tive in producing activation, further supporting the hypothesis of Schiff-base formation for which a terminal primary amine group is required. It is hoped that results of these studies may provide further information concerning the metabolism of dopamine and norepinephrine in terms of endogenous aldehyde levels and agents that alter these levels.

REFERENCES

(1) G. Cohen and M. Collins, *Science*, **167**, 1749(1970).

(2) V. E. Davis and M. J. Walsh, *ibid.*, **167**, 1005(1970).

(3) M. Sandler, S. B. Carter, K. R. Hunter, and G. M. Stern, *Nature*, **241**, 439(1973).

(4) H. C. Sabelli and W. J. Giardina, *Biol. Psychiat.*, **2**, 119(1970).

(5) A. C. Collins, V. E. Davis, and J. Cashaw, Abstracts for the Third Meeting of the American Society for Neurochemistry, Seattle, Wash., Mar. 1972, p. 66.

(6) J. Axelrod and R. Tomchick, *J. Biol. Chem.*, **233**, 702(1958).

(7) J. Axelrod and E. S. Vesell, *Mol. Pharmacol.*, **6**, 78(1970).

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Synthesis and Screening of Potential Antimalarial Agent α-(2-Piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol Hydrochloride

JAROSLAV NOVOTNY, CAROL H. COLLINS, and FRED W. STARKS[x]

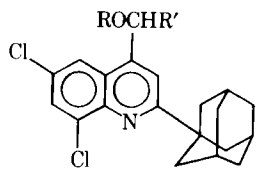
Abstract □ The synthesis and biological testing of α-(2-piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol hydrochloride and its *O*-acetyl and *N*-acetyl derivatives are reported. Direct hydrogenation of the α-pyridyl ketone gave very low yields. A novel procedure was developed which permits formation of piperidyl quinolinemethanols in satisfactory yields.

Keyphrases □ α-(2-Piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol hydrochloride (and *N*-acetyl and *O*-acetyl derivatives)—synthesized and screened as potential antimalarial agents □ Quinolinemethanols, α-(2-piperidyl) analog and *N*-acetyl and *O*-acetyl derivatives—synthesized and screened as potential antimalarial agents □ Antimalarial agents, potential—synthesis and screening of α-(2-piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol hydrochloride and *N*-acetyl and *O*-acetyl derivatives

Antimalarial activity has been reported for many derivatives of the quinine analog 4-quinolinemethanol. Mono- or disubstitutions at the 6-, 7-, or 8-position of the quinoline nucleus enhance activity relative to the unsubstituted compound, while substitution at the 2-position appears necessary to retard metabolic oxidation of the quinoline skeleton (1–4).

Unfortunately, the more active 2-aryl-4-quinolinemethanols also have undesirably high phototoxicity, which might detract from their use as antimalarial agents in humans (3, 5–8). Recently, a number of 4-quinolinemethanols were prepared with nonaryl substitution at the 2-position (9–11). Mixed results indicated further search for appropriate substitution at this position. Use of an adamantyl substituent at position 2 was suggested by the enhanced biological activity of this substituent in comparison to more conventional saturated moieties in other medicinal agents (12–14). Synthesis of several 2-adamantylquinolinemethanols has been reported (15). The promising antimalarial activity of α-(di-*n*-butylaminomethyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol (I*a*) (15) suggested that the α-(2-piperidyl) analog (I*b*) should be synthesized and tested.

The synthesis and biological screening of α-(2-piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol (I*b*) as well as the related *N*-acetyl (I*c*) and *O*-acetyl (I*d*) derivatives are reported here. Preparation of (I*d*) was necessitated when the usual selective catalytic hydrogenation of the pyridyl ketone (4, 16) produced the desired product in very small yields. The modification, a two-step reduction, permits good yields of the α-2-piperidyl-4-quinolinemethanol (I*b*).



I*a*: R = H, R′ = $CH_2N(C_4H_9)_2$
I*b*: R = H, R′ = 2-piperidyl
I*c*: R = H, R′ = *N*-acetyl-2-piperidyl
I*d*: R = CH_3CO, R′ = 2-piperidyl

CHEMISTRY

Compound I*b* was prepared as illustrated in Scheme I. Acetyladamantane (II) (17, 18) was obtained in 59% yield, by the method of Tegner (19), from the addition of methyllithium to adamantane-1-carboxylic acid followed by hydrolysis. A by-product of this reaction, 2-(1-adamantyl)propan-2-ol (20), was also isolated in low yield (about 4%). The formation of this product was somewhat surprising, because Tegner (19) suggested that methyllithium should not react further with the dilithium salt of the ketone, even though phenyllithium has been shown to give tertiary alcohols in its reaction with carboxylic acids and their derivatives (21).

