$NaNO_2$ was added, agitation was continued for an additional hr at 0–10°. The material was obtained by filtration on a sintered glass funnel, and washed with small portions of cold 1:1 EtOH–Et_2O (v/v) followed by cold Et_2O. The product was dried at 2 mm at 35° overnight, and a yield of 7.5 g (95%) of crude compound as the difluoroborate was obtained, mp 210–215 dec. The dried material was spread in a thin layer over the bottom of a Fernbach flask fixed with an air condenser and combusted with a flame. The product was heated with 30 ml of 10% H_2SO_4, cooled, diluted to 100 ml with H_2O, brought to pH 5 with dilute NaOH, and steam distilled. The crude product (0.5 g) was recovered by filtration and drying at 70° overnight, mp 147–155°. After sublimation (150° (2 mm)), 330 mg of compound was obtained, mp 167–170°.

5-Bromo-7-fluoro-8-quinolinol. 7-Fluoro-8-quinolinol[5] (2.5 g, 0.015 mole) in 100 ml of chloroform was stirred with *N*-bromosuccinimide (3.1 g, 0.0175 mole) for 1 hr. The chloroform was evaporated and the residue was slurried in 100 ml of H_2O and filtered. The product was dried at 70° overnight and weighed 3.5 g, mp 169–170°.

7-Fluoro-5-iodo-8-quinolinol was prepared from 2.0 g (0.012 mole) of 7-fluoro-8-quinolinol[5] and 3.0 g (0.12 mole, 90%) of *N*-iodosuccinimide in chloroform in the same manner as 5-bromo-7-fluoro-8-quinolinol. The yield of product was 1.8 g, mp 164–165°.

5-Bromo-7-chloro-8-quinolinol. To 11.2 g (0.05 mole) of 5-bromo-8-quinolinol,[14] dissolved in 300 ml of 10% NaOH, was added 100 ml of 5.25% sodium hypochlorite solution. The mixture was agitated for 2 hr and adjusted to pH 5 with acetic acid. The product was obtained after filtering, washing (H_2O), and drying at 70° overnight. The yield of product was 7.8 g, mp 188–195°. Purification was achieved by vacuum sublimation followed by crystallization from MeOH–DMF.

7-Bromo-5-iodo-8-quinolinol. 7-Bromo-8-quinolinol[6] (22.4 g, 0.1 mole) and fused potassium acetate (9.8 g, 0.1 mole) were dissolved in 250 ml of boiling 96% EtOH. I_2 (25.4 g, 0.1 mole), dissolved in 300 ml of 96% EtOH, was added dropwise with stirring to the boiling quinolinol solution over 0.5 hr. The mixture was kept under reflux for an additional 10 min, after completion of addition of the I_2. Aqueous $NaHSO_3$ was added to the mixture to reduce any unreacted I_2, and the mixture was refrigerated overnight. The product was removed by filtration, washed (96% EtOH), and dried under vacuum. The yield of compound was 29.8 g, mp 195–200° dec.

5-Bromo-7-iodo-8-quinolinol was prepared from 5-bromo-8-quinolinol[14] in the same manner as 7-bromo-5-iodo-8-quinolinol.

References

(1) H. Gershon and R. Parmegiani, *Appl. Microbiol.*, 11, 62 (1963).
(2) H. Gershon, R. Parmegiani, A. Weiner, and R. D'Ascoli, *Contrib. Boyce Thompson Inst.*, **23**, 219 (1966).
(3) H. Gershon, *J. Med. Chem.*, 11, 1094 (1968).
(4) H. Gershon, M. W. McNeil, and Y. Hinds, *ibid.*, **12**, 1115 (1969).
(5) H. Gershon and M. W. McNeil, *J. Heterocycl. Chem.*, 8, 821 (1971).
(6) H. Gershon, M. W. McNeil, and A. T. Grefig, *J. Org. Chem.*, **34**, 3268 (1969).
(7) H. Gershon and M. W. McNeil, *J. Heterocycl. Chem.*, 8, 129 (1971).
(8) A. F. Helin and C. A. Vanderwerf, *J. Org. Chem.*, 17, 229 (1952).
(9) Gesellschaft für Chemische Industrie in Basel, German Patent 556,324 (1930).
(10) M. K. Bose, *J. Indian Chem. Soc.*, **22**, 169 (1945), in "Oxine and Its Derivatives," Vol. 3, R. G. W. Hollingshead, Butterworths, London, 1956, p 741.
(11) F. Boedecker and L. Cassel, German Patent 767,098 (1951); *Chem. Abstr.*, **52**, 5483 (1958).
(12) K. Matsumura and M. Ito, *J. Amer. Chem. Soc.*, 77, 6671 (1955).
(13) A. L. Coll and G. P. Coll, *Afinidad*, **28**, 101 (1951).
(14) H. Gershon, M. W. McNeil, and S. G. Schulman, *J. Org. Chem.*, **36**, 1616 (1971).
(15) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, 88, 3390 (1966).
(16) W. W. Heseltine and F. M. Freeman, *J. Pharm. Pharmacol.*, 11, 169 (1959).
(17) G. O'Dom and Q. Fernando, *Anal. Chem.*, **38**, 844 (1966).

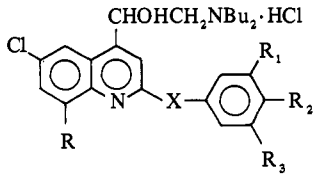
Antimalarial Potency of 2-Benzoyl-4-quinolinemethanols†

Andrew J. Saggiomo,* Shinzo Kano, Toyohiko Kikuchi, Kazumi Okubo, and Masafu Shinbo

Germantown Laboratories,‡ Philadelphia, Pennsylvania 19144.

