Test compounds were typically administered 60 min prior to challenge by 5 mg/kg ip of amphetamine. The ED_{50} was calculated as the dose that produced a 50% decrease from control values in amphetamine-induced circlings.

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References and Notes

(1) (a) For paper 1 of this series, see V. J. Bauer, B. J. Duffy, D. Hoffman, S. S. Klioze, R. W. Kosley, Jr., A. R. McFadden, L. L. Martin, H. H. Ong, and H. M. Geyer, III., *J. Med. Chem.*, 19, 1315 (1976); (b) for paper 2, see S. S. Klioze, V. J. Bauer, and H. M. Geyer, III *ibid.*, 20, 610 (1977); (c) for paper 3, see S. S. Klioze and W. J. Novick, Jr., *ibid.*, 21, 400 (1978).

(2) G. M. Shutske, *J. Org. Chem.*, 42, 374 (1977).

(3) A. Marxer, H. R. Rodriguez, J. M. McKenna, and H. M. Tsai, *J. Org. Chem.*, 40, 1427 (1975).

(4) (a) M. Sidman, *Science*, 118, 157 (1953); (b) *Ann. N.Y. Acad. Sci.*, 65, 282 (1956).

(5) C. J. E. Niemegeers, F. J. Verbruggen, and P. A. J. Janssen, *Psychopharmacologia*, 16, 161 (1969).

(6) (a) L. Cook and E. Weidley, *Ann. N.Y. Acad. Sci.*, 66, 740 (1957); (b) L. Cook and A. C. Catania, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 23, 818 (1964).

(7) H. M. Hanson, C. A. Stone, and J. J. Witoslawski, *J. Pharmacol. Exp. Ther.*, 173, 117 (1970).

(8) A. Carlsson, *J. Psychiatr. Res.*, 11, 57 (1974).

(9) N.-E. Anden, *J. Psychiatr. Res.*, 11, 97 (1974).

(10) S. Fielding and H. Lal, "Industrial Pharmacology, Neuroleptics", Vol. 1, S. Fielding and H. Lal, Ed., Futura Publishing Co., Mount Kisco, N.Y., 1974, p 64.

(11) A. M. Ernst, *Psychopharmacologia*, 10, 316 (1967).

(12) R. J. Stawarz, H. Hill, S. E. Robinson, P. Setler, J. V. Dingell, and F. Sulser, *Psychopharmacologia*, 43, 125 (1975).

(13) J. O. Cole and D. J. Clyde, *Rev. Can. Biol.*, 20, 565 (1961).

Three-Dimensional Mapping of the Sweet Taste Receptor Site

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The active sites of the receptors for sweet and bitter tastants are shown to be related by a simple symmetry operation. This relationship, in turn, allows the identification of the critical geometrical features of both receptor sites. The model proposed for the sweet site is shown to be consistent with a large number of (conformationally rigid) sweet molecules.

Two of the so-called primary taste qualities,[1] i.e., sweet and bitter, can be elicited by a wide variety of apparently unrelated molecules.[1,2] It is the purpose of the present work to show that the active sites of sweet and bitter receptors are related by a simple symmetry operation and that it is possible to find the main geometrical features of both sites by using the shapes of conformationally rigid molecules as idealized molds.

Although the existence of common features among tastants had been suspected long ago, in relation with the theory of selective adsorption[3] of membrane proteins, it has been only in comparatively recent times that one of these features has been actually identified.

Shallenberger and Acree[4] have shown that a characteristic common to nearly all known sweet substances is an entity composed of a basic (B) and acidic (AH) group spaced of about 0.3 nm that should interact with a similar (complementary) entity of the receptor site, possibly through a pair of hydrogen bonds. Shallenberger has also shown[5] that the drastic differences in taste existing between amino acid enantiomers may be explained by the presence in the receptor site of a spatial barrier located at approximately 0.3 nm from the line joining AH and B. That is, sweet amino acids must have an R configuration since their side chain would otherwise "invade" the spatial barrier.

