Tetrahedron Letters,Vol.24,No.24,pp 2495-2496,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

THE ACID-CATALYSED RING CONTRACTION OF TETRAHYDRO-1-BENZOXEPIN-3-OL TO 2-HYDROXYMETHYLCHROMAN DERIVATIVES.

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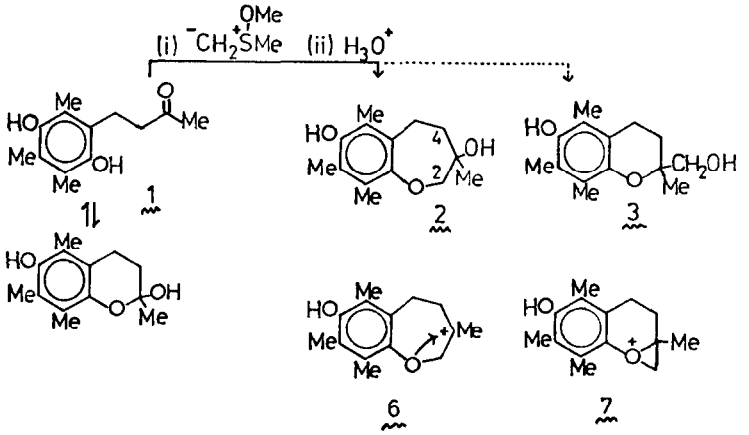
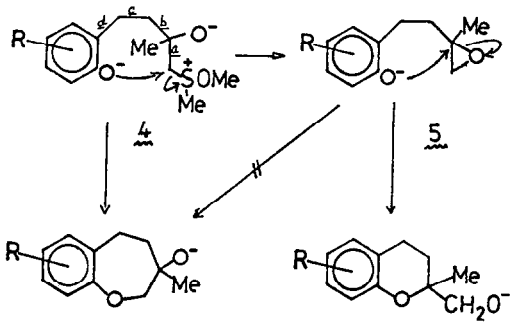
ABSTRACT : Derivatives of 2,3,4,5-tetrahydro-3-methyl-1-benzoxepin-3-ol are readily isomerised by acids into the corresponding derivatives of 2-hydroxymethyl-2-methyl chroman.

During their extensive studies on the use of sulphur ylides to synthesise heterocyclic systems, Italian workers[1] examined the interaction of phenolic ketones like (1) (or their 2-hydroxychroman tautomers) with methoxymethylsulphonium methylide in dimethyl sulphoxide. They always obtained derivatives of 1-benzoxepin such as (2), in good yield, but often variable amounts of the isomeric chroman derivatives such as (3) were also encountered. They suggested the reaction sequence shown in the Scheme in which the main feature is the initial formation of an adduct (4) which was considered to lead directly to the benzoxepin ring system. Formation of epoxides (5) was thought to be minimal and to lead specifically to the 2-hydroxymethylchroman derivatives.

In our view the well known conversion of ketones into epoxides would be the main, not the subsidiary, feature. In the intermediate (4) epoxide formation requires organisation about bond a only, whereas cyclisation to the 7-membered ring requires organisation about the four bonds a - d simultaneously, a very unfavourable requirement. Either ring size might now result from nucleophilic substitution of oxiran oxygen by phenoxide anion, but since S_N2 character is probable only substitution at the primary site should be important and this leads specifically to the oxepin, not to the chroman.





Scheme

Hence the chroman derivatives must have some other origin. We find that the oxepinol (2) is quantitatively converted into the chroman by trifluoroacetic acid at 19°C for some hours, and rapidly on heating. According to NMR and IR results, the immediate product is actually the trifluoroacetate, not the alcohol (3) itself, but aqueous workup yields only the alcohol. In the methylide reaction, the chroman appeared to a variable extent if the workup is left slightly acid instead of exactly neutral. It seems probable that the ring contraction involves the tertiary carbenium ion (6), the warp of the tetrahydrooxepin ring bringing together the oxygen atom and the carbenium centre so that the intermediate oxonium ion (7) can be formed. This cyclisation may well be reversible, but whenever a nucleophile attacks the primary centre (methylene group) the product will be a derivative of the chroman (3) and this cannot return to (7) or (6) because primary carbenium ions are not so readily formed and the chroman ring is in any case relatively free from strain and distortion. A somewhat similar rearrangement has been discussed by Paquette et al.,[2]. The shape of the tetrahydrooxepin ring is clearly evidenced by the quartet for the 2-methylene protons (δ 3.96 and 3.39, J 12.5 Hz), the former band also showing long-range splitting with one 4-methylene proton (J 1.5 Hz); this is possible if the two protons concerned are linked by a W-pathway, which happens if they are pseudo-equatorial in a step-like conformation for (2).

This ring contraction makes 2-hydroxymethylchroman derivatives available by a shorter route than the published one[4] and is of interest in connection with a number of natural products.[5]

REFERENCES AND NOTES

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2. L.A.Paquette, R.W.Begland, and P.C.Storm, *J.Amer.Chem.Soc.*, 1970, 93, 1971; L.A.Paquette and P.C.Storm, *J.Amer.Chem.Soc.*, 1970, 92, 4295.
3. These and all other analytical and physical characteristics noted by the earlier workers have been confirmed in full.
4. For a longer route see P.Bravo and C.Ticozzi, *J.Heterocycl.Chem.*, 1978, 15, 1051.
5. M.F.Grundon, *Tetrahedron*, 1978, 34, 143.

6. We thanks SERC and Fisons plc, Pharmaceutical Division, for financial support.

(Received in UK 25 February 1983)