ml. of glacial acetic acid and 28 ml. of 12 *N* hydrochloric acid; the solution was heated rapidly to boiling, treated with *ca.* 2 g. of Norite, filtered, and the cake washed with 57 ml. of glacial acetic acid. The amber-colored filtrate was diluted with its own volume of methanol and allowed to stand; Vd hydrochloride came down as a mass of well-formed microneedles, which were filtered off after an hour, rinsed with methanol, then ether, and air-dried, yield 15.9 g. of pale cream powder, m. p. 258–259° dec. The ethanol–acetone–ether washings (above) were concentrated to a sirup and dissolved in 80 ml. of glacial acetic acid and 16 ml. of 12 *N* hydrochloric acid and the solution diluted with twice its volume of methanol; an additional 8.7 g. of reasonably pure hydrochloride was obtained, total yield *ca.* 36.8% (11.8% over-all from Id). A portion was recrystallized from a mixture of acetic acid and water, light tan needle clusters, m. p. 227–229°, analysis for $C_{21}H_{19}Cl_3N_2O \cdot HCl \cdot H_2O$. Vd hydrochloride was found to have several melting points, depending on recrystallization conditions; the forms (probably solvated) were interchangeable, and all could be regenerated to the same free base. Vd was recrystallized from benzene, tiny, colorless needles, m. p. 241–242° dec.

Anal. Calcd. for $C_{21}H_{19}Cl_3N_2O$: C, 59.80; H, 4.54; N, 6.64. Found: C, 59.97; H, 4.64; N, 6.65.

Crude dibromo-IIId was ring-closed and reduced in the same manner; 33.6 g. (0.0482 mole) in 1.2 liters of ethanol was treated with 120 ml. of 14% sodium carbonate solution and 30 g. of anhydrous potassium carbonate. After shaking for one and one-half hours, 0.45 g. of catalyst was added, and the mixture reduced (five and one-half hours, 1.52 liters of hydrogen (2.57 one calcd.)); 4.2 g. (20.7%) of Vd was isolated.

Summary

(6 - Chloro - 2 - phenylquinolyl - 4) - α - piperidylcarbinol (and its N-methyl derivative), (8-chloro - 2 - phenylquinolyl - 4) - α - piperidylcarbinol, (6,8-dichloro-2-phenylquinolyl-4)-α-piperidylcarbinol and (6,8-dichloro-2-(*p*-chlorophenyl)-quinolyl-4)-α-piperidylcarbinol have been prepared.

PASADENA 4, CALIF. RECEIVED APRIL 5, 1946

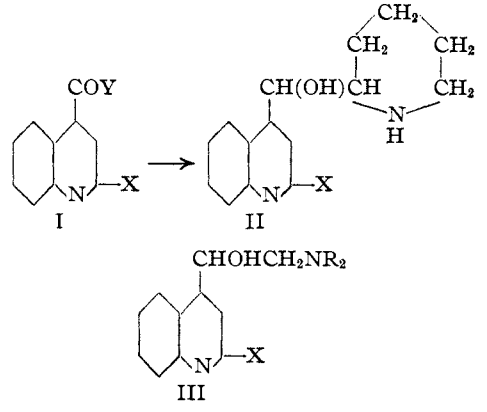
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

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

BY S. WINSTEIN, THOMAS L. JACOBS, EDWARD F. LEVY, DEXTER SEYMOUR, GUSTAVE B. LINDEN AND ROBERT B. HENDERSON

In exploring further variations[2] in the nature of the substituent blocking the 2-position of α-piperidyl-4-quinolinemethanol[3] II (X = H) we have prepared several such quinolinemethanols with so-called "negative" substituents. The aminoalcohols II contained either the 2-dialkylamino group (X = piperidino, morpholino and dibutylamino) which proved somewhat less effective than a phenyl group,[4] or the 2-hydroxyl group which produced complete loss of antimalarial activity as anticipated.[5] The preparation of the analogous 2-amino, 2-ethoxy and 2-phenylthio piperidylcarbinols was attempted and abandoned when it proved relatively easier to prepare the corresponding ethanolamines III.[6]

The general method of preparation of these α-piperidyl-4-quinolinemethanols was, as previously,[2] the one used by Ainley and King[3] and improved by Sargent,[4,7] the over-all yields from the appropriate cinchoninic ester I (Y = OC_2H_5) being approximately 10–20%, not allowing for recovered acid I (Y = OH).



