Synthesis and Pharmacological Evaluation of Some 3-Substituted Octahydropyrido[2,1-c][1,4]oxazines

Thomas N. Riley* and Gary O. Rankin

Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, Mississippi 38677.
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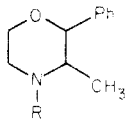
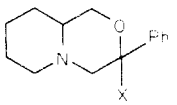
3-Phenyloctahydropyrido[2,1-c][1,4]oxazine hydrochloride and the 10*R* and 10*S* diastereomers have been synthesized from (±)-, (+)-, and (−)-2-piperidinemethanol. Treatment of 2-piperidinemethanol with α-bromoacetophenone gave 3-hydroxy-3-phenyloctahydropyrido[2,1-c][1,4]oxazine which was readily converted to the 3-phenyl derivative by catalytic hydrogenolysis. These compounds were shown to possess a depressant action on the CNS which was quantitated in terms of reduction of locomotor activity in mice. Qualitative differences were noted in the central effects of the 3-phenyl compound and its hemiketal derivative. Further, qualitative differences in the effects of the diastereomers of the 3-phenyl compound on locomotor activity of mice were also noted. The results of this study suggest that the octahydropyrido[2,1-c][1,4]oxazine system may provide a useful molecular framework for the construction of agents exhibiting pharmacologically useful actions in the CNS.

The β-arylethanolamine moiety is a structural unit common to numerous pharmacologically active agents, particularly those agents that affect the central nervous system.[1-3] Appropriate structural modification of this moiety can confer either central stimulatory or central inhibitory action on the resultant molecule. Of particular interest to this report is the incorporation of the β-arylethanolamine moiety into the cyclic morpholine system.[4] This structural modification results in a partial rigidification of the β-arylethanolamine moiety facilitating a study of the stereochemical factors involved in the pharmacological actions of β-arylethanolamine derivatives. In addition, it would appear that such a structural modification might also confer greater selectivity of action on CNS-active β-arylethanolamines as typified by the morpholine derivatives, phenmetrazine (**1a**) and phendimetrazine (**1b**), that are claimed to possess fewer peripheral adrenergic effects as compared to amphetamine in relation to their central anorexic actions.[5-7]



1a, R = H
b, R = CH_3

The present study describes the results of incorporating the β-phenethanolamine moiety into the octahydropyrido[2,1-c][1,4]oxazine system. The resulting bicyclic compound, 3-phenyloctahydropyrido[2,1-c][1,4]oxazine (**2a**), could conceivably offer advantages as compared to the morpholine derivatives as a result of increased lipophilic character and also because the bicyclic system provides a conformationally restrained framework for the β-phenethanolamine moiety that could confer greater selectivity of CNS action on the compound. Hence, the present study deals with an initial investigation of the CNS actions of **2a** and two diastereomers of **2a** in which the C-10 epimers were obtained. The importance of configurational isomerism in the action of β-arylethanolamines in the CNS is typified by the stereoselectivity of action of the diastereomers of **1a** and **1b**.[8] In the course of synthesis of **2a** the hemiketal derivative **2b** was obtained and subjected to pharmacological evaluation.



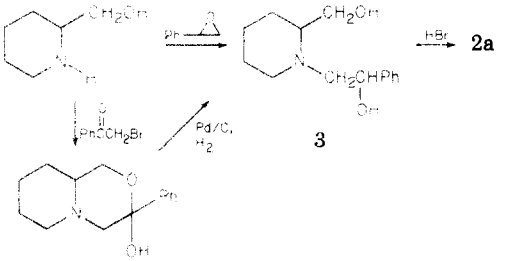
2a, X = H
b, X = OH

Synthesis. The synthesis of octahydropyrido[2,1-c][1,4]oxazine has been described by Rink and Eich.[9,10] Winterfeld and Geschonke have prepared **2a** by treatment of 2-piperidinemethanol with ethyl phenylchloroacetate followed by hydride reduction of the lactam.[11] Since future studies required the preparation of variously substituted 3-aryl analogs of **2a**, the authors have chosen the following synthetic scheme for the preparation of the desired compounds (Table I).

