

OXYGEN HETEROCYCLES BY SULPHUR YLIDE ANNULATION: REACTION OF
O-HYDROXYBENZALKETONES WITH DIMETHYLOXOSULPHONIUM METHYLIDE

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Abstract - Beside the expected cyclopropanes IV and 2,3-dihydrobenzofurans V, 2-(*o*-hydroxyphenyl)-2,3-dihydro-6H-pyrans X and 3-substituted-2,3-dihydrobenzofurans XII arise by transfer of methylenes, through the quinone methide intermediates IX, from dimethyloxosulphonium methylide on *o*-hydroxybenzalketones I.

During the study of annulation reactions induced by sulphur ylides on suitable substrates leading to the formation of oxygenated heterocyclic rings¹, we have been able to ascertain that *o*-hydroxybenzalketones show an unusual behaviour. In the two previous communications, in fact, we reported how they give good yields of 2-(*o*-hydroxyphenyl)-2,5-dihydrofurans through reactions with dimethylsulphonium methylide², while with dimethyloxosulphonium methylide they give as main products, complex compounds VI or VII, according to the relative amounts of substrate ylide used^{3,4}.

We have now newly examined the second reaction in order to decide on the structure and the formation way of some other products which, in variable amounts, always accompany the sulphoxides VI and VII.

Whenever the reaction of ylide II on a *o*-hydroxybenzalketone I is followed through thin layer chromatography, the presence of three additional, less polar, substances is also detected in addition to VI and VII. The quantity of these products was found to vary with conditions such as substitution at the carbonyl, reaction time and ylide-substrate ratio. If a chromatographic examination on a silica column is made, using hexane and ethyl ether, on the reaction raw material, the products eluted are, first a compound having a molecular weight equal to that of the starting product plus 28 (containing two more methylenes), then a second one having a molecular weight plus 14 (containing one more methylene), finally a third one having a molecular weight plus 42 (containing three more methylenes than the respective starting product). The structure of the new compounds have been drawn above all from the H-1 and C-13 nuclear magnetic resonance data, here reported.

For instance, 2-hydroxy-3-methoxybenzalacetone has first given a compound, m.p., 52-53 °C (benzene), *m/e*, 220 (M⁺), the H-1 nuclear magnetic resonance spectrum of which shows the following signals: δ (CDCl₃), 1.64 (3H, m, CH₃C=), 2.27 (2H, m, CH₂CH=), 3.87 (3H, s, OCH₃), 4.20 (2H, m, CH₂O), 4.76 (1H, dd, J=6.5, J=7.0 Hz, OCH₂CH₂) and 5.60 (1H, m, CH=), which are in agreement with the proposed structure Xa⁵. To the product diluted second, m.p., 55-56 °C, which exhibited the following