In this study, the Pfitzinger (22) condensation of 5,7-dichloroisatin and II produced the cinchoninic acid (III) (15) in 48% yield. Slow addition of III to α-pyridyllithium (23, 24) at −74° followed by hydrolysis gave pyridyl ketone (IV) in 84% yield. When this reaction was carried out at −60°, according to literature directions (4), the yield was only 46%.

When the one-step selective hydrogenation (4, 16) of IV to *Ib* was attempted, the desired compound was obtained in only 4% yield. This occurred in conjunction with a theoretical absorption of hydrogen. Similar low product yields and the formation of side-products have been reported in the selective hydrogenation of several other 2-pyridyl quinolyl ketones that lacked a 2-aryl substituent (10, 11).

A satisfactory yield of *Ib* ensued by first reducing the carbonyl with sodium borohydride (99% yield), acetylating the carbinol (60%), hydrogenating this (59%), and, finally, hydrolyzing the reduced *O*-acetyl compound (*Id*) in 52% yield. Compound *Id* hydrolyzed smoothly to *Ib* in either sodium methoxide or concentrated hydrochloric acid. However, in ammonium hydroxide at room temperature, the acetyl group migrated to the piperidyl nitrogen. The molecular arrangement of the piperidyl nitrogen and methanol oxygen made probable the facile formation of a six-membered ring as an intermediate in this intramolecular migration under the mild conditions employed. Use of stronger reagents hydrolyzes either the *N*-acetyl or the *O*-acetyl compound.

BIOLOGICAL ACTIVITY

Compound *Ib* and the several intermediates were tested[1] for antimalarial activity against *Plasmodium berghei* in mice and against *P. gallinaceum* in chicks. Assessment of activity was based on the influence of various doses of the compounds upon the survival times of groups of mice in comparison with untreated controls (mean survival time 6.2 days). Those surviving more than 60 days were adjudged "cured." Compound *Ib* was active at the 320-mg/kg level against *P. berghei*, effecting two (out of five) cures at this level. None of the other compounds (*Ic*, *Id*, IV, V, and VI) showed antimalarial activity (Table I).

Compounds *Id*, *Ic*, and *Ib* were also evaluated against blood-induced *P. gallinaceum* infections in chicks (25)[1]. They showed no significant activity. A similar response to *P. berghei* and *P. gallinaceum* has been reported for the di-*n*-butylaminomethyl analog (*Ia*) (15).

Table I—Antimalarial Activity in Blood-Induced Infections

Dose, mg/kg	Increase in Survival Time, Days: Evaluation against *P. berghei* KBG Malaria in Young Noninbred ICR/HA Swiss Mice[a]		Evaluation against *P. gallinaceum* Brumpt 8A in 9–12-day-old White Leghorn Chicks[a]
	Ib	*Id*	*Ib*
10	0.3		
20	0.3 0.3	0.1	0.0
40	0.5 0.3	0.3	0.0
80	0.5 0.5	0.3	0.0
160	2.1 1.9	0.7	0.0
320	2/5C[b]	1.9	0.0
640	2/5C[b]	5.9	3.4

[a] The test results were provided by the Walter Reed Army Institute of Research through the courtesy of Dr. T. R. Sweeney and Dr. B. T. Poon. [b] C = cures, the number of mice surviving 60 days after infection.

EXPERIMENTAL[2]

1-Acetyladamantane (II)—In a modification of the method of Tegner (19), an excess of methyllithium (2 *M* in ether) was added dropwise to a stirred solution of 721 g (4.0 moles) of adamantane-1-carboxylic acid[3] in 6 liters of ether, maintained under nitrogen at from −10 to 0° by partial immersion in a dry ice–acetone bath. The mixture was stirred at room temperature for 1 hr and then hydrolyzed by dropwise addition of wet ether followed by water. The organic layer was separated, washed with water, and dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the crude product was recrystallized from methanol to give 420 g (59%) of analytically pure material, mp 51–53° [lit. (17, 18) mp 53–54°]. The product was homogeneous to VPC with a retention time of 14.2 min.