Nucleophilic displacements of a group such as chloride proceed well at the 2-carbon atom in the quinoline nucleus. This was convenient in connection with the preparation of cinchoninic acids or derivatives of the type I, but troublesome in other phases of the work. 2-Chlorocinchoninic acid I (X = Cl, Y = OH), readily available[3,8] from N-acetylisatin by way of the 2-hydroxycinchoninic acid I (X = OH, Y = OH), was readily converted by heating with the appropriate amine, to the 2-piperidino-, morpholino-, dibutylamino- and novalaminocinchoninic acids.

The 2-aminocinchoninic acid I (X = NH_2, Y = OH) was prepared by treatment of the 2-chlorocinchoninic acid with ammonia and am-

(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.

(2) Brown, Jacobs, Winstein, Kloetzel, Spaeth, Florsheim, Robson, Levy, Bryan, Magnusson, Miller, Ott and Terek, THIS JOURNAL, **68**, 2705 (1946).

(3) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(4) Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

(5) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(6) Winstein, Jacobs, Linden, Seymour, Levy, Day, Robson, Henderson and Florsheim, THIS JOURNAL, **68**, 1831 (1946).

(7) Sargent, *ibid.*, **68**, 2088 (1946).

(8) Camps, *Arch. Pharm.*, **237**, 659 (1899).

monium carbonate after the manner used by Claus and Schaller[9] for 2-aminoquinoline. At the proper temperature, little 2-hydroxycinchoninic acid is produced and this preparation of large amounts of 2-aminocinchoninic acid is more convenient than previous methods.[10,11]

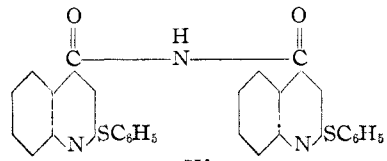
The displacement reactions are faster on the ethyl 2-chlorocinchoninate I (X = Cl, Y = OC_2H_5) than on the 2-chlorocinchoninate ion and it proved most convenient to employ the former for the preparation of the ethyl 2-phenylthio- and 2-phenoxycinchoninates I (X = SC_6H_5, OC_6H_5; Y = OC_2H_5). The preparation of the necessary ethyl 2-chlorocinchoninate was best carried out from 2-hydroxycinchoninic acid by esterification and subsequent treatment with phosphorus oxychloride.

For preparation of ethyl 2-ethoxycinchoninate and 2-aminocinchoninamide, where both X and Y of formula I are either OC_2H_5 or NH_2, it was most convenient to treat 2-chlorocinchoninyl chloride I (X, Y = Cl) either with sodium ethylate in especially dry alcohol or with ammonia.

The piperidino, morpholino and dibutylamino groups were stable to the treatment with sodamide and ε-benzamidocaproic ester and later long heating with aqueous acid, the procedures used in the synthesis[3,7] of the α-piperidyl-4-quinolinemethanols II. This was not true of other 2-substituents. The 2-ethoxy group in the ethyl cinchoninate I (X, Y = OC_2H_5) survived treatment with sodamide in benzene, but was cleaved to 2-hydroxy with aqueous acid. Thus the α-piperidyl-2-hydroxy-4-quinolinemethanol II (X = OH) was obtained from the attempted preparation of the corresponding 2-ethoxy compound. The 2-phenoxy group in ethyl 2-phenoxycinchoninate I (X = OC_6H_5, Y = OC_2H_5) was similar in behavior to the 2-ethoxy group. The 2-phenylthio group in ethyl 2-phenylthiocinchoninate I (X = SC_6H_5, Y = OC_2H_5) was seemingly more resistant to cleavage than the ethoxy group. Also, it was easily oxidized to a benzenesulfonyl group which was then very easily replaced by a group such as hydroxyl even in the determination of the saponification equivalent. The cleavage in this case gave rise to 2-hydroxycinchoninic I (X, Y = OH) and benzenesulfinic acid. This easy oxidation and displacement of a phenylthio group offered some promise of preparation of various 2-substituted α-piperidyl-4-quinolinemethanols from the 2-phenylthio compound. However, the phenylthio group was displaced in the Ainley–King–Sargent synthesis so that the 2-hydroxy compound was again produced.

