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THE ACID CATALYZED CYCLIZATION OF CITRAL

B. C. Clark, Jr.,* C. C. Powell and T. Radford
Corporate Research and Development Department, The Coca-Cola Company, Atlanta, GA 30301, U.S.A.

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Abstract—Fourteen compounds have been identified as products of the acid catalyzed cyclization of citral under mild aqueous acid conditions. Three major products of the reaction, 1,8-epoxy-*p*-menth-2-ene (**11**) and *trans*- and *cis*-*p*-menth-2-ene-1,8-diol (**16** and **18**) are reported here for the first time as products from citral. Possible mechanistic pathways leading to the products are discussed.

It had long been accepted that the acid catalyzed cyclization of citral (**1**) gives rise to *p*-cymene (**5**) as the single, end product, with intermediate formation of piperitenol (**2**) and/or isopiperitenol (**3**) and mentha-2,4(8),6-triene (**4**).[1] However, unequivocal evidence to confirm this sequence appears to be lacking.

Recently, several investigators have questioned the validity of this reaction pathway.[2-4] Thus, it has been reported[2] that treatment of citral with aqueous acid gives a mixture of hydrocarbons and unidentified alcohols in which *p*,α-dimethylstyrene (**10**) is a major product.

In a more detailed investigation it was determined that a mixture of **5** and **10** results from complete reaction of citral with aqueous acid.[4] Both piperitenol (**2**) and isopiperitenol (**3**) were detected when the reaction was arrested at intermediate stages. Identification of **2** was based on an interpretation of its mass spectrum in the absence of an authentic sample.[4,5] Mass spectral data reported by the authors for **3** have been questioned.[6]

It is evident that questions still exist regarding the acid catalyzed cyclization of citral. As a contribution to the understanding of this reaction, we are prompted to report the results of our investigation of the acid catalyzed cyclization of citral under mild aqueous acid conditions.

RESULTS AND DISCUSSION

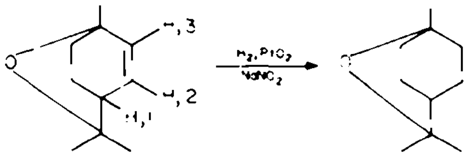
Citral reactions were carried out at various pH values between 2.4 and 3.2. The data shown in Table 1 were obtained for a typical reaction in which a vigorously stirred 4.3×10^{-2} molar aqueous suspension of citral, adjusted to a pH of 2.5 with hydrochloric acid, was allowed to react under nitrogen in the dark until essentially all the citral had been consumed (approximately 35 days). In this and other reactions the work-up always included washing the product with mild base. The structures, retention indices and area percent of the products obtained from citral under the above conditions are given in Table 1. Products previously reported[2-4] are marked with an appropriate reference number.

For identification, the products were separated by preparative column chromatography on silica gel into six major fractions: (1) hydrocarbons (dienes and trienes), (2) hydrocarbons (aromatic), (3) an ether, (4) monoalcohols, (5) 3,8-diols and (6) 1,8-diols. Usually, individual compounds were isolated *via* preparative glc from the appropriate fraction for identification. The 14 products discussed below accounted for 86% of the volatile (glc detectable) products in the particular example cited in Table 1.

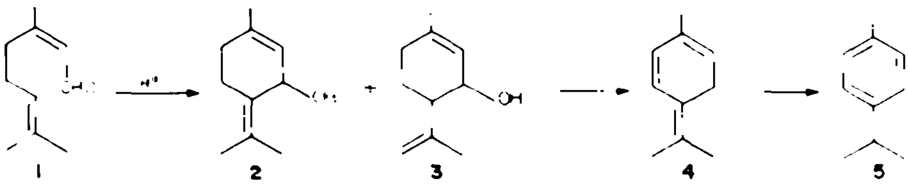
In the first fraction, α-terpinene (**6**) was identified by glc peak enrichment and MS. Terpinolene (**7**) was identified by glc peak enrichment and comparison of IR and MS with published spectra. The compound with retention index 5.8 gave a MS, UV and glc retention index that were compatible with the structure *p*-mentha-1,5,8-triene (**8**). Compound **9** was not identified, but on the basis of a molecular weight of 134, retention index, reaction mechanism and consideration of other reaction products, it is tentatively formulated as *p*-mentha-1(7),2,8-triene.

The aromatic hydrocarbons present in fraction 2 were identified as *p*-cymene (**5**) and *p*,α-dimethylstyrene (**10**) by glc peak enrichment and by IR and MS comparisons with authentic samples.