Anal.—Calc. for $C_{12}H_{18}O$: C, 80.85; H, 10.18; O, 8.97. Found: C, 80.62; H, 10.18; O, 9.16.

2-(1-Adamantyl)propan-2-ol—The mother liquor from recrystallization of crude 1-acetyladamantane was spin evaporated to an oil which was distilled (bp 65–67°/10 mm). An analytically pure product was obtained by crystallization from aqueous ethanol, mp 65–67° [lit. (20) mp 77–80°]. The product was homogeneous to VPC with a retention time of 14.8 min and was identical to a sample synthesized independently from methylmagnesium iodide and acetyladamantane.

Anal.—Calc. for $C_{13}H_{22}O$: C, 80.36; H, 11.41. Found: C, 80.45; H, 11.50.

6,8-Dichloro-2-(1-adamantyl)cinchoninic Acid (III)—A mixture of 178 g (1.00 mole) of II, 197 g (0.910 mole) of 5,7-dichloroisatin[3], 1 liter of ethanol, 340 ml of water, and 161 g (2.90 moles) of potassium hydroxide was refluxed for 17 hr, cooled, and then evaporated *in vacuo* to a residue (22). The residue was partitioned between water and ether. The aqueous layer was separated, washed with ether, and then acidified by addition of concentrated hydrochloric acid to precipitate the product. The solid was collected, washed by resuspension in hot ethanol, dried, and recrystallized from acetone to yield 166 g (48%), mp 260–263° dec. [lit. (15) mp 258–261°]; λ_{max} ($\epsilon \times 10^{-3}$): 241 (29.0), 298 (4.6), and 332 (4.6) nm.

Anal.—Calc. for $C_{20}H_{19}Cl_2NO_2$: C, 63.84; H, 5.09; N, 3.72. Found: C, 64.07; H, 5.05; N, 3.68.

2-Pyridyl-2-(1-adamantyl)-6,8-dichloro-4-quinolyl Ketone (IV)—An ethereal solution of 2-pyridyllithium was prepared, according to the method of Wibaut *et al.* (23), from 166 g (1.05 moles) of 2-bromopyridine, 1000 ml of ether, and 425 g (1.00 mole) of a 15% solution of *n*-butyllithium in hexane. While maintaining the nitrogen atmosphere, the ethereal solution was cooled to −74° and 125 g (0.333 mole) of III was added portionwise over 1.25 hr. After the addition, the mixture was stirred for 1 hr at −73°, for 1 hr at between −70 and −68°, for 1 hr at between −68 and −63°, and for 1 hr between −63 and −59°. After warming slowly to 10°, 500 ml of water was cautiously added. After separating the layers, the aqueous portion was extracted several times with ether. The combined ether solution was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was triturated with ethanol to yield crude product, which was recrystallized from ethanol, yielding 122 g (84%), mp 138–140°, homogeneous to TLC; λ_{max} ($\epsilon \times 10^{-3}$): 232 (38.6) and 332 (4.0) nm.

