Antispasmodics. III.[1] Esters of Basic Bicyclic Alcohols and Their Quaternary Salts

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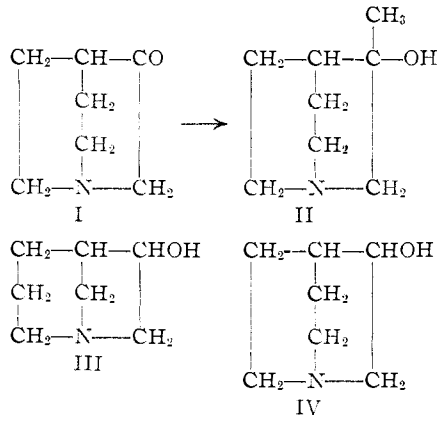
In continuation of our studies of ester type antispasmodics a new amino alcohol, 3-methyl-3-quinuclidinol (II), was prepared by treating 3-quinuclidone (I) with methyllithium. This tertiary alcohol II was esterified with diphenylacetic acid and the ester quaternized with methyl bromide. Since neither this ester nor its methobromide showed high antiacetylcholine activity, no other esters of tertiary alcohols were investigated.



However, two new esters were prepared from previously described bicyclic basic secondary alcohols.[2] They were the benzilic acid ester of 1-azabicyclo-[3.2.1]-6-octanol (III), prepared from the corresponding sodium alcoholate and diphenylchloroacetyl chloride, and 3-O-acetylmandelyloxyquinuclidine, prepared from 3-quinuclidinol (IV) and the corresponding acid chloride. The acetylmandelyl derivative was obtained as a mixture of two racemic enantiomorphs. They were not separated, and an analytically pure hydrochloride melting over a range of 9 degrees was used for the pharmacological testing.

The new benzilic acid ester (Ro 2-4569) and some of the formerly described esters were quaternized with methyl bromide. The benzilic[1] and diphenylacetic[1] acid esters of 3-quinuclidinol (IV) were also treated with other alkyl bromides, as well as with allyl bromide and benzyl bromide. One of these quaternary compounds, the methobromide of the benzilic ester of 3-quinuclidinol (Ro 2-3773), was resolved into optical antipodes. Two isomeric *d*-camphorsulfonates were obtained after metathesis of the bromide with silver *d*-camphorsulfonate. They gave a mixed melting point depression, and showed specific optical rotations of $[\alpha]^{30}D$ $+30.5 \pm 0.5°$ and $[\alpha]^{30}D$ $-13.5 \pm 0.5°$. This corresponds to a molecular rotation of the N-methylbenziloyloxyquinuclidinium ion of $+128.6 \pm 2.9°$ and $-125.9 \pm 2.4°$, respectively. These isomers were prepared in order to study possible differences in their pharmacological properties.

The physical properties, analyses and antiacetylcholine activities of these compounds are listed in Table I.

Pharmacological Activity.[3]—The spasmolytic activities of the various esters (Table I) were determined on the isolated rabbit intestine in a spasm induced by acetylcholine bromide. The potencies were estimated from the doses which produced relaxation equivalent to those caused by known amounts of atropine.

The benzilic acid ester of 1-azabicyclo[3.2.1]-octanol-6 (Ro 2-4569) showed antiacetylcholine activity of the same order as that of atropine. The acetylmandelic acid ester of 3-quinuclidinol (Ro 2-4344) and the diphenylacetic acid ester of 3-methyl-3-quinuclidinol (Ro 2-3631/2) were, however, only about $^1/_{10}$ as active. Quaternization of the diphenylacetic acid esters caused in all cases a considerable decrease in activity. On the other hand, most of the quaternary salts of the benzilic acid esters approximately equaled the non-quaternized compounds in potency.

The two isomeric 1-methyl-3-benziloyloxyquinuclidinium *d*-camphorsulfonates (Ro 2-5044 and Ro 2-5109) showed no significant difference in their antiacetylcholine activity.

Experimental[4]

3-Methyl-3-quinuclidinol (II).—A benzene solution (50 cc.) containing 5 g. of 3-quinuclidone (I) was added to an ether solution (about 50 cc.) of methyllithium, prepared from 1.4 g. of lithium metal and an excess of methyl bromide. The mixture was stirred and refluxed for 2 hours, then decomposed by the addition of 10–20 cc. of water. Sufficient potassium hydroxide and carbonate was added to convert the aqueous layer into a paste. This paste was extracted 3 times with 50 cc. each of benzene. The combined organic solutions were dried, concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether, forming prisms melting at 109–111°. The yield was 65%.

Anal. Calcd. for $C_8H_{15}ON$: C, 68.04; H, 10.71. Found: C, 68.03; H, 10.28.

