experiment indicated a significant capacity on the part of serotonin to reduce thyroid activity. This suggests that the thyroid effects of chronically administered reserpine are accomplished through the intermediation of serotonin. If this were true it might be expected that LSD through serotonin antagonism (16, 17) would increase thyroid activity, and that an increase in serotonin blood level induced by monoamine oxidase inhibition and 5HTP would reduce thyroid activity. However, the data obtained in testing these assumptions were not conclusive or consistent. There are possible explanations for failure of these attempts at confirmation. That both LSD and serotonin decreased I^{131} uptake by thyroid on *in vitro* administration may be only further evidence for the lack of specific antagonism between the two. In evaluating the role of free serotonin maintained in excess as presumably was accomplished by use of the drug combination, the possibility that toxicity may have altered parameters must be considered.

The evidence for a thyroid inhibiting effect for LSD is consistent with results obtained by others (9, 10). The significance of this in relation to the reserpine mechanism is not apparent. The finding that reserpine *in vitro* significantly increased I^{131} uptake by thyroid slices was not in agreement with Mayer, *et al.* (1), who used calf thyroid and a considerably higher concentration of reserpine. This phase of the work will receive further attention as also will the lethality of the combined effects of iproniazid and 5HTP.

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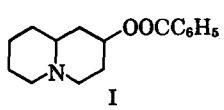
Esters of Bicyclic Aminoalcohols IV

Local Anesthetic Esters Derived from 2-Hydroxyquinolizidine

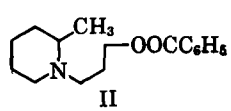
By CHANDULAL N. PATEL and TAITO O. SOINE

Several pairs of substituted benzoate esters derived from 2-hydroxyquinolizidine and 3-(2-methylpiperidino)propanol were synthesized in order to enable comparison of each pair for relative duration of local anesthetic activity in the rabbit cornea. The tests indicate, in general, the 2-hydroxyquinolizidine esters provided a greater duration of activity than the corresponding esters of 3-(2-methylpiperidino)-propanol. Some of the implications of this increase in duration of action with respect to the structures are discussed.

RHODES AND SOINE (1), in 1956, reported the synthesis of a series of 2-hydroxyquinolizidine esters specifically designed as anticholinergics. The selection of 2-hydroxyquinolizidine as the aminoalcohol was based on its formal relationship to tropine with respect to the relative positions of the amine and alcohol functions. No mention was made of local anesthetic activity although the relationship of 2-hydroxyquinolizidine to ecgonine would be analogous. In 1960, Counsell and Soine (2) described the preparation of selected esters of 1-, 2-, and 3-hydroxyquinolizidines and (among the activities reported) noted local anesthetic activity associated with most of their esters. In connection with the comparative local anesthetic activities, two observations were of particular significance with respect to the present report: *a*, the activity of 2-hydroxyquinolizidine benzoate (I) was 3 and 5 times greater, respectively, than the activities of the isomeric 1- and 3-hydroxyquinolizidine benzoates, and *b*, the activity of I was 1.72 times greater than that of piperocaine (II) which was used as the standard for compari-



I



II

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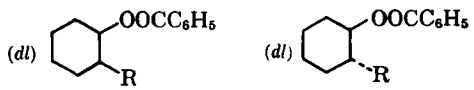
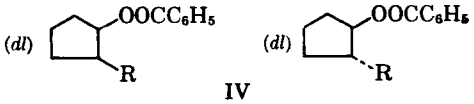
son. The latter observation was of interest because I could be looked upon as a closed ring analog of II. It was of further interest to note that the 2-methyl group in the piperidine moiety of II seems to have a direct influence upon activity inasmuch as its absence leads to inactivity (3). If one considers that the 2-methyl group of II imposes a degree of steric restriction to the esterified alkyl chain attached to the nitrogen of II it is immediately apparent that the closure of the esterified alkyl chain into a ring system as in I imposes still further steric restriction. That steric requirements for local anesthetic activity may be of importance is illustrated by several observations. Among these may be cited the findings of Mannich, *et al.* (4), with respect to the differing activities of the *cis* and *trans* isomers of III and IV wherein one form



