Structure–Affinity Relationships of Arylquinolizines at α-Adrenoceptors

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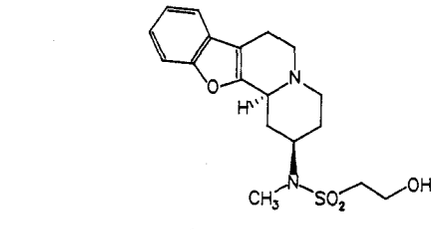
Hexahydroaryl[a]quinolizines comprise a prominent structural element in several α_2-adrenoceptor antagonists. Eight hexahydroheteroarylquinolizines were prepared as minimal ligands to investigate the relationship between the nature of the aromatic ring and affinity of these molecules for α-adrenoceptors. Affinity for α_1- and α_2-adrenoceptors was assessed by displacement of [^{3}H]prasozin and [^{3}H]clonidine, respectively. Lipophilicity of the aryl portion of the molecules, reflected by their partition coefficient between octanol and pH 7.4 buffer, correlated well with affinity at both receptor subtypes. Although some compounds showed nanomolar affinity for α-adrenoceptors, no subtype selectivity was observed. These results suggest that the aromatic ring enhances binding at both receptors chiefly through hydrophobic interactions and contributes little to subtype selectivity.

We recently reported that compound **1** is a potent and selective α_2-adrenoceptor antagonist.[1] The design of this compound was based in part on the observation that the bicyclic quinolizine nucleus comprises a prominent structural element of several other selective α_2-adrenoceptor antagonists such as yohimbine, rauwolscine, and WY-26703.[2,3] In each case the quinolizine is fused to an aromatic ring at the *a* face and substituted with additional functionality at C-2. At the conceptual level, the reduced quinolizine ring system may be viewed as a dual-purpose template. The rigid bicyclic structure provides a basic nitrogen atom, common to all adrenergic ligands, and simultaneously enforces a favorable topographical relationship among the aromatic ring, the basic nitrogen, and polar functionality located in the vicinity of C-2. Previous studies concerning structure–affinity relationships of yohimbine alkaloids have noted the importance of these three structural features.[4]

Early in the course of developing compound **1** we attempted to acquire some insight into the relative contribution made by the aryl portion of such molecules to α-adrenoceptor binding. Eight arylquinolizines were prepared as minimal ligands. This series, lacking the potentially confounding effects of additional functionality, allows direct comparison of the various aromatic rings with respect to their effects on affinity. Binding affinity at both α_1- and α_2-adrenoceptors significantly correlated with lipophilicity of the aryl group, suggesting that the aromatic ring enhances binding at both receptors chiefly through hydrophobic interactions and contributes little to subtype selectivity.



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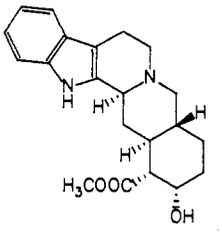
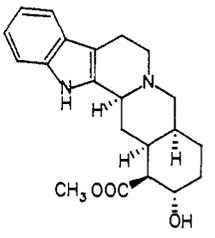
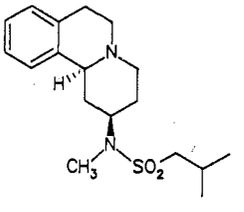


YOHIMBINE



RAUWOLSCINE



WY 26703

Chemistry

The arylquinolizines in this study were obtained by one of two synthetic strategies. In the first, ketoquinolizine **2**[5] served as a starting point for compounds **4**, **7**, **8**, and **10**. Alkylation of **2** with 2-(2-bromoethyl)-1,3-dioxolane and subsequent decarboxylation afforded the keto acetal **3**. Hydroxylamine effected cyclization of the latent 1,5-keto aldehyde, and under the mildly acidic conditions of the reaction, the product aromatized to yield pyrido[2,3-*a*]-quinolizine, **4** (Scheme I).

Acid-mediated decarboxylation of **2** gave the ketoquinolizine **5**, which readily condensed with dimethylformamide dimethyl acetal to yield **6**. Michael addition of hydrazine followed by cyclodehydration effected conversion to pyrazolo[3,4-*a*]quinolizine **7**.

Treatment of **5** with 2-hydrazinopyridine under conditions of the Fischer indole synthesis afforded the 7-azaindoloquinolizine **8** (Scheme I).

