International Symposium on Pteridines, Toba, July 1969," International Academic Printing Co., Ltd., Tokyo, Japan, 1970, p 357.
(55) J. I. DeGraw, V. H. Brown, M. Cory, P. Tsakotellis, R. L. Kisliuk, and Y. Gaumont, *J. Med. Chem.*, 14, 206 (1971).
(56) C. L. Maddock, G. J. D'Angio, S. Farber, and A. H. Handler, *Ann. N. Y. Acad. Sci.*, 89, 386 (1960).
(57) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 68, 1670 (1946).

2-Substituted Cinchoninic Acids as Intermediates in Quinolinemethanol Syntheses†

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The synthesis of six 2-substituted 4-quinolinemethanols *via* 4-hydroxyquinolines and cinchoninic acids as intermediates is described. A new synthetic scheme has been developed which proceeds from two readily available types of starting materials, substituted anilines and carboxylic acids, making possible the production of 4-quinolinemethanols bearing a wide variety of substituents in the 2, 6, and 8 positions. The present examples contain *tert*-butyl and 1-adamantyl groups in the 2 position. Five of the compounds showed antimalarial activity against *Plasmodium berghei*; the most active compound was α-di-*n*-butylaminomethyl-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol.

Discussion

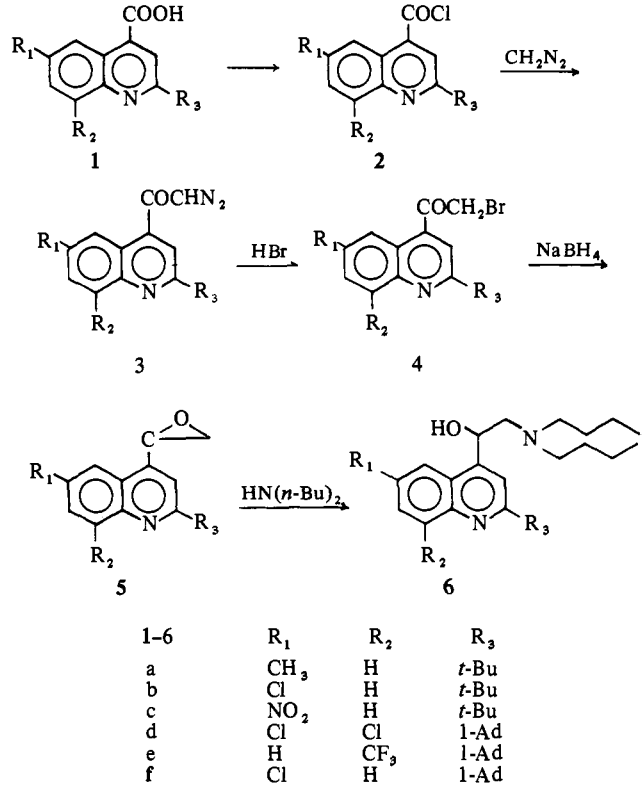
In recent years, the field of 4-quinolinemethanol antimalarials has been extensively researched with respect to the preparation of new compounds of this class. We wish to present our own findings in this area and to report an improved synthesis of 2-substituted cinchoninic acids, which are key intermediates in 4-quinolinemethanol preparation.

The importance of providing the 2 position of the quinoline nucleus with a stable substituent has been emphasized by Lutz,[1] Mead,[2] Schaefer,[3] and Boykin[4] and their coworkers. Consequently, those reactions which yield a 2-substituted quinoline nucleus, such as the Pfitzinger Synthesis,[5] have been frequently employed by a number of investigators in the quinolinemethanol field.[1,6-10,‡] In this connection, a number of 2-aryl-4-quinolinemethanols have been prepared[1,6-11] and while significant antimalarial activity has been demonstrated, the problem of phototoxicity[3,12-15] has precluded their significant utilization as antimalarial agents. Consequently, recent efforts in this field have been directed toward the preparation of quinolinemethanols bearing other than aryl groups in the 2 position. The use of the 2-trifluoromethyl group by Ohnmacht[16] is a case in point.

The low phototoxicity and curative properties of α-di-*n*-butylaminomethyl-2-(1-adamantyl)-6,8-dichloroquinolinemethanol[§] suggested that the substitution of the quinoline nucleus by a bulky alkyl group at the 2 position might provide a solution to the problem of phototoxicity. In addition to the adamantane structure, the *tert*-butyl group represents a bulky alkyl structure which is relatively inert and has the additional advantage of providing an economical model for preliminary experiments in the adamantyl series.

