Esters of Bicyclic Aminoalcohols as Potential Anticholinergics III

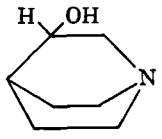
Synthesis of Some Isomeric Hydroxy-1-azabicyclononanes and Certain of Their Esters†

By MICHAEL J. MARTELL, JR.‡ and TAITO O. SOINE

Attempts to improve upon the literature preparation of 3-oxo-1-azabicyclo[3.2.2]-nonane failed. The previously unknown aminoalcohol 3-hydroxy-1-azabicyclo-[3.3.1]nonane (VI) was synthesized in good yield. The described synthesis of 8-hydroxy-1-azabicyclo[4.3.0]nonane (VII) was improved considerably and a series of nineteen esters of VI and VII was prepared using five acids. The pharmacological testing of the esters is reported.

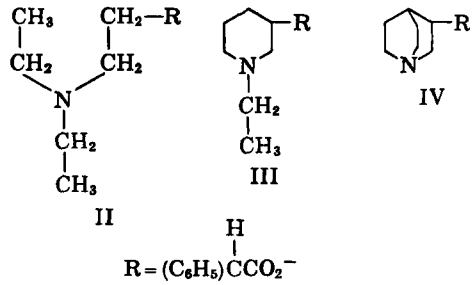
THESE laboratories have been engaged for some time (1) in the synthesis of esters of bicyclic aminoalcohols as potential spasmolytics. The paucity of information in this area has been discussed in the earlier papers.

Referring to the work of Sternbach and Kaiser (2), one can see from models that 3-quinuclidinol is arranged in a compact, rigid cage-type structure, the piperidine ring of which exists in the boat form (I).



I

The inflexibility of the molecule may have some bearing on the marked spasmolytic activity of its esters when one considers the differences in activity between 2-diethylaminoethyl diphenylacetate[1] (II), piperidolate[2] (III), and the diphenylacetate of 3-quinuclidinol (IV). 2-Diethylaminoethyl diphenylacetate has roughly the same order of activity as piperidolate (3), and is about 1/4 as active as atropine (4). However, racemic IV is equal in activity to atropine and the (−) enantiomorph is twice as active.



II III IV

R = $(C_6H_5)CCO_2^-$

To further explore the subtle effects of molecular flexibility on spasmolytic activity, it was decided to synthesize the aminoalcohols V, VI, and VII, if possible, and to prepare a representative selection of esters from them to be tested for anticholinergic activity. These isomeric bicyclic aminoalcohols are all β-aminoalcohols, esters of which have been shown to be the most active, particularly in the bicyclic series (5).

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† Paper II in this series, Counsell, R. E., and Soine, T. O., THIS JOURNAL, 49, 289(1960).

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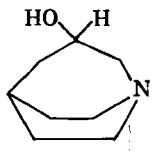
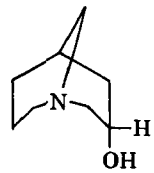
[1] Marketed as Trasentine by Ciba Pharmaceutica Products Inc., Summit, N. J.

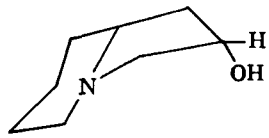
[2] Marketed as Dactil by Lakeside Laboratories, Inc., Milwaukee, Wis.



V



VI



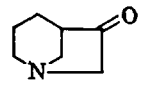
VII

The stereochemistry of 3-hydroxy-1-azabicyclo-[3.2.2]nonane (V) [and quinuclidine (6)], as well as 3-hydroxy-1-azabicyclo[3.3.1]nonane[3] (7, 8) (VI), and 8-hydroxy-1-azabicyclo[4.3.0]nonane[4] (VII) (as a special azahydrindane (9)) has been adequately discussed in the literature. Suffice it to say that, as one passes from V to VII, the molecular flexibility is increased among these isomers.

The aminoalcohols in this study were prepared by the Dieckmann synthesis for aminoketones possessing a bridgehead nitrogen (10, 11). It was found impractical, according to this method, to prepare suitable quantities of V and esters of this aminoalcohol were not prepared. The other two aminoalcohols, VI and VII, were prepared in good yield, however.

