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HYDROFORMYLATION OF SAFROLE: THE MECHANISM OF RING CLOSURE AND FORMATION OF A TETRALIN DERIVATE

J. PALÁGYI, Z. DÉCSY*, G. PÁLYI and L. MARKÓ

(Department of Organic Chemistry, Veszprém University of Chemical Engineering)

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5,6,7,8-tetrahydro-2,3-methylenedioxy naphthalene is formed from safrole through γ-(3,4-methylenedioxy phenyl)-butyraldehyde as an intermediate under hydroformylation conditions in the presence of $Co_2(CO)_8$ as catalyst. Ring closure is regarded as an intramolecular electrophilic substitution catalyzed by $HCo(CO)_4$.

The hydroformylation reaction, a typical petrochemical industrial process, has also increased in importance in synthetic organic chemistry. Hydroformylation of natural products can lead to new substances with unusual biological activity.

Eugenol reacts under hydroformylation conditions (120-180°C, 200-400 atm. CO + H , $Co_2(CO)_8$ as catalyst) forming - among other more usual products - 5,6,7,8-tetrahydro-3-methoxy-2-naphthol with 30-40 % yield [1]. The results reported gave no conclusive evidence for the mechanism of ring closure in the formation of the tetralin carbon skeleton.

Experiments performed under similar conditions (150°C, 200-300 atm. CO + H_2, 0.4 mole % $Co_2(CO)_8$ as catalyst) have now shown that the same ring closure also takes place in the case of

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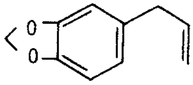
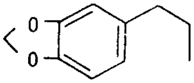
*Hungarian Oil and Gas Research Institute, Veszprém safrole (I) as the starting material. The product of a typical experiment had the following composition:

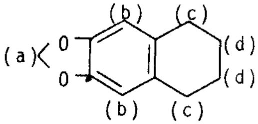
dihydrosafrole (II)	48 %
5,6,7,8-tetrahydro-2,3-methylenedioxy naphthalene (III)	24 %
C_{11} aldehydes (IVa, Va, VIa)	4 %
C_{11} alcohols (Vb, VIb)	3 %
high boiling products	21 %



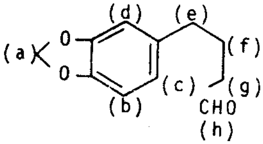
I



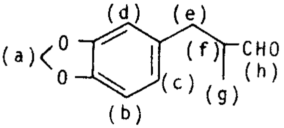
II



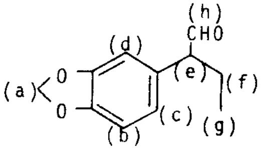
III



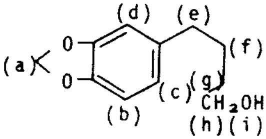
IVa



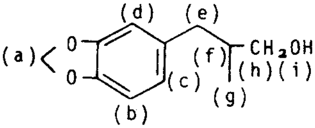
Va



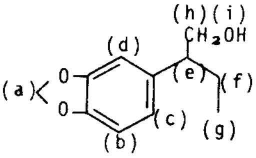
VIa



IVb



Vb

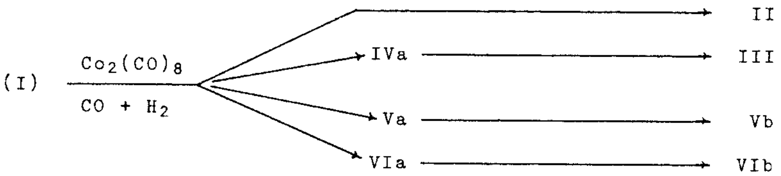


VIb

If the reaction was followed by taking samples from the autoclave at regular intervals, aldehydes IVa, Va and VIa were found to be the intermediates whereas dihydrosafrole (II), the cyclic reaction product III and the alcohols Vb and VIb the end products. This observation suggested the following scheme of reactions:

