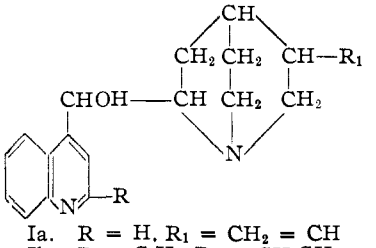
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1046]

The Synthesis of Potential Antimalarials. The Reaction of Organic Lithium Compounds with Quinolinemethanols[1]

BY J. F. MEAD, M. M. RAPPORT AND J. B. KOEPFLI

The reaction of organic lithium compounds with certain quinolinemethanols was undertaken in the hope of obtaining, without recourse to total syntheses, compounds related to cinchonine (Ia) but featuring a quinoline-2 substituent. Such compounds were desired for testing as antimalarials for reasons elaborated upon in another paper.[2]

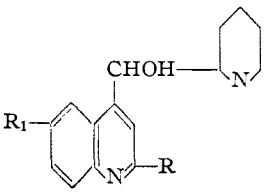


Ia. R = H, R_1 = CH_2 = CH
Ib. R = C_6H_5, R_1 = CH_3CH_2

The first attempts were made with cinchonine (Ia) using butyllithium and phenyllithium, respectively. In both instances products were formed which gave satisfactory elementary analyses. However, in the case of the so-called butylcinchonine, a quantitative hydrogenation with platinic oxide indicated a hydrogen uptake of only about one-third of the theoretical. Furthermore, neither the butyl nor phenyl derivative of cinchonine gave a precipitate with cuprichloride[3] and it therefore seemed probable that the vinyl group had been partially reduced in each instance to yield a mixture. These attempts were therefore abandoned in favor of the reaction of phenyllithium with dihydrocinchonine; this was successfully carried out and the structure of the resulting dextrorotatory 2′-phenyl-3-ethylruban-9-ol (Ib) was confirmed by oxidation to 2-phenylcinchoninic acid by the method of John.[4]

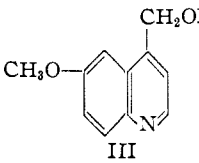
Previous to the synthesis of 2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (IIb)[2] from 2-phenylcinchoninic ester, the feasibility of obtaining such a 2-substituted Ainley and King type of quinolinemethanol directly from the unsubstituted analog IIa[5,6] by means of phenyllithium was explored.

The reaction of phenyllithium with IIa at room temperature gave the desired 2-phenyl analog,



IIa. R = R_1 = H
IIb. R = C_6H_5, R_1 = H
IIc. R = H, R_1 = CH_3O
IId. R = C_6H_5, R_1 = CH_3O

IIb. When, however, the reaction of phenyllithium with 6-methoxy-α-(2-piperidyl)-4-quinolinemethanol (IIc)[5] was carried out at 80°, the principal product was apparently 6-methoxy-4-quinolinemethanol (III) accompanied by only a small amount of the desired 6-methoxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (IId).[2]



III

The above product III of m. p. 135–136° was probably a result of hydrogenolysis at the bond between the piperidyl ring and the quinoline methanol group in IIc. A similar hydrogenolysis was postulated by Ainley and King,[5] who reported obtaining a compound of the same structure and like properties, but of m. p. 83–84°, during ring closure and catalytic reduction of ε-bromo-ε-(6-methoxycinchoninyl)-*n*-amylamine. Their compound analyzed for two moles of water of crystallization and thus may not be identical with that reported here.

Experimental[7]

Dextrorotatory 2′-Phenyl-3-ethylruban-9-ol (Ib), (SN 10,285).[8]—From 30 g. of cinchonine (Ia), 27.8 g. (93%) of dihydrocinchonine was prepared[9] and after recrystallization from 650 ml. of benzene (using a Soxhlet extractor) the compound was obtained as colorless needles, m. p. 270.5–273° (dec.).

A solution of 0.02 mole of phenyllithium in 30 ml. of ether was prepared[10] and added to a suspension of 5.9 g. (0.02 mole) of dihydrocinchonine in 40 ml. of dry ether in an ice–water-bath. The mixture was stirred and after five minutes the temperature was allowed to rise to room temperature over a period of thirty minutes. Most of the solid having dissolved, the dark yellow-green reaction mixture was poured into 500 ml. of ice water and the ether removed by warming. The insoluble solid which separated was collected, washed with water, dried and extracted with 500

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

(3) Cohen, *J. Chem. Soc.*, 999 (1933).

(4) John, *Ber.*, **63**, 2657 (1930).

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

(6) Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946).

(7) All melting points are corrected. The microanalyses were performed by Dr. Gertrude Oppenheimer and Mr. Alan Swinhart.

(8) The Survey number, designated SN, identifies a drug in the Records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

(9) Skita and Franck, *Ber.*, **44**, 2866 (1911).