Since Lutz had worked out a smooth sequence for the preparation of 4-quinolinemethanols from cinchoninic acids[1] (Scheme I), it was our decision to prepare the appropriate 2-substituted cinchoninic acids (**1**) and then to convert these to the corresponding 4-quinolinemethanols (**6**) through application of Lutz's scheme.

Scheme I



1-6	R_1	R_2	R_3
a	CH_3	H	*t*-Bu
b	Cl	H	*t*-Bu
c	NO_2	H	*t*-Bu
d	Cl	Cl	1-Ad
e	H	CF_3	1-Ad
f	Cl	H	1-Ad

While the Pfitzinger synthesis of substituted cinchoninic acids has been shown to work satisfactorily in several instances,[1,7,17] in others it has not worked well at all.[§,18] The lack of success experienced in our laboratory in the Pfitzinger synthesis of 2-(1-adamantyl)-8-trifluoromethylcinchoninic acid is a case in point. In our hands, condensation of 7-trifluoromethylisatin[19] and acetyladamantane never gave 2-(1-adamantyl)-8-trifluoromethylcinchoninic acid in greater than 8% yield.

After several failures, a reaction scheme (Scheme II) based upon the earlier work of Shah and coworkers[20,21] was devised which provided in good yield the desired 2-substituted quinoline nucleus. This scheme has the additional advantage of utilizing readily available starting materials, specifically carboxylic acids and aromatic amines. Consequently, one can foresee a wide variety of 2-substituted cinchoninic acids as being accessible through this scheme.

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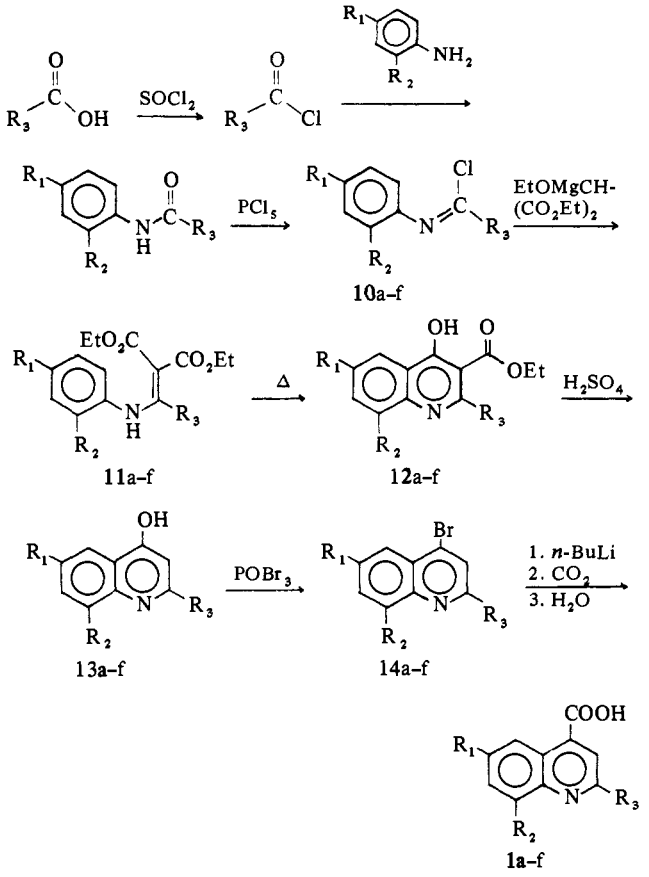
‡For a more comprehensive review of the synthesis and structure of quinolinemethanol antimalarials, see ref 9.

§This compound was prepared earlier in our laboratories by Dr. T. Yamamoto and it was tested for antimalarial activity prior to initiation of this work.

Scheme II



These authors had originally reported that various imide chlorides (**10**) would yield substituted carbethoxyacrylates (**11**) upon treatment with sodioethyl malonate and that these acrylates could be cyclized to 3-carbethoxy-4-quinolinols (**12**) upon heating. It was found that substitution of the ethoxymagnesium salt of malonic ester for the sodium salt gave markedly improved yields of the acrylic ester, and, in addition, the reported cyclization was found to occur so easily with the crude acrylate that it was not necessary to isolate and purify it prior to the cyclization.