Table 1. Hydroformylation of safrole with $Rh_4(CO)_{12}$ (0.003 mole %), or $Co_2(CO)_8$ (0.5 mole %) + + PBu_3 (4 mole %) as catalysts

Catalyst	Temperature °C	CO + H_2 pressure atm.	Composition of reaction product, %								
			II	III	IVa	Va	VIa	IVb	Vb	VIb	high boiling
$Rh_4(CO)_{12}$	110	200-300	2	1	24	41	23	-	-	-	9
$Rh_4(CO)_{12}$	180	200-300	3	1	-	-	-	24	39	16	17
$Co_2(CO)_8$ + PBu_3	180	40-60	81	-	-	-	-	-	-	-	19

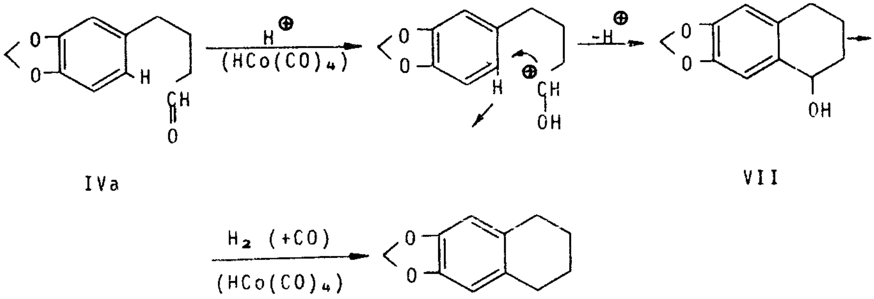


With the exception of IVa ⟶ III, all steps of the above scheme fit into the usual pattern of reactions observed during hydroformylation of olefins and therefore require no comment.

To investigate the mechanism of the ring closure reaction, safrole was also hydroformylated with $Rh_4(CO)_{12}$ as a catalyst. As shown in Table 1, rhodium forms only negligible amounts of compound III. If the $Co_2(CO)_8$ catalyst was modified by adding $P(\underline{n}\text{-}C_4H_9)_3$, dihydrosafrole was the only product of the reaction. Obviously unsubstituted cobalt carbonyls are the favoured catalysts for ring closure.

Regarding the pathway of ring closure, evidently there are two alternatives: both the n-butanol derivate IVb and the n-butyraldehyde derivate IVa may be visualized as intermediates. To clarify this point, two reaction products obtained with $Rh_4(CO)_{12}$ as catalyst at 110 and 180°C were subjected (after distillation to remove dissolved Rh) to further treatment with CO and H_2 in the presence of $Co_2(CO)_8$ as a catalyst. Table 2 shows the results which within the errors of GLC analysis prove aldehyde IVa to be the intermediate compound during the formation of III.

WENDER and co-workers [2] have found that pinacol is transformed under hydroformylation conditions in the presence of $Co_2(CO)_8$ to products which can best be explained by acid catalysis due to $HCo(CO)_4$, a strong acid in polar solvents. Our results can also be interpreted by intramolecular electrophilic substitution of the benzene ring caused by the protonation of aldehyde IVa and the subsequent hydrogenation [3, 4] of the benzyl alcohol derivate VII to the corresponding tetralin derivate, both reactions catalyzed by $HCo(CO)_4$:



IVa

VII

III

Table 2. Treatment of the aldehydes IVa-VIa (experiment A) and of the alcohols IVb-VIb (experiment B) with CO + H_2 ($150^{\circ}C$, 200-300 atm.) in the presence of 0.4 mole % $Co_2(CO)_8$ as catalyst

Compound	In starting mixture, %		In reaction product, %	
	Exp. A	Exp. B	Exp. A	Exp. B
II	2	3	4	8
III	< 1	< 1	33	2
IVa	27	-	4	-
Va	45	-	3	-
VIa	25	-	2	-
IVb	-	29	-	33
Vb	-	47	13	40
VIb	-	20	9	11
high boiling	-	-	32	6

