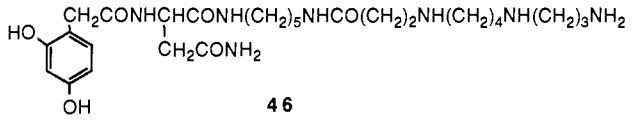
and found to have effects on glutamatergic receptors, particularly those of invertebrates.[149] Examples include the Joro spider toxin (46)[150] from *Nephila clavata* and the argiotoxins (47)[151] from the orb-web spider, *Argiope fasciata*. Both of these toxins contain the (2,4-dihydroxyphenylacetyl)asparagine moiety within their structures and act as noncompetitive glutamic acid receptor inhibitors, possibly by blocking the open cation channels.[151-153] These toxins as well as others that have been isolated, but have yet to be characterized, have the potential to serve as valuable pharmacological tools in the study of excitatory amino acid neurotransmission.



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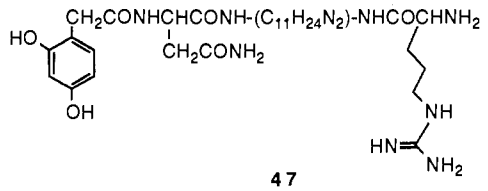

47

Acknowledgment. We acknowledge the support of the National Institutes of Health through Grants NS17944 and NS23935.

(149) Shinazaki, H. *Prog. Neurobiol.* **1988**, *30*, 399.
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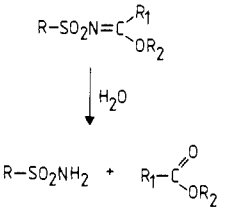
Communications to the Editor

N-Sulfonyl Imidates as a Novel Prodrug Form for an Ester Function or a Sulfonamide Group

Sir:

In recent years, chemical transformation of drug substances into per se inactive derivatives (prodrugs) that convert to the parent compounds by virtue of enzymic or chemical lability within the body system has become a useful approach to improve drug delivery.[1-3] A basal requisite for this prodrug approach is the ready availability of chemical derivative types satisfying the prodrug requirements, the most prominent of these being reconversion of the prodrug to the parent drug in vivo. Although several types of bioreversible derivatives have been exploited for utilization in designing prodrugs of various functional groups or chemical entities occurring in a variety of drug molecules,[4,5] no bioreversible derivatives for the ester group have been explored. In contrast, esters are probably the best known prodrug derivatives for drugs containing carboxyl or hydroxyl groups because of the ready availability of enzymes in the organism capable of hydrolyzing most esters.[3,4] However, numerous drugs contain an ester group as an essential part of their structure, e.g. various calcium antagonists like nifedipine and nicardipine, steroid derivatives, and anticholinergic agents. To solve delivery problems associated with some of such drugs due to e.g. unfavorable solubility and lipophilicity characteristics or extensive first-pass metabolism, by the prodrug concept, the availability of a prodrug type for the ester functionality is desirable. In this paper we report that *N*-sulfonyl imidate esters may be a prodrug type for drugs containing an ester function. In addition, the derivatives may serve as prodrug forms for primary sulfonamides (Scheme I).

Scheme I



A series of *N*-sulfonyl imidate esters (**1-19**) (Table I) were synthesized, by reacting *p*-toluenesulfonamide, used as a model sulfonamide, with the appropriate ortho ester (compounds **1-6**) or orthocarbonate ester (**18**, **19**) according to literature methods,[6] or by reacting *N*-(*p*-tolylsulfonyl)benzimidoyl chloride, obtained from *p*-toluenesulfonamide and phenyltrichloromethane as described previously,[7] with the appropriate alcohol (compounds **7-12**), phenol (**13**), or amino alcohol (**14-17**) in acetone solutions in the presence (**7-13**)[8] or absence (**14-17**) of pyridine.[9] Compounds **14-17** were isolated as water-

(1) Bundgaard, H., Ed. *Design of Prodrugs*; Elsevier: Amsterdam, 1985.
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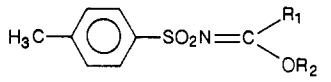
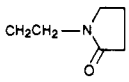
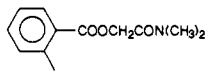
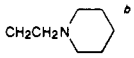
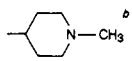
Table I. Properties of Various *N*-Sulfonyl Imidate Esters