Basic hydrolysis of the resultant 3-carbethoxy-4-quinolinol could not be realized under a variety of conditions, and mild acid hydrolysis did not work either. It was found that heating with concentrated H_2SO_4 effected both hydrolysis and decarboxylation. The bromination of the 4 position was initially carried out on 2-*tert*-butyl-4-hydroxy-6-methyl- and 2-*tert*-butyl-4-hydroxy-6-chloroquinoline with triphenylphosphine dibromide[22] with good results. However, this reagent would yield only tar when the transformation was attempted on the three adamantyl derivatives. At the elevated reaction temperatures necessary for the successful use of this reagent with aromatic substrates (250–300°), it is possible that the moderately strained adamantyl group[23] may undergo random carbonium ion isomerizations[24] under the initiating influence of the hydrogen bromide liberated during the reaction. Kaslow and March[25] reported the conversion of hydroxyquinolines to bromoquinolines using phosphorus pentabromide, but no product other than tar was obtained when their technique was applied to the 2-(1-adamantyl)-quinolinols. Again, high reaction temperatures were involved, and it is likely that the same factors which precluded the use of triphenylphosphine dibromide were active in this case also. The reagent finally chosen was phosphoryl bromide as used by Goldring and Senear on several hydroxypyrimidines.[26] This reagent gave very satisfactory results in the bromination of all the hydroxy quinolines (**13**) used in this work. Similar good results have been reported by Ohnmacht[16] and by Pinder and Burger.[27]

The halgen–metal interconversion reaction to produce a 4-lithioquinoline worked well in all but one case. No cinchoninic acid could be recovered from the carbonation of the reaction mixture of butyllithium and 2-*tert*-butyl-4-bromo-6-nitroquinoline. Owing to this difficulty it was necessary to utilize the reaction of cuprous cyanide in DMF to form the 4-cyano compound and then to hydrolyze the nitrile to the correpsonding cinchoninic acid.

Once the 2-substituted cinchoninic acids had been prepared, no difficulty was encountered in the subsequent application of Lutz's[1] procedures for the formation of α-dialkylaminomethyl-4-quinolinemethanols from the cinchoninic acids. This procedure leads from the acid to a 4-bromomethyl ketone by way of the acid chloride and diazomethyl ketone. The bromomethyl ketone is reduced to an epoxide from which the final α-di-*n*-butylaminomethyl product is produced by heating with di-*n*-butylamine.

Experimental Section

All C and H analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The exact mass measurements were taken on a Du Pont (CEC) 21-110 high-resolution mass spectrometer at *ca.* 70 eV.# The determination of the exact molecular mass was accomplished by peak matching at a resolution of approximately 2×10^4.

Imide Chlorides (**10a–f**).[28] In a large flask equipped with a reflux condenser protected by a $CaCl_2$ tube, the appropriate anilide (prepared from the amine and acid chloride by conventional procedures) was mixed with 10% molar excess of phosphorus pentachloride. The initial reaction was rather vigorous for those members of the series with the less electronegative aryl substituents and was moderated by immersing the reaction vessel in a cold water bath. Once the initial reaction had subsided, external heating was applied and maintained until hydrogen chloride evolution was no longer significant, usually 4–8 hr. Phosphoryl chloride was removed under aspirator vacuum with gentle warming to remove residual traces of phosphoryl chloride and hydrogen chloride. No further isolation was carried out.

3-Carbethoxy-4-hydroxyquinolines (**12a–f**). These compounds were prepared by the condensation of the imide chloride with ethoxymagnesium ethylmalonate prepared after the method of Reynolds and Hauser,[29] with the modification that the ether solvent was removed by distillation and replaced by an equal volume of dry toluene upon completion of the reaction.

To the refluxing toluene solution of the malonate salt was gradually added an equimolar amount of the appropriate imide chloride dissolved in an equal volume of dry toluene. Upon completion of the addition, the reaction mixture was allowed to stir at reflux temperature for 8 hr. After cooling to room temperature, enough cold, dilute hydrochloric acid was slowly added to just dissolve the magnesium salts. The two-phase mixture was extracted with ether, and the ether extracts were washed with water and dried ($MgSO_4$). The ether and toluene were removed under aspirator vacuum with gentle heating, and the residual dark oil was heated at about 150° under aspirator vacuum for about 8 hr or until the mixture was so thick with solid that magnetic stirring was difficult. The mixture was then allowed to cool and was diluted with petroleum ether (bp 60–80°) or, in the case of the *tert*-butyl-6-chloro derivative, with absolute alcohol and filtered. The product thus obtained was sufficiently pure for subsequent reaction. The filtrate was returned to the original flask and heated at 150° as before. This procedure was repeated until no additional product was obtained. The melting points and other data pertaining to the products are given in Table I.

