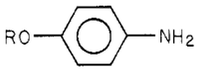
Table III *p*-Aminophenyl Ethers



no.	yield, %	recrystn solvent	mp, °C	formula	anal.
8	74	CH_2Cl_2/hexane then C_2H_5OH	128.8-135.8	$C_{20}H_{25}NO$	C, H, N
11	29	CH_2Cl_2, then ethanol	231.1-238.8	$C_{20}H_{25}NO$	C, H, N
14[a]	57	$(CH_3)_2CHOH$	>250 dec	$C_{16}H_{24}ClNO$	C, H, N, Cl
17[a]	17	C_2H_5OH	205 dec	$C_{16}H_{24}ClNO$	C, H, N, Cl
20[a]	92	$(C_2H_5)_2O$[b]	112.1-114.3	$C_{12}H_{20}ClNO$	C, H, N; Cl[c]
23[a]	97	$(C_2H_5)_2O$	94.8-96.1	$C_{14}H_{24}ClNO$	C, H, N, Cl
26[a]	74	1:1 benzene/Skelly B	92.0-94.2	$C_{16}H_{28}ClNO$	C, H, N, Cl

[a] Data reported are for the hydrochloride salt. The yield is based on the corresponding nitro compound. [b] The salt was generated in ether but not recrystallized. [c] Cl: calcd, 15.43; found, 15.95.

Acknowledgment. The authors are indebted to P. E. Marlatt and M. C. Moerman for the preparation of 4-diamantanol, R. L. Pederson for the preparation of *cis*- and *trans*-9-decalols, M. A. Rebenstorf for the hydrogenation reactions, Dr. W. Morozowich for helpful discussion on the isolipophilicity of compounds **2** and **23**, R. C. Anderson and D. J. Liggett for microanalyses, B. Story, H. Sanders, G. Louthan, T. A. Scahill, and P. A. Meulman for other analytical work, and J. K. Woods for typing the manuscript.

Analogues of 3-Quinuclidinyl Benzilate

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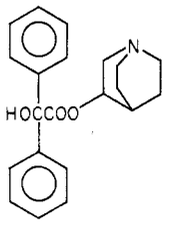
A number of analogues of 3-quinuclidinyl benzilate (QNB) have been synthesized and their affinities to muscarinic receptor from rat or dog ventricular muscle measured. We have determined that the muscarinic receptor can to a different degree accomodate either a halogen in the ortho, meta, or para position of one phenyl ring or the replacement of one phenyl ring with an alkyl group. Our in vitro competition studies show that the affinities lie within a 270-fold range, from the highest affinity compound, 3-quinuclidinyl α-hydroxy-α-cyclopentylphenylacetate (**2**), to the lowest affinity compound, 3-quinuclidinyl α-hydroxy-α-2-propargylphenylacetate (**11**).

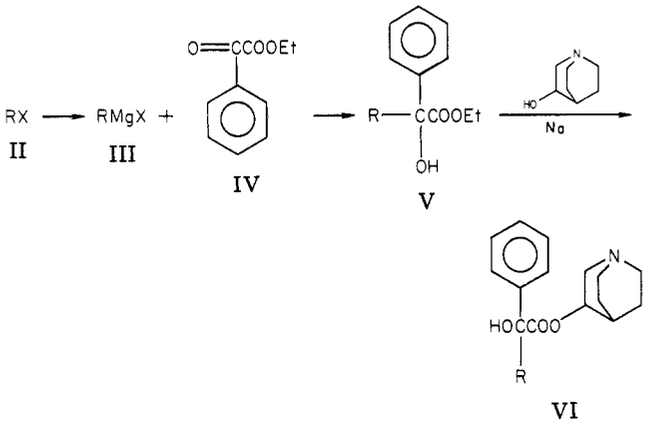
3-Quinuclidinyl benzilate (QNB, I), synthesized by



I

Sternbach and Kaiser,[1] is one of the most potent muscarinic antagonists.[2] Recently,[3,4] our group disclosed the potential use of QNB analogues for myocardial imaging. The proposed[5] "three points of attachment" model of the interaction of the muscarinic antagonist with the receptor explains neither the role of the second aromatic ring nor the role of substitution in the ring. Some impairment of binding has been reported at the receptor level due to ring substitution.[6] It has also been reported that the replacement of one of the aromatic rings with the cyclopentyl or cyclohexyl[7,8] group does not change the biological activity when tested in an intact animal[2] or isolated tissue preparations.[7,8] Recently, we reported a halogenated QNB

