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.

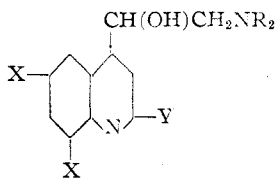
CHARLOTTESVILLE, VA. RECEIVED APRIL 5, 1946

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

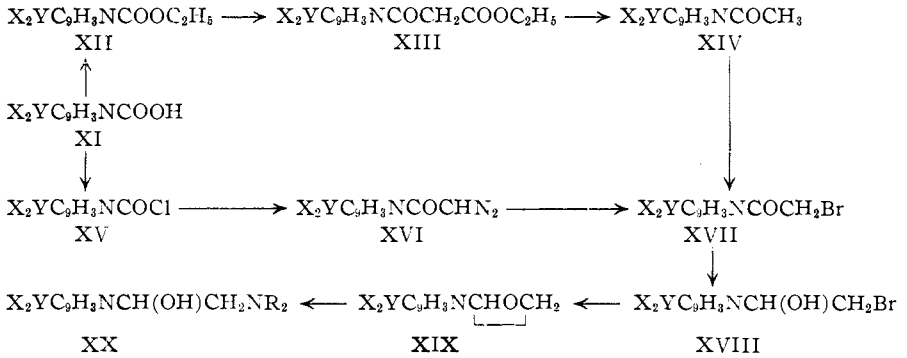
α-Dialkylaminomethyl-4-quinolinemethanols Substituted in the 2-Position[1]

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).

XIII before hydrolysis and decarboxylation to the ketone XIV.

The condensation proceeded well with ethyl 2-ethoxycinchoninate XII (X = H, Y = OC_2H_5), but decarboxylation under the acid conditions normally used was sure to proceed with cleavage of the 2-OC_2H_5 group to a 2-hydroxyl.[2b] It was hoped prior bromination would make decarboxylation enough easier to leave the 2-ethoxyl group uncleaved. Bromination of the ketoester and hydrolysis to the brominated ketoacid was possible. Again, more vigorous treatment with acid to effect decarboxylation cleaved the ethoxyl group to yield 2-hydroxy-4-bromoacetoquinoline XVII (X = H, Y = OH). However, the synthesis of the desired bromoketone XVII (X = H, Y = 2-OC_2H_5) proceeded in 73% yield from the acid by way of the diazoketone XVI (X = H, Y = 2-OC_2H_5).

The 2-phenylthio series of compounds was somewhat difficult. The yield of ketone XIV (X = H, Y = SC_6H_5) from the condensation of ethyl acetate with the ethyl cinchoninate XII (X = H, Y = SC_6H_5) was rather low and erratic. At least part of the difficulty was due to replacement of the phenylthio group by ethoxyl since 2-ethoxycinchoninic acid was obtained in working up the reaction mixture. This may have been produced by nucleophilic displacement[2b] of phenylmercaptide ion by ethylate ion in the ketoester XIII (X = H, Y = SC_6H_5) followed by reversal of the condensation to yield 2-ethoxycinchoninic ester which was later saponified. The yield of 2-phenylthio-4-chloroacetoquinoline by way of the diazoketone XVI (X = H, Y = SC_6H_5) was also not high.

Except for the use of bromine on the 2-phenylthio ketone XIV (X = H, Y = SC_6H_5), bromination of the ketones XIV to the bromoketones XVII in nearly quantitative yield was carried out elegantly by treatment of the ketones with sodium bromate and hydrobromic acid. In one case a perbromide was isolated and then warmed to complete the halogenation. With the 2-aminoketone XIV (X = H, Y = NH_2), it proved best to acetylate the amine group before bromination.

Reduction of the bromoketones XVII and conversion to the oxides made available the interestingly substituted ethylene bromohydrins XVIII and oxides XIX. These conversions were accomplished by the methods we developed for analogous naphthalene derivatives.[3,5] Reduction with aluminum isopropoxide was carried out in yields of 78–98%. In one case where the bromoketone hydrobromide was very insoluble it was necessary to add triethylamine to free the bromoketone. In the conversion to oxide the yields were 72–99%. It was usually simpler to purify the oxides XIX rather than the bromohydrins XVIII.

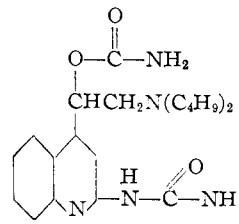
(4) Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946).

(5) Winstein, Jacobs, Henderson, Robson and Day, *ibid.*, **11**, 157 (1946).

The opening of the oxides XIX with amine to yield the desired antimalarials XX proceeded as in the case of the naphthylethylene oxides[5] in yields of 56–83%. For solubility reasons it was sometimes necessary to use a large excess of the amine as a solvent. To produce VII, it was necessary to remove the protecting acetyl group by hydrolysis in working up the reaction mixture. Compound VI was obtained on treatment of V with acid, the ethoxy group being cleaved.[2b]

In opening the oxides XIX, we did not encounter mixtures corresponding to the opening of the oxides in the two possible ways. The structure XX is assigned to the products on the basis of analogy with other arylethylene oxides.[5] However, the quinoline nucleus is enough different electronically from the other aryl nuclei to make this analogy somewhat questionable. Lutz and co-workers,[6] who have prepared aminoalcohols XX similar to ours, report experiments on this question.

The amino group in the aminoalcohol VII (Y = NH_2) was converted in poor yield to an ureido group by treatment with nitrourea by the method of Davis and Blanchard.[7] At the same time the hydroxyl group reacted so that there was obtained 2-ureido aminoalcohol carbamate XXI.



XXI

Three additional ketones XIV were prepared with Y = $N(C_4H_9)_2$, X = H; Y = $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ (novalamino), X = H; and Y = 4-C_5H_4N, X = Cl, but were not carried on to final aminoalcohols.

Table I summarizes the new compounds prepared in the course of this work.

Experimental

Condensation of Cinchoninic Esters with Ethyl Acetate and Preparation of Ketones.—The condensation[8] was carried out by refluxing for the specified time a mixture of the stated amount of cinchoninic ester,[2] two molecular proportions of ethyl acetate and one and one-half molecular proportions of sodium ethoxide in benzene (30 ml. for 0.1 mole of cinchoninic ester unless otherwise specified). The individual preparations are described below.

