3-Aryl-3-hydroxyquinolizidines with Potential Hypotensive, Antidepressant, and Analgetic Activity†

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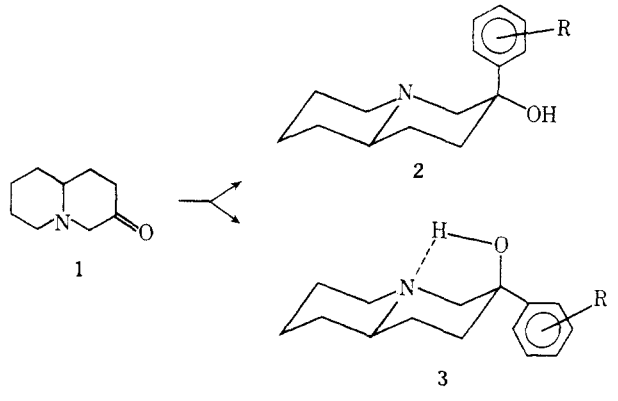
The synthesis, structure elucidation, and pharmacological evaluation of some 3-aryl-3-hydroxyquinolizidines as semirigid phenethylamines are described. Some antidepressant and analgetic activity was noted in several of the derivatives; no marked blood pressure effects were observed.

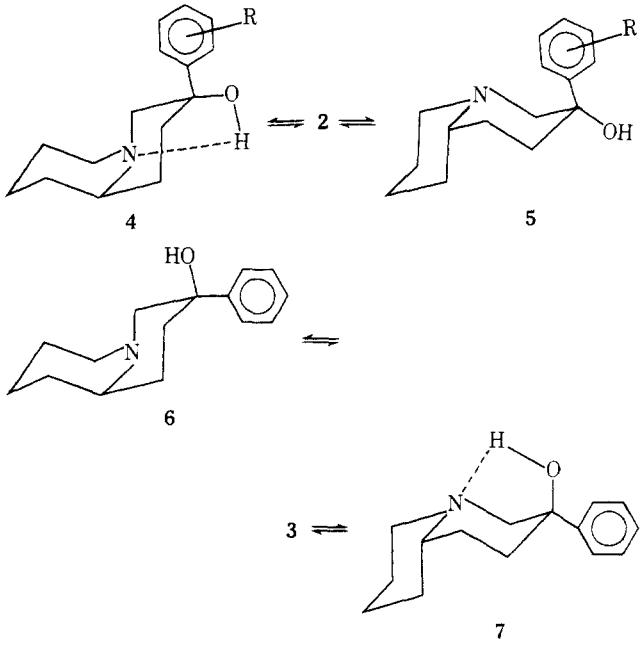
The biological activity of medicinal agents is dependent, in part, on steric dimensions.[1] The preparation and biological evaluation of compounds possessing fixed steric dimensions similar to various conformations of known biologically useful materials should lead to a better understanding of structural requirements for optimum biological activity.

Because the quinolizidine ring system possesses a degree of rigidity various derivatives (**2**, **3**) resembling conformations of adrenergic and analgetic agents were investigated. Previous reports[2-4] described the preparation and preliminary biological properties of some 1- and 2-arylquinolizidines.



Two cis (**4**, **5** and **6**, **7**) and one trans (**2** and **3**) forms, existing in chair conformations, are possible for each epimer of 3-aryl-3-hydroxyquinolizidine. The stability of the trans-fused system, the steric strain caused by an axially oriented aryl group, and the stability imparted by an intramolecular hydrogen bond are factors which affect the energy barrier between trans and cis forms. Although the cis-fused as well as boat and twisted conformers are possible, it is likely that the epimers exist predominantly in the trans-fused forms.[5] The position of equilibrium has been estimated only for a few of the quinolizidine derivatives.[6,7]

