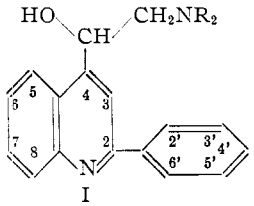
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials.[1] α-Alkyl and Dialkylaminomethyl-2-phenyl-4-quinolinemethanols

BY ROBERT E. LUTZ, PHILIP S. BAILEY,[2a] MARION T. CLARK,[2b] JOHN F. CODINGTON,[2c] ADOLPH J. DEINET,[2j] JAMES A. FREEK, GRANT H. HARNEST,[2d] NORMAN H. LEAKE,[2k] TELLIS A. MARTIN, RUSSELL J. ROWLETT, JR.,[2e] JASON M. SALSBURY,[2f] NEWTON H. SHEARER, JR.,[2g] J. DOYLE SMITH[2h] AND JAMES W. WILSON, III[2i]

This paper deals with the synthesis of twenty-eight series of compounds comprising a total of one hundred and two simple and substituted α-monoalkyl and α-dialkylaminomethyl-2-phenyl-4-quinolinemethanols of the type I. These compounds, which are listed in Table VI, are closely related structurally to quinine; they were made in connection with the search for superior antimalarial drugs and for the purpose of evaluating the activating effect of one or more chlorines and of certain other groups, notably methyl and methoxyl, at as many as possible of the different nuclear positions.



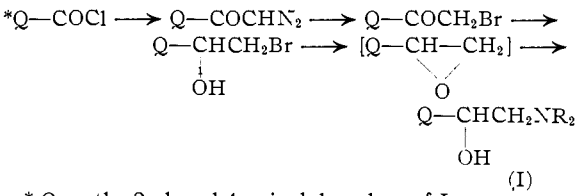
I

All but one of these compounds are new. A few of the type were described in the literature[3] over twenty-five years ago and include five based on cinchophen and three on 6-ethoxycinchophen. However, these compounds were made without application to the malaria problem.

Our program was begun at the request of the Panel on Synthesis of Antimalarial Drugs[1] and it stemmed from the discovery of the high antimalarial activity of many of the α-piperidyl-2-phenyl-4-quinolinemethanols, compounds which had been made[4] in an extension of the earlier work on the α-piperidyl-4-quinolinemethanols by Ainley and King[5a] and on the α-dialkylaminomethyl-4-quinolinemethanols by King and Work.[5b] The blocking of the 2-position with phenyl had been suggested by the observation of the biological oxidation of quinine in the rabbit to the carbostyril analog.[6]

The field of the relatively simple monoalkyl and dialkylaminomethyl 4-quinolinemethanols possesses some advantages over the α-piperidylmethanols, notably, the absence of diastereoisomerism, and the relative ease of varying the aliphatic amino group which is introduced in the last step of the synthesis and consequently can be modified with a minimum of labor. In each series, as far as was practical under the circumstances, a number of representative homologs were made in order to bring out with reasonable certainty the maximum antimalarial activity of which the series was capable; also in some of the series an attempt was made to determine the effect of branching the N-alkyl chain and to evaluate the relative effectiveness of secondary as compared with tertiary aliphatic nitrogen.

The general synthetic method used in this investigation starts with the appropriate cinchophen and involves the reactions: diazomethylation of the acid chloride to the diazomethyl ketone,[5a] hydrobromination to the α-bromomethyl ketone,[5b] aluminum isopropoxide reduction to the bromohydrin,[7a] and condensation with the appropriate amine to the amino alcohol[7b] usually without isolation of the intermediate ethylene oxide.[7c]



(I)

* Q = the 2-phenyl-4-quinolyl nucleus of I.

A second synthetic path used in a few cases was the Claisen condensation between the cinchophen ester and ethyl acetate to the β-ketoester,[5b,8] fol-

(1) (a) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia. (b) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which the Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(2) Present addresses: (a) University of Texas, Austin, Texas; (b) Birmingham-Southern College, Birmingham, Ala.; (c) National Institute of Health, Bethesda, Md.; (d) Middlebury College, Middlebury, Vt.; (e) Jackson Laboratory, du Pont de Nemours and Co., Wilmington, Del.; (f) American Cyanamid Co., Stamford, Conn.; (g) Tennessee Eastman Corp., Kingsport, Tenn.; (h) Medical College of Virginia, Richmond, Va.; (i) Smith, Kline and French, Philadelphia, Pa.; (j) Heyden Chemical Corp., Fords, N. J.; (k) Rohm and Haas Co., Phila., Pa.

(3) (a) Miescher, U. S. Patent 1,434,306 (1922); (b) Soc. Anon. pour l'Industrie Chimique á Bâle, Swiss 92,001, 92,607–819; *C. A.*, **17**, 2118 (1923); (c) Soc. Anon. pour l'Industrie Chimique á Bâle, Swiss 98,482, 98,712 and 98,713; *C. A.*, **18**, 2174 (1924).

(4) (a) Rapport, Senear, Mead and Koepfli, *ibid.*, **68**, Nov. (1946); (b) Brown, Jacobs, Winstein, Kloetzel, Spaeth, Florsheim, Robson, Levy, Bryan, Magnusson, Miller, Ott and Terek, *ibid.*, **68**, Nov. (1946); (c) Buchmann, Sargent, Myers and Howton, *ibid.*, **68**, Nov. (1946).

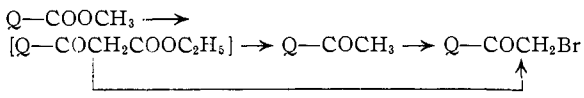
(5) (a) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 61 (1938); (b) King and Work, *J. Chem. Soc.*, 1312 (1940).

(6) (a) Kelsey, Geiling, Oldham and Dearborn, *J. Pharm.*, **80**, 391 (1944); (b) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(7) (a) "Organic Reactions," II, Wiley and Sons, Inc., 1944, p. 193; (b) Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946); (c) Winstein, Jacobs, Henderson, Robson and Day, *ibid.*, **11**, 157 (1946).

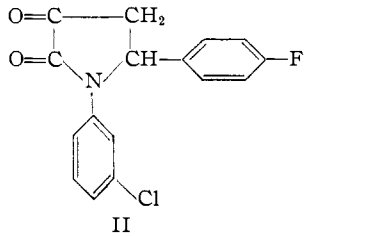
(8) (a) Winstein, Jacobs, Linden, Seymour, Levy, Day, Robson, Henderson and Florsheim, THIS JOURNAL, **68**, 1831 (1946); (b) Gilman and co-workers, *ibid.*, **68**, 1848 (1946)

lowed either by simultaneous bromination and hydrolysis[5b] to the bromomethyl ketone, or by ketone hydrolysis to the methyl ketone and subsequent bromination in a second step to the bromomethyl ketone.

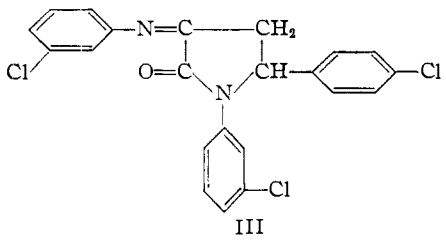


I. The Preparation of the Cinchophens

Nineteen new cinchophens have been made; seven of these, including all of those with an 8-chlorine, were made through the corresponding isatins by the Pfitzinger method,[9] and the other twelve including those carrying an 8-methyl, were made by the Doebner–Miller synthesis.[10] Of the two methods, the Pfitzinger gave by far the best yields but the isatins were sometimes difficult to obtain. The Doebner–Miller method, on the other hand, gave uniformly low yields, sometimes very low, and oftentimes there was formed along with the desired product, the diketopyrrolidine (II) or the anil (III), which in some instances became the dominant and occasionally the only isolable product. In spite of the relatively low yields usually involved, the Doebner–Miller method was preferred when the materials were readily available.



II



III

Several of the ketopyrrolidineanils (those bearing SN numbers) were tested against avian malaria and were found to be inactive.

The Doebner–Miller reaction, in the case of unsymmetrically substituted meta derivatives of aniline in which both ortho positions are free to react, apparently can be relied upon to give almost exclusively the 7-chloro derivative when the meta substituent is ortho-para directing.[11] To make sure of the mode of ring closure in three cases in this investigation, namely, the 7-chloro-4′-methoxy, 7-chloro-4′-fluoro and 4′,7-dichloro compounds, where rigorous structural proof was not available, the cinchophens in question were made also by the unequivocal Pfitzinger method. In three other cases, namely, the 4′-chloro-7-methyl, 7-chloro-6-methoxy and 4′,7-dichloro-6-methoxy compounds, we have relied on the absence of the characteristic steric hindrance toward alcoholysis of the acid chlorides as evidence for the structure (see section II).

(9) *Cf.* Lindwall, Bandea and Weinburg, THIS JOURNAL, **53**, 317 (1931).

(10) *Cf.* John, *J. prakt. Chem.*, **130**, 314 (1931).

(11) Roberts and Turner, *J. Chem. Soc.*, 1832 (1927).

Experimental[12]

Typical syntheses of three new cinchophens are given below as illustrations of the important modifications employed. Specific information on the diketopyrrolidines is given at the end of the description of method (B).

A. Preparation of Cinchophens by the Pfitzinger Reaction.—(Modification of Lindwall's[9] procedure): The condensations were effected in the usual excess of aqueous 30–33% potassium hydroxide solution with sufficient ethanol present to insure solution of the isatin alkali salt. An excess (2–18 mole per cent.) of the acetophenone was employed. The following methods were used in isolating and purifying the cinchophens.

1. Where only a very slight excess of the acetophenone was used, a part or all of the ethanol was distilled from the reaction mixture. The residual paste or solution was diluted with a large volume of water and acidified to liberate the cinchophen.

2. When a larger excess of the acetophenone was present, all of the ethanol was distilled and the residual paste was dissolved (or suspended) in a relatively small volume of water. Excess ketone was removed by extraction with benzene or di-isopropyl ether and the cinchophen precipitated by acidification.

3. Some of the cinchophens were purified by recrystallizing the sodium or potassium salt from water. This procedure is not recommended for the cinchophens having only one substituent because their salts, especially the potassium salts, are so soluble that considerable loss is entailed. However, in the case of cinchophens with two or more substituents this operation has been used to advantage.

B. A Typical Doebner–Miller Reaction Involving the Formation of the By-product Ketopyrrolidineanil. 4′,7-Dichlorocinchophen.—The effect of various factors on the yield of this cinchophen was studied. It was found necessary to use freshly distilled pyruvic acid for best yields. If the pyruvic acid was added to the *p*-chlorobenzaldehyde and the solution was refluxed before the addition of *m*-chloroaniline, the yield of cinchophen was negligible (less than 1%). The yield of the acid was not significantly changed by increasing the time of the preliminary refluxing of the *p*-chlorobenzaldehyde and *m*-chloroaniline from ten minutes to one hour. Optimum yields were obtained by the following procedure.

A solution of 421.8 g. (3 moles) of *p*-chlorobenzaldehyde in 1.2 l. of warm absolute ethanol was stirred[13] and gently heated; to this 382.8 g. (3 moles) of *m*-chloroaniline was added rapidly and the resulting solution was refluxed for ten minutes; a solution of 264.3 g. (3 moles) of freshly distilled pyruvic acid (b. p. 55–56°/1 mm.) in 265 ml. of absolute ethanol was added under stirring over a period

(12) (a) Throughout this research it has been necessary to produce finished drugs as quickly as possible. Consequently in many, perhaps most, of the experiments, the yields do not represent the best that can be expected, nor do the conditions described necessarily represent the optimum. (b) All melting points reported herein are corrected.

(13) An efficient stirrer was made by riveting a curved section of stainless steel rod onto a 2-foot length of the same type rod in the shape of an anchor and riveted loosely enough to allow folding and insertion into the neck of a flask.

of one hour. Five minutes after all of the acid had been added a yellowish precipitate formed which increased in amount as the reaction proceeded. The resulting mixture was refluxed and stirred continuously for an additional six hours, cooled to room temperature, stirred overnight, and filtered. The residue was washed on the funnel with 95% ethanol until the washings were pale yellow. This cream-colored solid was a mixture of the cinchophen and 1-(3-chlorophenyl)-5-(4-chlorophenyl)-3-(3-chlorophenylimino)-2-ketopyrrolidine (III).

The acid was extracted from the dry, powdered mixture by digestion for thirty minutes in a hot (95–98°) well-stirred solution of 160 g. of sodium carbonate monohydrate in a 2.2 l. of water. The *hot* slurry was filtered (the salt crystallizes on cooling); the residue of ketopyrrolidineanil was washed with 200 ml. of hot water and extracted a second time with a hot solution of 32 g. of sodium carbonate monohydrate in 240 ml. of water.

The cinchophen was obtained from the aqueous solution of the sodium salt upon acidification. Two methods of treatment were used, however; the more common procedure [(1) below] was to precipitate the acid directly and to purify it by digesting and washing with an organic solvent; the other, used more recently and probably the better method in those cases where the salt crystallizes out easily [procedure (2) below], involves crystallization of the sodium salt and further purification by washing it with benzene, followed by liberation of the nearly pure acid.

1. The aqueous solution of the sodium salt was diluted to 9 l. and acidified slowly with glacial acetic acid; a precipitate of the crude cinchophen was obtained. The acid was filtered (with difficulty) and purified by digestion with 2.1 l. of boiling butanone for one hour and allowing the mixture to cool slowly and to stand overnight. The mixture was then cooled in an ice–salt-bath for two hours, and the product was filtered (with difficulty), washed with acetone and dried.

2. When the aqueous solution of the sodium salt was cooled to 0°, the salt crystallized almost completely. It was filtered and pressed dry. The filtrate, which contained a negligible amount of the acid, was discarded.

To remove the small amount of resinous material adhering to the crystals, the sodium salt was slurried with benzene at 50°, cooled, and filtered. The 4′,7-dichloro cinchophen was precipitated from a well-stirred, *hot* solution of the purified salt in 1.5 l. of water by the slow addition of glacial acetic acid. The pale yellow acid was filtered and dried; yield 278 g. (29%); m. p., 271–278°.

A sample of the cinchophen, liberated from sodium salt which had been recrystallized from water several times, was purified further by repeated recrystallizations from ethanol; colorless prismatic rods; m. p. 281–282.5°.

Diketopyrrolidines Obtained in the Doebner–Miller Reaction.—In seven cases diketopyrrolidines were isolated from Doebner–Miller reaction mixtures. Six of these seven by-products were anils of the type III. One of them, the fluoro compound, appears to be the diketopyrrolidine itself (II).

Preparation of 1-(4-Chlorophenyl)-3-(4-chlorophenylimino)-5-phenyl-2-ketopyrrolidine (SN-13523).[1b]—The yield was 42%. It crystallized from glacial acetic acid as colorless rectangular rods; m. p., 202–203°.[14]

1-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-(3-chlorophenylimino)-2-ketopyrrolidine (III) (SN-13,572).—Yield, 32%; crystallized from glacial acetic acid; needles; m. p. 206–208°.

Anal. Calcd. for $C_{22}H_{16}Cl_3N_2O$: C, 61.48; H, 3.52. Found: C, 61.63; H, 3.74.

1-(2,5-Dichlorophenyl)-3-(2,5-dichlorophenylimino)-5-phenyl-2-ketopyrrolidine.—The yield was 31%. It crystallized as colorless plates from glacial acetic acid; m. p. 177–179°.

Anal. Calcd. for $C_{22}H_{16}Cl_4N_2O$: N, 6.03. Found: N, 5.75.

(14) Borsche, *Ber.*, **41**, 3884 (1908).

1-(3-Chlorophenyl)-3-(3-chlorophenylimino)-5-(4-methoxyphenyl)-2-ketopyrrolidine (SN-13,586).—Yield, 21%; plates from glacial acetic acid; m. p. 178–179°.

Anal. Calcd. for $C_{23}H_{18}Cl_2N_2O_2$: N, 6.59. Found, 6.68.

1-(3-Chloro-4-methoxyphenyl)-3-(3-chloro-4-methoxyphenylimino)-5-phenyl-2-ketopyrrolidine.—Yield 4.5%; prismatic rods from glacial acetic acid; m. p. 191–192°.

Anal. Calcd. for $C_{24}H_{20}Cl_2N_2O_3$: N, 6.19. Found: N, 5.95.

1-(3-Chloro-4-methoxyphenyl)-3-(3-chloro-4-methoxyphenylimino) - 5 - (4 - chlorophenyl) - 2 - ketopyrrolidine.—Yield, 17%; prismatic rods from glacial acetic acid; m. p. 204.5–206.5°.

Anal. Calcd. for $C_{24}H_{19}Cl_3N_2O_3$: N, 5.72. Found: N, 5.92.

1-(3-Chlorophenyl)-5-(4-fluorophenyl)-2,3-diketopyrrolidine (II).—Yield, 10%; needles from glacial acetic acid; m. p. 195–198°.

Anal. Calcd. for $C_{16}H_{11}ClFNO_2$: C, 63.27; H, 3.65. Found: C, 63.68; H, 3.61.

C. The Doebner–Miller Reactions in which no By-Product Diketopyrrolidineanil is Obtained.—When the crude product of the reaction, carried out according to (B), was found to dissolve with no (or a negligible) residue in hot sodium carbonate solution, the carbonate extraction was eliminated and the crude acid was purified by recrystallization or by digestion with some organic solvent.

Controlled experiments run on the preparation of **4′-chloro-6,8-dimethylcinchophen** again showed the sensitivity of the reaction toward impurities in the reactants, especially in the pyruvic acid. With other conditions held constant, freshly distilled pyruvic acid gave a 35% yield (m. p. 261–264°) whereas distilled pyruvic acid which had been standing on the shelf for some time gave a 21% yield (m. p. 257–263°).

II. The Cinchophen Acid Chlorides

The acid chlorides were prepared by the action of an excess of thionyl chloride on the cinchophens, usually by refluxing for a suitable period of time, and then distilling and sweeping out the excess of reagent by means of benzene or petroleum ether. They were usually handled as the hydrochlorides, although oftentimes these salts were somewhat unstable and tended to lose hydrogen chloride upon heating under reduced pressure. The 8-substituted cinchophen acid chlorides did not form stable isolable salts and these compounds were invariably handled as the free bases.