Bromination of **5** with phenyltrimethylammonium tribromide afforded the unstable bromo ketone **9**, which was not purified, but condensed directly with thiourea to yield 2-aminothiazolo[4,5-*a*]quinolizine **10** (Scheme I).

The remaining arylquinolizines were prepared by Wolff–Kishner reduction of the corresponding ketones (Scheme II), which, in turn, were obtained by previously reported cycloaddition chemistry.[6] For example, 3-(2-aminoethyl)thiophene was formylated, and the resulting formamide cyclized to yield dihydrothienopyridine **12**. Lewis acid catalyzed cycloaddition of 2-[(trimethylsilyl)-oxy]butadiene and the imine afforded the desired ketone **13**. Wolff–Kishner reduction gave thieno[2,3-*a*]quinolizine

(1) Huff, J. R.; Anderson, P. S.; Baldwin, J. J.; Clineschmidt, B. V.; Guare, J. P.; Lotti, V. J.; Pettibone, D. J.; Randall, W. C.; Vacca, J. P. *J. Med. Chem.* **1985**, *28*, 1756.
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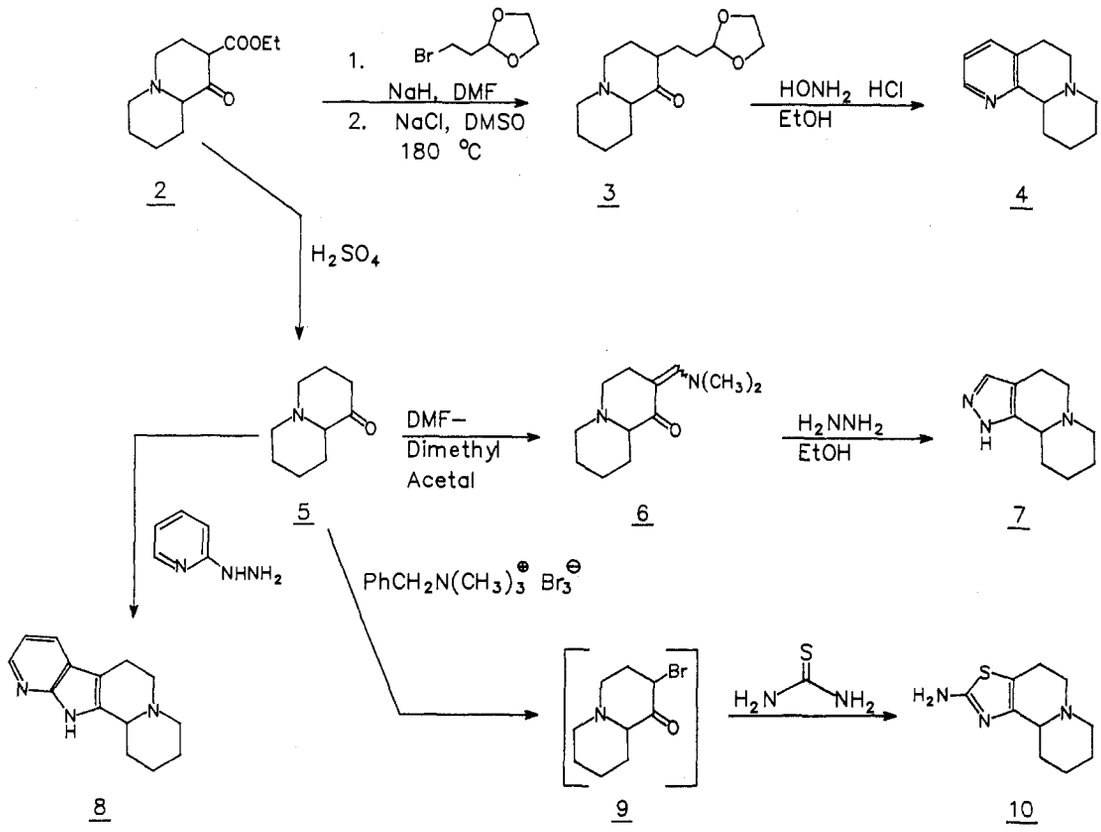
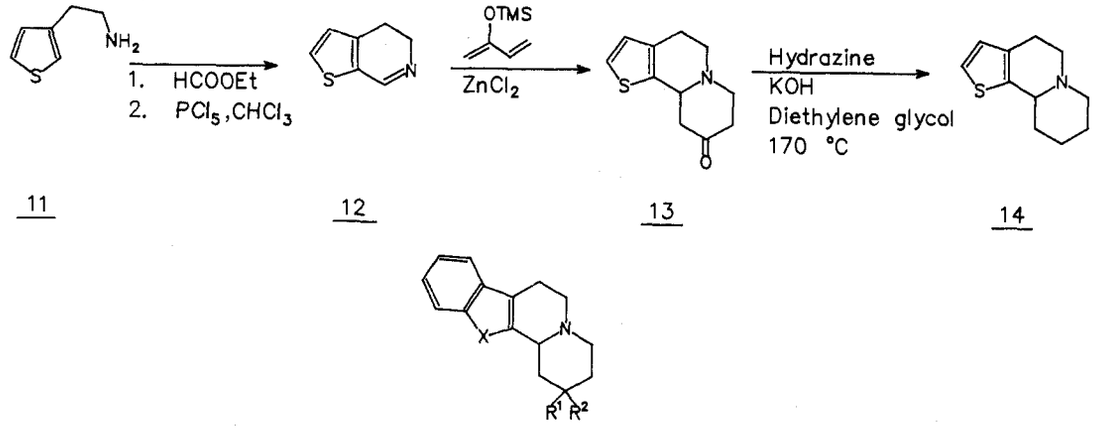
Scheme I