The alcohols (Table I) were prepared by the reaction of the appropriate arylmagnesium halides with 3-ketoquinolizidine. Approximately a 1:1 ratio of epimers was obtained (Table II). This was in contrast to the predominance of equatorial aryl isomers obtained in a related series of 1-aryl-1-hydroxyquinolizidines prepared from 1-ketoquinolizidine.[4] The latter was explained on the basis of complexation between the Grignard reagent and the nitrogen



lone pair, blocking the axial attack of the Grignard reagent on 1-ketoquinolizidine. Since the 1 and 3 positions are the same distance from nitrogen, complexation also should hinder axial attack at C-3. The observed results for the 3-substituted series may be due to the reaction of the ketone in a cis form or to the greater flexibility of C-3 over C-1 which is adjacent to a bridgehead. No attempt was made to determine the influence of solvent in the Grignard reaction; however, as noted in Table II, a solvent effect was observed in the preparation of **2a** and **3a**.

The various axial and equatorial isomers were separated by fractional recrystallization and/or column chromatography. The 3(a)-aryl-3(e)-hydroxyquinolizidines are fairly high-melting solids, whereas the corresponding equatorial aryl epimers are oils or low-melting solids. The axial aryl epimers generally are less soluble in nonpolar solvents and more soluble in polar solvents than the equatorial aryl epimers. Some of the axial aryl isomers can be isolated by recrystallization of a mixture from petroleum ether. The R_f values from tlc of the axial aryl epimers on silica gel are greater than those for the equatorial aryl epimers and, using SE-30 as a stationary phase, the axial aryl isomers have shorter glc retention times than the corresponding equatorial aryl isomers.

The axial and equatorial isomers are easily distinguished by either their ir or nmr spectra. The axial isomers (**2**), exhibit free OH and intermolecular hydrogen bonding in their ir spectra, while the equatorial isomers (**3**) show only intramolecular H bonding; all showed Bohl-

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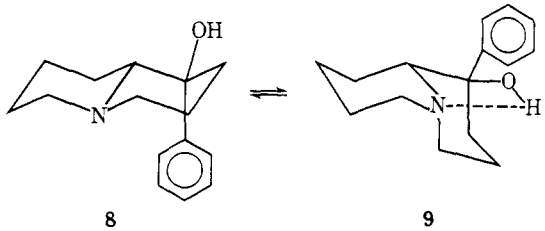
Table I. 3-Aryl-3-hydroxyquinolizidines

No.	R	Recrystn solvent[a]	Yield, %	Mp, °C	Formula[b]
2a	H	PE	50	123–124	$C_{15}H_{21}NO$
2a propionate	H	ACN	78	190–191	$C_{18}H_{25}NO_2 \cdot HCl$
3a	H	ACN	23	197–198	$C_{15}H_{21}NO \cdot HCl$
3a propionate	H	ACN–E	37	193–194	$C_{18}H_{25}NO_2 \cdot HCl$
2b	2′-OCH_3	PE–E–AC	33	140–141	$C_{16}H_{23}NO_2$
3b	2′-OCH_3	AC–ACN	39	213–215[c]	$C_{16}H_{23}NO \cdot HCl$
2c	3′-OCH_3	PE	18	96–97	$C_{16}H_{23}NO_2$
3c	3′-OCH_3	AC	28	175–176	$C_{16}H_{23}NO_2 \cdot HCl$
2d	4′-$OCH_2C_6H_5$	PE-BZ	11	113–115	$C_{22}H_{27}NO_2$
3d	4′-$OCH_2C_6H_5$	Et	50	94–95	$C_{22}H_{27}NO_2$
2e	4′-OH[d]	EAC	76	167–168	$C_{15}H_{21}NO_2$
3e	4′-OH[e]	*f*	72	154–155	$C_{15}H_{21}NO_2$
2f	4′-OCH_3	PE–BZ	19	97–98	$C_{16}H_{23}NO_2$
3f	4′-OCH_3	ACN	28	190–192	$C_{16}H_{23}NO_2 \cdot HCl$
2g	3′,4′-OCH_3	PE–E	26	127–129	$C_{17}H_{25}NO_3$
3g	3′,4′-OCH_3	PE	22	79–80	$C_{17}H_{25}NO_3$

[a]PE = petroleum ether; ACN = acetonitrile; E = ether; AC = acetone; BZ = benzene; ET = ethyl alcohol; EAC = ethyl acetate. [b]Analyzed for C, H, and N. [c]Melting point of free base 69–70°. [d]Prepared from **2d**. [e]Prepared from **3d**. [f]From column chromatography.

mann bands indicating trans fusion.[8] The ortho aromatic protons in **2** are deshielded and thus shifted downfield in their nmr spectra, distinguishing the axial and equatorial isomers and providing support for the trans-fused isomer (Table III).

