TABLE XV[a]

Exposure	Day	ϵ_{355}[b]	ϵ_{290}[c]	$\epsilon_{355}/\epsilon_{290}$
Light	1	20,600	8250	2.5
Light	3	10,200	7700	1.3
Light	10	10,300	7480	1.4
Light	17	8,250	7100	1.2
Dark	24	10,100	7050	1.4
Dark	31	13,000	7090	1.8

[a] Changes in the uv spectrum of *trans*-**76** on exposure to (i) diffuse daylight, fluorescent lighting for 17 days, and (ii) after exposure to light and storage in the dark for 14 days. [b] Calculated ϵ value at 355 mμ, a maximum in spectrum of **76**. [c] Calculated ϵ value at 290 mμ, another maximum in the spectrum.

TABLE XVI[a]

Sample	Exposure	% redn of *N. dubius* —burden at 25 mg/kg— Day 1	Day 3	Day 17
76	Dark	99	93	82
	Light	99	90	89
Pyrantel	Dark	99	99	96
	Light	99	78	15

[a] Table is explained in the text.

dramatic change in chemical structure. In the parallel experiment, the pyrantel solution lost activity upon exposure to light. From previous experience[2] it is known that pyrantel is readily converted to its *cis* isomer by the action of light, and that the *cis* isomer is only about 0.03 times as potent as the *trans* isomer.

That the apparent isomerization of **76** is reversible is indicated by the continuation of the experiment. The light-exposed solution was placed in the dark box, and was allowed to stand there at room temperature for 2 weeks. The uv spectrum was determined after 7 and 14 days in the dark. Although little change was observed after 1 week, it was apparent that by 2 weeks the original spectrum of the *trans* isomer was beginning to emerge (see Table XV). However, the uncatalyzed rate of conversion back to the *trans* isomer is too slow to account for the observed activity of the presumed *cis* isomer. In one effort to isolate the *cis* isomer of the free base **38**, an oil was obtained; an attempt to crystallize this material resulted only in the isolation of unchanged *trans* isomer.[12] Thus, it appears that whatever change **76** undergoes on exposure to light, it is readily reversible and is therefore unlikely to involve an oxidative cyclization or a similar irreversible change of structure. The common experience that light induces the isomerization of *trans*-olefins to the *cis* isomers and the analogy to pyrantel's reaction to light strongly suggest that the light-induced change in **76** is also to the *cis* isomer.

Acknowledgments.—The authors wish to thank Messrs. P. N. Gordon, R. B. James, G. F. Smith, R. W. Sumner, and T. F. Estabrooks of the Pfizer Medical Research Laboratories for valuable assistance rendered during the course of this investigation.

(12) P. N. Gordon, private communication.

Quinoxaline Studies. XV.[1a] Potential Antimalarials. Some (*RS*)-α-(Dialkylaminomethyl)-2-quinoxalinemethanols[1b]

HENRY R. MORENO AND HARRY P. SCHULTZ

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received September 5, 1969

Six (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols were prepared from 2-tetrahydroxybutylquinoxaline *via* an eight-step sequence. Neither intermediates nor target compounds (diethylamino through di-*n*-heptylamino derivatives) possessed antimalarial activity against *Plasmodium berghei* in mice.

Certain quinolinemethanols,[2] long used as antimalarial agents, frequently have less activity toward newer strains of malaria organisms. Because of the similarity of quinoline and quinoxaline, as well as the presence of the quinoxaline moiety in some broad spectrum (but toxic) antibiotics,[3] it was hoped that quinoxaline analogs of quinoline antimalarials would exhibit antimalarial activity. The purpose of this paper is to report the synthesis of a series of (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols, incorporating diethylamino through di-*n*-heptylamino groups, for testing as antimalarials.

Chemistry.—The desired synthetic objective was attained *via* the sequence D-*arabino*-2-tetrahydroxybutylquinoxaline (**1**),[4] 2-quinoxalinecarboxylic acid (**2**),[4] 2-quinoxaloyl choride (**3**),[4] 2-diazoacetylquinoxaline (**4**), 2-chloroacetylquinoxaline (**5**), (*RS*)-α-(chloromethyl)-2-quinoxalinemethanol (not analyzed) (**6**), (*RS*)-2-quinoxalinepoxyethane (**7**), and (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols (**8**).

2-Quinoxalinecarboxylic acid was prepared from **1** by a considerable improvement of existing procedures, the material being isolated and purified as its Na salt. Treatment of **3** with CH_2N_2 gave **4** (not isolated), which was transformed by standard methods into **5**. A variety of reaction conditions failed to transform secondary amines and **5** into the corresponding amino ketones; only red, irresolvable tars were obtained.