The 60 MHz NMR spectrum of ether **11**, detected in fraction 3, exhibited three, 3-proton singlets at δ0.98, 1.28 and 1.33, corresponding to three Me groups. In addition, the vinylic protons (H, 2 and 3) appeared as a quintuplet with additional fine splitting centered at 6.4. Decoupling of H_1 (2.26) yielded the vinylic protons as an AB quartet centered at 6.4 (J = 8 Hz). The structure of **11** was confirmed as 1,8 - epoxy - *p* - menth - 2 - ene (2 - dehydro - 1,8 - cineole) by reduction to 1,8-cineole (**12**) and by comparison of the IR and NMR spectra of **11** with published values.[7]



11 **12**



1 **2** **3** **4** **5**

Table 1. Citral reaction products[†]

Compound	Compound number	Retention index (I_E)	Area %*	Compounds previously identified (ref.)
α-terpinene	(6)	5.6	Trace	2
1,8-epoxy-p-menth-2-ene	(11)	5.6	3.7	
p-mentha-1,5,8-triene	(8)	5.8	0.9	
a menthatriene -- possibly p-mentha-1(7),2,8-triene	(9)	6.1	0.7	
p-cymene	(5)	6.3	1.1	2, 4
terpinolene	(7)	6.5	1.5	
p,α-dimethylstyrene	(10)	7.7	0.7	2, 4
p-mentha-1,5-dien-8-ol	(13)	10.4	17.8	3
p-mentha-1(7),2-dien-8-ol	(14)	10.9	11.0	3
p-cymen-8-ol	(15)	11.4	7.5	3, 4
trans-p-menth-2-ene-1,8-diol	(16)	13.8	20.0	
trans-p-menth-1-ene-3,8-diol[x]	(17)	14.2	1.6	
cis-p-menth-2-ene-1,8-diol	(18)	14.3	14.8	
cis-p-menth-1-ene-3,8-diol[x]	(19)	15.0	4.3	

[†] For reaction conditions see text.

[*] Peak area as a percent of total area corrected for response factors.

[x] The assignment of stereochemistry has not been rigorously proved; see text.

The dienols **13** and **14** in fraction 4 were identified as follows. The IR spectra were identical with those provided by Rogers.† The NMR spectrum of alcohol **13** exhibited a 6-proton singlet at δ 1.2 ($\mathrm{OCMe_2}$), a 3-proton multiplet at 1.71 (C=CMe), a 1-proton broad multiplet at 5.42  $(\mathrm{H{-}C{=}\overset{\overset{C}{|}}{C}{-}C})$ and a narrow 2-proton multiplet at 5.88 (HC=CH).

The NMR was in accord with a published[8] spectrum of **13** except that the 5.42 multiplet did not appear in the published spectrum. The IR spectrum of **13** was identical with that obtained for an authentic sample of the dienol synthesized from verbenol by a published procedure.[9]

The dienol **14** showed two, 3-proton singlets at δ 1.13 and 1.20 ($\mathrm{OCMe_2}$), a broad 2-proton singlet at 4.73 ($\mathrm{C{=}CH_2}$), and a broad 2-proton quartet at 6.03 with considerable secondary splitting (HC=CH). In addition, the IR of **14** was identical to an authentic sample of the dienol from verbenol.[9] Alcohol **15** was identified by comparison of its IR to a published spectrum[10] and MS to published values.[11]

The structure proofs of compounds **16**–**19** found in fractions 5 and 6 can be discussed together. Examination of the IR spectra indicated the compounds to be diols similar in structure to 1,8-terpin. The diols gave identical MS except for slight differences in relative peak intensities, suggesting they were isomers. The possibility that diols **16** and **18** and diols **17** and **19** constituted isomeric pairs was suggested by their elution times on silica gel. The diols **17** and **19** eluted in fraction 5 and the diols **16** and **18** eluted later as a separate fraction (fraction 6).

Confirmation of the close structural similarity between **16** and **18** was provided by NMR which showed them to be most likely *trans* - *p* - menth - 2 - ene - 1,8 - diol and *cis* - *p* - menth - 2 - ene - 1,8 - diol, respectively. NMR of **16** in deuterated dimethylsulfoxide showed three, 3-proton singlets at δ 1.02, 1.08 and 1.13 (Me–C–O) and a 2-proton singlet at 4.15 (OH protons). A singlet OH is a strong indication of tertiary OH, especially when the spectrum is run in deuterated dimethylsulfoxide.[12]

The NMR and m.p. of diol **18** compared well with published values[11,14] for *cis* - *p* - menth - 2 - ene - 1,8 - diol. The stereochemistry and structures of the diols were unequivocally determined by reduction of a 3:2 mixture of **16**:**18** to form a 3:2 mixture of *trans* - 1,8 - terpin:*cis* - 1,8 - terpin, which exhibited identical IR to authentic materials.

