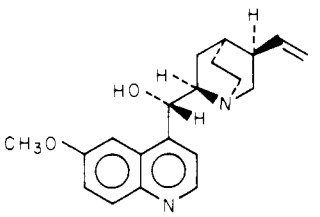
Mono- and Diaryl-2-quinuclidinylcarbinols with Local Anesthetic and Antiarrhythmic Activity[1]

P. H. Nelson,* A. M. Strosberg, and K. G. Untch

Institutes of Organic Chemistry and Pharmacology and Metabolism, Syntex Research, Palo Alto, California 94304.
Received July 9, 1979

The reaction between 2-carboethoxyquinuclidine and various aryl- and heteroaryllithium reagents gave mixtures of aryl 2-quinuclidinyl ketones and diaryl-2-quinuclidinylcarbinols. Diborane reduction of the ketones gave the *erythro*-carbinols, stereochemically analogous to quinidine. Several of the mono- and diarylcarbinols exhibited potent local anesthetic and antiarrhythmic activity, in some cases greater than that of quinidine. Diphenyl-2-quinuclidinylcarbinol and a (bromomethoxyphenyl)(methoxyphenyl)-2-quinuclidinylcarbinol were particularly active in reverting ouabain-induced arrhythmia in dogs, showing a potency and duration of action equal to or greater than that of propranolol.

Quinidine (1) is a member of a group of antiarrhythmic

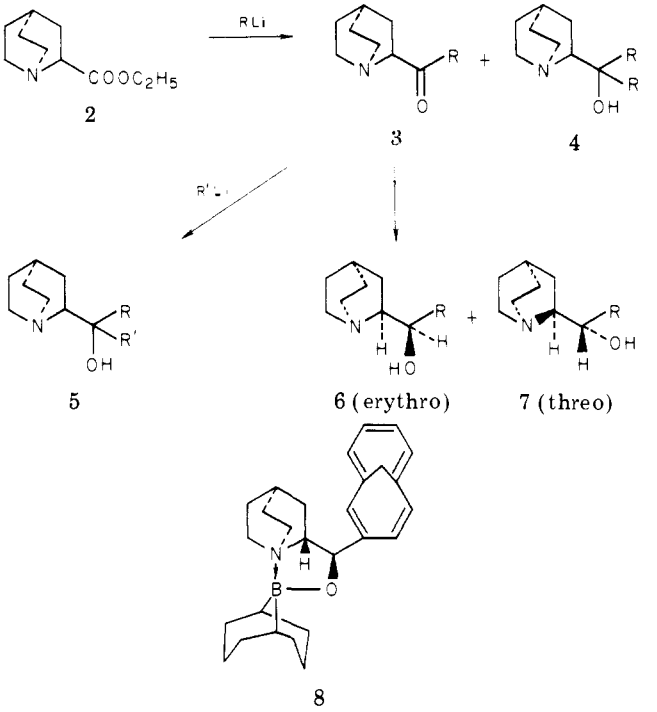


1

agents which also possess local anesthetic activity.[2] Structurally, quinidine can be regarded as an aryl-2-quinuclidinylcarbinol in which the two asymmetric centers adjacent to the quinoline ring have the erythro configuration.[3] We report here the synthesis and local anesthetic/antiarrhythmic activities of a series of *erythro*-aryl-2-quinuclidinylcarbinols, and also of some related diaryl-2-quinuclidinylcarbinols.

Chemistry. The compounds were prepared as shown in Scheme I. The reaction of ethyl quinuclidine-2-carboxylate[4] (2) with various alkyl-, aryl-, and heteroaryllithium compounds gave mixtures of the ketones 3 and the carbinols 4, which were separated by chromatography. Even in the presence of a large excess of the organometallic reagent, appreciable quantities of the ketonic products could, in most cases, be isolated. Presumably, this is because a proportion of the ketone is converted to the lithium enolate under the basic reaction conditions and thereby protected from further reaction. Indeed, in some cases, little or no carbinol was produced. The organometallic reagents, if not commercially available, were made by halogen–metal exchange between *n*-butyllithium and the appropriate bromo compound or, in the cases of furan,[5] *N*-methylimidazole,[6] and 1,6-methano[10]annulene, by proton abstraction from the unsubstituted aromatic compound, using *n*-butyllithium. Tetramethylenediamine was used in some cases to activate the butyllithium.[7] Attempted halogen–metal exchange with 4-bromoanisole gave, in addition to 4-lithioanisole, 2-lithio-4-bromoanisole, by proton abstraction ortho to the methoxyl group.[8] Reaction of this mixture with the ester 2 gave all four of the possible diarylcarbinols, including the two diastereomeric (methoxyphenyl)(bromomethoxyphenyl) compounds, and neither of the two expected ketones.