III



IV

(R = —$CH_2N(CH_3)_2$)

(not specified) possesses strong activity and the other has either no activity or a greatly lessened activity. Likewise, the recent findings of Nachmansohn in connection with his demonstrations of the chemical basis of nerve activity (5) would seem to imply that structural specificity is important in interaction of the anesthetic base with receptor protein. Apparently, however, the structural specificity does not encompass optical isomers inasmuch as these have been shown in virtually all cases to be of essentially the same activity. Another factor in enhanced activity may be envisioned because esters of secondary alcohols, for steric reasons, are less rapidly hydrolyzed than corresponding esters of primary alcohols which would be expected *a priori* when comparing I and II.

These observations have led us to attempt to determine whether an enhanced duration of anesthetic activity of the 2-hydroxyquinolizidine-type esters over the 3-(2-methylpiperidino)-propanol esters was a general trend. To accomplish this purpose it was necessary to synthesize not only selected esters of the former but also the corresponding esters of the latter for direct comparison. The esters to be synthesized were selected on the basis of the previously reported activities by McElvain and Carney (6) of the 3-(2-methylpiperidino)propanol esters. The rabbit cornea as utilized by McElvain and Carney was the test object in the present study.

DISCUSSION

The synthetic method employed for 2-hydroxyquinolizidine was essentially that of Counsell and Soine (2) with incorporation of certain modifications in the synthesis of the intermediate ethyl 2-pyridyl acetate as described by Winterfeld and Flick (7). 3-(2-Methylpiperidino)propanol was synthesized by the method of McElvain and Carney (6). The necessary methyl esters were purchased where possible or synthesized by standard methods wherever necessary. The synthesis of esters of both aminoalcohols was carried out most conveniently by the ester-interchange method as described by Counsell and Soine (2). This method, for benzoate esters, has proved to be superior to the usual method of interacting an acid chloride with the aminoalcohol. All esters were prepared as hydrochlorides and crystallized to constant melting points. In general, it was found that the ester hydrochlorides derived from 2-hydroxyquinolizidine were less water soluble than the corresponding esters derived from 3-(2-methylpiperidino)propanol. Indeed, it was found impossible to carry out suitable anesthetic tests on several of the 2-hydroxyquinolizidine ester hydrochlorides for this reason.

Testing of the esters for their comparative anesthetic duration times was accomplished by a comparison of the corneal anesthetic duration time ratios on several rabbits. The methods employed are described in the experimental section. The results show conclusively that there is a significant enhancement of the duration of corneal anesthesia by using 2-hydroxyquinolizidine as the esterified aminoalcohol rather than 3-(2-methylpiperidino)-propanol. The average enhancement ratio appears to be approximately 1.40 with a variation from a low value of 1.09 (*o*-hydroxybenzoate) to a high value of 2.38 (*o*-*n*-butoxybenzoate). It should be pointed out that this high value was the only one of its magnitude with the exception of the *o*-benzoylbenzoate which was 2.12. Most of the values were clustered closely around a narrower range centering on 1.30.

The reasons for the enhancement of duration can be speculated upon only. The steric factor has already been mentioned, and it is entirely possible that a better fit at the receptor site is obtainable with molecules that are relatively more fixed sterically than with more flexible molecules. Also one can reasonably assume two major mechanisms whereby the activity of a local anesthetic ester can be terminated. The first of these would be by diffusion from the site of action and the second would be enzymatic inactivation through esterase hydrolysis. Both processes can be assumed to operate at any one site of activity but probably influence the disposal of the ester in varying proportions depending on the particular locus of action. In the present instance, if one assumes that enzymatic activity has at least some role in the disposal of the ester, then it becomes reasonable to assume that steric inhibition to hydrolysis should lead to greater duration of activity. Such steric