That the compound **19** was an isomer of diols **16** and **18** was indicated by its identical MS and similar IR. The NMR of **19** in D-DMSO showed two, 3-proton singlets, ($\mathrm{Me_2CO}$) at δ 1.10 and 1.15, a 3-proton narrow multiplet at 1.63 (MeC=C), a broad 1-proton multiplet at 4.23 (C=C–CH–O), a 1-proton singlet at 5.10 (3°OH), a 1-proton doublet at 5.12 (J = 3.2 Hz; 2°OH) and a broad 1-proton vinylic multiplet at 5.28. These values suggest that the structure of compound **19** is *p* - menth - 1 - ene - 3,8 - diol. Other compatible structures (**20**, **21**) can be ruled out on mechanistic grounds.

No spectral data were obtained on pure compound **17**. Its structure was tentatively formulated as a *p* - menth -

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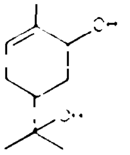
†We thank James A. Rogers, Fritzsche, Dodge & Olcott, Inc. for sharing with us the IR spectra of the alcohols 13, 14 and 15 and other data on the reaction of citral prior to publication.[3]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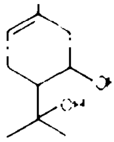
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1 - ene - 3,8 - diol on the basis of its elution in the fraction with diol **19**.

Further structural information was provided by catalytic hydrogenation of a mixture of **17** and **19** which yielded a mixture of four isomers (**22**) as expected, three major diols and one minor one. All the reduction products were not characterized, but the first major reduction product based on glc R_t was identical by IR with a major isomer isolated from hydrolysis of isopulegol (**23**). The 3,8-diol structure is consistent with these data.

The stereochemistry of the minor diols **17** and **19** was not resolved, but is most likely as assigned since the *cis* product (**19**) would be expected to have the longer glc R_t as is the case with the isomeric 1,8-diols.

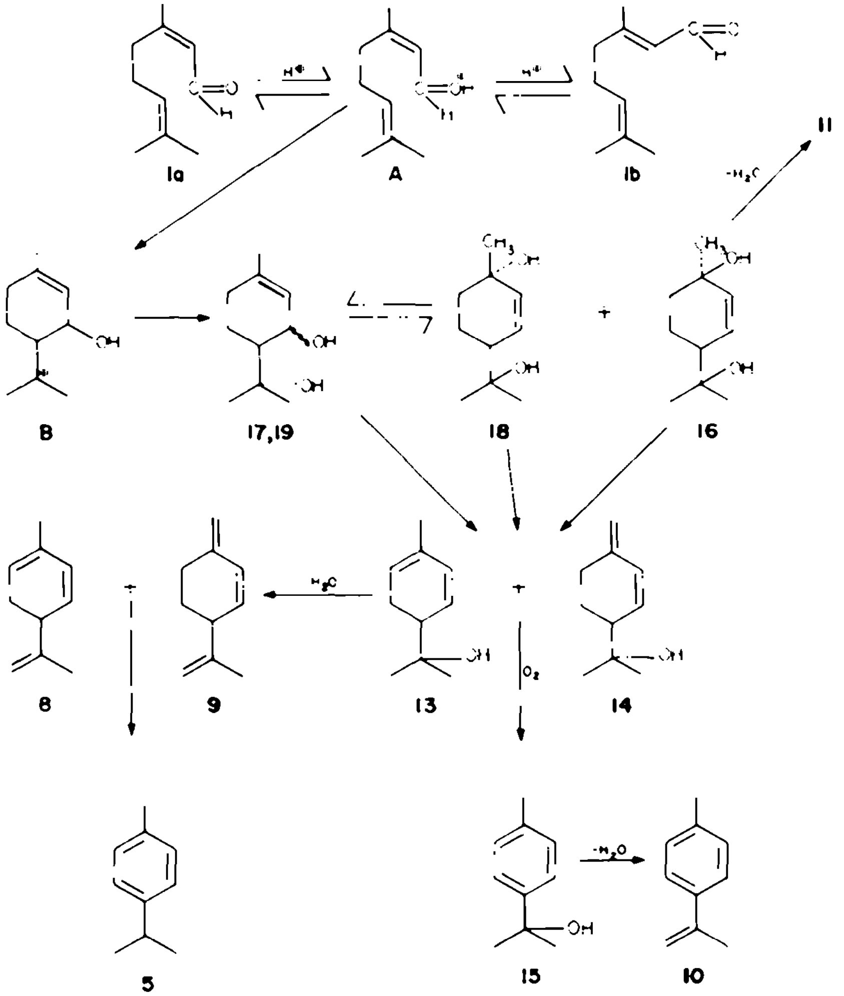
We have proposed a reaction scheme (Scheme 1) to account for our results. First, the formation of a common charged species such as **A** from both citral isomers, neral (**Ia**) and geranial (**Ib**), is postulated. **A** can undergo cyclization to carbonium ion **B** followed by hydration to 3,8-diols **17** and **19**. The diols **16** and **18** may be formed by allylic rearrangement of **17** and **19**. This process has been shown to be quite facile in the *p* - menth - 2 - en - 1 - ol (**24**) ⇌ piperitol (**25**) equilibration and other similar reactions.[15]