In testing the stability of the various 2-substituents in the cinchoninic esters I (Y = OC_2H_5) to treatment with sodamide in benzene followed by addition of water we found all of them uncleaved. However, there was a great tendency for the production of acid[12] from the ester in the process, which may have contributed to a lowered yield of condensation product even in the presence of benzamidocaproic ester.

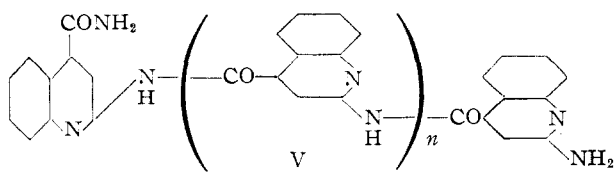
The mechanism by which acid is produced from ester is still not clear. For example, in the case of the ethyl 2-phenylthiocinchoninate I (X = SC_6H_5, Y = OC_2H_5) which was investigated a little more thoroughly than some of the others, treatment with sodamide, followed by addition of water gave acid in high yield. The amide of 2-phenylthiocinchoninic acid I (X = SC_6H_5, Y = NH_2) cannot be an intermediate here because it was shown to be stable to the conditions used in working up the reaction mixture. Addition of aqueous acetic acid instead of water to the reaction mixture after treatment of ester with sodamide in benzene produced in considerable amount a material which appeared to be an impure form of the imide IV.



IV

Heating of this material for five minutes with dilute base yielded approximately equal amounts of acid I (X = SC_6H_5, Y = OH) and amide I (X = SC_6H_5, Y = NH_2).

The situation was more complex in the case of the 2-aminocinchoninic esters. On treatment with sodamide the 2-amino group proved reactive and no condensation product could be obtained with ε-benzamidocaproic ester, only 2-aminocinchoninic acid I (X = NH_2, Y = OH) being obtained after hydrolysis. After treatment of butyl 2-aminocinchoninate I (X = NH_2, Y = OC_4H_9-*n*) with sodamide in benzene in the absence of benzamidocaproic ester, addition of water gave rise to acid and butyl alcohol, although ester and corresponding amide were both stable to the conditions used in working up the reaction mixture. Addition of the cooled reaction mixture from treatment of butyl 2-aminocinchoninate I (X = NH_2, Y = OC_4H_9) with sodamide to dilute acetic acid gave rise to butyl alcohol and what appeared to be a polyamide V.



V

The polyamide was more reactive to hot dilute base than the amide and a modified Kjeldahl analysis for volatilized ammonia indicated an average value of 8 for *n*. Treatment of 2-amino-

(9) Claus and Schaller, *J. prakt. Chem.*, [2] **56**, 206 (1897).

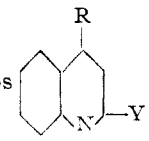
(10) Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(11) Renshaw and Friedman, THIS JOURNAL, **61**, 3320 (1939).

(12) For similar observations with ethyl benzoate, see Titherley, *J. Chem. Soc.*, **81**, 1520 (1902).