2-*p*-Chlorophenyl-4-acetoquinoline. The reaction mixture (0.20 mole, sixteen hours) was poured into 580 ml. of 5% sodium hydroxide and ice to precipitate the sodium salt[9] of the ketoester. This salt was warmed with 300 ml. of gl. acetic acid, the resulting solution being poured into 1.2 liters of ice and water. The precipitated ketoester, m. p. 97–99°, weighed 53.5 g. (76%) after recrystallization from ethanol. Two additional recrystallizations gave the analytical material, m. p. 99.8–100.3°.

(6) Lutz, THIS JOURNAL, *et al.*, **68**, in press (1946).

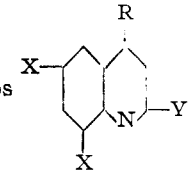
(7) Davis and Blanchard, *ibid.*, **51**, 1794 (1929).

(8) Koelsch, *J. Org. Chem.*, **10**, 34 (1945).

(9) See Gilman, *et al.*, THIS JOURNAL, **68**, in press (1946).

TABLE I

SUMMARY OF COMPOUNDS



SN	Y[a]	R	M. p., °C. (cor.)	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	p-ClC$_6$H$_4$	—COCH$_2$COOC$_2$H$_5$	99.8-100.3	C$_{20}$H$_{18}$NO$_3$Cl	67.89	67.70	4.56	4.51
	p-ClC$_6$H$_4$	—COCH$_3$	102-103	C$_{17}$H$_{12}$NOCl	72.47	72.60	4.30	4.35
	p-ClC$_6$H$_4$	—CH(O)CH$_2$	70.5-71.5	C$_{17}$H$_{12}$NOCl	72.47	72.37	4.30	4.25
14332	*p*-ClC$_6$H$_4$	—CH(OH)CH$_2$N(CH$_2$CH$_2$OH)$_2$·2-HCl·2H$_2$O	170-172	C$_{21}$H$_{29}$N$_2$O$_5$Cl$_3$	50.87	51.05	5.89	5.69
13723	*p*-ClC$_6$H$_4$	—CH(OH)CH$_2$NHCH(CH$_3$)(CH$_2$)$_3$[b] N(C$_2$H$_5$)$_2$C$_{23}$H$_{16}$O$_6$·2H$_2$O	180-190 dec.	C$_{49}$H$_{54}$O$_9$N$_3$Cl	68.08	67.92	6.30	6.51
	α-C$_{10}$H$_7$	—COCH$_3$	106-108	C$_{21}$H$_{15}$ON	84.82	85.15	5.09	5.11
	α-C$_{10}$H$_7$	—CH(O)CH$_2$	120-121	C$_{21}$H$_{15}$ON	84.82	84.97	5.09	5.40
	α-C$_{10}$H$_7$	—CH(OH)CH$_2$N(C$_2$H$_5$)$_2$	93-94	C$_{25}$H$_{26}$ON$_2$	81.04	80.85	7.07	7.25
	α-C$_{10}$H$_7$	—CH(OH)CH$_2$N(C$_2$H$_5$)$_2$·H$_3$PO$_4$·H$_2$O	183-186	C$_{25}$H$_{31}$O$_5$N$_2$P	61.71	61.79	6.42	6.20
	β-C$_{10}$H$_7$	—COCH$_2$COOC$_2$H$_5$	91-93	C$_{24}$H$_{19}$NO$_3$	78.03	78.19	5.18	5.11
	β-C$_{10}$H$_7$	—COCH$_3$	97-98	C$_{21}$H$_{15}$NO	84.82	85.07	5.09	5.15
	β-C$_{10}$H$_7$	—CH(OH)CH$_2$N(C$_2$H$_5$)$_2$·H$_3$PO$_4$·H$_2$O	190-194	C$_{25}$H$_{31}$O$_5$N$_2$P	61.71	61.93	6.42	
	—OC$_2$H$_5$	—COCH$_2$COOC$_2$H$_5$	56-57[c]	C$_{16}$H$_{17}$NO$_4$	66.88	67.00	5.97	5.96
	—OC$_2$H$_5$	—COCHBrCO$_2$H	161-162[c]	C$_{14}$H$_{12}$NO$_4$Br	49.72	49.98	3.58	3.63
	—OC$_2$H$_5$	—COCH$_2$Br	100-101.5[c]	C$_{13}$H$_{12}$NO$_2$Br	53.08	53.20	4.11	4.29
	—OC$_2$H$_5$	—CH(OH)CH$_2$Br	114.5-115.5[c]	C$_{13}$H$_{14}$NO$_2$Br	52.71	53.03	4.76	4.77
13783	—OC$_2$H$_5$	—CH(OH)CH$_2$N(C$_4$H$_9$)$_2$	40-42[c]	C$_{21}$H$_{32}$N$_2$O$_2$	73.21	73.20	9.36	9.38
	—OH	—COCH$_2$Br	190-192[c]	C$_{11}$H$_9$NO$_2$Br	49.65	49.67	3.03	2.86
	—OH	—CH(OH)CH$_2$N(C$_4$H$_9$)$_2$	133.5-134.5[c]	C$_{19}$H$_{28}$N$_2$O$_2$	72.11	72.22	8.92	8.95
	—NH$_2$	—COCH$_3$	194-195	C$_{11}$H$_{10}$N$_2$O	70.95	71.18	5.41	5.46
	—NHCOCH$_3$	—COCH$_3$	207.5-212.5	C$_{13}$H$_{12}$N$_2$O$_2$	68.40	68.32	5.30	5.26
	—NHCOCH$_3$	—COCH$_2$Br	146.5-149.5	C$_{13}$H$_{11}$N$_2$O$_2$Br	50.83	50.64	3.61	3.68
	—NHCOCH$_3$	—CH(O)CH$_2$	202-203	C$_{13}$H$_{12}$N$_2$O$_2$	68.40	68.07	5.30	5.31
13716	—NH$_2$	—CHOHCH$_2$N(C$_4$H$_9$)$_2$	84.2-85.0	C$_{19}$H$_{29}$ON$_3$	72.34	72.39	9.27	9.50
13803	—NHCONH$_2$	—CH(OCONH$_2$)CH$_2$N(C$_4$H$_9$)$_2$·H$_2$O	165-166	C$_{21}$H$_{33}$N$_5$O$_4$	60.12[d]	59.84	7.93	7.99
	—N(C$_4$H$_9$)$_2$ CH$_3$	—COCH$_3$	Oil[e]	C$_{19}$H$_{26}$N$_2$O	76.47	76.27	8.78	8.81
	—NHCH(CH$_2$)$_3$— N(C$_2$H$_5$)$_2$	—COCH$_3$·C$_{23}$H$_{16}$O$_6$[b]·H$_2$O	153-166 dec.	C$_{43}$H$_{47}$N$_3$O$_8$	70.37	70.00	6.46	6.62
	—N(COCH$_3$)CH(CH$_3$)— (CH$_2$)$_3$N(C$_2$H$_5$)$_2$	—COCH$_3$·C$_{23}$H$_{16}$O$_6$[b]·H$_2$O	120-160 dec.	C$_{45}$H$_{49}$N$_3$O$_9$	69.66	70.05	6.37	6.44
	—SC$_6$H$_5$	—COCH$_3$	82-83	C$_{17}$H$_{13}$NOS	73.09	72.86	4.69	4.69
	—SC$_6$H$_5$	—COCH$_2$Cl	131-133	C$_{17}$H$_{12}$ONSCl	65.06	64.76	3.86	4.01
	—SC$_6$H$_5$	—COCH$_2$Br	132-134	C$_{17}$H$_{12}$ONSBr	57.00	57.07	3.38	3.41
	—SC$_6$H$_5$	—CHOHCH$_2$Cl	144-146	C$_{17}$H$_{14}$ONSCl	64.65	65.16	4.47	4.67
	—SC$_6$H$_5$	—CHOHCH$_2$Br	135-146	C$_{17}$H$_{14}$ONSBr	56.67	56.51	3.92	3.99
	—SC$_6$H$_5$	—CHOHCH$_2$N(C$_2$H$_5$)$_2$·2HCl	200-204 dec.	C$_{21}$H$_{26}$ON$_2$SCl$_2$	59.29	59.03	6.16	6.19
	p-ClC$_6$H$_4$[a]	—COCH$_3$	179-181	C$_{17}$H$_{10}$NOCl$_3$	58.23	58.33	2.88	3.21
	p-ClC$_6$H$_4$[a]	—COCH$_2$Br	181-190	C$_{17}$H$_9$NOCl$_3$Br	47.53	47.58	2.11	2.29
	p-ClC$_6$H$_4$[a]	—CH(O)CH$_2$	191-193	C$_{17}$H$_{10}$NOCl$_3$	58.23	58.36	2.88	3.11
13724	*p*-ClC$_6$H$_4$[a]	—CH(OH)CH$_2$N(CH$_2$CH$_2$OH)$_2$	164-166	C$_{21}$H$_{21}$N$_2$O$_3$Cl$_3$	55.34	55.28	4.65	4.84
	3-C$_5$H$_4$N[a]	—COCH$_3$	189-190	C$_{16}$H$_{10}$N$_2$OCl$_2$	60.59	60.95	3.17	3.37
	3-C$_5$H$_4$N[a]	—COCH$_2$Br[f]		C$_{16}$H$_{10}$N$_2$OCl$_2$Br$_2$	40.28	40.26	2.11	2.13
14129	3-C$_5$H$_4$N[a]	—CHOHCH$_2$N(C$_4$H$_9$)$_2$	157-159	C$_{24}$H$_{29}$N$_3$OCl$_2$	64.57	64.83	6.55	6.61
	4-C$_5$H$_4$N[a]	—COCH$_3$	**202-204**	**C$_{16}$H$_{12}$N$_2$OCl$_2$**	**60.59**	**60.24**	**3.17**	**3.12**

