-methyl-2-trifluoromethyl-4-quinoyl-

(18) P. W. Sadler, *J. Org. Chem.*, **21**, 169 (1956).

TABLE III

4-FUNCTIONALIZED SUBSTITUTED QUINOLINES



No.[a]	R	R'[b]	R''[c]	Mp, °C[d-g,p]	Yield, %	Analysis[q-z]
23	6-Me	CF_3	H	89		$C_{11}H_8F_3N$[r,v]
18a	6-F	CF_3	OH	255–260	74	$C_{10}H_5F_4NO$
18b	8-F	CF_3	OH	144–145	69	$C_{10}H_5F_4NO$
18c	6,8-F_2	CF_3	OH	164–165	63	$C_{10}H_4F_5NO$[s]
19a	6-F	CF_3	Br	93–95	78	$C_{10}H_4BrF_4N$
19b	8-F	CF_3	Br	68–69	94	$C_{10}H_4BrF_4N$
19c	6,8-F_2	CF_3	Br	84–85	96	$C_{10}H_3BrF_5N$
14a	8-CF_3	COOH	COOH	230–232 dec	92	$C_{12}H_6F_3NO_4$
14b	7-CF_3	COOH	COOH	235–237 dec	85	$C_{12}H_6F_3NO_4$
14c	7-F	COOH	COOH	240–242 dec	91	$C_{11}H_6FNO_4$
14d	7-Br	COOH	COOH		94	Not anal.
15a	8-CF_3	H	COOH	232–235 dec[e]	85	$C_{11}H_6F_3NO_2$
15b	7-CF_3	H	COOH	283–286 dec[e,h]	91	$C_{11}H_6F_3NO_2$
15c	7-F	H	COOH	289–290 dec[e]	35	$C_{10}H_6FNO_2$
15d	7-Br	H	COOH	247–250 dec[f]	86	$C_{10}H_6BrNO_2$
15e	6-F	PhMe	COOH	274–275	92	$C_{17}H_{12}FNO_2$
20a	6-F	CF_3	COOH	207–209	65	$C_{11}H_5F_4NO_2$
20b	8-F	CF_3	COOH	218–220	78	$C_{11}H_5F_4NO_2$
25	7-CF_3	H	COOEt	67–69[i]	91	Not anal.
26	6,8-Me_2	PhMe	COOMe	122–123	88	$C_{20}H_{19}NO_2$
27	6,8-Me_2	PhMe	COOEt	117–118	97	$C_{21}H_{21}NO_2$
4a	6,8-Me_2	PhMe	COCl	138–139[j]	67	$C_{19}H_{16}ClNO$
6a	6,8-Me_2	PhMe	COMe	123.5–124.5	72	$C_{20}H_{19}NO$
6b	6-Me	PhMe	COMe	117–118	86	$C_{19}H_{17}NO$
6c	6-Me	PhOMe	COMe	123–124	83	$C_{19}H_{17}NO_2$
6d	6-Me	PhF	COMe	116–118	68	$C_{18}H_{14}FNO$
6e	6-Me	PhCl	COMe	133–134	85	$C_{18}H_{14}ClNO$
6f	6,8-Me_2	PhOMe	COMe	101–102	81	$C_{20}H_{19}NO_2$
24	6,8-Me_2	PhCl	COEt	120–121	65	$C_{20}H_{18}ClNO$,
28	6,8-Me_2	PhMe	$COCHN_2$	159–160	78	$C_{20}H_{17}N_3O$
5a[y]	6,8-Me_2	PhMe	$COCH_2Br$	145–147	88	$C_{20}H_{18}BrNO$
5b	6-Me	PhMe	$COCH_2Br$	132–135	71	$C_{19}H_{16}BrNO$
5c	6-Me	PhOMe	$COCH_2Br$	106–108	75	$C_{19}H_{16}BrNO_2$
5d	6-Me	PhF	$COCH_2Br$	134–136	72	$C_{18}H_{13}BrFNO$
5e	7-CF_3	H	$COCH_2Br$	203–205 dec[k]	63	$C_{12}H_7BrF_3NO \cdot HBr$[t]
7a	7-CF_3	H		60–62[l]	72	$C_{12}H_8F_3NO$[r]
9a	6-Me	CF_3	CH_2CONH_2	200	20	$C_{13}H_{11}ClF_3N_2O$[r]
9b	6-Cl	CF_3	CH_2CONH_2	260–261	50	$C_{12}H_8ClF_3N_2O$[w]
21a	6-F	CF_3	COPy	121–122	90	$C_{16}H_8F_4N_2O$
21b	8-F	CF_3	COPy	130–132	62	$C_{16}H_8F_4N_2O$
21c	6-F	PhMe	COPy	172–174	49	$C_{22}H_{15}FN_2O$
11a	8-CF_3	H	COPy	141–141.5	76	$C_{16}H_9F_3N_2O$
11b	7-CF_3	H	COPy	118–119.5	16	$C_{16}H_9F_3N_2O$
17	7-CF_3	Py	COPy	170–172[m]	12	$C_{21}H_{12}F_3N_3O$
22a	6-F	CF_3	CHOHPy	123–128	97	$C_{16}H_{10}F_4N_2O$
22b	8-CF_3	H	CHOHPy	133–134	76	$C_{16}H_{11}F_3N_2O$
2a	6-F	PhMe	CHOHPip	165–168	33	$C_{22}H_{23}FN_2O$
2b	6-F	CF_3	CHOHPip	256–258 dec	73	$C_{16}H_{16}F_4N_2O \cdot HCl$
2c	8-F	CF_3	CHOHPip	275–278 dec	62	$C_{16}H_{16}F_4N_2O \cdot HCl$[z]
2d	8-CF_3	H	CHOHPip	204–206 dec[n]	4	$C_{16}H_{17}F_3N_2O \cdot HCl$[r]
16[a]	8-CF_3	H	CHOHPip	182–185[m]	6–46	$C_{16}H_{21}F_3N_2O$[r]
1a	6,8-Me_2	PhMe	$CHOHH_2NEt_2$	217–219 dec[o]	92	$C_{24}H_{30}N_2O \cdot HCl$[r]
1b(·HCl)	6,8-Me_2	PhMe	$CHOHCH_2NBu_2 \cdot HCl$	200–202[k]	93	$C_{28}H_{38}N_2O \cdot HCl$[r]
1b(base)			$CHOHCH_2NBu_2$	78–79[l]		$C_{28}H_{38}N_2O$
1c	7-Cl	H	$CHOHCH_2NEt_2$	135–138 dec[m]	42	$C_{15}H_{15}ClN_2O \cdot HCl$[r]
1d	7-CF_3	H	$CHOHCH_2NBu_2 \cdot S$[c]	96–97[p]	51	$C_{24}H_{33}F_3N_2O_5$[r]