TABLE I

SUMMARY OF COMPOUNDS



SN	Y	R	M. p., °C. (cor.)	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	Piperidino	—COOH	230–232	70.29	70.04	6.29	6.46
	Piperidino	—COOH.$2H_2O$	230–232[a]	61.63	62.06	6.90	7.04
	Piperidino	—$COOC_2H_5$	80.3–80.9	71.80	71.81	7.09	7.23
	Piperidino	—$CO(CH_2)_5NH_2$·2HBr[b]	dec.	49.29	49.22	6.00	6.34
10001	Piperidino	—CH(OH)-2-piperidyl·HBr	226–226.5	59.11	59.05	6.94	7.05
	Morpholino	—COOH	221–222				
	Morpholino	—$COOC_2H_5$	125.0–125.6	67.11	66.93	6.33	6.50
10002	Morpholino	—CH(OH)-2-piperidyl·HCl	219–220	62.71	62.78	7.20	7.35
	$N(C_4H_9)_2$	—$COOC_2H_5$	Oil[d]	73.13	73.45	8.59	8.69
	$N(C_4H_9)_2$	—CHOH-2-piperidyl(monobenzoyl)	149–150	76.07	75.67	8.30	8.27
13087	$N(C_4H_9)_2$	—CHOH-2-piperidyl·H_3PO_4	150–151.5	59.08	59.29		
	OC_6H_5	—COOH	218–220[e] dec.				
	OC_6H_5	—$COOC_2H_5$	67–68[e]	73.70	73.67	5.15	5.09
12089	OH	—CH(OH)-2-piperidyl	248–249[e] dec.	69.74	70.09	7.02	7.10
	SC_6H_5	—COOH[f]	210–212	68.31	68.89	3.94	4.14
	SC_6H_5	—$COOC_2H_5$	54–56	69.88	70.27	4.89	4.93
	SC_6H_5	—$COOCH_3$	98.5–99.5	69.13	68.98	4.43	4.67
	SC_6H_5	—$COOCH(CH_3)_2$	75–77	70.56	70.49	5.30	5.30
	SC_6H_5	—$CONH_2$	231–233	68.55	68.33	4.32	4.46
	$SO_2C_6H_5$	—$COOC_2H_5$	154.5–155.5	63.33	63.39	4.43	4.56
	NH_2	—$COOCH_3$	203.5–205.5	65.34	65.34	4.98	5.07
	NH_2	—$COOC_4H_9$	155–156	68.83	68.98	6.60	6.61
	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	—$COOC_2H_5$	Oil[g]	70.55	70.34	8.74	8.61

[a] Melting point after loss of water. [b] Equivalent wt. (Volhard): calcd., 244; found, 247. [c] Equivalent wt. (Volhard): calcd., 363; found, 370. [d] B. p. 204–210° (2 mm.), $n^{23}D$ 1.5710. Saponification equivalent: calcd., 328; found, 327. [e] Uncorrected. [f] Equivalent wt.: calcd., 281; found, 281, 284. [g] B. p. 230° (2–3 mm.); 165–170° (bath) (5×10^{-5} mm.).

cinchoninamide I (X, Y = NH_2) with sodamide and decomposition of the reaction mixture with dilute acetic acid gave nearly complete recovery of unchanged amide.

In Table I are listed the new compounds prepared in the course of the work.

Experimental

All melting points are corrected unless marked otherwise. Analyses were carried out by Bruce F. Day and Richard Nevé.

2-Aminocinchoninic Acid and Amide.—A mixture of 70.0 g. (0.338 mole) of 2-chlorocinchoninic acid,[3,8] 70.0 g. (0.728 mole) of powdered ammonium carbonate and 230 ml. of 18 *N* ammonium hydroxide in a high-pressure bomb was brought to 145°, shaken for fifteen minutes and then kept at 140–150° for six and one-half hours.

The cooled reaction mixture was treated with 1000 ml. of 6 *N* sodium hydroxide and the resulting solution was charcoaled and filtered. The cool filtrate was acidified to litmus with glacial acetic acid and the 2-aminocinchoninic acid was collected, washed and dried. The yield was 46.6 g. (74%) of light yellow powder which could be purified without loss by reprecipitation from base after treatment with Nuchar; m. p. 386–387° (uncor.), 408–409° (cor.) (dec.) (reported 350–352°[10] and 362°[11]).

Acidification of the original filtrate to congo red with 6 *N* sulfuric acid produced 11.0 g. (17%) of 2-hydroxycinchoninic acid.[3,8]

The acid chloride from 20.7 g. (0.100 mole) of 2-chlorocinchoninic acid and thionyl chloride was added in small portions to 200 ml. of liquid ammonia in a high-pressure bomb which was then heated at 110–120° for twenty-one hours. The ammonia was released when the bomb cooled. The crude dry product yielded 16.0 g. (85%) of crude amide. Recrystallization from ethanol with use of Nuchar gave 13.5 g. (72%) of pure 2-aminocinchoninamide, m. p. 218–219° (reported[13] 218–218.5°).

