Esters of Aminoalcohols Derived from 3-Azabicyclo[3.2.2]nonane

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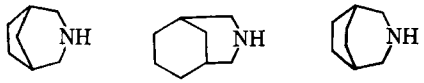
A series of esters of the type I and II was prepared utilizing 3-azabicyclo[3.2.2]nonane. The pharmacological testing of one of these esters is reported.

COMPOUNDS having interesting pharmacological activity have been prepared from one or more of the parent amines, 3-azabicyclo[3.2.1]-octane (I), 3-azabicyclo[3.3.1]nonane (II), and 3-azabicyclo[3.2.2]nonane (III) (1).



I II III

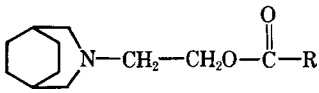
The use of 3-azabicyclo[3.2.2]nonane, extended in other areas of research, was initiated earlier at this institution by Blanton and Nobles (2, 3). These authors investigated the ketonic Mannich bases and their derivatives obtained from 3-azabicyclo[3.2.2]nonane. The ketonic Mannich bases have been shown to exhibit activity against *Staphylococcus aureus, Candida albicans, Trichophyton mentagrophytes,* and *Trichomonas foetus* (4).

Krieger (5) has demonstrated the usefulness of the guanidine derivative of 3-azabicyclo[3.2.2]-nonane as a possible hypotensive agent. Moreover, Martell and Soine (6) have reported that the esters of 3-hydroxy-1-azabicyclo[3.3.1]-nonane and 8-hydroxy-1-azabicyclo[4.3.0]nonane are potent anticholinergic agents.

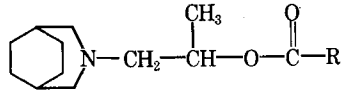
These observations prompted the investigations reported in this paper. The object of the present work was to prepare and examine some of the esters of the amino alcohols obtainable from 3-azabicyclo[3.2.2]nonane and to determine whether they possessed significant pharmacological action.

DISCUSSION

Types of compounds prepared from 3-azabicyclo[3.2.2]nonane are shown as types I and II.

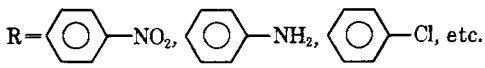


Type I



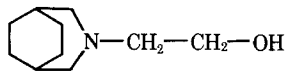
Type II

where



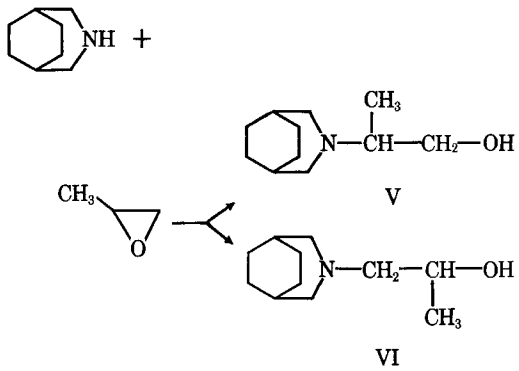
The preparation of 20 new esters of types I and II, starting with 3-azabicyclo[3.2.2]nonane,[1] was accomplished by well-known methods described in the literature.

A modification of the procedure described by Horne and Shriner (7), utilizing ethylene oxide at a lower temperature, was employed to obtain 3-azabicyclo[3.2.2]nonane-3-ethanol (IV) from 3-azabicyclo[3.2.2]nonane (8).



IV

When propylene oxide is treated with 3-azabicyclo[3.2.2]nonane using the same conditions as those used for ethylene oxide, there is a possibility of forming either 2-(3-azabicyclo[3.2.2]nonyl)-3-propanol (V) or 3-(3-azabicyclo[3.2.2]nonyl)-2-propanol (VI) or a mixture of both of these isomers, depending upon the point of ring opening (Scheme I).