These facts (which henceforth shall be referred to as "Shallenberger's theory") do not account satisfactorily for all aspects of sweet taste. In particular, Shallenberger's theory gives no clues for the understanding of the large differences in relative sweetness among known tastants and does not explain why substances with the right AH–B entity (such as simple geometric isomers of known sweeteners) are completely tasteless. A dramatic example of this type is afforded by the two isomers of the oxime of anisaldehyde; the anti isomer is very sweet but the syn isomer is tasteless.[2]

A trivial way to overcome these difficulties may be to invoke the existence of multiple (specialized) sites for a given taste sensation. Evidence in favor of the existence of multiple sites both for the bitter and sweet taste has, in fact, been given by various authors.[6,7]

On the other hand, rather than attributing every peculiarity to an increasing number of distinct receptors it is certainly more fruitful to deepen the analysis of the properties of a given receptor site, trying to explain the taste of the greatest possible number of molecules in terms of a single site if it can be clearly identified.

In fact, the number of sweet molecules described by Shallenberger[4] in terms of the AH–B entity is large enough to justify the reference to a common receptor site. For the sake of clarity it may be convenient to classify the features of the active site as electronic or geometric although in some instances such a classification can appear somewhat artificial. The main "electronic" feature of this site is obviously represented by the AH–B entity itself, whereas the spatial barrier represents a simple geometric feature. It is the purpose of this paper to show how this view of
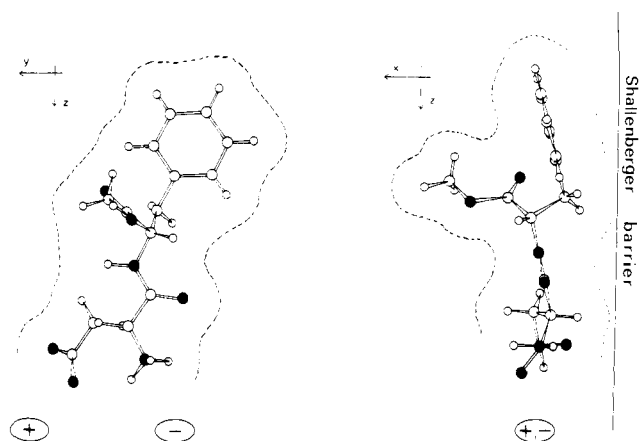
Figure 1. Molecular models of the most populated conformer of α-L-aspartyl-L-phenylalanine methyl ester. The axes of projection are respectively perpendicular and parallel to the spatial barrier proposed by Shallenberger.[5] The AH–B entity of the site is represented by the symbols (+) and (−). Open balls of different diameters represent carbon and hydrogen atoms; full balls represent heteroatoms. (The same symbols are adopted throughout, sulfur atoms being represented by full balls of larger diameter.)

the active site can be substantially improved.

When classes of chemically homologous substances are examined,[2] it is possible to notice that although, in some instances, vast differences in relative sweetness can be related to slight changes in chemical constitution, an increase in size is generally accompanied by a parallel increase in sweetness. It is also observed that beyond a critical value of the molecular size, sweetness is lost altogether. Should it be true that steric factors are critical for the interaction of sweet molecules with the receptor, it may be possible to identify the essential geometric features of the receptor site using the shape of many very sweet and bulky molecules as idealized molds of the site. This approach has been of rather limited usefulness in many problems of substrate–receptor interactions, but a few favorable circumstances render it very promising in our case.

First of all, unlike most substrate–receptor interactions the sweet taste response can be triggered by an enormous number of "substrates" of quite different chemical constitution and geometrical shape, so that any model of active site will be subject to a very severe test. Secondly, we can start from a reasonable working hypothesis by combining the findings of Shallenberger with a partial mapping of the site we have recently performed through the conformational analysis of α-L-aspartyl-L-phenylalanine methyl ester[8] (henceforth called α-APM), the prototype of a new class of sweeteners, the dipeptides of general formula α-L-Asp-X (where X is, in general, an amino acid residue with steric features similar to those of L-Phe). This molecule is a very useful "molecular mold" since it combines the properties of a very high sweetness and a very large molecular volume. It has been shown[8] that only the most populated conformer in aqueous solution has a molecular shape consistent with Shallenberger's theory. Figure 1 shows two projections of the molecular model of this conformer properly oriented with respect to the AH–B entity and the spatial barrier. The outer shape of the model, as dictated by the van der Waals radii of the atoms, should give an approximate contour of the minimal dimension of the receptor site. The main features of the site, emerging from the conformational analysis of α-APM, can be summarized as follows: it should have a flat shape coincident with the yz plane of Figure 1 (and containing
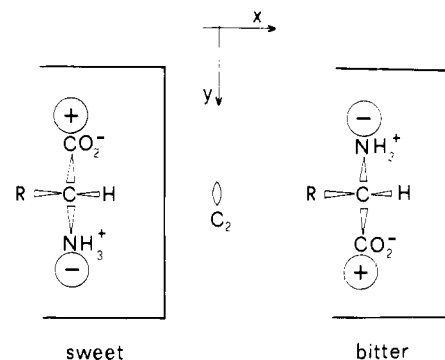

