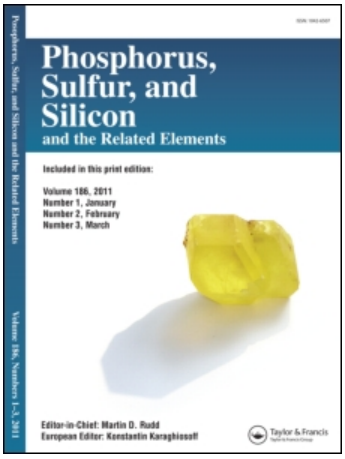

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A NEW, SULFONE GROUP CONTAINING, CLASS OF ARTIFICIAL SWEETENERS

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A NEW, SULFONE GROUP CONTAINING, CLASS OF ARTIFICIAL SWEETENERS

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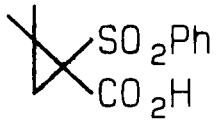
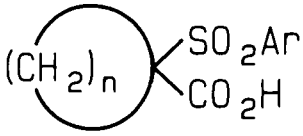
Abstract A new class of artificial sweeteners has been developed on the basis of 2,2-dimethyl-1-phenylsulfonylcyclopropanecarboxylic acid.

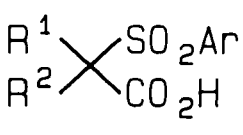
On the basis of the structure of 2,2-dimethyl-1-phenylsulfonylcyclopropanecarboxylic acid I, whose intensely sweet taste had been disclosed by chance in the sixties [1], we have performed the systematic /Q/SAR analysis of the series II and III.



I



II



III

We have attempted a synthesis of 32 compounds of the above mentioned series as shown on scheme /Fig. 1/. In particular, it has been found that ethyl arylsulfonylacetates could be easily dialkylated or cyclodialkylated in the catalytic two-phase system /CTP/ of the Mąkosza type with concentrated aqueous sodium hydroxide, suffering no hydrolysis in the reaction condition. Monosubstituted on C_α /R_1=H/ derivatives react in the CTP conditions to form unsymmetrical disubstituted analogues. The latter could be obtained directly from ethyl arylsulfonylacetates in some particular CTP systems using one-pot procedure. The PTC solid-liquid system of toluene/K_2CO_3 selectively furnishes

triangle test procedure with a four member panel. Thus ten active compounds which are generated exclusively by the acyclic analogues III indicate an about 10 - 440 fold sweet intensity of sucrose.

Most of the glucophores are monosubstituted on C_α analogues. A very simple method of discriminative structural analysis, within phenyl analogues of III, involving steric /STERIMOL/ and hydrophobic related parameters has been developed /Fig. 2/. Since the active, unlike the inactive compounds cluster in a striped A'A'' zone and both L/STERIMOL of R group and Σf parameters can be easily derived from the molecular structure, the analysis of the interdependence of L vs Σf enables prediction of the taste of the derivatives anticipated for the synthesis.

The method has been successfuly used to forecast the taste and to select the optimal analogues for further syntheses. The syntheses of the designed derivatives VII /predicted taste - sweet/, and VIII /predicted taste - not sweet/ confirm their predicted taste.

A stepwise selection for the synthesis of aryl /Ar-Ph/ analogues has been realised by means of the manual Topliss method in a series of 2-arylsulfonylisovaleric acids /III : R^1 = i-Pr/. None of the generally used "Topliss parameters" was identified to indicate the sequence of the sweet intensity changes in the first set of the synthetised derivatives. Instead, B_1^2 /STERIMOL/ parameter has been used as a leading one in selecting the analogues for further synthesis. The "4-EtPh" analogue appeared to be the most active.

A comparative analysis seems to preve that the class fits into the Shallenberger and Kier glucophore-receptor interaction model.

