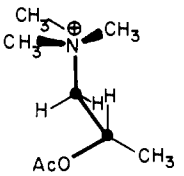
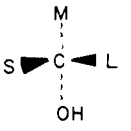
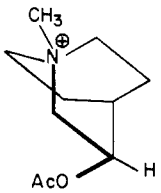
formula II yield an excess of the (−)-(*S*)-enantiomer of methyl *p*-tolyl sulfoxide. Having obtained an excess of the latter from (+)-3-quinuclidinol,[1] it follows that configuration II where S = H, M = CH_2N^+ and L = $CH(CH_2)_2$ applies. In the *RS* nomenclature, however, the substituent sequence in decreasing order of priorities is HO, CH_2N^+,$CH(CH_2)_2$ and H (III).



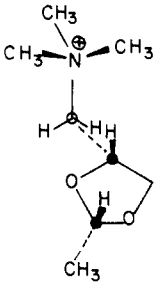
(I)



(II)



(III)



(IV)

Hence, (+)-3-quinuclidinol has the (*S*) configuration and of the two enantiomeric 3-acetoxyquinuclidine methiodides, that which acts as a substrate for AChE and which is the most active as a muscarinic agent[1] has the (*R*) (−) configuration (III). Therefore, the bridgehead carbon of the latter *does not occupy a position equivalent to that of the β-methyl group of I so that one is here dealing with another case of apparent inversion of optical specificity of the receptor and enzyme binding sites.*[6] The steric relations are as shown in I and III where the methyl group of the former assumes an orientation very close to that in the crystal.[3] The relative orientations of the acetoxy and quaternary moieties in I cannot be maintained in (*R*)-(−)-β-methylacetylcholine (the enantiomer of I) owing to prohibitive repulsions between the β-methyl and trimethylammonium groups.

We wish to emphasize that eclipsed conformations of this type were considered improbable[1] and at best one might admit a skewed conformation for the groups concerned.[1] It can now be stated with an increased degree of confidence that such high energy conformations appear not to be favored in the bound state at the AChE and muscarinic receptor levels. We can further conclude in the light of the present analysis that the muscarinic agonist L-*cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide,[8] whose crystal structure has recently been analyzed,[7] probably assumes conformation IV at the receptor level. This conformation is in fair agreement with the recent observations of Garrison, *et al.*,[8] on structure–activity relationships among constrained analogs.

(6) B. Belleau and J. Puranen, *J. Med. Chem.*, **6**, 325 (1963).
(7) P. Paoling and T. J. Petcher, *Chem. Commun.*, 1258 (1969).
(8) D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle, *J. Med. Chem.*, **12**, 130 (1969).

Our previous arguments regarding the possible stabilization of strained conformations by receptor proteins[1] remain valid in principle, although our results with the quinuclidine analogs of I give no evidence that this is the case at the AChE and receptor levels. It is significant that the β-methyl group of I fails to modify the biological activity of ACh only because it cannot interfere with the chirality of the latter in the bound state. In the (*R*)-(−) analog III, the rigid ring system would simply serve to force the inactive (*R*)-(−)-β-methylacetylcholine pattern into the proper chirality about the acetoxy and the quaternary moieties for productive interaction with the ACh binding sites. The present correct interpretation strongly supports conformation I for receptor and enzyme bound ACh (β-Me absent). A similar conformation has recently been proposed by Chothia[9] on the basis of extrapolations from crystallographic data. However, dioxolane IV, the most active muscarinic agent known to date, was not discussed in detail, and it is interesting to note that its crystal structure[7] does not quite fit the sought-for general patterns.[9] The X-ray structure of III will be reported in due course by one of us (P. P.).

Acknowledgments. The experimental part of this work (ref 1) was supported by the Defense Research Board of Canada and the National Research Council of Canada.

(9) C. Chothia, *Nature*, **225**, 36 (1970).