Scheme I



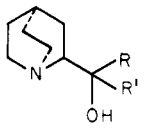
2 3 4 5 6 (erythro) 7 (threo) 8

Reduction of 2-benzoylquinuclidine with methanolic sodium borohydride gave approximately equal amounts of the two possible carbinols. These were separated and assigned erythro and threo configurations on the basis of their NMR spectra as follows: the benzylic hydrogen of the erythro isomer exhibited a 6.5-Hz doublet at 4.77 ppm; that of the threo isomer a 9.5-Hz doublet at 4.37 ppm. These values compare well with those observed[9] for the benzylic hydrogens of ephedrine (erythro stereochemistry), a 4.07-Hz doublet at 4.70 ppm, and pseudo-ephedrine (threo stereochemistry), an 8.23-Hz doublet at 4.16 ppm. Since the separation of the phenylcarbinols was difficult, a number of reducing agents were examined in attempts to obtain cleanly the erythro isomer, as it was believed that this stereochemistry, present in quinidine, was necessary for optimum biological activity. Most reducing agents gave mixtures (see Experimental Section), but it was found that either diborane or 9-BBN[10] gave almost exclusively the desired isomer. If it is assumed that the quinuclidine nitrogen coordinates to the boron, examination of Dreiding models clearly shows that hydride would be delivered

(1) Contribution no. 532 from the Syntex Institute of Organic Chemistry.
(2) Davis, W. G. *J. Pharm. Pharmacol.* **1970**, *22*, 284.
(3) Prelog, V.; Häfliger, O. *Helv. Chim. Acta* **1950**, *33*, 2021.
(4) Prelog, V.; Cerkovnikov, E. *Justus Liebigs Ann. Chem.* **1940**, *545*, 259.
(5) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216.
(6) Shirley, D. A.; Alley, P. W. *J. Am. Chem. Soc.* **1957**, *79*, 4922.
(7) Mulvaney, J. E.; Newton, D. J. *J. Org. Chem.* **1969**, *34*, 1936.
(8) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1939**, *61*, 106. Gilman, H.; Langham, W. *ibid.* **1940**, *62*, 2327.
(9) Portoghese, P. S. *J. Med. Chem.* **1967**, *10*, 1057.
(10) 9-Borabicyclo[3.3.1]nonane; Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280.

0022-2623/80/1823-0180$01.00/0

Table I. Local Anesthetic Activity of Arylquinuclidinylcarbinols



compd	R	R'	local anesthetic act. × propranolol (95% CL)
9	H	Ph (threo)	0.18 (0.14–0.23)
10	H	Ph (erythro)	0.25 (0.18–0.33)
11	H	2-thiazolyl[a]	0.80 (0.73–0.89)
12	H	1-Me-2-imidazolyl[a]	0.61 (0.48–0.78)
13	H	1,6-methano[10]annulen-2-yl[a]	0.99 (0.82–1.25)
14	H	2-furyl[a]	0.09 (0.05–0.13)
15	H	4-pyridyl[a]	0.08 (0.04–0.12)
16	H	*p*-ClC_6H_4[a]	0.43 (0.31–0.55)
17	H	*p*-MeC_6H_4[a]	0.23 (0.20–0.27)
18	H	*t*-Bu[a]	0.13 (0.05–0.21)
19	Ph	Ph	0.85 (0.74–0.98)
20	2-furyl	2-furyl	0.27 (0.20–0.35)
21	*p*-MeC_6H_4	*p*-MeC_6H_4	0.86 (0.60–1.22)
22	*p*-ClC_6H_4	*p*-ClC_6H_4	1.04 (0.94–1.15)
23	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	0.54 (0.37–0.72)
24	2-MeO-5-BrC_6H_3	2-MeO-5-BrC_6H_3	0.92 (0.70–1.28)
25[b]	p-$OMeC_6H_4$	2-MeO-5-BrC_6H_3	1.20 (1.02–1.42)
26[b]	2-MeO-5-BrC_6H_3	*p*-$OMeC_6H_4$	1.23 (0.99–1.55)
27	Ph	2-thiazolyl	0.25 (0.18–0.31)
quinidine sulfate			1.15 (0.59–2.51)
lidocaine			0.66 (0.18–1.94)

[a] Erythro isomer. [b] Compounds 25 and 26 are diastereomeric.

preferentially to one face of the carbonyl carbon to give the erythro product. The occurrence of coordination could be inferred from monitoring of the reduction reaction: the initial product—the N–B coordinated species—was relatively nonpolar, and the polar hydroxyamine could be released only after treatment with dilute hydrochloric acid at 60–70 °C. In the case of the 1,6-methano[10]annulene ketone (3, R = 1,6-methano[10]annulen-2-yl), the intermediate complex **8** was isolated. With the exception of the *N*-methylimidazolyl and the 2-furyl ketones, the other ketones also could be reduced with 9-BBN to give the *erythro*-carbinols. The two exceptions gave predominently the erythro products, with an appreciable amount of the threo isomer. The structures were assigned as previously described.[11] The decreased specificity of these reductions may be due to the occurrence of coordination between the reducing agent and one of the heteroatoms in the aromatic moiety. One example of a phenyl(heteroaryl)carbinol was made by reacting phenyllithium with 2-quinuclidinyl 2-thiazolyl ketone. Only one product was formed, though clearly two diastereomers are possible; the yield was low, evidently because enolization of the ketone predominated over 1,2 addition to the carbonyl group.

