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1 AUTHOR:

Abdel-Nasser Ahmed El-Shorbagi
University of Sharjah

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Model for delivery of amines through incorporation into a tetrahydro-2*H*-1,3,5-thiadiazine-2-thione structure

A-NA El-Shorbagi

Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, University of Assiut, Assiut-71515, Egypt

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Summary — Phenethylamine **1a** (**a**; $n = 2$) and benzylamine **1b** (**b**; $n = 1$) are known in medicinal chemistry as strong vasopressors. Both are excellent substrates for the enzyme monoamine oxidase (MAO). The 2 compounds were incorporated in a highly lipid-soluble and hydrolysis-vulnerable tetrahydrothiadiazine (THTT) target structure in order to modify their pharmacokinetics. Better partition correlations, expressed as log *P* (calculated and observed) for the synthesized products THTT in comparison to the original compounds **1a**, **b** have been found. One of the THTT derivatives was tested for its liability for chemical hydrolysis and the structure of the hydrolytic product was determined.

tetrahydro-2*H*-1,3,5-thiadiazine-2-thione / phenethylamine / benzylamine / prodrugs / monoamine oxidase inhibitors / partition coefficient / hydrolysis

Introduction

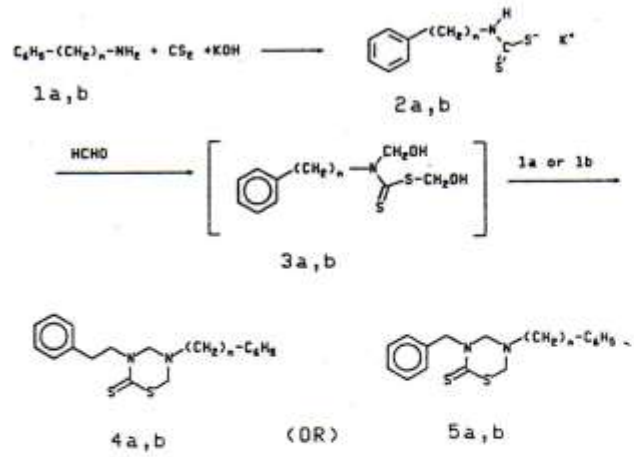
Since the discovery that the anti-depressant activity of iproniazide is due to its high *in vivo* monoamine oxidase (MAO) inhibition, many compounds embodying amine or hydrazine moieties in their structures have been synthesized and found to be efficient anti-depressants [1–3]. A useful study of the techniques associated with pattern recognition for several MAO inhibitors has claimed that: a) compounds having aromatic rings and a 2-carbon side chain are the most potent; and b) the length of the side chain seems to be fairly critical in aromatic compounds [4, 5]. The adverse pharmacological effects of aralkylamines [1–3, 6], and their inconsistent absorption by the gastrointestinal tract (GIT) [7, 8] have limited their clinical applications. It has also been noted [7–9] that the absorption rates of aralkylamines in the GIT are closely correlated with physico-chemical properties such as partition data [7].

In this study, phenethylamine **1a** and benzylamine **1b** were incorporated in a tetrahydrothiadiazine (THTT) structure (**4a, b, 5a, b**), in order to modify the partitioning of the drugs between the lipid and aqueous phases in the body. Such chemical modification led to more lipophilic THTT compounds, which constituted an entirely different group of compounds in their structure, ionization and electronic properties. The absorption of the THTT derivatives by the GIT was as expected increased, and might provide a more receptor site-oriented system through increased lipid solubility in the CNS. On the other hand, the production of formaldehyde as an expected biotransformation product for THTT derivatives in the body was assessed and compared with the small doses (50–100 mg daily dose) of the aralkylamines in chemotherapy.

Abbreviations: MAO: monoamine oxidase; THTT: tetrahydro-2*H*-1,3,5-thiadiazine-2-thione; GIT: gastrointestinal tract; CNS: central nervous system.

Chemistry

Phenethylamine **1a** and benzylamine **1b** were allowed to react with carbon disulfide in the presence of KOH to yield their corresponding potassium dithiocarbamate derivatives **2a, b**. Addition of formalin to the dithiocarbamates resulted – *in situ* – in compounds **3a, b** which were allowed to react further with **1a, b** in the presence of phosphate buffer (pH = 7.8) to form the designated THTT derivatives **4a, b** and **5a, b** (scheme 1; tables I–III). The structures of the prepared compounds were established by elemental analyses, UV, IR, ^{1}H- and ^{13}C-NMR, in addition to 2-D HH COSY spectral data. Under UV the tetrahydrothiadiazine-2-thione structure showed an absorption band at