The ether **11** may be formed by cyclodehydration of the diol **16**.

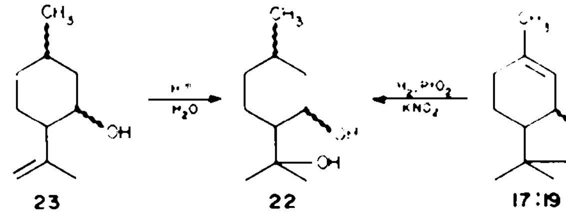
Dienols **13** and **14** may be produced by elimination of water from diols **16** and **18** and/or by rearrangement and elimination of water from **17** and **19**. In both cases the driving force is creation of a conjugated system. Even though the reaction was run under nitrogen, rigorous precautions to obtain a completely inert atmosphere were not taken, and apparently some oxidation occurred. We have subjected a mixture of **13** and **14** to air oxidation at 5°C and found that they are transformed to *p*-cymen-8-ol (**15**) as the major product.

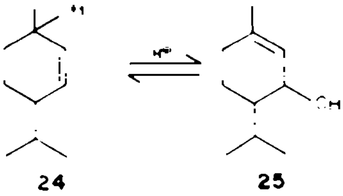
The dienols **13** and **14** could also dehydrate to the menthatrienes **8** and **9** which are known to isomerize readily to *p*-cymene (**5**). Dehydration of *p*-cymen-8-ol (**15**) may lead to *p*,α-dimethylstyrene (**10**) or the latter could be formed by disproportionation of unspecified compounds to yield the small amounts of α-terpinene (**6**) and terpinolene (**7**) found.

It will be noted that the data given in Table 1, and



Scheme 1.





consequently the mechanism proposed for acid catalyzed cyclization of citral (Reaction Scheme 1), differ significantly from those discussed previously.[2,4] For example, the hydrocarbons *p*-cymene (**5**) and *p*,α-dimethylstyrene (**10**), reported to be the major products from the reaction of citral with acid,[2] appear as minor constituents in the reaction mixture (Table 1). The contrast in these results is probably associated with differences in reaction conditions. The conditions used in our investigations were chosen to provide product and mechanistic information about the cyclization of citral under mild conditions. In fact, we found that higher concentrations of citral and acid gave increased yields of hydrocarbons.

Of greater significance is the identification by other workers of piperitenol (**2**) and isopiperitenol (**3**) (in the reaction products) and proposals that these alcohols are important intermediates in the cyclization of citral.[4] We did not detect **3** either at the intermediate stages checked or after complete reaction of citral with acid. Based on the detection limits inherent in our investigation, these observations suggest that **3**, if present, constitutes less than 1% of the reaction products. A sample of **2** was not available to us and consequently we are unable to comment on whether this alcohol is present in our reaction mixture. However, based on the compositional data in Table 1 and the relative areas of unassigned gas chromatographic peaks, it is believed that **3** can only be a relatively minor component of our reaction mixture.

The two most important features of the data given in Table 1 are probably (1) the presence of three major products, diols **16** and **18** and the ether **11**, which have not previously been identified as products of the cyclization of citral, and (2) the formation of the alcohols **13** and **14** and diols **16** and **18** as major products, which is supported by the results of periodic analyses of the reaction mixture. It was found that **13**, **14**, **16** and **18** are major products even in the early stages of the reaction.