Biological Results. The mono- and diarylcarbinols were tested for local anesthetic activity using a modification of the guinea pig intracutaneous wheal method.[12] Some compounds were also tested for their ability to abolish ouabain-induced arrhythmia in dogs.[13] The local anesthetic results, with 95% confidence limits,[14] are shown in Table I. It had been expected that the monoarylcarbinols would show the greatest activity, since they are more clearly analogous in structure to quinidine itself. However, the most potent compounds are actually in the diarylcarbinol series. In the monoaryl series, the *erythro*- and *threo*-phenylcarbinols **9** and **10** are of comparable potency, in contrast to the expectation that the erythro compound would be superior, based on the erythro stereochemistry of quinidine. The compound in the quinidine series which has threo stereochemistry is known as 9-epiquinidine. It occurs naturally[15] but its local anesthetic activity has not been reported. Several of the diarylcarbinols are equal to or more potent than propranolol in local anesthetic activity. Since propranol exhibits activity equal to or greater than that of the common local anesthetic agents[16] (e.g., lidocaine, Table I), the activity displayed by these quinidine analogues is very significant. The local anesthetic activities in both the mono- and diaryl series varied in a manner not obviously attributable to changes in lipophilicity or bulk. The most active compound in the monoaryl series, the 1,6-methano[10]-annulene compound **13**, is probably the most lipophilic, but the more hydrophilic thiazole and *N*-methylimidazole compounds **11** and **12** are only slightly less active. The apparent activity of **11** may be enhanced by a peripheral vasoconstriction exerted by the compound.[17] Since the *tert*-butylcarbinol **18** is of comparable activity to the phenyl compounds **9** and **10** and to the furyl and 4-pyridyl derivatives **14** and **15**, it cannot even be deduced that an

(11) The *erythro*-*N*-methylimidazol-2-ylcarbinol showed an 8.0-Hz doublet at 4.76 ppm; the threo isomer had a 10.0-Hz doublet at 4.50 ppm. The *erythro*-2-furylcarbinol had an 8.0-Hz doublet at 4.73 ppm; the threo isomer had a 10.0-Hz doublet at 4.42 ppm.

(12) Bülhbring, E.; Wajda, I. *J. Pharmacol. Exp. Ther.* **1945**, *85*, 78.

(13) Somani, P.; Lum, B. K. B. *J. Pharmacol. Exp. Ther.* **1965**, *147*, 194.

(14) Finney, D. J. "Statistical Methods in Biological Assay"; Hofner: New York, 1964.

(15) Rabe, P. *Chem. Ber.* **1941**, *74*, 725.

(16) Local anesthetic activity decreases in the order: propanolol, quinidine, lidocaine, procaine, procaine amide (unpublished results from these laboratories). See also Baum, T.; Eckfield, D. K.; Shropshire, A. T.; Rowles, G.; Varner, L. L. *Arch. Int. Pharmacodyn. Ther.* **1971**, *193*, 149.

(17) The compound induced transient increases in blood pressure in the pentobarbital-anesthetized dog at dose levels of 0.1 to 3.16 mg/kg. Vasoconstrictors are known to prolong and intensify the action of local anesthetics: Goodman, A. S.; Gilman, A. "The Pharmacological Basis of Therapeutics", 3rd ed.; McMillan: New York, 1965; p 372.

Table II. Antagonism of Ouabain-Induced Ventricular Arrhythmia

compd	no. of dogs used	no. of dogs reverted	ouabain, μg/kg	dose, mg/kg, to reverse arrhythmia	duration of reversal, min	heart rate, min⁻¹ control	heart rate, min⁻¹ after ouabain	heart rate, min⁻¹ after drug
13	1	1	70	15	>120[a]	144	216	156
16	1	0[b]	70	15	0	90	222	160
19	2	2	70 ± 10.0[c]	5	>120	160 ± 15	228 ± 6	186 ± 6
20	1	1	70	15	>120	110	240	180
21	3	3	83 ± 6.7	11.7 ± 3.3	85 ± 34.3	151 ± 6	220 ± 13	134 ± 19
22	4	4	75 ± 6.5	11 ± 3.1	116 ± 3.8	121 ± 16	213 ± 9	142 ± 12
23	1	1[d]	60	5	14[d]	144	240	168
24	1	1	70	10	>120	108	210	162
25	1	0	100	15	0	123	180	160
26	1	1	80	5	>120	132	204	123
27	2	1	75 ± 5.0	6.4 ± 1.4	>120	116 ± 16	207 ± 3	150 ± 12
propranolol	5	5	72 ± 7.4	5	80 ± 24.3	146 ± 16	211 ± 19	138 ± 6
lidocaine[e]	5	5	74 ± 2.4	5	51 ± 28.1	129 ± 14	223 ± 5	169 ± 22
quinidine[e]	13	10	59 ± 1	9 ± 1	31 ± 5	136 ± 9	211 ± 5	170 ± 8

[a] >120 min implies that ventricular tachycardia did not reappear during the 2-h observation period following the last dose of test compound. Since the tachycardia persisted for 128 min after ouabain in test animals, the duration of reversal caused by the drug may have been somewhat shorter than 120 min. [b] Occasional normal sinus beats were seen after drug administration. [c] Data are expressed as plus or minus the standard error of the mean where appropriate. [d] Dog suddenly fibrillated and died after 14 min of reversion. [e] Data from ref 15.

aromatic ring is necessary for activity. There is a similar lack of obvious trends in the data obtained for the diarylcarbinols, though once again the furan-containing compound is of notably low activity.