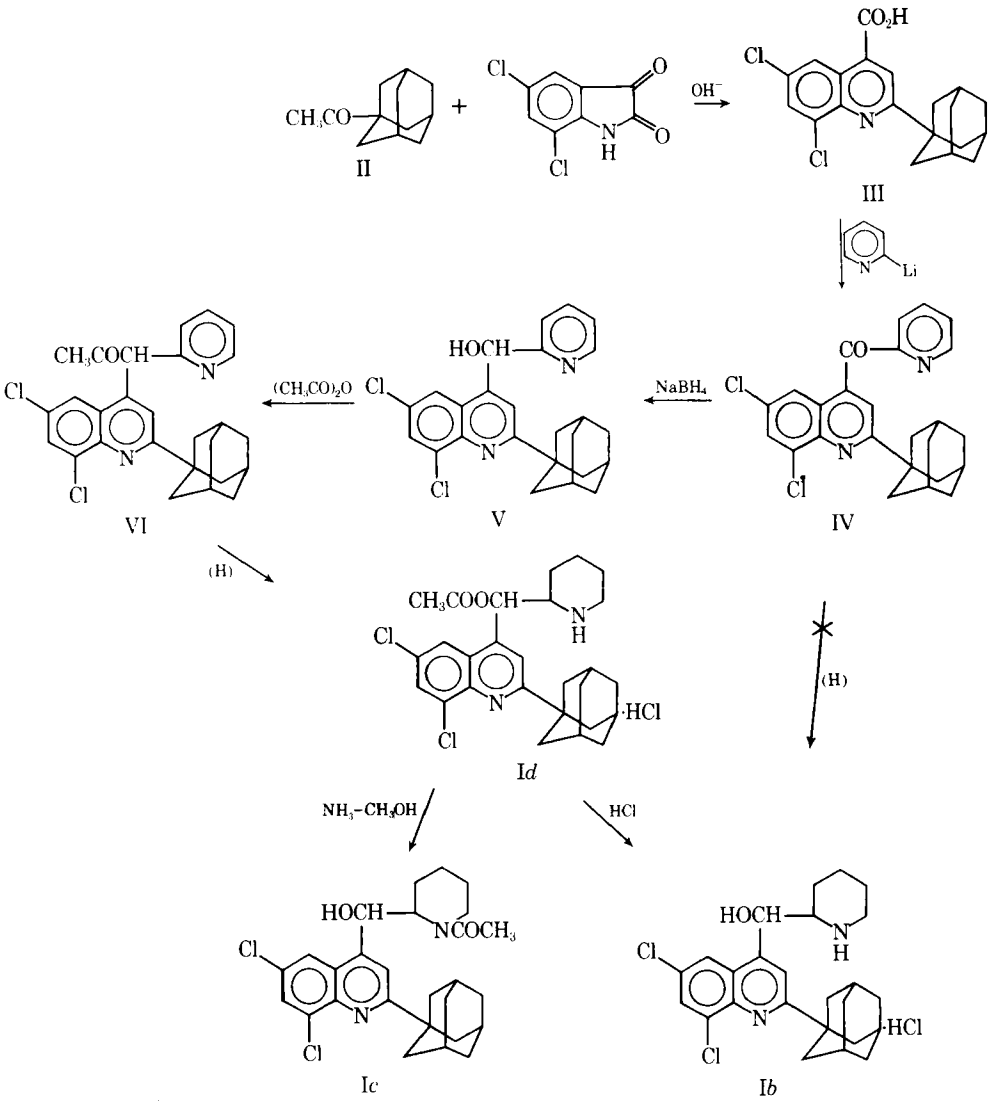
Anal.—Calc. for $C_{25}H_{22}Cl_2N_2O$: C, 68.66; H, 5.07; Cl, 16.21; N, 6.40. Found: C, 68.60; H, 5.24; Cl, 16.06; N, 6.60.

α-(2-Pyridyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol (V)—Sodium borohydride (51.3 g, 1.35 moles) was added portionwise to a stirred solution of 593 g (1.35 moles) of IV in 9 liters of ethanol. The mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in chloroform, which was then washed with water, dried (magnesium sulfate), and removed by spin evaporation *in vacuo*. The residue was recrystallized from methanol to give 587 g (99%) of product, pure to TLC (four systems), mp 177–177.5°; λ_{max} ($\epsilon \times 10^{-3}$): 238 (31.2), 262 (4.3), 268 (4.3), 284 (4.2), 316 (2.2), and 330 (2.3) nm.

[1] By Dr. L. Rane of the Malaria Screening Laboratory, University of Miami (25). The test results were provided by the Walter Reed Army Institute of Research through the courtesy of Dr. T. R. Sweeney and Dr. B. T. Poon.

[2] Melting points were determined on a Fisher-Jones apparatus. Those below 230° are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. UV spectra were determined in ethanol with a Bausch and Lomb Spectronic 505 spectrophotometer. TLC was run on Eastman silica gel chromagram sheets 6060, using at least three different solvent systems for each compound. Vapor phase chromatography (VPC) was carried out using a Hewlett-Packard model 5750B, temperature programmed at 10°/min from 40 to 250°, using a 2-m × 3-mm column packed with 10% UC-W982 on 80–100-mesh Diatoport S.

[3] Aldrich Chemical Co.



Scheme I

Anal.—Calc. for $C_{25}H_{24}Cl_2N_2O$: C, 68.34; H, 5.51; Cl, 16.14; N, 6.38. Found: C, 68.38; H, 5.36; Cl, 16.10; N, 6.23.

α-(*O*-Acetyl)-α-(2-pyridyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol (VI)—A solution of 461 g (1.05 moles) of V in 1690 ml of acetic anhydride was heated at approximately 100° for 45 min. While still hot, the excess acetic anhydride was hydrolyzed with water. After cooling, the reaction mixture was poured into additional water. The white solid that separated was collected, washed with water, and recrystallized from ethanol to give 303 g (60% yield) of pure product (TLC), mp 174–175°; λ_{max} ($\epsilon \times 10^{-3}$): 240 (48.2), 268 (6.3), 286 (6.4), 319 (3.7), and 333 (3.8) nm.

