Table III—Micellar Molecular Weight of Each Bile Salt Determined from Literature Data and Calculated Using Eq. 5 from Dissolution-Rate Data and Measured Diffusion-Coefficient Data

	—Micellar Molecular Weight—		
	Dissolution-Rate Data	Diffusion Coefficient Data	Literature[a]
Sodium taurodeoxycholate	14,148	13,306	12,500
Sodium taurocholate	2,662	3,072	2,689
Equimolar mixture	7,848	7,189	7,945

[a] From *Reference 15.*

where R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, N is Avogadro's number, M is the molecular weight, and $\bar{v}$ is the partial specific volume. Equation 4 predicts an inverse cube-root relationship between the diffusion coefficient and molecular weight. Therefore, estimation of micellar molecular weight can be made by means of the following relationship:

$$(M)^{1/3}\text{micelle-drug} = \frac{(M)^{1/3}\text{drug} \cdot D}{D_m} \qquad \text{(Eq. 5)}$$

The calculations were made for each bile salt solution studied from both diffusion and dissolution data (Table III). Several studies in the literature report the micellar molecular weights of a number of bile salts (12–15). Carey and Small (16) presented a detailed study of the micellar properties of sodium taurocholate and sodium taurodeoxycholate. By using the molecular weight of each individual bile salt and the rounded-off aggregation number at 20° and 0.15 M sodium chloride concentration, it was possible to calculate the molecular weight of each bile salt micelle. An estimation of the molecular weight of the mixed micelle of the equimolar mixtures of the bile salts was obtained by multiplying the aggregation number by the mean of the bile salt molecular weights. Since the molecular weights of each bile salt are similar, little error should be involved in this estimation. The molecular weight contributed by the moles of salicylamide solubilized by each mole of bile salt was then subtracted from the experimentally measured values of micellar weights to obtain the molecular weight of micelle (Table III). As can be seen in Table III, the agreement between the literature values and those calculated from Eq. 5 is excellent.

The cube-root relationship may only be used for an estimate of colloid molecular weight under those conditions where the interaction between the colloid and the drug molecule does not interfere with the organization of the colloid. If this is the case, one can determine the molecular weight of the colloid independent of the drug molecule, which is being used strictly as a probe.

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Aminotetrahydrofuranol Derivatives

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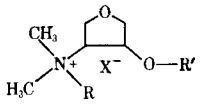
Abstract □ Some esters of 4-dimethylamino-3-tetrahydrofuranol are reported along with a methyl and benzyl quaternary ammonium salt. Compound VI possessed about one-fifth the anticholinergic activity of atropine sulfate.

Keyphrases □ 4-Dimethylamino-3-tetrahydrofuranol, esters—synthesis as possible anticholinergic agents, pharmacological evaluation □ Aminotetrahydrofuranol derivatives—synthesis, pharmacological screening as possible anticholinergic agents □ Anticholinergic agents, potential—synthesis of aminotetrahydrofuranol derivatives, pharmacological evaluation

The ethanolamine moiety is a prominent feature of most cholinergic and anticholinergic agents. The goal of this investigation was to determine whether tetrahydrofuran analogs containing a sterically restricted ethanolamine moiety would possess a greater specificity of biological activity.

Generally, 4-dimethylamino-3-tetrahydrofuranol was prepared from dimethylamine and 4-chloro-3-tetra-

