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 $C_{25}H_{28}ON_2$: 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]

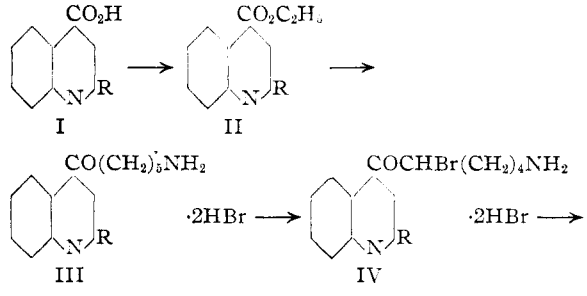
BY RONALD F. BROWN, THOMAS L. JACOBS, S. WINSTEIN, MILTON C. KLOETZEL, EARL C. SPAETH, WARNER H. FLORSHEIM, JOHN H. ROBSON, EDWARD F. LEVY, GEORGE M. BRYAN, ALAN B. MAGNUSSON, STANLEY J. MILLER, MELVIN L. OTT AND JOSEPH A. TEREK

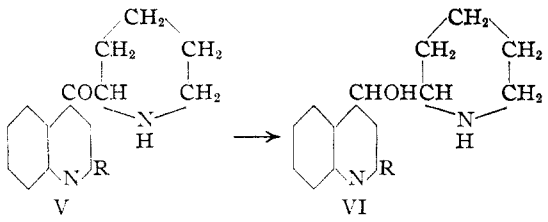
The discovery that α-(2-piperidyl)-2-phenyl-4-quinolinemethanol was much more effective against avian malaria than the corresponding compound without the 2-phenyl group[2] suggested the synthesis of a number of analogous compounds containing substituted 2-aryl groups of different types. It was found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





V VI

the corresponding methoxy compound (VI, R = *p*-methoxyphenyl) with hydrobromic acid.

Most of the 2-arylcinchoninic acids (I) were obtained in 50–95% yields by means of the Pfitzinger condensation[3] of isatin and the appropriate methyl ketone. The Doebner[4] synthesis was used to prepare 2-(*p*-diethylaminophenyl)-cinchoninic acid from *p*-diethylaminobenzaldehyde, pyruvic acid and aniline.

Table I summarizes the quinolinemethanols synthesized and Tables II and III list other new compounds prepared during this work.

The condensation of ethyl 2-(α- or β-naphthyl)-cinchoninate with ethyl ε-benzamidocaproate was erratic and the product was difficult to purify. A final product (VI, R = α-naphthyl) could be obtained in only one run and it was insufficient for testing. The synthesis of these compounds was abandoned when it was found that α-diethylaminomethyl-2-(α- and β-naphthyl)-4-quinolinemethanols could be obtained without difficulty.[5]

No success attended attempts to prepare α-(2-piperidyl)-4-quinolinemethanols substituted in both the 2 and 3 positions. 2,3-Diphenyl-[3] and 2-phenyl-3-methyl-cinchoninic acids[6] were readily available but their esters failed to condense with ethyl ε-benzamidocaproate, probably due to the hindrance of the group in the 3-position. These