TABLE I.—SYNTHESIZED METHYL BENZOATES

Benzoic Acid from Which Derived	Formula	Method of Prepn.	M.p., °C. or B.p., °C., (mm. Hg)	Yield, %	Analysis[a] —Carbon— Calcd.	Found	—Hydrogen— Calcd.	Found	Ref.
p-Phenyl	$C_{14}H_{12}O_2$	2	117–118	93	...	...	...	...	(18)
o-(*n*-Butoxy)	$C_{12}H_{16}O_3$	1	130–132 (6)	63	...	...	...	...	(19, 20)
p-(*n*-Butoxy)	$C_{12}H_{16}O_3$	1	105–110 (0.2)	61	...	...	...	...	(12)
p-iso-Butoxy	$C_{12}H_{16}O_3$	1	110–115 (0.4)	24	69.20	68.96	7.74	7.83	...
p-*sec*-Butoxy	$C_{12}H_{16}O_3$	1	95–100 (0.25)	53	69.20	68.96	7.74	7.77	...
p-iso-Amyloxy	$C_{13}H_{18}O_3$	1	124–125 (1.4)	63	...	...	...	...	(19)
p-(*n*-Hexyloxy)	$C_{14}H_{20}O_3$	1	132–137 (0.5)	59	71.15	71.25	8.53	8.59	...
p-Phenoxy	$C_{14}H_{12}O_3$	2	60	81	...	...	...	...	(14)
p-Benzyloxy	$C_{15}H_{14}O_3$	1	99	74	...	...	...	...	(19)
p-(4-Methoxyphenyl)	$C_{15}H_{14}O_3$	2	172–174	86	...	...	...	...	(16)

[a] New compounds.

inhibition combined with a possible better receptor fit may account for the observed longer duration of activity of the hydroxyquinolizidine esters in the present study.

EXPERIMENTAL

2 - Hydroxyquinolizidine.—*2 - Pyridylacetonitrile.*—This compound was prepared according to the method of Winterfeld and Flick (7) in 77.4% yield as a light yellow oil, b.p. 95–97° (3.7 mm.), n_D^{29} 1.5192 reported, b.p. 79–81° (0.4 mm.)(7); b.p. 80–85° (0.5 mm.), n_D^{29} 1.5193 (8); n_D^{25} 1.5224 (9). A picrate was formed in and recrystallized from absoute ethanol, m.p. 160–162° (reported, m.p. 155–157° (9)).

Ethyl 2-Pyridylacetate.—It was prepared according to the Winterfeld and Flick procedure (7) in a yield of 75.1% as a greenish-yellow liquid, b.p. 90–91° (0.3 mm.), n_D^{29} 1.4921. These properties, together with the picrate, m.p. 137–138°, corresponded in close detail to those previously reported in the literature (1, 10, 11).

2-Hydroxyquinolizidine.—Using ethyl 2-pyridyl acetate as the starting material, the synthesis of this aminoalcohol was carried out essentially as described by Rhodes and Soine (1) employing modifications suggested by Counsell and Soine (2). The yields of all intermediates and of the final product closely approximated those found by the above authors.

3-(2-Methylpiperidino)propanol.—This aminoalcohol was prepared from 2-methylpiperidine and trimethylene chlorohydrin according to the general procedure outlined by McElvain and Carney (6) in 60% yield, b.p. 110–115° (10 mm.) (reported, b.p. 112° (15 mm.) (6)).

Methyl Benzoates (see Table I).—Methyl benzoate, ethyl *o*-benzoylbenzoate, methyl *p*-(*n*-amyloxy)-benzoate and methyl *o*-hydroxybenzoate were purchased from commercial sources. The following examples describe the methods that were used for the synthesis of the other esters.

Alkoxybenzoates.—These were prepared by two methods: *1*, the methyl ester of the phenolic acid was alkylated with the appropriate alkyl halide in absolute methanol in the presence of sodium methoxide, and *2*, the appropriate benzoic acid was esterified with methanol and sulfuric acid. These are illustrated by the following examples.

Methyl p-(n-Butoxy)benzoate.—Sodium (4.6 Gm., 0.2 mole) was dissolved in 100 ml. of absolute methanol. Methyl *p*-hydroxybenzoate (30.4 Gm., 0.2 mole) and 36.8 Gm. (0.2 mole) of *n*-butyl iodide were added. The mixture was refluxed for 12 hours, cooled, and filtered free of inorganic salts. About half of the methanol was distilled off under reduced pressure, and the precipitated inorganic salts were removed by filtration. The solution was rendered alkaline with 5 ml. of 10% sodium hydroxide solution to dissolve unaltered methyl *p*-hydroxybenzoate, and the mixture was treated with 100 ml. of ether and 50 ml. of water. The ether layer and second ether extract were combined. The ether extracts were dried over anhydrous sodium sulfate and, after removal of solvent, the product was distilled to give 25.4 Gm. (61%) of product; b.p. 105–110° (0.2 mm.) (reported, b.p. 190–195° (20 mm.)(12)).

