# Oxime Analogs of Physostigmine†

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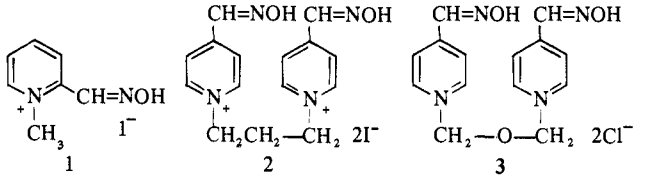
A series of ketoximes based on the structure of physostigmine was prepared as potential reactivators of phosphorylated cholinesterase. When tested *in vivo* no activity was noted and only limited *in vitro* reactivation was observed with bovine erythrocyte acetylcholinesterase.

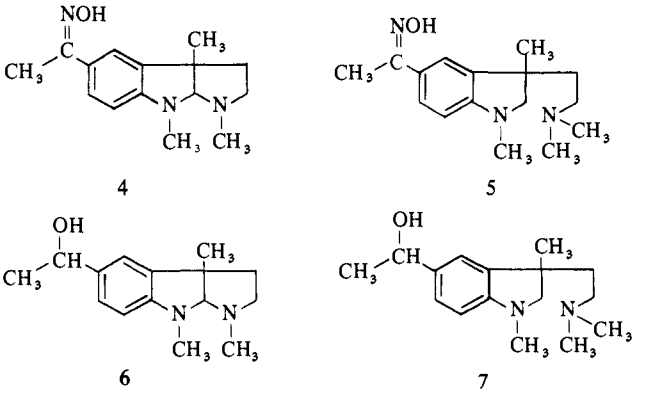
The effective reactivation of phosphorylated cholinesterase by 2-pyridine carbaldoxime methiodide (2-PAM) (**1**) has been attributed to the high affinity of the quaternary amine for the anionic center on the enzyme. This interaction could place the aldoxime oxyanion in a favorable position to carry out a nucleophilic attack on the phosphorylated esteratic site.[1] Trimethylenebis(1-pyridinium-4-carbaldoxime iodide) (TMB-4) (**2**) and bis(4-hydroxyiminomethylpyridinium-1-methyl) ether dichloride (Lu H6) (**3**) have also proven to be potent reactivators.[2,3] Several groups have, however, reported



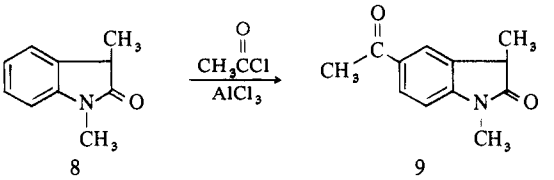
a low order of reactivation of brain cholinesterase using the quaternary amino oximes as antidotes.[4-8] Experiments have shown that 2-PAM does not penetrate all areas of the brain to the same extent, but the test animals are still protected from the lethal effects of paraoxon.[9]

Amino compounds with increased lipophilic character might be expected to overcome the shortcomings of 2-PAM and as a result provide more information about the essential role of brain cholinesterase. Oxime analogs of arecoline,[10] a tertiary amine, and the *N*-dodecyl homolog of 2-PAM[11] exhibit a limited ability to reactivate the enzyme. Also, no reactivating potential was observed for an oxime analog of atropine.[12] Since physostigmine has been demonstrated to significantly decrease *in vivo* brain cholinesterase activity in rats,[13] replacement of the carbamate with an oxime moiety might result in a compound with central reactivating properties. Two oxime analogs, **4** and **5**, have been synthesized for pharmacological testing.

Because of the moderate reactivating properties shown by choline,[14] the synthesis and biological evaluation of the alcohols, **6** and **7**, were also studied.