Synthesis of Compounds Related to Muscimol (Pantherine, Agarin)

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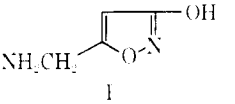
Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

Received October 29, 1969

The mushroom *Amanita muscaria* contains a number of biologically active compounds including a substance which has central nervous system effects and produces narcosis in flies.[1] This substance is known as pantherine, pyroibotenic acid, agarin, and muscimol; the latter is the preferred name.[2] The isolation and elucidation of the structure of this material (I) has been



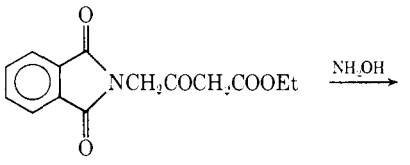
I

described by four independent groups of workers,[3] and its synthesis has been reported by Gagneux, *et al.*[4] In

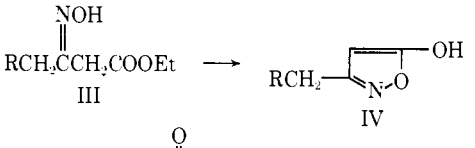
(1) C. H. Eugster, F. Häfliger, R. Deuss, E. Girod, *Helv. Chim. Acta*, **41**, 205, 583, 705 (1958); C. H. Eugster, *Publ. Naturforsch. Ges. Zurich*, Dec 31, 1966; T. Wieland, *Science*, **159**, 946 (1968).
(2) C. H. Eugster and T. Takemoto, *Helv. Chim. Acta.*, **50**, 126 (1967).
(3) (a) M. Onda, H. Fukushima, and M. Akagawa, *Chem. Pharm. Bull.*, **12**, 751 (1964); (b) T. Takemoto, T. Nakajima, and T. Yokobe, *J. Pharm. Soc. Jap.*, **84**, 1232 (1964); (c) C. H. Eugster, G. F. R. Muller, and R. Good, *Tetrahedron Lett.*, **23**, 1813 (1965); (d) K. Bowden and A. C. Drysdale, *ibid.*, **12**, 727 (1965).
(4) A. R. Gagneux, F. Häfliger, C. H. Eugster, and R. Good, *ibid.*, **25**, 2077 (1965); see also Belgian Patent 656,754 (1964) and Netherlands Patent 6,414,138 (1965); *Chem. Abstr.*, **63**, 16356*b* (1965).

this communication we describe the synthesis of a derivative of the "iso" analog IV and the synthesis of the "aza" analog X.

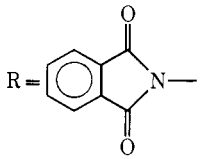
For the synthesis of "isomuscimol," the reaction of ω-phthalimidoacetoacetic ester (II)[5] with $HONH_2$ was examined. This reaction would be expected to proceed *via* III, as shown, since only one reference is



II



III IV



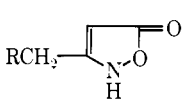
known[6] in which an acetoacetic ester reacts with $HONH_2$ to form the hydroxamic acid rather than the oxime. If reaction were to proceed *via* the latter course, the product would be the *N*-phthaloyl derivative of muscimol.

The reaction of II with $HONH_2$ proved to be very sensitive to reaction conditions, and gave a complex mixture of products. When $HONH_2 \cdot HCl$, NaOAc, and AcOH were used, only tars were obtained; $HONH_2 \cdot HCl$ and NaOAc in EtOH gave V and VI; on refluxing for 2 hr with $HONH_2 \cdot HCl$ in EtOH–H_2O, the product was largely VI. The reaction of II with $HONH_2 \cdot HCl$

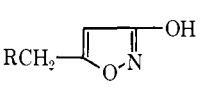
$$\text{II} \xrightarrow{NH_2OH} \underset{\text{V}}{RCH_2COCH_3} + \underset{\text{VI}}{RCH_2C(=NOH)CH_3} + \text{III} + \text{IV}$$

in hot EtOH after 5 min gave mostly III; the same solution on longer heating gave IV as the major product in addition to small amounts of III, V, and VI. Compound IV was best prepared from $HONH_2 \cdot HCl$ and II in EtOH at room temperature, or by treatment of III with acid.