Received March 23, 1972

A major effort in the potent antimalarial series of 2-phenyl-4-quinolinemethanols[1,2] has been the design of effective members without phototoxicity.[3-5] Since the majority of agents causing phototoxic reactions are conjugated aromatic structures,[4-7] it seemed desirable in the above series to insulate the 2-phenyl substituent from the quinoline nucleus by a C atom. For this purpose we investigated, initially, the 4-quinolinemethanol derivatives (Ia, b, and j where R = Cl; R_{1-3} = H). Test results§ revealed that although



Ia, X = CH_2; R = Cl; R_{1-3} = H
Ib–i, X = CO; R and R_{1-3} = H, Cl, CF_3
Ij, X = CF_2; R = Cl; R_{1-3} = H

each lacked phototoxic effects, only Ib possessed a moderate level of antimalarial activity. Based on these findings, we proposed to enhance the antimalarial potency of Ib by incorporation of Cl and CF_3 substituents. The efficacy of such modification was reported in our earlier work.[8] The present communication, therefore, describes the synthesis and biological properties of 2-benzyl-, 2-benzoyl-, 2-(α,α-difluorobenzyl)-4-quinolinemethanols (Ia, b, j) and affirms the potent antimalarial action of Cl, CF_3 members (Ic–i) of the 2-benzoyl series.

Chemistry. The Pfitzinger condensation[9,10] of 5,7-dichloroisatin and $C_6H_5CH_2COCH_3$ afforded (18%) the desired 2-benzylcinchoninic acid[11] (IIIa, Table I). The latter was converted to the corresponding amino alcohol (Ia, Table II) *via* the usual reaction sequence.[10] Difficulty in preparing the acid chloride of IIIa with $SOCl_2$ was circumvented by means of PCl_5 in C_6H_6.

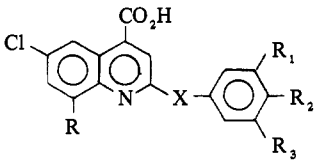
A convenient synthesis (Scheme I) of Cl, CF_3 containing 2-benzoylcinchoninic acids (IIIc–i, Table II) was developed which utilized appropriate phenylglyoxals (II, Table III) in the Doebner reaction[10,12] with commercial anilines. Requisite glyoxals (II) were obtained by DMSO oxidation[13] of the corresponding phenacyl bromides. Verification of the Doebner route to IIIc–i was provided by the unambiguous Pfitzinger synthesis of IIIc (Scheme II). The latter reaction also produced IIIb which had been previously obtained from IIIa and SeO_2 (47%), alkaline $KMnO_4$ (38%), or Br_2–

†This investigation was supported by the U.S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2950 and is Contribution No. 1051 from the Army Research Program on Malaria.

‡Affiliated with the Franklin Institute.

§Phototoxicity tests were carried out by Col. William E. Rothe, Division of Medicinal Chemistry, WRAIR, Walter Reed Army Medical Center, Washington, D.C. For details of the test procedure see ref 4. Antimalarial evaluation was conducted by Dr. L. Rane and coworkers, University of Miami, Miami, Fla. All test results were supplied by Drs. T. R. Sweeney and R. E. Strube, Walter Reed Army Institute of Research.

Table I. Cinchoninic Acids

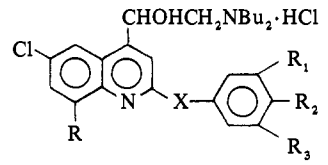


III

III	X	Substituents R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[d]
a	CH_2	Cl	H	H	H	178.5–180.5	C_6H_6	18[a]	$C_{17}H_{11}Cl_2NO_2$
b	CO	Cl	H	H	H	248–250	AcOH	69[a]	$C_{17}H_9Cl_2NO_3$
c	CO	Cl	H	Cl	H	325–326 dec	Dioxane	40,[a] 21[b]	$C_{17}H_8Cl_3NO_3$
d	CO	Cl	H	CF_3	H	284–285	Dioxane	23[b]	$C_{18}H_8Cl_2F_3NO_3$
e	CO	Cl	CF_3	H	CF_3	294–296	Dioxane	33[b]	$C_{19}H_7Cl_2F_6NO_3$
f	CO	CF_3	H	Cl	H	275–276	AcOH	24[b]	$C_{18}H_8Cl_2F_3NO_3$
g	CO	CF_3	Cl	Cl	H	276.5–278.5	AcOH	38[b]	$C_{18}H_7Cl_3F_3NO_3$
h	CO	CF_3	Cl	H	Cl	285–286.5	Dioxane	39[b]	$C_{18}H_7Cl_3F_3NO_3$
i	CO	CF_3	CF_3	H	H	226–228	AcOH	25[b]	$C_{19}H_8ClF_6NO_3$
j	CF_2	Cl	H	H	H	204–206 dec	Ligroin	65[c]	$C_{17}H_9Cl_2F_2NO_2$

[a]Pfitzinger method. [b]Doebner synthesis. [c]See Experimental Section. [d]*Anal.* for C, H, N.