compd	R_1	R_2	mp, °C	$t_{1/2}$,[a] min pH 6.0	pH 7.4	80% human[d] plasma
1	H	C_2H_5	51–53	1.2	0.8	<1
2	CH_3	CH_3	74–75	150	83	8.1
3	C_3H_7	CH_3	42–44	-	145	32
4	C_4H_9	CH_3	~25	-	160	28
5	CH_3	C_2H_5	52–53	175	144	6.4
6	C_2H_5	C_2H_5	43–44	-	108	24
7	C_6H_5	CH_3	123–124	-	114	7.0
8	C_6H_5	C_2H_5	74–75	220	175	23
9	C_6H_5	C_3H_7	86–87	-	175	20
10	C_6H_5	i-C_3H_7	73–74	1380	1045	195
11	C_6H_5	$CH_2CON(CH_3)_2$	166–167	-	144	2.0
12	C_6H_5		106–107	-	75	4.8
13	C_6H_5		164–165	93	91	0.6
14	C_6H_5	$CH_2CH_2N(CH_3)_2$[b]	144–145	35[c]	2.7	<1
15	C_6H_5	$CH_2CH_2CH_2N(CH_3)_2$[b]	156–157	53[c]	11	4
16	C_6H_5		134–135	35[c]	1.3	<1
17	C_6H_5		165–167	90	89	36
18	OCH_3	CH_3	149–152	870	255	32
19	OC_2H_5	C_2H_5	70–71	4.4×10^3	1580	78

[a] Half-lives of hydrolysis at 37 °C. [b] HCl salt. [c] At pH 4.0 (pH minimum of hydrolysis). [d] Human plasma diluted to 80% with 0.01 M phosphate buffer of pH 7.40.

soluble HCl salts.

The kinetics of decomposition of the *N*-sulfonyl imidate esters was determined in aqueous buffer solutions of various pH values as well as in freshly prepared human plasma solutions at 37 °C. The rates of hydrolysis were followed by reversed-phase HPLC methods[10] capable of separating the imidate esters and their products of hydrolysis. At constant pH and temperature the reactions followed strict first-order kinetics over several half-lives. Except for compounds **18** and **19** the sulfonyl imidates can exist as *Z* or *E* isomers. The exact configuration of the compounds is not known. The good linear first-order kinetics observed indicate, however, that if a compound is a mixture of *Z* and *E* isomers, the reactivity of these does not differ significantly.

The pH–rate profiles for all the derivatives studied were U-shaped as illustrated in Figure 1, indicating the occurrence of specific acid and base catalysis as well as a water-catalyzed reaction. Maximal stability was generally achieved at pH 5–6. The half-lives of hydrolysis at pH 6 and 7.4 are listed in Table I along with the half-lives of decomposition in 80% human plasma solutions. As it appears from the rate data obtained, hydrolytic enzymes in plasma markedly accelerate the rate of hydrolysis.

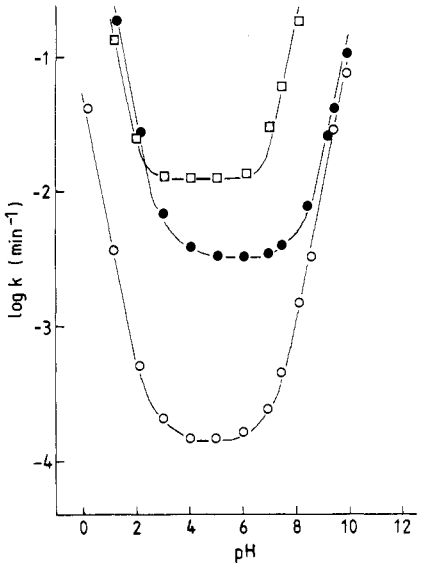


Figure 1. The pH–rate profiles for the hydrolysis of the *N*-sulfonyl imidate esters **8** (●), **15** (□), and **19** (○) in aqueous solution (μ = 0.5) at 37 °C.

As is the case for carboxylic acid esters, electronic and steric effects within the substituents R_1 and R_2 influence the rate of hydrolysis. Thus, the sterically hindered isopropyl group in **10** is seen to decrease the rate of hydrolysis as well as the ease of enzymatic hydrolysis. The formimidate ester **1** is more reactive than the corresponding alkyl imidates **5** and **6**, which is analogous to the behaviour of formate esters relative to alkyl esters. The water-soluble sulfonyl imidate esters derived from amino alcohols (**14**–**17**) are more reactive than the other esters, which most likely is due to intramolecular assistance by the amino function in analogy with the hydrolysis of carboxylic acid esters of

(9) Spectral and elemental analysis of all the compounds were consistent with their structures. Compounds **3**, **4**, **6**, **11**–**17**, and **19** have not been described before. The remaining compounds are described in ref 6–8. The melting points observed (Table I) were in good agreement with those reported.