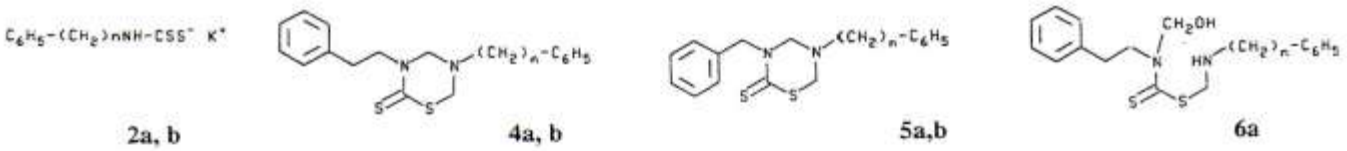
Scheme 1. In formulae: (**a**; $n = 2$, **b**; $n = 1$).

280–290 nm. With IR spectra **6a** showed the characteristic stretching absorptions of the OH and NH at 3480 and 3340 cm^{-1}. In ^1H-NMR spectra, the synthesized derivatives showed the C-4 and C-6 methylenes as singlets, where there was no interaction between each other as shown by the 2-D HH COSY spectral data (table II). In carbon-13 and DEPT experiments, compounds **4a** and **6a** showed 6 methylene groups as triplets, 6 methines as doublets, and 3 quaternary carbons as singlets, the most downfield of which was that for the (C=S) at 190.5 and 191.1 ppm for **4a** and **6a**, respectively. The observed chemical shifts in ppm of the C-4 and C-6 carbons (table III) agreed with those calculated for similar methylene groups [10].

Partition studies

The experimental partition coefficients expressed as observed log P data (table IV) were determined according to a previously described method (octanol/

Table I. Physico-chemical data of the synthesized derivatives.

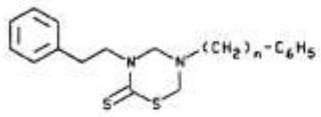


2a, b **4a, b** **5a,b** **6a**

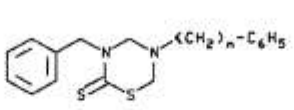
Compd No	*n*	*Yield (%)*	*Mp (°C)*	*Formula*	*Elemental analysis*
2a	2	94	172–173	$C_9H_{10}KNS_2$	N, S
2b	1	92	180–183	$C_8H_8KNS_2$	N, S
4a	2	88	139–140	$C_{19}H_{22}N_2S_2$	C, H, N, S
4b	1	85	145–147	$C_{18}H_{20}N_2S_2$	C, H, N, S
5a	2	81	119–120	$C_{18}H_{20}N_2S_2$	C, H, N, S
5b	1	78	101–103	$C_{17}H_{18}N_2S_2$	C, H, N, S
6a	2	36	138–141	$C_{19}H_{24}N_2OS_2$	C, H, N, S

All elemental analyses (C, H, N, S) were satisfactory and within ± 0.4% of the calculated values except for **2a, b**. The (NS) for **2a, b** were satisfactory to within ± 0.55% of the calculated values, but that for carbon was less than the calculated value due to the formation of a potassium carbonate or potassium bicarbonate residue upon combustion.

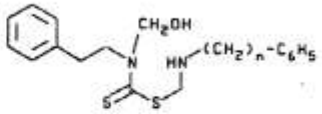
Table II. ^{1}H-NMR spectral data of the synthesized derivatives.



4a, b



5a, b



6a

Compd No	*n*	*Chemical shifts (δ values) ppm, J = Hz*						
		4-CH_2	*6-CH_2*	*N3-α-CH_2*	*N3-β-CH_2*	*N5-α-CH_2*	*N5-β-CH_2*	*Arom (10H)*
4a	2	4.53 s	4.47 s	4.08 t *J* = 9.1, 8.0	2.93 t *J* = 9.1, 8.1	2.89 t *J* = 7.9, 6.9	2.80 t *J* = 7.6, 7.8	7.17–7.37 m
4b	1	4.35 s	4.22 s	4.15 t *J* = 8.9, 8.6	3.03 t *J* = 9.1, 8.7	3.88 s	–	7.28–7.50 m
5a	2	4.57 s	4.28 s	4.38 s	–	2.93 t *J* = 7.8, 7.5	2.85 t *J* = 7.7, 7.6	7.21–7.47 m
5b	1	4.58 s	4.20 s	4.36 s	–	3.83 s	–	7.30–7.52 m
6a[a]	2	4.48 bs	4.12 s	3.93 t *J* = 8.7, 8.2	3.00 t *J* = 9.1, 7.9	2.84 t *J* = 8.1, 7.8	2.78 t *J* = 7.8, 7.6	7.20–7.39 m

s: Singlet, bs: broad singlet, d: doublet, t: triplet, m: multiplet; [a]in addition, an NH group as a broad singlet at 3.32 ppm and a sharp singlet for the OH group at 5.23 ppm (exchangeable by D_2O).

water) [11, 12]. Solutions of the appropriate **4a**, **b**, **5a**, **b** (0.2% w/v in octanol) and the buffer solutions (pH = 6, 7.4) were shaken for 2 h at ≈ 37°C. After centrifugation, the concentrations of the compounds remaining in the organic phases were determined spectrophotometrically at 287 nm.