Aarons has interpreted the existence of intramolecular H bonding in 1(e)-hydroxy-1(a)-phenylquinolizidine as evidence for a cis form.[7] By integrational analysis of the OH stretching bands in the ir, Aarons concluded that **8** and **9** exist in carbon tetrachloride as a 60:40 mixture.



8 **9**

A similar possibility exists and would be expected for **2**; however, only **2c** and **2g** show intramolecular H bonding giving evidence for cis conformers (**4**). Assuming the free OH band is due only to **2c** or **2g**, an analysis of the O–H stretching bands of **2c** and **2g** in dilute solution indicates the presence of four parts of trans (**2**) to one part of cis isomers (**4**).

The reaction of **2a** and **3a** with propionic anhydride provided the corresponding esters listed as **2a** propionate and **3a** propionate, respectively, in Table I.

Biological Data.§ The analgetic potency of **2a** propionate and **3a** propionate (Table IV) was determined by the hot-plate method.[9] The codeine-like analgetic activity of the 2-substituted derivatives is not surprising in view of their chemical similarity to prodine. However, in view of the rather surprising codeine-like activity of the 1-substituted compound, it was interesting to note the low activity in the 3-substituted derivatives. These compounds cannot provide the receptor with an unsubstituted carbon chain as can the 1- and 2-substituted compounds. As noted in Table IV, the epimeric 3-propionates show no significant difference in the activity while the epimeric 2-propionates exhibit a significant difference; the equatorial aryl derivative is approximately twice as active as the axial aryl epimer.

Table II. Epimeric Ratios of 3-Aryl-3-hydroxyquinolizidines

		Ratio of **2** to **3**	
No.	R	By glc of crude product	By product recovery
2a, 3a	H	62:38[a] (50:50[b])	68:32
2b, 3b	2′-OCH_3	44:56[b]	46:54
2c, 3c	3′-OCH_3	48:52[b]	38:62
2d, 3d	4′-$OCH_2C_6H_5$		18:82
2f, 3f	4′-OCH_3	47:53[b]	40:60
2g, 3g	3′,4′-OCH_3	52:48[b]	54:46

[a]Prepared in ethyl ether. [b]Prepared in tetrahydrofuran.

The potential antidepressant activity of the compounds listed in Table V was evaluated by their effects in the modified Dopa test.[10] This test consists essentially of a potentiated motor response in mice pretreated with a low dose of a monoamine oxidase inhibitor (pargyline, Eutonyl, orally, 40 mg/kg), a challenging dose of *dl*-Dopa (200 mg/kg ip), and the test compound (administered orally). As noted in Table V, compounds **2b,g** and **3a,b,f** exhibited a moderate to marked Dopa response at oral doses of 25 and 100 mg/kg. These compounds are less active in the Dopa potentiation test than imipramine, a known antidepressant, which exhibits a marked response at both dose levels. With the exception of **2g** all of the compounds with a free alcoholic group were inactive. In the equatorial aryl derivatives (**3**) the alcoholic group hydrogen bonds with the nitrogen. The activity of **2b** may be due to the presence of **4** and/or the hydrogen bonded species involving the 2′-methoxy group. Additional studies to delineate the effect of the alcoholic group on Dopa response activity are in progress.

The compounds listed in Table V, with the exception of **2a** propionate and **3a** propionate also were screened for blood pressure effects. The blood pressure was measured directly from the cannulated caudal artery in normotensive, unanesthetized, restrained rats. Each compound was tested, by the intraperitoneal route at a dose of 30 mg/kg, in one rat. Two compounds, **2b** and **2g**, showed activity in this test and were therefore each retested, by the oral route at a dose of 10 mg/kg, in two spontaneously hypertensive rats. The compounds were found to be inactive at intervals of 3 and 24 hr after drug administration.