For these aminoalcohols the three isomeric pyridylacetic esters were required as key intermediates in good quantity.[5]

Although VII had been prepared previously (12), the synthesis was impracticable in part. Ethyl 2-pyridylacetate was best prepared by the method of Winterfeld and Flick (13). Reduction of the pyridine ring was carried out as described (1), followed by alkylation with ethyl chloroacetate in the presence of anhydrous potassium carbonate (12). The diester thus obtained was best cyclized to the aminoketone using high dilution methods and employing potassium *tert*-butylate in a nitrogen atmosphere (14, 15). Reduction of the aminoketone to the alcohol in water by sodium borohydride was accomplished in nearly quantitative yield. Although the aminoketone was rapidly air-oxidized, the aminoalcohol was quite stable. The reduction product appears identical with the product prepared by Clemo and Metcalf (12) by sodium and alcohol reduction.[6]



i

Although several syntheses of 3-pyridylacetic ester are published in the literature, none appeared to be suitable without modification as an intermediate to VI. A sample of 3-pyridylthioacetmorpholide (16, 17) prepared from 3-acetylpyridine (18, 19) was converted directly to ethyl 3-pyridylacetate. Refluxing the thiomorpholide with concentrated hydrochloric acid (18) and replacement of the acid with alcohol and sulfuric acid gave good yields of the desired ester. Quaternization of the ester with ethylbromoacetate proceeded smoothly as did the subsequent reduction to the diester. Cyclization with potassium *tert*-butylate as described (14) gave the desired aminoketone in 74% yield. Sodium borohydride reduction in water afforded only one isomer.[7]

The preparation of the aminoketone corresponding to V according to the procedure of Leonard and co-workers (14) failed to give better yields than the 0.7% conversion reported in the Dieckmann reaction. Attempts to improve the yield by employing other catalysts or changing reaction conditions were fruitless. It would seem that perhaps the three carbon atom bridge increases greatly the extent of nonbonded interactions in the piperidine ring over that of quinuclidine (6).

Substantial improvements in the published methods for the preparation of ethyl 4-pyridylacetate were developed and 4-pyridylthioacetmorpholide was conveniently prepared by the reaction of 4-vinylpyridine, sulfur, and morpholine in the presence of hydroquinone. The thiomorpholide was converted directly to the ester by simply refluxing with equal weights of

[3] Although *Chemical Abstracts* catalogs this nucleus under the name 1-isogranatanine, in accordance with the nomenclature suggested by McElvain and Adams, *J. Am. Chem. Soc.*, **45**, 2744(1923), the authors prefer the 1-azabicyclo terminology to maintain consistency and to demonstrate the correlation among isomers.

[4] *Chemical Abstracts* prefers the name octahydropyrrocoline for this nucleus (see above). Other trivial names include piperolidine, indolizidine, and δ-coniceine.

[5] The 2, 3, and 4-pyridylacetic acids are now commercially available (Aldrich Chemical Co.). For a review of methods of synthesizing the isomeric pyridylacetic acids and their derivatives see M. J. Martell, Jr., Ph.D. thesis (University of Minnesota, 1958).

[6] These authors also reported the isolation of another "isomeric aminoalcohol" as a by-product of the Clemmensen reduction of the aminoketone. However, such a product seems unlikely, and, although no reinvestigation of this result was undertaken, it would seem that cleavage during reduction had taken place, probably to 2-piperidylacetone, isomeric with the aminoalcohol. Leonard and co-workers (14) have shown that *i* is cleaved during Clemmensen reduction to 3-acetylpiperidine.

[7] The reduction of bicyclic aminoketones of the bicyclo-[3.3.1]type has been investigated recently and excellently reviewed [Zirkle, C. L., Gerno, F. R., Pavloff, A. M., and Burger, A., *J. Org. Chem.*, **26**, 395(1961)] and shows that attack with large reducing groups is from the unhindered side giving the less thermodynamically stable axial conformer, which indeed VI may well be. Reduction with sodium and amyl alcohol gives the more stable equatorial conformer. We are presently investigating this reduction in greater detail.

absolute alcohol and sulfuric acid (23). Formation of the quaternary salt and subsequent reactions followed those described by Leonard, *et al.* (14).

The acid chloride method, as described by Counsell and Soine, was used for the preparation of the esters of diphenylacetic and xanthene-9-carboxylic acids. Transesterification in *n*-heptane, using a trace of sodium hydride as catalyst, conveniently transformed the methyl esters of benzilic, phenyl-2-thienylglycolic, and 9-hydroxyfluorene-9-carboxylic acids to the corresponding esters of the respective aminoalcohols.