Scheme II



15 X=O; $R^1=R^2=O$
16 X=S; $R^1=R^2=O$
17 X=O; $R^1=R^2=H$
18 X=S; $R^1=R^2=H$
19 X=NH; $R^1=R^2=H$

14 (Scheme II). Similarly, the previously reported ketones **15** and **16** were converted to the corresponding arylquinolizines **17** and **18**.

Radioligand Binding and Partition Coefficients

Relative affinities of the arylquinolizines for central α-adrenoceptors were determined by measuring radioligand displacement from membrane binding sites of calf cerebral cortex.[7] Displacement of [^{3}H]clonidine served as a measure of interaction with α_2-adrenoceptors while [^{3}H]prazosin displacement was used as an assay for α_1-

Table I. Radioligand Binding Results

	K_i,[a] nM		
no.	[^{3}H]clonidine (α_2)	[^{3}H]prazosin (α_1)	selectivity[b]
4	2000 (2500, 1600)	3250 (4300, 2400)	1.6
7	9600 (11400, 8000)	24000 (30600, 19000)	2.5
8	660 (810, 530)	540 (740, 390)	0.8
10	350 (420, 290)	2800 (3300, 2500)	8.0
14	195 (270, 140)	1100 (1900, 660)	5.6
17	16.2 (17.2, 15.3)	110 (220, 130)	6.8
18	4.3 (6.0, 3.1)	16.1 (17.5, 14.7)	3.7
19	60 (67, 53)	38 (50, 30)	0.6

[a] Values are the geometric means for at least three determinations. The 95% confidence limits are shown in parentheses. [b] K_i([^{3}H]prazosin)/K_i([^{3}H]clonidine).

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Table II. Parameters Relating Affinity for α-Adrenoceptors to log P

no.	obsd log P	obsd log $1/K_i(\alpha_1)$	calcd log $1/K_i(\alpha_1)$	Δ log $1/K_i(\alpha_1)$	obsd log $1/K_i(\alpha_2)$	calcd log $1/K_i(\alpha_2)$	Δ log $1/K_i(\alpha_2)$
4	0.39	5.49	5.55	−0.06	5.70	5.92	−0.22
7	0.16	4.62	5.30	−0.68	5.02	5.65	−0.63
8	0.16	6.27	5.30	0.97	6.18	6.65	0.53
10	0.39	5.55	5.55	0.00	6.46	5.92	0.54
14	1.51	5.96	6.76	−0.80	6.71	7.23	−0.52
17	1.80	6.96	7.08	−0.12	7.79	7.57	−0.22
18	2.09	7.79	7.39	0.40	8.37	7.90	−0.47
19	1.83	7.42	7.11	0.31	7.22	7.60	−0.38

adrenoceptor affinity. The results are shown in Table I.

Experimental partition coefficients were determined in octanol and pH 7.4 phosphate buffer by the standard shake-flask method,[8a] employing a pH 7.4, 0.1 ionic strength phosphate buffer as the aqueous phase.[8b] The concentration of a compound in each phase was measured by UV absorption. The results are shown in Table II.