Figure 2. Scheme of the symmetry relationship between the active sites for sweet and bitter tastants. The binary axis interchanges only the (+) and (−) groups of the sites. The figure shows that the C_2 relationship may explain the selectivity toward enantiomers if the interaction of the side chain of the amino acid with the lateral walls of the site is not critical.

the AH–B entity); the vertical dimension of the site (i.e., that parallel to the z axis of the reference system of Figure 1) is critically connected with the relative sweetness of the molecules.

Thirdly, the puzzling relationship existing between the taste of certain enantiomers[5] points to a simple symmetry relationship between the sites of sweet and bitter tastes and confirms the essentially bidimensional nature of the active sites of both receptors.

Symmetry Considerations. It has been pointed out by many authors[5,9,10] that a change of the configuration of the α carbon of amino acids changes their taste from sweet (characteristic of the R configuration) to bitter or flat (S configuration). Some authors[9,11] even claim that the relative bitterness corresponds quantitatively to the relative sweetness. A similar behavior is exhibited also by the quoted dipeptides of general formula Asp-X.[12] For instance, α-L-Asp-L-PheOMe is sweet, whereas α-D-Asp-D-PheOMe is bitter. These observations would lead to the paradoxical conclusion that the active sites of the two receptors are related by mirror plane symmetry. It is clear that the evolution of two proteins related by such a symmetry transformation would require an impossibly high evolutionary effort if, as it is inevitable, they must be built up of residues of only one given configuration.

However, there is a simple way out of this paradox if the active site, as partly indicated by the quoted conformational study of α-APM,[8] is essentially a hemihedral cavity, i.e., if its depth in one dimension is much smaller than in the other two dimensions. Figure 2 indicates that, in this case, we can view the bitter and sweet sites as two very similar cavities in which only the AH–B entities are related by a C_2 axis. This model explains immediately even the quantitative relationship between the taste of enantiomers, since while only R isomers of amino acids can enter the sweet site without invading the "Shallenberger barrier"[5] (and only S isomers can enter the bitter site) both isomers would interact in the same way with the upper part of the site (i.e., approximately along the z direction) since the dimension of the molecule is not affected by the C_2 symmetry operation. On the other hand, we must assume that the interactions along other directions, including the y direction, are not critical, since otherwise we would end up again with two active sites related by mirror plane symmetry.

It is interesting to note that the 180° inversion of the AH–B entities may be accomplished by substituting only two amino acids in the sequence of the receptor protein. It is obviously possible that the bitter and sweet sites differ in a number of other electronic and/or steric features but
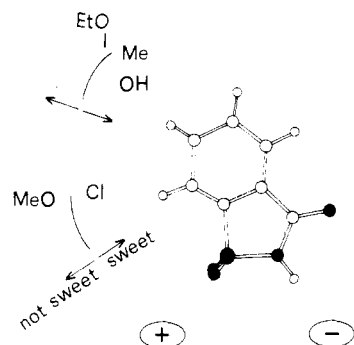
Figure 3. Identification of the spatial walls in the yz section of the sweet site. The location of the walls is based on the van der Waals radii of halogen atoms[14] (see text). Other substituted saccharins are correctly discriminated by the wall. The molecular models are based on the crystal structure of saccharin itself.[15]

it is worth emphasizing that our model represents the simplest explanation of the relationship between the taste of optical enantiomers.

Stereochemical Mapping. These considerations point to a model of the active site whose validity can be easily tested with the shapes of all rigid sweet molecules. In fact, both the symmetry relationship between sweet and bitter tastes and the study of α-APM lead to the fact that the active site ought to be nearly bidimensional. Should this be true, we can restrict the search of "molecular molds" only to molecules that are (geometrically) flat and conformationally rigid.