The reduction of **5** with $NaBH_4$ gave **6**, unstable, flaring within 1–10 hr of drying to black ash, from which small flakes of 2-acetylquinoxaline were isolated manually. Nonetheless, freshly isolated **6** was treated immediately with Et_2NH in an attempt to form a target compound **8**, either *via* a substitution reaction on **6**, or *via* transformation *in situ* of **6** into **7**, which in turn could react with Et_2NH to yield **8**. However, only 2-acetylquinoxaline was obtained, possibly by a reaction mechanistically related to the hydramine fission (Scheme I). Alternatively, elimination of HCl from **6** may have been spontaneous (*vide supra*), or promoted by basic N atoms of the quinoxaline nucleus.

The amino ketone or chlorohydrin (**6**) derivatives of quinoxaline were thus eliminated as direct intermediates

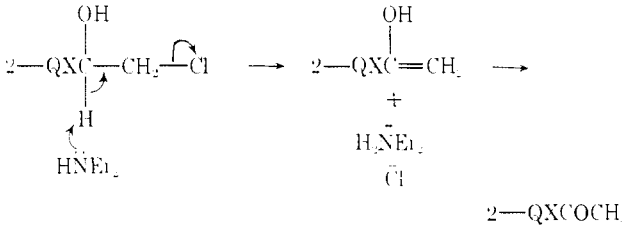
(1) (a) Paper XIV of this series: S. Gerchakov and H. P. Schultz, *J. Med. Chem.*, **12**, 141 (1969). (b) Contribution No. 691 from the Army Research Program on Malaria, supported by the U. S. Army Medical Research and Development Command *via* Contract DADA 17-67-C-7064.

(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, Survey of Antimalarial Agents, Public Health Monograph No. 9, U. S. Government Printing Office, Washington, D. C., 1953.

(3) H. Otsuka and J. Shoji, *Tetrahedron*, **23**, 1535 (1967), and references therein.

(4) S. Gerchakov, P. J. Whitman, and H. P. Schultz, *J. Med. Chem.*, **9**, 266 (1966). 2-Quinoxaloyl chloride is now commercially available.

SCHEME I

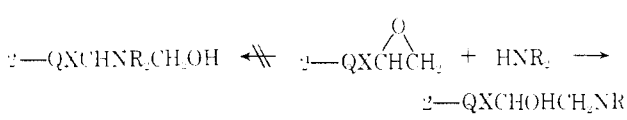


for making **8**. The epoxide **7** remained by default the *sine qua non* for the preparation of **8**. Dehydrohalogenation of **6** with EtOH–NaOH gave **7**, which was stable. Attempts to transform **5** directly into **7**, without isolating **6** from the $NaBH_4$ reduction mixture, yielded only tars.

Target compounds **8** were stable oils at room temperature, but slowly decomposed at elevated temperatures. Hence, the extent of formation of **8** by condensation of secondary amines with **7** was carefully monitored by observing the change in pmr spectra of the reaction solutions as the reactions progressed. The downfield shift of the 3-H of the quinoxaline unit as **7** was transformed into **8** was obvious, amounting to δ 0.6 ppm. Best yields of **8** were obtained when reactions were interrupted at 80–90% completion.

Pmr spectra of the target compounds **8** provided further essential data, proof that the secondary amines reacted with **7** to give secondary alcohols and not primary alcohols (Scheme II).

SCHEME II



Dyer[5] refers to the deshielding influence that the OAc group has upon adjacent carbinol H, $\Delta\delta$ 1.1 ppm for secondary and $\Delta\delta$ 0.5 ppm for primary alcohol acetates, as well as the change in splitting patterns. Each target compound, from crude reaction mixture as well as final product, contained only desired **8**, for the pmr resonance of the carbinol H changed from a quartet at δ 4.88 ppm in the secondary alcohol to a broad triplet at δ 5.98 ppm in the corresponding OAc derivative. One OAc derivative of a target substance (the NBu_2 compound) was isolated and analyzed as its pamoate [4,4′-methylenebis(3-hydroxy-2-naphthoate)] salt; in all other instances Ac_2O was added directly to solutions of **8** in CCl_4. These solutions exhibited the pmr spectra of the secondary alcohol OAc derivatives of **8** within 15 min at 24°.