The proposed S_E mechanism is supported by the observation that the ring closure reaction is strongly dependent on the polarity of the reaction medium. In two parallel experiments performed in hexane and 1,2-dimethoxy ethane as solvent the yield of III was 7 % and 33 %, respectively. At the same time, the amount of high boiling products was much higher in hexane (25 % and 10 %, respectively) showing that aldehyde IVa - which is transformed mainly into III in a polar medium - is very reactive under hydroformylation conditions and polymerizes if the conditions are unfavourable for ring closure.

Our experiments performed with eugenol as a substrate also revealed a similar mechanism for the ring closure reaction in this case. Typical experimental results which show that the n-butyraldehyde derivative is the precursor of the compound with the tetraline skeleton are summarized in Table 3.

Table 3. Treatment of the aldehydes IVa'-VIa' (experiment A) and alcohols IVb'-VIb' (experiment B) formed from eugenol with CO + H_2 (150°C, 200-300 atm.) in the presence of 0.3 mole % $Co_2(CO)_8$ as catalyst

Compound*	In starting mixture, %		In reaction product, %	
	Exp. A	Exp. B	Exp. A	Exp. B
II'	9	12	5	10
III'	-	22	40	19
IVa'	37	-	-	-
Va'	47	-	14	-
VIa'	7	-	4	-
IVb'	-	14	-	14
Vb'	-	35	-	35
VIb'	-	17	-	14
high boiling	-	-	37	8

*The numbering of eugenol derivatives is based on that of the analogous safrole derivatives, the primes indicating that these compounds contain a methoxy and a hydroxy group instead of the methylenedioxy group in safrole.

The treatment of isosafrole and isoeugenol with synthesis gas in the presence of $Co_2(CO)_8$ at 150° yielded almost exclusively the corresponding dihydro derivatives, whereas with $Rh_4(CO)_{12}$ as catalyst at 100° only the branched chain aldehydes were formed.

EXPERIMENTAL

Hydroformylation of Safrole

162 g safrole and 1.3 g $Co_2(CO)_8$ (0.4 mole %) were charged in a 1000 ml stainless steel rocking autoclave in which a carbon monoxide + hydrogen mixture (1:1) was compressed to 230 atm. The autoclave was heated to 150 ± 5° and maintained at this temperature for 4 hrs. 56 Nl of gas was consumed during this time which amounts to 2.5 mole of gas per mole of safrole. The reaction product (184 g) was discharged and distilled at 140-190°C at 10 Hgmm. The distillate (145 g) was analyzed by GLC (Chromosorb P with 10 % QF-1 at 180°C). The bottom (34 g) was decanted from the metallic cobalt formed by the decomposition of $Co_2(CO)_8$ and was investigated by IR spectroscopy which showed the presence of oligomeric derivatives of safrole or its carbonylated derivatives.

If desired, samples can be taken during the high pressure reaction from the autoclave, and processed and analyzed as indicated above.

Experiments with $Rh_4(CO)_{12}$ or $Co_2(CO)_8$ + PBu_3 as catalyst, as well as the hydroformylation of eugenol were performed similarly.

Identification of the Tetraline Derivative III

The compound was isolated by fractional distillation (bp. 109°C/7 Hgmm). It forms white crystals and melts at 39°C (uncorrected).

The cryoscopic MW determination (in benzene) gave 172 ± 5, the mass spectrometric mole peak (Finnigan Mod. 3000) was at m/e = = 176, these suggested the formula $C_{11}H_{12}O_2$ (calc.: 176).

The structure was assigned on the basis of the ^{1}H-NMR spectra (CCl_4 solution, TMS, 60* and 100** MHz).The signals observed were: δ_1 = 1.66 ppm, br. multiplet at 60 MHz, ill-resolved quintet at 100 MHz with J_1= 0.3 cps, J_2 = 0.4 cps, 4 H, (d)***; δ_2 = 2.53 ppm ill-resolved multiplet, 4 H, (c); δ_3= 5.66 ppm, singlet, 2 H, (a); δ_4 = 6.30 ppm, singlet (even at 100 MHz), 2 H, (b).