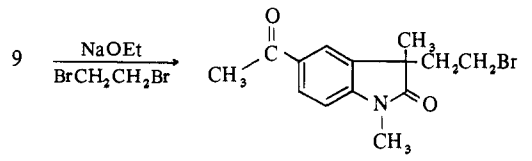


Of the several known syntheses of physostigmine, a modification of the approach described by Julian and Pikl proved to be quite applicable to this study.[15] In order to follow this method, a 5-acylated oxindole, which could eventually be converted into compounds **4-7**, was required as starting material. Following the conditions for the synthesis of 1,5-diacetylindoline,[16] 5-acetyl-1,3-dimethyloxindole (**9**) was obtained by Friedel-Crafts acylation of 1,3-dimethyloxindole (**8**).[17] The ethylene ketal of **9** was prepared by the

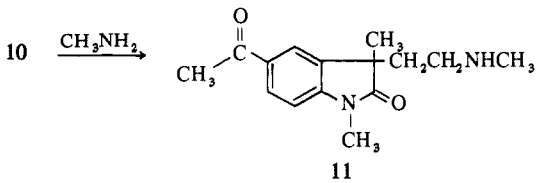


standard procedure but attempts to prepare the anion of this ketal, needed for the next step, using a suspension of sodium sand in benzene were unsuccessful.[15]

Upon treatment of a mixture of **9** and 1,2-dibromoethane with sodium ethoxide[17] in ethanol, 5-acetyl-3-(2-bromoethyl)-1,3-dimethyloxindole (**10**) was formed in good yield.



This material in the presence of a large excess of methylamine was converted into 5-acetyl-3-(2-methylaminoethyl)-1,3-dimethyloxindole (**11**).



A standard method of ketalization[18] of **11** in refluxing toluene met with limited success. The poor solubility of the amine salt probably accounted for the low yield of **12**. However, the yield of **12** was greatly improved by first preparing the ethylene ketal of **10** and treating this product with methylamine to give **12**.

The method of cyclization to the tetrahydropyrrolo[2,3-*b*]indole ring system employed by Julian and Pikl involved the use of sodium and alcohol.[15] A similar type of cyclization has been achieved with lithium aluminum hydride as the last step in the synthesis of chimonanthine.[19] The greater convenience of the hydride method made it the method of choice for this study.

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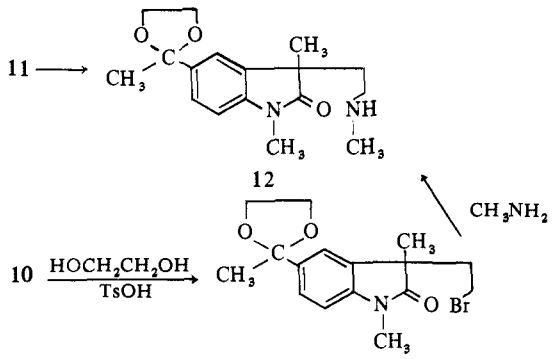
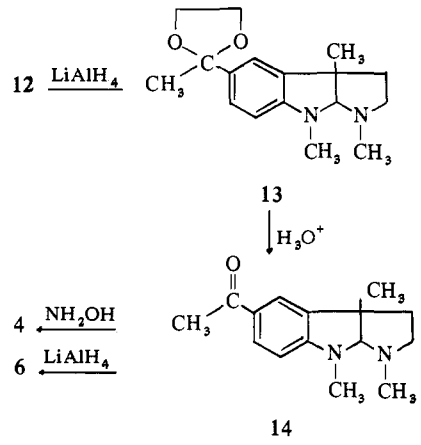
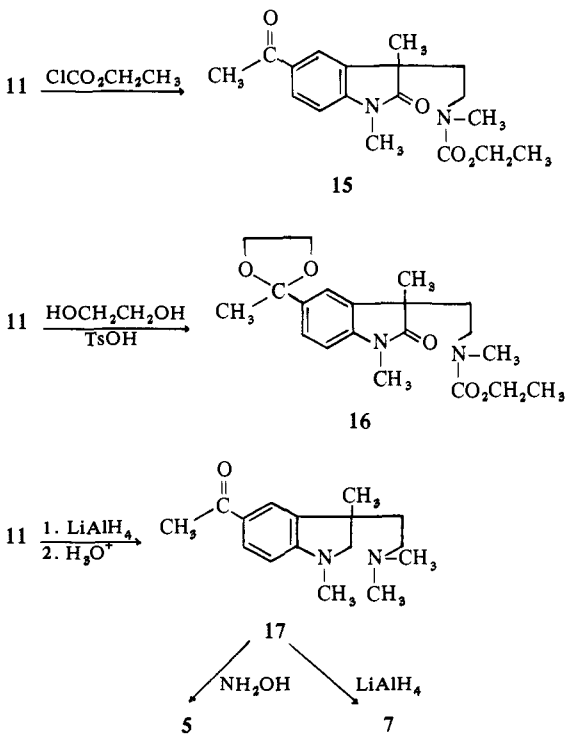



