Boron Trifluoride Ethyl Ether as an Effective Catalyst in the Synthesis of Alkyl *p*-Aminobenzoates

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Abstract □ Commercial boron trifluoride ethyl ether functions as an effective catalyst in the synthesis of a number of alkyl esters of *p*-aminobenzoic acid. Unlike earlier procedures, the present method offers a convenient single step reaction and does not call for special reaction conditions and equipment.

Keyphrases □ *p*-Aminobenzoic acid alkyl esters—synthesis □ Boron trifluoride-ethyl ether, catalyst—*p*-aminobenzoic acid alkyl esters

In the course of the authors' studies on potential local anesthetic agents (1), it became necessary to prepare a number of alkyl esters of *p*-aminobenzoic acid (PABA). A literature survey indicated that in practice, the preparation of PABA esters is usually accomplished by reduction of the previously esterified 4-nitro compounds. The 4-nitrobenzoic esters have been obtained in the conventional manner by reaction of 4-nitrobenzoyl chloride and the appropriate alcohol in a basic medium (2–6). Reduction to the *p*-aminobenzoates has been achieved generally by catalytic hydrogenation using platinum oxide or Raney nickel (3, 6), or palladium (4, 5) as catalyst, or occasionally using other reducing agents such as ferrous sulfate–ammonia (6) or tin and hydrochloric acid (2).

Though some attempts have been made at direct esterification of PABA, a general method of esterification for the different alkyl esters has not been formulated. The ethyl ester has been obtained using anhydrous ethanol and dry hydrogen chloride (7), and boron trifluoride-methanol reagent has been found to be quite suitable in the preparation of the methyl ester (8). Boron trifluoride-ethyl ether has also been found to give satisfactory results in the preparation of the methyl ester (9), though in low yield; however, with this exception, the possibility of using commercial boron trifluoride-ethyl ether as an effective catalyst in the synthesis of alkyl esters of PABA, in general, has not been investigated.

The authors have now found that good yields of the various alkyl esters of *p*-aminobenzoic acid can be obtained very conveniently in a single step by merely refluxing the acid with the appropriate alcohol in the presence of boron trifluoride-ethyl ether as catalyst. Unlike the methods outlined above, the simple procedure described here constitutes a direct and convenient method for the synthesis of alkyl *p*-aminobenzoates; it does not call for special conditions and equipment for catalytic hydrogenation or require the use of pungent hydrogen chloride gas which makes for inconvenience in handling.

Reported in Table I are a number of simple alkyl esters of *p*-amino benzoic acid. These have been characterized by their melting points and IR absorption spectra. The intact presence of the primary amino group has been established by reaction with 2,4-dichlorobenzaldehyde to yield the *N*-(2,4-dichlorobenzylidene) derivatives in very high yields (Table I).

It is evident from the results presented in Table I, that higher yields are obtained by using two equivalents of boron trifluoride-ethyl ether to one equivalent of acid in a 15-fold excess of alcohol, the additional equivalent of boron trifluoride being necessary to complex with the amino group of the acid.

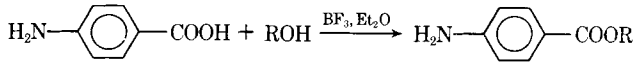

Table I—Alkyl p-Aminobenzoates,

R	Reflux Time, hr.	M.p., °C.[a] (Crude)	M.p., °C.[b] (Recrystallized)	Yield, %	Schiff Base Derivatives M.p. °C.	Schiff Base Derivatives Yield, %
Methyl	48	110–114 (114)	111–114 (E)	Quantitative[c]	165–67	91.0[d]
Ethyl	48	89–90 (90)	89–90 (E)	93	91–93[e]	84.5
	48	86–90	89–92 (E)	86[f]	—	—
	24	86–90	89–92 (E)	69[f]	—	—
	24	89–90	89–90 (E)	56[g]	—	—
n-Propyl	48	69–73 (75)	72–75 (E-H_2O)	62	73–75	91.5[h]
iso-Propyl	48	83–84 (84)	—	42.5	—	—
n-Butyl	48	55–58 (58)	57–60 (Et-Pet)	96	69–71	60.0[i]
iso-Butyl	48	63–64 (64)	63–64 (Et-Pet)	68[j]	—	—
sec-Butyl	48	53–54 (55)	53–54 (Et-Pet)	47	—	—
tert-Pentyl	48	187–188	187–188 (Et-Pet)	51[k]	—	—