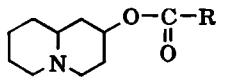
Methyl p-Cyclohexyloxybenzoate.—*p*-Cyclohexyloxybenzoic acid[1] (5 Gm.) absolute methanol (75 ml.), and 7.5 ml. of concentrated sulfuric acid were combined in a 100-ml. round-bottom flask and gently refluxed for 2 hours. The excess of methanol was removed under reduced pressure and the red-colored residue was treated with water. The insoluble ester was extracted from the aqueous mixture with ether and the ether washed with 5% aqueous sodium bicarbonate solution. The ether layer was dried over anhydrous sodium sulfate and after removal of the solvent, provided 3.5 Gm. of an orange-colored liquid. Attempts to distill this material resulted in decompositon and, therefore, it was used in the crude state for further synthesis for which it proved satisfactory.

Miscellaneous Benzoates.—*Methyl p-Phenoxybenzoate.*—A solution of 52.8 Gm. (0.335 mole) of potassium permanganate in 1500 ml. of water was added to a mixture of 20 Gm. (0.0704 mole) of 3-(*p*-phenoxybenzoyl)-propionic acid[2] and 20 Gm. (0.357 mole) of potassium hydroxide in 200 ml. of water. The mixture was heated on a steam bath for 5 hours. At the end of this time the mixture was cooled and carefully acidified with sulfuric acid. The mixture was heated for 30 minutes and cooled. The precipitated manganese dioxide was removed by the addition of a slight excess of 10% sodium bisulfite solution. The precipitated acid was removed by filtration and recrystallized from ethanol; yield, 14.0 Gm. (92.9%), m.p. 159–160° (reported, m.p. 160° (13)).

[1] The authors express their appreciation to Eli Lilly and Co., Indianapolis, Ind., for a generous gift of *p*-cyclohexyloxybenzoic acid.

[2] Distillation Products Industries, Rochester, N. Y.

TABLE II.—ESTERS OF 2-HYDROXYQUINOLIZIDINE



No.	R	Recrystallized from[a]	M.p., °C.	Molecular Formula	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	—C_6H_5	A	265–266	$C_{16}H_{21}NO_2 \cdot HCl$	64.96	65.17	7.50	7.54
II	—$C_6H_4C_6H_5(p)$	B	283–285 dec.	$C_{22}H_{25}NO_2 \cdot HCl \cdot {}^1/_2\text{-}C_2H_5OH$	69.94	69.78	7.40	7.32
III	—$C_6H_4OH(o)$	C	238–239	$C_{16}H_{21}NO_3 \cdot HCl$	61.63	61.58	7.11	7.19
IV	—$C_6H_4O(CH_2)_3CH_3(o)$	D	171–172	$C_{20}H_{29}NO_3 \cdot HCl$	65.29	64.75	8.22	8.22
V	—$C_6H_4O(CH_2)_3CH_3(p)$	A	195–197	$C_{16}H_{21}NO_3 \cdot HCl$	65.29	65.19	8.22	8.20
VI	—$C_6H_4OCH_2CH(CH_3)_2(p)$	D	221–222	$C_{20}H_{29}NO_3 \cdot HCl$	65.29	65.02	8.22	8.14
VII	—$C_6H_4OCH(CH_3)C_2H_5(p)$	A	192–193	$C_{20}H_{29}NO_3 \cdot HCl$	65.29	64.89	8.22	8.22
VIII	—$C_6H_4O(CH_2)_4CH_3(p)$	A	198–199	$C_{21}H_{31}NO_3 \cdot HCl$	66.04	65.65	8.44	8.60
IX	—$C_6H_4O(CH_2)_2CH(CH_3)_2(p)$	D	217–218	$C_{21}H_{31}NO_3 \cdot HCl$	66.04	66.04	8.44	8.45
X	—$C_6H_4O(CH_2)_5CH_3(p)$	A	193–194	$C_{21}H_{31}NO_3 \cdot HCl$	66.73	66.52	8.66	8.59
XI	—$C_6H_4OCH(CH_2)_4CH_2(p)$	D	213–215	$C_{22}H_{31}NO_3 \cdot HCl$	67.07	66.57	8.19	8.19
XII	—$C_6H_4OC_6H_5(p)$	A, F	197–198	$C_{22}H_{25}NO_3 \cdot HCl$	68.12	67.85	6.76	6.70
XIII	—$C_6H_4OCH_2C_6H_5(p)$	B	265–267	$C_{23}H_{27}NO_3 \cdot HCl$	68.72	68.56	7.02	7.07
XIV	—$C_6H_4COC_6H_5(o)$	D	194–195	$C_{23}H_{25}NO_3 \cdot HCl$	69.07	69.11	6.55	6.54
XV	—$C_6H_4C_6H_4OCH_3(pp')$	B	276–278	$C_{23}H_{27}NO_3 \cdot HCl$	68.73	68.72	7.02	7.34