Table 1. Racemic and Diastereomeric 3-Phenyloctahydropyrido[2,1-c][1,4]oxazines and 3-Hydroxy-3-phenyloctahydropyrido[2,1-c][1,4]oxazine

Compd	Mp, °C[a]	Formula	Analyses
2a	212-214	$C_{14}H_{20}ClNO$	C, H, N
(3*RS*,10*R*)-2a	209-211	$C_{14}H_{20}ClNO$	C, H, N[b]
(3*RS*,10*S*)-2a	209-211	$C_{14}H_{19}NO$	C, H, N[c]
2b	166-167	$C_{14}H_{20}ClNO_2$	C, H, N

[a] HCl salts. [b] N: calcd, 5.52; found, 6.00. [c] Free amine.



2b

The C-10 epimers of **2a** were obtained by treating the enantiomers of 2-piperidinemethanol with styrene oxide followed by acid cyclization of the diol **3**. Trans fusion of the bicyclic system in **2a** is suggested by the presence of Bohlmann bands in the ir spectrum. The finding of a doublet of doublets (δ 4.65) for the benzylic proton (J = 3 and 11 Hz) provides evidence for a predominance of the equatorial phenyl isomer of **2a**. Treatment of 2-piperidinemethanol with α-bromoacetophenone provided the hemiketal **2b** as evidenced by the absence of carbonyl absorption in the infrared spectrum of the product. Further, the presence of Bohlmann bands (2700 cm^{-1}) in the ir spectrum of **2b** lends further support to a hemiketal structure as opposed to a keto alcohol product. Beckett and co-workers encountered similar results in their studies of 2-arylmorpholines and noted that a hemiketal was the sole product upon treatment of secondary amino alcohols with α-bromoacetophenone.[12] The hemiketal **2b** was readily converted to the diol **3** via reductive cleavage in acidic media.

Pharmacology. Compounds **2a** and **2b** and the C-10 epimers of **2a** were tested as the HCl salts and adminis-

Table II. Toxicity and Effect on Locomotor Activity of Racemic and Diastereomeric 3-Phenyloctahydropyrido[2,1-c][1,4]oxazine and 3-Hydroxy-3-phenyloctahydropyrido[2,1-c][1,4]oxazine

Compd	LD_{50}, mg/kg (confidence limits)[a]	Effect on locomotor act. Dose, mg/kg	% redn[b]
2a	217 (204-230)	10	25
		20	56
		40	78
(3*RS*,10*R*)-2a	223 (200-248)	10	53
		20	50
		40	49
(3*RS*,10*S*)-2a	217 (194-242)	10	7
		20	15
		40	31
2b	265 (252-278)	10	0
		20	10
		40	45
Morphine sulfate		5	28
Chlorpromazine hydrochloride		5	83

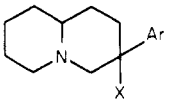
[a] Litchfield-Wilcoxon method. [b] Percent reduction in locomotor activity in mice 40 min postinjection as compared to saline control. Significance is reported at the 5% confidence level.

tered intraperitoneally in distilled water. Initial general CNS screening of these compounds indicated a cental depressant effect which was then quantitated in terms of effects on locomotor activity in mice. Changes in locomotor activity were measured in the test animals housed singly in photobeam cages containing six beams arranged in a circular fashion. The compounds were administered in doses of 10, 20, and 40 mg/kg ip in groups of eight mice per dose and the number of beam interruptions was determined at 10-min intervals for 30 min for both saline control and treated groups. A 10-min stabilization period was employed immediately after administration of the test compounds and prior to the 30-min test period. Table II summarizes the data obtained from this study in terms of percent reduction of locomotor activity produced by increasing doses of the test compounds 30 min after insertion into the photobeam cages as compared to the saline controls.

Discussion

All of the test compounds produced significant reduction in locomotor activity of the treated animals at doses of 40 mg/kg after a 30-min period (Table II). Compound **2a** produces a greater reduction in locomotor activity at all doses than its hemiketal analog **2b** possibly because of the greater lipid solubility of the former compound resulting in greater concentration in the CNS. Racemic **2a** is also seen to be more potent at 40 mg/kg in reducing locomotor activity in mice than either of its C-10 epimers and is approximately equipotent at the 40 mg/kg dose level to a 5 mg/kg dose of chlorpromazine hydrochloride. A significant degree of stereoselectivity of action is observed for C-10 epimers of **2a** in that the diastereomer of **2a** having the 10*R* configuration is considerably more active in reducing locomotor activity than the 10*S* diastereomer at all dose levels.