The hydrochloride, prepared with the calculated amount of hydrochloric acid and recrystallized from a mixture of ethanol and acetone, forms prisms melting at 291–292°.

Anal. Calcd. for $C_8H_{16}ONCl$: C, 54.07; H, 9.08. Found: C, 53.88; H, 8.76.

Procedures A, B, C and D for the preparation of basic esters and their salts are identical with those described in paper II[1] of this series.

Procedure E. Quaternization of Basic Esters.—To a solution of 0.01 mole of the basic ester[5] in 15 cc. of chloroform was added 0.05 mole of the organic bromide (methyl bromide was used as a 30% solution in acetone). The mixture was left at room temperature for 24 hours and then concentrated *in vacuo*. The residue was recrystallized.

Procedure F. *d*- and *l*-1-Methyl-3-benziloyloxyquinuclidinium *d*-Camphorsulfonate.—A solution of silver *d*-camphorsulfonate was prepared by heating an excess of silver carbonate (6 g.) for a few minutes with an aqueous solution of 4.65 g. (20 mmoles) of *d*-camphorsulfonic acid. The mixture was filtered and the filtrate added to an aqueous solution of 8.65 g. (20 mmoles) of 1-methyl-3-benziloyloxyquinuclidinium bromide. The precipitated silver bromide was filtered off and the solution concentrated *in vacuo*. The

(1) Paper II, L. H. Sternbach and S. Kaiser, THIS JOURNAL, **74**, 2219 (1952).

(2) L. H. Sternbach and S. Kaiser, *ibid.*, **74**, 2215 (1952).

(3) The pharmacological studies were carried out by Drs. W. M. Benson, L. O. Randall and their associates in the Pharmacology Department of Hoffmann-La Roche, Inc., Nutley, N. J., to whom the authors are greatly indebted for the data discussed here. Part of the results have been published in detail by L. O. Randall, W. M. Benson and P. L. Stefko, *J. Pharmacol. Exptl. Therap.*, **104**, 284 (1952).

(4) All melting points are corrected.

(5) In the case of Ro 2-3951 the basic ester was liberated from its hydrochloride with aqueous alkali, and extracted with chloroform. The chloroform solution was used for the quaternization without isolation of the free base.

TABLE I

Ro 2-	Esters of Alcohol	Acid	Salt	Procedure	Recrystallized from	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd.	Found	Activity atr. = 1
3631	II	Diphenylacetic		B	Pet. ether	65	85–87	$C_{22}H_{25}O_2N$	C, 78.77 H, 7.51	78.68 7.43	
3631/2	II	Diphenylacetic	H_2SO_4	D	Acetone[a]	90	205–206	$(C_{22}H_{25}O_2N)_2 \cdot H_2SO_4$	C, 68.72 H, 6.82	68.55 6.51	1/10
4201	II	Diphenylacetic	CH_3Br	E	Acetone	80	176–177	$C_{23}H_{28}O_2NBr$	C, 64.18 H, 6.56	64.27 6.61	1/50
3951	III	Diphenylacetic	CH_3Br	E	Isopropanol + acetone + ether	80	165–167	$C_{22}H_{26}O_2NBr$	C, 63.46 H, 6.30	63.04 6.33	1/50
4569	III	Benzilic		C	Acetone + ether + pet. ether	15	156–157	$C_{21}H_{25}O_3N$	C, 74.75 H, 6.87	74.39 6.51	1–2[b]
4570	III	Benzilic	CH_3Br	E	Methanol + acetone + ether	85	231–233	$C_{22}H_{26}O_3NBr$	C, 61.11 H, 6.06	61.10 6.14	1–2
3203	IV	Diphenylacetic	CH_3Br	E	Ethanol + ether + pet. ether	90	212–213	$C_{23}H_{28}O_2NBr$	C, 63.46 H, 6.30	63.31 6.38	1/5
3528	IV	Diphenylacetic	C_2H_5Br	E	Ethanol + ether	90	205–206	$C_{23}H_{28}O_2NBr$	C, 64.18 H, 6.56	63.82 6.43	1/100
5205	IV	Diphenylacetic	$CH_2{=}CHCH_2Br$	E	Acetone[a]	80	149–150	$C_{24}H_{28}O_2NBr$	C, 65.15 H, 6.38	65.05 6.12	1/10
4157	IV	Diphenylacetic	$C_6H_5CH_2Br$	E	Isopropanol	40	171–173	$C_{28}H_{30}O_2NBr$	C, 68.29 H, 6.14	68.70 6.37	1/100
3773	IV	Benzilic	CH_3Br	E	Methanol + acetone + ether	90	240–241	$C_{22}H_{26}O_3NBr$	C, 61.11 H, 6.06	61.25 6.33	1
	IV	Benzilic	CH_3picr.[c]	G	Ethanol		182–183	$C_{28}H_{28}O_{10}N_4$	C, 57.93 H, 4.86	57.77 4.62	
5044	IV	Benzilic	CH_3CS[d]	F	Methanol + acetone + pet. ether	56	221–223	$C_{32}H_{41}O_7NS$	C, 65.84 H, 7.08	65.48 7.04	1
5109	IV	Benzilic	CH_3CS[d]	F	Methanol + acetone + pet. ether	20	209–210	$C_{32}H_{41}O_7NS$	C, 65.84 H, 7.08	65.93 7.29	1
4174	IV	Benzilic	C_2H_5Br	E	Methanol + acetone	90	229–230	$C_{23}H_{28}O_3NBr$	C, 61.88 H, 6.23	61.86 6.19	1
4665	IV	Benzilic	C_3H_7Br	E	Methanol + acetone + ether	90	251–254	$C_{24}H_{30}O_3NBr$	C, 62.60 H, 6.57	62.92 6.51	1
4550	IV	Benzilic	C_4H_9Br	E	Methanol + acetone + ether	80	246–247	$C_{26}H_{32}O_3NBr$	C, 63.29 H, 6.80	63.14 6.60	1
5084	IV	Benzilic	$CH_2{=}CHCH_2Br$	E	Methanol + acetone + pet. ether	80	181–182	$C_{24}H_{28}O_3NBr$	C, 62.88 H, 6.16	62.48 6.23	1
4148	IV	Benzilic	$C_6H_5CH_2Br$	E	Isopropanol[e]	37	223–224	$C_{28}H_{30}O_3NBr$	C, 66.14 H, 5.95	65.85 5.82	1/25
4344	IV	Acetylmandelic	HCl	A	Ethanol + acetone + ether	65	169–178	$C_{17}H_{21}O_4N \cdot HCl$[f]	C, 60.08 H, 6.53	59.90 6.52	1/25