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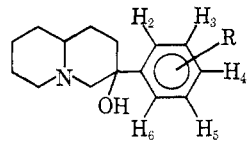
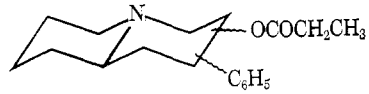
Table III. 3-Aryl-3-hydroxyquinolizidines, Chemical Shifts (δ) of Aromatic Protons



No.	R	Chemical shifts of aromatic protons				
		H_2	H_3	H_4	H_5	H_6
2a	H	7.90[a]	7.39[a]	7.37[a]	7.39[a]	7.90[a]
3a	H	7.40[a]	7.40[a]	7.40[a]	7.40[a]	7.40[a]
2b	2′-OCH_3		6.94	→	7.59[b]	8.35[c]
3b	2′-OCH_3		6.92	→	7.52[b]	7.82[c]
2c	3′-OCH_3	7.11 → 7.57[b]		6.83[a]	7.11	→ 7.57[b]
3c	3′-OCH_3	6.70 → 7.47[b]		6.70	→	7.47[b]
2d	4′-$OCH_2C_6H_5$	7.82[c]	7.02[c]		7.02[c]	7.82[c]
3d	4′-$OCH_2C_6H_5$	7.42[c]	6.88[c]		6.88[c]	7.42[c]
2e	4′-OH	7.79[d]	6.94[c]		6.94[c]	7.79[c]
3e	4′-OH	7.59[c]	6.98[c]		6.98[c]	7.59[c]
2f	4′-OCH_3	7.84[c]	6.98[c]		6.98[c]	7.84[c]
3f	4′-OCH_3	7.60[c]	7.04[c]		7.04[c]	7.60[c]
2g	3′,4′-OCH_3	7.63[a]			7.02[c]	7.63[a]
3g	3′,4′-OCH_3	7.44[d]			7.15[a]	7.15[a]

[a]Multiplet. [b]The arrow indicates a broad multiplet between indicated values. [c]Doublet. [d]Singlet.

Table IV. Analgetic Potency of Phenylpropionoxyquinolizidines



C_6H_5 position	$OCOCH_2CH_3$ position	ED_{50}, mg/kg[a]		OPD[b]	
3-Axial	3-Equatorial	37.0 (27.2–50.3)[c]	3.2	21.1	126.1
3-Equatorial	3-Axial	33.1 (26.0–42.1)[c]	3.9	24.0	140.3
2-Axial	2-Equatorial	8.0 (6.3–10.2)[c,d]	4.2	18.0	118.4
2-Equatorial	2-Axial	3.1 (2.5–3.9)[d]	3.6	23.6	130.9
1-Equatorial	1-Axial	8.5	3.9	27.2	138.7
Codeine		7.5 (6.8–8.2)	4.0	22.8	147.6

[a]Subcutaneous; numbers in parentheses are 95% confidence limits. [b]Onset, peak and duration of action in minutes. [c]Hydrochloride. [d]Reference 3.

Experimental Section

All melting points were taken on a Mel-Temp and are corrected. Infrared spectra were determined on a Perkin-Elmer Model 257 spectrometer. Solution infrared spectra were taken in sodium chloride cells of widths 1.058 mm (reference) and 1.091 mm (sample). Dilution studies were performed in $CHCl_3$ and CCl_4 using matched sodium chloride cells of widths 10 mm for 0.01 *M* solutions and 25 mm for 0.002 *M* solutions. The nmr spectra were taken on a Jeolco Model C-60-HL spectrometer (Me_4Si). Thin-layer chromatography was performed using silica gel thin-layer sheets (Brinkman, Polygram Sil G) and ethyl acetate (with 1% ammonium hydroxide). Gas chromatographic analyses were performed on a Varian Aerograph Model 600D fitted with a flame ionization detector and a 5 ft by ⅛ in. column packed with Varaport No. 30 (100–120 mesh) coated to a concentration of 3% with SE-30; column temperatures of 180–225° were used with injection temperatures 80–100° above the column temperature; a nitrogen carrier flow rate of approximately 30–40 ml/min was used; quantitative measurements were made using the ratio of peak heights method and are not corrected for detector response for all isomers. However, glc of a 52–48 solution of **2b:3b** showed a ratio of **2b** to **3b** of 53:47, approximately a 1:1 response. Column chromatography was performed using neutral alumina (Woelm), basic alumina (Brockman), or silica gel (Woelm, 0.05–0.20 mm); the chromatograms were monitored by tlc or glc; like fractions were combined and concentrated. Elemental analyses were performed by the A. H. Robins Co., Richmond, Va.