When allowed to react with lithium aluminum hydride, **12** was converted into the ethylene ketal of 5-acetyl-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (**13**). Molecular models indicate that only the cis ring fusion will




form. The ketone **14** was isolated after acid hydrolysis of the ketal. The alcohol **6** and the oxime **4** were prepared from **14** by the standard procedures.

The synthesis of the two open-chain compounds, **5** and **7**, followed a sequence similar to that used for the preparation of **4** and **6**. Reaction of **11** with ethyl chloroformate produced the carbamate **15** which was then converted into the ethylene ketal **16**.



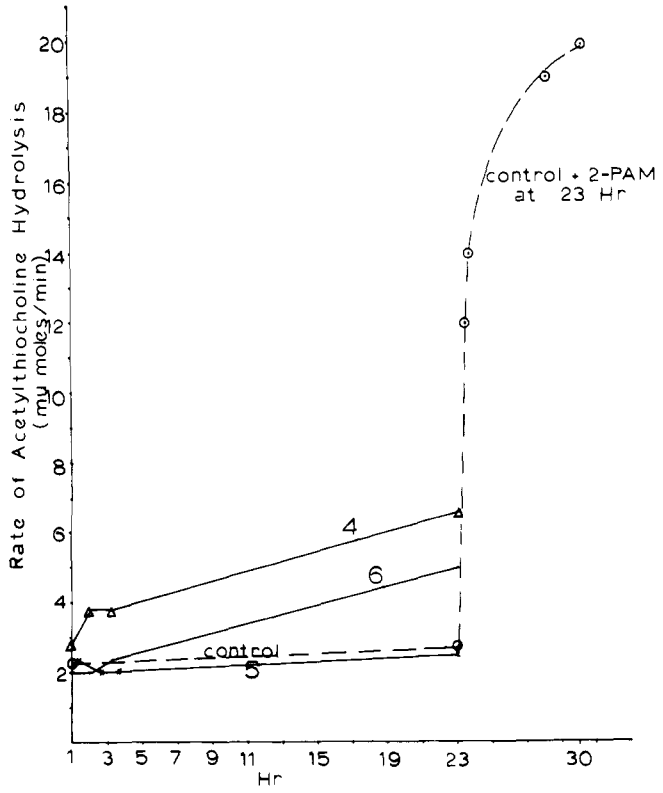




Figure 1. Reactivation of phosphorylated (paraoxon) bovine erythrocyte acetylcholinesterase by 4, 5, and 6 in 10 m*M* histidine buffer (pH 7.4). Control (without reactivator) still showed significant activity upon addition of 2-PAM at 23 hr. Test compounds did not cause spontaneous breakdown of substrate.

Following lithium aluminum hydride reduction of **16** and acidic work-up of the intermediate amino ketal, 5-acetyl-3-(2-dimethylaminoethyl)-1,3-dimethylindoline (**17**) was isolated as the major product. Conversion of this material into **5** and **7** was accomplished by the methods used for the syntheses of **4** and **6** from **14**. While the purification and characterization of the oxime **5** was readily accomplished, **7** could not be induced to crystallize, probably due to a mixture of diastereomeric isomers. Elemental analysis of this compound was not obtained.