Published methods (20, 21) for the synthesis of phenyl-2-thienylglycolic acid were unsatisfactory for our purposes and therefore a direct synthesis of its methyl ester was developed. Thus, the action of 2-thienyl magnesium bromide on methyl phenylglyoxylate gave fair yields of methyl phenyl-2-thienylglycolate.

Examination of the pharmacological data presented in Tables I and II readily reveals that whatever differences in activity exist between corresponding esters of VI and VII are small indeed, and lie well within the errors presented by the testing methods. The compounds, however, are quite potent anticholinergic agents.

All of the esters were tested in Shay (pyloric ligated) rats (22) and their effects on gastric secretion noted. Only five esters were either sufficiently active or well absorbed orally to demonstrate significant activity. The benzilate and xanthene-9-carboxylate methobromides of VII showed minimal action on gastric acid and no effect on gastric secretion volume at 40 mg./Kg. The phenyl-2-thienylglycolate methobromide of VII had minimal action on both acid and volume at 20 mg./Kg. The phenyl-2-thienylglycolates of VI showed unusually high activity. The methobromide was effective at only 40 mg./Kg. but the hydrochloride was active at 10 mg./Kg. These last two compounds were tested in Heidenhain denervated and Thomas innervated chronic fistula dogs, and the effect on the gastric secretion observed. The methobromide in oral doses of 0.1–0.25 mg./Kg. produced slightly delayed onset of acid secretion. However 0.5 mg./Kg. caused suppression of gastric acid output by at least 50% in two dogs. At 0.05–0.1 mg./Kg., taken intravenously, the acid secretion was completely suppressed in two dogs. The hydrochloride in dogs was very potent. Oral doses of 0.5 mg./Kg. completely inhibited secretion of acid for 5 hours in 4 dogs (3 denervated, 1 innervated), but serious side effects probably resulting from central stimulation (5) were observed. At doses of 0.1 mg./Kg., side effects were reduced and the gastric secretion was still abolished for at least 5 hours. In this type of test, atropine abolishes gastric secretion at about 0.065 mg./Kg.[8]

EXPERIMENTAL[9]

4-Pyridylthioacetmorpholide.—A mixture of redistilled morpholine (45.7 Gm., 0.525 mole), freshly distilled 4-vinylpyridine[10] (50.0 Gm., 0.475 mole) containing 1% of hydroquinone, and sulfur (31.0 Gm., 0.95 Gm. atom) were placed in a 200-ml. flask equipped with a reflux condenser. The sulfur dissolved and the temperature of the solution rose to 110°. The solution was then heated at 160° for 2 hours, during which time hydrogen sulfide evolved. The solution was poured into cracked ice, stirred until solid, filtered, pressed as dry as possible, washed with ice water, dried and recrystallized from absolute ethanol. This procedure gave 56.0 Gm. (53%) of slightly impure material, m.p. 103–106° [m.p. 104–105.5° lit. (17)].

Ethyl 3-Pyridylacetate.—3-Pyridylthioacetmorpholide (195 Gm., 0.88 mole) (16, 17) was dissolved in concentrated hydrochloric acid (200 ml.) and the solution refluxed for 2.5 hours. The solution was cooled, filtered until clear, and evaporated to dryness *in vacuo*. The residue was dissolved in absolute ethanol (400 ml.) and the solvent distilled under reduced pressure to remove traces of water. The solid was again dissolved in absolute ethanol (500 ml.) and concentrated sulfuric acid (200 ml.) was added with cooling. The solution was allowed to stand for 24 hours at room temperature, after which it was refluxed for 1 hour. The cooled solution was poured slowly with stirring into 600 ml. of ice-cold concentrated ammonium hydroxide solution in an ice bath and the ester extracted with five 150-ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. The product was distilled to give 92.5 Gm. (64%) of a light greenish liquid, b.p. 65° (0.1 mm.), n_D^{20} 1.5000 [b.p. 121–122° (10 mm.), lit. (17)].