V VI

Scheme I

When the alcohol was chromatographed on plates coated with Silica Gel G in solvent systems such as ethanol, methanol, chloroform, benzene, and benzene–methanol (40:60), it demonstrated only one sample spot upon visualization with acidic potassium permanganate solution, indicating the formation of only one isomer.

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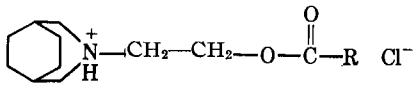
[1] 3-Azabicyclo[3.2.2]nonane was supplied through the courtesy of Eastman Chemical Products, Inc., Kingsport, Tenn.

TABLE I.—COMPOUNDS OF TYPE I



Compd.	R	Yield, %[a]	M.p., °C.[b]	Molecular Formula	Anal.[c] Calcd.	Found
1	Phenyl	61.5	230 dec.	$C_{17}H_{23}NO_2 \cdot HCl$	C, 65.91	65.71
					H, 7.81	7.84
					N, 4.52	4.45
2	*p*-Nitrophenyl	67.3	203 dec.	$C_{17}H_{22}N_2O_4 \cdot HCl$	C, 57.54	57.12
					H, 6.57	6.54
					N, 7.90	7.77
3	*p*-Aminophenyl	89.0	256 dec.	$C_{17}H_{24}N_2O_2 \cdot HCl$	C, 62.85	62.08
					H, 7.76	7.89
					N, 8.62	8.45
4	Benzilic	98.0	198 dec.	$C_{24}H_{29}NO_3 \cdot HCl$	C, 69.30	70.02
					H, 7.27	7.58
					N, 3.37	3.52
5	Mandelic	96.5	136 dec.	$C_{18}H_{25}NO_3 \cdot HCl$	C, 63.61	63.46
					H, 7.71	7.95
					N, 4.12	4.27
6	Cinnamyl	68.9	241 dec.	$C_{19}H_{26}NO_2 \cdot HCl$	C, 67.74	67.74
					H, 8.08	7.89
					N, 4.15	4.46
7	*m*-Bromophenyl	64.3	219–220 dec.	$C_{17}H_{22}BrNO_2 \cdot HCl$	C, 52.52	52.75
					H, 5.96	6.02
					N, 3.60	3.26
8	*p*-Chlorophenyl	64.7	252–253 dec.	$C_{17}H_{22}ClNO_2 \cdot HCl$	C, 59.29	59.37
					H, 6.73	6.65
					N, 4.07	4.20
9	*o*-Nitrophenyl	64.7	204–205 dec.	$C_{17}H_{22}N_2O_4 \cdot HCl$	C, 57.54	57.68
					H, 6.57	6.65
					N, 7.89	7.79
10	*o*-Aminophenyl	84.8	244 dec.	$C_{17}H_{24}N_2O_2 \cdot HCl$	C, 62.85	63.08
					H, 7.75	8.26
					N, 8.62	8.78

[a] All the compounds were recrystallized from ethanol–ethylacetate and ether mixture. [b] All the melting points are uncorrected. [c] Elemental analyses were done through the courtesy of Dr. P. N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa.

The NMR data[2] (see under *Experimental*) indicated the formation of 3-(3-azabicyclo[3.2.2]-nonyl)-2-propanol (VI). Contrary to expectations, this alcohol failed to undergo the haloform reaction. Fuson and Bull (9) have indicated that only certain secondary alcohols undergo a haloform reaction.

The alcohol, 3-(3-azabicyclo[3.3.2]nonyl)-2-propanol, on oxidation (10) with chromic acid and sulfuric acid below 20°, gave a compound which reacted with 2,4-dinitrophenylhydrazine to form a 2,4-dinitrophenylhydrazone derivative. The oxidation product did not reduce either Tollen's reagent or Schiff's reagent. The infrared spectrum of the oxidation product showed a strong peak in the region of 1725 to 1705 cm.$^{-1}$. These qualitative tests strongly suggest that the compound thus obtained is a ketone; therefore, the alcohol formed by the reaction of propylene oxide and 3-azabicyclo[3.2.2]-nonane should be 3-(3-azabicyclo[3.2.2]nonyl)-2-propanol.