[a] X = H except cases marked "a" where X = Cl. [b] Salt of methylene-bis-(2-hydroxy-3-naphthoic) acid. [c] Uncorrected. Unless specified, all melting points are corrected. [d] Calcd.: N, 16.70; found: N, 16.99. Nitrogen analysis performed through courtesy of Dr. Byron Riegel at Northwestern University. Carbon–hydrogen analyses by Bruce Day and Richard Nevé at University of California, Los Angeles. [e] Boiling point, 191–193° (1 mm.). [f] Hydrobromide.

A mixture of 18.8 g. (0.053 mole) of the above ketoester, 60 ml. of water, and 30 ml. of concd. sulfuric acid was warmed on the steam-bath until evolution of carbon dioxide ceased and then poured into 600 ml. of ice and water. After neutralization of the acid with potassium carbonate, the crude ketone was collected, dried and recrystallized from ethanol to give 10.8 g. (0.0384 mole, 72%) of product, m. p. 95–100°. Two more recrystallizations yielded an analytical sample, m. p. 102–103°.

When the ketoester was not isolated, the over-all yield of ketone from cinchoninic ester was 61%.

2-α-Naphthyl-4-acetoquinoline.—To the reaction mixture (0.209 mole, twenty-four hours) was added 100 g. of ice and slowly with stirring a cold solution of 70 ml. of concd. sulfuric acid in 100 ml. of water. The mixture was carefully brought to a boil, and after the benzene was distilled off, refluxed two hours. Then it was carefully made basic with 170 ml. of concd. ammonium hydroxide and

allowed to cool with stirring. A brown oil formed which solidified. Crystallization from methanol yielded 54 g. (87%) of ketone, m. p. 106–108°.

2-β-Naphthyl-4-acetoquinoline.—The reaction mixture (0.100 mole, forty-eight hours) was poured into 200 g. of ice and 80 ml. of glacial or acetic acid. Filtration yielded 29.5 g. of ketoester, m. p. 90–93°, and ether extraction yielded 3.6 g. more, m. p. 80–96°, to make the crude yield 90%. Recrystallization gave rise to analytical material, m. p. 91–93°.

Decomposition of 11.0 g. (0.030 mole) of the above ketoester as for the 2-*p*-chlorophenyl-4-acetoquinoline and addition of the equivalent amount of ammonium hydroxide to the cool reaction mixture gave rise to the ketone which was taken up in 500 ml. of ether. Evaporation of the ether and crystallization of the residue from methanol gave rise to 8.45 g. (95%) of ketone, m. p. 95–96°. Recrystallization gave rise to an analytical sample, m. p. 97–98°.