The structure assigned to IV is consistent with its elemental analysis, with the fact that intermediates III and VI can be isolated, and with the intense purple $FeCl_3$ test it gives. Its sensitivity to nucleophilic reagents (described below) is also consistent with the structure, since IV in its tautomeric form (IVa) is, in



IVa



VII

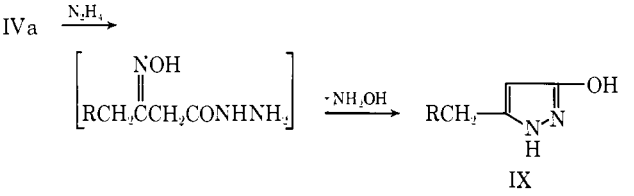
fact, an *O*-acylhydroxylamine, and such compounds are known to be highly reactive acylating agents.[7] Finally, the isomeric substance, *N*-phthaloyl muscimol (VII) was prepared and shown to be different from IV. It does not give a color with $FeCl_3$.

(5) S. Gabriel and J. Colman, *Ber.*, **42**, 1243 (1909).

(6) A. R. Katrizky and S. Øksne, *Proc. Chem. Soc.*, 387 (1961).

(7) G. H. L. Nefkens and G. I. Tesser, *J. Amer. Chem. Soc.*, **83**, 1263 (1961); G. T. Young and B. O. Handford, British Patent 1,085,916 (1967).

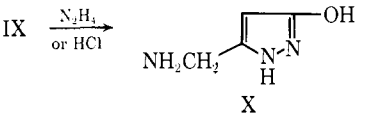
In an attempt to remove the phthaloyl group, IV was heated with 1 equiv of hydrazine; the product was IX the phthaloyl derivative of "azamuscimol." This product is consistent with a reaction in which highly reactive IVa gives the intermediate VIII, which then cyclizes to the pyrazole IX.



IX

Compound IX was also readily obtained by direct reaction of II with 1 equiv of hydrazine hydrate in EtOH. IX exists in a variety of tautomeric forms; the form obtained varied with the solvent used for recrystallization, but all had the same melting point.

Attempts to remove the phthaloyl group in IV by heating with HCl led to complete decomposition; the only products isolated were phthalic acid and NH_4Cl. The phthaloyl group in IX was readily removed by heating with hydrazine or with excess HCl, giving azamuscimol (X).



X

The ease with which the phthaloyl group was removed from IX is in marked contrast with the report of Bradshaw, *et al.*,[8] who found that a phthaloyl group could *not* be removed from the closely related compound, 2-phenyl-5-phthalimidomethylpyrrazolone.

Since the syntheses of muscimol described in the literature[4] are lengthy, the use of II in a potential 2-step synthesis of muscimol was further investigated. II was converted in high yield into the ethylene ketal, XI, using BF_3 etherate and ethylene glycol in dioxane, and into the thioketal, using BF_3 etherate and ethylenedithiol in $CHCl_3$; other methods of preparing the ketals failed.

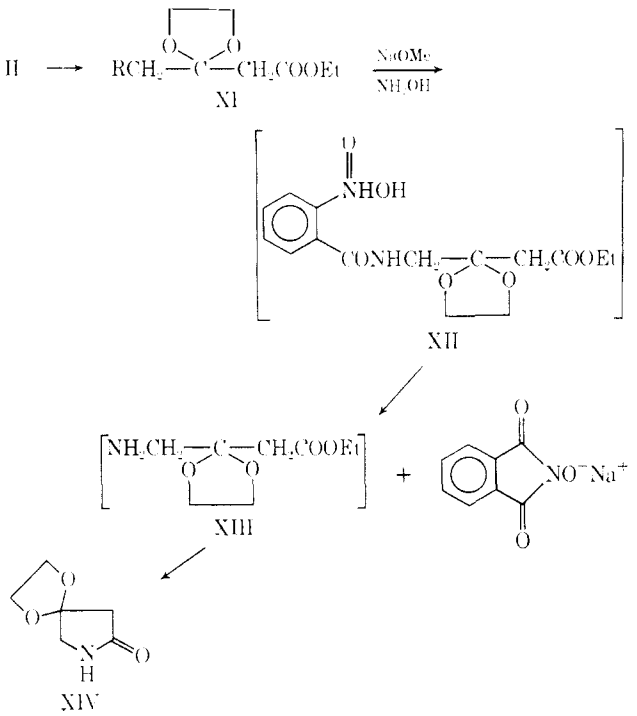
The ketal XI did not react with free $HONH_2$. However, when NaOMe was added a rapid series of reactions occurred. Shortly after all reagents were mixed the solution gave a positive $FeCl_3$ test; several minutes later the Na salt of *N*-hydroxyphthalimide precipitated and the solution no longer gave a positive $FeCl_3$ test. On work-up, the product isolated was the pyrrolidone ketal XIV.

