Tetrahedron Letters No. 36, pp 3175 - 3178, 1974. Pergamon Press. Printed in Great Britain.

A CONVENIENT SYNTHESIS OF SAFRANAL

W.M.B. Könst*, L.M. van der Linde and H. Boelens
Research Department NAARDEN INTERNATIONAL
Postbox 2, Bussum, The Netherlands

(Received in UK 15 July 1974; accepted for publication 31 July 1974)

Saffron, obtained by drying stigmas of Crocus sativus L. is a spice used for the flavouring and colouring of food and contains a bitter principle glycoside picrocrocin from which by hydrolysis safranal (6) is liberated[1]. This compound possesses the characteristic aroma of saffron.

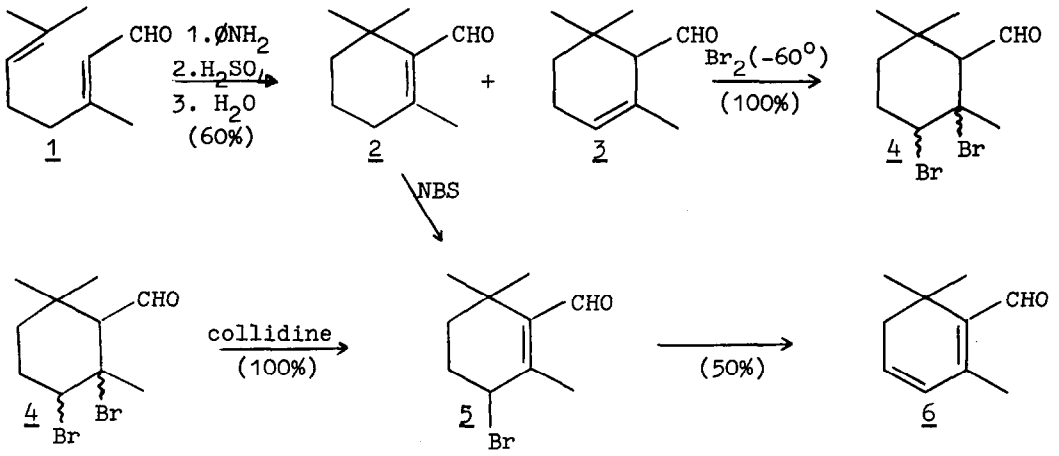
After the isolation and identification in 1935[2], several synthetic routes to this compound have been published, but non of these has much practical value.

Kuhn and Wendt[3] oxidized β-cyclocitral (2) with SeO_2 in one step to 6 in 2% yield. Bächli and Karrer[4] used a lengthy five-step synthesis starting from the methylester of α-cyclogeranylic acid. In the last step safranol was oxidized with MnO_2, but this led mainly to dehydrogenation and methyl shift, while safranal (6) was isolated in a very low yield. Karrer and Ochsner[5], in their attempted synthesis, started from α- or β-cyclocitral (3 resp. 2). Using a NBS bromination, dehydrobromination sequence, safranal (6) could not be isolated: the isomeric 2,2,6-trimethyl-3,5-cyclohexadiene-1-carboxaldehyde was the only compound identified.

Recently Mousseron-Canet and co-workers[6] claimed a method starting from α-cyclocitral (3). Bromination with NBS or phenyl trimethyl ammonium tribromide allegedly proceeded to the intermediate 8, which however was neither isolated nor identified. A subsequent dehydrobromination was claimed to give safranal (6) in "good yield". β-Cyclocitral (2) however, afforded only complex mixtures.

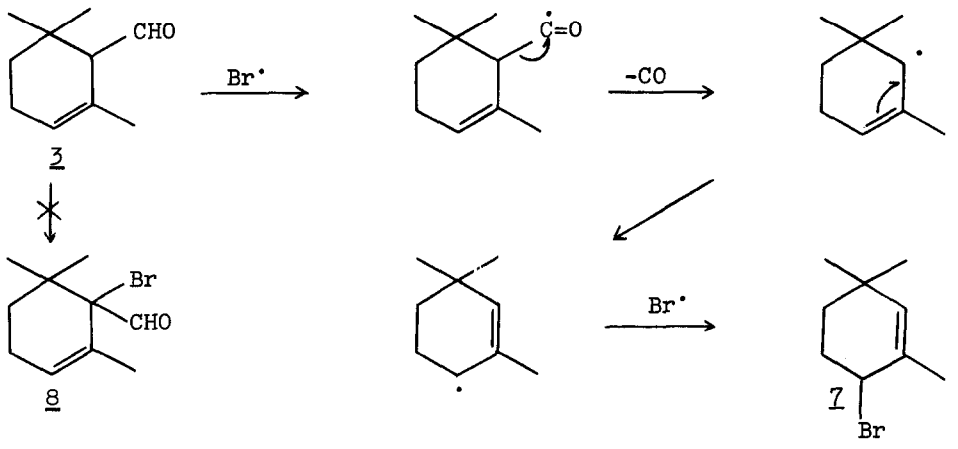
Although no experimental conditions were given, we have performed a number of experiments, but under no circumstances we were able to confirm their observations.