Scheme I



II III IV V VI

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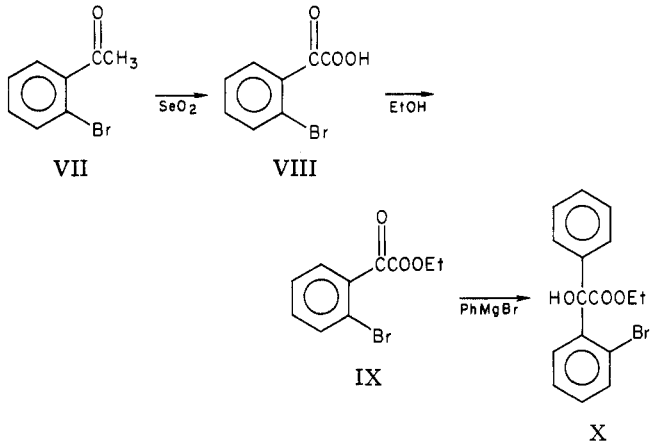
Scheme II



analogue, 3-quinuclidinyl 4′-iodobenzilate.[4]

To expand our understanding of the molecular requirements for binding to the muscarinic receptor, we synthesized QNB and 12 analogues. The apparent equilibrium association constants, K_A, of QNB and of the 12 analogues for the muscarinic receptor from rat or dog ventricular muscle were compared to those obtained for two other muscarinic receptor agents, atropine and scopolamine.

Chemistry. Commercially unavailable esters of corresponding glycolic acids were synthesized according to Scheme I. The corresponding aryl or alkyl halide II was converted to Grignard reagent III, which was allowed to react[9,10] with ethyl benzoylformate IV to give the desired glycolate V. A minor modification of Kadin and Cannon's[11] transesterification of glycolate with sodium 3-quinuclidinylate provided the desired analogue VI. Because of the instant elimination of halogens ortho to each other,[12] we were unable to synthesize the ortho-substituted analogues via the Grignard reaction. For that reason, the 2-bromo analogue (**6**) was synthesized according to Scheme II. An oxidation of 2-bromoacetophenone VII with selenium dioxide[13] gave 2-bromobenzoylformic acid[14] VIII. Its esterification to ethyl ester IX and consequent reaction with phenylmagnesium bromide gave ethyl 2-bromobenzilate X. Transesterification with 3-quinuclidinol gave **6**.

The substrate for the propargyl analogue (**11**) was obtained by the Reformatskii reaction[15] of ethyl benzoylformate and propargyl bromide in the presence of zinc dust.

Transesterification of the ethyl ester of commercially available xanthene-9-carboxylic acid gave its 3-quinuclidinyl ester QNX.[16] QNB and its analogues were obtained and studied in their racemic forms. (−)-[^{3}H]QNB at 33 Ci/mmol was obtained from New England Nuclear, Inc.

Pharmacology. The association constants (K_A) for the QNB derivatives were determined by competitive ligand binding assay with (−)-[^{3}H]QNB as the radiotracer and rat ventricular muscle or left ventricular muscle from dog as the source of muscarinic acetylcholine receptor. Each K_A is the result of at least five separate studies in duplicate, and the association constants are determined by the LIGAND program of Munson and Rodbard[17] with pooled data (see Experimental Section).

Results and Discussion

Despite the great interest[18-20] in the binding of QNB to the muscarinic receptor, no extensive structure–activity relationship study of its analogues has been performed at the receptor level. The intact animal and physiological studies using isolated tissues are obscured by protein binding, metabolism, and secretion, making any comparison with the in vitro receptor studies impossible. In our receptor study, QNB and its cyclohexyl (**1**), cyclopentyl (**2**), and *n*-butyl (**3**) analogues are almost equipotent within the 95% limit of confidence. The cyclopentyl analogue (**2**) shows the highest affinity and, consequently, the highest relative binding index.