2-Ethoxycinchoninylactic Ester.—The reaction mixture from the 2-ethoxycinchoninic ester (0.20 mole, 17.5 hours) yielded, as in the 2-*p*-chlorophenyl-4-acetoquinoline case, the solid sodium salt of the ketoester which was suspended in water acidified with acetic acid. An oil formed which solidified on standing to yield 46.8 g. (81.5%) of crude ketoester. Recrystallization from aqueous ethanol yielded 42.7 g. (74%) of ketoester, m. p. 55–57°. Two more recrystallizations yielded analytical material, m. p. 56–57° (uncor.).

2-Amino-4-acetoquinoline.—In this case the cooled reaction mixture (0.300 mole, 26.5 hours, volume of benzene twice usual, proportion of sodium ethoxide 30% greater than usual) was decomposed as for the 2-α-naphthyl-4-acetoquinoline (96 ml. concd. sulfuric acid, 168 ml. water, four hours). The homogeneous reaction mixture was cooled by the addition of ice and, with stirring and cooling, it was made alkaline by the addition of concd. sodium hydroxide solution. There was obtained 17.2 g. (30.8%) of crude 2-amino-4-acetoquinoline, m. p. 179.0–186.5°. Two recrystallizations from methanol yielded bright yellow prisms, m. p. 194.0–195.0°. Acidification of the aqueous filtrate gave a 69% recovery of 2-aminocinchoninic acid.[2b]

2-Dibutylamino-4-acetoquinoline.—The reaction mixture (0.10 mole, seventeen hours) was treated as in the above case (40 ml. concd. sulfuric acid, 55 ml. water, three hours) to yield after addition of the sodium hydroxide solution, an oily product which was taken up in chloroform. The chloroform solution was washed well with water and distilled at reduced pressure. There was obtained a 48% yield of yellow ketone, b. p. 191–193° (1 mm.), $n^{23}D$ 1.5847.

The oxime, crystallized from aqueous methanol, m. p. 108.5–111.2°.

Anal. Calcd. for $C_{19}H_{27}ON_3$: C, 72.80; H, 8.68. Found: C, 72.89; H, 8.75.

2-Phenylthio-4-acetoquinoline.—The reaction mixture (0.43 mole, sixteen hours) was poured into a solution of 100 g. of sodium hydroxide in 1500 ml. of ice water. The organic material was taken up in ether and the extracts were washed with water and dried over magnesium sulfate. Evaporation of solvent left an oil which was decomposed as in the above case (65 ml. concd. sulfuric acid, 195 ml. water). After the mixture was made alkaline with concd. sodium hydroxide, it was refluxed thirty minutes to saponify any esters, then cooled and extracted with ether.

The aqueous solution was acidified after decolorization to yield 29.5 g. of acidic material, m. p. 50–120°. Recrystallization from toluene gave only one pure acid, m. p. and mixed m. p. with authentic 2-ethoxycinchoninic acid,[2b,10] 144–146°.

From the ether extracts was obtained a red oil which turned partly crystalline on standing overnight. Trituration with 50 ml. of hexane yielded 23 g. of crystals, m. p. 78–80.5°. On cooling, the hexane solution yielded 24.4 g. more solid, m. p. 75–79°, for a total of 47.5 g. (40%) of crude ketone. Recrystallization from hexane yielded pure ketone, m. p. 82.0–82.7°.

(10) Koenigs and Körner, *Ber.*, **16**, 2152 (1883).

2-*p*-Chlorophenyl-6,8-dichloro-4-acetoquinoline.—The reaction mixture (0.150 mole, nineteen hours, volume of benzene twice usual) was treated with a solution of 50 ml. of concd. sulfuric acid in 85 ml. of water, 170 ml. of solvent being distilled off. To the resulting mixture was added 400 ml. of dioxane. Then it was refluxed four hours. The mixture was next poured with stirring into 400 ml. of iced 3 *N* sodium hydroxide solution. The solid crude ketone was crystallized from ethyl acetate to yield 21.9 g. (41.7%) of material, m. p. 178.5–180.5°. Recrystallization from dilute acetone gave an analytical sample, m. p. 179.2–181.0°.

2-(3-Pyridyl)-6,8-dichloro-4-acetoquinoline.—In this case (twenty-four hours, volume of benzene three times usual) the cooled reaction mixture from 100 g. of ethyl cinchoninate was poured into excess 5% sodium hydroxide to yield a solid which was heated to 95° for forty minutes with a mixture of 180 ml. concd. sulfuric acid and 270 ml. water. The precipitated solid was stirred with dilute ammonia and recrystallized twice from butyl alcohol to give material, m. p. 189–190°, in 41% yield.

2-Novalamino-4-acetoquinoline.—To the reaction mixture (0.05 mole, eighteen hours, volume of benzene three times usual) was added 40 ml. of 12 *N* sulfuric acid, benzene was distilled off, and the remainder was refluxed for four hours. The mixture was poured onto ice and neutralized with sodium carbonate to yield an oil which was taken up in benzene. The benzene layer was dried and concentrated to 12.0 g. (75%) of crude ketone. A sample of the ketone (1.05 g., 0.0032 mole) was dissolved in 100.0 ml. of 0.0907 *N* sulfuric acid and precipitated by addition of a solution of 1.24 g. (0.0032 mole) of methylene bis-(2-hydroxy-3-naphthoic acid) in 47.24 ml. of 0.192 *N* sodium hydroxide. After drying, the product weighed 2.07 g. (90%). Regeneration of the ketone and reprecipitation yielded 1.67 g., m. p. 153–166°, apparently a monohydrate.

2-(4-Pyridyl)-6,8-dichloro-4-acetoquinoline.—In this case, the yield was quite low in preliminary work.

2-Acetamido-4-acetoquinoline.—A mixture of 46.0 g. (0.247 mole) of crude 2-amino-4-acetoquinoline and 325 ml. of acetic anhydride was refluxed for five hours and then treated with ice cold water containing a little sulfuric acid. The mixture was made alkaline with cold concentrated ammonium hydroxide, and the product was collected by filtration, washed well with water and air dried. Recrystallization from ethyl acetate with use of Nuchar yielded 41.7 g. (74%) of material, m. p. 206–212°. One more crystallization from ethyl acetate yielded an analytical sample, m. p. 207.5–212.5°.[11]

2-(N-Acetylnovalamino)-4-acetoquinoline.—The ketone (9.0 g.) was refluxed five hours with 200 ml. of acetic anhydride and then the reaction mixture was poured onto ice and left a day. Neutralization with concd. sodium hydroxide and extraction with ether gave rise to 8.36 g. (83%) of an oil after drying of the ether extract and evaporation of the solvent. The oil gave a solid salt with methylene-bis-(2-hydroxy-3-naphthoic acid).