[a] A, Ethanol, isopropyl ether; B, ethanol; C, absolute ethanol; D, methylene chloride, ethyl acetate; E, ethyl acetate, ether; F, isopropanol, ether.

The esterification of the phenoxybenzoic acid was carried out essentially as described above for *p*-cyclohexyloxybenzoic acid (*q.v.*) to yield 6.5 Gm. (81%) of colorless crystals after recrystallization from a methanol-water mixture, m.p. 60° (reported, m.p. 59.5 to 60° (14)).

Methyl p-(4-Methoxyphenyl)benzoate.—The first step in this synthesis was the preparation of *p*-(4-methoxyphenyl)acetophenone according to the procedure of Johnson, *et al.* (15). The product was prepared in a 53% yield, m.p. 145–147° and following recrystallization gave pure material, m.p. 153–154° (reported, m.p. 153–154° (15)).

The above product was then oxidized as described by Fieser and Bardher (16) with permanganate to provide a 56% yield of *p*-(4-methoxyphenyl)benzoic acid, m.p. 248–249° (m.p. reported 248–249° (16)).

The above acid was esterified with methanol and sulfuric acid in the manner described above for alkoxybenzoates to give a product, recrystallized from methanol, m.p. 172–174° (reported, m.p. 172–173° (16)). The yield was 86%.

2-Hydroxyquinolizidine Esters.—These esters were all synthesized by the ester-interchange method as described by Counsell and Soine as Method 2 (2). The analytical and physical constants are recorded in Table II.

3-(2-Methylpiperidino)propanol Esters.—These esters were also synthesized by the ester-interchange method according to the above method of Counsell and Soine (2). They all agreed within a few degrees with the reported melting points of McElvain and Carney (6) and from the constancy of their melting points were assumed to be identical with the products of the former workers and of a suitable purity for pharmacological testing.

Pharmacological Testing

Solutions.—All of the salts were dissolved in distilled water in identical concentrations for each pair of compounds tested. The solutions were made on the day of use in every case. These solutions represented essentially equimolar concentrations because of the negligible difference in molecular weights between each pair. The hydrochlorides of *p*-phenylbenzoic, *p*-(4-methoxyphenyl)benzoic, *p*-phenoxybenzoic, and *p*-benzyloxybenzoic acid esters were too insoluble to allow preparation of solutions at the concentration required and thus were not included in the comparison studies.

TABLE III.—LOCAL ANESTHETIC DURATION COMPARISONS

Ester Pair Corresponding to the Esters as Numbered in Table II.	Concentration, %	Duration,[a] min. A	Duration,[a] min. B	Duration Ratio[b] A/B
I	1.00	14	9	1.54 (±0.29)
III	1.00	34	32	1.09 (±0.11)
IV	0.30	38	16	2.38 (±0.36)
VII	0.25	43	35	1.25 (±0.06)
XIV	0.20	58	29	2.03 (±0.63)
X	0.10	24	18	1.29 (±0.09)
XI	0.10	26	21	1.24 (±0.08)
VI	0.10	29	23	1.25 (±0.10)
IX	0.10	31	24	1.32 (±0.33)
V	0.10	53	43	1.28 (±0.13)
VIII	0.10	58	40	1.44 (±0.17)

[a] A = 2-Hydroxyquinolizidine esters. B = 3-(2-methylpiperidino)propanol esters. [b] 95% confidence limits.