Diethyl Pyridinium-1,3-diacetate Bromide.—Ethyl 3-pyridyl acetate (92.5 Gm., 0.56 mole), ethyl bromoacetate (94.0 Gm., 0.56 mole), and absolute ether (200 ml.) containing absolute ethanol (10 ml.) were mixed, briefly stirred, and left at room temperature for 24 hours. The oil that separated solidified upon scratching. The solid was separated by filtration, washed well with anhydrous ether, and dried to give 176 Gm. (94.5%) of product suitable for reduction. A sample was crystallized

[8] Dr. T. M. Lin, Eli Lilly and Co., personal communication.

[9] All melting points were determined on a calibrated Kofler micro hot stage apparatus unless otherwise specified, in which case they are uncorrected as are the boiling points. The microanalyses were performed by Wm. Kuryla and Mrs. Olga Hamerston of the Microanalytical Laboratories, School of Chemistry, University of Minnesota, or by Drs. Weiler and Strauss, Microanalytical Laboratories, Oxford, England. The infrared spectra were determined by the Spectroscopy Laboratory, School of Chemistry, University of Minnesota, on a Perkin-Elmer model 21 doublebeam spectrophotometer using sodium chloride optics.

[10] From the Reilly Tar and Chemical Co., Indianapolis, Ind.

several times from butanone to give hygroscopic colorless prisms, m.p. 81–82°.

Anal.—Calcd. for $C_{13}H_{18}BrNO_4$: C, 47.00; H, 5.46. Found: C, 47.27; H, 5.49.

Diethyl Piperidyl-1,3-diacetate.—Crude diethyl pyridinium-1,3-diacetate bromide (50 Gm., 0.15 mole) in glacial acetic acid (150 ml.) and water (50 ml.) was hydrogenated at 2–3 Atm. at room temperature, using 0.7 Gm. of platinum oxide catalyst. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the solution evaporated to a syrup *in vacuo*. The syrup was neutralized with 25% aqueous sodium hydroxide solution and the diester extracted with five 50-ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate and the ether removed under reduced pressure. The residue was distilled to give 33.6 Gm. (87% yield) of product as a colorless oil, b.p. 110–111° (0.15 mm.), n_D^{25} 1.4607.

Anal.—Calcd. for $C_{13}H_{23}NO_4$: C, 60.67; H, 9.01. Found: C, 60.65; H, 8.97.

The picrate was formed in and recrystallized from absolute ethanol, m.p. 92–93°.

Anal.—Calcd. for $C_{19}H_{26}N_4O_{11}$: C, 46.92; H, 5.39. Found: C, 46.90; H, 5.53.

3 - Oxo - 1 - azabicyclo[3.3.1]nonane. — Anhydrous xylene (2500 ml.) and freshly trimmed potassium (45.6 Gm., 1.17 Gm. atoms) were placed in a 5-L. three-neck flask, equipped with a mechanical stirrer, reflux condenser fitted with a drying tube, and a dropping funnel. The xylene was heated and the potassium pulverized with vigorous stirring under a stream of dry nitrogen, which was maintained throughout the reaction. The heat was removed and *tert*-butyl alcohol (freshly distilled from calcium hydride) (325 ml., 3.5 moles) was added at such a rate as to maintain a gentle reflux. The mixture was then stirred and refluxed until all the potassium had reacted. The excess alcohol was removed by collecting 1200 ml. of azeotrope by means of a Dean-Stark trap. A solution of diethyl piperidyl-1,3-diacetate (120 Gm., 0.47 mole) in anhydrous xylene (800 ml.) was added over a period of 10 hours with vigorous stirring followed by a period of 20 hours of refluxing and stirring, the ethanol-xylene azeotrope being removed the entire time. The mixture, which by now was reduced in volume to about 1 L. was cooled in ice, and 400 ml. of 6 *N* hydrochloric acid was added with vigorous stirring. The xylene layer was extracted twice more with 200-ml. portions of 6 *N* acid, and the combined acid extracts refluxed for 8 hours. The cooled solution was basified to pH 9 with 50% aqueous potassium hydroxide, with cooling, saturated with solid potassium carbonate, and extracted with six 200-ml. portions of benzene. The combined benzene extracts were dried and the solvent removed at slightly reduced pressure. The solid residue was sublimed at 70° and 0.1 mm. pressure to give 47.7 Gm. (73.5%) of product as tiny colorless prisms. A sample was recrystallized twice from Skellysolve B and sublimed for analysis, m.p. 123–125° (capillary with slight decompn.). The infrared spectrum (potassium bromide) showed carbonyl absorption at 1705 cm.$^{-1}$.