The antiarryhthmic results are shown in Table II. Because of the large number of parameters involved, it is not possible from the available data to determine the relative potencies of all the compounds. However, based on the effective dose and the duration of the resultant return to sinus rhythm, the diphenylcarbinol **19** and the (bromomethoxyphenyl)(methoxyphenyl)carbinol **26** appear to be the most active compounds. Surprisingly, the diastereomeric carbinol **25**, which differs from **26** only in the stereochemistry at the carbinol carbon, was inactive at 15 mg/kg, three times the effective dose for **26**. This result seems to indicate a very demanding configurational requirement at the carbinol carbon. The fact that the bis(bromomethoxyphenyl)carbinol **24** is quite active in the antiarrhythmic assay also indicates the considerable effect of subtle changes in the substitution pattern at this carbon. A comparison of the local anesthetic data and antiarrhythmic data of **25** and **26**, as well as that of **20** and **27**, suggests that there is no correlation between the two assays. The *erythro*-*p*-chlorophenylcarbinol **16** has low activity in both assays and perhaps indicates that in the monoarylcarbinols, which are more structurally analogous to quinidine, the two assays do correlate. Among the diarylcarbinols, the phenylthiazolyl compound **27** also caused prolonged reversion to sinus rhythm. Because of limited compound availability, the diastereomers **25** and **26** could only be studied in one dog each. Nevertheless, sharp differences in antiarrhythmic activity were apparent. In view of these differences, it is unfortunate that only one diastereomer of **27** was obtained (see Experimental Section).

The more active compounds described show local anesthetic and antiarrhythmic activity equal to or greater than propranolol, the most active of the reference compounds. Compared to quinidine, with which they are most structurally analogous, several of the compounds showed a markedly superior antiarrhythmic activity. The occurrence of such high activity in diaryl-, rather than monoaryl-, quinuclidinylcarbinols is especially noteworthy.

Experimental Section

Melting points are uncorrected. The NMR spectra were measured on a Varian A-60 or HA-100 spectrometer in $CDCl_3$ unless otherwise stated. The chemical shifts are expressed in parts per million (ppm) on the δ scale from internal Me_4Si. The IR spectra were measured on a Perkin-Elmer Model 137 spectrophotometer and are quoted to the nearest 10 cm^{-1}. The spectroscopic data for all new compounds were consistent with the assigned structures. Microanalytical results were within ±0.4% of theory. All compounds are racemic.

Ethyl Quinuclidine-2-carboxylate (2). Quinuclidine-2-carboxylic acid hydrochloride[18] (15.0 g, 0.078 mol) was stirred in thionyl chloride (200 g, 1.67 mol) containing DMF (1.0 g, 0.014 mol) for 24 h, to give a clear solution. The solvents were removed under vacuum to give a white residue of quinuclidine-2-carbonyl chloride hydrochloride, which was refluxed for 2 h in EtOH (200 mL). The solvent was removed under vacuum, and EtOAc and dilute aqueous Na_2CO_3 were added. The aqueous layer was saturated with NaCl and extracted several times with EtOAc. The combined organic extracts were dried and evaporated, and the residual oil was distilled to afford **2**: bp 60–64 °C (0.4 mm), lit.[4] 122–123 °C (12 mm); yield 13.5 g (95%).

Diphenyl-2-quinuclidinylcarbinol (19) and 2-Benzoylquinuclidine. To a solution of the ester (**2**; 3.0 g, 0.0164 mol) in Et_2O (15 mL) was added 2.2 M PhLi in 70:30 C_6H_6–Et_2O (19.0 mL, 0.041 mol). After 10 min, water and EtOAc were added; the organic solution was dried and evaporated, and the residue was chromatographed on silica gel (200 g; $CHCl_3$–MeOH, 95:5) to afford 2-benzoylquinuclidine: yield 1.0 g (28%); mp 83–84 °C (Et_2O–hexane), lit.[19] 88–89.5 °C. Further elution gave the carbinol **19**: yield 1.04 g (21%); mp 106–108 °C (hexane), lit.[20] (HCl) 265 °C.

***threo*- and *erythro*-Phenyl-2-quinuclidinylcarbinol (9 and 10).** Reduction of 2-benzoylquinuclidine with a wide variety of reducing agents gave mixtures of **9** and **10**; the isomers were separable by TLC (alumina; 19:1 $CHCl_3$–MeOH), and the ratio of **9** to **10** could be estimated by I_2 development. Sodium borohydride gave 30–60% of the threo isomer, depending on solvent. Lithium aluminum hydride, sodium cyanoborohydride, catalytic hydrogenation (Pd/C) and diisobutylaluminum hydride all gave mixtures. Reduction with diborane gave an estimated 95:5 erythro/threo mixture. Since no reagent gave exclusively the threo isomer **9**, this compound was obtained by chromatography of the mixture obtained by sodium borohydride reduction.

