Tetrahedron Letters Vol. 21, pp 617 - 619 0040-4039/80/0208-0617$02.00/0

USE OF POLYMERIC NUCLEOPHILES FOR THE SELECTIVE BINDING AND REMOVAL OF α-METHYLENE-γ-BUTYROLACTONE ALLERGENS FROM COMPLEX MIXTURES.

Annie CHEMINAT and Claude BENEZRA*

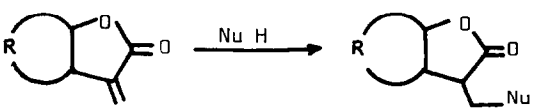
Laboratoire de Dermato-Chimie, Associé au CNRS, Université Louis Pasteur, Clinique Dermatologique, CHU de Strasbourg, 67005 Strasbourg, France

M Jean FARRALL and Jean FRECHET*

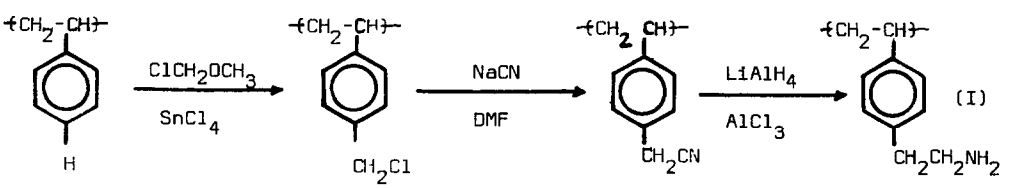
Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 9B4, Canada

Summary An insoluble polymer containing primary amines selectively removed α-methylene-γ-butyrolactone allergens from solutions.

Numerous cases of contact dermatitis have been linked to an allergic reaction to the sesquiterpene lactones which are found in a number of Compositae plants[1,2]. The allergenic properties of these lactones appear to be due in part to the presence of an α-methylene group exocyclic to the γ-lactone, and the mechanism of action of these sensitizers is thought to involve their reaction with nucleophiles such as amines or thiols in a Michael addition as shown below[2-4]

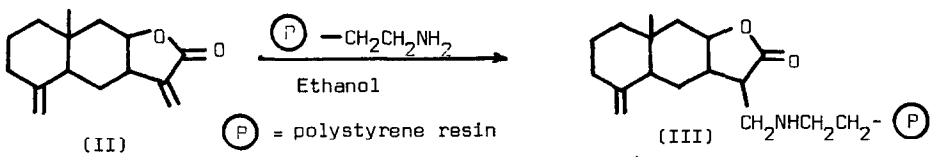


Our process for the binding of these conjugated lactones to polymer supports rests on their high reactivity towards nucleophiles Thus, it is expected that α-methylene-γ-butyrolactone can effectively be "fished out" from solutions by reaction with an insoluble polymer containing nucleophilic functional groups. The polymer we chose to test first was a modified polystyrene containing 2-aminoethyl functionalities on a fraction of its aromatic rings. This polymer was prepared easily by chemical modification of 1 % cross-linked polystyrene in three steps



Elemental analysis of the polymer and its infrared spectrum confirmed the assigned structure (I).

The polymer was tested by using a suspension of the resin in a dilute solution of the known allergen, isoalantolactone (II) with stirring at room temperature. Depending on the solvent (dioxane,acetone, benzene, chloroform, ethanol,ethanol-dioxane and ethanol-dichloromethane mixtures were used) from 10 (acetone) to 99 % (pure ethanol) of the lactone remained bound after 24h reaction. Although the polymer (I) does not swell appreciably in ethanol, this did not seem to overly affect the reactivity of aminoethyl sites. With ethanol, 96 % of the lactone remained bound after 7h stirring at room temperature. Progress of the reaction was followed by UV spectroscopy and gas chromatography of the liquid phase.



(II) (III)

The infrared spectrum of resin (III) showed peaks at 1 770 cm^{-1} (γ-lactone) and 1 640 cm^{-1} (C=C). The gain in weight of the polymer was consistent with that expected from an essentially complete binding of isoalantolactone (II)

Additional experiments using columns packed with resin (I) showed that they could be used effectively for the complete removal of isoalantolactone (II) from ethanol solutions (several recyclings were necessary).

A number of other nucleophilic resins containing amine, phenol or thiol functionalities have also been prepared[5-8], and are currently being tested[8] with (II) and other unsaturated lactones[4]. A preliminary study of the application of resin (I) to the selective removal of α-methylene-γ-butyrolactone allergens which are present as minor components in natural oils such as Costus oil[9], shows the great potential of the technique[8]. These results as well as the study of the cleavage of the bound lactones from the polymer support will be detailed in a forthcoming complete report

ACKNOWLEDGEMENTS.
The authors thank NATO for grant n° 1687. Additional support of this grant through a National Science and Engineering Council of Canada (NSERCC) operating grant (to JMJF) and postdoctoral fellowship (to MJF) is also acknowledged. Finally, thanks are due to INSERM, France (Contrat Libre 77-1-097-3).

REFERENCES.

1. J.C. MITCHELL, G. DUPUIS and T.A. GEISSMAN, Brit. J. Dermatol., 87, 235-240 (1972).
2. J.C. MITCHELL and G. DUPUIS, Ibid., 84, 139-150 (1971).
3. J.C. MITCHELL, T.A. GEISSMAN, G. DUPUIS and G.H.N. TOWERS, J. invest. Dermatol., 56, 98-101 (1971).
4. G SCHLEWER, J.L. STAMPF, C. BENEZRA, Can. J.Biochem., 56, 153-157 (1978) , J.P.CORBET and C. BENEZRA, Tetrahedron Letters, 4003-4006 (1979) , G. SCHLEWER, J.L. STAMPF and C. BENEZRA, unpublished results.
5. J.M.J. FRECHET, M.D. DE SMET and M.J. FARRALL, J. Org. Chem., 44, 1774-1779 (1979)
6. J.M.J. FRECHET, M.D. DE SMET and M.J. FARRALL, Tetrahedron Letters, 137-138 (1979) , J.T. AYRES and C.K. MANN, Polym. Letters, 3, 505-508 (1965).
7. J.M.J. FRECHET, M.D. DE SMET and M.J. FARRALL, Polymer, 20, 675-680 (1979).
8 A. CHEMINAT, C. BENEZRA, M.J. FARRALL and J.M J. FRECHET, unpublished results.
9. J.C. MITCHELL and W.L. EPSTEIN, Arch. Dermatol., 110, 871-873 (1974)

(Received in France 7 December 1979)