Table I—Derivatives of 4-Dimethylamino-3-tetrahydrofuranol



Compound	R	R′	X	Melting Point	Yield, %	Formula	Analysis[a], % Calc.	Found
I[b]	H	CH_3CO	Cl	159–160.5°	82	$C_8H_{16}ClNO_3$	C, 45.83 H, 7.69 N, 6.68	C, 45.83 H, 7.96 N, 6.72
II[b]	CH_3	CH_3CO	Br	184.5–186°	94	$C_9H_{18}BrNO_3$	C, 40.31 H, 6.76 N, 5.22	C, 39.86 H, 6.82 N, 5.17
III[c]	$C_6H_5CH_2$	CH_3CO	Br	170–171°	76	$C_{15}H_{22}BrNO_3$	C, 52.33 H, 6.44 N, 4.07	C, 51.97 H, 6.19 N, 4.01
IV[c]	H	p-$O_2NH_6H_4CO$	Cl	188.5–190°	38	$C_{13}H_{17}ClN_2O_5$	C, 49.30 H, 5.41 N, 8.84	C, 49.38 H, 5.53 N, 8.70
V[b]	H	p-$H_2NC_6H_4CO$	Cl	180.5–182°	80	$C_{13}H_{19}ClN_2O_3$	C, 54.45 H, 6.68 N, 9.77	C, 54.59 H, 6.69 N, 9.80
VI[c]	H	Benziloyl	Cl	204–206°[d]	65[e]	$C_{20}H_{24}ClNO_4$	C, 63.57 H, 6.40 N, 3.71	C, 63.87 H, 6.46 N, 3.54

[a] Elemental analyses for C and H were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Elemental analyses for N were performed by the Analytical Department, Research Laboratories, A. H. Robins Co., Inc., Richmond, Va. [b] Recrystallized from ethanol. [c] Recrystallized from a mixture of methylethylketone and methanol. [d] Lit. (2) m.p. 186° dec. [e] The reported yield is for the free base, m.p. 78–80°.

hydrofuranol or by the method of Reppe *et al.* (1) using 3,4-epoxytetrahydrofuran. The aminoalcohol was then esterified with the appropriate reagents. Both methods of preparation are considered stereospecific routes leading to *trans*-3,4-disubstituted analogs[1].

The acetate ester was easily quaternized with methyl bromide or benzyl bromide. Unsuccessful attempts to quaternize the benzilate ester led to the respective quaternary ammonium alcohol.

None of the compounds reported in Table I exhibited cholinergic activity in the isolated guinea pig ileum screen. All the compounds showed negligible anticholinergic activity, except Compound VI which possessed about one-fifth the potency of atropine sulfate. Compound V, an analog of procaine, possessed no significant local anesthetic activity.

EXPERIMENTAL[2]

4-Dimethylamino-3-tetrahydrofuranol—A solution of dimethylamine (162 g., 3.6 moles) and 4-chloro-3-tetrahydrofuranol (116 g., 0.94 mole) in absolute ethanol (250 ml.) was heated in a steel bomb at 126° for 18 hr. The cooled solution was concentrated *in vacuo* to an oil, which was added to a 25% solution of sodium hydroxide (200 ml.). The basic solution was extracted with chloroform (2 × 100 ml.), and the combined chloroform extracts were concentrated *in vacuo*. The residue was distilled, 74.5 g. (60.5%), b.p.$_{0.6}$ 77–80° [lit. (2) b.p.$_{0.7}$ 87–88°], and used without further purification.

Esters of 4-Dimethylamino-3-tetrahydrofuranol—The benzilate ester was prepared by transesterification (2). The acetate and *p*-nitrobenzoate esters were prepared by refluxing a chloroform solution of 4-dimethylamino-3-tetrahydrofuranol and an excess of either acetic anhydride or *p*-nitrobenzoyl chloride for 2–3 hr. After a routine acid–base wash, the respective free base was converted to the hydrogen chloride salt and recrystallized.

4-Dimethylamino-3-tetrahydrofuryl *p*-aminobenzoate was prepared by hydrogenating the corresponding nitro compound in the presence of a catalytic amount of 10% palladium-on-charcoal in methanol.

Quaternary Ammonium Bromides—A solution of the appropriate amine in methylethylketone was stirred while a solution of excess bromo compound in methylethylketone was added. After the suspension was stirred at ambient temperature for several hours, the product was isolated by filtration and recrystallized.

[1] While this paper was in preparation, the paper of Nelson *et al.* (3) was published.

[2] Melting points are uncorrected. Spectral data, NMR and IR, are in agreement with the proposed structures. Carbon-hydrogen analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and nitrogen analyses were performed by Analytical Department, Research Laboratories, A. H. Robins Co., Inc., Richmond, Va.

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