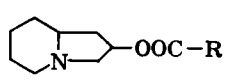
Anal.—Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 68.79; H, 9.40.

The hydrochloride salt melted at 292–293° (decompn. and sublimation, capillary) after several recrystallizations from *iso*propyl alcohol.

Anal.—Calcd. for $C_8H_{14}ClNO$: C, 54.70; H, 8.00. Found: C, 54.91; H, 7.93.

3 - Hydroxy - 1 - azabicyclo[3.3.1]nonane.—

TABLE I.—ESTERS OF 8-HYDROXY-1-AZABICYCLO[4.3.0]NONANE (VII)



Acid (R-COOH) Used for the Esterification	M.p., ° C.	Molecular Formulas	Salt	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Activity[a] Muscle Strip[b]	Cat Blood Pressure[c]
Phenyl-2-thienylglycolic[d]	237–238[e]	$C_{20}H_{23}NO_2S$	HCl[f,g]	60.98	60.74	6.14	6.21	100	20
	227–229[e]		CH_3Br[h]	55.75	55.47	5.79	6.03	100	10
Benzilic	217–219	$C_{22}H_{25}NO_3$	HCl[f]	68.12	68.35	6.76	6.68	20	0
	237–238[e]		CH_3Br[f]	61.88	62.11	6.31	6.21	10	0
9-Hydroxyfluorene-9-carboxylic	272–273[e,i]	$C_{22}H_{23}NO_3$	$HCl \cdot {}^1/_2C_2H_5OH$[f,g,k]	67.55	67.66	6.66	6.50	50	1
	249–250[e,i]		CH_3Br[h]	62.15	62.10	5.90	6.00	50	10
Xanthene-9-carboxylic	142–144	$C_{22}H_{23}NO_3$	HCl[l]	68.47	68.15	6.27	6.34	50	0
	234–235[e]		CH_3Br[h]	62.16	62.28	5.90	5.83	100	100
Diphenylacetic	...	$C_{22}H_{25}NO_2$	HCl[m]	...	...	...	...	...	...
	219–220		CH_3Br[f]	64.18	63.91	6.56	6.77	20	0

[a] Expressed as percentage of activity of atropine sulfate. [b] Alleviation due to blocking spasm, induced by 1:10,000,000 dilutions of methacholine, on an isolated guinea pig ileum. [c] Alleviation due to blocking depressor response to 1 mcg./Kg. intravenously of methacholine on the blood pressure of an anesthetized cat. [d] The free base was ether insoluble, so methylene chloride was added following hydrolysis and the salts were prepared in methylene chloride. [e] With decomposition. [f] Recrystallized from ethyl acetate–absolute alcohol–*iso*propyl ether. [g] Slowly soluble in absolute alcohol so the solution was concentrated after filtration. [h] Recrystallized from acetone–absolute alcohol–*iso*propyl ether. [i] Capillary. [j] The melting point is dependent on the rate of heating. The temperature must be raised very slowly over the range 190–250°. [k] Air-dried sample. [l] Recrystallized from ethyl acetate–tetrahydrofuran–*iso*propyl ether. [m] Was an oil which resisted crystallization. Other salts were equally as unsuitable.

A solution of the aminoketone (22.5 Gm., 0.162 mole) in water (50 ml.) was slowly added to a solution of sodium borohydride (1.68 Gm., 0.0445 mole) in water (50 ml.). The solution was allowed to stand at room temperature overnight. Concentrated ammonium hydroxide (50 ml.) (24) was added and the solution allowed to stand for 1.5 hours, after which it was saturated with sodium chloride. The aminoalcohol was extracted with seven 50-ml. portions of benzene. The extracts were dried over anhydrous sodium sulfate and the benzene was removed under slightly reduced pressure to give 20.0 Gm. (87.5%) of product. A sample was recrystallized twice from Skellysolve B and sublimed for analysis at 100° and 0.1 mm. The material was very hygroscopic and a good analysis could not be obtained, m.p. 148–151° (capillary). An infrared spectrum (potassium bromide) showed hydroxyl bands at 3400 cm.$^{-1}$ and 3150 cm.$^{-1}$.

Anal.—Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 67.43; H, 10.69.