The acid chlorides in the main had normal properties and reacted readily with alcohol to give esters. The less soluble analogs often appeared to be a little slower to react than the soluble types, but the differences were not significant. In contrast the 5-chloro compounds showed characteristic steric hindrance effects of a high order. As has already been noted by others[4] the Claisen condensation which is the first step in the synthesis of the 2-piperidyl analogs of (I) is prevented. We have found in addition that two 5-substituted acid chlorides, namely, the 5-chloro and the 5,8-dichloro compounds, were very resistant toward hydrolysis and were slowly alcoholized by the action of boiling alcohols from which they could be recrystallized. So striking was this behavior that we have been able con-

TABLE I

THE CINCHOPHENS

Substituent	Formula	Prep.[a]	React. time, hr.	%	Cryst. from	M. p., °C. (cor.)	Analyses, % Calcd.		Found	Calcd.	Found
7-Methyl (amide)	$C_{17}H_{14}N_2O$	*y*	12	..	Dioxane	237–238	N	10.68	10.28	..	..
4'-Chloro-6-methoxy	$C_{17}H_{12}ClNO_3$	C	5	33	EtOH	269–272	NE[b]	314	323	N 4.46	4.47
4'-Chloro-6,8-dimethyl[c]	$C_{18}H_{14}ClNO_2$	C	4	35	Butanone	262–263	C	69.33	69.27	H 4.53	4.77
4'-Chloro-7-methyl	$C_{17}H_{12}ClNO_2$	C	1	50	*d*	254–255	C	68.57	68.22	H 4.06	4.25[b1]
methyl ester	$C_{18}H_{14}ClNO_2$	*e*	0.1	..	CH_3OH	136–139	N	4.50	4.38	..	..
4'-Chloro-8-methyl	$C_{17}H_{12}ClNO_2$	C	3	26	EtOH	246–248	C	68.57	68.90	H 4.06	4.07
4'-Chloro-8-phenyl	$C_{22}H_{14}ClNO_2$	C	21	19	*f*	273–274	NE	360	365	N 3.89	3.87
5-Chloro[b]	$C_{18}H_{10}ClNO_2$	A(2)	16	46	EtOH	232–234	C	67.73	67.38	H 3.55	3.46[b2]
ethyl ester[g,b]	$C_{18}H_{14}ClNO_2$	*h*	5	..	EtOH	62-63	C	69.32	69.31	H 4.53	4.73
methyl ester	$C_{17}H_{12}ClNO_2$	*i*	4	..	MeOH	112–113	C	68.55	68.78	H 4.06	4.08
amide	$C_{16}H_{11}ClN_2O$	*j*	0.5	..	Abs. EtOH	232	N	9.91	9.88	..	..
7-Chloro (amide)	$C_{16}H_{11}ClN_2O$	*g*	100	..	Abs. EtOH	260–261	N	9.91	9.71	..	..
7-Chloro-4'-methoxy	$C_{17}H_{12}ClNO_3$	*k*	5	46	H_2O[l]	222–225	C	65.08	65.09	H 3.84	3.69[b3]
7-Chloro-6-methoxy	$C_{17}H_{12}ClNO_3$	B(1)	4	20	*m*	267–272	NE	314	309	N 4.46	4.29
methyl ester	$C_{18}H_{14}ClNO_3$	*t*	0.1	98	CH_3OH	192–193	N	4.27	4.55	..	..
7-Chloro-8-methyl	$C_{17}H_{12}ClNO_2$	C	7	24	*m*	278–279	NE	298	290	N 4.71	4.52
3',4'-Dichloro[4c]	$C_{16}H_9Cl_2NO_2$	A(1)	19	82	*n*	255–256 dec.	..	...	...	..	..
4',5-Dichloro	$C_{16}H_9Cl_2NO_2$	A(2)	14	71	EtOH	260 dec.	C	60.40	60.38	H 2.85	2.55
4',5-Dichloro-2'-methyl	$C_{17}H_{10}Cl_2NO_2$	A(2)	28	76	IsoprOH	243	C	61.46	61.03	H 3.34	3.23
4',6-Dichloro	$C_{18}H_9Cl_2NO_2$	A(3)	30	86	H_2O	273–275	NE	318	321	N 4.40	4.25
4',7-Dichloro	$C_{16}H_9Cl_2NO_2$	B(2)[k]	6	22	EtOH	278–279	C	60.39	60.23	H 2.85	2.96
ethyl ester	$C_{18}H_{13}Cl_2NO_2$	*o*	6	94	EtOH	130–131	C	62.44	62.75	H 3.78	3.66
4',7-Dichloro-6-methoxy	$C_{17}H_{11}Cl_2NO_3$	B(2)	5	22	EtOH	284–286	C	58.64	58.93	H 3.19	3.11
ethyl ester	$C_{19}H_{15}Cl_2NO_3$	*p*	0.1	..	EtOH	146–148	C	60.66	60.71	H 4.02	3.84
4',7-Dichloro-8-methyl	$C_{17}H_{11}Cl_2NO_2$	C	9	22	Butanone	300–301	C	61.46	61.18	H 3.34	3.47
methyl ester	$C_{18}H_{13}Cl_2NO_2$	*o*	20	98	Butanone	164–165	C	62.44	62.15	H 3.77	3.51
4',8-Dichloro	$C_{16}H_9Cl_2NO_2$	A(1)	10	51	EtOH[r]	265–267	N	4.40	4.28	..	..
5,8-Dichloro	$C_{16}H_9Cl_2NO_2$	A(2)[s]	24	65	EtOH	215–216	NE	318	327	N 4.40	4.62
methyl ester	$C_{17}H_{11}Cl_2NO_2$	*z*	24	..	EtOH	97–99	C	61.47	61.47	H 3.32	3.05
ethyl ester	$C_{18}H_{13}Cl_2NO_2$	*z*	24	96	EtOH	104–105	C	62.44	62.19	H 3.78	3.56
6,8-Dichloro[4a]	$C_{16}H_9Cl_2NO_2$	A(1,3)	17	91	H_2O	250–252	..	...	...	..	..
methyl ester	$C_{17}H_{11}Cl_2NO_2$	*o*	22	90	Benz.-CH_3OH	143–144	C	61.46	61.13	H 3.34	3.28
7-Chloro-4'-fluoro	$C_{16}H_9ClFNO_2$	*v*, *w*	16	24	AcOH	281–285	C	63.69	63.49	H 3.00	3.13[b4]
ethyl ester	$C_{18}H_{13}ClFNO_2$	*w*	2	..	Abs. EtOH	121–124	C	65.58	65.53	H 3.97	3.81
4',5',7-Trichloro-2'-methyl	$C_{17}H_9Cl_3NO_2$	A(2)	28	45	IsoamOH	292–294	C	55.69	55.57	H 2.75	2.74
4',6,8-Trichloro[4a]	$C_{16}H_8Cl_3NO_2$	A(2)	24	87	EtOH–diox.	276–279 dec.	..	...	...	..	..
3',4',6,8-Tetrachloro	$C_{16}H_7Cl_4NO_2$	A(1)[x]	21	53	Dioxane	295–296 dec.	N	3.62	3.42	..	..

[a] The capital letters, A through D, refer to the general descriptive paragraphs in the experimental section. [b] NE is the symbol for neutral equivalent. [b1] Calcd., 298; found, 291. [b2] Calcd., 284; found, 284. [b3] Calcd., 314; found, 316; [b4] Calcd., 302; found, 309. [c] The sodium salt of the acid forms a hydrate. *Anal.* Calcd. for $C_{18}H_{13}ClNNaO_2 \cdot H_2O$: C, 61.46; H, 4.29. Found: C, 61.84; H, 4.39. [d] Diisobutyl ketone. [e] The acid chloride reacted exothermically with absolute methanol at room temperature. This is strong evidence that the methyl group is in the 7 rather than the 5 position; the latter isomer which is a possible product in the preparation of the acid would have required long heating to react (*cf.* footnote *h*). [f] Ethylene glycol. [g] This acid chloride was allowed to react with 28% NH_4OH for five days. [h] The acid chloride can be recrystallized from absolute ethanol. However, if the solution is heated for four hours, the ester is produced. [i] The ester was obtained both from the acid chloride and from the silver salt of the acid by treatment with methyl iodide. [j] The acid chloride was heated in 28% NH_4OH for half an hour. [k] The acid was prepared in quantity by method (B); a small sample of the acid was prepared also by method (A) as a proof of structure. [l] The sodium salt of the acid was crystallized as the monohydrate, first from water and then from ethanol. *Anal.* Calcd. for $C_{17}H_{11}ClNNa \cdot H_2O$: C, 57.73; H, 3.70. Found: C, 57.77; H, 3.56. [m] Digested and washed with ethanol. [n] Digesting and washing with ethanol–ethyl acetate mixture; and then dissolving in excess potassium hydroxide solution, filtering and precipitating by addition of hydrochloric acid. [o] Prepared by acid catalyzed esterification of the cinchophen. [p] The acid chloride was heated in absolute ethanol. It readily dissolved and the ester precipitated when the solution was chilled. This high degree of reactivity is strong evidence that the chlorine is in the 7 rather than the 5 position (*cf.* footnotes *e* and *h*). [q] The ester was prepared both through acid catalyzed esterification of the cinchophen and through the ready reaction of the acid chloride with ethanol. The latter path again serves as strong evidence that the chlorine is in the 7 rather than the 5 position. [r] Recrystallization involved considerable loss of product; recrystallization of sodium salt from water would probably have been better. [s] An attempted preparation by the Doebner–Miller method gave only ketopyrrolidineanil. [t] Prepared by dissolving the acid chloride in methanol (*cf.* footnotes *c*, *h* and *p*). [v] The acid was purified by dissolving it in boiling excess *N* potassium hydroxide, filtering and acidifying with acetic acid while still hot. The solid obtained in this way filters much more rapidly than the gel-like suspension obtained when the acetic acid is added to the filtrate after it has cooled. [w] The acid was prepared by both method (A-3) and method (B). Samples from each preparation were converted through the acid chloride to the ester to furnish lower melting compounds in which identification by mixture melting was unequivocal. [x] About twice the usual quantity of ethanol was used in the reaction medium because of the unusually high insolubility of the product. [y] This acid chloride was allowed to react with 15% NH_4OH for twelve hours. [z] The acid chloride can be recrystallized from absolute ethanol. However, heating with absolute ethyl or methyl alcohol for twenty-four hours gives the corresponding ester.

fidently to use the ease of alcoholysis of the acid chloride to distinguish between 5- and 7-substituted cinchophens and thereby to establish the mode of ring closure in the Doebner–Miller synthesis where rigorous structural proof was lacking and hard to obtain.

TABLE II

2-PHENYLCINCHONINYL CHLORIDES

Substituents	Formula	React. time, hr.	%	Cryst. from	M. p., °C. (cor.)	Analyses, % Calcd.	Found
7-Methyl	$C_{17}H_{12}ClNO\cdot HCl$	1	..	Xylene[c]	155–156	Cl[a] 22.27	22.10
8-Methyl	$C_{17}H_{12}ClNO$	1	56	Ligroin	94–96	..[i]	...
8-Phenyl	$C_{22}H_{14}ClNO$	2.5	98	Ligroin[d]	174–176	N 4.08	3.95
4'-Chloro	$C_{16}H_8Cl_2NO$	4	85	Benzene	130–132	Cl[b] 11.71	11.55
4'-Chloro-6-methoxy	$C_{17}H_{11}Cl_2NO_2\cdot HCl$	1.5	92	$SOCl_2$	166–169	Cl[a] 19.3	18.6
4'-Chloro-6,8-dimethyl	$C_{18}H_{13}Cl_2NO$	3	96	Ligroin	169–171	Cl[b] 10.74	10.84
4'-Chloro-7-methyl	$C_{17}H_{11}Cl_2NO\cdot HCl$	3	..	Xylene[c]	179–181	Cl[a] 20.50	20.82
4'-Chloro-8-methoxy	$C_{17}H_{11}Cl_2NO_2$	6	95	.....	143–160	..[i]	...
4'-Chloro-8-phenyl	$C_{22}H_{13}Cl_2NO$	4.5	99	Ligroin[d]	198–200	N 3.70	3.70
5-Chloro	$C_{16}H_9Cl_2NO$	5	..	Ligroin	118–120	C[f] 63.59	63.72
6-Chloro	$C_{16}H_9Cl_2NO$	4	75	Ether	76–78	..[i]	...
7-Chloro	$C_{16}H_9Cl_2NO\cdot HCl$	1	..	.....	128–130	..[i]	...
7-Chloro-4'-methoxy	$C_{17}H_{11}Cl_2NO_2$	4	72	.....	164–167	..[i]	...
7-Chloro-6-methoxy	$C_{17}H_{11}Cl_2NO_2\cdot HCl$	2.5	92	$SOCl_2$	194–198	N 3.82	3.64
7-Chloro-8-methyl	$C_{17}H_{11}Cl_2NO$	3	97	$SOCl_2$	145–149	Cl[b] 11.2	11.4
8-Chloro	$C_{16}H_9Cl_2NO$	2	100	.....	116–120	..[i]	...
3',4'-Dichloro	$C_{16}H_8Cl_3NO$	4	98	Benzene	142–144	N 4.16	4.20
4',6-Dichloro	$C_{16}H_8Cl_3NO$	2	93	Ether	.....	..[i]	...
4',7-Dichloro	$C_{16}H_8Cl_3NO$	0.75	96	.....	159–161	N 4.16	4.34
4',7-Dichloro-6-methoxy	$C_{17}H_{10}Cl_3NO_2$	16	81	Toluene	243–245	N 3.82	3.89
4',7-Dichloro-8-methyl	$C_{17}H_{10}Cl_3NO$	3	99	.....[e]	148–150	Cl[b] 10.11	10.17
4',8-Dichloro	$C_{16}H_8Cl_3NO$	6	97	Benzene	161–162	N 4.16	4.16
5,8-Dichloro	$C_{16}H_8Cl_3NO$	20	86	Pet. eth.	140–141	C[h] 57.09	57.12
6,8-Dichloro	$C_{16}H_8Cl_3NO$	5	96	Benzene	141–142	N 4.16	4.06
7-Chloro-4'-fluoro	$C_{16}H_8Cl_2FNO$	1	96	.....	178–198	..[i]	...
4',5',7-Trichloro-2'-methyl	$C_{17}H_8Cl_4NO\cdot HCl$	7	..	Xylene[c]	151–153	Cl[a] 18.40	18.71
4',6,8-Trichloro	$C_{16}H_7Cl_4NO$	1	..	.....	167–170	..[i]	...
3',4',6,8-Tetrachloro	$C_{16}H_6Cl_5NO$	17	99	Benzene	197–198	C[g] 47.38	47.08

[a] The analysis is for both available chlorine atoms (ionic chloride and acid chloride). [b] The sample was analyzed for the single chlorine atom (acid chloride). [c] The sample lost HCl and dissolved as it was heated in xylene. The solution was cooled and ethereal HCl was added to precipitate the salt. [d] The solvent was a mixture of ligroin and benzene. [e] The solvent was β,β'-dichloroethyl ether. [f] Calcd. for H, 3.00; found, 3.16. [g] Calcd. for H, 1.49; found, 1.63. [h] Calcd. for H, 2.38; found, 2.09. [i] An analytical sample was not prepared. The compound, however, was sufficiently pure to give satisfactory yields, when treated with diazomethane.

Experimental[12]

Three typical preparations of new acid chlorides are given below in brief outline, illustrating three categories, one (A) a case where the product was obtained as the free base, the second (B) involving a difficultly soluble free base, and the third (C) a case where the hydrochloride formed readily and was used.

A. 2-(4-Chlorophenyl)-6,8-dimethylcinchoninyl Chloride (free base).—A suspension of 155.7 g. (0.5 mole) of 4'-chloro-6,8-dimethylcinchophen in 600 ml. of redistilled thionyl chloride was refluxed gently for three hours. An orange solution resulted. The thionyl chloride was evaporated under reduced pressure. The remaining yellow-brown solid was slurried with 500 ml. of dry benzene and the benzene was evaporated under reduced pressure. The residual yellow solid was digested with 750 ml. of ligroin and the crusty lumps were broken up as finely as possible. The mixture was filtered and the solid was repeatedly washed with ligroin and dried in a desiccator; brilliant yellow solid; yield 160 g. (96%); m. p. 169–171°.

B. 6,8-Dichloro-2-(3,4-dichlorophenyl)-cinchoninyl Chloride [a difficultly soluble acid chloride (free base)].—A mixture of 125 g. (0.32 mole) of 3',4',6,8-tetrachlorocinchophen and 400 ml. of thionyl chloride was refluxed for sixteen hours without stirring and was then refluxed for one additional hour with mechanical stirring.[15] Stirring was continued while the mixture was cooled to 0°. The pale yellow acid chloride was filtered, washed with 200 ml. of ligroin and dried; yield 130 g. (100%); m. p. 197–198°. Two crystallizations from dry benzene gave bright yellow crystals melting at 197–198°.

C. 7-Chloro-6-methoxy-2-phenyl-cinchoninyl Chloride Hydrochloride.—A suspension of 82.0 g. (0.262 mole) of 7-chloro-6-methoxycinchophen in 500 ml. of thionyl chloride was heated under reflux until a clear solution was obtained (eight minutes) and for an additional two hours. The excess thionyl chloride was distilled under reduced pressure. The orange residue was digested with 200 ml. of dry benzene which was then distilled under reduced pressure to sweep out traces of thionyl chloride. The residue was triturated with 300 ml. of absolute ether containing a trace of hydrogen chloride, cooled at −15° for two hours, filtered, washed with petroleum ether, and dried *in vacuo;* 88 g. (92%). A sample, dissolved in thionyl chloride and precipitated by the addition of ether, consisted of orange rods melting at 194–198°.

III. The Diazomethyl 2-Phenyl-4-quinolyl Ketones

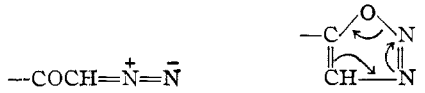
The diazomethyl ketones were made from the acid chlorides by the action of diazomethane (di-

(15) It would doubtless be better to stir the mixture throughout.

azomethylation). For this purpose diazomethane has been prepared on a large scale and used either in ethyl ether or methylene chloride[16] as the solvent. The latter solvent was of advantage in eliminating the fire hazard, and to some extent also in its greater solvent action on the compounds used; curiously, however, this solvent in some cases appears to have a very deleterious effect on the yields and quality of the products, and in three cases it was found to be advantageous or even necessary to use the more hazardous solvent, ether, in order to achieve reasonably good yields.