4-Hydroxyquinolines (**13a–f**). Decarbethoxylation of all six 3-carbethoxyquinolines was carried out in the same manner. A sample of the 3-carbethoxy compound was treated with 1.6 times its weight of concentrated sulfuric acid under aspirator vacuum at 120–125° with stirring until no more bubbles of carbon dioxide were observed. The hot acid solution was then poured into a large volume of

#The high-resolution mass spectrometer was purchased with funds provided by the National Science Foundation in Grant GP-8509.

Table I. Quinoline Derivatives

Compd[a]	Reaction conditions: Temp, °C	Time, hr	Purifn solvent	Yield, %	Mp, °C	Analyses
12a	Reflux	7		83	255–258	C, H
12b	105	9		63	264–266	C, H
12c	Reflux	12		61	278–281	C, H
12d	86	16		74	157–160	C, H
12e	100	8		68	230–233	C, H
12f	Reflux	8		73	315–318	C, H
13a	120	4	EtOH (recrystd)	92	284–286	C, H
13b	124	5	EtOH–H_2O (recrystd)	87	307–309	C, H
13c	124	4.5	EtOH (triturated)	95	>400	C, H
13d	125	4	EtOH (triturated	96	254–256	C, H
13e	124	7	EtOH–H_2O (recrystd)	90	196–198	C, H
13f	124	4.5	EtOH (triturated)	89	370–373	C, H
14a	155	5.5	MeOH (recrystd)	91	75–80	C, H
14b	155	5,5	MeOH (recrystd)	56	83–85	Mass[b]
14c	153	4.0	EtOH (recrystd)	97	118–120	C, H
14d	155	7.0	Benzene–EtOH (recrystd)	91	232–233	Mass[b]
14e	150	4.0	EtOH (recrystd)	88	149–151	C, H
14f	120	4.5	Benzene–EtOH (recrystd)	97	170–173	Mass[b]
1a	−40	25	EtOH–H_2O (recrystd)	77	223–225	C, H
1b	−40	25	EtOH–H_2O (recrystd)	76	212–214	C, H
1c			EtOH–H_2O (recrystd)	94[c]	220–225	Mass[b]
1d	−40	23	EtOH (recrystd)	89	258–261	Mass[b]
1e	−40	30	Benzene–petroleum ether (bp 60–80°) (recrystd)	77	249–252	C, H
1f	−40	35	Benzene–petroleum ether (bp 60–80°) (recrystd)	52	263–265	C, H
2a	Reflux	5.5		95	*d*	
2b	Reflux	7.5		76	103–105[b]	
2c	Reflux	6.0			*d*	
2d	Reflux	5.5		97	162–165[e]	
2e	Reflux	5.5		96	120–122[e]	
2f	Reflux	5.5		99	*d*	
4a	0	4.0	THF (triturated)	79	*f*	Mass
4b	0	4.0	THF (triturated)	29	*f*	Mass[b]
4c	0	4.0	THF (triturated)	95	125–129[f]	Mass[b]
4d	0	6.0	Petroleum ether (bp 60–80°) (recrystd)	86	114–117	Mass[b]
4e	0	3.5	Hexane (recrystd)	95	139–143	Mass[b]
4f	0	3.5	THF (triturated)	41	*f*	Mass[b]
5a			CH_3CN	100	56–59	Mass[b]
5b			CH_3CN	98	66–68	Mass[b]
5c				84	96–98	Mass[b]
5d				98	155–157	Mass[b]
5e				86	125–128	Mass[b]
5f			$(CH_3)_2CO$	95	165–166	Mass[b]
6a	100–110	10.5		63		C, H
6b	100–110	11.5		77		C, H
6c	100–110	10.5		98		C, H
6d	100–110	12.0		94		C, H
6e	100–110	10.0		98		C, H
6f	100–110	11.0		74		C, H