To a solution of 2-benzoylquinuclidine (0.8 g, 0.0036 mol) in MeOH (10 mL) was added sodium borohydride (0.3 g, 0.008 mol). After 30 min, dilute hydrochloric acid was added and the mixture

(18) Rubstov, M. V.; Dorokhova, M. I. *Zh. Obsch. Khim.* **1953**, *23*, 706.
(19) Braschler, V.; Grob, C. A.; Kaiser, A. *Helv. Chim. Acta.* **1963**, *46*, 2646.
(20) This compound was originally prepared by the reaction of phenylmagnesium bromide with the ester **2**; see ref 19.

was stirred for 30 min and then basified (aqueous Na_2CO_3) and extracted three times with EtOAc. The extract was dried and evaporated and the residue was chromatographed on ten 20 × 20 cm × 0.5 mm neutral Al_2O_3 plates (50:1 $CHCl_3$–MeOH); the upper band was removed to give **9**: yield 0.29 g (36%); mp 70–71 °C (EtOAc–hexane), lit.[21] 75–76.5 °C. Anal. ($C_{14}H_{19}NO$) C, H, N.

The erythro isomer **10** was obtained as follows: 2-Benzoylquinuclidine (0.5 g, 0.0022 mol) was dissolved in Et_2O (10 mL) and a 1.0 M solution of borane in THF (3 mL, 0.003 mol) was added. After 30 min, the solvents were removed and the residue was refluxed for 30 min in 15 mL of 1:1 THF–2 N hydrochloric acid. The solution was basified with aqueous Na_2CO_3 and extracted with EtOAc to afford, after recrystallization, 0.38 g (76%) of **10**: mp 143–144 °C (EtOAc–hexane), lit.[21] 142–144 °C.

***erthro*-2-Quinuclidinyl-2-thiazolylcarbinol (11).** A solution of 1.6 M *n*-butyllithium in hexane (19.6 mL, 0.031 mol) was added to Et_2O (40 mL) at −78 °C, 2-bromothiazole (4.8 g, 0.029 mol) was added, and after 10 min at −78 °C tetramethylethylenediamine (TMEDA; 2.59 g, 0.022 mol) was added. The solution was left at −78 °C for 20 min, and then the ester **2** (4.1 g, 0.022 mol) was added. After 1 h at −78 °C, the mixture was warmed and water and EtOAc were added. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel (1:1 C_6H_6–Me_2CO) to afford 2.93 g (59%) of 2-quinuclidinyl 2-thiazolyl ketone as an oil, characterized as the hydrochloride: mp 255 °C dec (2-propanol–Et_2O); NMR (D_2O) δ 5.20 (t, J = 10 Hz, 1 H), 8.14 (s, 2 H). Anal. ($C_{11}H_{15}ClN_2OS$) C, H, N. The ketone was reduced with diborane, as described above, and the product (ca. 90:10 erythro/threo) was recrystallized from EtOAc to afford 41% of **11**: mp 145–146 °C; NMR δ 5.03 (d, J = 7 Hz, 1 H), 7.22 (d, J = 3 Hz, 1 H), 7.68 (d, J = 3 Hz, 1 H). Anal. ($C_{11}H_{16}N_2SO$) C, H, N.

***erythro*-2-Quinuclidinyl-2-(1-methylimidazolyl)carbinol (12).** A solution of 1.6 M *n*-butyllithium in hexane (15.7 mL, 0.025 mol) was added to Et_2O (40 mL), then 1-methylimidazole (2.03 g, 0.024 mol) and TMEDA (2.2 g, 0.019 mol) were added, and after 2 h the mixture was cooled to −78 °C and the ester **2** (4.17 g, 0.022 mol) was added. The reaction was warmed to 25 °C and water and EtOAc were added. The organic solution was dried and evaporated. The product contained unreacted **2** which was removed by overnight hydrolysis in aqueous methanolic Na_2CO_3. The purified product was recrystallized from hexane to afford 2.0 g (40%) of 2-quinuclidinyl 2-(1-methylimidazolyl) ketone: mp 69–71 °C; IR (Nujol mull) 2600, 1670 cm^{-1} (keto–enol mixture); NMR δ 3.96 (s, 3 H), 5.08 (t, J = 10 Hz, 1 H), 7.20 (s, 1 H), 7.67 (s, 1 H). Anal. ($C_{12}H_{17}N_3O$) C, H, N. The carbinol **12** was obtained by reduction of the ketone with 9-BBN,[10] since a higher proportion of the erythro product was obtained with this reagent than with diborane. To a solution of the ketone (1.0 g, 0.0046 mol) in THF (5 mL) was added 0.5 M 9-BBN in THF (15 mL, 0.0075 mol). After 6 h, dilute hydrochloric acid was added, and the mixture was left for 16 h and then extracted with EtOAc. The aqueous solution was basified with aqueous NaOH and then extracted with CH_2Cl_2. The extract was dried and evaporated and the residue recrystallized from EtOAc–hexane to afford 0.3 g (30%) of **12**: mp 150–153 °C; NMR δ 4.76 (d, J = 8 Hz, 1 H). Anal. ($C_{12}H_{19}N_3O$) C, H, N. The NMR of the mother liquors showed the presence of ca. 50% of the threo isomer (10-Hz doublet at 4.50 ppm).