(10) A Chromosphere C 18 column (100 × 3 mm) was eluted with mixtures of 0.01 M acetate, pH 4.5, and methanol or acetonitrile. The column effluent was monitored at 215 nm. The kinetic runs were initiated by adding 100 μL of freshly prepared stock solutions of the compounds in acetonitrile or water (compounds **14**–**17**) to 10 mL of preheated buffer solutions to give initial concentrations of about 10^{-4} M.

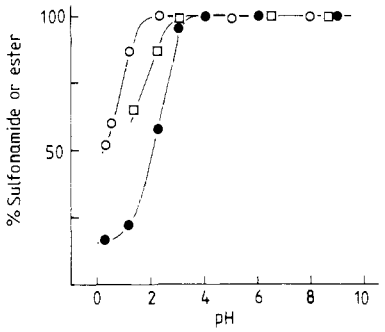
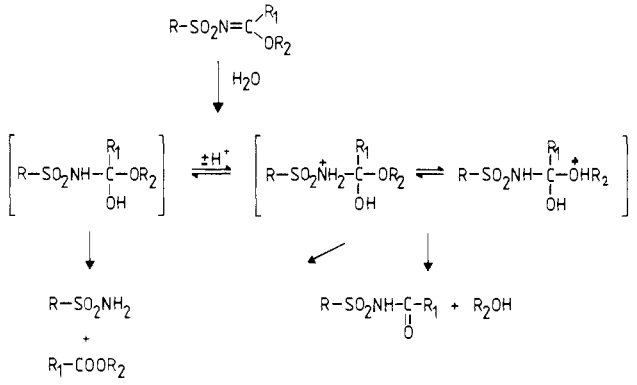


Figure 2. The effect of pH on the yield of *p*-toluenesulfonamide or ester formed upon hydrolysis of the *N*-sulfonyl imidate esters 8 (●), 14 (○), and 15 (□) in aqueous solution at 37 °C.

Scheme II



similar amino alcohols.[11] In **17** the amino function is placed in a position that makes it unable to exhibit intramolecular catalysis, and its stability is somewhat higher than that of the imidates **14–16**.

The identity of the products formed upon hydrolysis of compounds **1–19** was verified by HPLC analysis by comparison with *p*-toluenesulfonamide and the corresponding *N*-acyl-*p*-toluenesulfonamides[12] and esters. In agreement with earlier findings reported[13] for the hydrolysis of compound **2**, the product distribution varied with pH of solution (Figure 2). At pH <3–4 the compounds degraded to yield a mixture of *p*-toluenesulfonamide and *N*-acyl-*p*-toluenesulfonamide whereas at pH >4 the hydrolysis was found to proceed with the quantitative formation of *p*-toluenesulfonamide and the corresponding ester except for compound **13** (Scheme II). The same was observed for the plasma-catalyzed hydrolysis, which in fact is of essential importance for the consideration of sulfonyl imidate esters as prodrugs for carboxylic acid esters. In the case of compounds **18** and **19** the products of hydrolysis at pH 4–8 as well as in plasma solutions were shown to be *p*-toluenesulfonamide and the corresponding dialkyl carbonate esters. The sulfonyl imidate ester **13** derived from a phenol, i.e. the *N,N*-dimethylglycolamide ester of salicylic acid, differed from the other imidate esters derived from alcohols by hydrolyzing exclusively to *N*-benzoyl-*p*-toluenesulfonamide and the parent phenol in neutral and alkaline solutions a well as in the presence of plasma. This differential behavior may be ascribed to the better leaving ability of a phenol as compared with that of an alcohol. A similar route of degradation was observed for the *p*-toluenesulfonyl imidate ester derived from phenol (R_1 = R_2 = C_6H_5).[8]

According to previous investigations[13,14] on the hydrolysis of imidate esters, the degradation proceeds through rate-limiting formation of tetrahedral addition intermediates in acid–base equilibrium (Scheme II). At low pH the protonated intermediate decomposes mainly by expulsion of R_2OH with the formation of the stable *N*-acyl sulfonamide whereas at higher pH values the neutral intermediate expels *p*-toluenesulfonamide anion (pK_a = 10.2)[15] in preference to alkoxide ion (pK_a = 15–16).[16] When the acidity of R_2OH becomes equal to or greater than that of the sulfonamide as in the case of phenols (pK_a = 9–10), the reverse expulsion may become favored. Accordingly, a sulfonyl imidate ester may expectedly serve as a prodrug for a phenolate ester if a sulfonamide with a pK_a lower than that of the phenol is selected. For compound **13**, this requirement is not met and no ester is formed upon its hydrolysis as described above.

