Equation 11 yields Eq. IV-2 after addition of its two terms.

5. Substitution of Q for $Q(j\tau)$ in Eq. V-1 shows that the sum of its first two terms becomes identical to Eq. IV-1, except for the difference between $FX_0k_a/(Vk_a - Q)$ and X_0/V. Correspondingly, the first term in Eq. V-2 is equal to Eq. IV-2 (except for $X_0/V \neq FX_0k_a/(Vk_a - Q)$. The third term in Eq. V-1 becomes the second term in Eq. V-2 after substitution of Q for $Q(t)$.

Thus, it appears that for all of the input modes considered, the equations commonly used for the one-compartment model with constant clearance represent only particular cases of the corresponding equations involving a time-dependent clearance. This direct correspondence provides further validation of the equations proposed to describe drug levels when metabolic clearance increases exponentially.

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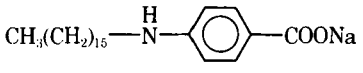
Cetaben Sodium, an Antiatherosclerotic Agent

Keyphrases □ Cetaben sodium—synthesis, antiatherosclerotic activity □ Antiatherosclerotic agents—cetaben sodium, synthesis □ Sodium 4-(hexadecylamino)benzoate—synthesis, antiatherosclerotic activity

To the Editor:

We wish to report the synthesis of cetaben sodium [sodium 4-(hexadecylamino)benzoate], a substance that shows promise as an antiatherosclerotic agent.

Ethyl 4-(hexadecylamino)benzoate (mp 85–86°) was prepared (yield 65–85%) from hexadecyl bromide or mesylate and 2 moles of ethyl 4-aminobenzoate at 135° in hexamethylphosphoric amide. Of the liquid amides, hexamethylphosphoric amide was the best reaction solvent (faster rate and fewer by-products); however, some dialkylation did occur. With dimethylformamide or *N,N*-dimethylacetamide at 135–150° as solvents, *N*-formyl and *N*-acetyl products were obtained as well as some 4-(hexadecylamino)-*N,N*-dimethylbenzamide by-product. Among various alternative synthetic methods, the diborane reduction of ethyl 4-(hexadecanoylamino)benzoate gave ethyl 4-(hexadecylamino)benzoate in good yield and can be used for preparing various isomers and analogs.



cetaben sodium

Cetaben sodium can be obtained directly from the quantitative alkaline hydrolysis of the ester but is generally prepared from 4-(hexadecylamino)benzoic acid (double mp 108–110 and 126–128°) since the latter is more easily purified. This salt, which is moderately soluble (about 2%) in 75% alcohol, is crystallized from a solution of the acid and a slight sodium hydroxide excess in aqueous ethanol in 95% yield.

The 4-(alkylamino)benzoic acids (1) are substantially less toxic and more hypolipidemic than the 4-alkoxybenzoic acids (2, 3) and 4-alkylbenzoic acids (3). Extensive studies have elucidated the structure–activity relationships in the aminobenzoic acid series, which are different from those in the alkoxybenzoic acids. The tabulated data show the hypolipidemic activity of representative aminobenzoic acids as well as of clofibrate under the same test conditions (Table I). The hypocholesterolemic activity falls off as the alkyl chain is increased to 20 or decreased to eight carbon atoms (1). However, the hypotriglyceridemic activity is relatively unaffected by the alkyl chain length. Cetaben is also the most effective member of the series in inhibiting ^{14}C-acetate and ^{3}H-glycerol incorporation into liver triglycerides, phospholipids, and cholesterol in rats. It is not esterogenic, and its hypocholesterolemic mechanism of action does not involve inhibition of a late stage in cholesterol biosynthesis. Hypocholesterolemic activity has been demonstrated also in the rabbit and monkey.

The considerable therapeutic potential of cetaben is suggested by its activity in two experimental atherosclerosis models in laboratory animals. First, cetaben sodium was shown to possess antiatherosclerotic activity in a rabbit model (4). Average reductions of 32–73% in the incidence of atherosclerotic lesions and of 24–28% in abdominal aortic cholesterol accumulation were observed in treated animals at doses below those that were hypolipidemic[1]. The reductions in aortic cholesterol were essentially all due to the decreases in cholesterol ester.

Second, Hollander *et al.* (5) reported on the antiatherosclerotic activity of cetaben sodium in the cynomolgus monkey. Serum cholesterol concentrations were reduced by 37% in the treated animals as compared to controls fed the atherogenic diet alone. This change was reflected in an altered lipoprotein distribution with decreases in very low density lipoproteins (by 30%) and low density lipoproteins (by 38%) but an increase in high density lipoproteins (by 96%). Such a shift in lipoprotein concentrations in humans is considered to be antiatherogenic (6, 7). Antiatherosclerotic activity was manifested by changes in the disease incidence and severity as well as in the chemical composition of the lesions present in the drug-treated monkeys.