Table II. α-(Di-*n*-butylaminomethyl)-4-quinolinemethanols

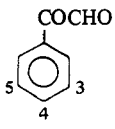


I

I	X	Substituents R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[e,f]
a	CH_2	Cl	H	H	H	126–128	*a*	47	$C_{26}H_{33}Cl_3N_2O$
b	CO	Cl	H	H	H	167–168.5	*b*	5	$C_{26}H_{31}Cl_3N_2O_2$
c	CO	Cl	H	Cl	H	159–161	*c*	59	$C_{26}H_{30}Cl_4N_2O_2$
d	CO	Cl	H	CF_3	H	157–159	*d*	14	$C_{27}H_{30}Cl_3F_3N_2O_2$
e	CO	Cl	CF_3	H	CF_3	194–195	*d*	11	$C_{28}H_{29}Cl_3F_6N_2O_2$
f	CO	CF_3	H	Cl	H	165–169.5	*a*	12	$C_{27}H_{30}Cl_3F_3N_2O_2$
g	CO	CF_3	Cl	Cl	H	185–188 dec	*d*	15	$C_{27}H_{29}Cl_4F_3N_2O_2$
h	CO	CF_3	Cl	H	Cl	173–175	*c*	10	$C_{27}H_{29}Cl_4F_3N_2O_2$
i	CO	CF_3	CF_3	H	H	165–166	*c*	13	$C_{28}H_{30}Cl_2F_6N_2O_2$
j	CF_2	Cl	H	H	H	142–144	*a*	37	$C_{26}H_{31}Cl_3F_2N_2O$

[a]C_6H_6-petroleum ether (20–40°). [b]*i*-PrOH-petroleum ether (20–40°). [c]C_6H_6. [d]C_6H_6-hexane. [e]*Anal.* for C, H, N. [f]Ir: OH absorption at 3.05–3.10 μ, NH+(broad) at 3.8–4.0 μ, C=O at 5.95–6.05 μ.

Table III. Phenylglyoxal Derivatives[a]



II

II	Substituents	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Precursor phenacyl bromides: Yield, % Method A	Method B[c]	Mp or bp (mm), °C
c	4-Cl	120–122[b]	C_6H_6	77	*d*	*d*	
d	4-CF_3	83–85[d,e]	Et_2O-petr ether (20–40°)	25	98		52–55[f]
e	3,5-$(CF_3)_2$	70–75 (2)		55		95	43–45[g]
g	3,4-Cl_2	103–105[h]	C_6H_6-petr ether (20–40°)	50	60		60–62[i]
h	2,5-Cl_2	65–67	C_6H_6-hexane	74	52		146–149 (1)[j]
i	3-CF_3	85–95 (1.1)		26	71		95–104 (1.1)[k]

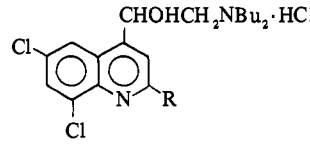
[a]These compounds were hygroscopic and, in most cases, were difficult to purify for analysis. Consequently, they were used as such to prepare the cinchoninic acids (III, Table I). Ir bands (OH at 2.9 μ, C=O at 5.9 μ) were as expected for the hydrated glyoxals. [b]Lit. mp of monohydrate 120–122°.[19] [c]Method A: $RCOCH_3 + Br_2$; method B: $RCOCl + CH_2N_2 + HBr$. [d]Aldrich Chemical Co. [e]Lit. mp of monohydrate 90–105°.[20] [f]Lit. mp 54–55°.[21] [g]Bp 80–85° (2 mm); recrystd from 90–120° ligroin. Ir bands were as expected. Analysis was omitted. [h]*Anal.* ($C_{16}H_{10}Cl_4O_5$) C, H. For a discussion of the structure of glyoxal hemihydrates see ref 22. [i]Lit. mp 54–56.5°.[23] [j]Prepd from *p*-aminoacetophenone in 3 steps as described by Lutz.[24] [k]Lit. mp 22°.[25]

Table IV. Biological Activity of 2-Benzyl- and 2-Benzoyl-4-quinolinemethanols

	Antimalarial test data,[a] ΔMST, days, or cures (C)								Photoxocity,[b] MED, mg/kg	
	Dose, mg/kg									
I	5	10	20	40	80	160	320	640	Ip	Oral
a			0.2	0.6	1.0	5.0	6.8	9.2	>450	>450
b			1.0	6.2	6.4	9.4	1C	4C	>400	>400
c	5.5	1C	3C	5C	5C	5C	5C	5C		
d	1C	3C	3C	3C	5C	5C	5C	5C	<15	15
e	7.8	2C	3C	5C	5C	5C	5C	5C	<300	<50
f	9.0	1C	1C	2C	3C	5C	5C	5C		<100
g	7.6	14.0	3C	5C	5C	5C	5C	5C	>500	<50
h	9.4	3C	5C	5C	5C	5C	5C	5C		
i	7.9	15.1	4C	5C	5C	5C	5C	5C	<200	<200
j			0.5	1.7	4.1	5.5	7.5	9.1	>600	>500

[a] Activity against *P. berghei* in 5 mice. The mean survival time of infected control mice is 6.5 ± 0.5 days. Extension in survival time (ΔMST) of treated mice is interpreted as evidence of antimalarial activity. The number of mice surviving (out of 5) at 60 days postinfection are considered as cures. For details of test procedure, see ref 17. [b] Expressed as the minimum effective phototoxic dose (MED) in test procedure reported in ref 4.