[a] Dissolved in alcohol; solvent removed *in vacuo*. Residual oil crystallized by trituration with acetone. [b] A solution of the base in the calculated amount of dilute hydrochloric acid was used for the pharmacological studies. [c] Picrate. [d] *d*-Camphorsulfonates of optical antipodes. Ro 2-5044 is the dextrorotatory, Ro 2-5109 the levorotatory isomer. [e] Dissolved in methanol; solvent removed *in vacuo*. Residual oil crystallized by trituration with isopropyl alcohol. [f] A direct oxygen determination (Calcd.: O, 18.82. Found: O, 18.75) showed that the compound was the hydrochloride of the acetylmandelic acid ester and not of the mandelic acid ester. The carbon and hydrogen values of these two ester hydrochlorides are very close.

residual thick sirup was dissolved in methanol. To this solution acetone and ether were added, causing the precipitation of crystals (needles, 2 g.) melting around 200°. Further additions of acetone, ether and petroleum ether caused precipitation of more material melting in the same range. These fractions were combined and recrystallized three times from a mixture of methanol, acetone and petroleum ether, giving finally 3.3 g. (56%) of fine needles (Ro 2-5044), having the constant melting point of 221–223° and a constant specific rotation of $[\alpha]^{30}D$ +30.5 ± 0.5° (*c* 5, in water). This corresponds to a molecular rotation of the *d*-1-methyl-3-benziloyloxyquinuclidinium ion of +128.6 ± 2.9°.

Anal. Calcd. for $C_{32}H_{41}O_7NS$: C, 65.84; H, 7.08. Found: C, 65.48; H, 7.04.

The mother liquors were concentrated and the residues crystallized from a mixture of methanol, acetone and petroleum ether. The lower melting fractions (180–185°) thus obtained were repeatedly recrystallized from the above solvents to yield finally 1.2 g. (20%) of needles having a constant melting point of 209–210° (Ro 2-5109) and giving a distinct mixed melting point depression with the other isomer. The specific optical rotation of this isomer was $[\alpha]^{30}D$ −13.2 ± 0.5° (*c* 5, in water). The molecular rotation of the *l*-1-methyl-3-benziloyloxyquinuclidinium ion calculated from this value is −125.9 ± 2.4°.

Anal. Calcd. for $C_{32}H_{41}O_7NS$: C, 65.84; H, 7.08. Found: C, 65.93; H, 7.29.

Procedure G. 1-Methyl-3-benziloyloxyquinuclidinium Picrate.—A solution of 0.4 g. of 1-methyl-3-benziloyloxyquinuclidinium bromide (Ro 2-3773) in 10 cc. of water was added to a hot aqueous solution (50 cc.) of 0.4 g. of picric acid. The mixture was cooled and the precipitated oil crystallized.

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Crystal Structures of Rare Earth Oxychlorides

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Compounds of the rare earth elements show the effects of ionic size on crystal structure with minimum interference from other factors. The ionic