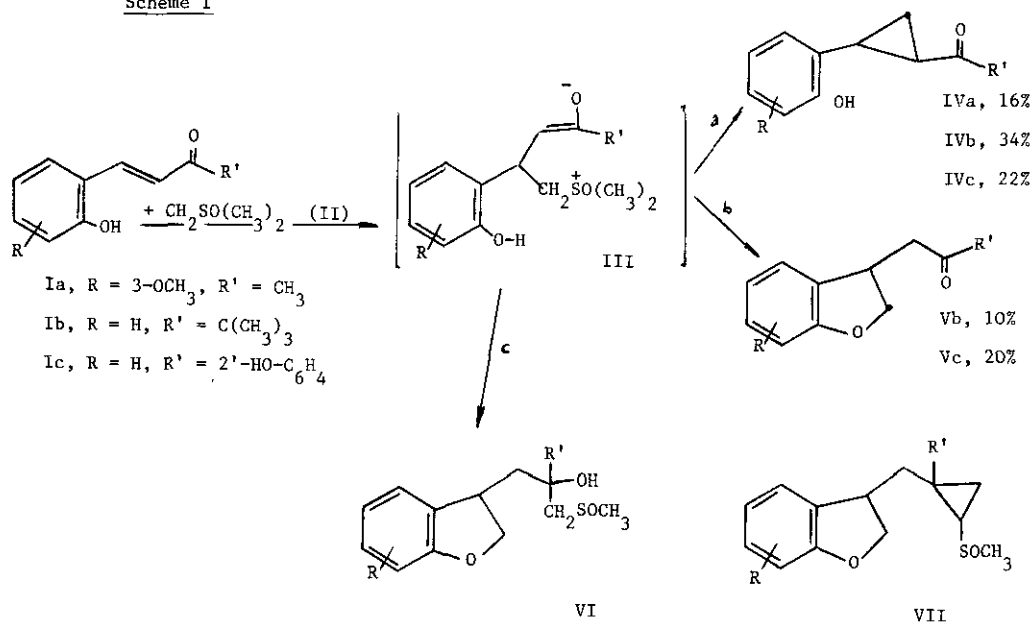
spectral data, m/e 206 (M^+), \int ($CDCl_3$) 1.24-1.80 (2H), 2.16 (1H) and 2.65 (1H), multiplets from the cyclopropane ring, 2.28 (3H, s, CH_3CO), 2.84 (3H, s, OCH_3), and 6.01 (1H, s, OH) has been given structure IVa. To the third product, a thick liquid which showed the following spectral data, m/e 234 (M^+), \int ($CDCl_3$) 1.62 (3H, broad s, CH_3C), 1.92 (1H, s, OH), 2.40 (2H, m, $CH_2CH=$), 3.52 (1H, m, CH_2CHCH_2), 3.85 (3H, s, CH_3O), 4.00 (2H, m, CH_2OH), 4.25 and 4.64 (1H, 1H, ABX , $J_{AB} = 8.2$, $J_{AX} = 6.0$, $J_{BX} = 8.5$ Hz, OCH_2CH), 5.44 (1H, m, $CH=$) has been given structure XIIa⁵. The value of the chemical shift of the methyl on the double bond, 13.9 ppm, in the C-13 NMR spectrum shows that the side chain and the methyl are in cis configuration⁶.

The 2-hydroxybenzal methyl-t-butylketone (Ib) gave, besides the cyclopropylketone IVb, m.p. 75-77 °C (hexane), a compound arising again from the transfer of one methylene from the ylide to Ib, the 3-substituted-2,3-dihydrobenzofuran Vb, liquid which showed the following spectral data, m/e 218 (M^+), \int ($CDCl_3$), 1.14 (9H, s, $(CH_3)_3C$), 2.76, 3.04 and 3.87 (1H, 1H, 1H, ABX , $J_{AB} = 18.0$, $J_{AX} = 8.0$, $J_{BX} = 5.0$, $COCH_2CH$), 4.02 and 4.76 (1H, 1H, ABX , $J_{AB} = 8.0$, $J_{AX} = 6.0$, $J_{BX} = 8.0$, OCH_2CH).

In our opinion compounds IV, V, X, and XII above mentioned, are formed from *o*-hydroxybenzalketone-ns I through the series of subsequent reactions reported in schemes 1 and 2.

Betaine III which is made by 1,4-addition of ylide on α,β -unsaturated ketone may lose a dimethylsulphoxide molecule in two different ways: by nucleophilic attack of the enolate anion on methylene, thus leading to the formation of cyclopropylketone IV (scheme 1, path a) or rather, by attack of the phenoxide anion giving rise to 2,3-dihydrofuran V (path b). On the other end the same dimethylsulphoxide molecule may be transferred inside betaine III on carbonyl in a way already somewhere else described³. In such a way compound VI is formed which, turns into VII in the presence of ylide excess (scheme 1, path c).