3-Hydroxy-3-arylquinolizidines. The procedure described by Sam and coworkers[2,4] was followed utilizing tetrahydrofuran, 0.40 mol of the appropriate bromoaryl compound, and 0.20 mol of 3-ketoquinolizidine.[10] The Grignard reaction mixture was cooled in an ice bath and treated dropwise over a 1-hr period with 150 ml of 15% NaOH. The THF layer was decanted from the reaction mixture and evaporated to dryness. The aqueous reaction mixture was extracted with three 100-ml portions of Et_2O. The Et_2O extractions and the residue from the THF layer were combined and extracted with three 50-ml portions of 3 *N* HCl. The acid solution was cooled in an ice bath, basified to pH 11–13 with 20% NaOH, and extracted with 200 ml of Et_2O. The Et_2O solution was dried over $MgSO_4$ and evaporated to dryness. The ratio of epimers present was determined by glc. The epimers were separated by fractional recrystallization and/or column chromatography.

3(e)-Hydroxy-3(a)-(4′-hydroxyphenyl)quinolizidine (3e) and 3(a)-Hydroxy-3(e)-(4′-hydroxyphenyl)quinolizidine (2e). Compound **3d** (3.8 g, 0.011 mol), 200 ml of MeOH, and 0.8 g of 10% Pd/C were hydrogenated at room temperature and 46 psi for 12 hr. The catalyst was removed by filtration and the MeOH evaporated to give 2.3 g of a viscous syrup. The latter was dissolved in a small amount of EtOAc and eluted through a column packed with 75 g of grade III alumina to give 2.1 g (72%) of white crystalline **3e**, mp 154–155°.

The debenzylation of 4.6 g (0.014 mol) of **2d** was conducted as described above to give 4.5 g of a viscous syrup. The latter was recrystallized from EtOAc to give 2.8 g (76%) of white crystalline **2e**, mp 167–168°.

3(a)-Phenyl-3(e)-propionoxyquinolizidine. The method of Sam, England, and Temple[3] was followed using 6.0 g (0.025 mol) of **2a**, 100 ml of dry pyridine, and 20 ml of propionic anhydride. The mixture was refluxed for 72 hr, then cooled at room temperature, and concentrated. The residue was chilled in an ice bath and thereafter stirred with saturated K_2CO_3 for 15 min. The mixture was extracted with three 50-ml portions of $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to yield 13.7 g of a crude oil: ir (film) no OH, 3090, 3065, 3030 (arom), 2800, 2765, 2735 (Bohlmann), 1815, 1740 (carbonyl), 1045 (ester), 769, 760, 703 cm^{-1} (arom). The material was dissolved in a few milliliters of petroleum ether and eluted onto a column of 30 g of grade I

Table V. Antidepressant Activity

Compd no.	Mouse approx LD_{50}, mg/kp ip	Dopa response mg/kg po	Dopa response Mouse act.[a]
2a	100	100	0
2a propionate	*b*	100	0
3a	300	100	+2
		25	0
3a propionate	*b*	100	0
2b	100	100	+2
		25	0
3b	300	100	+2
		25	0
2c	300	100	0
3c	300	100	0
2d	*b*	*b*	
3d	*b*	*b*	
2e	300	100	0
3e	300	100	0
2f	100	100	0
3f	300	100	+3
		25	+2
2g	300	100	+2
		25	0
3g	750	100	0
Imipramine		25	+3
		100	+3