Two different methods were employed to obtain the esters of 10 aromatic acids. The acid chloride method, as described by Martell and Soine (6), was used for the preparation of the esters of all acids except benzilic and mandelic acids. In general, the reaction proceeded smoothly to yield the expected products. It may be noted, however, that the yields obtained were between 60 and 70%.

A second method, as described in the literature (8), was employed to obtain esters from benzilic and mandelic acids. The yields were consistently in the range of 95–98%.

The esters of *p*-amino and *o*-amino acids were prepared by reducing the nitro groups of *p*-nitro and *o*-nitro benzoates, as described by Wright and Freifelder (11).

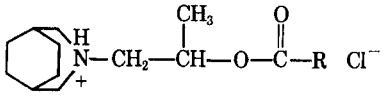
Pharmacological Results.—The compound 2-(3-azabicyclo[3.2.2]nonyl)-ethyl benzilate hydrochloride (Table I, compound *4*) was tested for biological activity. This compound was screened for potential pharmacodynamic properties. Intraperitoneal injection of 100 mg./Kg. of the compound in 12 mice resulted in weak central nervous system depression and in weak psychotrophic and anticonvulsant properties in 70% of the mice tested. The activity had its onset within 3 min. with an intraperitoneal injection of 500 mg./Kg., and the duration of the activity was observed to range from 24 to 72 hr.

The side effects of the compound with a dose of 500 mg./Kg. were characterized by marked ataxia, muscle weakness, and dyspnea.

When the same compound was tested for cardiovascular, somatic, and visceral effects in dogs anesthetized by pentobarbital, intravenous injections of

[2] The interpretation of the NMR data was done through the courtesy of Dr. R. L. Settine, Department of Chemistry, The University of Mississippi, University.

TABLE II.—COMPOUNDS OF TYPE II



Compd.	R	Yield, %[a]	M.p., °C.[b]	Molecular Formula	Anal.[c] Calcd.	Found
1	Phenyl	64.7	218 dec.	$C_{18}H_{25}NO_2 \cdot HCl$	C, 66.75	66.57
					H, 8.09	8.11
					N, 4.33	4.33
2	*p*-Nitrophenyl	63.8	247 dec.	$C_{18}H_{24}N_2O_4 \cdot HCl$	C, 58.60	58.35
					H, 6.83	6.93
					N, 7.60	7.63
3	*o*-Nitrophenyl	60.0	194 dec.	$C_{18}H_{24}N_2O_4 \cdot HCl$	C, 58.60	58.79
					H, 6.83	7.00
					N, 7.60	7.61
4	3,4,5-Trimethoxyphenyl	60.7	197–198 dec.	$C_{21}H_{31}NO_5 \cdot HCl$	C, 60.93	60.88
					H, 7.79	7.73
					N, 8.57	8.54
5	*p*-Aminophenyl	81.8	256 dec.	$C_{18}H_{26}N_2O_2 \cdot HCl$	C, 63.79	63.45
					H, 8.03	7.79
					N, 8.26	8.05
6	*o*-Aminophenyl	86.3	222 dec.	$C_{18}H_{26}N_2O_2 \cdot HCl$	C, 63.79	63.73
					H, 8.03	8.20
					N, 8.26	8.29
7	Benzilic	93.7	176 dec.	$C_{25}H_{31}NO_3 \cdot HCl$	C, 69.83	69.97
					H, 7.50	7.77
					N, 3.26	3.24
8	Mandelic	94.9	181 dec.	$C_{19}H_{27}NO_3 \cdot HCl$	C, 64.48	63.21
					H, 7.97	8.05
					N, 3.95	3.99
9	*m*-Bromophenyl	63.5	299 dec.	$C_{18}H_{24}BrNO_2 \cdot HCl$	C, 53.68	53.88
					H, 6.25	6.27
					N, 3.47	3.23
10	*p*-Chlorophenyl	66.6	246–247 dec.	$C_{18}H_{24}ClNO_2 \cdot HCl$	C, 60.40	60.33
					H, 7.08	6.99
					N, 3.91	3.89

[a] All the compounds were recrystallized from ethanol–ethylacetate and ether mixture. [b] All the melting points are uncorrected. [c] Elemental analyses were done through the courtesy of Dr. P. N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa.