***erythro*-2-Quinuclidinyl-2-(1,6-methano[10]annulenyl)carbinol (13).** To a solution of 1,6-methano[10]annulene[22] (2.0 g, 0.014 mol) in Et_2O (28 mL) at −78 °C was added TMEDA (1.26 g, 0.011 mol) and 1.6 M *n*-butyllithium in hexane (8.8 mL, 0.014 mol). The mixture was warmed to 25 °C to give a deep red solution containing some yellow solid;[23] this was cooled to −78 °C and the ester **2** (2.32 g, 0.013 mol) was added. The mixture was warmed to room temperature and water and EtOAc were added. The organic solution was dried and evaporated, and the residue was chromatographed on silica gel (95:5 $CHCl_3$–MeOH) to afford 2.0 g of a mixture of the desired ketone and unchanged **2**; the latter was removed by overnight hydrolysis in aqueous methanolic Na_2CO_3. The pure ketone so obtained was recrystallized from hexane to afford 0.82 g (23%) of 2-quinuclidinyl 2-(1,6-methano[10]annulenyl) ketone: mp 127–132 °C.[24] Anal. ($C_{16}H_{21}NO$) C, H, N. The ketone was reduced using 9-BBN as described above; a sample of the reaction mixture was worked up without acid treatment to afford the boronate complex **8**: mp 170–173 °C (EtOAc); MS m/e 401 (M^+) (100), 344 (24), 264 (64). The bulk of the reaction mixture was worked up as described above to afford 49% of the carbinol **13**: mp 169–170 °C (EtOAc); NMR δ 5.48 (d, J = 5 Hz, 1 H). Anal. ($C_{19}H_{23}NO$) C, H, N.

***erythro*-2-Quinuclidinyl-2-furylcarbinol (14) and 2-Quinuclidinylbis(2-furyl)carbinol (20).** To a solution of the ester **2** (5.0 g, 0.027 mol) in Et_2O (10 mL) at −78 °C was added a solution of 2-furyllithium[5] (0.027 mol) in Et_2O (31.5 mL). After 30 min at −78 °C, the mixture was warmed to 25 °C and EtOAc and water were added. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel (9:1 $CHCl_3$–MeOH) to afford 1.54 g (31%) of 2-quinuclidinyl 2-furyl ketone as an oil [NMR δ 4.08 (t, J = 10 Hz, 1 H), 6.48 (m, 1 H), 7.30 (m, 1 H), 7.54 (m, 1 H)] and 0.54 g (7%) of the carbinol **20**, mp 73–74 °C (EtOAc–hexane). Anal. ($C_{19}H_{14}NO_3$) C, H, N. The ketone was reduced with 9-BBN to afford 48% of the carbinol **14**: mp 87–88 °C (EtOAc–hexane); NMR δ 4.73 (d, J = 8 Hz, 1 H). Anal. ($C_{12}H_{17}NO_2$) C, H, N. The NMR of the mother liquors indicated the presence of the isomeric *threo*-carbinol (10.0-Hz doublet at 4.42 ppm).

***erythro*-2-Quinuclidinyl-4-pyridylcarbinol (15).** A solution of 1.5 M *n*-butyllithium in hexane (25 mL, 0.0375 mol) was added to Et_2O (100 mL) and 4-bromopyridine (5.9 g, 0.0375 mol) at −78 °C. After 30 min, TMEDA (4.35 g, 0.0375 mol) was added, followed by the ester **2** (4.8 g, 0.026 mol). After 1 h, the mixture was warmed to room temperature and water and EtOAc were added. The organic solution was dried and evaporated and the residue was triturated with Et_2O to afford 3.4 g (60%) of 2-quinuclidinyl 4-pyridyl ketone, mp 115–117 °C (Et_2O). Anal. ($C_{13}H_{16}N_2O$) C, H, N. The ketone was reduced using 9-BBN to afford 50% of the carbinol **15**: mp 161–162 °C (EtOAc); NMR δ 4.77 (d, J = 6.5 Hz, 1 H). Anal. ($C_{13}H_{18}N_2O$) C, H, N.