2-Ethoxycinchoninylbromoacetic Acid.—A solution of 3.20 g. (0.02 mole) of bromine in 20 ml. of chloroform was added at room temperature to a solution of 5.75 g. (0.02 mole) of ethyl 2-ethoxycinchoninylacetate in 25 ml. of chloroform. The solvent was evaporated on the steam-bath. Then the residual oil was stirred with 50 ml. of 10% hydrobromic acid on the steam-bath for fifteen minutes. The oil solidified to yield 6.68 g. (98.5%) of a yellow solid soluble in warm sodium bicarbonate solution. A small sample, after two recrystallizations from acetone–Skellysolve B softened at 155° and had m. p. 161–162° (uncor.).

2-Hydroxy-4-bromoacetoquinoline.—A 1.00-g. sample of 2-ethoxycinchoninylbromoacetic acid was refluxed ten minutes with 50 ml. of 48% hydrobromic acid. The reaction mixture was poured into ice and water, 0.73 g. of

(11) The wide melting range of this compound which persists even in the analytical sample possibly indicates a tautomerism at elevated temperatures. For a similar problem, see Woodward and Doering, THIS JOURNAL, **67**, 680 (1945).

material, m. p. 167–181°, being obtained. Two recrystallizations from acetone–Skellysolve F gave material, m. p. 190–192° (uncor.).

Other attempts at decarboxylation without cleavage of the 2-ethoxyl group using a high-boiling solvent without mineral acid or using various concentrations of hydrochloric acid led to difficult reaction mixtures.

2-Ethoxy-4-bromoacetoquinoline.—To the well-stirred ethereal diazomethane solution[12] prepared from 52 g. (0.50 mole) of N-nitroso-N-methylurea, cooled to −5° in an ice–salt-bath, was added in one hour 23.1 g. of powdered, crude acid chloride, m. p. 78–85°, prepared from 21.7 g. (0.10 mole) of acid.[13] The suspension was allowed to stir overnight as the ice-bath melted and came to room temperature. To the chilled suspension of diazoketone in ether was added 100 ml. of ethereal hydrogen bromide solution prepared from equal volumes of ether and 48% hydrobromic acid. After four hours of stirring, the ether was decanted and discarded. Residual ether was removed in a stream of air, then 200 ml. of water was added and the suspension was stirred briefly. The crude bromoketone was washed with water and dried *in vacuo* to yield 21.5 g. (73% based on 2-ethoxycinchoninic acid) of a yellow powder, m. p. 95–99°, m. p. 100.0–100.5° (uncor.) after two recrystallizations from acetic acid–water.

2-Phenylthio-4-chloroacetoquinoline.—2-Phenylthiocinchoninic acid was treated with excess thionyl chloride. After removal of thionyl chloride with the aid of benzene, finally at reduced pressure, the oil was taken up in ether, a small amount of solid being filtered off. The ether solution of 0.044 mole of the acid chloride was added to a cooled, stirred solution of diazomethane prepared from 50 g. of N-nitrosomethylurea. Stirring was continued for eighteen hours, during which time the ice-bath was allowed to come to room temperature. After cooling to 0°, an excess of ethereal hydrogen chloride was added and stirring continued for one hour with the cooling bath removed. Filtration gave 15.0 g. of a deep red hydrochloride. By dissolving in boiling ethanol, cooling and adding water, 5.8 g. (40%) of the chloroketone free amine was obtained, m. p. 130–132°. This compound is quite unstable. Warming above 50° causes decomposition, and recrystallization is attended by large losses.

2-*p*-Chlorophenyl-4-bromoacetoquinoline Hydrobromide.—To the vigorously stirred mixture of 10.95 g. (0.0389 mole) of 2-*p*-chlorophenyl-4-acetoquinoline, 1.96 g. (0.0130 mole) of sodium bromate, and 30 ml. of glacial acetic acid was added dropwise, 26.4 g. (0.156 mole) of 48% hydrobromic acid. The temperature was slowly raised with continuous stirring. When 75° was reached, the brick-red color began to change to a canary yellow and the temperature began to climb more rapidly. The heater was switched off and heating was soon resumed briefly to bring the temperature of the reaction mixture to 100°. The reaction mixture was poured into 500 ml. of ice and water and the precipitate was collected. After drying to constant weight, 16.36 g. (0.0371 mole, 95.3%) remained. The bromoketone salt which decomposed without melting above 250°, was used directly in the reduction step.

2-α-Naphthyl-4-bromoacetoquinoline Hydrobromide.—Bromination of 2-α-naphthyl-4-acetoquinoline was accomplished similarly except that the sodium bromate (0.0109 mole in 25 ml. of water) was added to the mixture of the other components (0.0328 mole of ketone, 40 ml. of 48% hydrobromic acid, 30 ml. of gl. acetic acid). There was obtained 14.9 g. (99%) of material with equivalent weight by Volhard titration, 428, calculated being 457.

2-β-Naphthyl-4-bromoacetoquinoline Hydrobromide.—Bromination as in the above case (0.040 mole of sodium bromate in 30 ml. of water, 0.122 mole of ketone, 100 ml. of gl. acetic acid, 80 ml. of 48% hydrobromic acid) gave 53.9 g. (96%) of material, m. p. 184–185°.

2-Acetamido-4-bromoacetoquinoline.—Sodium bromate (0.061 mole in 55 ml. of water) was added, as in the above cases, at 15–20° to ketone (0.183 mole, 380 ml. of 24% hydrobromic acid). The mixture was stirred for one hour. The orange product, collected by filtration, washed three times with water and dried *in vacuo* over calcium chloride, weighed 76.5 g. (89% based on ketone·HBr_3).