It was found that the diazomethylation of the 5-chloro and 5,8-dichloro cinchophen acid chlorides was subject to considerable hindrance, presumably steric. The diazomethane reacted slowly, and under the usual conditions considerable amounts of acid chloride escaped reaction. Where the reaction was prolonged using a large excess of diazomethane, a mixture resulted which analyzed very high in nitrogen, indicating the reaction of a large part of the material with a second molecule of diazomethane. In neither case have we obtained significant yields of authentic product, or samples which analyzed correctly.

The question of the structure of the diazomethyl ketones (IV or V) is of long-standing interest,[17] and the cyclic form is favored by many.



IV V

In this connection an accidental observation made in this investigation may have some significance. Several typical diazomethyl ketones were attacked only very slowly by aluminum isopropoxide under conditions which caused complete reduction of the bromomethyl ketones to the bromohydrins. Since this reagent appears to be specific for the aldehyde and ketone carbonyl this result may be compared with the known failure of typical diazomethyl ketones to react with hydroxylamine.[18] An alpha diazo group such as pictured in IV might well have a damping effect on the reactivity of the ketone carbonyl, but it is questionable whether it would account for such marked resistance as has been observed; on the other hand, the diazo compound in the cyclic oxadiazole arrangement (V) is not a simple ketone and would not be expected to react easily with aluminum isopropoxide.

One typical diazomethyl ketone upon bromination gave the dibromomethyl ketone (see section VI).

(16) Miescher and Kagi, *Helv. Chim. Acta*, **24**, 1474 (1941).

(17) *Cf.* Degering, "Outline of Organic Nitrogen Compounds," University Lithoprinters, 1945, pp. 258–286.

(18) Wolff, *Ann.*, **312**, 121 (1900).

Experimental[12]

Preparation of Diazomethane Utilizing Methylene Chloride as Solvent.[16]—A mixture of 3240 ml. of methylene chloride and 480 g. of 50% potassium hydroxide, cooled to 0°, was gently stirred mechanically[13] while 276 g. of moist nitrosomethylurea[19] [232 g. (2.25 moles) dry weight], was added portionwise at such a rate that the temperature of the reaction mixture did not exceed 5° (one-half hour). Addition of 960 ml. of ice water caused the lower potassium hydroxide layer to rise to the top. Gentle mechanical stirring was continued for ten minutes; then the lower, yellow, methylene chloride solution of diazomethane was siphoned out (forced by gentle pressure from a rubber bulb) and dried over sodium hydroxide pellets. Analysis by reaction with benzoic acid and titration of unused benzoic acid showed yields of 70–80%.

A. Diazomethyl 6-Methoxy-2-phenyl-4-quinolyl Ketone (formed in ether, but not isolated).—The powdered acid chloride (62 g.) was added slowly under efficient stirring over a period of ten minutes to a dried ether solution (1.5 l. at 0–5°) containing approximately 36 g. of diazomethane (0.86 mole). Frothing occurred as the orange-yellow color was replaced by the bright yellow of the rapidly precipitated diazomethyl ketone. The suspension was stirred overnight during which time it came slowly to room temperature; it was then treated directly with 48% hydrobromic acid to produce the bromomethyl ketone.

A sample of the diazomethyl ketone, taken from the above suspension and air dried, melted at 139°. Upon five recrystallizations from anhydrous ethyl acetate it was obtained as bright yellow hexagonal platelets melting at 148–148.5° (dec.).

B. 7-Chloro-2-(4-chlorophenyl)-4-quinolyl Diazomethyl Ketone (a diazomethyl ketone insoluble in methylene chloride).—One hundred grams of the cinchophen acid chloride was added portionwise to a 0.585 *N* solution of diazomethane (3.1 l.) in methylene chloride, under mechanical stirring. A moderate reaction occurred and a cream colored precipitate formed. The mixture was stirred and kept at 0° for nine hours (at higher temperatures the yield of diazomethyl ketone decreased); it was filtered, and the residue was washed twice with 350 ml. portions of anhydrous ether and pressed dry; colorless, crystals; 80 g. (86%). Repeated recrystallization of a small sample from ethyl acetate gave colorless needles; darkened at 159° and melted at 173°.

C. 2-(4-Chlorophenyl)-6,8-dimethyl-4-quinolyl Diazomethyl Ketone (a diazomethyl ketone which is appreciably soluble in methylene chloride).—A 0.5 *N* solution of diazomethane in methylene chloride (3.2 l.) was cooled in an ice-bath and 148.5 g. (0.45 mole) of 2-(4-chlorophenyl)-6,8-dimethylcinchoninyl chloride was added slowly with stirring. The mixture effervesced slowly and a yellow solution resulted. After a few minutes a white precipitate formed. The mixture was stirred overnight, cooled to −20°, allowed to stand at this temperature for one hour and filtered; brilliant yellow crystals; 89 g.; m. p. 162–165° (dec.). The filtrate was evaporated under reduced pressure and further crops of slightly less pure material melting over the range 155–159° (dec.) brought the total yield to 123.8 g. (82%).

IV. The Bromomethyl 2-Phenyl-4-quinolyl Ketones

The conversion of the diazomethyl ketones to the bromomethyl ketones by hydrobromination proceeded easily in all but one isolated case, namely, the 4′-chloro compound which formed unstable but isolable salts, the hydrochloride and hydrobromide. This case was particularly striking and somewhat disturbing because no reason such as steric hindrance could be seen to account

(19) "Organic Syntheses," Coll. Vol. II, p. 462. Large amounts of nitrosomethylurea were supplied by Dr. G. H. Coleman.

TABLE III

α-DIAZOMETHYL 2-PHENYL-4-QUINOLYL KETONES[a]

Substituent	Formula	M. p., (cor.)	N Analyses,[f] % Calcd.	Found
6-Methoxy	$C_{18}H_{13}N_3O_2$	149–150 dec.	13.86	13.65
7-Methyl	$C_{18}H_{13}N_3O$	152–153 dec.	14.63	14.53
8-Phenyl	$C_{23}H_{15}N_3O$	165 dec.	12.02	11.95
4'-Chloro	$C_{17}H_{10}ClN_3O$	123–125	13.68	13.87[i]
4'-Chloro-6-methoxy	$C_{18}H_{12}ClN_3O$	151–157 dec.	12.44	12.63
4'-Chloro-6,8-dimethyl[b]	$C_{19}H_{14}ClN_3O$	160–162 dec.	12.52	12.47
4'-Chloro-7-methyl[h]	$C_{18}H_{12}ClN_3O$	163–165 dec.	13.08	12.81
4'-Chloro-8-phenyl	$C_{23}H_{14}ClN_3O$	160 dec.	11.20	11.08
6-Chloro	$C_{17}H_{10}ClN_3O$	128–130 dec.	13.68	13.61
7-Chloro	$C_{17}H_{10}ClN_3O$	141–142 dec.	13.68	14.20[j]
7-Chloro-4'-methoxy	$C_{18}H_{12}ClN_3O$	169–170 dec.	12.44	12.03
7-Chloro-6-methoxy[b]	$C_{18}H_{12}ClN_3O_2$	157–159 dec.	12.44	12.04
3',4'-Dichloro	$C_{17}H_9Cl_2N_3O$	145 dec.	12.28	11.84[g]
4',6-Dichloro	$C_{17}H_9Cl_2N_3O$	172–173 dec.	12.28	12.10
4',7-Dichloro[c]	$C_{17}H_9Cl_2N_3O$	173	12.28	12.60
4',7-Dichloro-6-methoxy[d]	$C_{18}H_{11}Cl_2N_3O_2$	165–167 dec.	11.29	11.42
4',7-Dichloro-8-methyl[e]	$C_{18}H_{11}Cl_2N_3O$	160–162 dec.	11.80	11.59
5,8-Dichloro	$C_{17}H_9Cl_2N_3O$	155 dec.	12.28	12.50
7-Chloro-4'-fluoro	$C_{17}H_9ClFN_3O$	124–126 dec.	...[e]	...
4',5',7-Trichloro-2'-methyl[e]	$C_{18}H_{10}Cl_3N_3O$	179–180 dec.	10.75	10.64[g]
4',6,8-Trichloro	$C_{17}H_8Cl_3N_3O$	150–154 dec.	11.16	11.19[k]
3',4',6,8-Tetrachloro	$C_{17}H_7Cl_4N_3O$	179–180 dec.	10.22	10.01[g]

[a] Unless otherwise indicated these α-diazomethyl ketones were all prepared by method (A) of the experimental section. [b] Prepared according to method (C). [c] Prepared according to method (B). [d] This diazomethyl ketone was isolated before use in the next reaction. [e] We were unsuccessful in purifying this compound for analysis; however, it gave the desired compounds in the succeeding steps. [f] All the analytical samples were recrystallized from ethyl acetate unless indicated otherwise. [g] Recryst. from dioxane. [h] Also prepared according to method (C), but not isolated before use in the succeeding reaction. [i] Recryst. from methanol. [j] Recryst. from ethanol. [k] Recryst. from ethyl acetate–dioxane.

for the effect; however, the desired results could be obtained readily under somewhat more drastic conditions.

In view of the relative stability of the diazomethyl ketone of the 4'-chloro series, it seemed of interest to carry out a bromination of this compound; characteristically[20] the dibromomethyl ketone was produced (see section VI).

Experimental[12]

A. Bromomethyl 2-(4-Chlorophenyl)-6,8-dimethyl-4-quinolyl Ketone (an α-bromomethyl ketone which does not readily form a salt).—Eighty-four grams (0.25 mole) of 2-(4-chlorophenyl)-6,8-dimethyl-4-quinolyl diazomethyl ketone was suspended in 2 l. of absolute ether; 55 ml. of 48% hydrobromic acid was added slowly under stirring. The mixture was stirred for three hours during which time nitrogen was evolved slowly and there was an evident crystalline change in the suspended solid. Filtration gave 77.2 g. of yellow needles; m. p. 167–196°. The filtrate upon evaporation under reduced pressure gave 18.2 g. of yellow crystals; m. p. 150–153° (total crude yield, 98%). The product was recrystallized from a mixture of 400 ml. of ethanol and 1 l. of ethyl acetate (cooling to −20°); yellow needles; 75.5 g. (80%); m. p. 148–151°. (Probably salt formation accounted for the originally high melting point.) The α-bromomethyl ketone was recrystallized three times from 95% ethanol and ethyl acetate mixture; long needles; m. p. 147–148°.

B. Bromomethyl 6-Methoxy-2-phenyl-4-quinolyl Ketone Hydrobromide (an α-bromomethyl ketone made from unpurified diazomethyl ketone).—A mixture of equal volumes of 48% hydrobromic acid and absolute ether was added slowly with stirring to the ethereal suspension of unpurified diazomethyl ketone described in preparation (C) in the preceding section. Nitrogen was evolved copiously and at the same time the light yellow color of the diazomethyl ketone was replaced by the deep orange color of the precipitated bromomethyl ketone hydrobromide. An excess of the hydrogen bromide solution (10 ml.) was added above the amount required to give a positive congo red test. The bromomethyl ketone hydrobromide absorbed most of the water from the hydrobromic acid and tended to settle to the bottom as a pasty mass. Stirring was continued for four hours to ensure complete conversion of all of the diazomethyl ketone. The red-orange supernatant ether was decanted (upon evaporation it yielded less than a gram of dark red oil). The pasty orange residue in the flask was washed once with ether by decantation and then freed of the remaining ether and part of the water by evaporation under water pump suction for about thirty minutes. The crude bromomethyl ketone hydrobromide was then dissolved in boiling glacial acetic acid, from which it readily crystallized upon cooling. The crystallized solid was collected on a suction filter, washed once with glacial acetic acid and then washed free of acid with absolute ether. The bright orange solid, dried for two hours at 110°, melted at 200–203°, 66 g. (70% based on 6-methoxycinchophen). This material was used without further purification in subsequent experiments.

An analytical sample was made by repeatedly recrystallizing from glacial acetic acid containing a trace of hydrogen bromide; m. p. 205–206°.

C. Bromomethyl 2-(4-Chlorophenyl)-4-quinoyl Ketone (from an exceptionally stable diazomethyl ketone).—A mixture of 87 g. of 48% hydrobromic acid and 500 ml. of glacial acetic acid was heated to 90°; 105 g. of the crude diazomethyl ketone hydrobromide was added slowly with stirring. Nitrogen was evolved and the orange-colored diazomethyl ketone hydrobromide disappeared with the formation of the yellow-colored bromomethyl ketone hydrobromide. The heating was continued for ten minutes and the reaction mixture was cooled in ice and filtered.

(20) Curtis and Koch, *J. prakt. Chem.*, **38**, 484 (1888).

TABLE IV

α-BROMOMETHYL-2-PHENYL-4-QUINOLYL KETONES

Substituents	Empirical formula	Prepn. method	%[a]	Recrys. solv.	M. p., °C. (cor.)	Analyses, % Calcd.		Found	Calcd.	Found
6-Methoxy	$C_{18}H_{14}BrNO_2$	..	..	EtOH	120–121	C	60.69	60.84	H 3.96	3.77
	$C_{18}H_{14}BrNO_2 \cdot HBr$	B	70	AcOH	205–206 dec.	N	3.21	3.05	..	..
7-Methyl	$C_{18}H_{14}BrNO \cdot HBr$	B[p]	61	AcOH	204–205	C	51.33	51.00	H 3.35	3.54[i]
8-Methyl	$C_{18}H_{14}BrNO$	B	44	AcOH	101–102	C	63.55	63.25	H 4.15	4.25
8-Phenyl	$C_{23}H_{16}BrNO$	A	70	EtOH	133–134 dec.	N	3.48	3.49	..	..
4'-Chloro	$C_{17}H_{11}BrClNO$	..	..	CCl_4	121–122	C	56.70	56.83	H 3.07	3.17
	$C_{17}H_{11}BrClNO \cdot HBr$	C	70	...	259–261	C	46.24	46.58	H 2.51	2.72
	$C_{17}H_{11}Cl_2NO$[b]	..	..	CCl_4	117–119	C	64.57	64.98	H 3.51	3.61
	$C_{17}H_{11}Cl_2NO \cdot HCl$[b]	A	85	AcOH	212–214	Cl⁻	10.04	10.15	..	..
4'-Chloro-6-methoxy	$C_{18}H_{13}BrClNO_2 \cdot HBr$	B	83	AcOH	233–235 dec.	N	2.97	3.00	..	..
4'-Chloro-6,8-dimethyl	$C_{19}H_{15}BrClNO$	A	50	...[n]	147–148	C	58.71	58.73	H 3.89	3.89
4'-Chloro-7-methyl	$C_{18}H_{13}BrClNO \cdot HBr$	B[p,q]	46	AcOH	224–227 dec.	N	3.08	3.09	..	..
4'-Chloro-8-methyl	$C_{18}H_{13}BrClNO$	F	56	...[d]	108–109	C	57.70	57.96	H 3.50	3.47[j]
4'-Chloro-8-phenyl	$C_{23}H_{15}BrClNO$	A	70	EtOH	156–158	N	3.21	3.70	..	..
5-Chloro	$C_{17}H_{11}BrClNO$	..	..	EtOH	130–132	C	56.60	56.83	H 3.08	2.96
	$C_{17}H_{11}BrClNO \cdot HBr$	B	37	AcOH	220–226	C	46.24	47.66	H 2.74	3.07
6-Chloro	$C_{17}H_{11}BrClNO$	..	31	EtOH	140–141	N	3.88	3.75	..	..
	$C_{17}H_{11}BrClNO \cdot HBr$	B[o]	42	AcOH	210–212 dec.	N	3.17	3.09	..	..
7-Chloro	$C_{17}H_{11}BrClNO$	..	..	EtOH	106–107	C	56.70	57.01	H 3.07	3.08
	$C_{17}H_{11}BrClNO \cdot HBr$	B[p]	44	AcOH	210–213 dec.	C	46.24	46.27	H 2.74	2.90
7-Chloro-4'-methoxy	$C_{18}H_{14}BrClNO_2 \cdot HBr$	B	43	HCOOH	233–237 dec.	C	45.84	45.07	H 2.99	3.01[k]
7-Chloro-6-methoxy	$C_{18}H_{13}BrClNO_2 \cdot HBr$	B	56	Ac_2O	213–215 dec.	N	2.96	3.11	..	..
7-Chloro-8-methyl	$C_{18}H_{13}BrClNO$	F	63	...[c]	128–129	N	3.74	3.75	..	..
8-Chloro	$C_{17}H_{11}BrClNO$	B	63	...[d]	114–115	C	56.61	57.02	H 3.07	3.01
3',4'-Dichloro	$C_{17}H_{10}BrCl_2NO$	..	26	...[e]	114–116	C	51.67	51.79	H 2.55	2.49
	$C_{17}H_{10}BrCl_2NO \cdot HCl$	D	..	...[f]	189–191 dec.	N	3.25	3.11	..	..
4',6-Dichloro	$C_{17}H_{10}BrCl_2NO$	..	67	EtOH	170–171	N	3.54	3.40	..	..
	$C_{17}H_{10}BrCl_2NO \cdot HBr$	B[o]	86	AcOH	250–253 dec.	Br⁻	16.77	17.05	..	..
4',7-Dichloro	$C_{17}H_{10}BrCl_2NO \cdot HBr$	B[p]	63	AcOH	238–240	C	42.89	43.07	H 2.33	2.59
4',7-Dichloro-6-methoxy	$C_{18}H_{12}BrCl_2NO_2$	..	..	EtOAc	166–168	N	3.29	3.54	..	..
	$C_{18}H_{12}BrCl_2NO_2 \cdot HBr$	E	76	Ac_2O	233–235 dec.	N	2.76	2.71	..	..
4',7-Dichloro-8-methyl	$C_{18}H_{12}BrCl_2NO$	A	66	EtOAc	150–152	C	52.84	52.93	H 2.96	2.81
4',8-Dichloro	$C_{17}H_{10}BrCl_2NO$	B	55	AcOH	144–147	N	3.55	3.65	..	..
5,8-Dichloro	$C_{17}H_{10}BrCl_2NO$	B[o]	14	EtOH	181–182	C	51.67	51.64	H 2.55	2.49[m]
6,8-Dichloro	$C_{17}H_{10}BrCl_2NO$	B	78	...[g]	154–155 dec.	N	3.55	3.53	..	..
7-Chloro-4'-fluoro	$C_{17}H_{10}Cl_2FNO$[b]	B	69	EtOH	121–124	C	61.10	61.08	H 3.01	3.13
4',5',7-Trichloro-2'-methyl	$C_{18}H_{11}BrCl_3NO$	..	..	EtOH	138–139	C	48.74	49.31	H 2.50	2.52[l]
	$C_{18}H_{11}BrCl_3NO \cdot HBr$	B	72	...[h]	214–215	Br⁻	15.26	15.47	N 2.68	2.78
4',6,8-Trichloro	$C_{17}H_9BrCl_3NO$	B	57	Diox.	195	Br⁻	18.61	18.57	..	..
3',4',6,8-Tetrachloro	$C_{17}H_8BrCl_4NO$	D	71	...[e]	166–168	C	43.99	43.66	H 1.74	1.89

[a] Percentage yield based on acid as starting material. [b] α-Chloromethyl ketones, made by using concd. HCl in place of HBr–Et_2O. [c] Ethyl acetate–petroleum ether. [d] Ethanol–ethyl acetate. [e] Butanone–ligroin. [f] Butanone–acetic acid. [g] Butanone–isopropanol. [h] Glacial acetic acid with a trace of HBr. [i] Calcd. Br^-, 19.00. Found: 19.08. [j] Calcd. N, 3.74. Found: N, 3.60. [k] Calcd. N, 2.90. Found: N, 2.85. [l] Calcd. N, 3.16. Found: N, 3.01. [m] Calcd. N, 3.55. Found: N, 3.50. [n] Ethanol–acetic acid. [o] The α-diazomethyl ketone used was prepared according to method (C) in the foregoing reaction, but filtered and suspended in fresh ether before use. [p] Digested in and washed with hot acetic acid. [q] Also prepared according to method (G).