The CNS depressant actions of the 3-substituted octahydropyrido[2,1-*c*][1,4]oxazines of this study are in marked contrast to the CNS effects of structurally related agents. Smith and coworkers have reported that phenylation and diphenylation of the 1 position of the octahydropyrido[2,1-*c*][1,4]oxazine molecule provided compounds that lacked central stimulation and anorexic activities.[13] As previously noted, the 2-arylmorpholines (**1a,b**) possess marked amphetamine-like actions in the CNS. It is conceivable that the additional lipophilic groups in the octahydropyrido[2,1-*c*][1,4]oxazine derivatives (**2a,b**) could effect differential distribution in the CNS so as to produce a depressant effect rather than a stimulant action. However, in view of the findings of Sam and coworkers[14] that 3-arylquinolizidines (**4a,b**) exhibit amphetamine-like actions in CNS, it would appear that a combination of lipophilicity and introduction of an oxygen atom into the 2 position are the structural features of **2a** and **2b** that confer CNS depressant action on the compounds.



4a, X = H
b, X = OH

In view of the multiple pharmacological actions noted for **2a** and **2b** in the pharmacological screens, future studies of the 3-aryloctahydropyrido[2,1-*c*][1,4]oxazines will attempt to separate and magnify these actions via appropriate substitution on the 3-aryl substituent. These initial studies confirm the utility of the octahydropyrido[2,1-*c*][1,4]oxazine system as a molecular framework for useful CNS agents.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were determined using a Beckman IR-33 and the NMR spectra were taken using a C-60HL Jeolco spectrometer. All spectral data for intermediates and products were as expected. Optical rotations were determined as 1% ethanolic solutions at 25° using a Perkin-Elmer 141 polarimeter.

3-Phenyloctahydropyrido[2,1-*c*][1,4]oxazine (2a). Styrene oxide (24.0 g, 0.2 mol) was added to a solution of 2-piperidinemethanol (23.0 g, 0.2 ml) in 400 ml of EtOH and the solution was refluxed for 72 hr. The EtOH was removed in vacuo and the resultant oil dissolved in 10% HCl. The acidic solution was washed with ether several times to remove unreacted styrene oxide, neutralized (Na_2CO_3), basified to pH 10 (15% NaOH), and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated in vacuo to yield 44.0 g (94%) of **3** as a viscous, light yellow oil.

The diol **3**, without further purification, was combined with a solution of 48% HBr (41 ml) and the mixture refluxed for 2 hr. Excess HBr was removed in vacuo and the residue neutralized (K_2CO_3) and basified with 15% NaOH solution. Extraction of the basic material with ether, drying of the ether extract ($MgSO_4$), and concentration of the ethereal solution provided 3.8 g (76%) of **2a** as a brown oil. The HCl salt of **2a** was prepared by treatment with ethereal HCl and recrystallization from acetone–benzene: mp 212–214° (lit.[11] 238–241°).

Treatment of (*R*)- and (*S*)-2-piperidinemethanol as described above provided (+)-(3*RS*,10*R*)-**2a**·HCl and (−)-(3*RS*,10*S*)-**2a**·HCl, respectively. The 10*R* epimer [bp 113–115° (0.05 mm)] was prepared in 92% yield by this method and the HCl salt was recrystallized from acetone–benzene: mp 209–211°; $[\alpha]_D$ +31.2°. Similarly, the 10*S* epimer of **2a** [bp 119–120° (0.05 mm)] was prepared in 93% yield giving an HCl salt (acetone–benzene): mp 208–211°; $[\alpha]_D$ −10.0°.

3-Hydroxy-3-phenyloctahydropyrido[2,1-*c*][1,4]oxazine (2b). A solution of 2-piperidinemethanol (23.0 g, 0.2 mol) in ether (350 ml) was mixed with an ethereal solution (100 ml) of α-bromoacetophenone (19.9 g, 0.1 mol) and the resultant solution allowed to stand at room temperature for 48 hr. The 2-piperidinemethanol hydrobromide formed in the reaction was removed by filtration, the ethereal filtrate concentrated in vacuo, and the residue taken up in 10% HCl. The acidic solution was extracted with $CHCl_3$ and then basified with 15% NaOH. The alkaline mixture was extracted with ether, and the ethereal extract

was dried (Na_2SO_4) and concentrated in vacuo to yield a light yellow solid which upon recrystallization (*n*-hexane) gave 21.6 g (93%) of **2b** as a white powder: mp 67–69°. The HCl salt of **2b** was prepared and recrystallized (acetone): mp 166–167°. Anal. ($C_{14}H_{20}ClNO_2$) C, H, N.