The orange perbromide was added to 300 ml. of anhydrous benzene and the mixture was refluxed with stirring a half hour. Hydrogen bromide was copiously evolved while the orange solid changed to a heavy liquid and then to a light yellow bromoketone hydrobromide which was collected on a filter, washed with hexane and air dried. The equivalent weight of this crude material (Volhard) was: calcd. for $C_{13}H_{12}O_2N_2Br_2$: 388; found, 385.

This material was then dissolved by warming in 280 ml. of 50% ethanol and saturated sodium bicarbonate solution was added cautiously in excess. The mixture was diluted with 130 ml. of water and cooled a half hour in an ice-bath. The cream colored product was collected by filtration, washed well with water and dried over sulfuric acid *in vacuo*. There was obtained 47.0 g. (94% based on the perbromide) of bromoketone, m. p. 143.5–146.5°. After recrystallization from benzene–hexane there was recovered 88% of pure material melting at 146.5–149.5°.

2-Phenylthio-4-bromoacetoquinoline.—To a stirred solution of 5.0 g. (0.018 mole) of 2-phenylthio-4-acetoquinoline in 30 ml. of gl. acetic acid warmed to 60° was added dropwise a solution of 2.9 g. (0.018 mole) of bromine in 5 ml. of gl. acetic acid over a ten-minute period. The temperature was raised to boiling, and the hot solution was washed with 10 ml. of glacial acetic acid into an Erlenmeyer flask. Bromoketone hydrobromide which crystallized on cooling was filtered, dried, dissolved in boiling 95% ethanol and caused to crystallize as the free amine by adding water and cooling. Filtration and drying gave 4.0 g. (63%) of bromoketone, m. p. 132–134°. The free amine can be satisfactorily recrystallized by dissolving in cold benzene and adding several volumes of hexane.

2-*p*-Chlorophenyl-4-bromoaceto-6,8-dichloroquinoline.—Bromination as in the case of the 2-α-naphthyl-4-acetoquinoline (0.0622 mole of ketone, 100 ml. of glacial acetic acid, 100 ml. of 48% hydrobromic acid, 0.0208 mole of sodium bromate in 25 ml. of water) gave 26.2 g. (98%) of material, m. p. 171–181°. Three recrystallizations from ethyl acetate gave an analytical sample, m. p. 181.5–190.0°.

6,8-Dichloro-2-(3-pyridyl)-4-bromoacetoquinoline Hydrobromide.—Bromination was carried out as in the case of 2-α-naphthyl-4-acetoquinoline (0.0347 mole of ketone, 280 ml. of glacial acetic acid, 55 ml. of 48% hydrobromic acid, 0.0128 mole of sodium bromate in 20 ml. of water). The reaction mixture was cooled to room temperature in an ice-bath and stirred for one hour longer. The product was collected by filtration, washed well with acetic acid, then with water and dried over calcium chloride *in vacuo*. This yielded 15.5 g. (94%) of light yellow crystals which had no definite melting or decomposition point. An analytical sample was prepared by rubbing a small portion with water several times, the bromoketone hydrobromide being collected by centrifuging. This was dried over phosphorus pentoxide.

Preparation of Halohydrins.[4]—Reduction of the bromoketones or their hydrobromides was achieved using 5 moles of aluminum isopropoxide and 4–10 liters of isopropanol per mole of ketone and a reaction time of eight to ten minutes.

The reaction mixture from reduction of 2-*p*-chlorophenyl-4-bromoacetoquinoline hydrobromide (0.177 mole) was poured into ice and excess hydrochloric acid. Stirring gave 65.9 g. (93%) of crystalline bromohydrin hydrochloride with a neutralization equivalent weight of 194 (calculated 200).

Similarly, the yield of crude bromohydrin hydrochloride was 97% from 2-α-naphthyl-4-bromoacetoquinoline hydrobromide and 83% from the β-naphthyl analog.

Treated as in the above cases, 6,8-dichloro-2-*p*-chlorophenyl-4-bromoacetoquinoline gave directly the free bromohydrin, m. p. 139° (dec.) in 98.5% yield.

(12) Buchman and Struve, "Organic Reactions," Vol. I, Chap. 2, p. 50.

(13) Gardner and Hammel, THIS JOURNAL, **58**, 1360 (1936).

The reaction mixture from 2-ethoxy-4-bromoacetoquinoline was diluted with ice and the requisite amount of hydrochloric acid and extracted with ether. Evaporation of the ether gave rise to bromohydrin which crystallized on dilution of the residue with water. The yield of material, m. p. 114–115° was 79%. An analytical sample, m. p. 114.5-115.5° (uncor.), was obtained by three recrystallizations from aqueous isopropanol.

The reaction mixture from 0.014 mole of 2-phenylthio-4-bromoacetoquinoline was cooled in an ice-bath and poured onto 600 g. of ice and 50 ml. of concd. hydrochloric acid. This solution was diluted with 1200 ml. of water and extracted with three 200-ml. portions of ether. The collected ether phases were treated with ethereal hydrogen chloride to give 4.5 g. (81.5%) of a yellow hydrochloride, m. p. 182–185° (dec.). The free bromohydrin was prepared by dissolving the salt in 95% ethanol and adding water dropwise with constant swirling, until all the material was precipitated. Two recrystallizations of this product from an ether–hexane mixture gave white crystals, m. p. 135–146°.

The analogous reduction of 2-phenylthio-4-chloroacetoquinoline, possibly carried too far (fifteen minutes), gave rise to 4.5 g. of crude material from 0.015 mole of chloroketone. Repeated recrystallization from ethanol gave 1.0 g. of white product, m. p. 144–146°.

For the reduction of 6,8-dichloro-2-(3-pyridyl)-4-bromoacetoquinoline hydrobromide (0.200 mole) the apparatus was flushed with nitrogen and 0.205 mole of triethylamine was added just before addition of the hot aluminum isopropoxide solution. The mixture was cooled in ice, filtered, and the filtrate was added to 10 liters of ice and 600 ml. of 48% hydrobromic acid. After two hours, the product was collected by filtration, washed well with water and air dried. The yield was 74 g. (78%, assuming the product to be a hydrobromide) of material which could not be recrystallized and had no definite m. p. or decomposition point.