Anal.—Calc. for $C_{27}H_{26}Cl_2N_2O_2$: C, 67.36; H, 5.44; Cl, 14.72; N, 5.81; O, 6.64. Found: C, 67.44; H, 5.47; Cl, 14.83; N, 5.83; O, 6.69.

α-(*O*-Acetyl)-α-(2-piperidyl)-2-(1-adamantyl)-6,8-dichloro-4-quinolinemethanol Hydrochloride (I*d*-HCl)—A mixture of 71.2 g (0.148 mole) of VI, 900 ml of absolute ethanol, 25 ml of concentrated hydrochloric acid, and 0.8 g of platinum oxide was hydrogenated at 50 psi until the theoretical amount of hydrogen (3 moles) had been consumed (4 hr). The resulting suspension was dissolved in 1700 ml of absolute ethanol and filtered through a diatomaceous earth[4] pad. The filtrate and washings were concentrated *in vacuo* to give a crude product, which was recrystallized from absolute ethanol to give 42 g (59%) of pure product (TLC), mp 205.5–207.5° dec.; λ_{max} ($\epsilon \times 10^{-3}$): 239 (55.1), 285 (5.8), 320 (3.6), and 334 (3.7) nm.

Anal.—Calc. for $C_{27}H_{33}Cl_3N_2O_2$: C, 61.90; H, 6.35; Cl, 20.32; N, 5.35; O, 6.11. Found: C, 61.83; H, 6.43; Cl, 20.13; N, 5.26; O, 6.07.

α-[2-(1-Acetylpiperidyl)]- 2-(1-adamantyl)- 6,8-dichloro- 4-quinolinemethanol (I*c*)—Dry methanol (1000 ml), saturated with ammonia at 0°, was added to 10.0 g (0.020 mole) of solid I*d*-HCl at 0°. The mixture was kept at 0° overnight. Volatiles were removed by spin evaporation *in vacuo*, and the resulting solid was dissolved in 500 ml of chloroform. This solution was washed with water, dried (magnesium sulfate), and concentrated *in vacuo* to give a crude product, which was recrystallized from methanol to yield 4.4 g (44%), mp 246–249°, pure to TLC; λ_{max} ($\epsilon \times 10^{-3}$): 238 (46.7), 285 (6.0), 317 (3.1), and 331 (3.1) nm.

Anal.—Calc. for $C_{27}H_{32}Cl_2N_2O_3$: C, 64.41; H, 6.41; Cl, 14.08; N, 5.56; O, 9.53. Found: C, 64.35; H, 6.51; Cl, 14.19; N, 5.51; O, 9.22.

α-(2-Piperidyl)- 2-(1-adamantyl)- 6,8-dichloro-4-quinolinemethanol Hydrochloride (I*b*-HCl)—A solution of 237 g (0.487 mole) of I*d*-HCl in 2370 ml of concentrated hydrochloric acid was refluxed overnight, cooled to 15°, and neutralized to pH 12 with 33% aqueous sodium hydroxide. The white precipitate was collected, washed with water, and then dissolved in 20 liters of chloroform. The solution was dried (magnesium sulfate) and then saturated with 230 g (16.3 moles) of anhydrous hydrogen chloride. The white solid was filtered, washed with ether, and dried before being dissolved in 38 liters of ethanol containing 45 ml of concentrated hydrochloric acid. The solution was filtered hot, and the filtrate was reduced in volume to about 5.5 liters. The product crystallized on cooling to yield 122 g (52%) of material pure to TLC, mp 253–255° dec.; λ_{max} ($\epsilon \times 10^{-3}$): 237 (46.5), 283 (5.8), 317 (3.1), and 330 (3.4) nm.

Anal.—Calc. for $C_{25}H_{31}Cl_3N_2O$: C, 62.31; H, 6.48; Cl, 22.07; N,

[4] Celite.

5.81. Found: C, 62.15; H, 6.70; Cl, 21.80; N, 5.67.

An identical product was obtained by treating 10 g of Id-HCl with 40 ml of a 1 *M* solution of sodium methoxide in 1000 ml of dry methanol.

REFERENCES

(1) R. E. Lutz, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freck, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, Jr., J. M. Salsbury, N. H. Shearer, Jr., J. D. Smith, and J. W. Wilson, III, *J. Amer. Chem. Soc.*, **68**, 1813(1946).