8 - Oxo - 1 - azabicyclo[4.3.0]nonane. — Diethyl piperidyl-1,2-diacetate (12) was subjected to the Dieckmann conditions in a manner essentially like that of the 1,3-diacetate except that higher dilutions (2 times the volumes of xylene) were employed. The product was obtained in 60% yield as a colorless liquid that quickly turned to a brown tar upon exposure to air, b.p. 64° (1.25 mm.), n_D^{25} 1.4786 [b.p. 61° (1 mm.) lit. (12)]. The picrate was formed in absolute ethanol and recrystallized from water, m.p. 189° (capillary, with decompn.) [m.p. 187° (decompn.) lit. (12)]. The infrared spectrum (film) showed carbonyl absorption at 1756 cm.$^{-1}$.

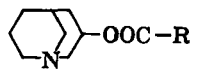
8 - Hydroxy - 1 - azabicyclo[4.3.0]nonane.— The aminoketone was reduced with sodium borohydride as was described for the preparation of 3-hydroxy-1-azabicyclo[3.3.1]nonane, in 89% yield, b.p. 73–74° (0.15 mm.), n_D^{25} 1.4950 [b.p. 95° (14 mm.), lit. (12)].

The picrate was formed in and recrystallized from absolute ethanol, m.p. 175–176° [m.p. 175° (reduction by sodium and alcohol), lit. (12)].

An infrared spectrum (film) showed broad hydroxyl absorption centering at 3400 cm.$^{-1}$.

Methyl Phenyl-2-thienylglycolate.—Methyl phenylglyoxylate (104 Gm., 0.635 mole) [prepared from methyl mandelate as described for the ethyl ester (25) in 97% yield] and anhydrous ether (400 ml.) were placed in a flask equipped with a mechanical stirrer and dropping funnel. The flask was cooled in an ice-salt mixture and a solution of 2-thienyl magnesium bromide [made from 2-bromothiophene (113.8 Gm., 0.7 mole) and magnesium (16.7 Gm., 0.7 Gm. atom)] in anhydrous ether (500 ml.) was siphoned into the dropping funnel and was added to the flask with stirring over a period of 2 hours. The mixture was stirred in the ice-salt bath for an additional hour and then for 3 hours at room temperature. The magnesium addition product was filtered off, washed well with anhydrous ether, and hydrolyzed by stirring it in ether (500 ml.) and cautiously adding a saturated aqueous solution of ammonium chloride (100 ml.) with ice cooling. The ether layer was decanted, washed with water (two 100-ml. portions), 2.5% hydrochloric acid (100 ml.), 5% sodium carbonate solution (two 100-ml. portions), and finally with water (two 100-ml. portions). The ether layer was treated, with charcoal, filtered, and dried over anhydrous sodium sulfate. The ether was removed *in vacuo* and the residue soldified upon scratching and cooling. This was dissolved in 3.5 liters of warm Skellysolve B and carefully cooled to room temperature, additional solvent being added if necessary to prevent oiling. Upon cooling to 10°,

TABLE II.—ESTERS OF 3-HYDROXY-1-AZABICYCLO[3.3.1]NONANE (VI)



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Phenyl-2-thienylglycolic	237–238[d,e]	$C_{22}H_{23}NO_3S$	HCl[f]	60.98	61.25	6.14	6.25	100	100
	225–228[d]		CH_3Br[g]	55.75	55.95	5.79	5.89	100	100
Benzilic	230–230.5	$C_{22}H_{25}NO_3$	HCl[f]	68.12	67.97	6.76	6.81	100	100
	225–226		CH_3Br[f]	61.88	61.70	6.31	6.54	100	100
9-Hydroxyfluorene-9-carboxylic	248–251	$C_{22}H_{23}NO_3$	$HCl \cdot {}^1/_2C_2H_5OH$[f,i]	67.55	67.89	6.66	6.93	50	<1
	239–240[d,h]		$CH_3Br.1{-}{}^1/_2C_2H_5OH$[g,i]	60.81	60.81	6.87	7.15	20	<1
Xanthene-9-carboxylic	201–203	$C_{22}H_{23}NO_3$	HCl[f]	68.47	68.24	6.27	6.43	100	10
	216–217		$CH_3Br \cdot {}^1/_2C_2H_5OH$[g,i]	61.67	61.80	6.25	6.11	50	10
Diphenylacetic	208–209	$C_{22}H_{23}NO_3$	HCl[f]	71.05	71.18	7.05	7.13	10	<1
	203–204		CH_3Br[g]	64.18	64.41	6.56	6.73	<10	0