[a] The melting points are for the crude products. The reported melting points for the pure products are given in parentheses. [b] The melting points are for recrystallized samples; solvent used is given in parenthesis: E, ethanol; Et, diethyl ether; Pet, petroleum ether. [c] Reference 8 has reported the preparation of the methyl ester using boron trifluoride-methanol reagent, in 75% yield. [d] *Anal.*—Calcd., %: C, 58.4; H, 3.6. Found: C, 58.3; H, 3.7. [e] *Reference* 1. [f] Using acid (Eastman, Practical grade) (0.05 mole), alcohol (0.5 mole), and $BF_3 \cdot Et_2O$ (0.075 mole). [g] Using acid (0.05 mole), alcohol (0.5 mole) and $BF_3 \cdot Et_2O$ (0.1 mole). [h] *Anal.*—Calcd., %: C, 60.7; H, 4.5. Found: C, 60.6; H, 4.5. [i] *Anal.*—Calcd., %: C, 62.3; H, 4.9. Found: C, 62.3; H, 4.8. [j] The product separated out as an oil and was extracted with ether and the ethereal solution was treated with petroleum ether, when crystallization was effected. [k] The excess alcohol was decanted off from the insoluble boron trifluoride-*tert*-pentyl ester complex, and the latter dissolved in water. Upon addition of sodium carbonate, there was effervescence followed by separation of the solid ester.

EXPERIMENTAL

Alkyl p-aminobenzoates—To a suspension of *p*-aminobenzoic acid (Eastman, White label) (6.9 g., 0.05 mole) in the appropriate alcohol (reagent grade) (40 ml., ~ 0.75 mole) was added boron trifluoride-ethyl ether (Eastman, White label) (12.6 ml., 0.1 mole) and the reaction mixture refluxed for 48 hr. The esters were precipitated by pouring the cooled, filtered solutions into an ice cold solution of sodium carbonate (5%, 400 ml.); these were sufficiently pure for most purposes and recrystallization increased the melting points only slightly (Table I). The compounds exhibited IR absorption frequencies characteristic of the C=O and NH_2 groups.

The methyl, *n*-propyl, and *n*-butyl esters were prepared using acid (Eastman, Practical grade) (0.05 mole), alcohol (0.5 mole), and boron trifluoride-ethyl ether (0.075 mole).

Under either experimental condition, when the reaction time was reduced to 24 hr. the yield was also reduced.

An attempt to prepare the methyl ester using diazomethane, yielded products with wide melting point ranges. Apparently, the diazomethane effects some *N*-methylation, giving rise to a mixture of products.

N-(2,4-Dichlorobenzylidene)-p-aminobenzoates—The Schiff base derivatives were prepared (1) by heating equimolar quantities of the *p*-aminobenzoic ester and the aldehyde in an ethanol solution (Table I).

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Inhibitors of Monoamine Oxidase V: Effect of Substitution on the Transport of Tetrahydro-β-Carboline Analogs to Mouse Brain

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Abstract □ Methyl substitution on the indolic nitrogen and halogen substitution on the indole nucleus of tetrahydro-β-carbolines were found to facilitate the transport of compounds into the brain. A correlation between the brain accumulation, the pKa, and the partition coefficient has been made. The 8-chloro-9-methyl-1,2,3,4-tetrahydro-β-carboline was assayed with mitochondrial monoamine oxidase from mouse brain and liver. Its inhibitory activity was two-fold greater than that reported using bovine liver enzyme.

Keyphrases □ Monoamine oxidase inhibitors—tetrahydro-β-carboline analogs, ^{14}C-labeled □ Tetrahydro-β-carboline analogs—substitution effect □ Transport, mouse brain—tetrahydro-β-carboline substitution effect

A number of substituted tetrahydro-β-carbolines have been found to be potent inhibitors of monoamine oxidase (MAO) *in vitro* (1–3). Methyl substitution on the position N-9, the indolic nitrogen, in most cases, enhanced the inhibitory activity *in vitro*. For instance, 9-methyltetrahydro-β-carboline (I) is a 34-fold better inhibitor than tetrahydro-β-carboline (II) (1), and 8-chloro-9-methyltetrahydro-β-carboline (III) is nearly 100-fold better than II (3). It was of interest to determine whether the methyl group could increase the lipid solubility of the tetrahydro-β-carboline and thus facilitate its entry into the brain. Furthermore, from previous metabolic studies, 1-methyltetrahydro-β-carboline (IV) was found to have undergone hydroxylation forming 6-hydroxy-1-methyltetrahydro-β-carboline (V) and 7-hydroxy-1-methyltetrahydro-β-carboline (VI) (4), see Scheme I. Halogen substitution on the C-6 (see VII) or C-8 (see III) position might retard 6- or 7-hydroxylation of the tetrahydro-β-carboline, and possibly prolong the biological action.

The object of this study was to demonstrate the enhancement of brain absorption of tetrahydro-β-carbolines by the introduction of a methyl group to the indolic nitrogen and the additional effect when halogen substitution was placed on the indole ring. A correlation of brain accumulation of the four analogs of tetrahydro-β-carboline (I, II, III, and VII) with the partition coefficient and the pKa was also made. This finding would