1 and 10 mg./Kg. resulted in slight hypotensive effects, characterized by moderate inhibition of the linguo-mandibular reflex, apparently not related to the hypotensive effect.

EXPERIMENTAL

Compounds of Type I (Table I)

3-Azabicyclo[3.2.2]nonane-3-ethanol.—A solution of 125 Gm. (1.0 mole) of 3-azabicyclo[3.2.2]-nonane in 125 Gm. of methanol was treated over a 1-hr. period with 59.5 Gm. (1.35 mole) of ethylene oxide. The temperature of the reaction was maintained below 47° by keeping the reaction mixture in ice water. The reaction mixture was stirred for 1.75 hr. after the addition of ethylene oxide had been completed. Distillation of the product after removal of the methanol yielded 139 Gm. (82%) of 3-azabicyclo[3.2.2]nonane-3-ethanol, b.p. 94°/1.8 mm.

Anal.—Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.93; H, 11.06; N, 8.29.

2-(3-Azabicyclo [3.2.2]nonyl)-ethyl Chloride Hydrochloride.—A solution of 33.8 Gm. (0.2 mole) of 3-azabicyclo[3.2.2]nonane-3-ethanol in 175 ml. of dry benzene was placed in a three-necked flask. The mixture was stirred as 32.1 Gm. (0.27 mole) of thionyl chloride in dry benzene was added dropwise. The reaction was slightly exothermic. After the addition of thionyl chloride had been completed, the mixture was refluxed for 3 hr. and then cooled. The solid product was collected by filtration and was washed with benzene yielding 42.0 Gm. (95%) of 2-(3-azabicyclo[3.2.2]nonyl)-ethyl chloride hydrochloride, m.p. 225° (sublimation).

2-(3-Azabicyclo [3.2.2]nonyl)-ethyl Benzilate Hydrochloride.—A 50-ml. ether suspension of 6.7 Gm. (0.03 mole) of 2-(3-azabicyclo[3.2.2]-nonyl)-ethyl chloride hydrochloride was treated with 1.5 Gm. of sodium hydroxide in 25 ml. of water. The aqueous layer was extracted with two 50-ml. portions of ether and discarded. The ether extracts and ether solution were combined, dried over anhydrous magnesium sulfate, and then poured into 6.6 Gm. (0.02 mole) of benzilic acid in isopropanol. The solvents were distilled at 80°. The reaction then was maintained under total reflux for 3 hr. The solid that recrystallized from the mixture was collected by filtration and recrystallized from isopropanol to yield 8.23 Gm. (98%) of 2-(3-azabicyclo[3.2.2]nonyl)-1-ethyl benzilate hydrochloride, m.p. 198° dec.

Anal.—Calcd. for $C_{18}H_{25}NO_3.HCl$: C, 63.61; H, 7.71; N, 4.12. Found: C, 63.43; H, 7.95; N, 4.27.

2-(3-Azabicyclo [3.2.2]nonyl)-ethyl Benzoate Hydrochloride.—A solution of 3.6 Gm. (0.021 mole) of 3-azabicyclo[3.2.2]nonane-3-ethanol was made in 150 ml. of dry benzene and 3 ml. of triethylamine.