TABLE I

α-(2-PIPERIDYL)-2-ARYL-4-QUINOLINEMETHANOLS

SN	2-Substituent	M. p., °C.	Yield,[a] %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Crystn. solvent
11449	*p*-Tolyl[m]	163.5–164	9	79.48	79.71	7.28	7.47	Ethyl acetate
		210–212 dec.[b]		65.18	65.08	6.47	6.71	70% Ethanol
13147	2,5-Dimethylphenyl	162–163	5–10	79.73	79.90	7.56	7.73	Ether and trace of methanol
11455	*o*-Chlorophenyl[m]	218–219.5	15	71.48	71.66	6.00	5.96	95% Ethanol
		215–216[b]		59.23	59.25	5.44	5.67	Ethanol–ether
11454	*m*-Chlorophenyl[m]	169.5–170		71.48	71.45	6.00	6.10	95% Ethanol
10000	*p*-Chlorophenyl	198–199.5	32	71.48	71.26	6.00	6.16	95% Ethanol
13521	2,4-Dichlorophenyl[m]	190–191	22	65.12	64.21	5.20	5.65	Benzene
		196–197[c]		50.82	50.36	5.28	5.43	Water
13486	2,5-Dichlorophenyl[m]	124–126	31	65.12	64.91	5.20	5.40	Acetic acid
		208–210[b,d]						
11456	3,4-Dichlorophenyl[m]	178–179	18					Benzene
		217–217.5[e]		59.52	59.29	5.00	5.06	80% Ethanol
		224.5–225[b]		54.80	54.72	4.82	4.90	80% Ethanol
12600	*p*-Bromophenyl	199–202	26	63.48	63.16	5.33	5.41	Methanol
11451	*p*-Methoxyphenyl[m]	154–154.5	10–15	75.83	75.96	6.94	7.14	Benzene–heptane
		203.5–204[b]						Dil. ethanol or dil. dioxane
12869	*p*-Hydroxyphenyl	124–126[f]	92[g]	71.56	71.64	6.86	6.99	Ethyl acetate
		275–276[b]		61.92	61.65	5.94	6.07	
11432	*p*-Diethylaminophenyl[m]	99–100[h]	24	74.44	74.11	8.56	8.55	Ethanol
		99–100[i]		74.79	75.01	8.74	8.53	2-Propanol
		175–175.5[j]		69.47	69.64	7.91	7.68	
13488	*p*-Xenyl[m]	168–169	30					Anh. ethanol
		199.5–200.5[k]		66.80	66.31	6.23	6.46	Dil. ethanol
14129	3-Pyridyl	210.5–211.5[l]	10	65.96	65.76	5.95	6.35	Ethanol–ether

[a] Over-all yields based on the cinchoninic esters. These are probably far from the optimum yields. [b] Dihydrochloride. [c] Dihydrochloride dihydrate. [d] Analysis for chloride ion: calcd. 15.8; found 15.9 (as silver chloride). [e] Monohydrochloride. [f] Monohydrate. Melts at 140–155° after resolidifying. [g] From the corresponding *p*-methoxyphenyl compound. [h] Monoethanolate. [i] Monoisopropanolate. [j] Monohydrochloride monoacetoneate. [k] Dihydrochloride monohydrate. [l] *p*-Toluenesulfonate. Other salts were hygroscopic or darkened in air. [m] The modified procedure described in the experimental section was used for these compounds.

TABLE II

CINCHONINIC ACIDS

2-Substituent	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2,5-Dimethylphenyl	207–208	78.00	77.74	5.45	5.67
m-Chlorophenyl	215–216				
2,4-Dichlorophenyl	279–280	60.40	60.17	2.85	2.99
2,5-Dichlorophenyl	257–259	60.40	60.68	2.85	3.01
3,4-Dichlorophenyl	257–257.5	60.40	60.61	2.85	2.91
p-Diethylaminophenyl	250.5–251	74.97	74.45	6.29	6.50
3-Pyridyl	320–321.5	71.99	71.69	4.03	4.33

(3) Pfitzinger, *J. prakt. Chem.*, [2] **56**, 283 (1897).

(4) Doebner, *Ber.*, **20**, 277 (1887).

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

(6) von Braun and Brauns, *Ber.*, **60**, 1253 (1927).