By orienting all of them in the same way in the yz plane of Figures 1 and 2, i.e., by forming the correct hydrogen bonds with the AH-B entity of the receptor site, it should be easy to identify an accurate shape of the yz section of the site.

The heuristic power of this approach is highest if we can use a very small number of molecules as molds and then be able to rationalize the sweet taste of all remaining sweet molecules.

The molecular models both of molecular molds and of the molecules used for testing the final shape of the active site were derived, whenever possible, from crystal structures. In all cases, however, when dealing with conformationally rigid molecules it is an easy job to build accurate molecular models from standard literature data. Specific sources for molecular parameters are quoted for each of the compounds appearing in the figures (vide infra).

A series of compounds that possess all the outlined requirements is the series of saccharins substituted on the benzene ring with halogen atoms. In particular let us examine the series of 6-halogenosaccharins. Sweetness is retained (although accompanied by an increasing bitter after taste) if we successively replace the hydrogen atom with F, Cl and Br and then drops to zero for 6-iodosaccharin.[13] It seems reasonable to connect this behavior with the presence (in the site) of a wall located approximately at the distance identified by the van der Waals radius of iodine. That is, if the reason for the observed trend in relative sweetness is mainly of sterical origin, the wall should discriminate also different molecules; e.g., saccharins with different substituents in position 6 should be sweet if they do not invade the wall.

Figure 3 shows that by means of this criterion it is possible to foresee the sweetness of 6-methyl-, 6-amino-, and 6-hydroxysaccharins, whereas 6-nitro- and 6-ethoxysaccharins are correctly predicted as not sweet.[13] In a similar way it is possible to extend the wall on the left-hand side of this section of the site by using the in-
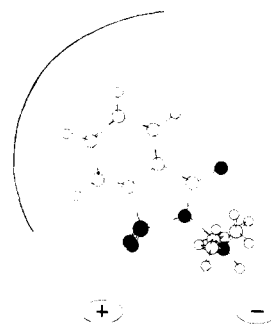

Figure 4. Approximate contours of the active site of the sweet receptor in the yz section, as derived by combining the shapes of some halogenosaccharins and of α-APM. The continuous line refers to identified walls; the dashed line shows only minimum contours. The Mannich base of saccharin was arranged by assuming for the grouping $O_2SNCH_2N^+(CH_3)_2H$ a conformation identical with that of the grouping $^-O_2CCHCH_2NH_3^+$ of α-APM. It is possible to see that interaction with the AH-B entity of the site (+, -) induces only a slight tilt of the rigid part of the molecule from the plane of saccharins unsubstituted at the nitrogen.

formation that 7-chlorosaccharin is sweet but 7-methoxysaccharin is not sweet.[13]

There are not many derivatives with substituents of different sizes on positions 4 and 5 of the benzene ring. Such a circumstance, however, is not critical for our mapping since the contours of the site in these directions are mainly outlined by the shape of α-APM. Notwithstanding we can use the shapes of 4- and 5-chlorosaccharins (that are sweet) to obtain minimum contours of the yz section in these directions.

Figure 4 shows the approximate contours of the site in section yz, derived by combining the information given by all mentioned saccharins and by α-APM. It must be noted that α-APM is the only representative of the class of sweeteners of general formula Asp-X of which we can use the shape, since it is the only one whose conformation has been studied in detail.[8] Accordingly it is probable that the contours determined solely on its shape represent only a lower limit. The shape of the site shown in Figure 4 is, however, sufficiently detailed for a meaningful comparison with the molecular models of other sweeteners. Figure 4 shows the fit in our model of the site of an "anomalous" saccharin, i.e., the Mannich base of saccharin with dimethylamine.[16] It has been found that the only N-substituted saccharins that have a sweet taste are hydroxymethylsaccharin and the Mannich bases of saccharins.[16] It is easy to see that the groupings O_2SNCH_2OH and $O_2SNCH_2N^+(CH_3)_2H$ represent AH-B entities almost identical with that of α-APM and that these saccharins can be fitted like saccharin itself in the receptor site, if the alkyl substituents can be kept essentially outside the site. It must be noted that the bulkiness of some of the amines of the Mannich bases that can be accommodated in the site[16] thus confirms that the side opposite to the Shallenberger's barrier is not critical or completely open.

