1,2,3,4,6,7,12,12a-Octahydro-2-phenylpyrazino-[2′,1′:6,1]pyrido[3,4-*b*]indole

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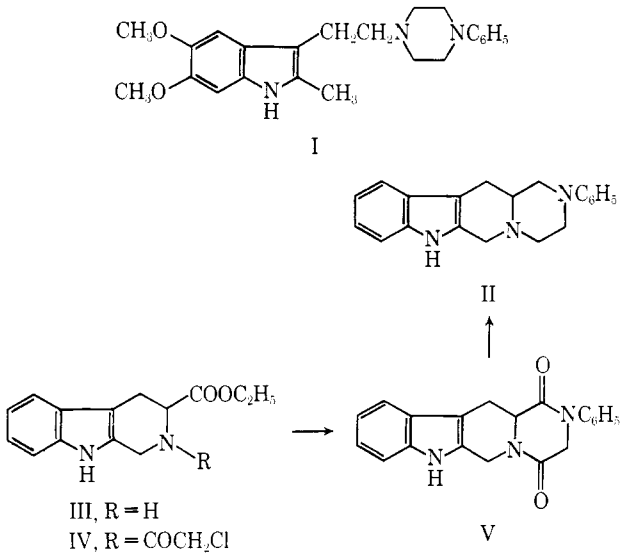
We wish to report the synthesis of the title compound (II) which we believe represents a new ring system. The indole II was of potential interest to us because of its structural relationship to the major tranquilizer oxypertine (I).[1]

The tricyclic ester III was prepared in two steps from tryptophane by a literature method.[2] Treatment of III with $ClCH_2COCl$ furnished the amide IV which was heated with $PhNH_2$ in Cellosolve to afford the cyclized product V. Reduction of V with LAH provided the desired amine II.

In contrast to oxypertine, compound II is not a CNS depressant. It failed to potentiate hexobarbital at 100 mg/kg po in mice.[1b] At a dose of 1 mg/kg po in mice, II produced a 91% increase in spontaneous activity, whereas oxypertine had caused a marked decrease.[1a,3]



Experimental Section[4]

Ethyl 2-(Chloroacetyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]-indole-3-carboxylate (IV).—A solution of 11.3 g (0.10 mole) of $ClCH_2COCl$ in 15 ml of $CHCl_3$ was added over 40 min to a stirred solution of 10.0 g (0.041 mole) of ethyl 1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole-3-carboxylate (III)[2] in 200 ml of $CHCl_3$. The mixture was refluxed for 6 hr, 20 ml of MeOH was added, and the solvent was removed *in vacuo*. The crystalline residue was recrystallized from C_6H_6–*n*-heptane (charcoal) to give 11.0 g (84%) of tan prisms, mp 143–145°. *Anal.* ($C_{16}H_{17}ClN_2O_3$) Cl, N.

2,3,6,7,12,12a-Hexahydro-2-phenylpyrazino[2′,1′:6,1]pyrido-[3,4-*b*]indole-1,4-dione (V).—A mixture of 18.0 g (0.056 mole) of IV (above), 6.7 g (0.072 mole) of $PhNH_2$, and 300 ml of Cellosolve was refluxed 18 hr. The solvent was removed *in vacuo*, the residue was extracted with hot EtOAc, and the extracts were washed with dilute aqueous HCl and aqueous NaCl. Removal of the EtOAc left a residue which could be crystallized directly. However, it was preferable to chromatograph the material on silica. Elution with EtOAc gave a solid which was washed with Et_2O, then recrystallized from EtOAc to furnish 10.3 g (56%) of tan prisms, mp 254–257°. *Anal.* ($C_{20}H_{17}N_3O_2$) C, H, N.

1,2,3,4,6,7,12,12a-Octahydro-2-phenylpyrazino[2′,1′:6,1]pyrido-[3,4-*b*]indole (II).—A mixture of 5.70 g (0.017 mole) of V, 3.3 g (0.088 mole) of LAH, and 500 ml of dry THF was refluxed for 48 hr. After cooling, aqueous THF was added, and the mixture was filtered. The insoluble material was washed with hot THF and the solvent was removed from the combined filtrates to give a dark residue which was chromatographed on silica. Elution with C_6H_6–Et_2O gave crystals which were recrystallized from C_6H_6–heptane to furnish 1.54 g (30%) of tan product, mp 228–232°. *Anal.* ($C_{20}H_{21}N_3$) C, H, N.

(1) (a) S. Archer, D. W. Wylie, L. S. Harris, T. R. Lewis, J. W. Schulenberg, M. R. Bell, R. K. Kullnig, and A. Arnold, *J. Amer. Chem. Soc.*, **84**, 1306 (1962); (b) D. W. Wylie and S. Archer, *J. Med. Pharm. Chem.*, **5**, 932 (1962).

(2) J. LeMen and C. Fan, *Bull. Soc. Chim. Fr.*, 1866 (1959).

(3) Data supplied by the Department of Pharmacology.

(4) Melting points were taken in capillaries and are uncorrected. Analytical results were determined by Mr. K. D. Fleischer and staff. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra of all compounds are compatible with the assigned structures.

Electronic Factors in Drug–Receptor Interactions

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The recent report by Cammarata[1] presented electronic mechanisms by which a drug and its receptor may interact. Pertinent equations for testing these mechanisms were also included. However, not all of the examples were tested statistically, and in one case a more rigorous analysis of the data was possible, yielding evidence in support of the mechanism. The following calculations have been performed on data in the above paper.

The relationship between frontier orbital charge density at the carbonyl carbon (f) and the potency of some nicotinic acid derivatives as inhibitors of acetylcholine esterase was noted[2] (Table I). The following equation

TABLE I
POTENCY OF NICOTINIC ACID DERIVATIVES AS INHIBITORS OF ACETYLCHOLINE ESTERASE[2]

Compound	Frontier orbital density, f	pI_{50} Obsd	pI_{50} Calcd, eq 1	pI_{50} Calcd, eq 2
Nicotinic acid	0.262	0.3	0.146	
Nicotinamide	0.616	1.2	2.03	1.23
3-Acetylpyridine	0.657	2.3	2.25	2.18
Ethyl nicotinate	0.699	3.1	2.47	3.15

was derived by us from the data by a least-squares technique. The correlation coefficient is not signifi-

$$pI_{50} = -1.247 + 5.322f \quad r = 0.868 \quad F_{1,2} = 6.16 \quad (t = 2.48) \qquad (1)$$

cantly different from zero.[3] If the nicotinic acid is omitted from the series (it is the only compound which would be in an ionic form at the pH of the studies) the

(1) A. Cammarata, *J. Med. Chem.*, **11**, 1111 (1968).

(2) A. Inouye, Y. Shinagawa, and Y. Takaishi, *Arch. Intern. Pharmacodyn.* **144**, 319 (1963).

(3) N. Draper and H. Smith, "Applied Regression Analysis," John Wiley & Sons, Inc., New York, N. Y., 1966.