The pmr resonance value for the secondary carbinol H quartet listed in footnote *b* of Table I was actually the value for two adjacent doublets (J = 5, 9 Hz). Exchange experiments with D_2O proved that under the circumstances of these pmr studies, the secondary carbinol H of **8** was not coupled with the adjacent hydroxy H; rather, the carbinol H was coupled only with the two adjacent diastereotopic primary H. For the same reason, the triplet listed in footnote *b* of Table I for the secondary carbinol H of the OAc derivatives of **8** was actually two overlapping doublets ($J_{HA} \simeq J_{HB} \simeq 6.5$ Hz).

All target compounds were oils, sensitive to heat and acid, hence requiring careful purification for analysis and testing. Each **8** was transformed into a solid derivative with pamoic acid (except the NEt_2 derivative of **8**, which formed a pamoate that was an unstable oil). The NMe_2 derivative of **8** was prepared, but was unstable as the free base, as the OAc, and as the pamoate.

The heat sensitivity of the **8** pamoates interdicted purification by usual recrystallization procedures; therefore, the bases and pamoate solutions were scrupulously purified before interaction. At best, the **8** pamoates were probably glasses, rather than true crystals, for the melting points of all the pamoates were observed to possess large temperature ranges with gradual softening and decomposition. Because of this, the only acceptable criterion of purity for the pamoate salts was elemental analysis. Table I summarizes data on the target compounds.

Biological Results.—All compounds were tested by the previously described procedure[6] for antimalarial activity against *Plasmodium berghei* in mice. All intermediates and target compounds were inactive and nontoxic. Data are recorded in Table I.

Experimental Section[7]

2-Quinoxalinecarboxylic Acid (2).—To a cold suspension of 40 g of Na_2O_2 (98.4%) in 135 ml of H_2O in a 1-l. flask equipped with a large paddle stirrer was added 26.8 g of D-*arabino*-2-tetrahydroxybutylquinoxaline monohydrate.[4] The thick sludge was heated to 75°, at which temperature the reaction became exothermic; for 20 min the temperature was kept at 80 ± 2° by occasional cooling of the flask. After the exothermic character of the reaction waned, the internal temperature of the reaction mixture was maintained for 30 min at 80 ± 2° by heating. The flask was stored at 10° for 12 hr, the product was filtered with suction, and the flask and filter cake of crude sodium 2-quinoxalinecarboxylate were rinsed twice with 25-ml portions of EtOH–Me_2CO (1:1), then with Me_2CO until the filtrate was colorless. The crude salt was dissolved in 300 ml of warm H_2O, treated with decolorizing carbon and filter aid, and filtered, and to the filtrate was added 120 ml of 1 *N* HCl to give 12 g (69%) of **2**, mp 211.5–212° dec (lit.[4] mp 215°).

2-Chloroacetylquinoxaline (5).—To 90 ml of 40% NaOH and 300 ml of USP Et_2O at 0°, 10.6 g of EXR-101 (Du Pont; *N*,*N*′-dinitroso-*N*,*N*′-dimethylterephthalamide in mineral oil) was slowly added with stirring, collecting the CH_2N_2 beneath 200 ml of Et_2O in a receiving flask cooled to 0°. The reaction mixture was warmed to 30–40°, while CH_2N_2 (about 2 g) continued to distil. The flask of CH_2N_2–Et_2O was adjusted for reflux and fitted with a stirrer, then 3.86 g of **3**[4] was added. The solution was stirred for 2 hr at 24° and cooled to 5°; anhydrous HCl was bubbled into the Et_2O solution of **4** at 5°. The solution darkened and a white precipitate formed, heralding conclusion of the reaction. H_2O (10 ml), followed by excess of solid $NaHCO_3$, were added. After removal of Et_2O by evaporation, the residual yellow solid was triturated with H_2O and filtered to give 4.15 g (100%) of **5**, mp

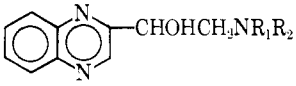
[5a] J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 87.

[6] T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). The authors thank the staff of the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for transmitting the test results provided by Dr. L. Rane, University of Miami.