2-Piperidino-, Morpholino-, Dibutylamino- and (4-Diethylamino-1-methylbutylamino)-cinchoninic Acids.—A mixture of 174 g. (0.84 mole) of 2-chlorocinchoninic acid[3,8] and 520 ml. of piperidine (redistilled), was refluxed for two and one-half hours. Then 220 ml. of piperidine was removed by distillation and the semi-solid residue taken up in 1100 ml. of water. The solution was barely acidified with 6 *N* sulfuric acid and allowed to stand a half hour. The product was collected by filtration, washed with water and air dried. The yield of 2-piperidinocinchoninic acid dihydrate was 226 g. (92%), m. p. 230–232° (melts after dehydration). On drying over phosphoric anhydride this material lost water and yielded the bright yellow anhydrous acid.

The other acids were prepared similarly[14] (yield 63% for morpholino). Precipitation with acid of the 2-dibutylaminocinchoninic acid gave a flocculent white solid which had no definite melting point and, on dehydration in vacuum, became a very viscous, bright yellow oil. Water was removed by distillation of benzene from the acid before esterification which gave an over-all yield of

(13) White and Bergstrom, *J. Org. Chem.*, **7**, 503 (1942).

(14) 4-Diethylamino-1-methylbutylamine was kindly supplied by Dr. Robert C. Elderfield and purified by the method of Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

68% from the 2-chlorocinchoninic acid. In the case of the 2-novalaminocinchoninic acid, 0.20 mole of sodium hydroxide was added for 0.10 mole of original 2-chlorocinchoninic acid, and water and excess novalamine were removed at reduced pressure. After this, esterification of the crude residue was carried out directly to give a 53% overall yield of ester from 2-chlorocinchoninic acid.

Esterification of the Cinchoninic Acids.—This was achieved in high yield either by way of the acid chloride prepared with thionyl chloride (2-phenylthio-, piperidino- and morpholinocinchoninic acids with methanol, ethanol or isopropanol), by the sulfuric acid method (2-amino-, novalamino- and dibutylaminocinchoninic acids with ethanol), or by the Fischer method (2-hydroxy- and 2-aminocinchoninic acids with methanol, ethanol and *n*-butanol).

Ethyl 2-Ethoxycinchoninate.—To the crude, solid acid chloride from 0.60 mole of 2-chlorocinchoninic acid and thionyl chloride was added a solution of 30.0 g. (1.30 g.-atoms) of sodium in 1000 ml. of 99.95% ethanol and the mixture was refluxed for two hours. Then 800 ml. of alcohol was distilled off and the residue was poured into ice and water to yield a solid product which was collected, washed with water, air-dried and recrystallized from ethanol to yield 124.0 g. (84%) of material, m. p. 85–86° (reported,[15] 87°).

Ethyl 2-Chlorocinchoninate.—This material was prepared in 83% yield by refluxing 73.3 g. of crude ethyl 2-hydroxycinchoninate with 250 ml. of phosphorus oxychloride for three and one-half hours and then pouring the reaction mixture into 4 liters of cracked ice. The solid was collected and sucked as dry as possible, after which it was extracted with a 1-liter and a 500-ml. portion of boiling hexane, decolorizing carbon being added. Filtration, concentration and cooling of the extracts yielded 66.0 g. of ethyl 2-chlorocinchoninate, m. p. 60–62, 62–63° after purification (reported[16] 63°).

Ethyl 2-Phenoxycinchoninate.—From the treatment of 23.6 g. (0.10 mole) of ethyl 2-chlorocinchoninate with a solution of 3.5 g. (0.15 g.-atom) of sodium in 100 g. of redistilled, molten phenol at 160° with stirring for twenty-four hours was isolated 14.8 g. (50.5%) of material, m. p. 61–64, 67–68° (uncor.) after recrystallization from hexane. Saponification of the ester gave the acid, m. p. 218–220° (dec.) (uncor.).

Ethyl 2-Phenylthiocinchoninate.—A solution of sodium thiophenolate was prepared by treating 27.5 g. (0.250 mole) of thiophenol with 125.0 ml. of 2.00 *N* (0.250 mole) sodium ethylate in especially dry ethanol. This was added to a solution of 58.9 g. (0.250 mole) of ethyl 2-chlorocinchoninate in 400 ml. of very dry ethanol. The mixture was refluxed with stirring and careful exclusion of moisture for four hours. Sodium chloride began to precipitate as the solution warmed up to the reflux temperature.