Table V. Antimalarial Comparison of 2-Phenyl- and 2-Benzoyl-4-quinolinemethanols



		Antimalarial test data,[a] ΔMST, days, or cures (C)					
		Dose, mg/kg					
Compd	R	5	10	20	40	80	160
WR 29252[b]	4'-ClC_6H_4	3.3	6.9	1C	4C	4C	5C
Ic	4'-ClC_6H_4CO	5.5	1C	3C	5C	5C	5C
AD 22902[b]	4'-$CF_3C_6H_4$			1C	2C	3C	5C
Id	4'-$CF_3C_6H_4CO$	1C	3C	3C	3C	5C	5C

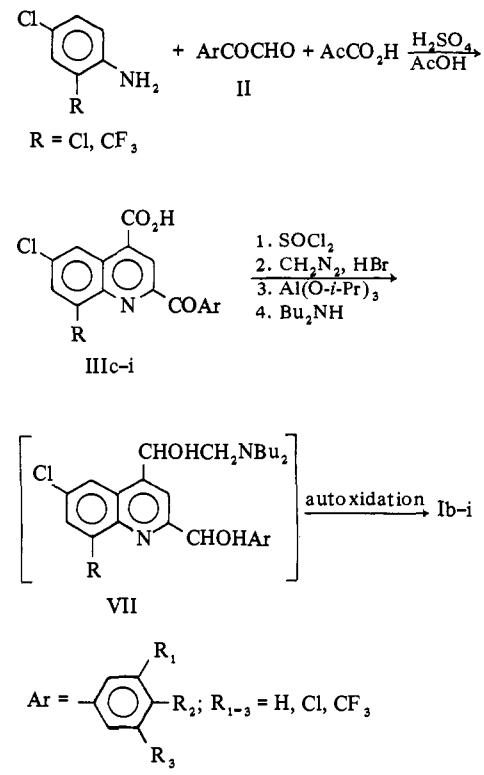
[a] Test method described in Table IV. [b] Walter Reed numbers supplied by Dr. T. R. Sweeney (WRAIR).

AcOH (69%). Conversion of IIIb–i to VII (Scheme I) and subsequent autoxidation[14,15] gave the target 2-benzoyl-4-quinolinemethanols (Ib–i, Table II). Our attempts to isolate pure VII from reaction 4 (Scheme I) or from the reduction of Ib–i were unsuccessful.

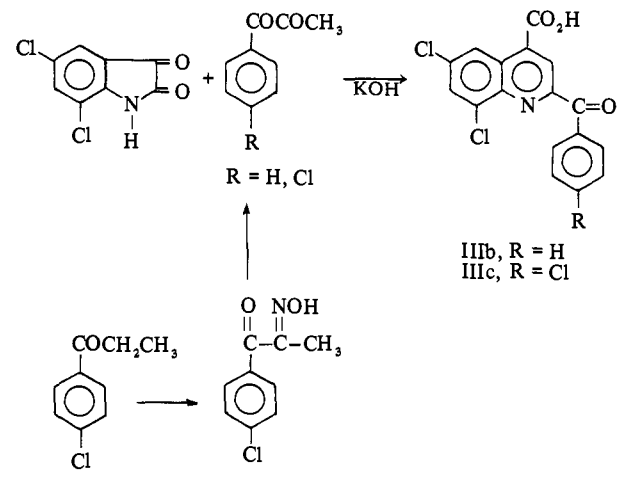
6,8-Dichloro-2-(α,α-difluorobenzyl)cinchoninic acid (IIIj, Table I) required in the synthesis of Ij was prepared from the ethyl ester of IIIb and SF_4–HF[16] followed by hydrolysis. The path from IIIj to the α,α-difluorobenzylamino alcohol (Ij, Table II) paralleled earlier methods.[10]

Biological Results. The quinoline amino alcohols (Ia, b, and j, Table IV) exhibited no significant phototoxicity. Of these, only the 2-benzoyl derivative (Ib) possessed moderate antimalarial activity. Substitution of Cl and CF_3 in the benzoyl series (Ic–i) produced in every case a striking enhancement of antiplasmodial action. However, this also led to a resurgence of phototoxic effects. Test data to date are presented in Table IV. In general, the 2-benzoyl-4-quinolinemethanols (Ic–i) were more potent antimalarials (Table V) and less phototoxic (based on ip data[4]) than the corresponding 2-phenyl analogs. Further consideration of the 2-benzoyl derivatives as therapeutic agents diminished, mainly due to phototoxicity in experimental animals and the availability in the Army program of nonphototoxic antimalarial agents.

Scheme I



Scheme II



Experimental Section

Melting points were determined with an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Micro-Analysis, Inc., Wilmington, Del. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

The following experimental methods are typical procedures for the designated groups of compounds. Generally, reactions were carried out under nitrogen. Starting materials were commercially available from Aldrich Chemical Co., Inc., Milwaukee, Wis., Distillation Products Industries, Rochester, N. Y., Research Organic Chemical Co., Sun Valley, Calif., and Pierce Chemical Co., Rockford, Ill.

Phenacyl Bromides. α-Bromo-4-trifluoromethylacetophenone (Table III, Method A). To a stirred soln of 4-trifluoromethylacetophenone (100 g, 0.54 mole) in AcOH (1 l.) was added dropwise at 20–25° Br_2 (91 g, 0.57 mole) in AcOH (200 ml). After 0.5 hr, the mixt was poured onto ice. The oil was extd with Et_2O, washed with H_2O, and dried over $MgSO_4$. Removal of the solvent *in vacuo* produced the phenacyl bromide (140 g, 98%) as an oil which solidified on standing.

α-Bromo-3,5-bis(trifluoromethyl)acetophenone (Table III, Method B). A stirred mixt of 3,5-bis(trifluoromethyl)benzoic acid (100 g, 0.39 mole) and $SOCl_2$ (150 g) was heated at reflux for 19 hr, and the excess $SOCl_2$ was removed *in vacuo*. After triturating the residue with dry C_6H_6, the solvent was evapd under reduced pressure to yield the acid chloride as a yellow oil (125 g).