Discussion

Radioligand binding data for the arylquinolizines demonstrate that the nature of the aryl group exerts a pronounced influence on the affinity of these compounds for α-adrenoceptors. The value of K_i varies more than 3 orders of magnitude for the eight compounds, with benzothieno- and benzofuro[2,3-*a*]quinolizines showing the highest affinity and pyrazolo[3,4-*a*]quinolizine showing the least. It may also be noted that while some compounds (**17** and **18**) show high affinity for α-adrenoceptors, none of the compounds are selective. This observation is consistent with the hypothesis that functionality substituted at C-2 of the quinolizine nucleus imparts adrenoceptor subtype selectivity.[9]

Recently, Hollister and co-workers reported that yohimbine binding to α_2-adrenoceptors is driven by a large increase in entropy (41.3 cal mol^{-1} deg^{-1}) with little change in enthalpy (0.99 kcal mol^{-1}).[10] A commonly accepted explanation of entropy driven binding phenomena suggests that, in order to preserve an equivalent number of hydrogen bonds, water molecules are more highly ordered at nonpolar surfaces than in bulk solution. As a hydrophobic molecule binds to a protein, water molecules ordered at the lipophilic surfaces of the ligand and protein are released into bulk solution, increasing the entropy of the system. In such cases, receptor affinity will be related to the lipophilicity of a series of homologous molecules within appropriate steric and conformational constraints.

On the basis of the structural similarity of the eight arylquinolizines in this study and yohimbine, we examined the relationship between lipophilicity and affinity for α-adrenoceptors. Regression analysis of data in Table II demonstrates a correlation ($p < 0.01$) between affinity for α_1-adrenoceptors and log P according to eq 1.

$$\log 1/K_i = 1.08\ (\pm 0.28) \log P + 5.13\ (\pm 0.36) \quad (1)$$

$$n = 8,\ r = 0.84,\ s = 0.622,\ F_{1,6} = 14.83$$

A strong correlation ($p < 0.005$) is also seen between affinity for α_2-adrenoceptors and log P as shown in eq 2.

$$\log 1/K_i = 1.17\ (\pm 0.24) \log P + 5.47\ (\pm 0.31) \quad (2)$$

$$n = 8,\ r = 0.89,\ s = 0.532,\ F_{1,6} = 23.67$$

In both cases, the coefficient of log P is approximately 1, suggesting, according to Hansch et al., that the molecules are almost completely desolvated when bound to the protein.[11] Evidence that ligand binding to β-adrenoceptors occurs in the hydrophobic, transmembrane core has been presented.[12]

For comparative purposes, log P of the eight arylquinolizines were also calculated by means of the MedChem computer program CLOGP (release 3.33) from Medicinal Chemistry Project, Pomona College, Claremont, CA. The values obtained also correlated with affinity for both α_1- ($r = 0.90$, $p < 0.005$) and α_2-adrenoceptors ($r = 0.92$, $p < 0.005$).

The results of this study suggest that the arylquinolizine substructure contains all of the basic molecular parameters required for recognition and binding to both subtypes of α-adrenoceptors. The structure of the aromatic ring plays an important role in determining affinity, and exerts its influence primarily through hydrophobic interactions.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus using open capillaries and are uncorrected. NMR spectra were recorded for all intermediate and final products on either a Varian EM-390 or Varian XL-300 instrument. Chemical shifts are reported in part per million relative to Me_4Si used as an internal standard. Microanalytical results are indicated by atom symbols and are within ±0.4% of theoretical values unless otherwise indicated. **1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (19)** was obtained from Professor Gordon Gribble, University of New Hampshire.

Ethyl 2-(2-(1,3-Dioxolan-2-yl)ethyl)octahydro-1-oxoquinolizine-2-carboxylate. Sodium hydride (1.5 g of a 50% dispersion in oil; 31.5 mmol) was washed twice with hexane and suspended in 200 mL of a 1:1 mixture of DMF and benzene. To this was added over 15 min a solution of ethyl octahydro-1-oxoquinolizine-2-carboxylate[13] (3.5 g, 15.5 mmol) in 25 mL of benzene. The reaction mixture was stirred an additional 30 min before 2-(2-bromoethyl)-1,3-dioxolane (5.71 g, 31.5 mmol) was added and the solution then refluxed for 10 h. The reaction mixture was cooled and poured into 500 mL of water. The aqueous layer was extracted with EtOAc, which was then dried over Na_2SO_4. Evaporation of the solvent yielded the crude product, which was chromatographed over silica gel with ethyl acetate as eluent to give 3.36 g (67%) of product as a 1:1 mixture of diastereomers. This mixture was decarboxylated without further purification. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.23 (t, 3 H, J = 12 Hz), 1.45–2.27 (m, 12 H), 2.45 (m, 3 H), 2.85 (m, 2 H), 3.89 (m, 4 H), 4.23 (q, 2 H, J = 12 Hz), 4.86 (m, 1 H).

