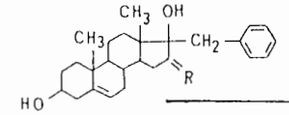
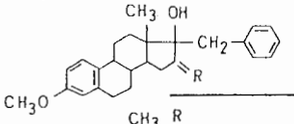
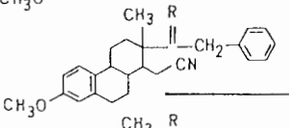
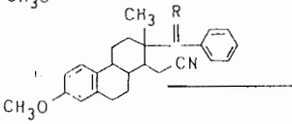
04-Crystallography of Biological Small Molecules

Molecular mechanic calculations were performed to provide and to determine minimum energy conformations. Computer aided modeling of the new structures with extended 17-side-chains has been attempted.

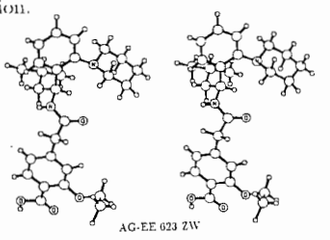
	COMPOUND	R	S.G.	Z	R
	1		$P2_12_12_1$	8	0.051
	2	=NOH	$P2_12_12_1$	4	0.058
	3	=O	$P2_1$	2	0.071
	4	=NOH	P1	2	0.069
	5	=O	$P2_12_12_1$	4	0.065
	6	=O	$P2_12_12_1$	4	0.048
	7		$P2_12_12_1$	4	0.069
	8	=O	$P2_1$	2	0.047
	9		$P2_1$	2	0.041

MS-0 .0 .08 X-RAY ANALYSIS OF THE NEW HYPOGLYCEM DRUG REPAGLINIDE: COMMON STRUCTURAL FEA1 RES WITH GLIBENCLAMIDE. By W. Grell, Department of Chemical Research, and M. Mark, Department of Biochemical Research, Dr. K. Thomae GmbH. Biberach, and P. Luger*, Institute for Crystallography, Freie Universität Berlin. Germany.

Repaglinide, (+)-2-ethoxy-α-[[(S)-α-isobutyl-o- piperidinobenzyl]carbamoyl]-p-toluic acid (1), AG-EE 623 ZW, (WHO Drug Inform. 1992, 6(3), List 32), being the most active representative of a series of novel hypoglycemic (B-cytotropic) benzoic acid derivatives, was found to display a 20 times higher blood sugar lowering activity than the sulfonylurea (s.u.) compound glibenclamide (2) in fasted rats. With the aim of obtaining more insight into common or different conformational aspects, the X-ray structure of (1) and of several related compounds was determined. The structure of (1) was computergraphically compared with that of (2) (Byrn,S.R.,McKenzie, A.T., Hassan,M.M.A. & Al-Badr,A.A., J. Pharm. Sci. 1986, 75, 596-600). The superposition was performed in such a way that functional groups which are known to contribute essentially to activity, and which are regarded as being involved in binding to the so called "s.u. receptor" (Kaubisch,N., Hammer,R.,Wollheim,C.,Renold, A.E. & Offord,R.E., Bioch. Pharmacol. 1982, 31, 1171-1174) fit best after having slightly rotated only a few bonds of each of the X-ray structures.

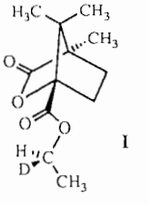
It was found that the acidic (-COOH / -SO2-NH-) and basic (piperidino -N / methoxy-O) functional groups, and the amino hydrogens (-H) are overlapping quite well. In contrast the amido oxo (=O) groups do not, but are yet in positions for enabling hydrogen bonds to the same (presumed) electron accepting binding site of the "s.u. receptor".

It is concluded that the conformations being realized in the superposition are compatible with a common three-point binding model. This, as an extension of the binding hypotheses discussed formerly (Rufer,C. & Losert,W., J. Med. Chem. 1979, 22, 750-752; Brown,G.R. & Foubister,A.J., J. Med. Chem. 1984, 27, 79-81), means that the three main functional groups [the acidic, the basic, and the (ambivalent) amido groups] bind simultaneously to corresponding binding sites of the "s.u. receptor". Additional lipophilic interactions are supposed to occur so that the particular groups of (1) [the (S)-positioned isobutyl group, the (whole) piperidino group, and the ethoxy group], and (2) [the cyclohexyl group], respectively, are binding into (presumed) different corresponding pockets of a given "s.u. receptor". This supports the speculation that "there exists more than one specific binding site for sulfonyl ureas and benzoic acid derivatives" (Verspohl, E.J., Ammon, H.P.T. & Mark, M., J. Pharm. Pharmocol. 1990, 42, 230-235). Possibly, even the existence of different (sub)types of "s.u. receptors" has to be taken into consideration. - Further investigations are necessary before coming to a decision between the various kinds of binding, and getting conclusive information about the "active conformations" of structurally different stimulators of insulin secretion.



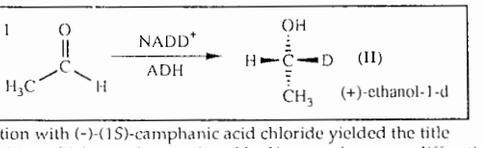
OPS-04.01.09 ABSOLUTE CONFIGURATION OF THE (-)-(1S)-CAMPHANATE ESTER OF (+)-ETHANOL-1-d BY NEUTRON DIFFRACTION by Robert Bau*, Tobias Metzenthin, Department of Chemistry, University of Southern California, Los Angeles, CA 90089, U.S.A., Thomas F. Koetzle, Department of Chemistry, Brookhaven National Laboratory, Upton, NY 11973, U.S.A., and Harry S. Mosher, Department of Chemistry, Stanford University, Stanford, CA 94305, U.S.A.

The absolute configuration of the (-)-(1*S*) camphanate ester (I) of (+)-ethanol-1-*d* has been determined by single-crystal neutron diffraction. (+)-Ethanol-1-*d* (II) was prepared (Scheme 1) via the reduction of acetaldehyde by the enzyme alcohol dehydrogenase (ADH) in the presence of deuterated nicotinamide adenine dinucleotide ($NADD^+$) by the method of Simon[1]:



I

Scheme 1



Esterification with (-)-(1S)-camphanic acid chloride yielded the title compound (I), which was then analyzed by X-ray and neutron diffraction. The neutron diffraction analysis of I, using the known[2] absolute configuration of the (-)-(1S) camphanate group as a reference, showed that the absolute configuration of the chiral CHD group is *R*.

We had earlier analyzed[3] the absolute configuration of (+)-neopentanol-1-*d* (III), prepared by the reduction of deuterated neopentanal by actively fermenting yeast[4] (presumably also involving alcohol dehydrogenase; Scheme 2) and converted to its phthalate half-ester (V):

Scheme 2