2-Acetamido-4-quinolyl Ethylene Oxide.—The cooled reaction mixture from reduction of 2-acetamido-4-bromoacetoquinoline (0.0342 mole bromoketone, fifteen minutes) was poured into a flask containing 650 g. of ice and 93 ml. (0.558 mole) of 6 *N* sodium hydroxide solution. The mixture was swirled well and then left in an ice-bath with occasional swirling for one hour. The suspended flocculent product was collected, washed well with water, and dried *in vacuo* over potassium hydroxide. This gave 4.70 g. of colorless oxide, m. p. 201.5–202.0°. The filtrate and washings were extracted with ether and the ether was evaporated at reduced pressure to give 2.38 g. of lightly colored oxide, m. p. 199.8–200.2°, for a total of 7.08 g. (90.8%). A small sample was crystallized for analysis from aqueous methanol: colorless plates, m. p. 202.0–203.0°.[14]

Preparation of Other Oxides.[5]—The bromohydrin or bromohydrin hydrochloride was dissolved or suspended in alcohol (3–7 liters per mole) and treated with approximately twice the theoretical amount of 6 *N* sodium hydroxide. The reaction mixture was shaken ten minutes with the 2-naphthyl derivatives, fifteen minutes with the 2-phenylthio compound, thirty minutes with the 2-ethoxy and 2-*p*-chlorophenyl compounds and one hour with the 6,8-dichloro-2-*p*-chlorophenyl compound. The reaction mixture was then diluted strongly with water and the oxide taken up in ether. After being washed with water, the ether extract was dried over magnesium sulfate or potassium carbonate. Removal of ether with the aid of a bath kept below 50°, finally under vacuum, left the residual oxide.

In the case of the 2-*p*-chlorophenyl compound, the yield of oil was 86%. Recrystallization from Skellysolve B gave a poor recovery of pure oxide, m. p. 70.5–71.5°.

The 2-α-naphthyl compound was directly crystalline, the yield of material, m. p. 115–118°, being 79%. Pure material, m. p. 120–121°, was obtained by recrystallization from hexane.

In the case of the 2-β-naphthyl compound the product was obtained as a red oil in 72% yield.

The yield of material which solidified on standing in the case of the 2-ethoxy compound was 92.8%, m. p. 55–59°.

The 2-phenylthio oxide was prepared in only small amounts as an oil and used directly for reaction with diethylamine.

With the 6,8-dichloro-2-*p*-chlorophenyl compound, the crude yield of material, m. p. 175–186°, was 99%. Recrystallization with considerable loss from acetone–hexane gave pure material, m. p. 191–193°.

α-Di-*n*-butylaminomethyl-6,8-dichloro-2-(3-pyridyl)-4-quinolinemethanol.—A mixture of 21.5 g. of the bromohydrin hydrobromide and 440 ml. of di-*n*-butylamine was heated at 85–100° for three days with occasional swirling. The deep brown solution was filtered and the dibutylamine hydrobromide washed with a little dibutylamine. The excess dibutylamine was distilled off at 5 mm. The residue solidified after drying over phosphoric anhydride *in vacuo* for a day. The dark crystalline mass was dissolved in hot methanol. On standing for two days exposed to the air 6.0 g. of brown crystals precipitated from this solution. No second crop could be obtained. Recrystallization from ethanol gave rise to 4.6 g. (22%) of material, m. p. 137–139°.

Reaction of Oxides with Amines.—The specified amount of oxide was heated at 100° (in a pressure bottle in the case of diethylamine) with the stated quantity of amine for the indicated time. Excess amine was removed by distillation in the case of diethylamine and dibutylamine or by pouring the reaction mixture into water in the case of diethanolamine. When hydrochlorides were desired, the product was taken up in ether, the ether solution was dried over sodium carbonate or sulfate and ethereal hydrogen chloride was added. Further details are given in the following sections.

α-Diethanolaminomethyl-2-*p*-chlorophenyl-4-quinolinemethanol.—The undried ether extract (0.0165 mole recrystallized oxide, 10 ml. diethanolamine, 16.5 hours) yielded 7.05 g. (0.0137 mole, 83%) of dihydrochloride dihydrate, m. p. 170–172°.

α-Novalaminomethyl-2-*p*-chlorophenyl-4-quinolinemethanol.—The crystalline hydrochloride (0.0344 mole crude oxide, 0.0344 mole of Novaldiamine,[15] eight hours) proved to be hygroscopic. This salt was converted to the free base giving 12.0 g. (0.0273 mole) of crude oil which was dissolved in 0.0819 mole of hydrogen chloride in 100 ml. of water. The solution was filtered. To the acidic filtrate was added a solution of 10.61 g. (0.0273 mole) of methylene *bis*-(2-hydroxy-3-naphthoic) acid in 0.0819 equivalent of dilute sodium hydroxide. After filtering and drying the salt weighed 19.50 g. It was too insoluble to recrystallize from any solvent tried.

Regeneration of the free base and reprecipitation of the salt gave 15.23 g. (0.0176 mole, 51%) of the dihydrate, m. p. 180–190° (dec.). Other preparations gave 51.7% from crude oxide and 70% from pure oxide. Other attempts were made to obtain solid, non-hygroscopic salts of this amine: the sulfate, phosphate and tartrate were hygroscopic solids; the hydrobromide, hydroiodide, lactate, salicylate, and *p*-toluenesulfonate were liquids.

α-Diethylaminomethyl-2-α-naphthyl-4-quinolinemethanol.—To the reaction mixture (0.0325 mole oxide, 12 ml. diethylamine, twelve hours) was added 150 ml. of methanol and 75 ml. was distilled to remove the excess amine, and 5 g. of phosphoric acid was added with swirling to the hot solution. The precipitated granular white solid was filtered off and recrystallized from 50% alcohol to yield 9.63 g. (61%) of monophosphate monohydrate, m. p. 183–186°. The free aminoalcohol was obtained as a crystalline solid, m. p. 93–94°, from ether–petroleum ether.

(14) The oxide decomposes at elevated temperatures and these recorded melting points were observed after immersing the melting point tube in the bath one to two degrees below the melting point.

(15) Kindly supplied by Dr. Robert C. Elderfield of Columbia University and purified by the method of Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

α-Diethylaminomethyl-2-β-naphthyl-4-quinolinemethanol.—To the reaction mixture (0.0365 mole oxide, 10 ml. of diethylamine, sixteen hours) after excess diethylamine was removed by distillation were added 75 ml. of ethanol and 10 g. of phosphoric acid in 20 ml. of ethanol. The separated crystals were recrystallized from aqueous alcohol to yield 10.0 g. (57%) of monophosphate monohydrate, m. p. 190–194°.