Besides being considered as a possible prodrug type for carboxylic acid or carbonate esters, *N*-sulfonyl imidates can also be thought of as a prodrug type for sulfonamides, in which case the ester component would act as the promoiety. As discussed in a previous paper,[12] surprisingly few useful bioreversible derivatives for the sulfonamide group have been explored, although several drugs contain such a group as the only distinct functionality amenable to derivatization, e.g. carboanhydrase inhibitors such as acetazolamide and ethoxzolamide. A potential objective for making a sulfonyl imidate ester prodrug of the latter may be to obtain a derivative with more favorable solubility or lipophilicity characteristics in order to get the compounds absorbed through the cornea for topical treatment of glaucoma.[12] It is also of interest to note that since compounds derived from phenols like **13** hydrolyze to yield the parent phenol in quantitative amounts, such sulfonyl imidate esters may serve as prodrugs of phenols.

In conclusion, *N*-sulfonyl imidate esters are shown to be a potentially useful prodrug type for carboxylic acid esters derived from aliphatic alcohols as well as for drugs containing a primary sulfonamide group. The imidate esters are rapidly hydrolyzed by plasma enzymes to yield a sulfonamide and ester in quantitative amounts. By varying the sulfonyl or ester portions of the derivatives it should be readily possible to control such physicochemical properties as water solubility and lipophilicity. Studies are in progress to delineate the structural factors within the sulfonyl part influencing these properties as well as the chemical stability and enzymatic lability with the purpose of expanding the potential application of sulfonyl imidate esters as a prodrug type for carboxylic acid esters.

Registry No. 1, 40597-41-9; **2**, 40412-03-1; **3**, 38383-80-1; **4**, 115561-72-3; **5**, 2881-15-4; **6**, 54819-57-7; **7**, 22158-84-5; **8**, 22158-85-6; **9**, 22158-86-7; **10**, 22158-87-8; 11, 115561-73-4; **12**, 115561-74-5; **13**, 115561-75-6; **14**, 115561-76-7; **15**, 115561-77-8; **16**, 115561-78-9; **17**, 115561-79-0; 18, 13063-51-9; **19**, 18093-19-1; $HOCH_2CON(CH_3)_2$, 14658-93-6; HO-*o*-$C_6H_4COOCH_2CON(CH_3)_2$, 114665-08-6; $HO(CH_2)_2N(CH_3)_2$, 108-01-0; $HO(CH_2)_3N(CH_3)_2$, 3179-63-3; *p*-toluenesulfonamide, 70-55-3; *N*-(*p*-tolylsulfonyl)-

(11) Hansen, B. *Acta Chem. Scand.* **1962**, *10*, 1927–1935. Ågren, A.; Hedsten, U.; Jonsson, B. *Acta Chem. Scand.* **1961**, *15*, 1532–1544. Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* **1966**, *20*, 1451–1455. Bruice, P. Y.; Mautner, H. G. *J. Am. Chem. Soc.* **1973**, *95*, 1582–1586.
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(15) Willi, A. V. *Helv. Chim. Acta* **1956**, *39*, 46–53.
(16) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798.

benzimidoyl chloride, 4513-27-3; 2-(2-oxopyrrolidinyl)ethanol, 3445-11-2; 2-piperidinylethanol, 3040-44-6; 1-methyl-4-piperidinol, 106-52-5.

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Received March 21, 1988

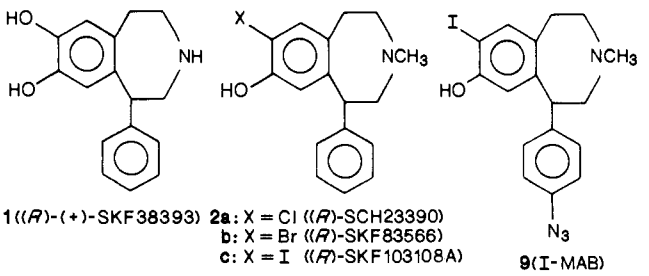
A Photoaffinity Label for the D-1 Dopamine Receptor, (*RS*)-7-[^{125}I]Iodo-8-hydroxy-3-methyl-1-(4′-azidophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine, Selectively Identifies the Ligand Binding Subunits of the Receptor

Sir:

Dopamine is a well-recognized neurotransmitter in the CNS as well as at some peripheral sites. Kebabian and Calne[1] proposed the classification of dopamine receptors into two categories: the D-1 and D-2 receptors. While the D-2 receptor has been studied extensively at both the pharmacological and molecular level,[2-5] the same is not true for the D-1 receptor owing, in large part, to the limited availability of potent, biospecific, and selective compounds. With the development of azidoclebopride[6] and azido-NAPS[7] as photoaffinity labels for the D-2 receptor, the need arose for similar photoaffinity labels to identify the ligand binding subunits of the D-1 receptor.