The probable sequence of reactions leading to XIV is shown in Scheme I. Compound XII accounts for the transient $FeCl_3$ test; it may be formed directly from XI or, more likely, from an intermediate methyl phthalamate (this could account for the necessity of methoxide). Ring closure then occurs liberating *N*-hydroxyphthalimide, which does not give a $FeCl_3$ test, and the ketal XIII which would spontaneously cyclize to XIV.

None of the compounds IV, VII, IX, or X showed the potent CNS depressant effects of muscimol, however, III and X produced a significant lowering of blood

(8) J. Bradshaw, H. Stephen, and C. Weizmann, *J. Chem. Soc.*, 803 (1915).

SCHEME I



pressure in the metacorticoid rat preparation.[9] Compound X produced a lowering of the systolic blood pressure of rats in which the control readings were 223 ± 10 mm/kg. There was a 37 and 19 mm drop 5 and 24 hr post drug administration of 48.6 mg/kg p.o. on day 1, and a 49 and 39 mm drop post drug administration of 48.6 mg/kg p.o. on day 2. In a similar test with III, using rats in which the control readings were 183 ± 15 mm/kg, there was a 15 mm drop 5 hr post drug on day 1, and a 20 mm drop 5 hr post drug on day 2 following administration of 80 mg/kg po. Neither of the compounds lowered blood pressure in the neurogenic dogs[10] at doses up to 10 mg/kg po.

Experimental Section[11]

Ethyl 3-Oximino-4-phthalimidobutyrate (III).—A solution of 3.81 g of $NH_2OH \cdot HCl$ in 20 ml of H_2O was added to a suspension of 15 g of II[5] in 135 ml of warm EtOH. The mixture was warmed on a steam bath with agitation until dissolution was complete (about 5 min). It was then chilled immediately in an ice bath, and the crystalline starting material was removed by filtration. The filtrate was diluted with 250 ml of H_2O. On standing, the product deposited. After washing with H_2O and drying, 8.8 g of crude III was obtained. Recrystallization from C_6H_6 gave 7.4 g of III, mp 133–135°. *Anal.* ($C_{14}H_{14}N_2O_5$) C, H, N.

3-(Phthalimidomethyl)-5-hydroxyisoxazole (IV).[12] **(a) From II.**—A suspension of II[5] (5 g) and 1.27 g of $NH_2OH \cdot HCl$ in 50 ml of EtOH was stirred at 25° for 18 hr. The mixture was filtered and washed (H_2O, EtOH) to give 2.8 g of crude product, mp 178–183°. Digestion with 80 ml of hot EtOH for 30 min gave 2.4 g of IV, mp 187–190°. *Anal.* ($C_{12}H_8N_2O_4$)C, H, N.

(b) From III.—A solution containing 0.5 g of III and 1 ml of satd Et_2O–HCl in 25 ml of EtOH was stirred at 25° for 18 hr. The precipitated product, 0.21 g, was isolated on dilution of the reaction mixture with H_2O. The melting point and ir spectrum were identical with those of the material obtained above.

Phthalimidoacetone (V) and Oxime (VI).—To the ester II (5 g, 0.017 mol) in 32 ml of EtOH was added a solution of 2.3 g of $NH_2OH \cdot HCl$ and NaOAc in 7 ml of H_2O, and the mixture was heated for 2 hr during which time the color turned red-brown. Concentrated HCl (2.5 ml) was added and heating was continued for 0.5 hr. On cooling, light orange crystals precipitated and were filtered, 2.5 g, mp 180–183. After recrystallization there was obtained 1.9 g of VI, mp 187–190°. *Anal.* ($C_{11}H_{10}N_2O_3$) C, H, N.