Three grams (0.021 mole) of benzoylchloride in 75 ml. of dry benzene was added dropwise over a period of 30 min. with stirring. The mixture was heated at 70° with stirring for 2.5 hr. The mixture was then cooled, and the triethylamine hydrochloride was removed by filtration. The benzene solution of the free base was washed with four 60-ml. portions of water, dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in 75 ml. of dry ether; the hydrochloride was formed by passing anhydrous hydrogen chloride through the solution. The product was recrystallized from ethanol, ethyl acetate, and ether, yielding 4.0 Gm. (61%) of 2-(3-azabicyclo[3.2.2]-nonyl)-1-ethyl benzoate hydrochloride, m.p. 230° dec.

Anal.—Calcd. for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.91; H, 7.81; N, 4.52. Found: C, 65.71; H, 7.84; N, 4.45.

2-(3-Azabicyclo [3.2.2]nonyl)-ethyl-(p-amino) Benzoate Hydrochloride.—A solution of 2.1 Gm. (0.006 mole) of 2-(3-azabicyclo[3.2.2]nonyl)-ethyl-(*p*-nitro) benzoate hydrochloride in 25 ml. of water was placed in a Parr low-pressure hydrogenator. The solution then was hydrogenated in the presence of 0.2 Gm. of 5% palladium-on-activated charcoal under 5 lb. of pressure of hydrogen. The reduction was complete in 40 min. The solution absorbed 2 lb. of hydrogen. The solution was then filtered from the catalyst and was concentrated under reduced pressure to a syrup. About 15 ml. of absolute ethanol was added to it, and the mass was triturated. The product so obtained was recrystallized from absolute ethanol, yielding 1.7 Gm. (89%) of 2-(3-azabicyclo[3.2.2]nonyl)-1-ethyl-(*p*-amino) benzoate hydrochloride, m.p. 256° dec.

Anal.—Calcd. for $C_{17}H_{24}N_2O_2 \cdot HCl$: C, 62.85; H, 7.76; N, 8.62. Found: C, 62.80; H, 7.89; N, 8.45.

Compounds of Type II (Table II)

3-(3-Azabicyclo[3.2.2]nonyl)-2-propanol.—A solution of 100 Gm. (0.8 mole) of 3-azabicyclo[3.2.2]-nonane in methanol was treated over a 1-hr. period with 48 Gm. (0.83 mole) of propylene oxide. The temperature of the reaction was maintained below 47° by keeping the reaction mixture in ice water. The reaction mixture was stirred for 1.75 hr. after the addition of propylene oxide had been completed. Distillation of the product after removal of the methanol yielded 135 Gm. (93%) of 3-(3-azabicyclo-[3.2.2]nonyl)-3-propanol, b.p. 96°/1.7 mm.

Anal.—Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.59; H, 11.69; N, 7.50.

The NMR spectrum in carbon tetrachloride was δ = 1.70 (d, probably CH_3—C, 3H), 1.70 (t, probably ring protons, 10H), 2.23 (d, probably N—CH_2, 2H), 2.65 (m, probably CH_2—N, 4H), 3.28 (s, probably C—OH, 1H), and 3.74 (m, probably —CH—O, 1H), p.p.m.

3-(3-Azabicyclo [3.2.2]nonyl)-propane-2-one.—To 13.7 Gm. (0.075 mole) of 3-(3-azabicyclo[3.2.2]-nonyl)-2-propanol in 35 ml. of acetone was added 7.35 Gm. of concentrated sulfuric acid in a few milliliters of water with cooling and stirring. Then 50 ml. of an aqueous solution containing 10 Gm. of CrO_3 and 16 Gm. of sulfuric acid was added dropwise below 20° by keeping the reaction mixture in an ice bath. The mixture was stirred for 3 hr., and then the solvent was evaporated. The residue was diluted with 250 ml. of water. The crystals formed were removed by filtration, washed several times with water, and recrystallized from water yielding 7.1 Gm. (51%) of 3-(3-azabicyclo[3.2.2]nonyl)-propane-2-one, m.p. 129–131° dec.

Anal.—Calcd. for $C_{11}H_{19}NO$: C, 72.81; H, 10.56; N, 7.72. Found: C, 72.56; H, 10.38; N, 7.61.

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