The benzazepines provide the most useful selective pharmacological probes of the D-1 receptor.[8] SKF 38393 (**1**) is the most widely used selective D-1 receptor agonist.[9] The benzazepines also provide the only examples of currently available selective antagonists of the D-1 receptor.[10] Several 7-halogenated N-methylated analogues of SKF 38393 have been shown to be potent, selective, stereospecific antagonists of the D-1 DA receptor. The chloro (**2a**, SCH 23390), bromo (**2b**, SKF 83566), and iodo (**2c**, SKF 103108A) analogues are all highly potent and selective with the activity residing in the *R*-(+) enantiomer. (*R*)-(+)-SKF 103108A ((*R*)-(+)SCH 23982) has been radiolabeled with high specific activity and is now the radioligand of choice for identifying the D-1 receptor.[11]

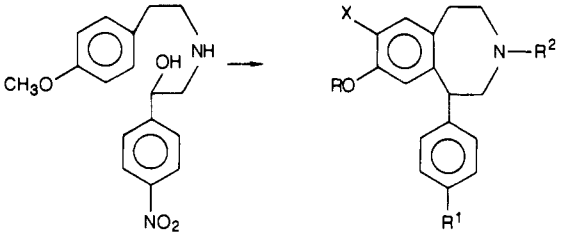
A retrospective structure–activity relationship (SAR) study of benzazepine agonists and antagonists indicated that the 1-phenyl ring could serve as the target for introduction of the amino and subsequently the azido functions for the development of a photoaffinity label. While this



1((*R*)-(+)-SKF38393) **2a**: X = Cl ((*R*)-SCH23390)
b: X = Br ((*R*)-SKF83566)
c: X = I ((*R*)-SKF103108A)

Figure 1.

Scheme I



3

4: X = H; R = CH_3; R^1 = NO_2; R^2 = H
5: X = H; R = CH_3; R^1 = NO_2; R^2 = CH_3
6: X = H; R = CH_3; R^1 = NH_2; R^2 = CH_3
7: X = H; R = H; R^1 = NH_2; R^2 = CH_3
8: X = H; R = H; R^1 = N_3; R^2 = CH_3(MAB)

study was in progress, Caron et al.[12] reported an iodinated 3-aminophenyl derivative of SCH 23390 for use in the identification of the ligand binding subunit of rat striatal D-1 receptors (M_r = 72000) via photoaffinity cross-linking with *N*-succinimidyl 6-[(4-azido-2-nitrophenyl)amino]-hexanoate (SANPAH). Since it is advantageous to have a radioactive photoaffinity label, racemic SKF 103108A was chosen for the introduction of the amino and subsequently the azido functions. A synthetic route was devised that could provide a photoaffinity label of high specific activity by permitting iodination and hence radioiodination at the terminal step.

The general synthetic route established by Walter and Chang[13] for the construction of the 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine skeleton was employed for the synthesis of the target compound. *p*-Nitrostyrene oxide was made by the method of Rafizadeh and Yates[14] in a one-pot synthesis starting from *p*-nitrobenzaldehyde. Condensation with 4-methoxyphenethylamine gave α-[[*N*-(4-methoxyphenyl)ethylamino]methyl]-4-nitrobenzyl alcohol (**3**) (mp 120–122 °C; 42% yield; $C_{17}H_{20}N_2O_4$: C, H, N). Attempted cyclization of **3** employing the standard sulfuric acid–TFA system failed in this case owing persumably to the destabilization of the incipient carbonium ion intermediate by the 4-nitro group. Cyclization with PPA proved successful and the required 8-methoxy-1-(4′-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**4**) (mp 132–134 °C; 78% yield; $C_{17}H_{18}N_2O_3$: C, H, N) was obtained. N-Methylation of **4** was carried out by the standard Eschweiler–Clarke procedure[15] to obtain **5** (mp 116–118 °C; 84% yield; $C_{18}H_{20}N_2O_3$: C, H, N). This was reduced with Raney Ni and hydrazine hydrate in ethanol to yield **6** (mp 190–192 °C; 92% yield), which was subjected to O-demethylation with boron tribromide to **7** (mp 230–232 °C; 55% yield; $C_{17}H_{20}N_2O{\cdot}2CH_3SO_3H{\cdot}2H_2O$: C, H, N; *m/z* 268 ($M^+$)). Diazotization of **7** with sodium nitrite in 6 N sulfuric acid at 0 °C yielded the diazonium

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