2-(2-(1,3-Dioxolan-2-yl)ethyl)octahydro-1-oxoquinolizine (3). The diastereomeric mixture from above (1 g, 3.1 mmol) was

(8) (a) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175. (b) Scherrer, R. A.; Howard, S. M. *J. Med. Chem.* **1977**, *20*, 53.
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dissolved in 25 mL of DMSO, and to it were added pulverized LiCl (0.289 g, 6.8 mmol) and water (0.122 g, 6.8 mmol). The reaction was heated at 170 °C for 4 h. After the mixture was cooled, the DMSO was distilled at 0.05 Torr, and the residue was dissolved in EtOAc, dried (Na_2SO_4), decolorized, and concentrated in vacuo to give a brown oil. Distillation of this oil gave **3** (0.694 g, 88%), bp 160–200 °C (0.05 Torr). ^1H NMR (90 MHz, $CDCl_3$): δ 1.10–2.72 (m, 15 H), 3.00 (m, 2 H), 3.91 (m, 4 H), 4.89 (t, 1 H, J = 8 Hz).

5,8,9,10,11,11a-Hexahydro-6*H*-pyrido[1,2-*h*]-1,7-naphthyridine (4). A solution of **3** (0.386 g, 1.5 mmol) and hydroxylamine hydrochloride (0.268 g, 3.8 mmol) in 10 mL of EtOH was refluxed for 18 h. The solvent was removed, and the residue was dissolved in 10 mL of water. The aqueous solution was made basic with solid $NaHCO_3$ and was extracted with EtOAc. Subsequent drying (Na_2SO_4) and evaporation of solvent yielded 0.063 g (22.3%) of **4** as a yellow oil. This was dissolved in 2 mL of 2-propanol and was treated with 0.03 g of oxalic acid. The mixture was diluted with EtOAc, an the solvent was evaporated in vacuo until crystallization occurred to give 0.049 g of the oxalate salt monohydrate, mp 54–56 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 1.61 (m, 2 H), 1.70–1.92 (m, 3 H), 2.73 (br s, 1 H), 2.98 (m, 2 H), 3.20 (m, 2 H), 3.41 (d, 2 H, J =12 Hz), 3.49 (m, 2 H), 4.16 (d, 1 H, J = 7 Hz), 7.32 (dd, 1 H, J = 4, 7 Hz), 7.65 (dd, 1 H, J = 2, 7 Hz), 8.46 (dd, 1 H, J = 2, 4 Hz). Anal. C, H, N.

1,3,4,6,7,10b-Hexahydro-2*H*-pyrazolo[3,4-*a*]quinolizine (7). A mixture of octahydro-1-oxoquinolizine (**5**)[13] (0.306 g, 2.0 mmol) and dimethylformamide dimethyl acetal (0.286 g, 2.4 mmol) was heated under an atmosphere of N_2 at 100 °C for 16 h. The dark residue was dissolved in 5 mL of absolute EtOH and was treated with anhydrous hydrazine (0.128 g, 4 mmol). The reaction mixture was stirred at ambient temperature overnight. After evaporation of the solvent, the residue was chromatographed over silica gel, eluting with 5% MeOH in $CHCl_3$ saturated with NH_3. A solution of the oily product in 2-propanol was acidified with HCl. Addition of Et_2O caused the product to crystallize as the monohydrochloride hemihydrate salt, mp 239–42 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 7.37 (s, 1 H), 4.46 (dd, 1 H), 3.7–3.4 (m, 4 H), 3.4–3.2 (m, 2 H), 3.01 (dd, 1 H), 2.72 (br d, 1 H), 2.3–2.15 (m, 2 H), 2.15–1.9 (m, 2 H). Anal. C, H, N.