[1] A. S. Katocs, Jr., and S. A. Schaffer, unpublished results.

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Table I—Hypolipidemic Effect of 4-(*n*-Alkylamino)benzoic Acids and Clofibrate in Normal Rats

n-Alkyl Group	Oral Dose in Diet[a], mg/kg/day	Percent Lowering[b] of Serum	
		Sterol	Triglyceride
C_{12}	86	11[c]	68[d]
	47	20[e]	60[d]
	25	14[f]	49[d]
C_{14}	82	9	47[d]
	46	9	49[d]
	23	9	36[d]
C_{16} (cetaben)	89	44[d]	69[d]
	64	30[d]	48[f]
	42	26[d]	40[f]
	22	27[d]	38[f]
	10	27[d]	29[d]
C_{18}	91	18[g]	40[e]
	48	6	28[c]
	23	14[f]	29[c]
Clofibrate	375	26[d]	43[c]
	106	5	30
	33	0	32

[a] The method used was described in detail in Ref. 2. Oral dosing was by normal rat chow containing drug; 0.05% in the diet corresponds to a measured average daily dosage of 46 mg/kg, *etc.* [b] Percent lowering of the mean serum concentrations relative to the mean values in control animals in the same test; control groups averaged 75 ± 3 mg % sterol and 85 ± 6 mg % triglyceride. The significant level (p), determined by the Student t test, is denoted by the appropriate footnote. Numbers without a footnote are not statistically significant lowerings. [c] $p < 0.05$. [d] $p < 0.001$. [e] $p < 0.005$. [f] $p < 0.02$. [g] $p < 0.01$.

Most important was the presence of only half as much luminal narrowing in four major coronary arteries (5). Accompanying this effect on lumen size were increases in myocardial blood flow in the nonstressed and stressed heart. In the stressed heart, regional blood flow toward the endocardium was improved as well. Reductions in luminal narrowing and incidence of atherosclerotic lesions also were seen in several major peripheral arteries. In the aortas of treated monkeys, average 48% reductions in cholesterol accumulation resulted predominantly from decreases in esterified cholesterol. Additionally, there was complete prevention of a 2.5-fold calcium increase in the aortic wall and a 70% inhibition of the increase in aortic fibrous connective tissue. Up to now, such pronounced therapeutic effects on this atherosclerosis model (5, 8, 9) have not been reported with any other drug.

The reduced cholesterol ester content in the rabbit and monkey aortas may result from cetaben inhibition of the cholesterol-esterifying enzyme in the aortic wall. With a cell-free preparation of fatty acyl-CoA: cholesterol acyl transferase (ACAT) from rabbit aortas, cetaben sodium substantially inhibited the enzyme at therapeutically obtainable concentrations[1] (~5 μg/ml). This effect is especially significant in view of the greater proportion of esterified to free cholesterol in atheromatous lesions in humans (10) as well as the lower experimental reversibility of ester deposition in rabbits (11).

In a series of papers, we shall fully report on the biological activity described here and elaborate the structure–activity relationships of alkyl size; branching, cyclization, substitution, and unsaturation of the alkyl group; further substitution of the amino nitrogen and its position isomers; additional substitution on the benzene ring and its replacement with other rings; and carboxyl group derivatization, modification, and extension.

Effective atherosclerosis therapy probably will require drugs that have several modes of action such as those displayed by cetaben sodium. Cetaben sodium is now undergoing clinical trials as an antiatherosclerotic agent in humans.

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pKa of 2-Methylamino-5-chlorobenzophenone, a Diazepam Hydrolysis Product

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To the Editor:

The compound 2-methylamino-5-chlorobenzophenone (I) is the aromatic product of diazepam (II) hydrolysis in acidic aqueous solution (1). It was of interest to estimate the pKa of I because of its importance in kinetic stability and analytical studies of prazepam (2) and II (1, 3–8).

The pKa of I[1] was determined spectrophotometrically[2] at 25° at 415 nm in a concentration of 4.07×10^{-5} *M* (10 μg/ml). All samples contained 7% (v/v) ethanol. The pH was varied by preparing samples in 0.02–0.40 *N* HCl. The spectrum of the conjugate acid was obtained in 60% (w/w) H_2SO_4 ($H_0 = -4.4$), and that of the nonionized base was obtained in buffers of pH 7.20 and 9.23. The conjugate acid species showed no absorbance at 415 nm, and the base had an absorbance of 0.23. The other spectral characteristics included decreasing absorbance at 410–420 nm and a hypsochromic shift from ~268 to 238 nm with increasing

[1] Ro 5-4365, lot PP-4 Hoffmann-La Roche, Nutley, N.J.
[2] Beckman DB-GT grating spectrophotometer, Beckman Instruments, Fullerton, Calif.

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