To an ethereal CH_2N_2 soln [from 100 g (0.98 mole) of nitrosomethylurea] at 0–5° was added in 15 min a soln of the acid chloride in 100 ml of C_6H_6. The mixt was stirred at room temp overnight, and 67 ml of 48% HBr was added slowly with stirring, allowing the temp to rise to 20°. The organic layer was sepd, washed with H_2O, 5% $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concd to give, after vacuum distn, α-bromo-3,5-bis(trifluoromethyl)acetophenone (125 g, 95%). Ir bands were as expected. Elemental analysis was omitted.

Phenylglyoxal Derivatives (II, Table III). 4-Chlorophenylglyoxal Monohydrate (IIc). *p*-Chlorophenacyl bromide (100 g, 0.43 mole) was dissolved in DMSO (625 ml), and the soln was permitted to stand for 22 hr at room temp. The yellow soln was poured into H_2O (2 l.) and the resulting gummy ppt taken up in Et_2O. Evapn of the solvent gave white crystals (55 g, 77%), mp 100–110°. Recrystn from C_6H_6 afforded pure IIc.

Doebner Method. 2-Benzoyl-4-cinchoninic Acids (IIIc–i, Table I). 2-(4′-Chlorobenzoyl)-6,8-dichlorocinchoninic Acid (IIIc). To a stirred mixt of 2,4-dichloroaniline (61.6 g, 0.38 mole) and *p*-chlorophenylglyoxal monohydrate (70.8 g, 0.38 mole) in AcOH (160 ml) cooled by a H_2O bath at 15° was added dropwise H_2SO_4 (15 ml) during 20 min. The internal temp rose to 31°, and a thick white suspension (difficult to stir) formed. Pyruvic acid (33.5 g, 0.38 mole) was added in one portion, and the mixt was heated to 115° in 50 min (soln occurred at 60° and a solid pptd at 78°). The reaction was cooled to room temp, AcOH (160 ml) was added, and the ppt was filtered and washed with 20–40° petroleum ether to yield IIIc (26 g, 21%).

Pfitzinger Method. 2-Benzoyl-4-cinchoninic Acids (IIIb, c, Table I). 2-(4′-Chlorobenzoyl)-6,8-dichlorocinchoninic Acid (IIIc). Na (1.0 g, 0.042 g-atom) was dissolved in EtOH (100 ml) and the anhyd K salt of 5,7-dichloroisatin [prepd by evapn of equimolar quantities of KOH and the isatin (4.1 g, 0.015 mole) in EtOH] was added with stirring. To this soln was admitted in one portion 1-(4-chlorophenyl)-1,2-propanedione[18] (7.0 g, 0.038 mole). The reaction was heated at reflux for 2 hr, 10% HCl (600 ml) was added, and the tan ppt was collected and washed with H_2O. Recrystn from dioxane provided IIIc as white needles (2.5 g, 40%). The latter was identical with the product from the Doebner synthesis.

2-Benzyl-6,8-dichlorocinchoninic Acid (IIIa, Table I). A stirred mixt of 34% KOH soln (750 ml), 1.2 l. of H_2O, and 5,7-dichloroisatin (324 g, 1.5 moles) was heated at 60–90° for 0.5 hr. To the brown soln was added dropwise during 20 min, 1-phenyl-2-propanone (210 g, 1.57 moles). After refluxing for 24 hr, the reaction was poured into 3 l. of H_2O, and the mixt was treated with carbon. Acidification of the filtrate with HCl (300 ml) gave a tan ppt which, after digestion with EtOH (3 l.), produced 6,8-dichloro-2-methyl-3-phenylcinchoninic acid (IIIa) (244 g, 54%), mp 276–278° dec. The analytical sample melted at 269–272° dec (AcOH). *Anal.* ($C_{17}H_{11}Cl_2NO_2$) C, H, N.

The EtOH filtrate was brought to dryness, and the residue was extd with hot C_6H_6 (3 l.). After filtration, concn of the C_6H_6 soln gave IIIa (82 g, 18%) as tan solid, mp 174–176.5° (analytical sample, mp 178.5–180.5°). The structure of IIIa was substantiated by nmr analysis.

2-Benzoyl-6,8-dichlorocinchoninic Acid (IIIb) from IIIa. To a stirred mixt of IIIa (37 g, 0.111 mole), KOAc (52 g, 0.532 mole), and AcOH (380 ml) at 90–95° was added Br_2 (36 g, 0.225 mole) in AcOH (70 ml) during 45 min. After an additional 1.5 hr at 95°, the reaction was cooled, and the ppt collected, washed with H_2O, and recrystd from AcOH yielding (69%) IIIb, mp 248–250°, identical with the Pfitzinger product. Alcoholation of the acid chloride provided the ethyl ester (IIIb′, 84%), mp 152–154° (EtOH). *Anal.* ($C_{19}H_{13}Cl_2NO_3$) C, H, N.

6,8-Dichloro-2-(α,α-difluorobenzyl)cinchoninic Acid (IIIj) and Ethyl Ester (Table I). In a 250-ml Hastelloy "C" stainless steel autoclave was agitated a mixt of IIIb′ (37.4 g, 0.1 mole) SF_4 [0.552 mole, precondensed (34.1 ml) in a Dry Ice trap and vacuum transferred to the reactor], and H_2O (5.76 g, 0.32 mole) at 120° for 8 hr. The autoclave was cooled and vented, and the mixt was treated with 10% Na_2CO_3. The insol product on recrystn yielded (68%) the difluoro ester (IIIj′) as pale yellow needles (EtOH), mp 124–126°. *Anal.* ($C_{19}H_{13}Cl_2F_2NO_2$) C, H, N. Sapon of IIIj′ in EtOH (10% NaOH, reflux 2 hr), removal of the solvent, and recrystn afforded IIIj as yellow crystals.