The product was converted directly into the free base by treatment with sodium carbonate solution; it was extracted with ether; evaporation of the ether gave tan-colored crystals; 60 g.; m. p. 119–131°. Repeated recrystallization from carbon tetrachloride gave cream-colored crystals; m. p. 121–122°.

D. Bromomethyl 2-(3,4-Dichlorophenyl)-4-quinolyl Ketone (from a moderately stable diazomethyl ketone in acetic acid as solvent).—Seventy milliliters of 32% hydrobromic-glacial acetic acid was added slowly to 40 g. of the diazomethyl ketone in 100 ml. of glacial acetic acid. A vigorous reaction occurred as the diazomethyl ketone dissolved; nitrogen was evolved and cooling became necessary. After the reaction had subsided the mixture was allowed to stand at room temperature for three hours. The mixture was then cooled to 10°, and the precipitate was filtered and washed with water. Dilution of the filtrate with water yielded more product which was added to the main batch. The base was set free with dilute sodium carbonate solution and extracted into ether. This ether solution was dried over anhydrous sodium sulfate and evaporated, leaving 33 g. (72%) of free base; m. p. 114–116°.

E. Bromomethyl 7-Chloro-2-(4-chlorophenyl)-6-methoxy-4-quinolyl Ketone (from a moderately stable diazomethyl ketone in ethyl acetate as solvent).—Forty-five grams of the diazomethyl ketone was dissolved in 1.8 l. of boiling ethyl acetate and filtered to remove 4.8 g. of insoluble fibrous material. After cooling the filtrate to room temperature 100 ml. of 32% hydrobromic–acetic acid was added portionwise. Nitrogen was evolved and the bright orange-red bromomethyl ketone hydrobromide precipitated. After stirring for four and one-half hours this was filtered, washed with ether and dried; yield, 54 g. (87%), m. p. 185–189°.

F. Bromomethyl 7-Chloro-8-methyl-2-phenyl-4-quinonyl Ketone (formation in methylene chloride as a solvent).—A solution of the diazomethyl ketone, made from 78 g. (0.247 mole) of acid chloride according to method (A) of the preceding section, in 1.6 l. of methylene chloride, was treated with a mixture of 123 ml. of 48% hydrobromic acid and 123 ml. of ether, added slowly with stirring and cooling in ice. Nitrogen was evolved and stirring was continued for four hours; a dark red solution resulted. The aqueous layer was drawn off and the methylene chloride solution was washed with sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent at atmospheric pressure gave 79 g. (86%) of the free base of the bromomethyl ketone, m. p. 105–118°. Recrystallization from 95% ethanol gave 58 g. (64%); m. p. 125–127°.

G. α-Bromomethyl 2-(4-Chlorophenyl)-7-methyl-4-quinolyl Ketone (formation in methylene chloride by means of hydrogen bromide).—The methylene chloride solution of the diazomethyl ketone (0.66 mole) prepared according to method (C) was cooled in an ice-bath to 10° or less. Dry hydrogen bromide was passed in at a moderate rate under vigorous stirring and nitrogen was evolved. After a short time the bromomethyl ketone hydrobromide began to separate out, and the reaction was stopped when the mixture became strongly acidic. The brownish-yellow solid was filtered off, washed with ether and air dried; yield 137 g. (46%); m. p. 221–223°. After two recrystallizations from glacial acetic acid it melted at 224–227°.

V. The 2-Phenyl-4-quinolyl Methyl Ketones

Nine new methyl ketones in this field have been made and are described below. Two of these were made by hydramine fission of amino alcohols (see section IX); they were identified by analysis and preparation in a second way by stannous chloride reduction of the bromomethyl ketones. Three were made by pyrolysis of the bromohydrins (see section VII) and they also were identified by stannous chloride reduction of the bromomethyl ketones.

In several instances where large quantities of bromomethyl ketones were required in the preparation of samples of amino alcohols for clinical studies and where synthesis via the diazomethyl ketone involved large quantities of diazomethane, it was found advantageous to follow the Claisen condensation route through the methyl ketone with subsequent bromination to the bromomethyl ketone. Two methyl ketones were made in this way in good yields, namely, the 6,8-dichloro-2-phenyl-4-quinolyl and 6,8-dichloro-2-(4-chlorophenyl)-4-quinolyl methyl ketones.

Experimental[12]

6-Methoxy-2-phenyl-4-quinolyl Methyl Ketone.—Five grams of α-bromomethyl 6-methoxy-2-phenyl-4-quinolyl ketone hydrobromide was suspended in 48 ml. of 4 *N* hydrochloric acid containing 6.7 g. of stannous chloride dihydrate and the mixture was heated on a boiling water-bath for five hours (when the heating period was half over, the hard pellets which had formed were removed, crushed and returned to the reaction mixture). The solid residue was filtered, suspended in ether and shaken with 20% sodium hydroxide until all solids had dissolved. The ether solution was washed, dried, and evaporated to a dark sirup which crystallized on cooling. The solid mass was triturated with petroleum ether and filtered; yield 2.65 g. (83.5%); m. p. 98–101°. The product was recrystallized five times by dissolving in hot ethyl acetate, adding hot ligroin and allowing the solution to cool slowly. The glistening yellow needles thus obtained melted at 103–104° and did not depress the melting point of a sample prepared via the Claisen condensation route.[21]

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.44. Found: C, 77.81; H, 5.33.

6-Chloro-2-phenyl-4-quinolyl methyl ketone was prepared by stannous chloride reduction of the bromomethyl ketone in the usual way (heating on a hot water-bath for three hours); m. p. 89–90° mixture m. p. 84–86°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: N, 4.97. Found: N, 4.85.

The compound was also formed by pyrolysis of the di-*n*-hexylamino alcohol at 165°. Isolation was accomplished in the manner described in section IX; m. p. 82–86°.

7-Chloro-2-phenyl-4-quinolyl methyl ketone was prepared by stannous chloride reduction of the bromomethyl ketone; m. p. of the hydrobromide 235–237° (*in vacuo*); m. p. of the free base 104–105°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29. Found: C, 72.45; H, 4.36.

6-Chloro-2-(4-chlorophenyl)-4-quinolyl methyl ketone was obtained by stannous chloride reduction of the bromomethyl ketone; recrystallized from ethanol; m. p. 157–159°.

Anal. Calcd. for $C_{17}H_{11}Cl_2NO$: C, 64.58; H, 3.48. Found: C, 64.24; H, 3.62.

This compound was also obtained by the pyrolysis of the bromohydrin by the method described in section VII; m. p. 154–156°; identified by mixture melting point.

6,8-Dichloro-2-(4-chlorophenyl)-4-quinolyl methyl ketone[8a] was prepared by stannous chloride reduction of the bromomethyl ketone; m. p. 182–183°.

Anal. Calcd. for $C_{17}H_{10}Cl_3NO$: N, 4.00. Found: N, 3.93.

The preparation of this compound by Jacobs, Winstein, *et al.*,[8a] via the Claisen condensation on the ester[8a] was repeated (yield of 68%). It was also obtained by pyrolysis of the bromohydrin according to the method described in section VII. Since the 8-position is substituted the hydrobromide could not be obtained. The product was recrystallized from acetone and melted at 182–183°; a mixture melting point with an authentic sample showed no depression.

6,8-Dichloro-2-phenyl-4-quinolyl Methyl Ketone.—This compound was prepared in good yields by a modification of the method developed by Winstein, Jacobs, *et al.*[8a] A mixture of 60.9 g. of sodium methoxide, 400 ml. of dry benzene, 347 g. of methyl 6,8-dichloro-2-phenylcinchoninate (the ethyl ester was equally satisfactory), and 133 g. of anhydrous ethyl acetate was stirred mechanically and heated to reflux temperature. Solution was effected within thirty minutes and refluxing was continued for four hours. The dark solution was cooled slightly and a mixture of 253 ml. of concd. sulfuric acid and 420 ml. of water was added dropwise with continual stirring. Heating was resumed and a total of 500 ml. of solvent was removed by distillation. The residue was treated with 650 ml. of dioxane and the mixture was refluxed for eighteen hours, cooled to room temperature and poured with cooling and stirring into a solution of 700 g. of sodium hydroxide in 4 l. of water. The yellow ketone was filtered, washed with water, dried, and recrystallized from butanone–isopropanol; yield 164 g. (70%); m. p. 129–131°. Further recrystallization raised the melting point to 133–134°.

Anal. Calcd. for $C_{17}H_{11}Cl_2NO$: C, 64.57; H, 3.51; N, 4.43. Found: C, 64.58; H, 3.52; N, 4.66.

Ethyl 7-Chloro-2-(4-chlorophenyl)-8-methylcinchoninoylacetate.—The Claisen condensation was carried out as above with methyl 7-chloro-2-(4-chlorophenyl)-8-methylcinchoninate. Attempts to hydrolyze and decarboxylate the resulting keto ester (which was not isolated at this point) with the sulfuric acid–dioxane mixtures as described in the preceding experiment yielded instead of the desired methyl ketone about a 30% yield of the keto ester (m. p. 130–133°) and 70% of the original 4',7-dichloro-8-methylcinchophen (identified by mixture melting point). The keto ester was recrystallized from a 3:2 mixture of absolute ethanol and ethyl acetate; colorless needles; m. p. 133–135°.

Anal. Calcd. for $C_{21}H_{17}Cl_2NO_3$: C, 62.69; H, 4.26. Found: C, 62.59; H, 3.84.

2-(4-Chlorophenyl)-4-quinolyl methyl ketone was prepared directly from the diazomethyl ketone by the action of stannous chloride in a 1:2:1 mixture of concd. hydrochloric acid, water and ethanol. Although the diazomethyl ketone in this case is unusually stable and forms a stable hydrobromide, doubtless the reaction proceeds through the chloromethyl ketone. The methyl ketone

(21) This reaction was carried out and the sample furnished by Dr. Henry Gilman and co-workers; see ref. 8h.

(crude yield 97%) was recrystallized from ethanol; m. p. 101–102°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: N, 4.98. Found: N, 4.95.

It showed no mixture melting point depression with a sample prepared by stannous chloride reduction of the bromomethyl ketone.

The **hydrochloride** was prepared by dissolving the methyl ketone in ether and adding ethereal hydrogen chloride. It was recrystallized from absolute ethanol; m. p. 212–214°.

Anal. Calcd. for $C_{17}H_{12}ClNO \cdot HCl$: Cl^-, 11.15. Found: Cl^-, 11.03.

5-Chloro-2-phenyl-4-quinolyl Methyl Ketone.—This compound was easily prepared by the stannous chloride reduction procedure. It was recrystallized from 80% ethanol; m. p. 120–122°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29. Found: C, 72.64; H, 4.45.

5,8-Dichloro-2-phenyl-4-quinolyl Methyl Ketone.—The usual stannous chloride reduction procedure was employed. The product was recrystallized from acetone and from ethanol; m. p. 143–144°.

Anal. Calcd. for $C_{17}H_{11}Cl_2NO$; C, 64.58; H, 3.48. Found: C, 64.37; H, 3.39.

VI. The Dibromomethyl 2-Phenyl-4-quinolyl Ketones

A typical dibromomethyl ketone has been made by bromination of the diazomethyl ketone of the 4′-chloro series; it was reduced by stannous chloride to the methyl ketone as a structural check and for identification.

$$Q\text{—}COCHN_2 \xrightarrow{Br_2} Q\text{—}COCHBr_2 \xrightarrow{SnCl_2} Q\text{—}COCH_3$$

A second dibromomethyl ketone was isolated in a very small yield as a by-product in the bromination of one of the methyl ketones, namely, 2-(4-chlorophenyl)-6,8-dichloro-4-quinolyl methyl ketone.

Experimental[12]

α,α-Dibromomethyl 2-(4-Chlorophenyl)-4-quinolyl Ketone.—A solution of 0.64 g. of bromine in 50 ml. of carbon tetrachloride was added over twenty minutes to a solution of 1.3 g. of the diazomethyl ketone (free base) in 50 ml. of ether at room temperature. Washing with sodium carbonate solution and evaporation gave a red oil which was dissolved in hot methanol; cooling precipitated resinous material and white crystals; 0.62 g. (33%); m. p. 118–120°. Repeated recrystallizations from absolute ethanol gave colorless needles which melted at 121–123°.

Anal. Calcd. for $C_{17}H_{10}Br_2ClNO$: C, 46.45; H, 2.29; N, 3.19. Found: C, 46.68; H, 2.19; N, 3.16.

The dibromomethyl ketone was reduced to the methyl ketone by stannous chloride in the usual way (see section V).

α,α-Dibromomethyl 2-(4-Chlorophenyl)-6,8-dichloro-4-quinolyl Ketone.—In one case a small amount of the dibromomethyl ketone was obtained along with the expected monobromomethyl ketone from the bromination of 2-(*p*-chlorophenyl)-6,8-dichloro-4-quinolyl methyl ketone by means of potassium bromate. It was isolated by fractional crystallization. In the reaction in which it was produced, 29.7 g. (0.0847 mole) of the methyl ketone was heated to refluxing and dissolved in a mixture of 125 ml. of glacial acetic acid and 85 ml. of 48% hydrobromic acid. Refluxing was continued and a solution of 4.7 g. (0.028 mole) of potassium bromate in 50 ml. of warm water was added dropwise with stirring. During the half hour period required for the addition, a yellow solid separated. Refluxing was continued for an additional half hour. The mixture was poured with stirring into 150 ml. of ice water; the yellow product was filtered, washed three times with water, dried superficially *in vacuo* (m. p. 167–173°) and recrystallized from acetone; 20.7 g. (55%); m. p. 178–189°. A solid of more deeply yellow color separated from the filtrate upon standing; 1.9 g.; m. p. 167–175°. This sample was twice recrystallized from ethyl acetate; m. p. 183–184°; it gave a mixture melting point depression with the methyl ketone and with the monobromomethyl ketone. Analysis indicated it to be the dibromomethyl ketone.

Anal. Calcd. for $C_{17}H_8Br_2Cl_3NO$: C, 40.17; H, 1.59. Found: C, 39.93; H, 1.81.

VII. The α-Bromomethyl-2-phenyl-4-quinolinemethanols

The α-bromomethyl ketones with the exception of the 5-chloro types were easily reduced to the bromohydrins by aluminum isopropoxide upon a few hours of heating.[7b] Over-reduction did not often complicate the method; this is in contrast to the reduction of the bromomethyl ketones of the quinolines without the 2-phenyl group[22] which were very easily over-reduced and where the reduction time had to be of the order of five minutes or less. The bromomethyl ketones were usually reduced in the form of the hydrobromides or hydrochlorides except where an 8-substituent prevented salt formation. In a number of cases, however, the free bases were used instead of the salts with equally good results. In general it was found best to use purified materials rather than crude products.

The bromohydrins often showed double melting points. In several cases this was shown to involve rearrangement. If the salt was used, the halogen acid was first expelled. The base then rearranged to the methyl ketone (or its hydrobromide).

$$Q\text{—}\underset{\displaystyle OH}{\underset{|}{CH}}\text{—}CH_2Br \longrightarrow Q\text{—}COCH_3 + HBr$$

In three cases (the 7-chloro, the 4′,6-dichloro and the 4′,6,8-trichloro series) the products were isolated and identified. In the case of the 4′,6-dichloro compound, the bromohydrin was pyrolyzed as the free base; the salt did not show the characteristic double melting point.

Experimental[12]

In the bromohydrin table (V) those notes which represent technique variations (1, 4, 6, 9, 10, 11, 12, 15 and 16) are referred to by appropriate numbers in the preparation column.

A. α-Bromomethyl-2-(4-chlorophenyl)-6,8-dimethyl-4-quinolinemethanol (a procedure which involves removal of the isopropanol).—A mixture of 73 g. (0.19 mole) of α-bromomethyl 2-(4-chlorophenyl)-6,8-dimethyl-4-quinolyl ketone (note 1), 200 ml. of 3 *N* aluminum isopropoxide and 400 ml. of dry isopropanol (note 2) was slowly distilled under partial reflux until the distillate gave no further test for acetone with 2,4-dinitrophenylhydrazine (note 3). Unless otherwise indicated (note 4) the hot solution was clear and homogeneous at this point. The remaining isopropanol was evaporated under reduced pressure [see (B) below]. To the residual dark viscous mass (or solid

(22) Lutz, Codington and Leake: reduction of the bromomethyl 6-and 7-chloroquinolyl ketones (unpublished results).

cake) was added, with stirring, 200 ml. of water and 200 ml. of concd. hydrochloric acid (note 5). The bromohydrin precipitated almost immediately as a tan solid (notes 6, 7, and 8). The product was filtered, washed repeatedly with water and used without recrystallization (notes 9, 10 and 11); yield 58.0 g. (78.9%); m. p. 178–179°. Recrystallization from absolute ethanol gave colorless diamond-shaped plates; m. p. 179–180°.