Since both syn and anti isomers of the oxime compounds were not isolated, one cannot speculate upon which was obtained. The nmr absorption at δ 7.29 (compound 4) and 7.22 ppm (compound 5) due to the aromatic proton at position 4 is, however, a sharp singlet. Since this proton in the anti isomer should resonate distinctly downfield from that of the syn isomer,[20] one can conclude that only one isomer was isolated.

Little to no effects were observed with the potential reactivators on inhibited rat brain enzyme. Incubation of compounds **4** and **6** for an extended period of time with phosphorylated bovine erythrocyte AChE (Figure 1) appears to give rise to relatively insignificant reactivation. 2-PAM, added to the control after this long incubation period, still caused the enzyme to recover. No attempt was made to determine the configuration of the oxime moiety in these compounds and it is possible that the lack of activity could be due to obtaining an inactive isomer. Another possibility which was not studied is the possibility that change in the basicity of the ring nitrogens due to the electron-withdrawing effect of the oxime compared to the electron-donating effect of the carbamoyl moiety of physostigmine led to inactive compounds.

## Experimental Section

Melting points were determined using a Mel-temp capillary melting point apparatus with open capillary tubes and are uncorrected. Ir, nmr, and mass spectra were consistent with all structures assigned. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

**5-Acetyl-1,3-dimethyloxindole (9).** In a three-necked flask equipped with a powerful stirrer, solid addition funnel, and condenser was placed 1,3-dimethyloxindole (20 g, 0.125 mol) (83). Aluminum chloride (48 g, 0.36 mol) was added in small portions to the stirred oxindole. The temperature was held constant by occasional cooling with an ice bath. Acetyl chloride (44 g, 0.56 mol) was added dropwise at a rate sufficient to maintain a smooth reflux. After the exothermic reaction had subsided, the mixture was heated carefully on the staem bath for 0.5 hr. At this point the mixture became very thick and could no longer be stirred. The reaction flask was cooled and ice (200 g) was carefully added to the mixture. The solid, which was collected by filtration, was recrystallized from $CH_3OH$–$H_2O$: 18 g (79% yield); mp 111.5–112°. *Anal.* ($C_{12}H_{13}NO_2$) C, H.

**5-Acetyl-3-(2-bromoethyl)-1,3-dimethyloxindole (10).** A solution of 5-acetyl-1,3-dimethyloxindole (9, 38.3 g, 0.19 mol) in ethylene bromide (142 g, 0.76 mol) was added dropwise with stirring to a cooled solution of NaOEt in absolute EtOH, prepared by reacting Na (4.3 g, 0.19 g-atom) with EtOH (75 ml). The mixture then was refluxed for 2 hr. The cooled mixture was poured over ice (50 g). The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($CaSO_4$) and the solvent removed *in vacuo* leaving a solid which was recrystallized from $CH_3OH$: 30.2 g (51% yield); mp 121–122°. *Anal.* ($C_{14}H_{16}BrNO_2$) C, H.

**5-Acetyl-3-(2-methylaminoethyl)-1,3-dimethyloxindole (11).** Methylamine (52.5 g, 1.7 mol) and 5-acetyl-3-(2-bromoethyl)-1,3-dimethyloxindole (10, 30.2 g, 0.10 mol) were placed in a Paar bomb and heated at 100° for 5 hr. The excess $CH_3NH_2$ was evaporated and the residue was dissolved in dilute HCl. This was extracted with $Et_2O$. The aqueous layer was made basic with dilute NaOH and extracted thoroughly with $Et_2O$. The $Et_2O$ solution was dried with $CaSO_4$ and the solvent removed *in vacuo* leaving a solid: 12 g (48% yield); mp 106–108°.