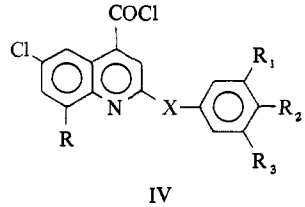
2-Benzoyl-4-cinchoninic Acid Chlorides (IVb–i, Table VI). 2-(4′-Chlorobenzoyl)-6,8-dichlorocinchoninic Acid Chloride (IVc). A stirred mixt of IIIc (11.4 g, 0.03 mole), $SOCl_2$ (20 ml), and C_6H_6 (100 ml) was heated at reflux for 18 hr. Excess $SOCl_2$ and C_6H_6 were removed *in vacuo*, and the yellow residue was washed with 20–40° petroleum ether to yield IVc (12 g, 100%).

2-Benzoyl- and 2-(α,α-Difluorobenzyl)-6,8-dichlorocinchoninic Acid Chlorides (IVa and j, Table VI). A suspension of the acid IIIa (28.5 g, 0.086 mole) and PCl_5 (18.2 g, 0.087 mole) in dry C_6H_6 (280 ml) was refluxed gently for 4 hr. The solvent was removed under reduced pressure, and the residue was slurried with petroleum ether. Extn of the insol product with C_6H_6 followed by solvent removal provided IVa. Compound IVj was prepared in similar fashion.

α-Bromomethyl 4-Quinolyl Ketones (V, Table VII). α-Bromomethyl 2-(4′-Chlorobenzoyl)-6,8-dichloro-4-quinolyl Ketone (Vc). To a well-stirred ethereal solution of CH_2N_2 [from 50 g (0.49 mole) of nitrosomethylurea] at 0–5° was added IVb (30 g, 0.075 mole) during 0.5 hr. After 2 hr, 48% HBr (80 ml) in Et_2O (80 ml) was admitted dropwise and the temp subsequently allowed to rise to 25°. The Et_2O layer was sepd, washed with 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and concd to yield Vc (20 g, 53%).

α-Bromomethyl-4-quinolinemethanols (VI, Table VIII). α-Bromomethyl-2-(α-hydroxy-4′-chlorobenzyl)-6,8-dichloro-4-quinolinemethanol (VIc). In a flask equipped with a Vigreux column and distn assembly was gently heated at reflux a mixt of Vc (5 g, 0.011 mole), predistd Al(*i*-PrO)$_3$ (8 g, 0.039 mole), and predried *i*-PrOH (150 ml). After 4 hr, the reaction was brought to dryness *in vacuo*, and the residue was placed in an ice bath. Upon

Table VI. Cinchoninic Acid Chlorides[a]

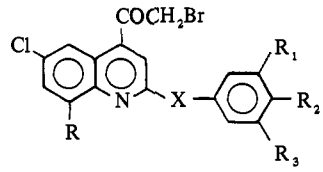


IV

IV	X	Substituents R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %
a	CH_2	Cl	H	H	H	86–89	*b*	75
b	CO	Cl	H	H	H	176–178.5	*b*	97
c	CO	Cl	H	Cl	H	280–282	*b*	100
d	CO	Cl	H	CF_3	H	151–154	*c*	96
e	CO	Cl	CF_3	H	CF_3	181–183	*c*	100
f	CO	CF_3	H	Cl	H	160–161	*b*	100
g	CO	CF_3	Cl	Cl	H	118.5–120.5	*b*	89
h	CO	CF_3	Cl	H	Cl	164–166	*c*	100
i	CO	CF_3	CF_3	H	H	*d*	*c*	96
j	CF_2	Cl	H	H	H	94–97	*b*	98

[a] Ir bands were as expected. Analysis was omitted. [b] Washed with 20–40° petroleum ether. [c] Washed with hexane. [d] Used immediately in the next reaction.

Table VII. α-Bromomethyl 4-Quinolyl Ketones

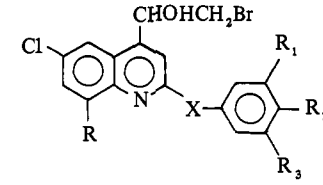


V

V	X	Substituents R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
a	CH_2	Cl	H	H	H	89–91	EtOH	66	$C_{18}H_{12}BrCl_2NO$
b	CO	Cl	H	H	H	150–152	EtOH	66	$C_{18}H_{10}BrCl_2NO_2$
c	CO	Cl	H	Cl	H	185–186	C_6H_6	53	$C_{18}H_9BrCl_3NO_2$
d	CO	Cl	H	CF_3	H	155–156	*i*-PrOH	47	$C_{19}H_9BrCl_2F_3NO_2$
e	CO	Cl	CF_3	H	CF_3	145–146	EtOH	55	$C_{20}H_8BrCl_2F_6NO_2$
f	CO	CF_3	H	Cl	H	160–161	Ligroin	60	$C_{19}H_9BrCl_2F_3NO_2$
g	CO	CF_3	Cl	Cl	H	133–134	Ligroin	88	$C_{19}H_8BrCl_3F_3NO_2$
h	CO	CF_3	Cl	H	Cl	159–161	*i*-PrOH	57	$C_{19}H_8BrCl_3F_3NO_2$
i	CO	CF_3	CF_3	H	H	110–111	EtOH	54	$C_{20}H_9BrClF_6NO_2$
j	CF_2	Cl	H	H	H	133–134	Ligroin	58	$C_{18}H_{10}BrCl_2F_2NO$

[a] *Anal.* for C, H, N.