[a] 16 is the 1,2,3,4-tetrahydroquinoline. [b] Ph = phenyl substituent para; Py = 2-pyridyl; Pip = 2-piperidyl. [c] 1d: S = succinic acid. [d] dec = melts with decomposition. [e] Decarboxylation solvent, Ph_2O; [f] $PhNO_2$. [g] Recrystallization solvent, EtOH, unless otherwise specified as follows: [h] 2-methoxyethanol; [i] hexane; [j] AcOEt; [k] AcOH; [l] isooctane; [m] MeCN; [n] *i*-PrOH–Et_2O; [o] EtOH–Et_2O; [p] Me_2CO–pentane. [q] Within ± 0.4%, and for C, H, except when otherwise specified: [r] for C, H, N; [s] for C, H, F; [t] for C, H, Br; [u] for N. [v] C: calcd 62.56, found 62.00. [w] C, H: calcd 49.91, 2.77; found, 49.32, 2.08. [z] C: calcd, 52.68 found, 53.29. [y] A. L. Crosby, M. S. Thesis, University of Virginia, Charlottesville, Va., 1950.

lithium in dry Et_2O under N_2 at −70°. After 2 hr the mixture was warmed to room temp and hydrolyzed (H_2O). The resulting α-(2-pyridyl) 6-methyl-2-trifluoromethyl-4-quinolyl ketone was recrystd from EtOH (30%) mp 155° (lit.[8] mp 153°). The results of these experiments are shown in Table II.

As might have been expected the reaction between 4-quinolyllithiums and pipecolenic acid which has two active hydrogens and would form a dianion with two proximate negative charges, failed to give the piperidyl ketone; in the case of the 6-Me derivative the corresponding parent quinoline was obtained in 55% yield.

The reaction of 4-cyano-6,8-dimethyl-2-trifluoromethylquinoline (**13**[8]) **with 2-PyLi** in Et_2O at −70° for 4 hr under N_2 and purification by column chromatography on silica gel ($CHCl_3$) gave 50% of 2-pyridyl 6,8-dimethyl-2-trifluoromethyl-4-quinolyl ketone, mp 94° (lit.[6] mp 98°).