For analysis the HCl salt was prepared and recrystallized from absolute EtOH, mp 239–240.5°. *Anal.* ($C_{15}H_{21}ClN_2O_2$) C, H.

**5-Acetyl-3-(2-methylaminoethyl)-1,3-dimethyloxindole Ethylene Ketal (12).** The ethylene ketal of 5-acetyl-3-(2-bromoethyl)-1,3-dimethyloxindole was prepared by a standard procedure.[18] Without further purification this material (33 g, 0.093 mol) was mixed with $CH_3NH_2$ (52.5 g, 1.69 mol) and heated in a Paar bomb for 5 hr. The reaction vessel was cooled and opened. The excess $CH_3NH_2$ was evaporated on the steam bath, and the remaining mixture was dissolved in $CHCl_3$ (200 ml). This solution was washed with 5 × 100 ml of dilute $Na_2CO_3$. After drying with $CaSO_4$ the solvent was removed *in vacuo* leaving a yellow oil. As noted by the odor, this substance contained $CH_3NH_2$. Additional washing with $H_2O$ and vacuum drying did not remove this impurity. The material was dissolved in $CHCl_3$ (100 ml) and treated with alumina III (15 g). After standing 3 hr the mixture was filtered and the solvent removed *in vacuo*. The resulting yellow oil (21 g, 75% yield) was used without further purification.

**5-Acetyl-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (14).** An $Et_2O$ solution (100 ml) of 5-acetyl-3-(2-methylaminoethyl)-1,3-dimethyloxindole ethylene ketal (12, 7.0 g, 0.023 mol) was added dropwise with stirring to a cooled mixture of $LiAlH_4$ (475 mg, 0.0125 mol) in $Et_2O$ (150 ml). This was then refluxed 16 hr. The mixture was cooled, and $H_2O$ (1.1 ml) was carefully added. The mixture was filtered and the insoluble material washed thoroughly with $Et_2O$. The filtrate was dried with $CaSO_4$ and the solvent removed *in vacuo*. The resulting oil (5.3 g) was placed over a column of alumina III (100 g) and eluted with benzene (500 ml). Evaporation of the solvent left an oil (1.9 g) which was dissolved in dilute HCl (20 ml) and allowed to stand 0.5 hr. Dilute NaOH was added until the mixture was basic. The aqueous mixture was extracted with $CHCl_3$. The $CHCl_3$ was removed *in vacuo* leaving yellow oil, 1.6 g (29% yield). This material was used without further purification. Starting material 12 (2.8 g) was recovered from the column by eluting with $CH_3OH$–$CHCl_3$ (1:3, 500 ml).

**5-Acetyl-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole Oxime (4).** A solution of aqueous EtOH (70%, 15 ml) containing 5-acetyl-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (650 mg, 2.7 mmol), $NH_2OH$·HCl (200 mg, 2.9 mmol), and NaOAc (240 mg, 2.9 mmol) was refluxed 10 hr. The EtOH was removed *in vacuo* and the mixture made basic with dilute NaOH. The mixture was extracted with 5 × 50 ml of $Et_2O$. The $Et_2O$ solution was dried with $CaSO_4$ and the solvent removed *in vacuo* leaving an oil which crystallized upon treatment with a mixture of $Et_2O$–petroleum ether (bp 30–60°). This solid was recrystallized from $Et_2O$–petroleum ether: 400 mg (56% yield); mp 125–127°. *Anal.* ($C_{15}H_{21}N_3O$) C, H.