The filtrate from the orange crystals was concentrated and extracted with EtOAc–C_6H_6. Concentration gave an oil which contained a large amount of V, as shown by comparison of the ir and tlc with that of authentic material.[5]

Reaction from Which III, IV, V, and VI Are Isolated.—A solution of 1.5 g of $NH_2OH \cdot HCl$ in 30 ml of H_2O was added to 5 g of II; 27 ml of EtOH was added and the mixture was heated on a steam bath. After 1.5 hr, a sample was removed which, on cooling and diluting with H_2O, gave a precipitate, mp 108–140°, containing III and IV (tlc and ir). After 2 hr, the solution was cooled, and 3.5 g of IV precipitated, mp 145–155°, after recrystallization from EtOH, mp 188–190°. The filtrate from IV was diluted with H_2O and extracted with $CHCl_3$, giving 1 g of solid, which was heated with C_6H_6. The insoluble material was filtered and recrystallized from EtOAc to give 0.1 g of IV, mp 186–87°. The filtrate was diluted with a large vol of petroleum ether and decanted from the gum. Concentration gave a solid which was recrystallized from *i*-Pr_2O to give V, mp 109–110° (lit.[5] mp 124°). *Anal.* ($C_{11}H_9NO_3$) C, H, N. All compounds were identified by comparison with samples prepared as described elsewhere (tlc, ir, and mmp).

***N*-Phthaloylmuscimol** (VII).—Muscimol (1) (1.14 g) was dissolved in 20 ml of H_2O containing 2.9 g of Na_2CO_3, then 2.2 g of *N*-carbethoxyphthalimide was added and the pH was adjusted to 1.5 by the addition of dil HCl. After 1 hr satd NaCl solution was added and white solid 3-hydroxy-5-(1-carboxybenzamidomethyl)isoxazole precipitated, 1.85 g, mp 192°. The melting point was unchanged after recrystallization from MeCN (resolidifies then remelts at 225–230° dec). *Anal.* ($C_{12}H_{10}N_2O_5$) C, H, N.

The acid (0.1 g) was suspended in PhMe (8 ml), 1 drop of Et_3N was added and the suspension was heated at reflux. The solid slowly dissolved then a new solid VII separated (70 mg), mp 225–230° dec. It was recrystallized from EtOH, 40 mg, mp 232–235°. *Anal.* ($C_{12}H_8N_2O_4$)C, H, N.

5-(Phthalimidomethyl)-2-hydroxypyrazole Dihydrochloride (IX). **(a) From II.**—A suspension of 27.5 g (0.1 mol) of II and 3.2 ml of 97% N_2H_4 in 500 ml EtOH was stirred at 25° for 18 hr. After 2 hr everything dissolved; after 4 hr product began to precipitate. The resulting yellow solid was filtered and washed with Et_2O to give 16.3 of IX, mp 293–295° dec. Concentration of the mother liquor gave an additional 3.6 g of crude IX, mp 255–270°. *Anal.* ($C_{12}H_9N_3O_2$) C, H, N.

(b) From IV. Hydrazine (0.43 ml of 33% solution) was added to a suspension of 1 g of IV in a mixture of 5 ml of EtOH and 5 ml of dioxane. The solid soon transposed to a yellow solid. After 4 days this converted into a new white solid (0.5 g) which was filtered. This was recrystallized from DMSO–H_2O, mp 296° dec, identical with the material described above.

3-Hydroxy-5-aminomethylpyrazole Dihydrochloride (X). **a.**—IX (5 g) in 75 ml of 20% HCl was heated at reflux for 3 hr. After cooling the precipitated phthalic acid was removed and the filtrate was concentrated. The crystalline residue was recrystallized from MeOH–*i*-Pr_2O to give X·2HCl, 1.7 g, mp 240–241°. *Anal.* ($C_4H_9Cl_2N_3O$) C, H, Cl, N.

b.—IX (6 g) and 1 ml of 85% N_2H_3 in 60 ml of EtOH was heated at reflux for 3 hr. The precipitate was filtered and redissolved in dilute HCl. The solution was concentrated and the product isolated as above, mp 240–241°.