α-Dibutylaminomethyl-2-ethoxy-4-quinolinemethanol.—The reaction mixture (0.075 mole oxide, 0.075 mole dibutylamine, nine hours) was freed of dibutylamine by steam-distillation. Then cooling and scratching the residual oil induced crystallization. Recrystallization from ligroin (b. p. 80–70°) yielded 16.0 g. (60%) of material, m. p. 40–43°. Two further recrystallizations produced the analytical sample, m. p. 40–42°.

Warming with aqueous hydrochloric acid converted the material to another compound, m. p. 133–134°, with a 2-hydroxy instead of ethoxy group.

α-Dibutylaminomethyl-2-amino-4-quinolinemethanol.—From the reaction mixture (0.0495 mole 2-acetamido-4-quinolyl ethylene oxide, 1100 ml. of anh. dibutylamine, sixty-eight hours) most of the excess dibutylamine was removed by distillation at reduced pressure and the rest by distillation from 250 ml. of 3 *N* sodium hydroxide solution. The remaining viscous oil was rinsed several times with water and dried *in vacuo* over conc. sulfuric acid. The dried oil was dissolved by warming in 120 ml. of cyclohexane. Cooling yielded 13.6 g. of material, m. p. 80.2–82.4°, probably not completely deacetylated.

The pure aminoalcohol was isolated by refluxing 15.0 g. of the above mixture with 150 ml. of 6 *N* sodium hydroxide solution and 100 ml. of 95% ethanol for three hours. Then 200 ml. of water was added and the mixture extracted three times with ether. The ether solution was washed with water and dried over potassium carbonate. The ether was removed and the resultant viscous oil was taken up in 25 ml. of cyclohexane. Cooling yielded 9.6 g., m. p. 84.2–85.0°. A second crop of 2.0 g. was isolated from the mother liquor to give an over-all yield from the oxide of 73%.

α-Diethylaminomethyl-2-phenylthio-4-quinolinemethanol.—From the oxide ring opening (oxide from 0.0050 mole of crude bromohydrin hydrochloride, 15 ml. of diethylamine, 15 hours) was obtained, after recrystallization from ethanol-ether, the aminoalcohol dihydrochloride, m. p. 196–200° (dec.), in 80% yield.

The reaction of bromohydrin hydrochloride with excess diethylamine for a 24-hour reflux period gave rise to the same product, m. p. 200–204° (dec.), in 43% yield.

α-Diethanolaminomethyl-2-*p*-chlorophenyl-6,8-dichloro-4-quinolinemethanol.—The crude product (0.0223 mole oxide, 150 ml. of redistilled diethanolamine, 20 hours) was dried over sodium hydroxide *in vacuo*. An unidentified oily impurity was removed by triturating the crude material with 60 ml. of hot ethyl acetate. After cooling, there was obtained 5.64 g. (56%) of aminoalcohol, m. p. 162–165°. Recrystallization from ethanol yielded 4.72 g. (46.5%) of colorless leaves, m. p. 164–166°.

1-(2-Ureido-4-quinolyl)-2-dibutylaminoethyl Carbamate.—A mixture of 3.9 g. (0.0124 mole) of α-dibutylaminomethyl-2-amino-4-quinolinemethanol, 1.30 g. (0.0124 mole) of nitrourea and 45 ml. of anhydrous dioxane was heated until the vigorous evolution of gas began and then refluxed a half hour after it subsided. Two more 1.30-g. portions of nitrourea were added at half-hour intervals and the mixture was refluxed forty-five minutes after the last addition.

The dioxane was removed on a steam-bath at reduced pressure leaving a viscous brown oil which crystallized on cooling. This material was triturated with 40 ml. of benzene and the solid isolated by centrifuging, the liquid layer being saved for recovery of starting material. Recrystallization from benzene–isopropanol gave 1.45 g. (28%) of material, m. p. 158.5–162.3°, and a second crop of 0.25 g. (5%).

Starting material was recovered by removal of solvent from the trituration mother liquor, refluxing the resultant oil three hours with alcoholic sodium hydroxide solution, extraction with ether and crystallization from cyclohexane. This yielded 0.70 g. (18%) of α-dibutylaminomethyl-2-amino-4-quinolinemethanol. The yield of product was 1.70 g. (50%, allowing for recovered starting material).

A small sample was recrystallized twice from benzene-isopropanol; m. p. 165.4–166.0°.

Summary

A series of α-dialkylaminomethyl-4-quinolinemethanols with various substituents in the 2-position of the quinoline nucleus has been synthesized.

The ethanolamines were derived from the corresponding 4-aceto- and 4-bromoacetoquinolines prepared from the appropriate 2-substituted cinchoninic acids or esters. Reduction of the haloketones to halohydrins and conversion of the latter to ethylene oxides proceeds satisfactorily. Opening of the oxide ring with dialkyl amine gave rise to the desired aminoalcohols.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. II. The Preparation of Some Dialkylaminomethyl-4-quinoline Methanols[1,2]

BY KENNETH N. CAMPBELL AND JAMES F. KERWIN[3,4]

As part of the extensive antimalarial research program carried out in this country during the war, it seemed desirable to prepare dialkylaminomethylquinoline methanols of various types; in this paper are recorded some of those with the side chain attached to the 4-position of the quinoline ring, and with methoxyl, chlorine or hydrogen attached at the 6-position, I.

Rabe[5] and Kaufmann[6] made a few compounds of this type some years ago, with dimethylamino, diethylamino and piperidino groups; more recently King and Work[7] prepared an extensive series. Other workers under the auspices of the

(1) Previous paper in this series: Campbell and Schaffner, THIS JOURNAL, **67**, 86 (1945).

(2) The work reported here was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame.

(3) A part of this material is abstracted from the Ph.D. dissertation of James F. Kerwin, June, 1944.

(4) Present address: Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

(5) Rabe, Pasternack and Kindler, *Ber.*, **50**, 144 (1916).

(6) Kaufmann, *ibid.*, **46**, 1831 (1913).

(7) King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942).