**5-(1-Hydroxyethyl)-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (6).** An $Et_2O$ solution (30 ml) of 5-acetyl-1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (14, 600 mg, 3.2 mmol) was added dropwise with stirring at 5° to a mixture of $LiAlH_4$ (199 mg, 2.6 mmol) in $Et_2O$ (50 ml). The mixture was then refluxed for 12 hr. Water (0.2 ml) was carefully added at 5°. The mixture was filtered, and the solid washed thoroughly with $Et_2O$. The filtrate was dried with $CaSO_4$ and solvent removed *in vacuo*. The resulting oil solidified upon standing in the cold. This was recrystallized from cyclohexane: 225 mg (38% yield); mp 79.5–81°. *Anal.* ($C_{15}H_{22}N_2O$) C, H.

**5-Acetyl-3-[2-(*N*-ethoxycarbonyl-*N*-methyl)aminoethyl]-1,3-dimethyloxindole Ethylene Ketal (16).** The ethyl carbamate of 5-acetyl-3-(2-methylaminoethyl)-1,3-dimethyloxindole (15) was prepared by a standard procedure.[19] This solid (13.8 g, 0.042 mol) was converted into the ethylene ketal by a manner analogous to the synthesis of 12. A yellow oil (13.6 g, 86% yield, ir and nmr consistent with 16) was obtained which was used without further purification.

**5-Acetyl-3-(2-dimethylaminoethyl)-1,3-dimethylindoline (17).** An $Et_2O$ solution (150 ml) of 5-acetyl-3-[2-(*N*-ethoxycarbonyl-*N*-methyl)aminoethyl]-1,3-dimethyloxindole ethylene ketal (16, 9.7 g, 0.026 mol) was added dropwise with stirring at 5° to a mixture of $LiAlH_4$ (1.4 g, 0.037 mol) in $Et_2O$ (100 ml). The mxiture was then refluxed for 12 hr. Water (2.8 ml) was carefully added at 5°. The mixture was filtered and the solid washed thoroughly with $Et_2O$. The filtrate was dried with $CaSO_4$ and the solvent removed *in vacuo* leaving an oil. This material was dissolved in dilute HCl (50 ml) and allowed to stand 1 hr. This mixture was extracted with $Et_2O$. The aqueous layer was made alkaline by the addition of dilute NaOH. The alkaline mixture was extracted thoroughly with $Et_2O$. After drying the $Et_2O$ solution with $CaSO_4$, the solvent was removed *in vacuo* leaving an oil, 3.7 g (54% yield).

**5-Acetyl-3-(2-dimethylaminoethyl)-1,3-dimethylindoline Oxime (5).** A mixture of 5-acetyl-3-(2-dimethylaminoethyl)-1,3-dimethylindoline (17, 1.7 g, 6.7 mmol), $NH_2OH$·HCl (0.56 h, 8 mmol), and NaOAc (0.70 g, 8.5 mmol) was refluxed 12 hr in a solution of EtOH (15 ml) and $H_2O$ (5 ml). The EtOH was removed *in vacuo* and the mixture made basic with dilute NaOH. This mixture was extracted thoroughly with $Et_2O$. The organic layer was dried with $CaSO_4$ and the solvent removed *in vacuo*. The remaining oil crystallized upon treatment with cold $Et_2O$ and was recrystallized from $Et_2O$: 0.8 g (42% yield); mp 124–125°. *Anal.* ($C_{16}H_{25}N_3O$) C, H.

**5-(1-Hydroxyethyl)-3-(2-dimethylaminoethyl)-1,3-dimethylindoline (7).** An $Et_2O$ solution (100 ml) of 5-acetyl-3-(2-dimethylaminoethyl)-1,3-dimethylindoline (17, 1.1 g, 4.2 mmol) was added dropwise with stirring at 5° to a mixture of $LiAlH_4$ (200 mg, 5.3 mmol) in $Et_2O$ (100 ml). The mixture was then refluxed for 12 hr. Water (0.5 ml) was carefully added to the cooled mixture which was filtered and the insoluble material thoroughly washed with EtOH. The $Et_2O$ solution was dried with $CaSO_4$ and the solvent removed *in vacuo*. A clear oil, which could not be induced to crystallize, was obtained, 775 mg (70% yield).