In this communication we describe how we arrived at a novel synthesis of safranal (6), which is rapid, economical en reproducible (scheme I).



SCHEME I

Our starting material is citral (1), a mixture of the Z/E isomers neral and geranial. The aldehyde function is protected by conversion in the anilide by stirring equivalent amounts of 1 and aniline with dry $MgSO_4$ for 3 hrs. After filtration, ring closure of the crude anilide is carried out in concentrated H_2SO_4 at 0° for 1 hr, according to a modified procedure of Gedye[7]. Extraction with chloroform is essential for a good yield. In this way α-cyclocitral (3) can be obtained in 60% yield, while in addition β-cyclocitral (2) is isolated in 5% yield. The first can be isomerized by base[7]. The reaction of α-cyclocitral (3) with freshly crystallized NBS in CCl_4 and monitored by NMR reveals to be very rapid. After 10 min at 60-70° the starting material has disappeared. Although α-cyclocitral (3) is partly isomerized to β-cyclocitral (2), which is brominated to the desired bromide 5, the rest of the starting material is largely destroyed in a decarbonylation reaction to 7 (scheme II).



SCHEME II

This decarbonylation is easily visualized in the NMR-spectrum: δ_{CCl_4} 5.22 =C<u>H</u>, m; 4.88 -C<u>H</u>Br, m; and a very low integration of the C<u>H</u>O at <u>δ</u> 10.09. In contrast to the statement of Mousseron-Canet et al., we have not been able to demonstrate the presence of the <u>α</u>-brominated aldehyde <u>8</u>. This CO-fission does not take place when <u>β</u>-cyclocitral (<u>2</u>) is treated with NBS. On micro scale this compound yields the isomeric bromide <u>5</u> as the sole product. On preparative scale however, the yield decreases dramatically.

Starting from <u>α</u>-cyclocitral (<u>3</u>) the decarbonylation can be circumvented by a direct bromination with bromine in $CHCl_3$ at -60° in the presence of quinoline. In 15 min <u>4</u> is formed quantitatively as a mixture of two stereo isomers; NMR δ_{CCl_4}: 1.10 and 1.22 gem C<u>H</u>$_3$, double d; 1.93 and 2.10 C<u>H</u>$_3$, double s; 4.49 and 4.78 C<u>H</u>Br, double t; 9.89 and 9.99 C<u>H</u>O, double d. This dibromide is relatively stable at low temperature in the absence of traces of acid, but when these are present it looses HBr rapidly. A controlled dehydrobromination can be achieved by refluxing <u>4</u> with 1 eq of collidine in toluene for 15 min. After removal of the precipitated collidine hydrobromide, the monobromide <u>5</u> is isolated quantitatively; NMR δ_{CCl_4}: 1.20 gem C<u>H</u>$_3$, d; 2.21 -C<u>H</u>$_3$, s; 4.63 C<u>H</u>Br, m; 10.11 C<u>H</u>O, s. To eliminate the second molecule HBr, more drastic conditions are

required. So after refluxing 5 in pure collidine for 30 min under nitrogen the calculated amount of collidine hydrobromide is formed. After filtration the reaction mixture is acidified and extracted with ether. The concentrated extract is distilled with steam and the steam-distillate after working up, purified by distillation on a spinning band column. A 50% yield of safranal (6) is obtained (calculated on starting α-cyclocitral); bp 72° (4 mm); n_D^{20} 1.524; NMR δ_{CCl_4}: 1.15 gem CH_3, s; 2.16 CH_3, s; 5.75-6.35 vinyl protons, m; 10.12 CHO, s. Other spectral data are also in accordance with the structure of safranal.

We are indebted to Prof. Dr. Th.J. de Boer, Laboratory for Organic Chemistry, University of Amsterdam, and to Dr. H.J. Takken, for their helpful discussions.

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