Identification of Aldehydes IVa, Va and VIa

The compounds were isolated by fractional distillation and subsequent preparative GLC using a 4 m × 8 mm column packed with 10 % QF-1 on 30/60 mesh Chromosorb W operated at 180°C with 0.9 atm. H_2 carrier inlet pressure. The fractions were collected at room temperature.

The mass spectrometric mole peaks (MS-902, AEI, 70 eV) correspond to the supposed formula $C_{11}H_{12}O_3$ (calc. 192).The M-15 peak is lacking at IVa, M-29 is the base peak at VIa, since M-29 are of very low - and nearly equal - intensity at Va and IVa, thus this process should be attributed to the loss of C_2H_5 and not to that of CHO. The base peak at IVa and Va is the methylenedioxytropylium ion (m/e 135). Other less pronounced features of the spectra are in agreement with this picture.

The ^{1}H-NMR spectra fully agree with the MS assignement. The main characteristics of the NMR spectra (CCl solution, TMS, 60 MHz) are as follows. IVa: δ_1 = 1.85 ppm, quartet, J_1 = 7 cps, J_2 = 8 cps, 2 H, (e); δ_2 ≈ 2.4 ppm, multiplet (6 visible peaks),

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*Varian T-60
**JNM PS-100 and XL-100
***for assignment see letters of the formulae

4 H, (f,g); δ_3 = 5.87 ppm, singlet, 2 H, (a); δ_4 = 6.65 ppm, one peak, 3 H, (b,c,d); δ_5 = 9.79 ppm, triplet, J = 1.4 cps, 1 H, (h); Va: δ_1 = 1.03 ppm, doublet, J = 6 cps, 3 H, (g); δ_2 = 2.2-3.2 ppm multiplet, 3 H, (e,f); δ_3 = 5.88 ppm, singlet, 2 H, (a); δ_4 = 6.64 ppm, one peak, 3 H, (b,c,d); δ_5 = 9.75 ppm, doublet, J = 1.0 cps; 1 H, (h); VIa: δ_1 = 0.88 ppm, triplet, J = 7 cps, 3 H, (g); δ_2 = = 1.30-2.15 ppm, multiplet, 2 H, (f); δ_3 = 3.26 ppm, triplet, J = 6 cps, 1 H, (e); δ_4 = 5.94 ppm, singlet, 2 H, (a); δ_5 = 6.67 ppm, one peak, 3 H, (b,c,d); δ_6 = 9.65 ppm, doublet, J = 1.6 cps, 1 H, (h). The most characteristic bands are those of the methyl groups for IVa and Va as well as the bands of the aldehydic protons with special regard to the multiplicity of these bands. These data together with the MS spectra reveal a consistent system of evidence which supports the structural assignment given in formulae IVa-VIa.

IR investigations were in accordance with the above statements; aldehydic ν(C-O) (1630 cm^{-1}) and ν(C-H) (2730 cm^{-1}) bands are present in the spectra of all the three compounds. Bands characteristic for methyl ν(C-H) and ν(C-H) vibrations are absent in the spectra of IVa, while present in those of Va and VIa. The bands characteristic for the $-OCH_2O-$ group (ν(C-H): 2780 cm^{-1}, C-O-C bands: 1248 and 1050 cm^{-1}) are present in all spectra while olefinic absorptions around 1000 cm^{-1} are missing.

Cryoscopic and osmometric (both in benzene) MW measurements (to control the order of magnitude of the MS mole peak measurements) gave 192 ± 6 which agrees well with the supposed formula ($C_{11}H_{12}O_3$) as well as with the mole peak (m/e = 192).