**Pharmacology *in Vivo*.** The compounds were evaluated for their ability to protect against TEPP toxicity as follows. The maximal sublethal dose of the compounds was injected intraperitoneally into white mice weighing about 25 g. Five minutes later, they were dosed with 1 mg/kg of TEPP subcutaneously in the back of the neck. TEPP alone resulted in 15 deaths of 15 mice dosed. In mice dosed with 50 mg/kg of 2-PAM, only 4 of 18 TEPP-treated mice died. Compounds 4, 6, and 7 were each injected into groups of 12 mice at doses of 200, 50, and 100 mg/kg, respectively. In contrast, no fatalities were observed in another control set of groups of eight mice treated with compounds 4, 6, and 7 at 200, 50, and 100 mg/kg, respectively. Slight loss of muscle tone and tremors were noted with compound 4. Increased muscle tone and activity, tremors, and Straub tail phenomena were noted with compound 6. Clonic convulsions with eventual recovery were noted with compound 7. All the mice succumbed to the subsequent dose of TEPP. Thus, at the maximum tolerated dose no protection against TEPP toxicity was observed with the physostigmine analogs.

*In Vitro.* Rat brains (6 mg) were homogenized in distilled water in a Sorvall blender at maximum speed for 2 min, filtered through four layers of cheese cloth, and centrifuged at 100,000g for 1 hr. The supernatant, containing 23% of the total activity (specific activity 600 nmol/mg protein/hr), was used for assaying the reactivators. Bovine erythrocyte AChE (Sigma) was prepared by dissolving the enzyme powder into histidine buffer (10 m*M*) adjusted to pH 7.4 to an activity of 0.1–0.2 μmol/min.

A standard assay was followed using 3.75 m*M* acetylthiocholine (Eastman recrystallized twice from ethanol) and 2.5 m*M* 5,5'-dithiobis(2-nitrobenzoic acid) in sodium phosphate buffer (0.1 *M*) at pH 8.[21] The enzyme was inhibited with 1 μ*M* paraoxon and excess inhibitor was removed by passing the enzyme mixture through a 1.2 by 12 cm Bio-gel column equilibrated in 10 m*M* histidine buffer (pH 7.4). The potential reactivator (1 m*M* in ethanol) or ethanol alone as control was then added to the inhibited enzyme and recovery monitored at room temperature.

## References


(1) I. B. Wilson, S. Ginsburg, and C. Quan, *Arch. Biochem. Biophys.*, 77, 286 (1958).
(2) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, 23, 714 (1958).
(3) N. Engelhard and W. D. Erdmann, *Arnzneim.-Forsch.*, 14, 870 (1964).
(4) R. I. Ellin and J. H. Wills, *J. Pharm. Sci.*, 53, 995 (1964).
(5) J. P. Rutland, *Brit. J. Pharmacol.*, 13, 399 (1958).
(6) F. Hobbiger, *ibid.*, 12, 438 (1957).
(7) H. Edery and G. Schatzberg-Porath, *Science*, 128, 1137 (1958).
(8) F. Hobbiger and V. Vojvodic, *Biochem. Pharmacol.*, 15, 1677 (1966).
(9) F. Hobbiger and V. Vojvodic, *ibid.*, 16, 455 (1967).
(10) J. N. Wells, J. N. Davisson, I. Boime, D. R. Haubrick, and G. K. W. Yim, *J. Pharm. Sci.*, 56, 1190 (1967).
(11) I. B. Wilson, *Biochim. Biophys. Acta*, 27, 196 (1958).
(12) G. L. Albanus, *Biochem. Pharmacol.*, 12, 218 (1963).
(13) F. Kalsbeek and J. A. Cohen, *Biochim. Biophys. Acta*, 4, 559 (1950).
(14) I. B. Wilson, *J. Biol. Chem.*, 190, 111 (1951).
(15) P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 57, 755 (1935).
(16) A. P. Terent'ev, M. N. Preobrazhenskaya, and G. M. Sorokina, *J. Gen. Chem. USSR*, 29, 2835 (1959).
(17) P. L. Julian, J. Pikl, and D. Boggess, *J. Amer. Chem. Soc.*, 56, 1797 (1934).
(18) M. Kuhn, *J. Prakt. Chem.*, 156, 103 (1940).
(19) J. B. Henrickson, R. Goschke, and R. Rees, *Tetrahedron*, No. 20, 565 (1964).
(20) E. J. Poziomek, D. N. Kramer, W. A. Mosher, and H. O. Michel, *J. Amer. Chem. Soc.*, 83, 3916 (1961).
(21) G. L. Ellman, K. D. Courtney, V. Andrews, and R. M. Featherstone, *Biochem. Pharmacol.*, 7, 88 (1961).