Conformational studies using X-ray crystallography[21] or NIH–EPA CIS CHEMLAB programs[22] indicate that the phenyl rings of QNB are perpendicular to each other. In an attempt to find the desired conformation for binding to cardiac muscarinic receptor, we resynthesized the 3-quinuclidinyl ester of xanthene-9-carboxylic acid (QNX) where both phenyl rings are in a plane. Our CHEMLAB calculations and HPLC studies indicate that QNB and QNX are isolipophilic. Therefore, the resulting 25-fold loss in binding indicates that that conformation is not favored by the cardiac muscarinic receptor. The replacement of one of the phenyl rings with the small and polar propargyl group (**11**) leads to an almost 175-fold loss in binding. Introduction of fluorine in the meta position on one of the phenyl rings (**4**) of QNB does not change the affinity significantly. Fluorine in the para position (**5**) does lower the affinity (**5** vs. QNB), but not significantly, using the 95% confidence limit. Substitution in the ortho, meta, or para position with bromine leads to a significant drop in the affinities. The affinities of the three bromo analogues (**6–8**) are almost identical. Surprisingly, the introduction of iodine in the para position (**10**) does not lead to a further loss in affinity. The affinity of that compound is actually higher than that of the bromo analogues. The *m*-iodo analogue (**9**) of QNB, on the other hand, is equipotent with the bromo analogues. The fact that the bulky and lipophilic 4-iodo analogue (**9**) regains some of the affinity lost due to para substitution may indicate the existence of an additional hydrophobic bonding area in the direct vicinity to the point of binding of one of the phenyl rings of the benzilate. That additional hydrophobic bonding region might compensate to a degree for the loss of binding caused by a steric obstacle in the para position. That finding and confirmation of the reported high affinity of the cyclo-

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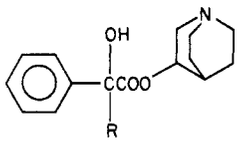
Table I. Chemical Properties and Binding Data



compd	R	mp,[a] °C	yield,[b] %	no. of determinations	K_A (10^9 M^{-1})[c]	confidence interval (95%)	RBI[d]
1[e,f]	c-C_6H_{11}	90-92	19.4	7	3.51	2.91-4.33	66
2[e,g]	c-C_5H_9	107-109	15.8	8	8.21	6.21-10.6	155
3	n-C_4H_9	75-77	13.6	5	2.91	1.76-4.95	55
4	3-FC_6H_4	132-134	20.0	6	5.03	3.48-7.21	95
5	4-FC_6H_4	151-153	15.2	6	3.03	2.34-3.91	57
6[h]	2-BrC_6H_4	75-78	15	5	0.401	0.28-0.57	8
7	3-BrC_6H_4	163-165	6.6	6	0.433	0.321-0.594	8
8	4-BrC_6H_4	175-177	25.0	7	0.608	0.435-0.834	11
9	3-IC_6H_4	54-56	22.1	5	0.482	0.320-0.715	9
10	4-IC_6H_4	135-137	21.6	6	1.22	0.87-1.7	23
11[i]	HC≡CCH_2	103-105	17	8	0.0303	0.021-0.043	0.6
(±)-QNX[j]		195-198	80	5	0.225	0.17-0.30	4
(±)-QNB				25	5.28	3.68-7.48	100
atropine				9	0.167	0.108-0.395	3
scopolamine				10	0.135	0.109-0.167	2

[a] Uncorrected. [b] Based on ethyl ester of corresponding glycolic acid. [c] Affinity constant from LIGAND program. [d] Relative binding index = $K_A/K_{A(\pm)\text{-QNB}}$. [e] Hemioxalate. [f] Reported in ref 8 as the hydrochloride. [g] Reported in ref 2 as the hydrochloride. [h] Hydrate. [i] Oxalate, $1.5H_2O$. [j] Hemioxalate, hydrate.

pentyl analogue warrant further investigation along those lines.

Experimental Section

Chemistry. IR spectra were recorded in KBr disks on a Perkin-Elmer spectrophotometer Model 700 and are consistent with the assigned structures. Liquid chromatography was performed on a Waters Associates ALC 202/6000 high-performance liquid chromatograph (HPLC) and by the dry column method using silica gel. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Optical activity of all synthesized compounds was checked by polarimetry using a Zeiss polarimeter. All compounds have shown absence of any optical activity; therefore, it was assumed that they have been isolated and purified in their racemic forms. Elemental analysis was performed by Galbraith Laboratories, Inc. The results obtained are within ±0.4% of the theoretical values. Typical preparation of an intermediate and an analogue are given below.

Ethyl *p*-Bromobenzilate. A solution of 12.0 g (0.05 mol) of *p*-dibromobenzene in 100 mL of dry ether was added dropwise to 1.0 g (0.042 mol) of magnesium turnings suspended in 30 mL of ether. After the addition, the reaction mixture was refluxed for 1 h, cooled in an ice bath, and added to 7.2 g (0.04 mol) of ethyl benzoylformate in 50 mL of ether. After an 18-h reflux, the cooled mixture was poured onto 500 mL of slurry (ice/6 N HCl, 1:1) and was stirred for 30 min. The ethereal layer was separated, and the aqueous layer was extracted with 50 mL of ether. The combined ethereal extracts were washed with water, 1 N sodium bicarbonate, and water and then dried over sodium sulfate. After filtration and evaporation of the solvent, the residual oil was chromatographed on a dry silica gel column in toluene. The purified ester (2 g, 12%) was used for transesterification without any further manipulation.