Taking into account the good yield of the syntheses,

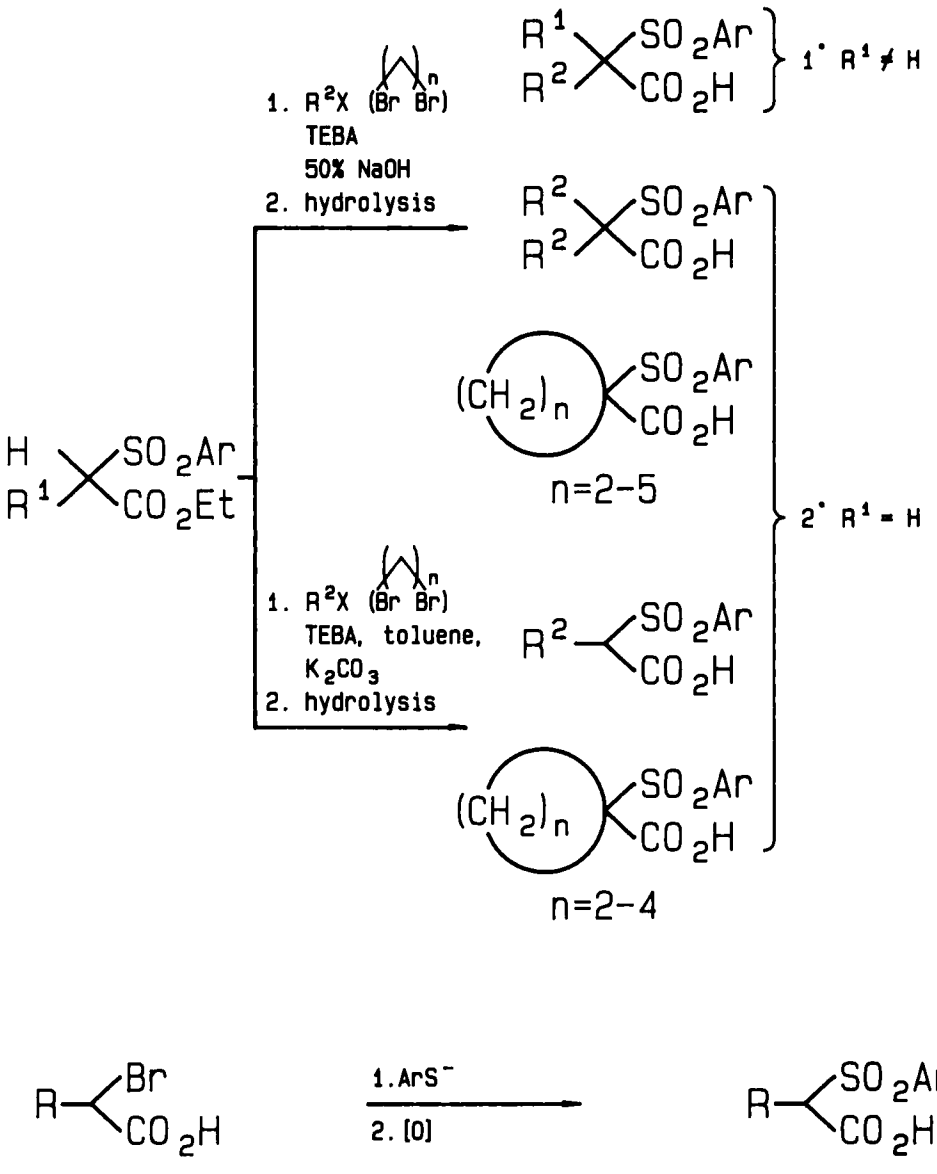
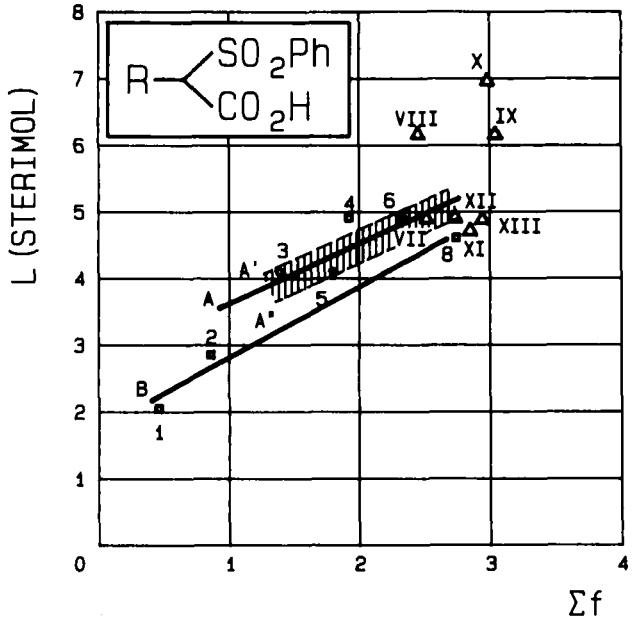


FIGURE 1 Scheme of the syntheses of 2-arylsulfonylalkanoic /III/ and 1-arylsulfonylcycloalkanecarboxylic acids /II/

monosubstituted on Cα derivatives, even when the excess of the alkylating agent is used.

Sensory properties of the active analogues have been estimated as recognition treshold values, using the Belitz



A: L=0.897Σf + 2.731 /3, 5, 6/
r=0.902, n=3

B: L=1.063Σf + 1.745 /1, 2, 8/
r=0.991, n=3

• sweet
▪ not sweet
▲ predicted

R = H(1); Me(2); Et(3); n-Pr(4); i-Pr(5); s-Bu(6); Bz(8); c-Pn(VII) n-Bu(VIII) ...

FIGURE 2 Interdependence of the R group L/STERIMOL parameter vs calculated Rekker hydrophobicity Σf

the accesibility of the synthetic precursors and the stability of the sulfone group, these compounds are a promising target of further search and good chance of using them as the artificial sweeteners is anticipated.

REFERENCES

1. D.J. Cram and A. Ratajczak, US Patent 3 598 868 /1971/