TABLE III

CINCHONINIC ESTERS[a]

Substituents	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-(2,5-Dimethylphenyl)	60–61.5	78.66	78.82	6.27	6.30
2-(*o*-Chlorophenyl)	80–82				
2-(*m*-Chlorophenyl)	116.5–117.5	69.34	69.48	4.55	4.62
2-(*p*-Chlorophenyl)[b]	88–88.5	69.34	69.31	4.53	4.50
2-(2,4-Dichlorophenyl)	157–157.5	62.44	62.63	3.78	3.95
2-(2,5-Dichlorophenyl)	128–130	62.44	62.11	3.78	3.81
2-(3,4-Dichlorophenyl)	69–70.5	62.44	62.68	3.78	3.88
2-(*p*-Bromophenyl)[b]	94.5–95	60.69	60.71	3.96	3.91
2-(*p*-Methoxyphenyl)	79–80				
2-(*p*-Diethylaminophenyl)	80–81	75.85	76.02	6.94	6.92
2-(*p*-Xenyl)	134.5–135.5	81.56	81.61	5.41	5.53
2-(α-Naphthyl)	107–108	80.71	80.78	5.24	5.28
2-(α-Naphthyl)[a]	127–128	80.50	80.31	4.83	5.02
2-(β-Naphthyl)[c]	73–75	80.71	80.60	5.24	5.15
2-(β-Naphthyl)[a]	113–115	80.50	80.27	4.83	4.88
2-(3-Pyridyl)	61.5–62.5	73.32	73.25	5.07	5.29
2-Phenyl-3-methyl[b]	42–44	78.39	78.46	5.88	5.89
2,3-Diphenyl[b]	96–96.5	81.56	81.83	5.41	5.49
2,2′-Bicinchoninic[b]	165.5–166	71.99	72.08	5.03	5.18
2-(3-Pyridyl)-6,8-dichloro	178–181	58.80	58.44	3.49	3.52
2-(4-Pyridyl)-6,8-dichloro	144–145	58.80	59.02	3.49	3.99

[a] This letter designates methyl esters. All others are ethyl. [b] Prepared through the acid chloride made with thionyl chloride. [c] The b. p. of the ester was 263–264° (2 mm.) uncor.

acids were not esterified by refluxing with alcohol and sulfuric acid, but methyl 2-phenyl-3-methylcinchoninate was hydrolyzed completely by refluxing with 16 *N* sulfuric acid for forty hours. Very little acid was recovered from the condensation of the acid chloride of 2-phenyl-3-methylcinchoninic acid with ethyl ε-benzamidocaproate in the presence of triphenylmethylsodium, but no pure products could be isolated.

Several attempts were made to convert α-(2-piperidyl)-2-(4-hydroxyphenyl)-4-quinolinemethanol to α-(2-piperidyl)-2-(3-diethylaminomethyl-4-hydroxyphenyl)-4-quinolinemethanol through a Mannich reaction. Although the reaction was carried out with both paraformaldehyde and 36% formaldehyde solution in such solvents as water, ethanol, nitromethane and nitrobenzene, none of the desired product was obtained.

It seemed possible that the marked increase in antimalarial activity obtained by blocking the 2-position of the quinoline nucleus with an aryl group would also result by introduction of the α-(2-piperidyl)-methanol side chain into 2,2′-biquinoline. 2,2′-Bicinchoninic acid has been prepared[7] by the condensation of isatin and acetoin. We found it more convenient to use 3-chloro-2-butanone instead of acetoin. Although the condensation of the ethyl ester of this acid with ethyl ε-benzamidocaproate in toluene followed by hydrolysis, bromination, ring closure and reduction seemed to go smoothly, the products were very insoluble and we were never able to purify the final compound.

(7) Lesesne with Henze, THIS JOURNAL, **64**, 1897 (1942).

Experimental

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

Cinchonic Acids.—Data for the new acids are given in Table II. Recrystallization solvents were ethanol, acetic acid and methyl cellosolve. The procedure usually employed for the Pfitzinger reaction was that given by Lindwall, Bandes and Weinberg[8] and yields of 75–95% were obtained. The substituted acetophenones needed as starting materials have all been reported.[9–13] Cinchoninic acids with the following 2-substituents have already been described: *p*-tolyl,[6,14] *o*-chlorophenyl,[15] *p*-chlorophenyl,[14] *p*-bromophenyl,[8,14] *p*-methoxyphenyl,[8] *p*-xenyl,[16,17] α-naphthyl[18,19,20] and β-naphthyl.[19,20]

The melting point of 2-(α-naphthyl)-cinchoninic acid was 223.5–224.5° when prepared from α-acetonaphthone purified through the picrate.