At the end of the reaction period, the mixture was poured slowly into a vigorously stirred slush of ice and water. The solid product was collected and dried in a vacuum, 73.2 g. (94.7%), m. p. 46–52°, being obtained. Recrystallization from hexane gave 58.8 g. (76.2%), m. p. 53–55° together with a second crop of 5.1 g. (6.6%), m. p. 50–53°.

2-Phenylthiocinchoninic Acid and Amide.—Refluxing of 45.5 g. of the ethyl ester for 1 hour in a mixture of 100 ml. of alcohol and 400 ml. of 10% sodium hydroxide and acidification to congo red of the cooled reaction mixture with hydrochloric acid gave 39.7 g. (96%) of acid, m. p. 207–209°, m. p. after recrystallization from toluene, 209–210°.

This material may also be prepared from 2-chlorocinchoninic acid and sodium thiophenolate.

The acid chloride from 14.0 g. (0.0498 mole) of 2-phenylthiocinchoninic acid was added in small portions to 200 ml. of liquid ammonia in a flask equipped with an all-glass stirrer and a Dry Ice reflux condenser protected by a potassium hydroxide tower. The mixture was refluxed two and one-half to three hours. Then the ammonia was allowed to evaporate. The dry residue yielded 13.8 g. (99%) of 2-phenylthiocinchoninamide, m. p. 229.5–233.0, 231–233.5° after two recrystallizations from dioxane.

Ethyl 2-Benzenesulfonylcinchoninate.[17]—To a mixture of 14.2 g. (0.046 mole) of ethyl 2-phenylthiocinchoninate, 25 ml. of glacial acetic acid and 25 ml. of acetic anhydride held at 0° with an ice–salt-bath was added slowly 15 ml. of 30% hydrogen peroxide with stirring. The ice melted and the bath slowly warmed to room temperature. The bath was necessary for six to eight hours to prevent acceleration of the reaction. After several days the reaction mixture was filtered to yield 9.3 g. (0.0273 mole, 59%) of ethyl 2-benzenesulfonylcinchoninate, m. p. 155–156°.

α-(2-Piperidyl)-4-quinolinemethanols.—The condensation of the cinchoninic esters with ethyl ε-benzamido caproate was carried out with 1.5 to 2.0 moles of sodamide, a reaction time of twenty-four to forty-eight hours and a hydrolysis time using sulfuric acid of forty-eight hours.[4,7]

The aminoketone hydrobromide was quite pure only in the piperidino case. In the case of the 2-ethoxy material, the aminoketone gave a negligible value for ethoxyl by the Zeisel method. Also, the recovered cinchoninic acid (45–61%) was the 2-hydroxycinchoninic acid.

After bromination, ring closure and hydrogenation, and filtration from catalyst, the reaction mixture was concentrated. The piperidino compound crystallized out as a hydrobromide which was recrystallized from ethanol. In the morpholino case, concentrated ammonium hydroxide was added and the carbinol was extracted with ether. A hydrochloride was precipitated from the dried ether solution with hydrogen chloride and reprecipitated from ethanol. In the dibutylamino case an oil separated which was taken up in chloroform and then freed of solvent. A diphosphate of the desired compound was precipitated from dioxane with phosphoric acid. Crystallization of a small sample from dioxane and ethanol yielded a monophosphate. A monobenzoyl derivative was prepared from the phosphate and benzoyl chloride in pyridine.

The final solution of the compound from the 2-ethoxycinchoninic ester was freed of alcohol and water with the aid of benzene. The carbinol was extracted from the precipitated solid with boiling absolute alcohol, precipitated from the alcohol by addition of acetone, and recrystallized from alcohol–acetone. The carbinol was insoluble in water or bicarbonate solution but soluble in dilute acid or base.

The condensation of ethyl 2-phenylthiocinchoninate with the benzamidocaproic ester proceeded in unusually low yield (13%). The recovered acid included 49% 2-hydroxycinchoninic acid and 1% 2-phenylthiocinchoninic acid. From the final steps was isolated α-piperidyl-2-hydroxy-4-quinolinemethanol, identical in melting point and mixed melting point with the material from the 2-ethoxycinchoninic ester.