# 10,11-Dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide, a Metabolite of Carbamazepine Isolated from Human and Rat Urine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The synthesis of 10,11-dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide from carbamazepine (Tegretol) is described and this is shown to be one of the metabolites of carbamazepine. The extraction procedure is described fully and further details about the metabolic pathway are discussed, in which carbamazepine epoxide is proposed as an intermediate. The synthesis of another possible metabolite, 10,11-dihydro-10-hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide, from carbamazepine epoxide is also described, although this has not been found as a metabolite in urine. The decomposition of 10,11-dihydroxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carboxamide to acridine-9-carboxaldehyde under glc conditions is also discussed.


To date the metabolic fate of carbamazepine (Tegretol) (**1**) in humans and the experimental animal has not been completely determined. In previous reports we have described the pharmacokinetics of the drug in animals and humans[1-4] and the isolation and chemical and physical characterization of another metabolite, 10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carboxamide 10,11-epoxide (**2**).[3-6] There was also evidence to suggest the presence of two hydroxylated derivatives in human urine following carbamazepine administration.[1-4] We report here the syntheses of 10,11-dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide (**3**) and 10,11-dihydro-10-hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide (**4**) and the isolation of one of these as a metabolite from rat and human urine. The mass spectrometric characterization of the dihydroxy compound **3** as well as the gas chromatographic behavior will be mentioned. The finding of metabolite **3** has also been very recently reported by other workers.[7,‡]

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## Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer 157 spectrophotometer as Nujol mulls and nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal reference and DMSO-$d_6$ as solvent. Mass spectra were obtained on an LKB 9000 instrument operating under the previously described conditions.[3] Thin-layer chromatography was carried out on silica gel plates (Woelm precoated F256/366). Gas chromatography was carried out on a Carlo Erba Fractovap G1 chromatograph using a 2-m, 3% OV-17 or SE-30 column operating at 220–250° with an injection port temperature of 270°. Radiochromatograms were scanned on a Packard Radiochromato-Scanner Model 7201 and radioactive determinations were made on a Nuclear Chicago Isocap 300 liquid scintillation system. Samples were counted in 15 ml of a scintillation solution of butyl PBD (7 g) in toluene–ethylene glycol monomethyl ether (2:1) (1 l.). Counts were corrected by the external standard procedure with a counting efficiency of 80–89%. Cold and labeled 10,11-[$^{14}C_2$]-carbamazepines were generously supplied by Ciba-Geigy, Basel.

**10,11-Dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide (3).** Carbamazepine (**1**)[8] (2.36 g, 10 mmol) in pyridine (1 ml) was added to a solution of $OsO_4$ (2.53 g, 10 mmol) in benzene (260 ml). The reaction mixture was stirred at room temperature for 2 days and the resulting dark precipitate collected and dried. Hydrolysis with a solution of *d*-mannitol (2.6 g) and NaOH (7 g) in water (50 ml) afforded a pale yellow solid which was washed with water and dried. Crystallization from EtOH gave **3** (1.5 g, 56%): mp 242–