[a]See ref 10. Ratings: 0 = inactive, +1 = slight potentiation, +2 = moderate, +3 = marked. [b]Not determined.

basic alumina. Elution was begun with petroleum ether at a flow rate of 5 ml/min. A combination of fractions gave 5.6 g (78%) of ester as an oil: ir (film) 3090, 3060, 3030 (arom), 2800, 2765, 2730 (Bohlmann), 1742 (ester carbonyl), 1176 (ester C–O), 769, 760, 702 cm^{-1} (arom); nmr (CCl_4) δ 1.00 (t, 3, CH_3), 2.20 (q, 2, CH_2), 7.20–7.48 (m, 2, arom), 7.52–7.90 (m, 2, arom).

3(e)-Phenyl-3(a)-propionoxyquinolizidine. The procedure described above was followed using 5.5 g (0.024 mol) of **2a**. The crude product was dissolved in 50 ml of 20% HCl and extracted with three 50-ml portions of Et_2O. The aqueous layer was cooled in an ice bath and basified to pH 11–13. The mixture was extracted with three 100-ml portions of Et_2O; the extract was dried over $MgSO_4$ and evaporated to give 4.9 g of a dark oil. The oil was chromatographed in a fashion similar to that described above to give 2.5 g (37%) of ester: ir (film, PE 137) 2750 (Bohlmann), 1740 (ester C=O), 1170 (ester C–O), 768, 756, 696 cm^{-1} (arom); nmr (CCl_4) δ 1.10 (t, 3, CH_3), 7.27 (s, 5, arom).

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Structure–Activity Relationships of the Mitomycins and Certain Synthetic Analogs

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1-Acetoxy-7-methoxymitosene was highly active against gram-positive and gram-negative bacteria in cultures but inactive in mice. It is partly inactivated in the presence of serum, but simple binding to serum proteins does not account for this inactivation. 1-Hydroxy-7-methoxymitosene also was active against bacteria in culture but inactivated by serum. Both it and 2,7-diamino-1-hydroxymitosene were inactive against L1210 leukemia, despite the activity of the latter compound and related 1-hydroxymitosenes against certain sarcomas. Lipid–water partition coefficients were measured for these compounds, related mitosenes and indoloquinones, and naturally occurring mitomycins in order to establish structure–activity relationships. Only limited correlations could be made. These included antileukemia activities of the mitomycins, in which activity increased with hydrophilicity, and antibacterial activity of 7-methoxymitosenes and related indoloquinones, in which the best activity was obtained at moderate lipophilicity. The unique physicochemical properties of mitomycin C are cited as essential to future studies.

Recently we reported the synthesis of 1-substituted 7-methoxymitosenes including **1** and **2**.[1] These compounds are close structural analogs to mitomycin hydrolysis products such as apomitomycin A (**3**),[2] which has moderate antibacterial and antitumor activity.[3-5] As shown in Table I, compounds **1** and **2** are highly active against both gram-positive and gram-negative bacteria in culture. Thus **1** was one-fourth to one-eighth as active as mitomycin C (**9**) against many bacteria, whereas **2** was as potent as mitomycin C against *Diplococcus pneumoniae* and *Streptococcus pyogenes* but less active than **1** against gram-negative bacteria.

In contrast to its high activity against bacteria in cultures, **1** was inactive at doses of 20 mg/kg (administered intramuscularly at 1 and at 3.5 hr postchallenge) in mice infected with *S. pyogenes* A 9604 and with *Klebsiella pneumonia* A 9977. This disparity between the activity of **1** in culture and in mice was surprising, especially since the closely related 1-unsubstituted analog **6** is active against *Staphylococcus aureus* in mice but much less active than **1** in bacterial culture.[6] The observation (Table I) that both **1** and **2** have decreased activities against *S. aureus* in the presence of serum suggested that serum protein binding might be at least partly responsible for their inactivation. In order to investigate this possibility we measured the binding to bovine serum albumin (BSA) of **1**, **2**, **6**, and a variety of naturally occurring mitomycins and synthetic analogs which were included for comparison purposes. At the relatively high concentration of BSA (4%) used in this study, the bindings of **1** and **2** were 60