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

(3) J. P. Schaefer, K. S. Kulkarni, R. Costin, J. Higgins, and L. M. Honig, *J. Heterocycl. Chem.*, **7**, 607(1970).

(4) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273(1968).

(5) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366(1968).

(6) I. G. Fels, *ibid.*, **11**, 887(1968).

(7) E. R. Atkinson and A. J. Puttick, *ibid.*, **13**, 537(1970).

(8) *Ibid.*, **11**, 1223(1968).

(9) R. M. Pinder and A. Burger, *J. Med. Chem.*, **11**, 267(1968).

(10) A. R. Patel, C. J. Ohnmacht, D. P. Clifford, A. S. Crosby, and R. E. Lutz, *ibid.*, **14**, 198(1971).

(11) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, **14**, 926(1971).

(12) K. Gerson and D. Kau, *ibid.*, **10**, 189(1967).

(13) A. N. Voldeng, C. A. Bradley, R. D. Kee, E. L. King, and F. L. Melder, *J. Pharm. Sci.*, **57**, 1053(1968).

(14) V. L. Narayana, *J. Med. Chem.*, **15**, 1180(1972).

(15) R. B. Fugitt and R. M. Roberts, *ibid.*, **16**, 875(1973).

(16) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459(1967).

(17) H. Stetter and E. Raucher, *Chem. Ber.*, **93**, 2054(1960).

(18) S. Hala and S. Landa, *Collect. Czech. Chem. Commun.*, **25**, 2692(1960).

(19) C. Tegner, *Acta Chem. Scand.*, **6**, 782(1952).

(20) E. C. Hermann and J. A. Snyder (to E. I. duPont de Nemours and Co.), U.S. pat. 3,284,445 (Nov. 8, 1966); through *Chem. Abstr.*, **66**, 28760(1967).

(21) H. Gilman and P. R. van Ess, *J. Amer. Chem. Soc.*, **55**, 1258(1933).

(22) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 383(1897); *cf.*, H. G. Lindwall, J. Bancles, and I. Weinberg, *J. Amer. Chem. Soc.*, **53**, 317(1931).

(23) J. P. Wibaut, A. P. de Jonge, H. G. P. Van der Voort, and P. P. H. L. Otto, *Rec. Trav. Chim.*, **70**, 1054(1951).

(24) H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, **62**, 446(1940).

(25) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431(1967).

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Binding of Quinidine to a Red Blood Cell Hemolysate Preparation

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Abstract □ A constant degree of binding of quinidine to a red blood cell hemolysate preparation was found for a clinically significant range of concentrations at 37° using the methods of equilibrium dialysis and ultracentrifugation. By repeating the binding experiments at 37° but over a much wider range of quinidine concentrations, it was possible to calculate an association constant (252 liters/mole) and the apparent number of binding sites (1.54). Quinidine appeared to be bound to a single binding site. In another series of experiments performed at therapeutic levels and 37°, the competitive binding of quinidine was studied in the presence of red blood cell hemolysate and serum, each placed in individual compartments of a dialysis cell but separated by a semipermeable membrane. Following attainment of equilibrium, free drug was separated from bound drug by ultracentrifugation. Calculations indicated that slightly more than half of the drug was contained within the serum compartment.

Keyphrases □ Quinidine—binding to a red blood cell hemolysate preparation, influence on protein binding of quinidine, binding parameters □ Binding—quinidine to a red blood cell hemolysate preparation, influence on protein binding of quinidine □ Erythrocyte binding—quinidine to a red blood cell hemolysate preparation, binding parameters

Quinidine has been shown to interact with various proteins contained within the body's vascular pool. For example, elucidation of a quantitative quinidine–albumin relationship at pH 7.4 established the existence of one receptor location on an albumin molecule and an association constant of 7.7×10^3 (1). There is also extensive binding of quinidine to human platelets as evidenced by its large accumulation within the platelet, much greater than would be expected on the basis of pH partitioning (2). Moreover, quinidine has been found to penetrate red blood cells (3), which might be expected to occur for an organic base with a pKa of 8.6 (4) whose unionized form is lipid soluble (5). Because of its potential for binding, the purposes of this study were to determine the binding affinity of quinidine to an erythrocytic preparation obtained from freshly drawn human blood samples and to determine its competitive influence on the protein binding of quinidine in human serum.