Further tests of the goodness of our model of the receptor site are afforded by molecules of entirely different chemical constitution. One of the most puzzling cases of the influence of geometrical isomerism on taste is represented by the two oximes of anisaldehyde;[2] as mentioned previously the anti isomer is intensely sweet and the syn isomer is tasteless. Figure 5 shows quite convincingly that, in fact, only the anti isomer can fit the receptor site. A class of very sweet molecules is that of m-nitroanilines.
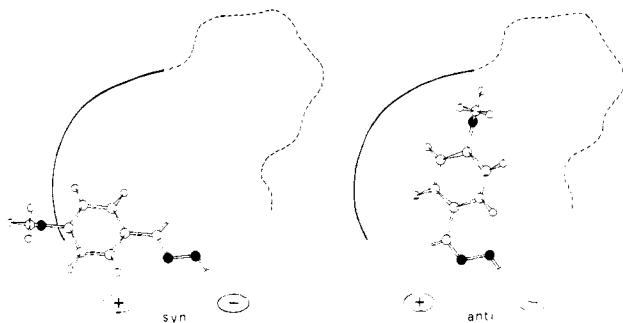
Figure 5. Arrangement in the sweet site of the two isomers syn (tasteless) and anti (very sweet) of the oxime of anisaldehyde. The nitrogen atom and the hydroxyl group are hydrogen bonded to (+) and (−) in a manner analogous to the oxygens and NH groups of saccharin, respectively. The molecular models were derived from the crystal structure of ref 17.
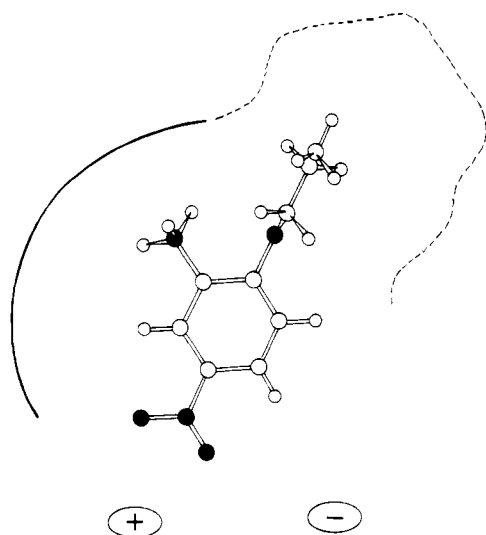

Figure 6. Arrangement in the sweet site of 2-propoxy-5-nitroaniline. The conformation of the propoxy chain is arbitrary but such as not to invade the spatial barrier proposed by Shallenberger. As for α-APM the good fit of a bulky hydrophobic portion of the molecule in the upper part of the site seems to be critically connected with the intensity of the sweet response (4100 times sweeter than sucrose[19]) This model was built using standard molecular parameters.[20]

Substitution of the hydrogen para to the nitro group with halogens and alkyl or alkoxy groups may increase the sweetness. This behavior has been explained on the basis of the relative hydrophobicity of the substituents.[18] Although this property may play a role it is clear from the models of Figure 6 that the main reason for the greater sweetness of the iodo- and propoxynitroanilines is the very good sterical fit of the receptor site.

Also in this case the bulkier (and flexible) substituents, if arranged not to invade the "spatial barrier",[5] can only point opposite to it, as if this side were completely open.

It must be noted that in order to fit the nitroanilines in the receptor site we must relax the requirements of Shallenberger[4] according to which both groups of the AH–B entity are essential, since the aromatic C–H groups can hardly be regarded as acidic (besides, also, many aliphatic nitro compounds are sweet[2]). In fact, if the AH–B entity has mainly the function of locking the sweet molecule, it is conceivable that only half the entity may be sufficient to lock a given molecule, provided that the sterical fit of the site is particularly good.