The log *P* for the synthesized derivatives **4a**, **b**, **5a**, **b** and **1a**, **b** were calculated according to equation [1] following Moriguchi *et al* [13] (table IV, eq 1).

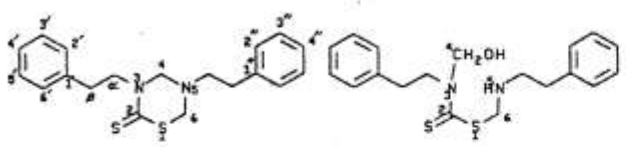
$$\log P = 1.244\,(CX)^{0.6} - 1.017\,(NO)^{0.9} + 0.406\,PRX - 0.145\,(UB)^{0.8} + 0.511\,HB + 0.268\,POL - 2.215\,AMP + 0.912\,ALK - 0.392\,RNG - 3.684\,QN + 0.474\,NO_2 + 1.582\,NCS + 0.773\,BLM - 1.041 \quad [1]$$

where *CX*: sum of numbers of carbon and halogen atoms weighted by C: 1; *NO*: total number of N, S and O atoms; *PRX*: proximity effect of N/O or N/S; *UB*: total numbers of unsaturated bonds; *HB*: dummy variable for the presence of hydrogen bonding; *POL*: number of aromatic polar substituents; *AMP*: amphoteric property; *ALK*: dummy variable for alkane, alkene, cycloalkane or cycloalkene; *RNG*: dummy variable for the presence of ring structures other than benzene; *QN*: quaternary nitrogens; NO_2: number of nitro groups; *NCS*: number of isithiocyanato or thiocyanato groups; *BLM*: dummy variable for the presence of β-lactam.

The observed and calculated log *P* data showed more lipid-soluble THTT derivatives than the corresponding aralkylamines; absorption by the GIT could therefore be increased as a result. The increased lipophilicity of a drug may affect its transfer to the CNS where its activity occurs.

The relation of the calculated log *P* using eq [1] and the corresponding observed values showed a good fit

Table III. ^{13}C-NMR spectral data for **4a** and **6a**.



4a **6a**

Carbon No	*4a*	*6a*
C=S	190.5 (s)	191.1 (s)
C-1'	139.4 (s)	138.6 (s)
C-1"	138.2 (s)	137.4 (s)
C-2'	128.7 (d)	128.0 (d)
C-4'	128.6 (d)	127.9 (d)
C-2"	128.4 (d)	127.6 (d)
C-4"	128.2 (d)	127.3 (d)
C-3'	126.4 (d)	126.0 (d)
C-3"	126.0 (d)	125.3 (d)
C-4	70.1 (t)	78.1 (t)
C-6	57.3 (t)	57.6 (t)
N3-α-CH_2	52.7 (t)	52.8 (t)
N5-α-CH_2	50.9 (t)	51.0 (t)
N3-β-CH_2	33.0 (t)	32.7 (t)
N5-β-CH_2	31.8 (t)	31.5 (t)

for this type of molecule. The absence of the possibility of dissociation and formation of intra- or intermolecular hydrogen bonding in the structure of the synthesized compounds helped to fit the observed and calculated data for log *P*.