Table VIII. α-Bromomethyl-4-quinolinemethanols[a]



VI

VI	X	Substituents R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[e]
a	CH_2	Cl	H	H	H	*b*		99	
b	CHOH	Cl	H	H	H	148–149 dec	EtOH	96	$C_{18}H_{14}BrCl_2NO_2$
c	CHOH	Cl	H	Cl	H	138–140	*i*-PrOH	93	$C_{18}H_{13}BrCl_3NO_2$
d	CHOH	Cl	H	CF_3	H	*c*		96	
e	CHOH	Cl	CF_3	H	CF_3	*b*		90	
f	CHOH	CF_3	H	Cl	H	122 dec	*d*	97	
g	CHOH	CF_3	Cl	Cl	H	127 dec	CCl_4	93	$C_{19}H_{12}BrCl_3F_3NO_2$
h	CHOH	CF_3	Cl	H	Cl	*b*		95	
i	CHOH	CF_3	CF_3	H	H	*c*		92	
j	CF_2	Cl	H	H	H	81–83 dec.		86	

[a] Ir bands (broad OH at 2.9–3.1 μ, absence of C=O absorption) were as expected. Analysis was generally omitted. [b] Viscous oil. [c] Semisolid. [d] Dried *in vacuo* over P_2O_5. [e] *Anal.* for C, H, N.

addn of 10% HCl (30 ml) an oil formed that gradually solidified. Recrystn from *i*-PrOH produced VIc (5 g, 93%) as white needles.

α-(Di-*n*-butylaminomethyl)-4-quinolinemethanols (I, Table II). α-(Di-*n*-butylaminomethyl)-2-(4'-chlorobenzoyl)-6,8-dichloro-4-quinolinemethanol Monohydrochloride (Ic). A mixt of VIc (2.0 g, 0.0043 mole) and Bu_2NH (3.36 g, 0.026 mole) was stirred magnetically and heated at 75–80° by an oil bath for 18 hr. The reaction was brought to room temp and Et_2O (20 ml) was added pptg insol $Bu_2NH_2^+Br^-$ (0.8 g, 93%). To the filtrate dild with Et_2O (50 ml) and stirred magnetically in an ice bath was added ethereal 0.89 *N* HCl (25 ml, 0.022 mole). The pptd $Bu_2NH_2^+Cl^-$ (3.4 g, 94%) was collected and washed with Et_2O. Further addn of ethereal HCl (4 ml, 0.0036 mole) to the filtrate produced on concn *in vacuo* Ic (1.3 g, 59%).

In the case of Ib, autoxidation was effected on neutral Al_2O_3 using C_6H_6 as the elution solvent.

Acknowledgment. We thank Col. William E. Rothe for permission to publish phototoxicity data and Drs. T. R. Sweeney and R. E. Strube for discussions and test results during the course of this program.

References

(1) F. Y. Wiselogle, "A Survey of Antimalarial Drugs 1941–1945," Vol. 1, J. W. Edwards, Ann Arbor, Mich., 1946.
(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953.
(3) T. N. Pullman, *et al.*, *J. Clin. Invest.*, **27**, 12 (1948).
(4) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, 11, 366 (1968).
(5) I. G. Fels, *ibid.*, 11, 887 (1968).
(6) W. Fowlks, *J. Invest. Dermatol.*, **32**, 233 (1959).
(7) M. Pathak, J. Fellman, and K. Kaufman, *ibid.*, **35**, 165 (1960).
(8) A. J. Saggiomo, K. Kato, and T. Kaiya, *J. Med. Chem.*, 11, 277 (1968).
(9) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).
(10) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).
(11) W. Borsche and O. Vorbach, *Justus Liebigs Ann. Chem.*, **537**, 22 (1938).
(12) O. Doebner, *ibid.*, **242**, 265 (1887).
(13) N. Kornblum, *et al.*, *J. Amer. Chem. Soc.*, 79, 6562 (1957).

(14) P. Dyson and D. Hammick, *J. Chem. Soc.*, 1724 (1937).
(15) B. R. Brown, *ibid.*, 2577 (1949).
(16) M. S. Raasch, *J. Org. Chem.*, 27, 1406 (1962).
(17) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).
(18) N. Kochetkov and N. Dudykina, *Zh. Obshch. Khim.*, 30, 3054 (1960); *Chem. Abstr.*, 55, 18652*a* (1961).
(19) P. Karrer and C. Musante, *Helv. Chim. Acta*, 18, 1140 (1935).
(20) E. L. Anderson, J. E. Casey, Jr., M. Emas, E. E. Force, E. M. Jensen, R. S. Matz, and D. E. Rivard, *J. Med. Chem.*, 6, 787 (1963).
(21) W. Caldwell and G. Schweiker, *J. Amer. Chem. Soc.*, 75, 5884 (1953).
(22) H. Becker and G. Russel, *J. Org. Chem.*, 28, 1895 (1963).
(23) R. Fuchs, *J. Amer. Chem. Soc.*, 78, 5612 (1956).
(24) R. Lutz, *J. Org. Chem.*, 12, 617 (1947).
(25) R. Laird and R. Parker, *J. Amer. Chem. Soc.*, 83, 4277 (1961).

Absolute Configuration of 3-Quinuclidinyl Benzilate and the Behavioral Effect in the Dog of the Optical Isomers

Anita Meyerhöffer

Research Institute of National Defence, 172 04 Sundbyberg, Sweden, and Department of Medical Physics, Karolinska Institutet, 104 01 Stockholm, Sweden. *Received January 17, 1972*

Usually, a great difference in potency is found between optical isomers of anticholinergic esters with asymmetric centers in the acid moiety.[1,2] But when the asymmetric center is situated in the alcoholic part of the ester, this effect is not always noted. Hence, five anticholinergic esters derived from the isomers of β-methylcholine showed *R/S* potency ratios close to one.[2] However, Sternbach and Kaiser[3,4] found a marked difference in antispasmodic action on isolated rabbit intestine between the enantiomers of quinuclidinyl diphenylacetate, although no difference was found between the two isomers of quaternized quinuclidinyl benzilate.