1,2,3,4,6,7,12,12b-Octahydropyrido[3′,2′:4,5]pyrrolo[2,3-*a*]quinolizine (8). Equimolar amounts of 2-hydrazinopyridine (0.20 g, 1.8 mmol) and **5** (0.28 g, 1.8 mmol) were heated at 100 °C under an atmosphere of N_2 for 1 h to form the intermediate hydrazone. Hydroxyethyl ether (2 mL) was added, and the mixture was heated at 245 °C for 18 h under N_2. The reaction mixture was poured into 5 mL of ice water, and the product was extracted into $CHCl_3$. The organic mixture was washed, dried (Na_2SO_4), and concentrated in vacuo. Chromatography over silica gel, eluting with 5% MeOH–CH_2Cl_2, yielded 45 mg (11%) of **8**. ^1H NMR (300 MHz, DMSO-d_6) of the free base: δ 8.11 (dd, 1 H, J = 2, 5 Hz), 7.76 (dd, 1 H, J = 2, 8 Hz), 6.98 (dd, 1 H, J = 5, 8 Hz), 3.15 (br d, 1 H), 2.94 (m, 2 H), 2.77 (m, 1 H), 2.60 (br d, 1 H), 2.51 (m, 1 H), 2.34 (m, 2 H), 1.82 (m, 1 H), 1.61 (m, 2 H), 1.5–1.3 (m, 2 H). An analytical sample was obtained as the maleate salt, mp 140 °C. Anal. C, H, N.

4,7,8,9,10,10a-Hexahydro-5*H*-thiazolo[4,5-*a*]quinolizin-2-amine (10). To a solution of ketone **5** (790 mg, 5.16 mmol) in 10 mL of CH_3CN was added phenyltrimethylammonium tribromide (1.94 g, 5.15 mmol). After 45 min the reaction was diluted with 50 mL of saturated $NaHSO_3$ solution and was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 163 mg (14%) of the unstable bromo ketone **9**, which was used immediately in the next step. ^1H NMR (90 MHz, $CDCl_3$): δ 4.8–4.4 (m, 1 H), 3.4–3.2 (m, 1 H), 3.0–1.2 (m, 12 H).

To a solution of **9** (170 mg, 0.73 mmol) in 5 mL of EtOH was added thiourea (55 mg, 0.73 mmol), and the reaction mixture was heated at 60 °C for 1 h. The solvent was evaporated, and ammonia saturated chloroform was added. This mixture was filtered through a pad of Celite, concentrated to dryness, and chromatographed (SiO_2, ammonia saturated chloroform) to give 54 mg (35%) of product as a brown waxy solid. ^1H NMR (300 MHz, $CDCl_3$-d_1): δ 2.92 (m, 4 H), 2.54 (dt, J = 6 Hz, 2 H), 2.28 (m, 2 H), 1.74 (m, 2 H), 1.68 (m, 2 H), 1.38 (m, 2 H); mass spectrum, m/e 209 (M^+).

An oxalate salt was crystallized from ethanol, mp 208–211 °C. Anal. C, H, N.

3,4-Dihydrothieno[2,3-*c*]pyridine (12). Ethyl formate (15 mL) and 3-(2-aminoethyl)thiophene[14] (0.72 g, 5.7 mmol) were heated at reflux under N_2 for 3 h and then were concentrated in vacuo to remove excess ethyl formate. The residue was partitioned between CH_2Cl_2 and H_2O, washed with 2 N HCl (1 × 25 mL), washed with brine (1 × 25 mL), and dried (Na_2SO_4). Filtration and subsequent evaporation to dryness gave 0.78 g (88%) of 3-(2-formamidoethyl)thiophene. This material was dissolved in 10 mL of CH_3CN and was treated with $POCl_3$ (0.5 mL, 5.5 mmol). After stirring at ambient temperature for 4 h, the reaction mixture was concentrated, dissolved in H_2O (20 mL), washed with EtO_2, and made basic with concentrated NH_4OH. The product was extracted with CH_2Cl_2 (3 × 20 mL), washed with saturated NaCl, and dried (Na_2SO_4). Filtration and concentration to dryness followed by trituration with EtOAc gave 0.38 g (56%) of **12**, mp 102-104 °C. ^1H NMR ($CDCl_3$): δ 2.82 (t, 2 H, J = 9 Hz), 3.76 (td, 2 H, J = 2, 9 Hz), 6.87 (d, 1 H, J = 4.5 Hz), 7.33 (d, 1 H, J = 4.5 Hz), 8.25 (m, 1 H).