[a] See Scheme II. [b] Exact mass measurement was satisfactory. [c] Prepared from the corresponding nitrile. See Experimental Section. [d] No isolation made. Crude acid chloride was used in the subsequent step. [e] Melting point of the free base. [f] Product isolated as the hydrobromide salt. Slow decomposition upon heating.

crushed ice, and the resulting tar was manually stirred until it solidified (1–5 min) and could be broken up. The crushed solid product was collected by suction filtration and then triturated with a 50:50 ethanol–water solution saturated with sodium bicarbonate and again collected by suction filtration. The resulting 4-hydroxyquinolines were all soluble in ethanolic sodium hydroxide and could be precipitated by saturating their solutions with carbon dioxide. Yield data, melting points, and other pertinent data are given in Table I.

4-Bromoquinolines (14a–f). The 4-bromoquinolines were prepared in good yield from the corresponding 4-hydroxy compounds by treatment with an excess of phosphoryl bromide. The general procedure involved dissolving the 4-hydroxy compound in an approximately one molar excess of phosphoryl bromide (most easily handled by freezing and weighing the solid). The exact excess of brominating agent was not critical; however, an amount sufficient to dissolve the quinolinol and permit efficient stirring was necessary to achieve a good yield. The bromination mixture was heated at 150–160° for 4.5–9 hr or until hydrogen bromide evolution had ceased, and the hot mixture was poured into ice. The resulting mass was stirred until it solidified and was then broken up and collected by filtration. The crude bromoquinoline was washed in saturated sodium bicarbonate and recrystallized. Table I gives reaction times, recrystallization solvents, and other data pertaining to the products.

Cinchoninic Acids (1a,b,d–f) (except 2-*tert*-Butyl-6-nitrocinchoninic Acid). The cinchoninic acids, with the one exception, were all prepared in acceptable yields from the corresponding 4-bromoquinolines by the methods of Gilman and Spatz.[30,31]

To a three-necked flask fitted with an internal thermometer, an addition funnel, and a magnetic stirrer was introduced a measured amount of 4-bromoquinoline. Anhydrous ether was added to the solid *via* syringe and serum cap in a volume equal to 25 times the weight of bromoquinoline used. The resultant reaction mixture was cooled to −42 to −45° by a Dry Ice–isopropyl alcohol bath, and the addition funnel was packed in Dry Ice by making an aluminum foil jacket around it. The reaction system was kept under a slight positive nitrogen pressure and 1.25 equiv of *n*-butyllithium in hexane (Ventron) was transferred to the addition funnel by syringe and

serum cap. The cold butyllithium solution was rapidly added to the bromoquinoline as the reaction temperature was maintained at −40°. After about 25 min the lithioquinoline was carbonated by the careful, but rapid, addition of solid Dry Ice to the cold reaction mixture. The carbonated solution was allowed to warm to room temperature and all the solvent was removed on a rotary evaporator. The residual solid was dissolved in 10% sodium hydroxide solution and twice extracted with ether. Some unchanged bromoquinoline was invariably recovered from the ether extracts at this stage of the work-up. The basic aqueous solution was acidified with glacial acetic acid and extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$). Removal of the solvent ether gave the crude cinchoninic acid. Table I gives reaction conditions, recrystallization solvents, and other pertinent data.

2-*tert*-Butyl-4-cyano-6-nitroquinoline. This nitrile was prepared after the method of Friedman and Schecter[32] but utilized a work-up in ferric chloride solution rather than by either of the two work-up methods offered by these authors. In a 100-ml flask containing 14.7 g (0.082 mol) of cuprous cyanide was added a solution of 20.0 g (0.065 mol) of 2-*tert*-butyl-4-bromo-6-nitroquinoline dissolved in 30 ml of dimethylformamide. The dark reaction mixture was heated at reflux temperature for 3.5 hr. The resulting dark liquid was poured into a solution of ferric chloride ($FeCl_3$, 40 g; concentrated HCl, 10 ml; water, 60 ml). This mixture was stirred to break up solid material and warmed at 60–80° for 30 min. The ferric chloride solution was then diluted with water and extracted thoroughly with ether. The yellow ether extracts were dried ($MgSO_4$) and the ether was removed on a rotary evaporator to give 13 g of crude, yellow 2-*tert*-butyl-4-cyano-6-nitroquinoline. The nitrile was recrystallized from 95% ethanol to give 10 g (61%) of yellow crystals, mp 161–164°.