3-Quinuclidinyl 4'-Bromobenzilate (4). 3-Quinuclidinol (1.5 g, 0.01 mol) was dissolved in 50 mL of dry benzene and refluxed for 30 min using a Dean–Stark reflux head to remove any traces of moisture. A 0.1-g piece of clean sodium metal was added, and the suspension was refluxed for 0.5 h. The remaining unreacted sodium was removed, and 3.2 g (0.01 mol) of ethyl *p*-bromobenzilate was added. The reaction mixture was refluxed for 18 h and then spin evaporated to dryness. The residue was dissolved in ethyl acetate and washed repeatedly with water. After drying over sodium sulfate, the solution was filtered and spin evaporated. The residue was recrystallized from acetonitrile until a single spot and a single peak were visible on TLC and HPLC, respectively. The TLC on silica gel was carried out in *n*-BuOH/AcOH/water (4:1:1). The HPLC was carried out on a Whatman Partisil PXS 5/25 ODS-3 column using 5 mM 1-octanesulfonic acid (pH 3.0) in MeOH/water (60:40). The purified sample (1.0 g, 25%) had mp 175–177 °C.

Tissue Preparation. Hearts were removed from freshly killed rats (cervical dislocation under light ether anesthesia), and the ventricular muscle was dissected free of atria, major vessels, and fat and minced with scissors. The tissue was homogenized (Brinkman Polytron PC-U) in 20 vol of ice-cold 10 mM Tris-buffered saline (pH 7.4) containing 10% sucrose. The homogenate was filtered through four layers of cheesecloth and used without further purification. The heart of a mongrel dog was removed, and the left ventricular muscle was dissected free of remaining tissue, fat, and vessels, frozen in liquid nitrogen, and stored at −80 °C until used. One-gram segments were prepared as above. Storage for up to 3 months did not change the binding characteristics of the muscarinic receptor. The concentration of muscarinic receptor in such preparations varies from 0.4 to 1.2×10^{-11} M.

The K_A for (±)-QNB (Table I) compares well with that reported for porcine atrial preparations ($K_A = 8.2 \times 10^9$ M^{-1})[23] but is 5-fold less than that reported for rabbit ventricular muscle.[24] The value of K_A has been shown to be affected by the concentration of receptor.[24] We used final receptor concentrations of 4×10^{-12} to 1.2×10^{-11} M. We did not observe significant differences in K_A as a function of receptor concentration.

Determination of Apparent Equilibrium Association Constants. The apparent equilibrium association constants for the muscarinic antagonists in Table I were determined by competition with (−)-[^{3}H]QNB. The compounds were dissolved in 95% EtOH and added to 5 mL of Tris–saline buffer (10 mM Tris, pH 7.4) containing 2×10^{-10} M (−)-[^{3}H]QNB at final concentration of 0.5% EtOH. Concentrations of EtOH under 2% do not affect the binding parameters of [^{3}H]QNB to its receptor. Competition curves were generated using 10 concentrations of unlabeled compound from 10^{-12} to 10^{-6} M for the QNB analogues with affinities within 5-fold of QNB and from 10^{-11} to 10^{-5} M for atropine, scopolamine, and QNB analogues with affinities that differed from the QNB affinity by more than 5-fold. Aliquots of 0.1 mL of tissue preparation were added, and the mixture was vortexed and incubated at room temperature for 2 h. Neither agitation nor increased incubation times altered the results. The

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incubation mixture was rapidly filtered on GF/C filter paper, washed with 10 mL of ice-cold saline, dried, placed in ACS liquid scintillation cocktail, and counted for 5 min each. Data were analyzed using the LIGAND program of Munson and Rodbard,[17] modified for use on an HP 3000 computer. Confidence intervals (95%) were calculated by the method of Munson and Rodbard.[25] K_A values are obtained from pooled data of at least five determinations. Although we used two species for the source of heart tissue (predominantly rat), we observed no species differences in affinities. For *p*-IQNB, $K_A = 1.24 \times 10^9$ M^{-1} (0.79 to 1.9×10^9) for dog, $K_A = 0.77 \times 10^9$ M^{-1} (0.38 to 1.6×10^9) for rat, and $K_A = 1.22 \times 10^9$ M^{-1} (Table I) for the combination of all data.