Ethyl ω-Phthalimidoacetoacetate Ethylene Ketal (XI). —Dry ethylene glycol (6.96 g, 0.112 mol) and 20 g of II were dissolved in dry dioxane and 23.2 ml of BF_3–etherate was added. After 3 days the solution was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2, washed with $NaHCO_3$ solution, dried, and concentrated to give 27 g of an oil which crystallized on stirring. The material could be purified by recrystallization from *i*-Pr_2O or by distillation, bp 186–189° (0.5 mm), yield 21 g, mp 74–75°. *Anal.* ($C_{16}H_{17}NO_6$) C, H, N.

(9) F. Del Greco, F. Olmstead, G. M. C. Masson, and A. C. Corcoran, *J. Lab. Clin. Med.*, **41**, 729 (1953).

(10) K. S. Grimson, *Arch. Surg.*, **43**, 284 (1941).

(11) All melting points are corrected. Analyses were performed by the Analytical Department of these laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(12) Compound IV was mentioned in an article by K. Bowden, G. Crank, and W. J. Ross, *J. Chem. Soc.*, 172 (1968) but neither synthesis nor properties were described.

Ethyl ω-Phthalimidoocetoacetate Ethylene Thioketal.—Ester II (5 g, 0.018 mol) and 2.7 g (0.028 mol) of ethanedithiol were dissolved in $CHCl_3$ and 5.8 ml of BF_3–etherate was added. The solution was stirred 3 hr at 25°, then was washed with $NaHCO_3$ solution, dried, and concentrated. After long standing it partly crystallized from *i*-Pr_2O, 3.1 g, mp 71–72°. *Anal.* ($C_{16}H_{17}NO_4S_2$) C, H, N, S.

Pyrrolidine-2,4-dione 4-Ethylene Ketal (XIV).—NaOMe (0.32 g, 0.006 mol) was added to a solution of 2 g of XI (0.006 mol) and 0.23 g (0.007 mol) of NH_2OH in MeOH. The solution turned pale yellow, then bright yellow, orange and, after 15 min, red. Shortly afterwards a solid precipitated. After 16 hr, the solid Na salt of *N*-hydroxyphthalimide (0.6 g) was filtered, the filtrate was diluted with a large volume of *i*-Pr_2O and more Na salt (0.25 g) was removed. The filtrate was concentrated giving 1.5 g of crude XIV, as an oil. This material slowly recrystallized and was then sublimed *in vacuo* and recrystallized from *i*-Pr_2O, to give 0.7 g of XIV, mp 98–101°. The compound shows a typical lactam absorption in the ir at 5.92 μ. *Anal.* ($C_6H_9NO_3$) C, H, N.

Acknowledgment.—We are indebted to Dr. Timothy Jen for the synthesis of *N*-phthaloylmuscimol, to Dr. Herbert Winicov for the muscimol, and to Mr. Edward Macko and Dr. Richard McLean for the biological test results.

Benzimidazole-5(6)-alanine and Related Compounds. 1. Synthesis of Amino Acids as Inhibitors of Norepinephrine Biosynthesis[1a]

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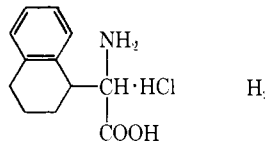
Received October 27, 1969

The potential usefulness of inhibitors of norepinephrine biosynthesis at the level of tyrosine hydroxylase is widely recognized. Inhibitors of phenylalanine hydroxylase offer a potential model for phenylketonuria.

1,2,3,4-Tetrahydronaphthyl-1-glycine hydrochloride (**3**) was prepared by standard reactions as described in the Experimental Section. 3-Nitro-4-aminophenylalanine (**6**) was prepared by standard reactions from *p*-nitrophenylalanine. Benzimidazole-5(6)-alanine dihydrochloride (**7**) was prepared by reduction of **6** and cyclization of the resulting *o*-phenylenediamine by the Phillips method.[2] The unstable intermediate *o*-phenylenediamine analog was not isolated. 3,4-Ethylenedioxyphenylalanine hydrochloride was obtained by the hydrogenation of the oxime formed from the reaction of isopropyl nitrite with the condensation product of 3,4-ethylenedioxybenzyl chloride and sodium diethyl malonate.