Identification of Alcohols IVb, Vb and VIb

The compounds were separated by means of preparative GLC using a 2 m x 8 mm glass column filled with 22 % QF-1 on 60/72 mesh Celite, at 220°C column temperature and with 140 ml/min Ar carrier. The fractions were collected at -14°C.

Our structural assignment is mainly based on the mass spectra (MS-902, AEI, 70 eV). The mole peaks m/e 194 (48, 29, and 30 respectively) correspond to the supposed formula $C_{11}H_{14}O_3$. The base peak is in all cases the formation of the methylenedioxytropylium ion, m/e = 135 (100). The loss of the hydroxymethylene group (M-31) shows a characteristic trend, the intensity of the corresponding peak decreases sharply with the distance of this group from the aromatic ring: 86 (IVb), 15 (Vb), 9.6 (VIb).

The mass spectral assignation was supported by IR and NMR spectra.

The presence of the ν(O-H) bands (3350 cm^{-1}, s, br.), the characteristic absorptions of the dioxymethylenephenyl group (ν(C-H) ($O-CH_2-O$) 2780 cm^{-1}, mw; ν(C-O) (C-O-C) 1248 vs and 1050 cm^{-1}, s) is a common feature of the three compounds. The absence of an olefinic double bond stretching band (∿1000 cm^{-1}) as well as aldehydic ν(C-H) and ν(C-O) bands indicates the change of the original safrole and intermediate aldehyde structure. ν(C-H) (methyl) bands are absent in the spectrum of IVb while present at Vb and VIb. The $CH_3:CH_2$ (C-H str. band) intensity ratio is 1:1 (as supposed) at VIb, while it is far from the theoretical at Vb which can be attributed to the frequency shift of the ν(C-H) absorptions of the methylene group directly attached to the aromatic ring.

The H^1-NMR spectra of the compounds show the following main features (CCl_4 solution, TMS, 60 MHz). IVb: δ_1 = 1.35-1.75 ppm, br. multiplet, 4 H, (f,g); δ_2 = 2.50 ppm, ill-resolved triplet, 2 H, (e); δ_3 = 3.08 ppm, singlet, 1 H, (i); δ_4 = 3.50 ppm, triplet, J = 6 cps, 2 H, (h); δ_5 = 5.86 ppm, singlet, 2 H, (a); δ_6 = 6.62 ppm, one peak, 3 H, (b,c,d). Vb: δ_1 = 0.85 ppm, doublet, J = 7.5 cps, 3 H, (g); δ_2 = 1.35 - 2.05 ppm, multiplet, 1 H, (f); δ_3 = = 2.35 ppm, doublet, J = 7.5 cps, 2 H, (e,i)*; δ_4 = 3.37 ppm, doublet, J = 6 cps, 2 H, (h); δ_5 = 5.89 ppm, singlet, 2 H, (a); δ_6 = 6.63 ppm, one peak, 3 H, (b,c,d). VIb: δ_1 = 0.83 ppm, triplet, J = 6 cps, 3 H, (g); δ_2 = 1.15 - 2.20 ppm, multiplet, 2 H, (f);

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*The OH signal is most probably concealed by the (e) doublet.

δ_3 = 1.95 ppm, singlet, 1 H, (i); δ_4 = 2.25 - 2.80 ppm, multiplet, 1 H, (e); δ_5 = 3.58 ppm, doublet, J = 7 cps, 2 H, (h); δ_6 = 5.90 ppm, singlet, 2 H, (a); δ_7 = 6.65 ppm, one peak, 3 H, (b,c,d).

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РЕЗЮМЕ

5,6,7,8 - тетрагидро - 2,3 - метилдвуокись нафталина образуется из сафрола через γ - (3,4-метилдвуокись фенил) - бутировый альдегид как переходное соединение в условиях гидроформилирования в присутствии катализатора $Co_2(CO)_8$. Закрытие кольца происходит внутримолекулярным электрофильным замещением, катализированным с $HCo(CO)_4$.