B. In some cases the *isopropanol* was only *partially evaporated* until the volume of solution was about half of that initially; the remaining mixture was then treated with water and hydrochloric acid.

C. α-Bromoethyl-7-chloro-2-(4-chlorophenyl)-4-quinolinemethanol Hydrochloride (a procedure involving a difficultly soluble salt).—A mechanically stirred suspension of 65.5 g. (0.137 mole) of α-bromomethyl ketone hydrobromide (note 12) in 275 ml. of dry isopropanol (note 2) was heated to boiling and 150 ml. of hot 3 *N* aluminum isopropoxide solution was added. The mixture slowly became black and a homogeneous solution resulted (notes 4 and 13). Isopropanol was slowly distilled through a short Vigreux column for forty minutes (no acetone was then detected in the distillate) (note 3). The solution was treated directly with 250 ml. of water and an oil separated. The mixture was stirred mechanically and cooled in an ice bath while 125 ml. of concd. hydrochloric acid was added (note 5). A brown homogeneous solution was obtained (note 14), but as the cooling and stirring was continued, a yellow crystalline hydrochloride separated (notes 7 and 15). This was filtered, washed with water, and digested with 225 ml. of boiling isopropanol for forty-five minutes (notes 9, 10, and 11); the mixture was then cooled in an ice-bath, filtered, washed with ether and dried in an evacuated desiccator; 49.2 g. (82%); m. p. 270–271°.

This compound was so insoluble in the common solvents that it could not be recrystallized conveniently; it analyzed correctly without further purification.

D. α-Bromomethyl-7-chloro-2-(4-methoxyphenyl)-4-quinolinemethanol Hydrochloride (a procedure involving insolubility in isopropanol of both the bromomethyl ketone and bromohydrin hydrobromides).—It is worthy of note that all of the compounds made by this procedure and involving the low solubility of starting material and product were methoxyl derivatives. A suspension of 161 g. (0.342 mole) of α-bromomethyl ketone hydrobromide in 1.2 l. (note 2) of anhydrous isopropanol in a 3-l. flask equipped with a mechanical stirrer and a ten-inch Vigreux column was vigorously stirred and heated to boiling. To the mixture was added 350 ml. of hot 1 *M* aluminum isopropoxide solution. The mixture darkened immediately and turned green within forty-five minutes; during this time acetone was evolved (note 13); the mixture was slowly distilled for 6.5 hours (note 3), cooled to room temperature and filtered. The green residue was washed with isopropanol (145 g.) and suspended in 1 l. of water and 500 ml. of concd. hydrochloric acid. This mixture was shaken mechanically for one hour and filtered; the residue was washed with dilute acid and then with water, and dried; yield 108.6 g. (75%); m. p. 185–190°. The crude bromohydrin hydrochloride was further purified by slurrying with 500 ml. of hot absolute alcohol (notes 9, 10 and 11), cooling the mixture in an ice–salt bath, filtering, washing with ether and drying; 103.8 g.; m. p. 188–190°.

A sample was recrystallized from absolute ethanol; yellow rods melting at 188–190°.

E. α-Bromomethyl-2-(4-chlorophenyl)-8-phenyl-4-quinolinemethanol (a special case where both bromomethyl ketone and bromohydrin (free bases) are difficultly soluble is isopropanol).—A solution of 2 g. of the α-bromomethyl ketone and 3 ml. of 3 *N* aluminum isopropoxide in 10 ml. of dry benzene (note 16) was refluxed for fifteen minutes. The resulting purple solution was cooled and poured with stirring into 25 ml. of 1.5 *N* hydrochloric acid. The benzene layer was removed and the water layer extracted with 20 ml. of benzene. The combined benzene extracts was washed with water, dried over sodium sulfate, treated with Darco and evaporated to dryness. The yield of bromohydrin after digestion and washing with ethanol was 2 g. (99%); m. p. 142–143°. Recrystallization from absolute ethanol and ethyl acetate did not change the melting point.

In other experiments in which the refluxing period was considerably longer, a mixture of products was obtained; this is being investigated.

F. The preparation of the free base of the bromohydrin from the hydrochloride was generally accomplished by suspending the salt in 10% sodium carbonate solution and extracting with ether. The ether solution was dried over sodium sulfate, evaporated, and the residual bromohydrin recrystallized.

Notes.—1. A few α-bromomethyl ketones in the form of their *salts* (see table references) were reduced under the conditions described in method (A).

2. The quantity of isopropanol used varied from compound to compound and depended on the solubility; some α-bromomethyl ketones and bromohydrins were soluble in relatively small amounts of isopropanol; some required relatively large volumes for solution; some were very difficultly soluble and in these cases the amount of isopropanol was immaterial.

3. The time of refluxing varied from fifteen minutes to eight and one half hours, as indicated in the table.

4. In some cases during the reflux period the α-bromomethyl ketone dissolved partially or almost completely (see table references); then the aluminum complex of the bromohydrin precipitated and had a different color or crystalline form.

5. The amount of concd. hydrochloric acid which was added to the aqueous mixture at the end of the reduction varied in different preparations; the final normality ranged from 2 to 6 *N*. In general the more dilute acid was used for the 8-substituted bromohydrins in order to prevent partial solution by salt formation. In other instances the more concd. acid was used to advantage.

6. In several cases (see table references) an oil or gum separated after the addition of water and acid, necessitating prolonged standing with scratching and stirring to induce crystallization.

7. The color varied from brown, tan, yellow, to white.

8. The bromohydrin hydrochloride separated at this point if the 8-position was unsubstituted.

9. These compounds were pure enough for use without recrystallization or digestion with solvents.

10. These compounds were purified by digestion and washing with ethanol before condensation with amines.

11. These compounds were recrystallized before condensation with amines.

12. In those cases where an 8-substituent was present and prevented salt formation, the free base was used as the starting material. The free base was also used in one other case.

13. Various color changes all the way from yellow, red, green, violet, brown, to black, have been observed at this point. The color change and final color of the solution or suspension depended on the compound being reduced, and did not appear to have any relationship to the yields.

14. In some cases the bromohydrin precipitated instead of forming a clear solution as soon as the water and hydrochloric acid was added.

15. In the one case (see table references) where there was an 8-substituent present, the free base separated at this point.

16. In the preparation of the bromohydrin of the 8-phenyl series (see table references), the solvent consisted of a mixture of isopropanol and benzene which was evaporated at the end of the reflux period. The residue was redissolved in the minimum quantity of isopropanol and treated with water and hydrochloric acid to precipitate the bromohydrin.

Pyrolysis of α-Bromomethyl-7-chloro-2-phenyl-4-quinolinemethanol Hydrochloride.—A stream of nitrogen was passed over a heated sample of the bromohydrin hydrochloride and bubbled through silver nitrate solution. At 165° silver chloride began to form, and after a half hour at 190° the evolution of hydrogen chloride was complete. No silver bromide was formed (shown by qualitative analy-

TABLE V

THE α-BROMOMETHYL-2-PHENYL-4-QUINOLINEMETHANOLS

Substituent	Empirical formula	Prep. method notes	Reflux period, hr.	Yield, %	Cryst. from	M. p., °C. (cor.)	Analyses, % Calcd.	Found	Calcd.	Found
None	$C_{17}H_{14}BrNO\cdot HCl$	A,1,1	4	85	EtOH	161–162	C 55.99	55.55	H 4.15	4.03[k1]
	$C_{17}H_{14}BrNO$	F	..	43	EtOH	132–133	C 62.21	62.00	H 4.30	4.43
6-Methoxy	$C_{18}H_{16}BrNO_2\cdot HCl$	D,10	..	84	..[a]	235–236 dec.	C 54.77	54.21	H 4.34	4.60
	$C_{18}H_{16}BrNO_2$	F		72	EtOAc	169–171	C 60.34	60.46	H 4.50	4.84[k2]
7-Methyl	$C_{18}H_{16}BrNO\cdot HCl$	A,1,6,11	4	49[b]	EtOH	129–130	Cl⁻ 9.37	9.24	..	..
8-Methyl	$C_{18}H_{16}BrNO$	A,4,6,9	1	87	..	69–81	..[p] ...	...	..	..
8-Phenyl	$C_{23}H_{18}BrNO$	E,16	8	77	$CHCl_3$–ligr.	123–124	..[p] ...	...	..	..
4′-Chloro	$C_{17}H_{13}BrClNO\cdot HCl$	B,6,9	1	97	MeOH–Et_2O	257–259 dec.	Cl⁻ 8.88	8.95	..	..
	$C_{17}H_{13}BrClNO$	F	..	..	80% EtOH	145–146	C 56.30	56.00	H 3.61	3.63[k3]
4′-Chloro-6-methoxy	$C_{18}H_{15}BrClNO_2\cdot HCl$	D,1,10	5	85	MeOH	227–229 dec.	N 3.26	3.16	..	..
4′-Chloro-6,8-dimethyl	$C_{19}H_{17}BrClNO$	A,4,9	2	79	Abs. EtOH	179–180	C 58.40	58.22	H 4.39	4.56
4′-Chloro-7-methyl	$C_{18}H_{15}BrClNO\cdot HCl$	A,1,6,11	3	60[d]	EtOH	139–141[j1]	C 52.20	52.33	H 3.91	4.71
4′-Chloro-8-methyl	$C_{18}H_{15}BrClNO$	A,11	4	71	EtOH	149–150[e]	C 57.39	57.93	H 4.01	3.91[k4]
4′-Chloro-8-phenyl	$C_{23}H_{17}BrClNO$	E	0.25	99	..[i]	142–143	C 62.97	63.10	H 3.91	3.79[k4]
6-Chloro	$C_{17}H_{13}BrClNO\cdot HCl$	C,12,9	2	91	Et glycol	168–170[j2]	Cl⁻ 8.90	8.80	N 3.51	3.20
	$C_{17}H_{13}BrClNO$	F	..	..	EtOH	135–136[j3]	N 3.87	3.68	..	..
7-Chloro	$C_{17}H_{13}BrClNO\cdot HCl$	A,11	1	63	EtOH	170.5[ej4]	N 3.51	3.77	..	..
7-Chloro-4′-methoxy	$C_{18}H_{15}BrClNO_2\cdot HCl$	D,10	6	64	..	188–190	C 50.37	50.37	H 3.76	3.70[k5n]
7-Chloro-6-methoxy	$C_{18}H_{15}BrClNO_2\cdot HCl$	D,10	6	84	..[a]	222-223 dec.[e]	26.9[n]	26.7	..	..
7-Chloro-8-methyl	$C_{18}H_{15}BrClNO$	A,11	2	78	EtOH	152–153	N 3.72	3.54	..	..
8-Chloro	$C_{17}H_{13}BrClNO$	A,11	4	76	EtOH	140–141	C 56.30	56.59	H 3.61	3.67
3′,4′-Dichloro	$C_{17}H_{12}BrCl_2NO$	B,F,6[f]	..	85	..[m]	149–150	N 3.53	3.46	..	..
4′,6-Dichloro	$C_{17}H_{12}BrCl_2NO\cdot HCl$	C,12,10	4	97	..	248–252 dec.	N 3.24	3.10	..	..
	$C_{17}H_{12}BrCl_2NO$	F	..	50	EtOH	139–140[j5]	N 3.53	3.53	..	..
4′,7-Dichloro	$C_{17}H_{12}BrCl_2NO\cdot HCl$	C,9	0.8	82	..	270–271	N 3.24	3.22	..	..
4′,7-Dichloro-6-methoxy	$C_{18}H_{14}BrCl_2NO_2\cdot HCl$	C,4,9	0.5	83	MeOH	225–226 dec.[q]	N 3.03	3.20	..	..
	$C_{18}H_{14}BrCl_2NO_2$	F	..	..	EtOAc	196–197[j6]	C 50.61	50.86	H 3.30	3.31
4′,7-Dichloro-8-methyl	$C_{18}H_{14}BrCl_2NO$	A,4,6,11	2	81	EtOH	152–154	Br⁻ 19.45	19.60	..	..
4′,8-Dichloro	$C_{17}H_{12}BrCl_2NO$	A,9	5	99	Toluene	154–155 dec.	N 3.53	3.57	..	..
6,8-Dichloro	$C_{17}H_{12}BrCl_2NO$	A,9	3	99	Diox.–ligr.	130–131	N 3.53	3.49	..	..
7-Chloro-4′-fluoro[h]	$C_{17}H_{12}Cl_2FNO\cdot HCl$	C,9	6	83	..	126–135[j8]	N 3.76	3.65	..	..
4′,6,8-Trichloro	$C_{17}H_{11}BrCl_3NO$	C,4,9	2	97	Acetone	130–131[j7]	C 47.31	47.73	H 2.57	2.52[k6]
3′,4′,6,8-Tetrachloro	$C_{17}H_{10}BrCl_4NO$	B,9	3	90	Diox.–ligr.	129–130 dec.	N 3.01	3.18	..	..

[a] Ethylene glycol–isopropanol. [b] Yield after two recrystallizations. [c] Range of one-half degree or less; the upper limit is reported. [d] After one recrystallization. [e] The compound was relatively insoluble in ethanol. [f] Under rapid rate of heating. [g] Converted to the free base for condensation with amines. [h] The m. p. varied in different preparations. [i] Chlorohydrin instead of bromohydrin. [j] *In vacuo*. [k] Resolidified soon after melting; the second melting points were as follows: [j1] 239–242°. [j2] 238–240° dec. [j3] 242–245°. [j4] 228–238° dec. [j5] 255–260°. [j6] 205–210° dec. [j7] 183°. [j8] 224–227; this is identical with the melting point of the acetyl derivative. [k] Additional analyses: [k1] Calcd.: Cl⁻, 9.72; N, 3.84. Found: Cl⁻, 9.79; N, 4.03. [k2] Calcd.: Br⁻, 22.31. Found: Br⁻, 22.50. [k3] Calcd.: N, 3.86. Found: N, 4.01. [k4] Calcd.: N, 3.72. Found: N, 3.68. [k5] Calcd.: Br⁻Cl⁻, 26.89. Found: Br⁻Cl⁻, 26.80. [k6] Calcd.: N, 3.25. Found: N, 3.25. [k7] Calcd.: N, 3.72. Found: N, 3.68. [l] Absolute ethanol–ethyl acetate. [m] Ether–petroleum ether. [n] Analysis for Br⁻Cl⁻; aliphatic bromine analyzed as bromide. [p] Insufficient purity for analysis, but satisfactory for preparation of amino alcohols. [q] Much sweating at 185–195°; sample inserted at 210° melted instantly and resolidified to melt again at 223–225° dec.

sis). The residue, which had solidified was digested with absolute ethanol, filtered, and recrystallized from the same solvent; m. p. 234–235° in *vacuo;* a mixture m. p. with authentic 7-chloro-2-phenyl-4-quinolyl methyl ketone hydrobromide was 233–235°.

The **free base** was liberated by dilute sodium hydroxide and extracted into ether. It was recrystallized from ethanol; m. p. 107–109°; a mixture melting point with the sample prepared as described in section V was 105–106°.

VIII. The 2-Phenyl-4-quinolyl Ethylene Oxides

Several ethylene oxides were prepared by treatment of the bromohydrins with alkali in the usual way. In three cases conditions for the condensation between the bromohydrin and the amine were not drastic enough to effect complete reaction and the ethylene oxides were isolated as by-products; the three series involved were the 8-chloro, 4′,6,8-trichloro and the 3′,4′,6,8-tetrachloro. In one case the ethylene oxide (of the 6-chloro series) was prepared directly from the bromomethyl ketone without isolation of the intermediate bromohydrin, by alkali hydrolysis of the complex from the aluminum isopropoxide reduction.

Experimental[12]

7-Chloro-2-(4-chlorophenyl)-8-methyl-4-quinolyl Ethylene Oxide.—A solution of 8 g. (0.143 mole) of potassium hydroxide in 30 ml. of water was added to a suspension of 41.1 g. (0.1 mole) of α-bromomethyl-7-chloro-2-(4-chlorophenyl)-8-methyl-4-quinolinemethanol in 700 ml. of absolute ethanol and immediately a heavy white precipitate formed. The mixture was allowed to stand for one hour with occasional shaking; it was then filtered and the residue was washed with water until the washings were neutral; yield, 31.2 g. (94.5%); m. p. 158–161°. The product was recrystallized from a 2:1 ligroin–ethyl acetate mixture; 24.3 g. (73.6%); light yellow rods; m. p. 165–166°. Repeated recrystallization did not change the melting point.

Anal. Calcd. for $C_{18}H_{13}Cl_2NO$: C, 65.47; H, 3.97. Found: C, 65.39; H, 3.77.

7-Chloro-2-(4-chlorophenyl)-4-quinolyl ethylene oxide was prepared by the method described above; recrystallized from acetone; m. p. 143–144°.

Anal. Calcd. for $C_{17}H_{11}Cl_2NO$: C, 64.59; H, 3.51. Found: C, 64.40; H, 3.37.

8-Chloro-2-phenyl-4-quinolyl Ethylene Oxide.—This compound was prepared as above and was also the chief product when an attempt was made to condense dicyclohexylamine with the bromohydrin by heating at 75° for twenty-six hours; m. p. 111–112°; a mixture melting point of the two samples showed no depression.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.48; H, 4.30; N, 4.97. Found: C, 72.34; H, 4.39; N, 4.98.

6,8-Dichloro-2-(3,4-dichlorophenyl)-4-quinolyl Ethylene Oxide.—This compound was prepared in the usual manner. When diethylamine was condensed with the bromohydrin in benzene (refluxing for twelve hours) the yield of amino alcohol was small and about three-fourths of the material was recovered as the ethylene oxide; m. p. 218–219°; identified by mixture melting point.

Anal. Calcd. for $C_{17}H_9Cl_4NO$: C, 53.03; H, 2.36; N, 3.64. Found: C, 52.75; H, 2.41; N, 3.76.

6,8-Dichloro-2-(4-chlorophenyl)-4-quinolyl Ethylene Oxide.—This oxide like the above was prepared by alkaline treatment of the bromohydrin and was also obtained from the bromohydrin–diethylamine reaction mixture (refluxing for two days). In another experiment where the ethylene oxide was heated with diethylamine under pressure at 95° for ten hours the amino alcohol was produced in 75% yield and no ethylene oxide was recovered from the reaction mixture. The ethylene oxide was recrystallized from ethyl acetate; m. p. 195–196°.