A solution of **2b** (5.0 g, 0.021 mol) was prepared in 100 ml of 1.13 *N* H_2SO_4, 1.0 g of 10% Pd/C was added, and the mixture was hydrogenated at 55–60° and 48 psi for 48 hr. The solution was filtered, basified (15% NaOH), and extracted with $CHCl_3$. The extract was then dried ($MgSO_4$) and concentrated in vacuo to provide 4.0 g (80%) of a viscous, yellow oil which was identified by spectral methods as the diol **3** which had been previously prepared from the reaction of 2-piperidinemethanol and styrene oxide. Treatment of **3** with 48% HBr provided **2b** having identical physical and chemical properties with the sample obtained by the previous synthetic method.

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Synthesis of *N*-Hydroxythiourea

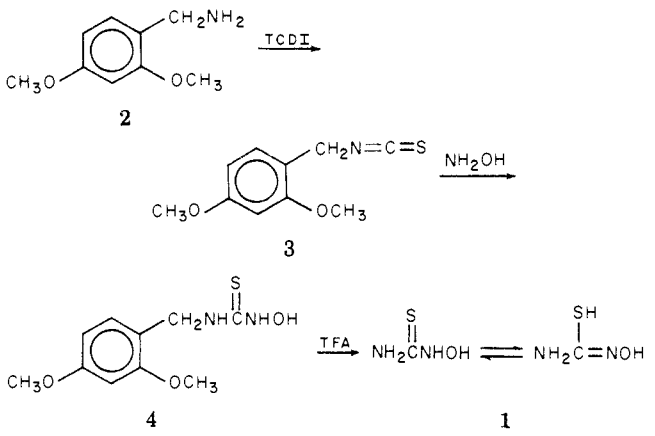
Masayuki Sato and Charles H. Stammer*

Department of Chemistry, University of Georgia, Athens, Georgia 30602. *Received June 12, 1975*

The synthesis of the title compound (1) was accomplished by the conversion of 2,4-dimethoxybenzylamine (**2**) into an isothiocyanate (**3**) using thiocarbonyl diimidazole. Treatment of **3** with hydroxylamine and removal of the DMB group with trifluoroacetic acid gave 1. *N*-Hydroxythiourea (1) showed no activity in the L1210 mouse tumor.

N-Hydroxyurea is a well-known and useful chemotherapeutic agent in the treatment of cancer.[1] It was of interest, therefore, to prepare the sulfur analog of this compound, *N*-hydroxythiourea (1), in order to examine its chemotherapeutic properties. The standard method for conversion of an amine to a thiourea, i.e., treatment with thiocyanic acid under rather vigorous conditions, would not suffice for the synthesis of 1 since neither hydroxylamine nor the product might be expected to withstand the conditions required for the reaction. In light of reports by Weygand,[2] who used the bis(2,4-dimethoxybenzyl), and Pietta,[3] who used the 2,4-dimethoxybenzyl (Dmb) protecting group for amide functions, we designed a synthesis of 1 in which the Dmb-protecting group was used (Scheme I).

Scheme I



The conversion of 2,4-dimethoxybenzylamine (**2**) into the isothiocyanate **3** turned out to be the most difficult step in the synthesis. Although Bach and Kjaer[4] reported the conversion of **2** into **3** using thiophosgene, these authors indicated that it decomposed on short-path distillation and were unable to report an elemental analysis for their product. In our hands also, thiophosgene was a poor reagent for the preparation of the isothiocyanate **3**. However, thiocarbonyldiimidazole (TCDI) smoothly converted the amine into **3**, which crystallized from hexane: mp 24–25°. Treatment of **3** with excess hydroxylamine in aqueous methanol afforded the thiourea **4** in excellent yield. The Dmb group was removed from **4** with trifluoroacetic acid giving 1 in almost 70% yield.

N-Hydroxythiourea (1) crystallized in two polymorphic forms when allowed to crystallize slowly but could be obtained in a single form when crystallization was rapid. The compound was unstable at ambient temperatures in the laboratory and was stored in a refrigerator freezer compartment. Its NMR spectrum indicated that it exists as a mixture of enthiol and thione tautomers and the ir spectrum indicated an azomethine function (C=N, 1610 cm^{-1}) but showed no strong band readily assignable to a thiocarbonyl group.

The use of the Dmb-protecting group in the synthesis of thiocarbonyl derivatives of very sensitive molecules is exemplified in this work. The very mild conditions used in this procedure should allow the synthesis of such de-