4,5,7,8,10,10a-Hexahydro-9*H*-thieno[2,3-*a*]quinolizin-9-one (13). $ZnCl_2$ (0.17 g, 1.25 mmol) and **12** (0.14 g, 1.0 mmol) in 10 mL of CH_3CN were heated to 60 °C with stirring in a flame-dried round-bottom flask under N_2. 2-[(Trimethylsilyl)oxy]butadiene (0.28 g, 2.0 mmol) in 5 mL of CH_3CN was added, and the mixture was heated at reflux for 20 h. Upon cooling, the reaction mixture was treated with 1 N HCl (20 mL) and was added to H_2O (150 mL). The acidic aqueous layer was washed with CH_2Cl_2, made basic with concentrated NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Column chromatography (silica gel, EtOAc) afforded 0.11 g (53%) of **13** as a yellow solid, mp 114–115 °C. IR ($CHCl_3$): 1720 cm^{-1} (s). ^1H NMR ($CDCl_3$): δ 2.3–2.8 (m, 8 H), 2.9–3.3 (m, 2 H), 3.4–3.7 (m, 1 H), 6.79 (d, 1 H, J = 4.5 Hz), 7.11 (d, 1 H, J = 4.5 Hz). Anal. C, H, N.

4,7,8,9,10,10a-Hexahydro-5*H*-thieno[2,3-*a*]quinolizine (14). Hydrazine hydrate (64% in H_2O; 0.73 mL, 15 mmol), **13** (0.5 g, 2.4 mmol), powdered KOH (0.74 g, 13.2 mmol), and diethylene glycol (25 mL) were stirred at 170 °C for 2 h. Heating was continued at 200 °C for 0.25 h without a condenser and then for 1 h at 200 °C under an ascending tube. After cooling, the reaction mixture was treated with 25 mL of H_2O and was extracted with CH_2Cl_2 (5 × 30 mL). The organic layer was washed with brine (1 × 35 mL), dried (Na_2SO_4), decolorized (Norit), and evaporated. Column chromatography (silica gel, hexane–EtOAc, 4:1) afforded 0.16 g (35%) of **14**. ^1H NMR ($CDCl_3$): δ 1.4–1.9 (m, 3 H), 2.0–2.1 (m, 1 H), 2.2–2.4 (m, 1 H), 2.5–2.7 (m, 2 H), 2.9–3.0 (m, 3 H), 3.14 (d, 1 H, J = 7 Hz), 6.77 (d, 1 H, J = 5.1 Hz), 7.09 (d, 1 H, J = 5.1 Hz); mass spectrum, m/e 193 (M^+). The hydrochloride salt was prepared by precipitation with EtOH–HCl from EtO_2. Anal. C, H, N.

1,3,4,6,7,12b-Hexahydro-2*H*-benzo[*b*]furo[2,3-*a*]-quinolizine (17) was obtained in 27% yield by Wolff–Kishner reduction of 1,3,4,6,7,12b-hexahydrobenzo[*b*]furo[2,3-*a*]-quinolizin-2-one[6] and was crystallized from EtOH as the maleate salt, mp 140 °C. ^1H NMR (300 MHz, CD_3OD): δ 7.58 (d, 1 H, J = 7.5 Hz), 7.51 (d, 1 H, J = 7.5 Hz), 7.39–7.26 (m, 2 H), 3.81 (m, 1 H), 3.68–3.53 (m, 2 H), 3.35 (br d, 1 H), 3.25–3.16 (m, 2 H), 3.06 (br d, 1 H), 2.1–1.75 (m, 6 H). Anal. C, H, N.

1,3,4,6,7,12b-Hexahydro-2*H*-benzo[*b*]thieno[2,3-*a*]-quinolizine (18)[15] was obtained in 65% yield from Wolff–Kishner reduction of 1,3,4,6,7,12b-hexahydrobenzo[*b*]thieno[2,3-*a*]-quinolizin-2-one.[6] ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 1 H, J = 9 Hz), 7.54 (d, 1 H, J = 9 Hz), 7.3 (t, 1 H, J = 6 Hz), 7.23 (t, 1 H, J = 6 Hz), 3.24 (d, 1 H, J = 8 Hz), 3.16–2.95 (m, 3 H), 2.79–2.6 (m, 2 H), 2.34 (m, 1 H), 2.06 (br d, 1 H, J = 12 Hz), 1.84 (br d, 1 H, J = 12 Hz), 1.8–1.4 (m, 4 H). A hydrochloride salt was obtained by treating an EtOAc solution of the product with EtOH–HCl, mp 265–268 °C dec; mass spectrum, m/e 234 (M^+). Anal. C, H, N.