Acknowledgment. This investigation was supported by Grant HL 19127 from the National Heart, Lung and Blood Institute.

Synthesis and Study of a Spin-Labeled Cyclophosphamide Analogue, 3-(1-Oxy-2,2,6,6-tetramethyl-4-piperidinyl)cyclophosphamide[1]

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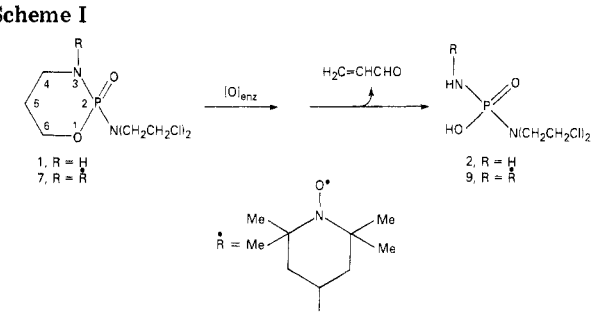
3-(1-Oxy-2,2,6,6-tetramethyl-4-piperidinyl)cyclophosphamide (**7**) was isolated in 36% yield following H_2O_2–Na_2WO_4 oxidation of 3-(2,2,6,6-tetramethyl-4-piperidinyl)cyclophosphamide (**6**), which was synthesized in three steps (25% yield) starting with 4-amino-2,2,6,6-tetramethylpiperidine. Binding of **7** to mouse liver microsomes was investigated by optical and electron spin resonance spectroscopy. Compared with the mouse liver microsomal metabolism of **1**, separate incubations of **6** and an ca. 1:1 mixture of **1** and **6** gave approximately 90 and 60% *less* acrolein, respectively. A spin-labeled metabolite of **7**, viz., *N*-(1-oxy-2,2,6,6-tetramethyl-4-piperidinyl)phosphoramide mustard (**9**), was synthesized and its intramolecular O-alkylation at pH 7.4, 37 °C, was studied by ^{31}P NMR spectroscopy. Compounds **7** and **9** were inactive in screening tests against L1210 lymphoid leukemia in mice.

While numerous analogues[2] of cyclophosphamide (**1**) have been employed for investigating the mechanism of action of this widely used anticancer prodrug,[3] spin-labeling[4,5] studies dealing with **1** have not been reported. On the other hand, spin-labeled analogues of the antitumor agents thio-TEPA[6-8] and 5-aziridino-2,4-dinitrobenzamide[9] have exhibited oncostatic selectivity;[8-10] moreover, the sterically protected, paramagnetic, 1-oxo-4-piperidinyl moiety in these molecules has been utilized for novel pharmacokinetic measurements by ESR spectroscopy.[9,10]

Scheme I



Two key features of cyclophosphamide metabolism[3] (Scheme I) are the initial "activation" (C-4 oxidation) of **1** by a liver microsomal mixed-function oxidase and the eventual release of the cytotoxic phosphoramide mustard (**2**) fragment. Attachment of a free radical to the endocyclic nitrogen (N-3) in **1** provides a spin-labeled analogue that could be used to probe metabolic and dynamic processes involving **1**, **2**, and intermediary phosphorus-containing metabolites—provided that the analogue undergoes efficient "activation" and that the paramagnetic center is persistent under biological conditions. In view of the success of the 1-oxy-2,2,6,6-tetramethyl-4-piperidinyl group as a spin-label,[6-10] 3-(1-oxy-2,2,6,6-tetramethyl-4-piperidinyl)cyclophosphamide (**7**) was investigated as a *prototype for appraising the feasibility of the ESR "reporter group" method in studies of cyclophosphamide metabolism.*

Results and Discussion

The strategy for conversion of starting material **3** into 3-(2,2,6,6-tetramethyl-4-piperidinyl)cyclophosphamide (**6**) was similar to that reported[11] for the synthesis of 3-(α-methylbenzyl)cyclophosphamide. A mixture of H_2O_2 and Na_2WO_4 selectively oxidized the nitrogen–hydrogen bond in **6** and, thus, afforded analytically pure **7** after silica gel chromatography. Since the utility of any spin-labeled analogue is dependent upon, inter alia, its ability to mimic the parent molecule, several lines of investigation were

(1) This paper is part 5 of a series on "Synthesis and Antitumor Activity of Cyclophosphamide Analogues". For part 4, see J. A. Brandt, S. M. Ludeman, G. Zon, J. A. Todhunter, W. Egan, and R. Dickerson, *J. Med. Chem.*, **24**, 1404 (1981). Systematic nomenclature is given under Experimental Section.

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