Short Communication

"FOOTPRINTS" IN ADSORBENTS

By A. H. Beckett and Patricia Anderson

From The School of Pharmacy, Chelsea College of Science and Technology, Manresa Road, London, S.W.3

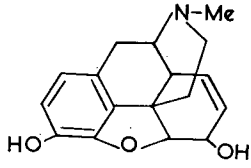
Received June 1, 1959

The investigation of the possible preparation of three dimensional footprints in adsorbents had a two-fold objective, namely, to provide a new method for the elucidation of the configuration of molecules and to try to produce models of biological receptor surfaces. A three-dimensional approach to the consideration of biological receptor surfaces and medicinal chemistry seemed imperative since the majority of chemical substances formed or broken down in normal metabolic processes are optically active.

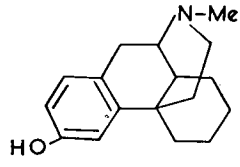
A preliminary report of the preparation and application of stereoselective adsorbents has already been given[1]. The method involves the preparation of "footprints" of the desired three-dimensional arrangement in silica gel by forming the gel in the presence of the reference molecule, drying and reducing to a powder and extracting the reference molecule from the surface layers of the adsorbent. These adsorbents distinguish stereoisomers of the same, from those of different configuration providing the molecule used to prepare the configurational footprint is not too dissimilar in structure from the molecules to be adsorbed. Very good discrimination was obtained using cinchona alkaloids as reference molecules[1].

The presence of configurational footprints to account for the increased uptake by stereoselective, as compared with blank adsorbents (prepared in the absence of the reference molecule), rather than an explanation based upon increased surface area of the former adsorbents is indicated by the stereoselectivity of the adsorbents, for example, a gel with a quinine footprint will adsorb quinine and cinchonidine (same configuration) more readily than quinidine and cinchonine (different configurations) but a quinidine adsorbent will adsorb quinidine and cinchonine more readily than quinine and cinchonidine. Also when molecules greatly dissimilar from the molecule used to make the footprint are adsorbed the specificity is decreased, for example, a gel with the quinine footprint will adsorb quinine, and to a lesser extent quinidine, much more readily than will a blank gel, but this difference is greatly diminished using 5-aminoacridine. Further support for the physical reality of footprints derives from storage experiment, for example, the storage of a blank gel and one with a quinine footprint for 6 months in a refrigerator gives no change in the adsorbent properties of either, but storage at 37° gives some loss of selectivity of stereoselective adsorbent compared with the blank adsorbent.

Further work has shown that stereoselective adsorbents may be prepared to distinguish between enantiomorphic analgesic type compounds, for example, a gel with footprints of levorphan (II) will adsorb levorphan better than its enantiomorph dextrorphan; the gel will adsorb both enantimorphs better than a blank gel prepared devoid of footprints. Morphine (I), the analgesically active isomer, is adsorbed on a gel with levorphan



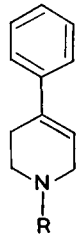
(I)



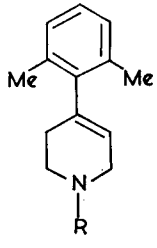
(II)

(analgesically active) footprints slightly better than on a gel with dextrorphan (analgesically inactive) footprints to indicate that probably morphine and levorphan have the same steric arrangement.

Molecular models indicate that the introduction of methyl groups into (III) to yield (IV) will restrict the rotation of the phenyl group so that the aryl group in (IV) will be held approximately at right angles to the general

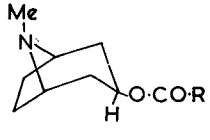


(III)

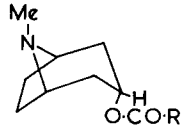


(IV)

plane of the tetrahydropyridine ring. Ultra-violet absorption measurements support this contention since the aryl-double bond conjugation exhibited by (III) is completely absent in (IV). As expected, planar compounds (III) are more readily adsorbed on silica gel than Type (IV) molecules. Footprints on silica of planar molecules (III) show even a greater selectivity for similar planar molecules than for out of plane molecules (IV) than do blank gels.



(V)



(VI)

Investigation of atropine-type molecules indicates that suitable stereoselective adsorbents may be prepared, for example, a gel with footprints of cinnamyltropine (V; R=C_6H_5CH=CH·), adsorbs this compound more readily than cinnamyl-ψ-tropine (VI; R=C_6H_5CH=CH–).

REFERENCE

1. Beckett and Anderson, *Nature, Lond.*, 1957, **179**, 1074.

After Dr. Beckett presented the communication there was a DISCUSSION. The following points were made.

Adsorbents other than silica gel had been tried initially with little success. Preparation of "footprints" in the gels was always good where rigid molecules were used. Flexible molecules did not give such satisfactory results. The molecules trapped in the gels could not be leached out in solution as they were associated with the gels by hydrogen bonding. The exposed surfaces of physically held crystalloids could still be a possible explanation for receptive surfaces. When two isomers were used in preparing the gel two types of "footprint" were formed. Reference molecules must be very stable, as there could be a build up of protons at the gel surface giving acid conditions.