Biologically Oriented Organic Sulfur Chemistry. 7. Carbonyl Disulfides as Inhibitory Agents for *Histoplasma capsulatum*[1a-d]

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Received August 14, 1970

Twenty-one unsymmetrical carbonyl disulfides, RC(O)SSR′, were synthesized by reaction of thio acids with thiolsulfonates (eq 1) or with sulfenyl chlorides (eq 2; usually preferred). Absence of symmetrical disulfides was demonstrated by tlc and occasionally by glpc also. Structures were confirmed by ir, nmr, and mass spectra, and by identity of 3 products synthesized using both eq 1 and 2. The reactivity of methyl acetyl disulfide (**1**) differed greatly under various conditions; for example, at 100°, half reacted during 78 days in dioxane but during only 0.2 day in the presence of thiolate ion and during only 0.3 day in 100% EtOH. The decomposition of **1** did not involve merely disproportionation to two symmetrical disulfides (eq 3), but was complex (eq 4). *In vitro* tests against *Histoplasma capsulatum* showed that minimum inhibitory concentrations ranged upward from 8 μg/ml (amphotericin B, **25**, showed 0.1 μg/ml; Table I), with best results when both R and R′ were short, unbranched alkyl or unsubstituted Ph moieties. The approximate LD_{50} ranged downward from *ca.* 430 mg/kg (LD_{50} for **25**, 280 mg/kg). Eight disulfides were unpromising *in vivo* in comparion with **25**, although **1** (the best) did result in approximately 17% prolongation of life, which was considered statistically significant. Several carbonyl disulfides afforded no protection against ionizing radiation.

An earlier paper reported the synthesis of carbonyl disulfides by the reaction of eq 1.[2] The compound in

$$RC(O)S^- + R'SSO_2R' \longrightarrow RC(O)SSR' + R'SO_2^- \quad (1)$$

which R = Me and R′ = Ph was considered "good" as an inhibitor of *Histoplasma capsulatum*, the causative organism of histoplasmosis; the compound in which R = R′ = Ph was "fair."[3] The present paper reports a structure–activity study of types of alkyl and aryl groups favorable as a backbone for carbonyl disulfides, onto which functional groups can be substituted later.

Chemistry.—The procedure of eq 1 (method A) was used to prepare several carbonyl disulfides, but purification proved to be difficult.[4]

An adaptation of a method of Hawley and Kittleson, shown in eq 2, gave a smoother preparation and was

$$R'SH \xrightarrow{0.5\ Cl_2} 0.5(R'S)_2 \xrightarrow{0.5\ Cl_2} R'SCl \xrightarrow{RC(O)SH} RC(O)SSR' \quad (2)$$

used in most instances (method B). Compounds prepared are shown in Table I. With **1**, **2**, and **19**, with which both methods A and B were used, A seemed to have an advantage only with **19** (with **1**, the seemingly higher yield by method A actually was offset by greater impurity).[4] In principle, however, method A does have an advantage over B if one wishes to vary the thio acid component (R) with R′ fixed, because the thiolsulfonate used in method A can be stored, whereas the sulfenyl chloride used in method B cannot. By circumstance, method A alone was used for **15** and **18**, but B probably would have served as well.

For method B, most sulfenyl chlorides were prepared by condensing an equivalent amount of Cl_2 and then allowing it to volatilize into a solution of the disulfide or thiol in CH_2Cl_2 at −20°; 2-methyl-2-propanesulfenyl chloride needed for the preparation of **6**, however, was prepared in hexane at room temp because a thiosulfenyl chloride, $(CH_3)_3CSSCl$, and *t*-BuCl form at low temp.[6] The solution of the sulfenyl chloride then was added to one of the thio acid at −20° (with **1**, when the solution

(1) (a) Paper VI, L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971); (b) this investigation was supported by Public Health Service Research Grants No. AM11685 from the National Institute of Arthritis and Metabolic Diseases (L. F.) and No. AI 08916 from the National Institute of Allergy and Infectious Diseases (I. M.), and by Biomedical Science Support Grant, National Institutes of Health Grant FR-07089 to Vanderbilt University (I. M.); (c) taken from part of the forthcoming Ph.D. dissertation of W. S. H., which may be consulted for greater detail; (d) reported in part at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968 (Abstracts, p 98), and at the Second National Conference on Histoplasmosis, Atlanta, Ga., Oct 6–9, 1969.

(2) (a) L. Field and J. D. Buckman, *J. Org. Chem.*, **32**, 3467 (1967); (b) *Chem. Abstr.* has named such compounds as *SS*-dithioperoxy esters. Thus MeC(O)SSPh is named "dithioperoxyacetic acid, *SS*-phenyl ester" [*cf. Chem. Abstr.*, **68**, 2763 (1968)]. However, nomenclature as disulfides has precedent in simple systems and is clearer for purposes of this paper.

(3) I. McVeigh and Z. Evans, *Mycopathol. Mycol. Appl.*, **35**, 313 (1968).

(4) Method A was much less satisfactory than method B with RC(O)SSR, when R and R′, respectively, were Me, Me; Me, Et; 1-adamantyl, Et; and *p*-$MeOC_6H_4$, Et. Crude yields were 34–89%, but none of these disulfides could be purified readily to the point of giving one spot by tlc.

(5) R. S. Hawley and A. R. Kittleson, U. S. Patent 2,553,777 (1951); *Chem. Abstr.*, **45**, 7742 (1951).

(6) W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).