Animals.—Young adult white rabbits, equal numbers of each sex, were used for the corneal testing. The eyelids were carefully trimmed to remove the eyelashes. In most tests they were used only once each day but on occasion were tested in the morning and again in the afternoon.

Test Procedure.—The usual method of instillation for corneal testing was employed in which 0.5 ml. of solution was introduced into the conjunctival sac from a blunt-tipped syringe and allowed to act upon the cornea for 1 minute before beginning the duration count. All compounds induced anesthesia within the 1-minute period as evidenced by the absence of the wink reflex when the cornea was stimulated with a blunt glass rod. The time re-

quired for the animal to regain the wink reflex when the stimulus was applied was recorded in minutes. In most cases six rabbits were used for each comparison although in a few cases five were used and in one case 12 were employed. Each pair of esters was tested on the same rabbit's eyes with the right eye being used for one-half of the tests on the hydroxyquinolizidine esters and the left eye for the other half. Concomitantly, the alternate eye of the rabbits was used for the other ester. At no time were both eyes subjected to anesthesia at the same time.

The duration ratio between the pairs of compounds in each animal was obtained by dividing the duration of the 2-hydroxyquinolizidine ester by that of the 3-(2-methylpiperidino)propanol ester. The mean of these ratios was determined and the 95% confidence limits of the mean were calculated assuming a normal distribution for the mean and a chi-square distribution for the squares of the deviations (17). These results are given in Table III.

Observations.—No irritation of the cornea was observed with either series of esters in the concentrations employed. Both the *p*-isoamyloxybenzoate and the *o*-benzoylbenzoate were erratic in the 2-hydroxyquinolizidine series with respect to the comparative durations. The latter, in particular, exhibited an unpredictable behavior with the duration ratios varying widely (0.83 to 3.86). For this reason, the 95% confidence interval varies more widely than any of the other pairs tested. A further observation of interest was that the 2-hydroxyquinolizidine esters induced much less xerophthalmia than the corresponding 3-(2-methylpiperidino)-propanol esters.

SUMMARY

1. Fifteen new substituted benzoate esters of 2-hydroxyquinolizidine have been synthesized and described because of an interest in their comparative local anesthetic activity with the corresponding esters of 3-(2-methylpiperidino)propanol.

2. Four new methyl esters of substituted benzoic acids have been synthesized and described in the course of the investigation.

3. Several of the newly synthesized esters have been compared with their counterparts obtained from the esterification of 3-(2-methylpiperidino)-propanol for duration of corneal anesthesia in the rabbit. The observed results indicate that an enhanced duration of action can be expected as a general trend when comparing the two esters derived from the same acid. The duration ratios varied from 1.09 (± 0.11) for the *o*-hydroxybenzoates to 2.38 (± 0.36) for the *o*-(*n*-butoxy)benzoates.

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Release of Drug from a Self-Coating Surface

Benzphetamine Pamoate Pellet

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The problem has been examined in which the rate of release in acid solution of an amine drug from a pellet of a weak acid salt of the amine is controlled by a coat which is formed by precipitation of a weak acid onto the pellet surface. A detailed mathematical analysis has been carried out and an expression for the rate of release is presented. The theory has been applied to data on the release of the drug from benzphetamine pamoate pellets.

RECENT STUDIES by Morozowich, *et al.* (1), on the release of benzphetamine from pellets of benzphetamine pamoate in 0.12 *N* hydrochloric acid medium led these investigators to propose that in this instance the rate was controlled by a layer of pamoic acid which was deposited on the pellet surface according to the reaction:

$$\text{benzphetamine pamoate (pellet)} \xrightarrow{H^+} \text{benzphetamine (solution)} + \text{pamoic acid (pellet surface)}.$$

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