As further *visual* evidence of the generality of the model on sterical grounds it may be interesting to see the fit of
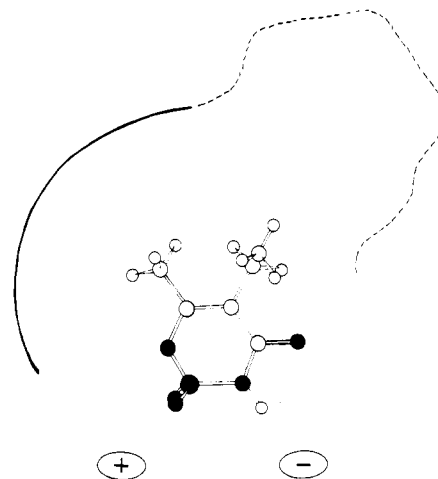

Figure 7. Arrangement in the sweet site of 5-ethyl-6-methyloxathiazinone dioxide (250 times sweeter than sucrose[21]). The model was built using standard molecular parameters.[20]

a member of a new class of sweeteners, oxathiazinone dioxides.[21] Figure 7 shows the arrangement in our site of 5-ethyl-6-methyloxathiazinone dioxide, the sweetest of these compounds.[21] We wish to point out that for this class of compounds it is also possible to rationalize the changes in relative sweetness linked to substitution in position 5 and 6 of the ring.[21]

Many other classes of sweet compounds[2] were also tested and found to fit consistently our model (e.g., ureas, benzonitriles, sulfonaphthimidazoles, etc.).

The self-consistency of our model is further emphasized by the mapping of the bitter site. As indicated previously, the bitter taste of many enantiomers of sweet compounds may be explained even by a bitter site of identical shape in which only the AH–B entity is related to the analogous entity of the sweet site by a C_2 axis.

Although this idea is very attractive, it is probably unrealistic to apply it too strictly. Accordingly, rather than taking the shape of the bitter site as identical with that of the sweet site, it is more sensible to retain only the critical features, i.e., the interchanged AH–B entity and the flat spatial barrier and the open side opposite to it, and to look for specific contours on the yz section. In fact, these contours can be found in a way completely analogous to that used for the sweet site. For the bitter site we can take advantage of the fact that 4,5,6,7-tetraiodosaccharin is faintly bitter[13] and thus its shape probably reproduces rather faithfully the lower part of the yz section of the site. The approximate shape of the bitter receptor site can thus be obtained from the combined shapes of D-Asp-D-Phe-OMe and of tetraiodosaccharin. It is easy to check that typical bitter compounds[2] such as quinine, 6-nitrosaccharin, and the naphthosaccharins fit the site very well, whereas 6-ethoxysaccharin or *syn*-anisaldehyde oxime (i.e., tasteless compounds) cannot be fitted at all.

Conclusion

The evidence presented seems sufficient to consider the models of sweet and bitter receptor sites as very close to the real ones. Obviously, our models are essentially static in nature and we do not claim that they represent the state of the site prior to the association with any accuracy. In essence, they describe the critical geometrical features of the sites when interacting with tastants. Accordingly, it is not possible to identify univocally the side from which tastants enter the site, although we strongly favor the side opposite to Shallenberger's barrier.

A careful comparison of many classes of sweet molecules

also points to the presence (in the active site) of other centers for acid–base (or hydrogen bond) interaction but the evidence is not comparable to that accumulated for the AH–B entity.

Another very important unsolved problem is the actual mechanism of nerve impulse triggering. Whether it is due to molecular motions of the tastants in the receptor site or by a conformational modification of the protein (that, in turn, induces a modification of the lipidic part of the membrane) it cannot be said on the basis of our data alone. The only thing we can say on the basis of our models (of the receptor sites) is that the intensity of the taste sensation may be correlated in part with the value of the association constants compatible with a critical geometrical fitting and with the apolar nature of the upper part of the site. This finding can prove to be quite relevant for future studies on the mechanism of the triggering of the nerve impulse.

At any rate, it seems fair to conclude that the model presented in this paper can be helpful in the choice of the first synthetic targets of prospective analogues of known sweeteners or even in the design of new tastants.