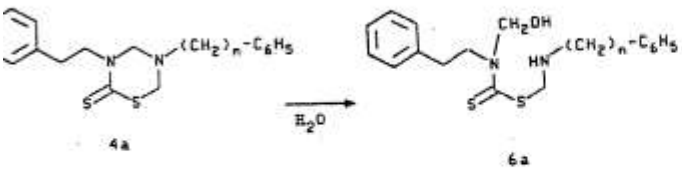
Hydrolytic studies

Hydrolysis and therefore the liberation of the required drug from its prodrug target in the body, thereby revealing its activity, is a prime factor in such prodrugs. Hydrolysis of the tetrahydrothiadiazine-2-thione structure is expected to produce the aralkylamine when hydrolysis occurs at the N-5 position of the ring system. When hydrolysis occurs at the N-3 position of the ring system, an isothiocyanate derivative of the aralkylamine results [14, 15]. When applied biologically, the hydrolase enzymes are therefore responsible for its biotransformation to aralkylamines. For this reason, compound **4a** was subjected to chemical hydrolysis. Hydrolysis was complete upon standing for 1 h at pH > 11, producing the aralkylamine **1a**. To investigate the intermediate hydrolytic product(s), mild hydrolysis was carried out at pH = 9 in 60% methanol for 6 h at rt. The organic solvent was removed *in vacuo* at rt and the remaining suspension extracted with methylene chloride, dried ($MgSO_4$), concentrated and chromatographed on a silica-gel column. Upon elution with chloroform, compound **6a** (scheme 2; tables II, III) was separated as a major product (R_f = 0.65, methanol/$CHCl_3$, 1:99). It is concluded from these experiments that enzymatic hydrolysis of the THTT structure thereby producing the aralkylamines may be possible. Further studies on the pharmacokinetics and enzymatic hydrolysis of the THTT target still need to be carried out.

Table IV. Calculated and observed log *P* of the synthesized compounds.

Compd No	*CX*	*PRX*	*POL*	*ALK*	*NCS*	*NO*	*UB*	*RNG*	*Calcd log P*	*Obs log P*
1a	8	1	1	–	–	1	3	–	3.63	3.7
1b	7	1	1	–	–	1	3	–	3.37	3.4
4a	19	4	1	2	0.5	4	7	1	5.26	5.3
4b	18	4	1	2	0.5	4	7	1	5.06	5.0
5a	18	4	1	2	0.5	4	7	1	5.06	4.9
5b	17	4	1	2	0.5	4	7	1	4.88	4.7

The parameters *HB*, NO_2, *BLM*, *AMP*, and *QN* in eq [1] were calculated as zero for all compounds and were therefore not listed.



Scheme 2. Hydrolysis of the tetrahydrothiadiazine-2-thione.

Results and discussion

The good statistical figures obtained for the THTT derivatives indicate optimum lipophilicity (calculated and observed) as a requirement for absorption by the GIT. On the other hand, the hydrolysis of **4a** to **6a** under mild hydrolytic conditions indicates that the tetrahydrothiadiazine structure may be considered a good target for the aralkylamines to be effectively absorbed as THTT prodrugs, but that it is vulnerable as regards hydrolysis by the hydrolase enzymes in the body.

Experimental protocols

Precoated silica-gel 60 F-254 plates (Merck) were used for TLC; spots were detected by UV light and/or iodine vapor staining. Melting points were determined in open capillary tubes using Electrothermal AI-9100 mp apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu 408 spectrometer. ^{1}H-, ^{13}C-NMR and 2-D HH COSY spectra were measured ($CDCl_3$) on JEOL JNM-GSX-500 (500 MHz) spectrometers. Chemical shifts are given in δ values downfield from Me_4Si as internal standard. Elemental analyses (C, H, N) were carried out at the Faculty of Science, Assiut University. Phenethylamine **1a** and benzylamine **1b** were available as commercial-grade bases. Solutions of (pH = 6, 7.4, 9) were prepared according to the British Pharmacopoea (BP 1973) by using analytical grade potassium acid phosphate, boric acid and sodium hydroxide.

3,5-Bis(2-phenethyl)tetrahydro-2H-1,3,5-thiadiazine-2-thione ***4a*** *and 5-benzyl-3-phenethyltetrahydro-2H-1,3,5-thiadiazine-2-thione* ***4b***

Carbon disulfide (60 mmol) was added to a stirred mixture of phenethylamine **1a** (10 mmol) and potassium hydroxide (20%, 10 mmol) in ethanol (10 ml). After stirring at rt for 3 h, formaldehyde solution (35%, 22 mmol) was added to the mixture and stirring continued for 1 h. The clear solution obtained was added portionwise over a 15-min period to a stirred solution of the appropriate aralkylamine **1a, b** (10 mmol) at pH 7.8 (20 ml phosphate buffer). After stirring for 4 h at ambient temperature, the reaction mixture was acidified to pH = 2 with dilute hydrochloric acid (5%, ≈ 18 ml). Methylene chloride (50 ml) was added and stirring was continued for 30 min. Washing with hydrochloric acid (0.5%), drying ($MgSO_4$), evaporation under reduced pressure, and crystallization from chloroform/methanol (7:3) afforded compounds **4a** and **4b** (scheme 1; tables I–III).

3,5-Bis(benzyl)tetrahydro-2H-1,3,5-thiadiazine-2-thione ***5a*** *and 3-benzyl-5-phenethyltetrahydro-2H-1,3,5-thiadiazine-2-thione* ***5b***

The above-mentioned procedure was utilized but with benzylamine instead of phenethylamine. Compounds **5a** and **5b** were obtained in good yield (scheme 1; tables I, II).

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