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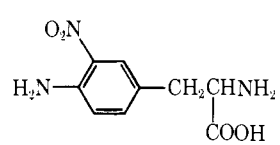

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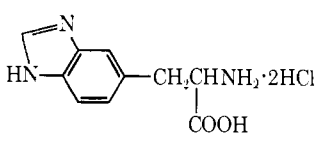

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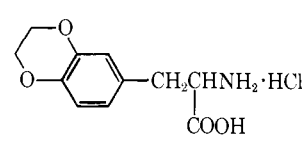

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Biological Activity.—Bovine tyrosine hydroxylase was prepared and purified by slightly modifying previously described methods.[3,4] Tyrosine hydroxylase inhibition was determined[5] using a concentration of 5×10^{-5} *M* L-tyrosine (see Table I).

TABLE I
PER CENT INHIBITION OF TYROSINE HYDROXYLASE[a]

Compd	10^{-3} *M*	10^{-4} *M*	10^{-5} *M*
3	32[a]		4
6	29	8	
7	97		22
12	15		6

[a] All values are the average of triplicate runs; iodotyrosine was run as a standard in each run and consistently yielded inhibition of approximately 50% at 10^{-5} *M* and 10% at 5×10^{-7} *M*.

Rat liver phenylalanine hydroxylase was prepared by the method of Kaufman[6] through the first $(NH_4)_2SO_4$ step and stored frozen in 200-μl fractions. Phenylalanine hydroxylase inhibition was carried out as described by Guroff and Abramowitz,[7] the tyrosine produced being measured spectrophotofluorometrically.[8] A K_m of 2.1×10^{-4} *M* for L-phenylalanine was obtained by a Lineweaver–Burke[9] plot of this enzyme preparation.

Compounds **3**, **6**, and **12** were tested at concentrations up to 2×10^{-3} *M* in a system containing 2×10^{-4} *M* L-phenylalanine and no inhibition was noted. The K_i of **7** determined by the method of Lineweaver and Burke, was found to be 2.1×10^{-4} *M* and appeared competitive.

Experimental Section[10]

1,2,3,4-Tetrahydronaphthyl-1-malonic acid (1) was obtained by hydrolysis of ethyl 1,2,3,4-tetrahydronaphthyl-1-malonate;[11]

(1) (a) Supported by Fellowship 4-F1-GM-18,614 and Grant AM-06480 from the National Institutes of Health, U. S. Public Health Service. (b) In partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Maryland, 1967. Present address: Merck, Sharp and Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N. J. 07065. (c) Department of Chemistry, University of Northern Illinois, Dekalb, Ill. 60115. (d) To whom inquiries should be addressed.

(2) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(3) T. Nagatsu, M. Levitt, and S. Udenfriend, *J. Biol. Chem.*, **239**, 2910 (1964).

(4) M. Ikeda, L. A. Fahien, and S. Udenfriend, *ibid.*, **241**, 4452 (1966).

(5) S. Udenfriend, P. Zoltzman-Nirenberg, and T. Nagatsu, *Biochem. Pharmacol.*, **14**, 837 (1965).

(6) S. Kaufman, *Methods Enzymol.*, **5**, 809 (1962).

(7) G. Guroff and A. Abramowitz, *Anal. Biochem.*, **19**, 548 (1967).

(8) T. D. Waalkes and S. Udenfriend, *J. Lab. Clin. Med.*, **50**, 733 (1957).

(9) J. L. Webb, "Enzyme and Metabolic Inhibitors," Vol. 1, Academic Press, New York, 1963, p 150.

(10) The melting points, all uncorrected, were determined on a Thomas-Hoover melting point apparatus. Ir spectra were obtained on a Perkin-Elmer Infracord, Model 137 and uv spectra on a Beckman DB spectrophotometer. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

(11) Synthesized as described by M. Protiva, J. Jilek, F. Vejdelek, and P. Finglova, *Chem. Listy*, **47**, 584 (1953).