References and Notes

(1) L. M. Beidler, *Adv. Chem. Ser.*, **No. 56**, 1 (1966).
(2) R. A. Moncrieff, "Chemical Senses", Leonard Hill, London, 1967.
(3) L. M. Beidler, *Prog. Biophys. Biophys. Chem.*, 11, 107 (1961).
(4) R. S. Shallenberger and T. E. Acree, *Nature (London)*, 216, 480 (1967).
(5) R. S. Shallenberger, T. E. Acree, and C. Y. Lee, *Nature (London)*, 221, 555 (1969).
(6) (a) L. M. Beidler and G. W. Gross in "Contributions to Sensory Physiology", Vol. 5, W. D. Neff, Ed., Academic Press, New York, N.Y., 1971, p 97; (b) M. J. Hall, L. M. Bartoshuk, W. S. Cain, and J. C. Stevens, *Nature (London)*, 253, 442 (1975).
(7) C. Pfaffmann in "Reinforcement and Behaviour", J. T. Tapp, Ed., Academic Press, New York, N.Y., 1969, p 226.
(8) F. Lelj, T. Tancredi, P. A. Temussi, and C. Toniolo, *J. Am. Chem. Soc.*, 98, 6669 (1976).
(9) J. Solms, *J. Agric. Food Chem.*, 17, 686 (1969).
(10) L. B. Kier, *J. Pharm. Sci.*, 61, 1394 (1972).
(11) A. Petritschek, F. Lynen, and H. D. Belitz, *Dtsch. Forsch. Lebensmittelchem.*, 5, 47 (1972).
(12) R. H. Mazur, J. M. Schlatter, and A. H. Goldkamp, *J. Am. Chem. Soc.*, 91, 2684 (1969).
(13) L. L. Bambas, *Chem. Heterocycl. Compd.*, 4, 318 (1952).
(14) "Lange's Handbook of Chemistry", 11th ed, McGraw-Hill, New York, N.Y., 1973.
(15) Y. Okaya, *Acta Crystallogr., Sect. B*, 25, 2257 (1969).
(16) H. Zinner, U. Zelch, and G. Rembarz, *J. Prakt. Chem.*, 8, 150 (1959).
(17) B. Jerslev, *Nature (London)*, 180, 1410 (1957).
(18) E. W. Deutsch and C. Hansch, *Nature (London)*, 211, 75 (1966).
(19) P. E. Verkade, C. P. Van Dijk, and W. Meerburg, *Recl. Trav. Chim. Pays-Bas*, 65, 346 (1946).
(20) "Tables of Interatomic Distances and Configuration in Molecules and Ions", *Chem. Soc., Spec. Publ.*, No. 11 (1958).
(21) K. Clauss and H. Jensen, *Angew. Chem., Int. Ed. Engl.*, 12, 869 (1973).

Notes

2-(Substituted phenyl)oxazolo[4,5-*b*]pyridines and 2-(Substituted phenyl)oxazolo[5,4-*b*]pyridines as Nonacidic Antiinflammatory Agents

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Some 2-(substituted phenyl)oxazolo[4,5-*b*]pyridines and 2-(substituted phenyl)oxazolo[5,4-*b*]pyridines have good antiinflammatory and analgesic activity. A few possess activity comparable to phenylbutazone or indomethacin without producing the irritation in the gastrointestinal tract that acidic antiinflammatory compounds cause.

In our continuing study of nonacidic antiinflammatory compounds[2] it was found that thiabendazole (4-thiazolyl-2-benzimidazole) has moderate antiinflammatory and analgesic activity.[3] In the course of testing compounds with similar ring systems (aryl-fused heterocycles) 2-phenyloxazolo[4,5-*b*]pyridine (I) and 2-phenyloxazolo-

I   II
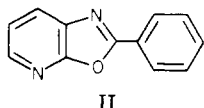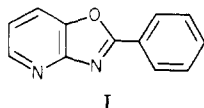
[5,4-*b*]pyridine (II) were found to have interesting activity in the carrageenan rat foot edema assay.[4] Both of the parent compounds are known in the literature;[5,6] however,

no biological activity is recorded for them. Thus, a number of substituted phenyloxazolopyridines in both series were prepared and compared, in several standard antiinflammatory assays, with known antiinflammatory compounds.

Chemistry. Fraser and Tittensor[5] prepared 2-phenyloxazolo[4,5-*b*]pyridine by heating 2-amino-3-hydroxypyridine with benzoic anhydride. We have found this procedure can be simplified by heating a mixture of the benzoic acid and the aminohydroxypyridine in polyphosphoric acid. After quenching in water, the desired compound is obtained.

It is necessary to use a stepwise procedure to prepare the oxazolo[5,4-*b*]pyridine derivatives. The amine is acylated first and ring closure of the product is accom-