(10) Gilman, Zoellner and Selby, THIS JOURNAL, **54**, 1957 (1932).

ml. of ether. The ether solution was taken to dryness and the residue crystallized from 95% ethanol. Two crops, obtained by concentration of the solution[11] and mother liquors, weighed 2.7 g. (36%). Recrystallization from ethanol gave colorless needles, m. p. 260–261° (dec.), $[\alpha]^{25}D$ +129° (1% solution of the base in water containing four equivalents of hydrochloric acid).

Anal. Calcd. for $C_{25}H_{25}ON_2$: C, 80.6; H, 7.6; N, 7.5. Found: C, 80.5; H, 7.7; N, 7.7.

The above base (1.0 g.) was oxidized by the method of John[4] and 0.31 g. (46%) of colorless needles, m. p. 214–215°, was isolated from the reaction mixture. A mixed melting point with an authentic sample of 2-phenylcinchoninic acid was 214–216°.

The Reaction of α-(2-Piperidyl)-4-quinolinemethanol (IIa)[5,6] with Phenyllithium.—To 0.06 mole of phenyllithium, prepared by the method of Evans and Allen,[12] from 1.1 g. of lithium and 12 g. of bromobenzene, was added with stirring at 0°, 4.8 g. (0.02 mole) of IIa suspended in 100 ml. of dry ether. The temperature was allowed to rise and the stirring continued for one-half hour at room temperature; the reaction mixture was then poured into water and rapidly stirred for an additional half hour. The ether phase was separated, dried and evaporated to dryness, the residue dissolved in a little absolute ethanol and treated with dry hydrochloric acid gas. The crystalline hydrochloride which precipitated was collected, washed with ethanol and dried to give 0.5 g. of a compound, m. p. 225–227° (dec.); the melting point of the dihydrochloride of 2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (IIb)[2] is 225° (dec.).

The above salt was converted to the free base which was obtained as colorless needles of m. p. 96–97° from absolute methanol. The free base showed no depression in melting point when mixed with an authentic sample of IIb.[2]

(11) The product when crude is much more soluble than after initial purification, making it necessary to concentrate the first ethanol solution to small volume.

(12) Evans and Allen, "Organic Syntheses," Coll. Vol. II, 1943, p. 517.

The Reaction of 6-Methoxy-α-(2-piperidyl)-4-quinolinemethanol (IIc)[5,13] with Phenyllithium.—The reaction between phenyllithium and IIc was carried out as described in the last experiment except that dry benzene was used as a solvent and the reaction mixture was warmed at 80° for one-half hour before pouring it into water. Long light-colored needles appeared on the oily phase, some of which (0.35 g.) were collected, crystallized twice from water, washed and dried to give colorless needles of m. p. 135–136°. The compound was soluble in hot water and dilute acids but insoluble in base; it formed a methiodide with methyl iodide and did not give any test for a carbonyl group.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.8; H, 5.9; N, 7.4; MeO, 16.4. Found: C, 69.6; H, 5.9; N, 7.7; MeO, 16.3.

The remaining solid and oil, obtained by evaporation of the benzene phase, was dissolved in ethanol and treated with hydrochloric acid gas. The resulting light brown precipitate (2 g.), m. p. 245° (dec.), was collected and converted to a free base, m. p. 134–136°, identical with the compound isolated above and is probably 6-methoxy-4-quinolinemethanol (III).

From the mother liquors of the hydrochloride (m. p. 245°) obtained above, there was isolated 0.25 g. of crystals of m. p. 234–236° (dec.) which did not depress the melting point when mixed with a sample of the dihydrochloride hemihydrate of 6-methoxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (IId)[2].

Summary

The preparation of dextrorotatory 2′-phenyl-3-ethylruban-9-ol from dihydrocinchonine by means of phenyllithium is reported. The reaction of phenyllithium with two Ainley and King type quinolinemethanols is described.

(13) Sargent, THIS JOURNAL, **68**, 2688 (1946).

PASADENA, CALIFORNIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE UNIVERSITY OF SOUTHERN CALIFORNIA]

α-(2-Piperidyl)-2-aryl-4-quinolinemethanols[1]

BY RONALD F. BROWN, THOMAS L. JACOBS, S. WINSTEIN, MILTON C. KLOETZEL, EARL C. SPAETH, WARNER H. FLORSHEIM, JOHN H. ROBSON, EDWARD F. LEVY, GEORGE M. BRYAN, ALAN B. MAGNUSSON, STANLEY J. MILLER, MELVIN L. OTT AND JOSEPH A. TEREK

The discovery that α-(2-piperidyl)-2-phenyl-4-quinolinemethanol was much more effective against avian malaria than the corresponding compound without the 2-phenyl group[2] suggested the synthesis of a number of analogous compounds containing substituted 2-aryl groups of different types. It was found that *p*-chlorophenyl was especially effective in increasing the quinine equivalent of these quinolinemethanols.

(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, and the University of Southern California. 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) Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

These compounds were prepared in 10–30% over-all yield by a slight modification of the procedure described by Koepfli and co-workers[2] (I → VI) except in the case of α-(2-piperidyl)-2-(*p*-hydroxyphenyl)-4-quinolinemethanol (VI, R = *p*-hydroxyphenyl) which was obtained from