[a] Expressed as a percentage of atropine sulfate. [b] Alleviation due to blocking spasm induced by 1:10,000,000 dilutions of methacholine on an isolated guinea pig ileum. [c] Alleviation due to blocking depressor response to 1 mcg./Kg. intravenously of methacholine on the blood pressure of an anesthetized cat. [d] With decomposition. [e] Capillary. [f] Recrystallized from ethyl acetate–absolute alcohol–*iso*propyl ether. [g] Recrystallized from acetone–absolute alcohol–*iso*propyl ether. [h] Release of ethanol and resolidification at 130–140°. [i] Air-dried sample.

there was deposited 47.5 Gm. of crude ester. Further cooling of the mother liquor gave an additional 17.0 Gm. for a total of 64.7 Gm. (41% yield) of crude ester. This material was recrystallized from warm cyclohexane to give 44.0 Gm. of pure ester, m.p. 62–63°. This material was identical to a sample of the methyl ester of phenyl-2-thienylglycolic acid (21, 26) which had been distilled and had solidified and been recrystallized, m.p. 61.5–62.5°.

Methyl 9-Hydroxyfluorene-9-carboxylate.—9-Hydroxyfluorene-9-carboxylic acid (27, 28) was converted to its methyl ester by the method of Clinton and Laskowski (29), m.p. 165° [m.p. 160° lit. (30)].

1-Azabicyclo[4.3.0]nonan-8-yl Benzilate Hydrochloride and Methobromide.—In a 250-ml. three-neck flask fitted with a mercury sealed stirrer, reflux condenser with drying tube, and a Dean-Stark trap, was placed 8-hydroxy-1-azabicyclo-[4.3.0]nonane (1.0 Gm., 7.1 mmoles), methyl benzilate (1.75 Gm., 7.1 mmoles) and Skellysolve C (freshly distilled from calcium hydride) (75 ml.). A trace of a 46% dispersion of sodium hydride in mineral oil (Metal Hydrides) was added to the refluxing solution with stirring and the mixture refluxed and stirred for 10 hours. Most of the solvent was removed *via* the trap, the mixture cooled, and water (25 ml.) and ether (25 ml.) added with stirring. The organic layer was extracted four times with water (20-ml. portions), and finally dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was taken up in 25 ml. of anhydrous ether. The hydrochloride was prepared by adding ethereal hydrogen chloride. The methobromide was formed by adding methyl bromide, stoppering the flask tightly, and allowing it to remain at room temperature for several days. The salts, in this case and in general, were recrystallized by the solvent mixtures listed in Tables I and II.

1-Azabicyclo[3.3.1]nonan-3-yl Xanthene-9-carboxylate Hydrochloride and Methobromide.—Xanthene-9-carboxylic acid[11] was converted to its acid chloride by refluxing the acid (1.6 Gm., 7.1 mmoles) in thionyl chloride (10 ml.) for 2 hours. The excess thionyl chloride was removed *in vacuo*, and the residue dissolved in dry benzene (15 ml.) and the solvent removed under reduced pressure. A solution was made of freshly sublimed 3-hydroxy-1-azabicyclo[3.3.1]nonane (1.0 Gm., 7.1 mmoles), anhydrous benzene (50 ml.) and triethylamine (1.0 ml.). A solution of the acid chloride in dry benzene (25 ml.) was added dropwise over a period of 1/2 hour, with stirring. The mixture was heated at 70° and stirred for 2 1/2 hours. The mixture was cooled, and the triethylamine hydrochloride filtered off (*ca.* 1 Gm.). The benzene solution of the free base was washed with four 20-ml. portions of water, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. The residue was dissolved in 25 ml. of dry ether and the hydrochloride or methobromide formed and recrystallized as outlined in the previous preparation.

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SUMMARY

1. The literature preparation of 3-oxo-1-azabicyclo[3.2.2]nonane could not be improved upon. Its isomers and their respective alcohols (3-hydroxy-1-azabicyclo[3.3.1]nonane and 8-hydroxy-1-azabicyclo[4.3.0]nonane) were synthesized in good yield.

2. A series of 19 esters of the named amino-alcohols using five acids was prepared.

3. The pharmacological testing of these esters show several to be potent anticholinergic agents.

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