The yield of 2,2′-bicinchoninic acid was 48% when 3-chloro-2-butanone[21] was used instead of acetoin in the condensation with isatin.

2-(*p*-Diethylaminophenyl)-cinchononic Acid.—*p*-Diethylaminobenzaldehyde (177 g.) and aniline (93 g.) were heated together on the water-bath for one hour while water vapor was blown out with a gentle stream of air, and 1750 ml. of anhydrous ethanol containing 30 drops

(8) Lindwall, Bandes and Weinberg, *ibid.*, **53**, 317 (1931).
(9) Claus and Wollner, *Ber.*, **18**, 1857 (1885).
(10) Lock and Böck, *ibid.*, **70**, 916 (1937).
(11) Crauw, *Rec. trav. chim.*, **50**, 753 (1931).
(12) Roberts and Turner, *J. Chem. Soc.*, 1832 (1927).
(13) Kolloff and Hunter, THIS JOURNAL, **63**, 490 (1941).
(14) DuPuis and Lindwall, *ibid.*, **56**, 471 (1934).
(15) Dohrn and Zöllner, German Patent 375,715, *Chem. Zentr.*, **95**, I, 967 (1924). We obtained a m. p. of 265° for this acid.
(16) Steinkopf and Petersdorff, *Ann.*, **543**, 119 (1940).
(17) White and Bergstrom, *J. Org. Chem.*, **7**, 497 (1942).
(18) Dohrn, U. S. Patent 1,197,462, *C. A.*, **10**, 2985 (1916).
(19) Bose and Guha, *J. Indian Chem. Soc.*, **13**, 700 (1936).
(20) Buu-Hoï and Cagniant, *Rec. trav. chim.*, **62**, 713 (1943).
(21) Forster and Fierz, *J. Chem. Soc.*, **93**, 669 (1908).

of sulfuric acid was then added. Heating was continued while 132 g. (50% excess) of pyruvic acid in 250 ml. of anhydrous ethanol was added dropwise during two hours with mechanical stirring. The mixture was heated for twenty hours, half the alcohol was removed by distillation and the residue was chilled and induced to crystallize by rubbing with methanol. Yields of 30–35% were obtained.

Cinchonic esters were prepared without difficulty by refluxing with alcohol and sulfuric acid except for the 2,3-disubstituted acids which were esterified through the acid chlorides. New esters are summarized in Table III. They were usually crystallized from ligroin, methanol or ethanol (sometimes dilute). Ethyl acetate was used for ethyl 2,2′-bicinchoninate and ether for ethyl 2-(3-pyridyl)-cinchoninate.

α-(2-Piperidyl)-2-aryl-4-quinolinemethanol. VI.—The condensations of ethyl 2-arylcinchoninates with ethyl ε-benzamidocaproate[22] in the presence of sodamide and the hydrolyses of the products to amino ketones (III) were carried out by the procedure used for the 2-phenyl compound.[2] A larger proportion of sodamide did not improve the yields and led to a more pasty reaction mixture which was harder to stir and which never reached an oily state. After the condensation was complete it was advantageous, especially in the case of the 2-(*p*-xenyl) compound, to cool the reaction mixture to 0° and treat with 50% sulfuric acid also at 0° with ice cooling. The cooling sometimes made stirring very difficult. A modified procedure for working up the hydrolysis mixture was used in some cases as indicated in Table I. In those cases the chloroform extract of the basified hydrolysis mixture was washed with 5% sodium hydroxide and water, the solvent removed, the residual oil treated with an amount of 5% acetic acid calculated on the basis of the weight of the oil to yield a diacetate and the mixture heated to boiling. There was usually a small undissolved residue which was removed by adding decolorizing carbon and filtering. The filtrate was cooled and made basic with a volume of 5% sodium hydroxide equal to that of the 5% acetic acid used. This insured the complete separation of the aminoketone (III) and provided an excess of base to retain any of the cinchoninic acid still present. The basic mixture was extracted with chloroform or better three times with ether which had less tendency to take up remaining cinchoninic acid. The ether extracts were dried over anhydrous sodium sulfate, the ether removed and the residue treated with sufficient 48% hydrobromic acid to form a dihydrobromide. The mixture was heated until solution was complete, an equal volume of isopropyl alcohol was added, and after heating to boiling the solution was allowed to cool. Usually the product crystallized and was separated by filtration and washed with isopropyl alcohol and with a little ether. The yield of dihydrobromide was 20–50% based on the cinchoninic ester and not allowing for recovered cinchoninic acid. The amount of recovered acid varied greatly from case to case; it was negligible for 2-(2,5-dimethylphenyl)-cinchoninic acid and 50% for 2-(*p*-bromo or *p*-chlorophenyl)-cinchoninic acid. A Volhard titration was carried out on each aminoketone salt, but in some cases these compounds were mixtures of mono- and dihydrobromides.