[7] Uv absorption spectra were obtained from samples at concentrations of 5 mg/l. of 95% EtOH with a Bausch and Lomb Spectronic 505 spectrophotometer using 1-cm silica cells. H nmr spectra, all referred to TMS, were determined on an Hitachi Perkin-Elmer R-20 spectrometer at 60 MHz, 34°; the δ values for multiplets were taken at the center of gravity. The pmr carbinol δ values are noted to be temperature, concentration, and solvent dependent. Melting points, determined on a Thomas-Hoover apparatus, were uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

TABLE I

(*RS*)-α-(DIALKYLAMINOMETHYL)-2-QUINOXALINEMETHANOLS[a-c]



No.	R_1, R_2	Formula	Reaction time, hr	Reaction solvent, reflux	% yield Base	% yield Pamoate	Pamoate mp dec, C[c]	Antimalarial act., life span increase, days, mouse, 640 mg/kg[e]
1	Et[d]	$C_{14}H_{19}N_3O$	3.3	Et_3NH	38			0.4
2	*n*-Pr	$C_{55}H_{62}N_6O_8$	9.5	Dioxane	68	29	100–150	0.2
3	*n*-Bu	$C_{59}H_{70}N_6O_8$	29	CCl_4	62	43	80–130	0.3
4	*n*-Pe	$C_{63}H_{78}N_6O_8$	38	CCl_4	47	28	78–105	0.9
5	*n*-Hex	$C_{67}H_{86}N_6O_8$	16	Dioxane	26	13	75–92	0.3
6	*n*-Hep	$C_{71}H_{94}N_6O_8$	13.5	Dioxane	89	41	65–85	0.0

[a] Uv spectra of pamoates were as expected; average λ_{max}[mμ (ε)] 237–238 (152,000), 278–279 (10,600), 289–290 (13,700), 301–302 (12,600), 318–321 (13,700). [b] H nmr spectra of bases were as expected; average δ[ppm(CCl_4)] 4.19 (s, 1 H, HCO*H*), 4.88 (q, 1 H, *H*COH), 8.05 (m, 4, H, aromatic), 9.18 (s, 1 H, heterocyclic); average δ (ppm) for OAc derivatives: 5.98 (t, 1 H, *H*COAc), 7.86 (m, 4 H, aromatic), 8.84 (s, 1 H, heterocyclic); also present, complex peaks of alkyl substituents. [c] Products, except the diethylamine compound, were isolated and analyzed as the diammonium pamoate salts. All analyses were C, H, and N; values were within ±0.4% of the theoretical values. [d] Uv spectrum, λ_{max} [mμ (ε)] 236 (26,400), 310 (5600), 318 (6700); $n^{23.5}$D 1.5700. [e] Average life span of control mice infected with *Plasmodium berghei*, 6.2 days.

145–147° dec. The material was dissolved in 40 ml of 9 *N* HCl, treated with decolorizing carbon and filter aid, and filtered into 80 ml of H_2O to give 3.94 g (95%) of **5**, mp 148–148.5° dec. Recrystallization of **5** from C_6H_6–hexane (1:2, 15 ml/g) gave 1.66 g (40%) of **5**: mp 147.5–148° dec; λ_{max} 209 mμ (ε 15,500), 240 (21,100), 251 (24,200), 310 (6900), 319 (7300). *Anal.* ($C_{10}H_7ClN_2O$) C, H, Cl, N.

(*RS*)-**2-Quinoxalineepoxyethane** (**7**).—A suspension of 20.7 g of **5** in 200 ml of THF–EtOH (1:1) was cooled to 0°. With stirring, 1.6 g of $NaBH_4$ was added; after 15 min, 1.6 g of $NaBH_4$ was added; after 45 min 400 ml of C_6H_6 was added; after 1 hr 1 l. of H_2O was added. The organic layer was washed three times with 100-ml portions of H_2O, dried ($MgSO_4$), treated with decolorizing carbon, filtered, and concentrated. The residue was triturated with 40 ml of MeOH, filtered, and washed with 10 ml of MeOH. The filtrate was evaporated to dryness, and the semisolid residue was triturated with 10 ml of MeOH, filtered, and washed with 5 ml of MeOH. The combined solids were dried (vacuum desiccator, NaOH) to give 13.6 g (65%) of **6**, mp 104–105° dec. Although unstable when dry, and flaring to a black ash within 1–10 hr, **6** could be stored under ligroin at 0° for 2 weeks.