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Acknowledgment. We thank Joan Murphy for NMR spectra, John Moreau for elemental analysis, and Vera Finley for the preparation of this manuscript.

Registry No. 2, 64757-13-7; 3, 112114-02-0; 4, 112114-03-1; 4·oxalate, 112114-12-2; 5, 10447-21-9; 7, 112114-04-2; 7·HCl, 112114-13-3; 8, 112114-05-3; 8·maleate, 112114-14-4; 9, 112114-06-4; 10, 112114-07-5; 10·oxalate, 112114-15-5; 11, 59311-67-0; 12, 28783-50-8; 13, 104535-60-6; 14, 112114-08-6; 14·HCl, 112114-16-6; 15, 97456-68-3; 16, 97456-71-8; 17, 112114-09-7; 17·maleate, 112114-17-7; 18, 29970-79-4; 18·HCl, 112114-18-8; 19, 4802-79-3; H_2C=CHC(OTMS)=CH_2, 38053-91-7; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; *cis*-ethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-octahydro-1-oxoquinolizine-2-carboxylate, 112114-10-0; *trans*-ethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)octahydro-1-oxoquinolizine-2-carboxylate, 112114-11-1; 2-hydrazinopyridine, 4930-98-7; 3-(2-formamidoethyl)thiophene, 28783-48-4.

Arteether, a New Antimalarial Drug: Synthesis and Antimalarial Properties

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Arteether (6) has been prepared from dihydroqinghaosu (3) by etherification with ethanol in the presence of Lewis acid and separated from its chromatographically slower moving α-dihydroqinghaosu ethyl ether (7). The absolute stereochemistry at C-12 has been determined by ^{1}H NMR data ($J_{11,12}$, NOESY). Ethyl ethers 6 and 7 showed potent in vitro inhibition of *Plasmodium falciparum*, and both compounds were highly potent antimalarials in mice infected with a drug-sensitive strain of *Plasmodium berghei*. Crystalline arteether (6) and its oily epimer 7 were 2–3 times more potent schizontocides than quinghaosu (1), but deoxy compounds 8, 9, and 11 were 100–300 times less potent in vitro than their corresponding peroxy precursors. Pharmacological studies have shown arteether (6) to have antimalarial activity in animals comparable to artesunate (2) and artemether (4), both of which are fast-acting blood schizontocides in humans. Arteether (6) has now been chosen for a clinical evaluation in high-risk malaria patients.

Qinghaosu (QHS, 1),[7] a sesquiterpene peroxide, is an active ingredient of *Artemisia annua* L. that has been used as an antimalarial preparation in China in the form of extracts for centuries.[8,9] Details on the isolation of QHS,[10] its structure determination,[11,12] and its antimalarial effects in infected animals[9,13] and malaria patients[9,13] have been reviewed.[13,14] QHS is only sparingly soluble in water or oils and not well absorbed by the gastrointestinal tract. A search for more potent analogues of QHS with better bioavailability was initiated in China, focusing attention on ethers and esters of dihydroquinghaosu (DQHS, 3).[15,16] DQHS, obtained by reduction of QHS with sodium borohydride, is an acetal and behaves in solution as a mixture of anomers.[17] Attention to possible clinical use of derivatives of QHS focused early on artesunate (2),[18] a sodium salt of a hemisuccinate of α-DQHS, which is soluble in water and was found to be a highly effective antimalarial in animal models.[19] Artesunate proved to be extremely sensitive to hydrolysis,[20] and therefore, it is unclear whether its pharmacological effects are due to the parent drug or its hydrolysis product DQHS. Artemether (4), on the other hand, an ether representative of the β-series,[17] obtained by etherification of DQHS with methanol in the presence of Lewis acids, was found to be much more stable, and when given by im injection in an oily solution to malaria patients, it had activity comparable to that of artesunate.[21]

The Steering Committee of the Scientific Working Group on Malaria Chemotherapy of the World Health Organization in Geneva, Switzerland (SWG-CHEMAL), responsible for the development of new antimalarial drugs,

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(7) We use in this report nomenclature which is derived from the Chinese name qinghaosu (1) to protect its origin and preferred by us over the name artemisinin, which is also used in the literature.
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0022-2623/88/1831-0645$01.50/0