In the cases where small or no differences have been found between the pharmacological effects of the isomers, quaternized drugs have always been used. The esters of quinuclidine appear to be exceptions to the findings which state that quaternization increases the activity of these types of drugs.[5] Hence, it was of interest to study the pharmacological effects of the enantiomers of 3-quinuclidinyl benzilate (QB) as a base. Moreover QB is a very potent drug, particularly as a central agent,[6] and because of the rigid structure of quinuclidine this compound might show a higher degree of stereospecificity than the esters of β-methylcholine.

In the present study the (+) and (−) enantiomers of 3-quinuclidinyl benzilate were isolated and their absolute configurations determined by the use of the X-ray anomalous dispersion technique.[7] In addition, a pharmacological test was performed on the enantiomers.

Experimental Section†

Resolution of (±)-3-quinuclidinol was performed according to Sternbach and Kaiser[3] using (+)-camphor-10-sulfonic acid. While this manuscript was being prepared, a method of isolating (+)-3-quinuclidinol in the pure state was published.[8] All experimental data are listed in Table I.

(−)-3-Quinuclidinyl benzilate was prepared from equivalent amounts of methyl benzilate and (−)-3-quinuclidinol in the presence of sodium hydride,[9,‡] yield 79%. After three recrystallizations from acetone, the product showed less than 0.1% of impurities according to glc (on 5% OV 210 column).

Crystals of (−)-3-quinuclidinyl benzilate hydrobromide were prepared from the base and hydrobromic acid solved in methanol and recrystallized from acetone–methanol with slow evaporation and cooling. After one week, crystals large enough for single crystal X-ray diffraction analysis were obtained, $[\alpha]^{22}D - 26.2°$ (*c* 0.6, 0.2 *M* HCl), which corresponds to $[\alpha]^{22}D - 32.5°$ for the free base.

(+)-3-Quinuclidinyl Benzilate. (+)-3-Quinuclidinol, partially resolved, was converted to the corresponding ester using the same method as described for the (−) isomer, yield 59%. The product was purified by fractional crystallizations from acetone–methanol, 30:1, the first fraction being richest in the (+) isomer. Five recrystallizations yielded a product with $[\alpha]^{22}D + 32.6°$. It was not possible to obtain higher optical purity for the last product by further recrystallizations from this solvent mixture. The glc analysis (on 5% OV 1 column) showed small amounts of methyl benzilate and benzophenone (together less than 1%).

Determination of the Absolute Configuration. The structure factors for the *R* configuration of QB hydrobromide were calculated with the positional atomic coordinates and temperature factors from the crystal structure determination.[10] The atomic scattering factors for Cu Kα radiation with corrections for the anomalous scattering of the bromine ions were taken from the International Tables.[11] The calculations were performed on an IBM 360/75 computer with the program system of Bergin.[12] From these data 20 Bijvoet pairs, which showed the effect of anomalous scattering most significantly, were selected in the *hk*1–*hk*3 layers. The observed intensities were obtained from a single crystal of (−)-quinuclidinyl benzilate hydrobromide. The crystal was trimmed to a sphere (radius 0.23 mm) in order to avoid differences in absorption for the two reflections of each Bijvoet pair. The reflections were recorded in an integrating Weissenberg camera with Ni-filtered Cu Kα radiation and multiple film technique. The intensities of the 20 pairs selected from the structure factor calculations were derived from microdensitometer data. Due corrections for background and film factors were made. The calculated structure factors were converted to I_{calcd} and scaled to I_{obsd}.

Pharmacological Tests. Behavioral and peripheral effects of the synthetized isomers have been studied in adult beagles according to a method described by Albanus.[6] Centrally active anticholinergic drugs elicit a typical behavioral syndrome in dogs called the central anticholinergic syndrome (CAS). This is manifested by symptoms such as ataxia and decreased environmental awareness, the latter being manifested as nonretreating behavior. The threshold dose to elicit these two symptoms is used as the index of central anticholinergic potency. In addition salivation and heart rate were recorded. Aqueous solutions of the enantiomers of QB were prepared in concentrations of 0.1–10 mg/ml. The solutions were equimolar with respect to hydrochloric acid and contained 10% methanol because of the low water solubility of the drugs. The injections were made subcutaneously with 0.1 ml/kg body weight. The threshold dose to elicit the CAS for the most inactive isomer was determined.

Results and Discussion

The observed Bijvoet pairs exhibited differences§ which agreed well with the calculated values based upon an *R* configuration. This shows unequivocally that (−)-QB hydrobromide possesses the *R* configuration. Belleau and Pauling[13] have determined the absolute configuration of (−)-quinuclidinol to be *R*. This indicates that no inversion occurred during the transesterification of methyl benzilate with 3-quinuclidinol.

The spatial arrangement of atoms for the *R* configuration of QB in crystals of the hydrobromide is illustrated in the perspective drawing of Figure 1. The ether oxygen atom is

†Melting points (uncorrected) were determined on a Leitz melting point microscope. Optical rotation measurements were carried out on a Perkin-Elmer 141 polarimeter and nmr spectra on a Varian A 60A spectrophotometer. Glc analyses were performed by I. Lindgren and elemental analyses were carried out by C. Lamrell both at this laboratory.

‡G. Wallerberg, *et al.*, unpublished work from this laboratory, 1970.

§Observed and calculated intensities for 40 reflections are on file in the offices of the ACS.