***erythro*-2-Quinuclidinyl-4-chlorophenylcarbinol (16) and 2-Quinuclidinylbis(4-chlorophenyl)carbinol (22).** 4-Bromochlorobenzene (8.38 g, 0.044 mol) was dissolved in Et_2O (40 mL) and 2.34 M *n*-butyllithium in hexane (19.1 mL, 0.044 mol) was added. After 30 min, the mixture was cooled to −78 °C and the ester **2** (4.0 g, 0.022 mol) was added. After 30 min, the mixture was warmed to room temperature and extracted with dilute hydrochloric acid. The extract was basified with aqueous Na_2CO_3 and extracted with EtOAc to afford the crude product, which was chromatographed on silica gel (95:5 CH_2Cl_2–MeOH) to afford 1.3 g (24%) of 2-quinuclidinyl 4-chlorophenyl ketone [mp 92–94 °C (Et_2O–hexane). Anal. ($C_{14}H_{16}ClNO$) C, H, N] and then 2.4 g (30%) of the carbinol **22** [mp 97–99 °C (hexane). Anal. ($C_{20}H_{21}Cl_2NO$) C, H, N]. The ketone was reduced with diborane in THF to afford 67% of the carbinol **16**: mp 143–145 °C (EtOAc); NMR δ 4.73 (d, J = 6.5 Hz, 1 H). Anal. ($C_{14}H_{18}ClNO$), C, H, N.

***erythro*-2-Quinuclidinyl-4-methylphenylcarbinol (17) and 2-Quinuclidinylbis(4-methylphenyl)carbinol (21).** The ester **2** was reacted with *p*-tolyllithium[25] as described above for 4-chlorophenyllithium, and the reaction product was chromatographed to give 28% of 2-quinuclidinyl 4-methylphenyl ketone [mp 73–74 °C (Et_2O–hexane). Anal. ($C_{15}H_{19}NO$) C, H, N] and 19% of the carbinol **21** [mp 76–78 °C (aqueous MeOH). Anal.

(21) This compound was originally prepared (ref 19) by fractional crystallization of the mixture obtained by reduction of 2-benzoylquinuclidine with lithium aluminum hydride.

(22) Vogel, E.; Roth, H. D. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 228. The compound was prepared as described by Nelson, P. H.; Untch, K. G. *Tetrahedron Lett.* **1969**, 4475.

(23) Nelson, P. H.; Bartsch, G. A.; Untch, K. G.; Fried, J. H. *J. Med. Chem.* **1975**, *18*, 583.

(24) The broad melting range of this compound is presumably due to the fact that, since the substituted annulene moiety is chiral, the ketone is a diastereomeric mixture. No indication of the diastereomeric composition could be obtained from the NMR spectrum.

(25) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327.

($C_{22}H_{27}NO$) C, H, N]. The ketone was reduced using diborane in THF to yield 72% of the carbinol 17: mp 151–153 °C (EtOAc–hexane); NMR δ 4.71 (d, J = 7 Hz, 1 H). Anal. ($C_{15}H_{21}NO$) C, H, N.

***erythro*-2-Quinuclidinyl-*tert*-butylcarbinol (18).** The ester **2** (2.2 g, 0.012 mol) was dissolved in Et_2O (5 mL) and 1.6 M *tert*-butyllithium in pentane (17.0 mL, 0.027 mol) was added. Water and EtOAc were added, and the organic solution was dried and evaporated to afford a crude product which upon chromatography on silica gel (9:1 CH_2Cl_2–MeOH) afforded 1.4 g (64%) of 2-quinuclidinyl *tert*-butyl ketone as an oil, characterized as the maleate: mp 165–166 °C (EtOH–Et_2O). Anal. ($C_{16}H_{25}NO_5$) C, H, N. Reduction of the ketone with 9-BBN gave a 55% yield of the carbinol 18: mp 109–110 °C (hexane); NMR δ 3.45 (d, J = 3.5 Hz, 1 H). Anal. ($C_{12}H_{23}NO$) C, H, N.

2-Quinuclidinylbis(4-methoxyphenyl)carbinol (23), 2-Quinuclidinylbis(2-methoxy-5-bromophenyl)carbinol (24), and the Diastereomeric 2-Quinuclidinyl(4-methoxyphenyl)(2-methoxy-5-bromophenyl)carbinols (25 and 26). To a solution of 4-bromoanisole (10.9 g, 0.058 mol) in Et_2O (40 mL) was added a 2.34 M solution of *n*-butyllithium in hexane (24.8 mL, 0.058 mol). After 30 min, the solution was cooled to −78 °C and the ester **2** (4.0 g, 0.022 mol) was added. The reaction was allowed to attain room temperature. The crude product was chromatographed on neutral alumina (400 g; hexane-acetone, 4:1) to give the carbinol **24** [yield 0.7 g (6%); mp 196–198 °C (MeOH). Anal. ($C_{22}H_{25}Br_2NO_3$) C, H, N] and then the carbinol **25** [yield 0.7 g (7%); mp 177–178 °C (MeOH). Anal. ($C_{22}H_{26}BrNO_3$) C, H, N], followed by the isomer **26** [yield 1.1 g (10%); mp 125–127 °C (acetone–hexane). Anal. ($C_{22}H_{26}BrNO_3$) C, H, N] and finally **23** [yield 1.7 g (22%); mp 128–129 °C (hexane). Anal. ($C_{22}H_{27}NO_3$) C, H, N]. No ketones were isolated.