2-*tert*-Butyl-6-nitrocinchoninic Acid (1c). To 9.00 g (0.035 mol) of the 4-cyano compound in a 100-ml flask was added 25 ml of 70% (by volume) sulfuric acid. The clear reaction mixture was heated at 120–130° for 1.5 hr and then poured onto ice. The crude cinchoninic acid was collected in almost quantitative yield by filtration and was recrystallized from ethanol–water: 9.0 g (94%) of yellow crystals; mp 220–225°.

Cinchoninoyl Chlorides (2a–f). All the acid chlorides were prepared by treatment with the minimum amount of redistilled thionyl chloride necessary to dissolve the acid upon warming. The acid–thionyl chloride solution was heated at reflux temperature for 5–7 hr. Afterward, the unchanged thionyl chloride was removed under aspirator vacuum with gentle warming until only a slurry of the cinchoninoyl chloride remained. Dry toluene (10–20 ml) was added and then removed under vacuum to flush out traces of thionyl chloride and dissolved gases. No further isolation was carried out, and it was not necessary to generate the free base from those acid chlorides which were formed as their hydrochloride salts. Table I lists the data for the cinchoninoyl chlorides.

Diazomethyl Ketones (3a–f). The quantity of diazomethane necessary to generate each of the diazomethyl ketones was calculated on the basis of the molar amount of cinchoninic acid used to prepare the acid chloride. *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide was used as the source of diazomethane by utilizing the procedure described in Aldrich Technical Bulletin No. D-2800-0.** The ethereal diazomethane was distilled directly into a three-necked flask cooled in an ice–salt bath and equipped with a Teflon-coated magnetic stirring bar. Rubber stoppers were used for all connections, and no equipment with ground glass joints was employed.**

When all the diazomethane had been collected in the three-necked flask, a dropping funnel with a Teflon stopcock was attached, as was a reflux condenser. The acid chloride (or its hydrochloride salt) was dissolved in dry tetrahydrofuran and was slowly added with stirring to the ice–salt-cooled ethereal diazomethane solution. This reaction mixture was allowed to stir for 18 hr and was then allowed to come to room temperature. At this point, the diazomethyl ketone was either isolated by filtering the ethereal solution and removing the solvent on a rotary evaporator, or the ethereal solution of the ketone was used directly in the next step, conversion to the bromomethyl ketone. It should be noted that the free bases were treated with 2.5 equiv of diazomethane, whereas 3.5 equiv was used with the hydrochloride salts.

Bromomethyl Ketones (4a–f). The bromomethyl ketones were prepared either from the crude ethereal solution of the diazomethyl ketone or by dissolving a previously isolated diazomethyl ketone in a volume of anhydrous ether equal to approximately 16 times the weight of diazo ketone used. Two molar equivalents of 48% HBr dissolved in an equal volume of anhydrous ether was slowly added to the ice-cold ethereal solution of diazo ketone, and the reaction mixture was allowed to stir for about 4 hr.

In the case of the 6,8-dichloro and the 8-trifluoromethyl compounds, the free base was formed and was isolated by diluting the reaction mixture with cold water and extracting the product into ether. Evaporation of the ether extracts gave the crude bromomethyl ketone. In the case of the two 6-chloro derivatives, the products were isolated by reducing the volume of ether almost to dryness and washing the crude hydrobromide salt with cold tetrahydrofuran.

The 6-methyl derivative was resistant to bromination in ethereal HBr, and it was necessary to dissolve this derivative in 100 ml of warm glacial acetic acid and then add a solution of 10 ml of 48% HBr in 10 ml of acetic acid. This reaction solution was allowed to stand for 10 min before the crude bromomethyl ketone hydrobromide was isolated by diluting the reaction mixture with tetrahydrofuran and filtering the resultant solid.

The 6-nitro derivative was isolated in both its hydrobromide salt and free base forms. The former was recovered by filtration, followed by washing the solid with tetrahydrofuran, while the latter was recovered by diluting the combined tetrahydrofuran washings and ether filtrate with water and separating the ether layer. After drying the ether extracts ($MgSO_4$), evaporation gave the remainder of the bromomethyl ketone as the free base. Additional data on the bromomethyl ketones are given in Table I.

