03.1–14 STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF 5-PHENYL-1,4-BENZODIAZEPINES. By H.J. Butcher, P. Chananont and T.A. Hamor, Department of Chemistry, University of Birmingham, Birmingham, England and I.L. Martin, M.R.C. Neurochemical Pharmacology Unit, Medical Research Council Centre, Cambridge, England.

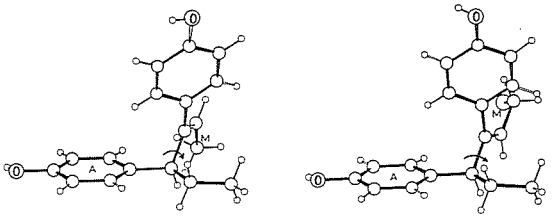
Certain members of the class of 5-phenyl-1,4-benzodiazepines possess a wide spectrum of psychotropic activity (anxiolytic, sedative/hypnotic, anticonvulsant, muscle relaxant). MNDO molecular orbital calculations have been made on twenty-five such compounds of known crystal structure and covering a wide range of biological activity as measured by their affinity for the specific benzodiazepine receptor in rat brain (Squires & Braestrup, Nature (1977) 266, 732). Electronic parameters including atomic π-electron charges, dipole moment components and molecular orbital energies derived from these calculations, together with geometrical parameters relating both to the overall conformation of the molecule and to bond length data derived from the X-ray analyses have been used in the structure-activity studies.

The results of statistical analysis of the data will be presented. Parameters which may be important in the correlation with affinity include HOMO energy (a measure of ionisation energy) LEMO energy (a measure of electron affinity), E(HOMO) + E(LEMO) (a measure of molecular electronegativity) and dipole moment. Extension to multiple regression analysis has yielded some promising results based on 3-parameter equations.

03.1–15 MOLECULAR CONFORMATION, RECEPTOR BINDING AND HORMONE ACTION OF DIETHYLSTILBESTROL DERIVATIVES. By W. L. Duax, J. F. Griffin and D. C. Rohrer, Medical Foundation of Buffalo, Buffalo, NY 14203 and K. S. Korach, NIEHS, Research Triangle Park, NC 27709.

Diethylstilbestrol (DES) is a potent synthetic estrogen whose action in the uterus is similar to estradiol (E) and is mediated by binding to an intracellular receptor. Pseudo-DES (PD) is a DES analog with similar receptor binding affinity (RBA) but poor uterotropic activity. When the Z and E isomers of pseudo-DES (Z-PD and E-PD) were tested separately, the Z isomer was found to have much higher uterotropic activity than the E isomer. The X-ray crystal structures of the anhydrous Z-PD and E-PD ethanol 1:1 complex were determined in order to compare their molecular conformations with those of estradiol and DES. Because of the fused ring system of E and the location of the central double bond in DES both of these active compounds are constrained to have an extended conformation in which their oxygen to oxygen distance is between 10Å and 12Å. Surprisingly both the moderately active Z-PD and the inactive E-PD were found to have bent conformations in the solid state. Molecular mechanics calculations (MM2/p) confirmed that the crystallographically observed conformations corresponded to local minimum energy structures. When the structures where mechanically altered by rotation about the central bond (see figures) to achieve an extended conformation and subjected to energy minimization, unfavorable interaction between the methyl substituent (M) and the A-ring forced the E-PD structure to revert to the crystallographically observed conformation. Under energy minimization Z-PD retained its extended conformation. This local minimum is of slightly higher energy than the observed (X-ray) conformation. These results together with data from previous investigations support the postulate that a phenolic ring is the major contributor to estrogen receptor binding and that an extended conformation is required for hormonal activity. Both Z-PD and E-PD have the essential phenolic ring required for binding but only Z-PD has a metastable conformational isomer in which the two hydroxyl groups are extended in a fashion similar to DES.

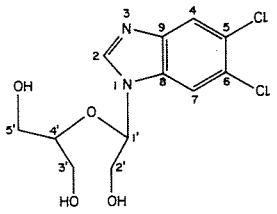
Crystal data: Z-PD, $C_{18}H_{20}O_2$, M_r = 268.3, monoclinic, $P2_1/c$, a = 10.349(3), b = 18.572(5), c = 7.815(2)Å, β = 96.66(2)°, V = 1492Å, Z = 4, D_x = 1.19 gm cm^{-3}, R = 7.7% for 2088 reflections with $F > 2\sigma_F$. E-PD, $C_{18}H_{20}O_2 \cdot C_2H_5OH$, M_r = 268.3·46.1, monoclinic, $P2_1/c$, a = 12.566(1), b = 11.945(1), c = 12.090(4)Å, β = 101.44(2)°, V = 1778Å^3, Z = 4, D_x = 1.15 gm cm^{-3}, R = 5.9% for 3267 reflections with $F > 2\sigma_F$.



E-PD
(E) 3,4-di-ρ-hydroxyphenyl-2-hexene

Z-PD
(Z) 3,4,-di-ρ-hydroxyphenyl-2-hexene

Research supported in part by Grant No. AM26546 from the National Institute of Arthritis, Metabolism and Digestive Disease.

03.2–1 CRYSTAL STRUCTURE AND CONFORMATION OF 5,6-DICHLORO-1-(β-D-2',3'-SECORIBOFURANOSYL)BENZIMIDAZOLE. By G.I. Birnbaum, R. Stolarski and D. Shugar, Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada, K1A 0R6, and the Institute of Biochemistry and Biophysics, Polish Academy of Sciences, 02-532 Warsaw, Poland.

5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) is an inhibitor of hnRNA/mRNA synthesis. Several compounds in another class of nucleoside analogues, viz. those containing an acyclic fragment of the sugar moiety, have been found to possess strong antiviral activity, e.g. the antiherpes drug acyclovir. We have carried out an X-ray analysis of the title compound, the first acyclonucleoside analogue to contain not only all the atoms of the ribose moiety but also the aglycon fragment of DRB. The crystals are monoclinic ($P2_1$) with cell dimensions a=11.861(2), b=7.897(1), c=14.527(3) Å, β=91.28(1)°; there are two molecules in the asymmetric unit. The structure was solved by direct methods and refined by least squares to R=0.036. The conformation of the acyclic moiety is different in each independent molecule. The results will be compared with solid-state conformations of analogous acyclonucleosides. An attempt will be made to correlate the structure and conformation of acyclonucleosides to their biological activity.