From the ethyl 2-aminocinchoninate or the corresponding methyl or butyl esters was isolated no condensation product, over 80% of 2-aminocinchoninic acid being recovered. Attempts at condensation in dimethylaniline as a solvent gave rise only to recoveries of acid of 79–90%.

From the condensation of ethyl 2-hydroxycinchoninate using refluxing xylene as a solvent and 2.5 moles of sodamide, was obtained only 4–5% of the aminoketone.

Stability of 2-Substituents to Acid or Base.—Refluxing with sulfuric acid comparable in strength to that employed in the Sargent[7] procedure gave from ethyl 2-phenylthiocinchoninate (forty-eight hours reflux) corresponding acid and hydroxy-acid in the ratio of 6 to 1. On similar treatment of ethyl 2-phenoxy- or 2-ethoxycinchoninates as well as on heating the latter with 9 *N* hydrochloric acid for as short a time as forty minutes, 2-hydroxycinchoninic acid was formed. Ethyl 2-ethoxycinchoninate was recovered largely unchanged after fifteen minutes on the steam-bath with 10% hydrobromic acid.

Ethyl 2-benzenesulfonylcinchoninate behaved abnormally in the determination of its saponification equivalent. The cleavage products were isolated from treatment of 4.0 g. of the ester with 5 ml. of 6 *N* sodium hydroxide in

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

(16) Thielepape, *ibid.*, **71B**, 387 (1938).

(17) Pomeranz and Connor, THIS JOURNAL, **61**, 3386 (1939).

40 ml. of water on the steam-bath overnight. Acidification of the cooled solution yielded 2.3 g. of 2-hydroxycinchoninic acid. Treatment of the remaining solution with concd. ferric chloride solution yielded 1.29 g. (47%) of solid which was redissolved in ammonium hydroxide. The ferric hydroxide was removed by filtration and the solution was acidified with hydrochloric acid to yield after thirty-six hours 0.52 g. (40%) of benzenesulfinic acid, m. p. 83–85° (reported,[18] 83–84°).

Treatment of Esters with Sodamide.—To the cooled reaction mixture from refluxing of 0.050 mole of ethyl 2-phenylthiocinchoninate with 0.100 mole of sodamide in benzene for twenty-four hours was added water and ether and the phases were separated. Acidification of the aqueous layer gave 11.6 g. (82%) of 2-phenylthiocinchoninic acid after precipitation from bicarbonate solution.

The 2-phenylthiocinchoninamide was recovered unchanged on treatment with sodium hydroxide, ammonium hydroxide, benzene and water under conditions comparable to those used in working up the above reaction mixture.

Another cooled reaction mixture from treatment of 0.050 mole of ethyl 2-phenylthiocinchoninate with 0.100 mole of sodamide was poured into ice and aqueous acetic acid. Ether was added and the mixture was separated into an ether extract, 4.6 g. (*ca.* 34%) of a solid obtained by filtration, and an aqueous layer which did not yield any material on acidification to congo red.

The solid, m. p. 224–233° after precipitation from dioxane by addition of water, showed a melting point lowering on mixing with either amide or acid. Boiling of the solid for five minutes with 3 *N* sodium hydroxide yielded *ca.* 90% of 2-phenylthiocinchoninamide, m. p. 229.5–232.5° after recrystallization from dioxane and *ca.* 80% of 2-phenylthiocinchoninic acid.

Evaporation of the ether layer yielded 8.6 g. of a gummy mixture from which the only pure material isolated was 1.28 g. of 2-phenylthiocinchoninic acid.

Treatment of ethyl 2-aminocinchoninate with 1.50 moles of sodamide in benzene for twenty-four hours, followed by addition of water to the cooled reaction mixture, gave a 32% recovery of ester and a 66% yield of acid. The much less soluble methyl ester gave a 74% recovery of ester and an 11% yield of acid. The butyl ester with 2 moles of sodamide gave no recovery of ester, no appreciable amount of butene or butylamine but a 92% yield of acid and a 76% yield of butyl alcohol.

The butyl ester was shaken with 3 *M* sodium hydroxide for five minutes and let stand thirty minutes, no acid being obtained, only a 95% recovery of ester being made. Treatment of 2-aminocinchoninamide with sodamide as for the esters gave a 93% recovery of unchanged amide.