Anal. Calcd. for $C_{17}H_{10}Cl_3NO$: N, 4.00. Found: N, 4.01.

6-Chloro-2-phenyl-4-quinolyl Ethylene Oxide.—A normal reduction was run on the bromomethyl ketone [see (A) of section VII] up to the point of hydrolysis of the aluminum complex. The residue was stirred with 30% sodium hydroxide for approximately one hour at room temperature and the resulting orange solid was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and evaporated. The orange residue was recrystallized from ethanol; yield 64%; m. p. 119°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: N, 4.98. Found: N, 5.19.

This oxide was also made by the usual method and gave no depression of the melting point when mixed with the above sample.

IX. The α-Alkyl and Dialkylaminomethyl-2-phenyl-4-quinolinemethanols

The amino alcohols listed in Table VI were made in every case by the direct condensation of the appropriate amine with the bromohydrin, the chlorohydrin or the oxide. The condensation temperatures varied between 25 and 140° and the period of heating from three to forty-seven hours. Troublesome side reactions were encountered at temperatures much above 100°. The best yields were usually realized by employing a temperature in the range of 70–95° and a time varying between ten and twenty hours. At temperatures considerably below 75°, the reactions were frequently incomplete even after prolonged heating and in several instances the intermediate oxides were isolated as the chief products. Dicyclohexylamine in one case under the optimum conditions employed above gave only the oxide, though doubtless, as in other cases, it would have reacted further under more drastic conditions; the failure of this amine to undergo condensation readily is due, presumably, to steric hindrance factors.

In those cases where high molecular weight amines were employed the amino alcohol produced and the excess of unreacted secondary amine were usually separated by fractional precipitation with standardized ethereal hydrogen chloride from an ether–acetone solution. With efficient stirring and a large volume of solvent, a clean-cut separation was usually possible. The secondary amine hydrochloride usually precipitated first (and immediately) upon addition of successive portions of acid, whereas the amino alcohol mono- or dihydrochloride usually crystallized slowly from the acid solution and only after cooling and stirring. The 8-substituted amino alcohols, of course, gave only monohydrochlorides.

Most of the dihydrochlorides and some of the monohydrochlorides after melting, partially solidified and melted again at a higher temperature. Those compounds, for which double melting points have been observed, are shown in Table VI. Certain others of the hydrochlorides listed would undoubtedly show this same behavior under the proper conditions, but the phenomenon was not studied exhaustively. The products formed were isolated in three typical cases, two in the 6-methoxy and one in the 6-chloro series (see section V), and these were shown to be the products of hydramine fission, namely, the dialkylamine hydrochloride and the 4-acetylquinoline.

$$Q\text{—}\underset{\displaystyle OH}{\underset{|}{CH}}CH_2NR_2\cdot HCl \longrightarrow Q\text{—}COCH_3 + R_2NH\cdot HCl$$

This fission is of the same type undergone by quinine itself, where rearrangement with ring opening occurs readily to give the aminomethyl ketone, quinotoxine.[23] Other examples of this fission are seen in the case of ephedrine and isoephedrine.[24]

The one weakness in the synthetic scheme used here, involving the bromohydrin, is the possibility that the intermediate ethylene oxide in the last step might react with the amines in two different ways. However, there is a definite theoretical reason for expecting the mode of cleavage to be as indicated.[7c] Furthermore the hydramine fission mentioned above may be taken as indication of the structure of the amino alcohols involved and as a means of distinction from the *iso* type amino alcohol, $Ar\text{—}CH(NR_2)CH_2OH$, which conceivably might have been formed. Also there are strong analogies for this mode of oxide ring fission. Styrene oxide reacts with di-*n*-propylamine to give α-di-*n*-propylaminomethylbenzyl alcohol in 91% yield,[25a] although Mannich[25b] has reported the opposite mode of ring opening with 3,4-dimethoxy-styrene oxide. A typical α-dialkylaminomethylaryl-methanol, namely, α-dioctylaminomethyl-4-chloro-benzyl alcohol,[26] has been

(23) Rabe, *Ann.*, **365**, 366 (1909).

(24) E. Schmidt and A. Goehring, *Arch. Pharm.*, **247**, 141 (1909); H. Emde and E. Ruune, *Arch. Pharm.*, **249**, 377 (1911).

(25) (a) Emerson, THIS JOURNAL, **67**, 516 (1945); (b) Mannich, *Arch. Pharm.*, **248**, 127–171 (1910).

(26) Lutz and co-workers, results to be published.

TABLE VI

α-(*s* AND *t*-AMINOMETHYL)-2-PHENYL-4-QUINOLINEMETHANOLS

SN[1]	Substituents	—N(R1)(R2)	Prep. method	Cond. Temp., °C.	Time, hr.	Cryst. solvent	Yield[a] crude, %	Yield[a] pure, %	M. p., °C. (cor.)	Empirical formula	No.[b]
10508	None	—N(ethyl)2	A[c]	140	4	abs. EtOH–Et2O	..	88	175–178[d]	$C_{21}H_{24}N_2O\cdot 2HCl$	1
10509		—N(*n*-butyl)2	A[c]	140	8	abs. EtOH–Et2O	..	88	70	$C_{25}H_{32}N_2O\cdot 2HCl$	2
10510		—N(*n*-amyl)2	A[c]	140	8	abs. EtOH–Et2O	..	75	138–139	$C_{27}H_{36}N_2O\cdot 2HCl$	3
11394		—N(*n*-hexyl)2	F	78	15	abs. EtOH–abs. Et2O	63	52	120–122	$C_{29}H_{40}N_2O\cdot HCl$	4
10511		—N(*n*-octyl)2	F	70	11	abs. EtOH	63	50	116–118	$C_{33}H_{48}N_2O\cdot HCl$	5
...[p]		—N(*n*-decyl)2	F	70	18	abs. EtOH–ligr.	23	15	113–114	$C_{37}H_{56}N_2O\cdot HCl$	6
10524	6-Methoxy	—N(ethyl)2	C[e]	141	6	abs. EtOH	90	56	192–194	$C_{22}H_{26}N_2O_2\cdot 2HCl$	7
10525		—N(*n*-butyl)2	E	130	3	abs. EtOH	75	61	203–212[f]	$C_{26}H_{34}N_2O_2\cdot 2HCl$	8
...			..	...	..	Pet. ether	..	..	66–68	$C_{26}H_{34}N_2O_2$	9
12213		—NH(*n*-octyl)	E	130	3	abs. EtOH	74	58	189–193	$C_{26}H_{34}N_2O_2\cdot HCl$	10
10526		—N(*n*-amyl)2	F	135	10	abs. EtOH	61	44	176–177	$C_{28}H_{38}N_2O_2\cdot HCl$	11
11395		—N(*n*-hexyl)2	F	125	12	abs. EtOH–abs. Et2O	74	48	163–165	$C_{30}H_{42}N_2O_2\cdot 2HCl$	12
10527		—N(*n*-octyl)2	E	130	3	abs. EtOH	80	52	165–171[e]	$C_{34}H_{50}N_2O_2\cdot 2HCl$	13
15029		—N(*n*-decyl)2	F	90	13	abs. EtOH–pet. eth.	80	49	118–119	$C_{38}H_{58}N_2O_2\cdot HCl$	14
13585	7-Methyl	—N(*n*-hexyl)2	F	72	20	Acet.–ligr.	52	42	138–140[e]	$C_{30}H_{42}N_2O\cdot 2HCl$	15
13524		—N(*n*-octyl)2	F	68	18	Acetone–Et2O	33	28	111–113	$C_{34}H_{50}N_2O\cdot 2HCl$	16
13373	8-Methyl	—N(*n*-octyl)2	F	80	8	EtOAc	66	56	128–130	$C_{34}H_{50}N_2O\cdot HCl$	17
13631	8-Phenyl	—N(*n*-butyl)2	F	80	19	abs. EtOH–Et2O	43	36	154–155	$C_{31}H_{36}N_2O\cdot HCl$	18
13409		—N(*n*-octyl)2	F	80	11	EtOH	68	45	149–150	$C_{39}H_{52}N_2O\cdot HCl$	19
...	4′-Chloro	—NH(ethyl)	F[f]	25	47	abs. EtOH–acet.	69	34	189–191[f]	$C_{19}H_{19}ClN_2O\cdot HCl$	20
14687		—N(ethyl)2	F	55	21	abs. EtOH	..	35	152–154[f]	$C_{21}H_{23}ClN_2O\cdot 2HCl$	21
14726		-4-methylpiperidyl	A	100	20	EtOH–acet.	58	53	170–172[f]	$C_{23}H_{25}ClN_2O\cdot HCl$	22
...			..	...	..		..	..	143–145	$C_{23}H_{25}ClN_2O$	23
13841		—N(*n*-butyl)2	F	84	14	Acetone	57	31	184–186[f]	$C_{25}H_{31}ClN_2O\cdot HCl$	24
13648		—N(*n*-hexyl)2	F	83	15	abs. EtOH	44	36	145–147[e]	$C_{29}H_{39}ClN_2O\cdot HCl$	25
13030		—N(*n*-octyl)2	F	90	16	80% EtOH	..	44	135–137[e]	$C_{33}H_{47}ClN_2O\cdot HCl$	26
...[p]	4′-Chloro-6-	—N(ethyl)2	C	55	31	abs. EtOH	79	42	117–118	$C_{27}H_{29}ClN_2O_2$	27
14285	methoxy	—N(*n*-butyl)2	E	70	20	abs. EtOH–Et2O	73	28	195–198	$C_{26}H_{33}ClN_2O_2\cdot HCl$	28
...[p]		—N(*n*-hexyl)2	F	70	19	abs. EtOH	82	24	168–169	$C_{30}H_{41}ClN_2O_2\cdot HCl$	29
13031		—N(*n*-octyl)2	F	80	13	abs. EtOH–EtOAc	79	50	156–157	$C_{34}H_{49}ClN_2O_2\cdot HCl$	30
14994	4′-Chloro-6,8-	—N(ethyl)2	B	55	12	abs. EtOH	43	28	209–210	$C_{23}H_{27}ClN_2O\cdot HCl$	31
...	dimethyl	—N(*n*-butyl)2	B	76	17	"Hexane"[g]	81	67	106–107	$C_{27}H_{35}ClN_2O$	32
14270			..	...		EtOH	..	64	202–204	$C_{27}H_{35}ClN_2O\cdot HCl$	33
15031		—N(*n*-hexyl)2	F	75	15	abs. EtOH	78	62	189–190	$C_{31}H_{43}ClN_2O\cdot HCl$	34
...[p]	4′-Chloro-7-	—N(*n*-butyl)2	F	70	18	EtOH–Et2O	..	20	175–176	$C_{25}H_{33}ClN_2O\cdot HCl$	35
13630	methyl	—N(*n*-hexyl)2	F	72	24	Acetone	..	24	161–162	$C_{29}H_{41}ClN_2O\cdot HCl$	36
13721	4′-Chloro-8-	—N(*n*-butyl)2	E	90	8	abs. EtOH	85	..	193–195	$C_{26}H_{33}ClN_2O\cdot HCl$	37
13649	methyl	—N(*n*-hexyl)2	F	90	15	*i*-PrOH	93	66	147–149	$C_{30}H_{41}ClN_2O\cdot HCl$	38
...	4′-Chloro-8-	—N(ethyl)2	C[q]	75	25	abs. EtOH	60	45	126–127	$C_{27}H_{27}ClN_2O$	39
13601	phenyl	—N(*n*-butyl)2	F	70	23	Benzene–ligr.	84	44	171–172	$C_{31}H_{35}ClN_2O\cdot HCl$	40
15209	6-Chloro	—N(*n*-butyl)2	F	70	10	abs. EtOH	45	22	166[e]	$C_{25}H_{31}ClN_2O\cdot HCl$	41
12714		—N(*n*-hexyl)2	F	70	10	abs. EtOH	78	43	160–161[e]	$C_{29}H_{39}ClN_2O\cdot HCl$	42
...	7-Chloro	—N(ethyl)2	F	55	15	Acetone	..	..	101–102	$C_{21}H_{23}ClN_2O$	43
...[p]			..	...	..	abs. Et2O[i]	53	46	178–179[f]	$C_{21}H_{23}ClN_2O\cdot HCl$	44
10521		—N(*n*-butyl)2	F	108	10	Butanone	62	..	108–110[e]	$C_{25}H_{31}ClN_2O\cdot 2HCl$	45
...			..	...	..	Butanone	..	..	181–183	$C_{25}H_{31}ClN_2O\cdot HCl$	46
13283		—NH(*n*-octyl)	E	68	18	Et2O–pet. eth.	32	25	100[h]	$C_{25}H_{31}ClN_2O$	47
10522		—N(*n*-amyl)2	F	130	3	Butanone–ligr.	58	49	114–115[e]	$C_{27}H_{35}ClN_2O\cdot 2HCl$	48
11441		—N(*n*-hexyl)2	F	108	8	Butanone	..	67	117[e]	$C_{29}H_{39}ClN_2O\cdot 2HCl$	49
10523		—N(*n*-octyl)2	F	68	18	Acetone	44	35	140[e]	$C_{33}H_{47}ClN_2O\cdot 2HCl$	50
12672		—N(*n*-decyl)2	F	68	18	EtOH	52	42	167	$C_{37}H_{55}ClN_2O\cdot HCl$	51
...[p]	7-Chloro-4′-	—N(ethyl)2	F[j]	80	21	Butanone	30	..	186–189	$C_{22}H_{25}ClN_2O_2\cdot HCl$	52
...[p]	methoxy	—N(*n*-butyl)2	F	75	12	Butanone	58	..	189–193[f]	$C_{26}H_{33}ClN_2O_2\cdot HCl$	53
...[p]		—N(*n*-hexyl)2	F	75	12	Butanone	60	..	166–169	$C_{30}H_{41}ClN_2O_2\cdot HCl$	54
13027		—N(*n*-octyl)2	F	75	12	Butanone	..	20	148–150	$C_{34}H_{49}ClN_2O_2\cdot HCl$	55
14626	7-Chloro-6-	—N(*n*-butyl)2	F	73	6	$CHCl_3$–Et2O	77	45	191–194	$C_{26}H_{33}ClN_2O_2\cdot HCl$	56
13599	methoxy	—N(*n*-hexyl)2	F	70	10	abs. EtOH–Et2O	52	40	182–183	$C_{30}H_{41}ClN_2O_2\cdot HCl$	57
13711	7-Chloro-8-	—N(*n*-butyl)2	F	70	16	abs. EtOH–EtOAc	88	58	189–191	$C_{26}H_{33}ClN_2O\cdot HCl$	58
13602	methyl	—N(*n*-hexyl)2	F	70	15	Acetone	83	67	156–160	$C_{30}H_{41}ClN_2O\cdot HCl$	59
...	8-Chloro	—N(ethyl)2	C[j]	75	25	*i*-PrOH–ligr.	..	..	155–156	$C_{21}H_{23}ClN_2O$	60
15028			..	...	..	Butanone–iPrOH	..	58	210–212	$C_{21}H_{23}ClN_2O\cdot HCl$	61
13633		—N(*n*-butyl)2	E	100	12	*i*-PrOH	87	75	173–174	$C_{25}H_{31}ClN_2O\cdot HCl$	62
12713		—N(*n*-hexyl)2	F	99	25	abs. EtOH	78	60	173–175	$C_{29}H_{39}ClN_2O\cdot HCl$	63
13085		—N(*n*-octyl)2	F	98	15	85% EtOH	65	49	117–119	$C_{33}H_{47}ClN_2O\cdot HCl$	64
...[p]	3′,4′-Dichloro	—N(*n*-butyl)2	E	82	17	Butanone	67	32	170–171	$C_{25}H_{30}Cl_2N_2O\cdot HCl$	65

TABLE VI (*Concluded*)