The bromination, ring closure and reduction (IV → V → VI) were carried out according to the procedure of Koepfli and co-workers.[2] Data on the final compounds are given in Table I.

α-(2-Piperidyl)-2-(*p*-hydroxyphenyl)-4-quinolinemethanol (VI, R = *p*-hydroxyphenyl) was prepared by refluxing 15 g. of the methoxy derivative (VI, R = *p*-methoxyphenyl) with 500 ml. of 48% hydrobromic acid for seventy-two hours. Crystals began to separate during the heating and upon cooling 16.3 g. (92%) of the dihydrobromide, m. p. 299–300° was obtained. The dihydrobromide was dissolved in 20% sodium hydroxide, the solution filtered and acidified with hydrochloric acid to yield the dihydrochloride which crystallized in fine yellow crystals (Table I). The free amine was liberated from a solution of the dihydrochloride in 20% sodium hydroxide by treatment with carbon dioxide. It seems unusual that the hydrobromic acid treatment did not alter the hydroxyl in the side chain, but the analytical results (Table I) indicate that the product had the structure assigned. Furthermore, the product was remethylated in ethanol solution by treatment with an ether solution of diazomethane, and the methylated product had the same melting point as the starting material (VI, R = *p*-methoxyphenyl). A mixture showed no melting point depression.

(22) This ester was supplied by Dr. C. C. Price and co-workers of the University of Illinois.

Summary

Fourteen new α-(2-piperidyl)-2-aryl-4-quinolinemethanols have been prepared for testing as antimalarials. Data are given for these and for a number of new cinchoninic acids and esters, which were synthesized as intermediates.

LOS ANGELES, CALIF. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1044]

The Synthesis of Potential Antimalarials. 2-Alkyl-α-(2-piperidyl)-4-quinolinemethanols[1]

BY J. F. MEAD, A. E. SENEAR AND J. B. KOEPFLI

For reasons elaborated upon in another communication,[2] it was of interest to prepare an Ainley and King type[3] of carbinol with a group (such as methyl) in the quinoline-2 position and this investigation was started with the limited objective of preparing IIId. While unsuccessful attempts were being made to synthesize IIId, the previously reported[2] (compare Brown, *et al.*,[4] and Buchman, *et al.*[5]) enhancement of the antimalarial activity of α-(2-piperidyl)-4-quinolinemethanol, occasioned by the introduction of an aryl group into the quinoline-2 position, became known and made advisable the broadening of the original scope of this investigation to include preparation of compounds with a secondary alkyl or alicyclic group in this position. The appropriate intermediate was also prepared with the hope of obtaining a

(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 California Institute of Technology.

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

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

(4) Brown, Jacobs, Winstein, *et al.*, THIS JOURNAL, **68**, 2705 (1946).

(5) Buchman, *et al.*, *ibid.*, **68**, 2692 (1946).