2-Quinuclidinyl(2-thiazolyl)(phenyl)carbinol (27). 2-Quinuclidinyl 2-thiazolyl ketone (3.0 g, 0.009 mol) was dissolved in Et_2O (10 mL) and cooled to −78 °C. A 2.2 M solution of phenyllithium in 70:30 C_6H_6–Et_2O (4.0 mL, 0.0088 mol) was added, and the reaction was warmed to room temperature; TLC examination (Al_2O_3; 1:1 hexane–EtOAc) showed largely unchanged ketone; so after cooling to −78 °C, a further 4.0 mL (0.0088 mol) of phenyllithium solution was added. The reaction was warmed to room temperature and the crude product was chromatographed on neutral alumina (400 g; 1:1 hexane–EtOAc) so as to isolate unreacted ketone (2.0 g, 67%) and 0.62 g (16%) of the carbinol **27**, mp 119–120 °C (EtOAc–hexane). Anal. ($C_{17}H_{20}N_2OS$) C, H, N.

Determination of Local Anesthetic Activity. A modification of the method of Bülbring and Wajda[12] was employed. Colored female guinea pigs weighing 300–350 g were used for the test. On the day preceding the experiment, the hair on the back of the guinea pigs was shaved. Injections were given intradermally with 26-gauge needles in a volume of 0.15 mL of saline at 0.2–2% concentration. Four animals were used for each test. Each animal received four injections: 2 doses of standard (propranolol, 0.6 and 0.2%) and two doses of test compound, one high (0.6–2%) and one low (0.2–0.67%). The wheals which developed at the injection site were marked with colored pens. Every 5 min, up to 30 min after each injection, the animals' skin was pricked lightly with a 23-gauge needle, six times outside the wheal and six times inside the wheal. Pricks were applied 3–5 s apart. The number of times the guinea pigs skin within the wheal did not react by twitching was recorded. The percentage of occasions on which the animal did not react to the stimulus within the wheal (out of a total of 36) was taken as a numerical indication of the local anesthetic activity of the compound. Standard potency estimates and 95% confidence limits were then determined.[14] Propranolol was selected as a standard in this assay because it exhibits prominent local anesthetic activity and is also highly active against ouabain-induced arrhythmia. The standard local anesthetic agent lidocaine is also included in Table I.

Antiarrhythmic Assay. Ouabain-induced ventricular tachycardia was elicited in pentobarbital (35 mg/kg) anesthetized dogs by an initial intravenous loading dose of 40 μg/kg, supplemented by 20 μg/kg 30 min later. These were followed by additional dose levels of 10 μg/kg at 15-min intervals until a persistent ventricular tachycardia was established. Test compounds were administered intravenously over 3 min, approximately 20 min following the last dose of ouabain. An initial dose of 5 mg/kg of test compound was administered. If reversion to sinus rhythm did not occur within 15 min, or if reversion did not last longer than 10 min (except for lidocaine), second or third doses of 5 or 10 mg/kg were administered at 15-min intervals until reversion occurred or until an arbitrary peak dose of 15 or 20 mg/kg had been achieved. All animals were observed for a period of 2 h following the last dose of test compound.

In 10 control dogs, the mean total dose of ouabain to establish the arrhythmia was 67 ± 2.1 (SE) μg/kg. Prior to ouabain treatment, the control heart rate of these animals was 136 + 4.4 beats per minute. After ouabain-induced ventricular tachycardia was established for 20 min, heart rate was 236 ± 4.0 beats per minute. The arrhythmia remained unabated for 128 ± 7.8 min.

Acknowledgment. We thank L. Johnson, L. Miller, and D. Van Antwerp for assistance with the pharmacological assays.

Quantitative Structure–Activity Relationships for *N*-[(*N*′,*N*′-Disubstituted-amino)acetyl]arylamines for Local Anesthetic Activity and Acute Toxicity

Françoise Heymans, Laurence Le Thérizien, Jean-Jacques Godfroid,*

Laboratoire de Pharmacochimie Moléculaire, Université de Paris 7, 75221 Paris Cedex 05, France

and Pierre Bessin

Département de Pharmacologie, Crephar, 4, rue de la Division Leclerc, 91380 Chilly-Mazarin, France. *Received May 11, 1979*

The synthesis and physicochemical properties of a series of *N*-[(*N*′,*N*′-disubstituted-amino)acetyl]arylamines are described. A QSAR method is applied to local anesthetic activity and acute toxicity by means of a "nonclassic" substituent variation involving a modification on both aryl and amino moieties. The choice of the different parameters (partition coefficient, pK_a, connectivity index, molar refraction, and molar volume) is discussed and their different methods of determination are described. Molar refraction is the parameter which explains best the variance of the local anesthetic activity, and the quadratic regression with MR leads to a "a posteriori" synthesis of one compound with optimized activity. However, the partition coefficient is the most explicative parameter for intravenous toxicity.

Numerous molecules are capable of inducing local anesthetic activity, and this property is often a secondary therapeutic effect of drugs active on the central nervous system, β-blocking drugs, antiarrhythmic drugs, etc. We have first tested anesthetic activity in a potentially antiarrhythmic series. In order to investigate the parameters which would explain the variance of local anesthetic activity, we have selected and synthetized compounds for

0022-2623/80/1823-0184$01.00/0