Quinolyl Epoxides (5a–f). The epoxides were prepared as described by Atkinson and Puttick.[15] The bromomethyl ketone, free base, or hydrobromide salt was treated over a 10-min period with 1.26 molar equiv of sodium borohydride after having been dissolved in a volume of absolute ethanol equal to 60 times the weight of borohydride used and cooled to 20° for 20 min upon completion of the borohydride addition. The reaction mixture was then treated with a volume of 10 *M* sodium hydroxide equal to ten times the weight of borohydride used. The basic reaction mixture was stirred for 30 additional minutes at 20° and the epoxide was isolated either by direct filtration and washing with water, as in the case of the 6,8-dichloro, 8-trifluoromethyl, and 6-nitro derivatives, or by dilution with water and ether extraction as in the three remaining cases. Additional data on the epoxides are given in Table I.

Di-*n*-butylaminomethyl-4-quinolinemethanols (6a–f). The final

Table II. 4-Quinolinemethanols. Evaluation against *P. berghei* in Mice[a]

Compd	Dose, mg/kg	Increase in survival time, days
6a	20	0.6
	40	1.4
	80	3.6
	160	5.0
	320	10.8
	640	11.6
6b	20	0.6
	40	1.6
	80	2.2
	160	12.0
	320	$^2/_5$ C,[b] $^1/_5$ T[b]
	640	$^3/_5$ C,[b] $^2/_5$ T[b]
6d	20	4.3
	40	7.5
	80	8.1
	160	12.5
	320	$^4/_5$ C[b]
	640	$^5/_5$ C[b]
6e	5	0.7
	10	8.7
	20	9.1
	40	14.3
	80	15.8
	160	$^4/_5$ C[b]
	320	$^5/_5$ C[b]
6f	5	1.6
	10	3.8
	20	5.8
	40	7.6
	80	13.0
	160	15.0

[a] Testing was done by Dr. L. Rane at University of Miami; data supplied by Walter Reed Army Institute of Research. [b] C, cure; T, toxic.

**Aldrich Technical Bulletin No. D 2800-0, Aldrich Chem. Co., Inc., Milwaukee, Wis. 53210.

aminomethanol products were prepared after the method of Atkinson and Puttick.[15] The epoxide was dissolved in a volume of dry dimethylformamide equal to approximately three times its weight, and 2 equiv of di-*n*-butylamine was added. The reaction was heated to 100–110°, stoppered, and allowed to stir at this temperature for 10–12 hr. The reaction mixture was then steam distilled until about 700 ml of water had been collected. The crude product was collected by extracting the pot residue with ether, drying the extracts ($MgSO_4$), and removing the solvent ether on a rotary evaporator. The products thus attained all gave satisfactory C and H analyses without further purification. Table I lists the reaction conditions and product yields. The products were generally obtained as light-colored waxes with very indistinct melting points.

Antimalarial Testing. The 4-quinolinemethanols were primarily evaluated in blood-induced *Plasmodium berghei* infections of mice. Assessment of activity was on the basis of influence of various doses of the compounds upon the survival times of groups of five mice in comparison with untreated controls (mean survival time 6.2 days). Those surviving more than 60 days were adjudged "cured." Table II shows the comparative data on compounds **6a**, **6b**, **6d**, 6e, and **6f**; **6c** was inactive at doses to 640 mg/kg. From the background available, antimalarial activity was greatest in 6b, 6d, and **6e**, of which 6e was best. That gave evidence of the worth of the 8-CF_3 grouping in enhancement of antimalarial activity among this series of 2-substituted 4-quinolinemethanols. Some of the intermediates (as, **1a**, 4a, 13e, 14e) were also tested against the murine malaria; all were inactive.

Compounds **6a** and 6b were evaluated against blood-induced *Plasmodium gallinaceum* infections in chicks.[33] Both were inactive. Patterns of activity in this series were not adequate to justify expanded testing or further extension of the present group.††