SN[1]	Substituents	—N(R1)(R2)	Prep. method	Cond. Temp., °C.	Time, hr.	Cryst. solvent	Yield[a] crude, %	Yield[a] pure, %	M. p., °C. (cor.)	Empirical formula	No.[b]
14995	4',6-Dichloro	—N(ethyl)$_2$	C	70	10	abs. EtOH	63	23	181[e]	$C_{21}H_{22}Cl_2N_2O\cdot HCl$	66
...			..	...	..	EtOH	..	..	103–104	$C_{21}H_{22}Cl_2N_2O$	67
14273		—N(*n*-butyl)$_2$	F	70	10	EtOH–*i*-PrOH	58	50	184–186[e]	$C_{25}H_{30}Cl_2N_2O\cdot HCl$	68
...			..	...	..	EtOH	..	..	83–84	$C_{25}H_{30}Cl_2N_2O$	69
14934		—N(*n*-hexyl)$_2$	F	70	10	abs. EtOH	54	41	174–176[e]	$C_{29}H_{38}Cl_2N_2O\cdot HCl$	70
...	4',7-Dichloro	—N(ethyl)$_2$	C	55	21	Acetone	33	23	105–106	$C_{21}H_{22}Cl_2N_2O$	71
...[p]			..	...	..	abs. Et$_2$O[i]	..	..	171–172[t]	$C_{21}H_{22}Cl_2N_2O\cdot HCl$	72
...		-piperidyl	A	72	11	Acetone	..	..	142–148	$C_{22}H_{22}Cl_2N_2O$	73
14996			..	...	..	CH_3OH	44	35	199–200[t]	$C_{22}H_{22}Cl_2N_2O\cdot HCl$	74
15060		(4-methylpiperidyl)	F	62	36	Acet.–CH_3OH	33	25	171–173[t]	$C_{23}H_{24}Cl_2N_2O\cdot 2HCl$	75
13710	4',7-Dichloro	—N(*n*-butyl)$_2$	E	74	10	abs. EtOH–EtOAc	82	..	188–189	$C_{25}H_{30}Cl_2N_2O\cdot HCl$	76
12711		—N(*n*-hexyl)$_2$	F	80	12	EtOAc	79	..	190–192	$C_{29}H_{38}Cl_2N_2O\cdot HCl$	77
14883	4',7-Dichloro-6-methoxy	—N(*n*-butyl)$_2$	F	70	9	abs. EtOH	63	45	205–207	$C_{26}H_{32}Cl_2N_2O_2\cdot HCl$	78
14070	4',7-Dichloro-	—N(ethyl)$_2$[r]	C[j]	80	16	abs. EtOH	64	30	218–220	$C_{22}H_{24}Cl_2N_2O\cdot HCl$	79
...[p]	8-methyl	—N(*n*-propyl)$_2$	F	70	19	abs. EtOH	82	56	209–211	$C_{24}H_{28}Cl_2N_2O\cdot HCl$	80
13815		—N(*n*-butyl)$_2$[r]	F	70	16	abs. EtOH	..	61	203–205	$C_{26}H_{32}Cl_2N_2O\cdot HCl$	81
...[p]		—N(iso-butyl)$_2$	F	70	19	abs. EtOH–Et$_2$O	59	46	196–198	$C_{25}H_{32}Cl_2N_2O\cdot HCl$	82
...[p]		—N(*n*-amyl)$_2$[r]	G	80	40	abs. EtOH–EtOAc	80	73	196–197[m]	$C_{28}H_{34}Cl_2N_2O\cdot HCl$	83
...[p]		—N(iso-amyl)$_2$	F	70	19	abs. EtOH	68	56	215–217	$C_{28}H_{36}Cl_2N_2O\cdot HCl$	84
13720		—N(*n*-hexyl)$_2$[r]	F	70	16	abs. EtOH	82	61	195–197	$C_{30}H_{40}Cl_2N_2O\cdot HCl$	85
...[p]	4',8-Dichloro	—N(ethyl)$_2$	C	58	11	EtOH	79	45	211–212[t]	$C_{21}H_{22}Cl_2N_2O\cdot HCl$	86
13634		—N(*n*-butyl)$_2$	E	95	7	*i*-PrOH	71	53	184–186	$C_{25}H_{30}Cl_2N_2O\cdot HCl$	87
12673		—N(*n*-hexyl)$_2$	F	95	12	*i*-PrOH	..	70	168–169	$C_{29}H_{38}Cl_2N_2O\cdot HCl$	88
12675		—N(*n*-octyl)$_2$	F	92	10	abs. EtOH	..	47	162–163	$C_{33}H_{46}Cl_2N_2O\cdot HCl$	89
12676		—N(*n*-decyl)$_2$	F	94	12	abs. EtOH	71	58	168–169	$C_{37}H_{54}Cl_2N_2O\cdot HCl$	90
...	6,8-Dichloro	—N(ethyl)$_2$	C[j]	75	11	*i*-PrOH	62	..	118–120	$C_{21}H_{22}Cl_2N_2O$	91
13571			..	...	..	AcOH	47	34	223–224	$C_{21}H_{22}Cl_2N_2O\cdot HCl$	92
13632		—N(*n*-propyl)$_2$	C[k]	85	15	Diox.–ligr.–abs. EtOH	62	43	212–213	$C_{23}H_{26}Cl_2N_2O\cdot HCl$	93
12209		—N(*n*-butyl)$_2$	E[k]	85	15	Cyclohexanone–ligr.	94	71	183–185	$C_{25}H_{30}Cl_2N_2O\cdot HCl$	94
13635		—N(*n*-amyl)$_2$	E[k]	85	15	EtOH	78	44	201–202[t]	$C_{27}H_{34}Cl_2N_2O\cdot HCl$	95
12674		—N(*n*-hexyl)$_2$	F	94	12	abs. EtOH	50	26	195–196	$C_{29}H_{38}Cl_2N_2O\cdot HCl$	96
...		—NH(*n*-dodecyl)	F[j]	80	18	EtOH	71	56	107–109	$C_{29}H_{38}Cl_2N_2O$	97
...[p]			..	...	..	AcOH–*i*-PrOH	..	35	206–207	$C_{29}H_{38}Cl_2N_2O\cdot HCl$	98
12208		—N(*n*-octyl)$_2$	F	83	13	abs. EtOH	70	47	192–193	$C_{33}H_{46}Cl_2N_2O\cdot HCl$	99
...[p]	7-Chloro-4'-fluoro	—N(ethyl)$_2$	C	80	16	abs. EtOH	63	41[l]	176–180	$C_{21}H_{22}ClFN_2O\cdot HCl$	100
...[p]		—N(*n*-butyl)$_2$	E	80	16	abs. EtOH–Et$_2$O	69	44[l]	189–191[e]	$C_{25}H_{30}ClFN_2O\cdot HCl$	101
...[p]		—N(*n*-hexyl)$_2$	F	80	16	abs. EtOH–Et$_2$O	36	29[l]	178–180[e]	$C_{29}H_{38}ClFN_2O\cdot HCl$	102
...	4',6,8-Tri-	—N(methyl)$_2$	D	78	16	Acetone	47	33	167–168	$C_{19}H_{17}Cl_3N_2O$	103
...[p]	chloro		..	...	..	abs. Et$_2$O	..	33	231–232	$C_{19}H_{17}Cl_3N_2O\cdot HCl$	104
...		—N(ethyl)$_2$	F[n]	48	22	*i*-PrOH	..	..	122–123	$C_{21}H_{21}Cl_3N_2O$	105
14182			..	...	..	abs. EtOH–diox.	..	33	221–223	$C_{21}H_{21}Cl_3N_2O\cdot HCl$	106
14220		—N(methyl)(isopropyl)	F	45	17	abs. EtOH–diox.	56	41	208–209	$C_{21}H_{21}Cl_3N_2O\cdot HCl$	107
14317		—NH(*n*-butyl)	F	73	16	*n*-BuOH	40	33	223–225[t]	$C_{21}H_{21}Cl_3N_2O\cdot HCl$	108
...		—morpholinyl	C	75	14	EtOAc	63	..	182–183	$C_{21}H_{19}Cl_3N_2O_2$	109
14935			..	...	..	*n*-AmOH	49	31	218–219	$C_{21}H_{19}Cl_3N_2O_2\cdot HCl$	110
14265		—N(ethyl)(CH_2CH_2OH)	F	73	17	*n*-BuOH	..	45	196–197[t]	$C_{21}H_{21}Cl_3N_2O_2\cdot HCl$	111
14062		—N(*n*-butyl)$_2$	F	73	8	CH_3OH–diox.	54	48	199–201[t]	$C_{25}H_{29}Cl_3N_2O\cdot HCl$	112
12678		—N(*n*-hexyl)$_2$	F	73	19	CH_3OH–diox.	68	54	182–184	$C_{29}H_{37}Cl_3N_2O\cdot HCl$	113
12679		—N(*n*-octyl)$_2$	F	70	14	Acet.–diox.	74	50	181–183	$C_{33}H_{45}Cl_3N_2O\cdot HCl$	114
...[p]	3',4',6,8-	—N(methyl)$_2$	D	75	36	Diox.–benz.–butanone	34	27	205–206	$C_{19}H_{16}Cl_4N_2O$[s]	115
...	Tetrachloro	—N(ethyl)$_2$	C[j]	80	24	Butanone–benz.	..	..	175–176	$C_{21}H_{20}Cl_4N_2O$	116
14912			..	...	..	Cyclohexanone	71	61	225–227	$C_{21}H_{20}Cl_4N_2O\cdot HCl$	117
...		—N(*n*-butyl)$_2$	E[k]	90	19	Dioxane	..	..	128–129	$C_{25}H_{28}Cl_4N_2O$	118
15068			..	...	..	*n*-BuOH	..	73	209–210	$C_{25}H_{28}Cl_4N_2O\cdot HCl$	119

[a] Crude-fairly pure. Based on bromohydrin unless otherwise indicated. [b] Numbers here refer to Table VII which contains the analytical data. [c] Xylene employed as solvent in condensation. [d] K. Miescher, U. S. pat. 1,434,306 (Oct. 31, 1922) reports m. p. 185° dec. [e] Melts and resolidifies. [f] Ether employed as solvent in condensation. [g] B. p. (760 mm.) 155–162°. [h] Under pressure. [i] Solution of the pure free base in ether was acidified with ethereal hydrogen chloride. The precipitated salt was not recrystallized. [j] Benzene employed as solvent in condensation. [k] Toluene employed as solvent in condensation. [l] Prepared from chlorohydrin. [m] This compound was also prepared from the bromohydrin but the product was contaminated with diamylamine hydrobromide and could not be purified satisfactorily. [n] This amino-alcohol free base was also prepared in 73% yield by condensing the oxide with diethylamine in a pressure bottle at 95° for fourteen hours. [p] This compound was tested but was not assigned a Survey Number. [q] Condensed in a pressure bottle. [r] The free base was a solid which could not be purified readily. [s] Attempts to prepare an analytically pure hydrochloride of this compound were unsuccessful. The pure white free base consistently gave a yellow salt showing the following analyses: Calcd. Cl^- 7.59. Found: Cl^- 7.37 and 7.12. [t] With decomposition.

TABLE VII

ANALYTICAL DATA FOR TABLE VI

No.[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	No.[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	No.[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Cl⁻, % Calcd.	Cl⁻, % Found	No.[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Cl⁻, % Calcd.	Cl⁻, % Found
6	76.44	76.30	9.71	9.54	92	59.23	59.47	5.45	5.37	31	..	..	8.45	8.38	78	..	..	6.93	6.90
8	65.27	65.26	7.52	7.71	97	69.45	69.39	7.63	7.34	33	..	..	7.46	7.44	79	6.37	6.25	8.06	8.12
9	76.80	77.04	8.43	8.52	100	61.62	61.58	5.66	5.82	34	..	..	6.67	6.64	80	..	..	7.58	7.60
11	71.37	71.51	8.34	8.48	101	64.51	64.37	6.71	6.76	35	..	..	7.70	7.57	81	..	..	7.15	7.19
13	69.02	68.89	8.86	8.84	102	66.79	66.40	7.54	7.44	36	..	..	6.85	6.93	82	..	..	7.15	7.11
20	62.81	62.03	5.56	5.64	103	57.67	57.65	4.33	4.27	37	..	..	7.68	7.98	83	..	..	6.77	6.78
23	72.53	72.37	6.61	6.54	105	59.51	59.17	5.00	4.71	38	..	..	6.85	6.89	84	..	..	6.77	6.76
27	68.65	68.60	6.55	6.37	106	54.80	54.35	4.82	4.53	39	6.50	6.53	...	...	85	..	..	6.42	6.44
32	73.87	73.71	8.04	8.01	113	60.84	61.09	6.52	6.78	40	..	..	6.77	6.78	86	6.58	6.37	8.33	8.30
35	67.66	67.38	7.43	7.35	114	63.05	63.31	7.22	7.38	41	..	..	7.93	7.87	87	..	..	7.36	7.31
37	67.65	67.36	7.43	7.12	115	53.04	53.04	3.75	3.72	42	..	..	7.03	7.05	88	..	..	6.59	6.64
38	69.61	69.48	8.18	8.09	117	50.98	51.12	4.28	4.23	44	..	..	9.07	9.12	89	4.72	4.80	5.97	6.07
39	75.26	75.13	6.32	6.01						45	..	..	14.66	15.07	90	4.31	4.39	5.45	5.57
41	67.11	66.83	6.98	7.16						46	6.26	5.98	...	...	91	7.19	7.47	..	..
42	68.84	69.06	7.79	7.90	No.[a]	Nitrogen, %		Cl⁻, %		47	6.82	6.91	...	...	92	..	..	8.33	8.36
43	71.07	71.16	6.53	6.53		Calcd.	Found	Calcd.	Found	48	..	..	13.84	13.97	93	6.18	6.01	7.81	7.82
50	66.48	66.75	8.29	8.36	1	7.12	6.93	18.03	18.01	49	5.19	5.38	...	...	94	..	..	7.36	7.46
51	72.03	71.28	9.10	8.83	2	6.23	6.31	15.79	15.84	50	4.71	4.53	11.90	12.06	95	..	..	6.95	7.00
52	62.77	62.81	6.23	6.13	3	5.87	6.07	14.85	14.75	51	..	..	5.76	6.00	96	5.21	5.10	6.59	6.81
53	65.40	65.57	7.18	7.03	4	5.97	6.29	7.56	7.62	52	..	..	8.42	8.51	97	5.59	5.82	..	..
54	67.54	67.41	7.94	8.07	5	5.52	5.59	6.76	6.88	53	..	..	7.43	7.47	98	5.21	5.06	6.59	6.52
55	69.25	69.12	8.55	8.55	6	4.82	5.37	6.10	6.25	54	..	..	6.65	6.60	99	4.72	4.57	5.97	5.99
62	67.10	66.79	6.98	7.20	7	6.62	6.60	...	...	55	..	..	6.03	6.04	100	..	..	8.66	8.68
64	70.95	70.91	8.65	8.41	8	...	...	14.79	14.55	56	..	..	7.44	7.48	101	..	..	7.62	7.57
65	62.32	62.60	6.49	6.62	10	...	...	8.01	8.09	57	..	..	6.65	6.71	102	..	..	6.75	6.80
66	59.24	58.89	5.44	5.24	12	...	...	13.24	13.27	58	..	..	7.68	7.68	104	..	..	8.22	8.20
68	62.31	62.03	6.48	6.31	13	4.74	4.87	...	...	59	..	..	6.85	6.91	106	6.09	5.86	7.70	7.67
69	67.41	67.24	6.74	6.89	14	...	...	5.80	5.81	60	7.89	7.90	...	...	107	..	..	7.70	7.72
71	64.78	64.62	5.70	5.55	15	...	...	13.65	13.43	61	..	..	9.06	8.99	108	..	..	7.70	7.54
73	65.84	65.73	5.53	5.51	16	...	...	12.29	12.18	62	..	..	7.92	7.96	109	6.40	6.45	..	..
76	62.30	62.20	6.48	6.63	17	5.20	5.31	6.58	6.57	63	5.56	5.78	7.04	7.21	110	..	..	7.48	7.43
78	60.85	61.05	6.50	6.32	18	5.73	5.48	7.25	7.32	64	..	..	6.35	6.45	111	..	..	7.45	7.48
79	60.07	59.59	5.73	5.60	19	4.66	4.86	5.90	5.89	65	..	..	7.36	7.38	112	..	..	6.87	6.81
80	61.61	61.51	6.25	6.23	20	...	...	9.76	10.11	66	..	..	8.33	8.35	113	..	..	6.19	6.23
81	62.97	62.39	6.71	6.83	21	...	...	16.55	16.80	67	7.19	7.31	...	...	114	..	..	5.64	5.57
82	62.97	62.58	6.71	6.54	22	...	...	8.50	8.57	68	..	..	7.36	7.38	115	6.51	6.25	..	..
83	64.18	63.71	7.12	7.09	24	...	...	7.93	7.90	70	..	..	6.60	6.63	116	6.12	6.00	..	..
84	64.18	64.30	7.12	7.03	25	...	...	7.24	7.31	72	..	..	8.33	8.28	117	5.66	5.37	..	..
85	65.27	65.10	7.49	7.25	26	...	...	6.52	6.58	74	..	..	8.11	8.33	118	5.45	5.19	..	..
87	62.31	62.45	6.48	6.52	28	...	...	7.43	7.73	75	..	..	14.52	14.46	119	..	..	6.44	6.35
88	64.74	65.04	7.31	7.44	29	...	...	6.65	6.60	76	5.81	6.03	7.37	7.36					
89	66.70	66.65	7.97	8.01	30	...	...	6.02	6.04	77	..	..	6.61	6.58					

[a] See footnote *b*, Table VI.

made by both the bromohydrin synthesis and by the unequivocal aminomethyl ketone synthesis. A similar synthesis of two typical drugs by both of these paths has been carried through in the α-dialkylaminomethyl - 1 - naphthalenemethanol series.[7,27] In the 2-phenyl-4-quinoline β-aminoethanol field itself, one compound, α-diethylaminomethyl-2-phenyl-4-quinolinemethanol, has been made by both methods, previously by catalytic reduction of the aminomethyl ketone,[3] and in this laboratory by the bromohydrin synthesis; but unfortunately here agreement in the melting points of the salts is the only identification of the two samples, and we have not had the opportunity to repeat the original preparation. However, we have made one other compound, α-dibutylaminomethyl-6-methoxy-2-phenyl-4-quinolinemethanol, by the two methods and the two samples thus obtained were shown to be identical by mixture melting points of the salts and of the free bases; and this amino alcohol underwent the hydramine fission to the expected methyl ketone.

On the basis of the above considerations and especially the analogies cited, we have relied with confidence on the assumed mode of oxide ring cleavage and have therefore avoided the less convenient synthetic path from the α-bromomethyl ketone through the aminomethyl ketone.

Most of the compounds listed in Table VI proved to be highly active against avian malaria and showed activities ranging from below one up to thirty-two times that of quinine. The details involved in these tests and the results obtained will be given in the forthcoming monograph.[1b] The quinine equivalents of twenty-two of the drugs are listed in Table VIII; these compounds were screened too late to be included in the monograph and are presented herewith in order that they may be recorded. These results are typical. One among them is particularly striking, namely, that with α-di-isobutylaminomethyl-7-chloro-2-*p*-chlorophenyl - 8 - methyl - 4 - quinolinemethanol, where the quinine equivalent against *Lophurae*

(27) Jacobs, Winstein, Ralls, Robson, Henderson, Akawai, Florsheim, Seymour and Seil, *J. Org. Chem.*, **11**, 21 (1946).