Scheme 1

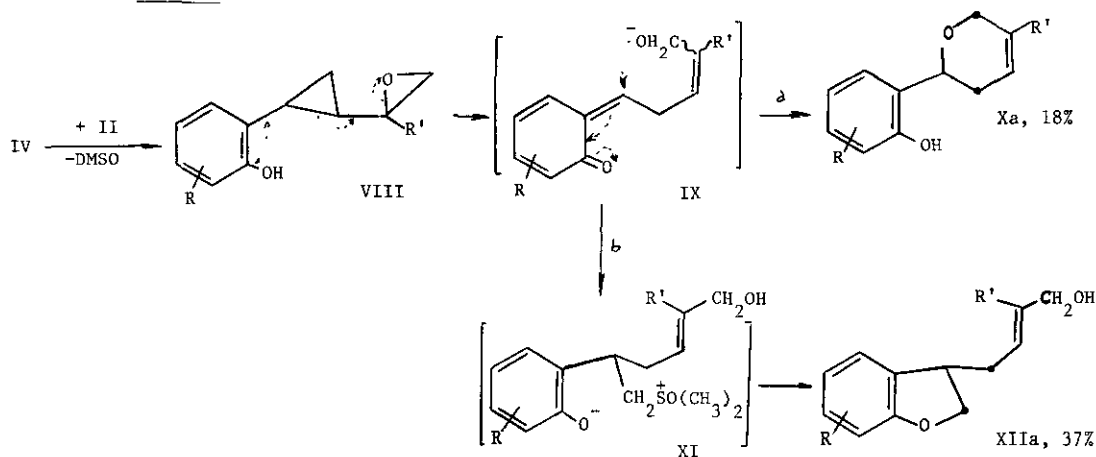


Ylide II, whenever present in excess in the reaction medium, may further react on the carbonyl of compound IV in order to give cyclopropyl- epoxy-intermediate VIII (scheme 2). Owing to a push-pull phenomena, (at one end, phenoxy anion pumps electrons into the system $O=C-CH-CH_2-CH-CR'-CH_2$, while at the other end the cyclopropyl and epoxide rings tend to open to release the ring strain and to receive electrons on the oxygen), compound VIII is converted to the quinone methide intermediate IX. That intermediate can evolve in two different ways. When the alkoxide group and the electrophilic end of the quinone methide are in a *cis* arrangement, they can easily interact, close to the dihydropyran ring and regenerate the aromatic ring system (scheme 2, path a)⁷. On the other end, a third mole of ylide can react on the electrophilic end of quinone methide IX giving rise to 3-substituted-2,3-dihydro-benzofuran XII through a usual annulation reaction (scheme 2, path b).

To support the complex reaction mechanism above described, we can report the following facts:

- IVa, made to react with ylide excess, under the same usual reaction conditions, gives a dihydropyran X and benzofuran XII mixture as expected;
- compounds Ib ($R' = t\text{-Bu}$) and Ic ($R' = C_6H_4-OH$) give only a mixture of compounds IV and V. The low reactivity of the carbonyl in cyclopropylketones IVb, due to steric hindrance, and IVc due to electronic effects of R' substituent, stop the reaction at the first stage;
- the hydroxymethyl group and the chain on the double bond in compound XII are in a *trans* configuration;
- compound Xa does not react with ylide II, and that demonstrates that reactions VIIIa to IXa and IXa to Xa are irreversible in nature;
- finally reactions between Ia and II when carried out with a ylide to substratum high ratio (about three to one) and for long times, give higher and higher yields in Xa and XIIa mixtures to the detriment of IV a.

Scheme 2



The methylenes transferred from the ylide molecule into the heterocyclic rings in compounds V, X and XII are pointed out in the formulae reported in schemes 1 and 2; it is interesting to note that the methylene close to the oxygen comes in all cases from the ylide⁹.

REFERENCES AND NOTES

1. The general principle underlining the hetero-annulation reactions promoted by sulphur ylides is illustrated in : P. Bravo, C. Ticozzi, G. Fronza, R. Bernardi and D. Maggi, Gazz. Chim. Ital., 1979, 109, 137 and references therein.
2. P. Bravo and C. Ticozzi, J. Chem. Soc., Chem. Comm., 1979, 438.
3. P. Bravo, G. Fronza, D. Maggi and C. Ticozzi, Tetrahedron Letters, 1977, 1077.
4. That is one of the few cases reported in the literature, where the whole ylide molecule is transferred to the substratum.
5. Decoupling experiments have allowed to obtain allylic and homoallylic coupling constants, still as small as 1.6 - 0.5 Hz, and to confirm the signals attribution.
6. The C-13 chemical shifts for a methyl on a double bond of type $RCH_2=CHCH_3$ have values of 17-18 ppm in the trans and 12-13 ppm in the cis configurations due to the effect of the chain on the cis methyl: F. Bohlmann, R. Zeisberg and E. Klein, Org. Magn. Res., 1975, 7, 426.
7. An analogous mechanism leads to the formation of 2-(o-hydroxy-m-methoxyphenyl)-4-methyl-2,5-dihydrofuran when Ia is made to react with dimethylsulphonium methylide; see reference 2.
8. Systematic studies have not been made to optimize the yields of every single compound. Yields varying from 5 to up 40% have been obtained.
9. Experiments with ylides marked on methylene to confirm what suggested are being made.

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