References

(1) R. E. Lutz, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freek, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, Jr., J. M. Salsbury, N. H. Shearer, Jr., J. D. Smith, and J. W. Wilson, III, *J. Amer. Chem. Soc.*, 68, 1813 (1946).
(2) J. Mead and J. B. Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).
(3) J. P. Schaefer, K. S. Kulkarni, R. Costin, J. Higgins, and L. M. Honig, *J. Heterocycl. Chem.*, 7, 607 (1970).
(4) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 11, 273 (1968).
(5) W. Pfitzinger, *J. Prakt. Chem.*, 33, 100 (1886).
(6) R. F. Brown, T. L. Jacobs, S. Winstein, M. C. Kloetzel, E. C. Spaeth, W. H. Florsheim, J. H. Robson, E. F. Levy, G. M. Bryan, A. B. Magnusson, S. J. Miller, M. L. Ott, and J. A. Terek, *J. Amer. Chem. Soc.*, 68, 2705 (1946).
(7) M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *ibid.*, 68, 2697 (1946).
(8) A. J. Suggiomo, K. Kato, and T. Kaiya, *J. Med. Chem.*, 11, 277 (1968).
(9) P. E. Thompson and L. M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology," Academic Press, New York, N. Y., 1972, Chapter 8.
(10) J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *J. Med. Chem.*, 11, 425 (1968).
(11) J. B. Wommack, Jr., and D. E. Pearson, *ibid.*, 13, 383 (1970).
(12) I. G. Fels, *ibid.*, 11, 887 (1968).
(13) W. E. Rothe and D. P. Jacobus, *ibid.*, 11, 366 (1968).
(14) E. R. Atkinson and A. J. Puttick, *ibid.*, 13, 537 (1970).
(15) E. R. Atkinson and A. J. Puttick, *ibid.*, 11, 1223 (1968).
(16) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, 14, 926 (1971).
(17) S. D. Lesesne and H. R. Henze, *J. Amer. Chem. Soc.*, 64, 1897 (1942).
(18) J. F. Mead, A. E. Senear, and J. B. Koepfli, *ibid.*, 68, 2708 (1946).
(19) P. M. Maginnity and C. A. Gaulin, *ibid.*, 73, 3579 (1951).
(20) K. D. Kulkarni and R. C. Shah, *J. Indian Chem. Soc.*, 26, 171 (1949).
(21) R. C. Shah and V. R. Heeramaneck, *J. Chem. Soc.*, 428 (1936).
(22) G. A. Wiley, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, 86, 964 (1964).
(23) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *ibid.*, **92**, 2377 (1970).
(24) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, 64, 277 (1964).
(25) C. E. Kaslow and M. M. Marsh, *J. Org. Chem.*, **12**, 456 (1947).
(26) D. V. R. Goldring and A. E. Senear, *ibid.*, **12**, 293 (1947).
(27) R. M. Pinder and A. Burger, *J. Med. Chem.*, 11, 267 (1969).
(28) S. A. Kulkarni and R. C. Shah, *J. Indian Chem. Soc.*, **27**, 111 (1950).
(29) G. A. Reynolds and C. R. Hauser, *Org. Syn.*, **30**, 70 (1950).
(30) H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, **62**, 446 (1940).
(31) H. Gilman and S. M. Spatz, *ibid.*, 63, 1553 (1941).
(32) L. Friedman and H. Schechter, *J. Org. Chem.*, **26**, 2522 (1961).
(33) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

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Quinazolines and 1,4-Benzodiazepines. 58.[1] The Azido Group, a Novel Pharmacophoric Substituent. 7-Azido-5-phenyl-1,4-benzodiazepines

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Some 7-azido-5-phenyl-1,4-benzodiazepines have been prepared. They showed, in animals, potent sedative and anticonvulsant properties. Analogs containing 7-(3,4,5-triazatricyclo[5.2.1.0]dec-4-en-3-yl), 7-(1*H*-tetrazol-5-yl), and 7-(1- and 2-methyltetrazol-5-yl) substituents (**10**, **11**, **12**, and **13**) were found to be inactive.

Substituents in the 7 position of the 1,4-benzodiazepine nucleus are known to have a paramount effect on the biological activity of these compounds.[2] In the search for novel substituents which might impart unusual pharmacological properties, we synthesized and studied 7-azido and related 1,4-benzodiazepines.†

We found that an azido (N_3) group in the 7 position of 5-phenyl-1,4-benzodiazepines imparted high pharmacological activity which compares favorably with that exhibited by the corresponding 7-halo and 7-nitro analogs and is vastly superior to that of the corresponding amino compounds. We wish to report on the preparation of these 7-azido compounds (Table I) along with compounds **10–13** which contain a triazole or tetrazole substituent in the 7 position.

Chemistry. The 7-azido group was introduced by di-

†This is, to our knowledge, the first case in which the effect of an azido group on the CNS activity of a drug molecule was studied.