To a stirred suspension of 12.54 g of **6** in 90 ml of 95% EtOH was added 10 ml of 6 *N* NaOH; after 5 min 10 ml of 6 *N* NaOH was added; after 20 min the reaction suspension was poured into 1.2 l. of H_2O, from which **7** was extracted five times with 250-ml portions of Et_2O. After drying ($MgSO_4$) and removal of Et_2O, the residue was dissolved in 100 ml of C_6H_6, dried ($MgSO_4$), treated with decolorizing carbon and filter aid, filtered, and concentrated. The solid residue was triturated with 20 ml of ligroin (bp 35–60°) and filtered to give 9.4 g (91%, based on **6**) of **7**, mp 94–95°. For analysis **7** was sublimed (80°, 0.1 mm): 94.5% recovery; mp 95.5–96°; λ_{max} 209 mμ (ε 9900), 239 (26,500), 320 (4900); pmr (CCl_4), δ (ppm) 3.12 (m, 2 H, C*H*$_2$), 4.08 (q, 1 H, C*H*),[8] 7.86 (m, 4 H, aromatic), 8.62 (s, 1 H, heterocyclic). *Anal.* ($C_{10}H_8N_2O$) C, H, N.

2-Acetylquinoxaline.—A solution of 1.8 g of **6** in 50 ml of Et_2NH was stirred for 70 hr at 25° and refluxed for 22 hr. Filtration of the reaction mixture gave 0.8 g of $Et_2NH_2^+$ Cl^-, and concentration gave 1.15 g of semisolid residue, only 0.1 g of which was soluble in 1 *N* HCl. The remainder was extracted with 90 ml of hot ligroin (bp 37–55°); the ligroin solution was clarified, filtered, and concentrated to give 0.85 g (57%) of 2-acetylquinoxaline, mp 76.5–77.5°. Sublimation of 0.5 g at 50° (1 mm) gave 0.35 g (40% total yield) of yellow crystals: mp 79–79.5°; positive haloform, negative Tollens test; λ_{max} 210 mμ (ε 9900), 247 (22,100), 311 (4500), 320 (4500); pmr (CCl_4), δ (ppm) 2.72 (s, 3 H, CH_3), 7.90 (m, 4 H, aromatic), 9.34 (s, 1 H, heterocyclic). *Anal.* ($C_{10}H_8N_2O$) C, H, N.

Di-(*RS*)-α-(di-*n*-butylammoniummethyl)-2-quinoxalinemethanol Pamoate (**8**).—A solution of 110 ml of CCl_4 containing 5.17 g of **7** and 3.88 g of Bu_2NH was refluxed under N_2 for 29 hr, until pmr data indicated the reaction was 75% complete. The cooled solution was treated with 0.71 ml of Ac_2O in order to transform unreacted Bu_2NH into Bu_2NAc. After 15 min the solution was extracted three times with 50-ml portions of 0.3 *N* HCl; the combined aqueous extract was treated with decolorizing carbon and filter aid and filtered. The filtrate was brought to pH 9–10 and extracted three times with 50-ml portions of CCl_4. The combined CCl_4 solution was counterextracted with saturated NaCl, dried ($MgSO_4$), treated with decolorizing carbon and filter aid, and filtered. Removal of the solvent gave 5.83 g (64.5%) of oily yellow product. The oil was redissolved in CCl_4 and again purified as outlined above. Removal of CCl_4 gave 5.6 g (62%) of clear oil whose pmr spectrum proved it to have the desired structure. The oil was dissolved in 100 ml of 0.185 *N* HCl, treated with decolorizing carbon and filter aid, and filtered three times and the filtrate was diluted to a final volume of 200 ml. A solution of 3.999 g of disodium pamoate in 50 ml of H_2O was likewise prepared, then diluted to 200 ml. The two solutions were simultaneously dripped into 400 ml of stirred water, giving instantaneous precipitation of 6.3 g (43%) of product.

In some instances acceptable analyses were obtained only after liberation of the free base with NaOH from the pamoate salt, repurification of the free base (alumina column), and reprecipitation of the pamoate salt. Physical data for all target compounds (**8**) are listed in Table I.

Di-(*RS*)-α-(di-*n*-butylammoniummethyl)-2-quinoxalinemethanacetoxide Pamoate.—A solution of 1.1 g of **8** (NBu_2 compound) and 0.31 ml of Ac_2O in 10 ml of CCl_4 stood 12 hr under N_2 at 25°. The product was purified and transformed into its pamoate salt by the same series of steps as outlined for the parent **8**: yield 0.95 g (48.4%); mp 80–140°; λ_{max} 237 mμ (ε 150,600), 279 (8500), 291 (11,700), 302 (10,100), 319 (7200); pmr average data, see footnote *b*, Table I. *Anal.* ($C_{63}H_{74}N_6O_{10}$) C, H, N.

(8) This H was coupled with two adjacent diasterentopic H; the quartet was actually 2 doublets, $J_{AB} \simeq 5.3$ Hz.

Acknowledgment.—The authors are indebted to Mr. John Oatis, Jr., for his skilled technical assistance.