TABLE VIII

QUININE EQUIVALENTS OF SOME OF THE α-DIALKYLAMINOMETHYL-2-PHENYL-4-QUINOLINEMETHANOLS[a]

Substituents (See formula I)	—NR_2	Cpd. no. (Table VI)	REL[b] no.	*Lophurae* (duck) Q^c	Test method	*Gallinaceum*[g] (chick) Q^c A-1[h]	D^i A-2[i]	D^i A-2a[i]	Chronic toxicity[k] (chick) Q^c(1-A[g])
None	—N(*n*-decyl)$_2$	6	582	0.25	D-1[d]	<0.03			<0.8
4′-Chloro-6-methoxy	—N(ethyl)$_2$	27	585	6	G-5[e]	4	<4.0	<0.5	6
	—N(*n*-hexyl)$_2$	29	584	5	G-5	2	<0.5	<0.06	1
4′-Chloro-7-methyl	—N(*n*-butyl)$_2$	35	596	7	F-1	2	<1.0	<0.12	2
				14	F-1(I. M.[f])				
4′-Chloro-8-phenyl	—N(ethyl)$_2$	39	594	1.5	G-5	....	....	....	...
7-Chloro	—N(ethyl)$_2$	44	588	1.5	G-5	0.5	....	....	1
7-Chloro-4′-methoxy	—N(ethyl)$_2$	52	578	0.8	G-5	2	<1.0	<0.12	2
	—N(*n*-butyl)$_2$	53	577	5	G-5	4	<1.0	<0.12	2
	—N(*n*-hexyl)$_2$	54	576	5	G-5	1	<0.25	<0.03	1
3′,4′-Dichloro	—N(*n*-butyl)$_2$	65	580	10	G-5	2	<1.0	<0.12	2
4′,7-Dichloro	—N(ethyl)$_2$	72	592	20	G-5	4	<1.0	<0.12	3
4′,7-Dichloro-8-methyl	—N(*n*-propyl)$_2$	80	570	10	G-5	8	<1.0	<0.12	2
	—N(iso-butyl)$_2$	82	571	1	G-5	2	<1.0	<0.12	2
	—N(*n*-amyl)$_2$	83	586	10	G-5	4	<0.5	<0.06	2
	—N(iso-amyl)$_2$	84	572	10	G-5	8	....	....	1
4′,8-Dichloro	—N(ethyl)$_2$	86	579	1	G-5	0.5	....	....	2
6,8-Dichloro	—NH(*n*-dodecyl)	98	581	32	D-1	1	<0.25	<0.03	<0.8
7-Chloro-4′-fluoro	—N(ethyl)$_2$	100	575	8	D-1	8	<2.0	<0.25	3
	—N(*n*-butyl)$_2$	101	573	16	D-1	4	<1.0	<0.12	...
	—N(*n*-hexyl)$_2$	102	574	32	D-1	....	....	....	...
4′,6,8-Trichloro	—N(methyl)$_2$	104	583	8	D-1	4	<2.0	<0.25	3
3′,4′,6,8-Tetrachloro	—N(ethyl)$_2$	116	556	2	D-1	4	<0.5	<0.06	1.5

[a] Compounds screened too late to be included in the survey monograph.[1b] The values reported are calculated on the basis of the base. The test procedures referred to in footnotes *a*–*k* are described in the forthcoming monograph.[1b] [b] Code number from this laboratory. [c] Q = quinine equivalent. [d] The D-1 tests were carried out by Dr. E. K. Marshall, Jr., at the Johns Hopkins Medical School. [e] The G-5 and F-1 tests were carried out by Dr. A. P. Richardson, Squibb Institute for Medical Research. [f] I. M. = administered intramuscularly rather than orally. [g] Determined by Dr. G. Robert Coatney, National Institute of Health. [h] Therapeutic. [i] Sulfadiazine equivalent. [j] Prophylactic. [k] At the maximum tolerated dose (calculated to base). All of these tests, except those on No. 98 (REL 581) were made at the maximum tolerated dose, and the results were negative.

(duck) is one as compared with thirty-two for the isomeric di-*n*-butylamino compound.[1b]

Further studies in this field in progress are designed on the one hand to document the existing data and on the other to improve the drugs, particularly in respect to absorption properties.

Experimental[12]

A. 2-(4-Chlorophenyl)-α-[1-(4-methylpiperidyl)-methyl]-4-quinolinemethanol Monohydrochloride (a condensation employing a low boiling water soluble amine).—A mixture of 19 g. of α-bromomethyl-2-(4-chlorophenyl)-4-quinoline methanol hydrochloride and 28 g. of 4-methylpiperidine was heated at 95° for twenty hours. The resulting solution when diluted with 150 ml. of ether and filtered yielded 13.5 g. (93%) of the mixed hydrohalides of 4-methylpiperidine. Excess 4-methylpiperidine was removed from the ether filtrate by six extractions with water. The white free base (10 g., m. p. 110–112°), obtained by partial evaporation of the ether, was converted to the monohydrochloride in absolute ether using the calculated volume of standardized ethereal hydrogen chloride; m. p. 166–169°. One recrystallization from ethanol–acetone gave white crystals (10.5 g.); m. p. 170–172° (dec.).

B.—In some cases both the secondary amine hydrohalide and the excess secondary amine were removed by pouring the initial condensation product into a large volume of water. The amino alcohol free base was then removed by filtration and handled as in (A).

C. 8-Chloro-α-(diethylaminomethyl)-2-phenyl-4-quinolinemethanol Monohydrochloride.—A mixture of 10 g. of α-bromomethyl-8-chloro-2-phenyl-4-quinolinemethanol, 30 g. of diethylamine and 65 ml. of benzene was refluxed (70–80°) for twenty-five hours. The mixture was diluted with 175 ml. of ether and the diethylamine hydrobromide (4.3 g., 100%) was removed by filtration. The solvents were removed completely from the filtrate by evaporation under reduced pressure. A very small portion of the residual solid free base upon two recrystallizations from *i*-propanol–ligroin gave a white crystalline analytical sample; m. p. 155–156°. The bulk of the crude free base was converted to the hydrochloride in absolute ether. One recrystallization from butanone–isopropanol gave white crystals (6.3 g., 57.9%); m. p. 210–212°.

D.—When dimethylamine was employed, a sealed tube was used for the initial condensation. Excess reagent was removed by spontaneous evaporation and the dimethylamine hydrobromide by trituration with water.

E. α-(Di-*n*-octylaminomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol Dihydrochloride (a condensation employing a high boiling water insoluble amine).—A mixture of 50 g. of α-bromomethyl-6-methoxy-2-phenyl-4-quinolinemethanol and 165 g. of di-*n*-octylamine was heated at 127–130° in an oil thermostat for three hours. The resulting red oily suspension when diluted with 500 ml. of ether and filtered yielded 45 g. (100%) of di-*n*-octylamine hydrobromide. After shaking the filtrate with aqueous sodium carbonate the ether was removed by evaporation under reduced pressure. The excess di-*n*-octylamine was removed from the residual oil by heating in a molecular still at 100° and 1×10^{-3} mm. for ten hours. The amino alcohol was precipitated under efficient stirring from ether–acetone as the monohydrochloride using one equivalent of ethereal hydrogen chloride; yield 52.6 g. (67.7%); melting range 124–140°. Conversion to the dihydrochloride was accomplished in absolute ethanol using

an excess of ethanolic hydrogen chloride. Recrystallization from absolute ethanol gave 42.7 g. (51.5%) of cream-colored crystals which melted at 163–169° when heated rapidly.

F. 8-Chloro-2-(4-chlorophenyl)-α-(di-*n*-decylaminomethyl)-4-quinolinemethanol Monohydrochloride.—A mixture of 95 g. of di-*n*-decylamine and 31.8 g. of α-bromomethyl-8-chloro-2-(4-chlorophenyl)-4-quinoline-methanol was heated at 94° for twelve hours. The addition of 850 ml. of ether followed by filtration gave 29.3 g. (97%) of di-*n*-decylamine hydrobromide. Employing effective mechanical stirring the excess di-*n*-decylamine was removed from the ether filtrate by fractional precipitation with standardized ethereal hydrogen chloride. After the addition of 100 ml. of acetone further acidification (*p*H 2–3) caused no immediate precipitation. However, after cooling in ice with stirring 37 g. of a white product was obtained. Two recrystallizations from absolute ethanol yielded 30 g. (58%) of white crystals; m. p. 168–169°.

G.—More satisfactory results were obtained in some cases by condensing the oxide,[7e] rather than the bromohydrin, with the amine. In this case no excess of amine was required. Any unreacted amine was removed as in (F) by fractional precipitation.

Preparation of α-Di-*n*-butylaminomethyl-6-methoxy-2-phenyl-4-quinolinemethanol Dihydrochloride through Condensation of the Bromomethyl Ketone with Dibutylamine and Reduction. (a) **Catalytic Reduction.**—Four grams of bromomethyl 6-methoxy-2-phenyl-4-quinolyl ketone was added to a solution of 5.8 g. of di-*n*-butylamine in 50 ml. of absolute ether. After gentle agitation for one and one-half hours the ketone dissolved. After standing for ten hours at 5° the precipitated dibutylamine hydrobromide (4.1 g., 86%) was removed by filtration and the amber-colored ether solution was evaporated under reduced pressure at room temperature. Hydrogenation of the residual red oil (0.05 g. of platinum oxide) at atmospheric pressure in 60 ml. of absolute ethanol with sufficient added ethanolic hydrogen chloride to bring the *p*H to 5, was complete in four and one-half hours. Filtration, evaporation of the solvent and dilution with absolute ether gave 3.4 g. of dibutylamine hydrohalide (from excess amine used originally). Upon addition of ethereal hydrogen chloride 2.3 g. (42.5%) of a dark red oil separated which solidified on standing overnight; m. p. 175–195°; two recrystallizations from absolute ethanol–ether gave bright yellow crystals; m. p. 197–200°. A mixture melting point with the amino alcohol dihydrochloride prepared through the bromohydrin (E) showed no depression. The free base was liberated into ether by sodium carbonate; evaporation and trituration of the product with petroleum ether gave a white solid (m. p. 63–65°); a mixture melting point of this and the analytical sample (m. p. 66–68°) prepared through the bromohydrin, was 65–67°.

(b) **Aluminum Isopropoxide Reduction.**—A sample of crude aminomethyl ketone prepared as above (except that the reaction mixture was allowed to stand for six days) was reduced in the usual way with aluminum isopropoxide (five hours). A yield of 14% of the amino alcohol dihydrochloride was isolated and identified by mixture melting point of the base with a sample obtained through the bromohydrin.

Hydramine Fission of α-(Di-*n*-octylaminomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol Dihydrochloride.—Five grams of the amino alcohol dihydrochloride was heated at 165° for ten minutes; the resulting melt solidified, was finely ground, suspended in ether and shaken with 10% sodium carbonate. The resulting ethereal solution was washed with water, dried, and the methyl quinolyl ketone and the di-*n*-octylamine fractionally precipitated with ethereal hydrogen chloride; yield of di-*n*-octylamine hydrochloride, 2.05 g. (87.5%), and of the methyl ketone hydrochloride, 1.73 g. (65.4%). The methyl ketone free base was liberated into ether and isolated as an oil which solidified; recrystallization from ethyl acetate–petroleum ether gave well-defined yellow crystals melting at 98–102°; identified by mixture melting point with an authentic sample (see section V).

The di-*n*-butylamino analog, α-(di-*n*-butylaminomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol dihydrochloride, upon pyrolysis at 215° gave dibutylaminehydrochloride and a small yield of the methyl ketone (very extensive decomposition was involved).

Acknowledgments.—The following assisted in various stages of some of the syntheses: Kent C. Nicodemus, John F. R. Kuck, Jr., George M. Shiflett, J. Samuel Gillespie, Jr., and James F. Hutson. The microanalyses were carried out by Misses Joyce Blume, Geraldine M. Alley, Messrs. Gilbert Ashburn, Curtis S. Floyd and Robert T. Hite. Supplies of some of the amines and other intermediates were furnished by the Columbia University C. M. R. group under Dr. R. C. Elderfield.

Summary

Twenty-eight series of antimalarial drugs of the quinine type have been developed, based on the 2-phenyl-4-quinolyl system. The synthesis of these drugs has involved in the main the following path: the preparation of the appropriate cinchophen, conversion to the acid chloride, diazomethylation, hydrobromination, reduction of the bromomethyl ketone by aluminum isopropoxide to the bromohydrin, and condensation with the appropriate primary or secondary amine. Two series were made through the Claisen condensation of the cinchophen esters with ethyl acetate followed by ketone hydrolysis and bromination to the bromomethyl ketones.

I. Nineteen new substituted cinchophens have been made, seven by the Pfitzinger and twelve by the Doebner–Miller method. In the latter group of reactions one new diketopyrrolidine and five ketopyrrolidineanils were obtained as by-products.

II. Twenty-eight new substituted cinchophen acid chlorides have been made.

III. Of the diazomethyl ketones involved, twenty-one have been isolated and analyzed. The resistance of several of these compounds toward aluminum isopropoxide reduction has been noted and is regarded as evidence favoring the cyclic oxadiazole rather than the linear structure.

IV. New bromomethyl ketones have been made by the hydrobromination of the diazomethyl ketones. Three of these were made also from the cinchophens by the Claisen condensation, hydrolysis and bromination.

V. Nine new methyl 4-quinolyl ketones were made involving preparation by four methods, hydramine fission of the amino alcohol, rearrangement of the bromohydrin, reduction of the bromomethyl ketone and ketone hydrolysis of the cinchophen ester Claisen condensation product.

VI. Two dibromomethyl ketones have been isolated, one by bromination of a diazomethyl ketone, and the other as a by-product in the bromination of a methyl ketone.

VII. Twenty-seven new substituted bromohydrins were made. Explanation of the double melting points shown by many of them was

found to be rearrangement to the methyl ketone which was isolated in a typical case.

VIII. Six typical nuclear substituted 2-phenyl-4-quinolyl ethylene oxides have been isolated.

IX. One hundred and two nuclear substituted α-dialkylaminomethyl-2-phenyl-4-quinoline-methanols have been made. These include representatives carrying the following substituted groups: none, 6-methoxy, 7-methyl, 8-methyl, 8-phenyl, 4′-chloro, 4′-chloro-6-methoxy, 4′-chloro-6,8-dimethyl, 4′-chloro-7-methyl, 4′-chloro-8-methyl, 4′-chloro-8-phenyl, 6-chloro, 7-chloro, 7-chloro-4′-methoxy, 7-chloro-6-methoxy, 7-chloro-8-methyl, 8-chloro, 3′,4′-dichloro, 4′,6-dichloro, 4′,7-dichloro, 4′,7-dichloro-6-methoxy, 4′,7-dichloro-8-methyl, 4′,8-dichloro, 6,8-dichloro, 7-chloro-4′-fluoro, 4′,6,8-trichloro, and 3′,4′,6,8-tetrachloro.

The choice of N-alkyl and N,N-dialkylamino groups as far as possible in each case was made to bring out the highest antimalarial activity of which the series was capable. The dialkylamino groups used were dimethylamino, diethylamino, dipropylamino, dibutylamino, diamylamino, dihexylamino, dioctylamino and didecylamino. The branch chain types included the methyl-isopropylamino, diisobutylamino and diisoamylamino. The morpholinyl and piperidyl type groups were used in a few instances, and the ethyl-ethanolamino group in one case. The secondary amino alcohols involved the groups butylamino, octylamino and dodecylamino.

Many of the salts of the amino alcohols showed double melting points; this was shown to be due to hydramine fission, by the identification of the methyl ketones produced in three cases.

The basis for the assumed mode of the ethylene oxide ring cleavage by the amines is discussed and analogies cited. One typical 2-phenyl-4-quinoline amino alcohol has been synthesized both through the bromohydrin and by the unequivocal path through reduction of the aminomethyl ketone.

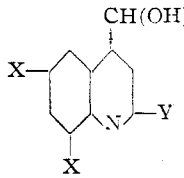
CHARLOTTESVILLE, VA. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

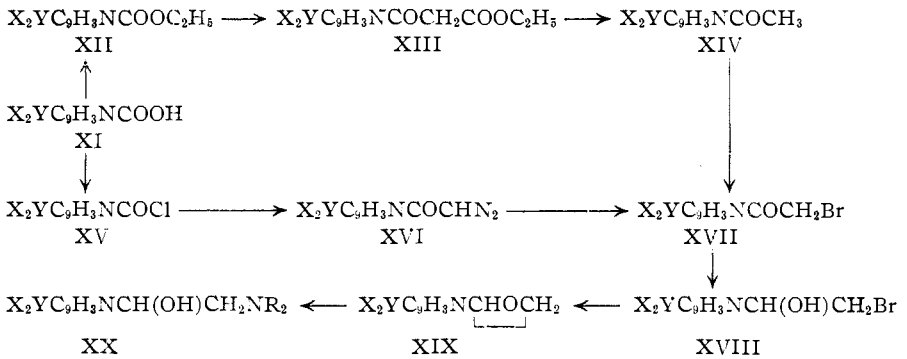
α-Dialkylaminomethyl-4-quinolinemethanols Substituted in the 2-Position[1]

BY S. WINSTEIN, THOMAS L. JACOBS, GUSTAVE B. LINDEN, DEXTER SEYMOUR, EDWARD F. LEVY, BRUCE F. DAY, JOHN H. ROBSON, ROBERT B. HENDERSON AND WARNER H. FLORSHEIM

As possible antimalarials we have prepared a number of ethanolamines I–X which carry the quinoline nucleus substituted in the 2-position.



I. Y = *p*-ClC$_6$H$_4$; R = CH$_2$CH$_2$OH; X = H
II. Y = *p*-ClC$_6$H$_4$; NR$_2$ = NHCH(CH$_3$)CH$_2$CH$_2$CH$_2$NEt$_2$ (novalamino); X = H
III. Y = α-C$_{10}$H$_7$; R = C$_2$H$_5$; X = H
IV. Y = β-C$_{10}$H$_7$; R = C$_2$H$_5$; X = H
V. Y = OC$_2$H$_5$; R = *n*-C$_4$H$_9$; X = H
VI. Y = OH; R = *n*-C$_4$H$_9$; X = H
VII. Y = NH$_2$; R = *n*-C$_4$H$_9$; X = H
VIII. Y = SC$_6$H$_5$; R = C$_2$H$_5$; X = H
IX. Y = *p*-ClC$_6$H$_4$; R = CH$_2$CH$_2$OH; X = Cl
X. Y = 3-C$_5$H$_4$N; R = *n*-C$_4$H$_9$; X = Cl



Several of these give information on the effect of a 2-substituent on antimalarial activity which we were unable to obtain in the α-piperidyl-4-quinolinemethanol series[2] because of synthetic difficulties.

The starting points for the syntheses of I, II, III, IV, V, VII, VIII and X were the parent cinchoninic acids XI or esters XII, which were available from previous work.[2] In the case of IX, the starting cinchoninic acid was prepared essentially by the directions of Buchman, Sargent, Meyers and Howton.[3] In most cases the ethyl ester XII was condensed with ethyl acetate with or without isolation of the ketoester

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

(2a) Brown, Jacobs, Winstein, Kloetzel, Spaeth, Florsheim, Robson, Levy, Bryan, Magnusson, Miller, Ott and Terek, THIS JOURNAL, **68**, in press (1946).

(2b) Winstein, Jacobs, Levy, Seymour, Linden and Henderson, *ibid.*, **68**, in press (1946).

(3) Buchman, Sargent, Meyers and Howton, THIS JOURNAL, **68**, in press (1946).