When the treatment of the butyl ester with sodamide was repeated and the cooled reaction mixture poured into dilute acetic acid, there was obtained *ca.* 93% of a solid, m. p. 213–221°. Precipitation of the material from dioxane by addition of water gave a product, m. p. 258–268° (dec.). Boiling of 4.86 g. of this material for five minutes with 30 ml. of 2 *N* sodium hydroxide gave after two precipitations from basic solution 3.91 g. of 2-aminocinchoninic acid. Heating the material with base in a modified Kjeldahl analysis gave 0.82 and 0.78% N (as —$CONH_2$), 0.815 being the theoretical for a polymeric amide of ten units. The same type analysis (forty-five minutes) on 2-aminocinchoninamide gave 7.51% N (as —$CONH_2$), the theoretical being 7.48.

(18) Otto, *J. prakt. Chem.*, [2] **30**, 177 (1884).

Summary

New cinchoninic acids and derivatives have been prepared which contain the 2-substituents: piperidino, morpholino, dibutylamino, novalamino, phenoxy, phenylthio and benzenesulfonyl.

As possible antimalarials, α-(2-piperidyl)-4-quinolinemethanols have been synthesized with the 2-position of the quinoline nucleus substituted by piperidino, morpholino, dibutylamino and hydroxy.

Observations have been reported on the stability to cleavage by acid or base of the various 2-substituents and on the behavior of certain of the cinchoninic esters toward sodamide in benzene.

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Potential Antimalarials. Additional (2-Phenylquinolyl-4)-α-piperidylcarbinols[1]

BY E. R. BUCHMAN AND D. R. HOWTON

The present paper reports the syntheses of three additional[2] (2-phenylquinolyl-4)-α-piperidylcarbinols (V) by conventional methods. The cinchoninic esters (I) were prepared *via* the Doebner reaction.[3]

$$\underset{\text{I}}{RCOOC_2H_5} \xrightarrow{\text{5 steps}} \underset{\text{V}}{RCHOH\text{-}\alpha\text{-piperidyl}}$$

Series a. R^4 = 6-Methyl-2-phenylquinolyl-4
b. R = 8-Methyl-2-phenylquinolyl-4
c. R = 2,8-Diphenylquinolyl-4

(1) 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 California Institute of Technology.

(2) For other substituted (2-phenylquinolyl-4)-α-piperidylcarbinols see: (a) Koepfli, *et al.*, THIS JOURNAL, **68**, 2697 (1946); (b) Brown, Jacobs, Winstein, *et al.*, *ibid.*, **68**, 2705 (1946); (c) Buchman, *et al.*, *ibid.*, **68**, 2710 (1946).

(3) *Cf.* Doebner and Gieseke, *Ann.*, **242**, 296, 298 (1887).

(4) Vb and Vc analogs of the type $RCHOHCH_2NR'_2$ have been prepared by Lutz and co-workers, THIS JOURNAL, **68**, 1813 (1946).

Experimental[5]

2-Phenylcinchoninic Esters

Ethyl 6-Methyl-2-phenylcinchoninate (Ia).[6]—The acid corresponding to Ia was prepared essentially as described in the literature[3] (glacial acetic acid in place of ethanol was less satisfactory) except that a technical (*ca.* 50% aqueous solution) pyruvic acid[7] was used. An equivalent of aqueous sodium hydroxide was added before removing the ethanol from the reaction mixture. The residue was extracted with *i*-propyl ether; acidification of the aqueous phase gave an oil which soon crystallized. This was dried and esterified with ethanolic sulfuric acid; after removal of solvent, the residue was basified with 15 *N* ammonium hydroxide and the oily Ia taken up in ether and recrystallized from ethanol at 0°; light yellow needles, m. p. 74.8–75.5° in agreement with the lit.[6]; yield 35.5% from *p*-toluidine.

(5) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by the Huffman Microanalytical Laboratories, Denver 2, Colorado.

(6) "Beilstein," 4th ed., Suppl. Vol. XXII, p. 520.

(7) Supplied by the Calco Chemical Division of the American Cyanamid Company.