It is clear from the results reported here that acid catalyzed cyclization of citral under these mild conditions proceeds by a different pathway and yields different products than those generally formulated for the reaction of citral with acid.

EXPERIMENTAL

All m.ps are uncorrected and were obtained in capillary tubes on a Thomas Unimelt apparatus. Analyses by glc were performed on a PE-900 equipped with dual 12 ft, 1/8 in. i.d. glass columns, modified for on-column injection, packed with 5% Triton X-305 on Chromosorb W. H.P. 80–100 mesh. The oven temp was programmed from 70° to 180° at 2°/min with 10 min initial hold. The injector and detector were maintained at 150° and 250° respectively. A flow rate of 35 ml/min of helium was employed. Compounds were in general isolated by collection with glass capillaries from an F & M 810 glc equipped with a TC detector, 1/4 in. glass columns, and generally operated as above. The reaction products were isolated on Triton X-305 or OV-17 liquid phases. IR spectra were determined using a PE-221; NMR, a Varian T-60; and MS, a CEC model 110.

Cyclization of citral. Citral (40% neral **1a** and 60% geranial **1b**), 20 g, was dispersed in 300 ml water (deaerated with N_2). The pH of the soln was adjusted to 2.5 with conc. HCl, the flask was placed under N_2 and stirred vigorously in the dark at room temp. The reaction was monitored by glc periodically and after all the citral had been allowed to react (35 days), a 200 ml aliquot of the mixture was then treated with 20 g of NaCl and extracted 4 times with ether. The ethereal layer was washed with sat $NaHCO_3$ aq, H_2O, sat NaCl aq, dried over Na_2SO_4 and concentrated to yield a yellow oil.

The citral reaction products were fractionated by preparative column chromatography generally on Woelm III silica gel as follows:

Fraction	Solvent	Compounds
1	Pentane	Hydrocarbons (**6**, **7**, **8**, **9**)
2	Pentane	Hydrocarbons (**5**, **10**)
3	Ether/pentane 1:8	Ether (**11**)
4	Ether/pentane 1:1	Monoalcohols (**13**, **14**, **15**)
5	Ether	*p*-menth-1-ene-3,8-diols (**17**, **19**)
6	Ethanol/ether 1:4	*p*-menth-2-ene-1,8-diols (**16**, **18**)

p-*Mentha-1,5,8-triene* (**8**). UV (EtOH), λ_{max} 263.5 nm (Lit.[9]; 265 nm); MS: *m/e* (relative abundance) 135(11), 134(100), 120(8), 119(79), 106(15), 105(27), 93(26), 92(26), 91(91), 79(27), 77(27,

1,8-*Epoxy*-p-*menth-2-ene* (*2-dehydro-1,8-cineole* **11**). See text for NMR details. IR (neat), ν_{max} 3010, 2950, 1618, 1380, 1230, 1142, 1108, 1070, 952, 840 cm^{-1}. MS *m/e* (relative abundance) 153(3), 152(25), 124(40), 109(100+), 94(70), 93(26), 91(22), 79(100), 77(35), 49(80).

Reduction of **11** *to 1,8-cineole* (**12**). Approximately 100 mg of **11** in a Parr apparatus was reduced in 95% EtOH with 7.3 mg. PtO_2 and 1.5 mg $NaNO_2$ at 65 psi H_2 using a standard procedure of Henbest.[16] The ether **11** was converted quantitatively to 1,8-cineole, identical to authentic material by glc peak enrichment and IR.

p-*Mentha-1,5-dien-8-ol* (**13**). See text for NMR data. UV (EtOH), λ_{max} 261 nm, ε 2735 (Lit.[9] isooctane λ_{max} 263 nm, ε 2340). IR (CCl_4), ν_{max} 3300, 2995, 2910, 1660, 1452, 1378, 1205, 1160, 1130, 922, 915, 853, 828, 775, 738 cm^{-1}. MS: *m/e* (relative abundance) 152(1), 134(22), 119(50), 117(10), 94(100), 93(40), 92(18), 91(48), 79(94), 77(28), 65(10), 59(72), 43(26).

p-*Mentha*-1(7),2-*dien*-8-*ol* (**14**). See text for NMR data. IR (CCl_4), ν_{max} 3450, 3120, 2075, 3010, 1650, 1610, 1380, 1205, 1155, 1132, 922, 878, 810 cm^{-1}. MS: *m/e* (relative abundance) 152(1), 134(28), 119(35), 94(100), 93(26), 91(42), 79(75), 77(24), 59(80), 43(17).

trans-p-*Menth*-2-*ene*-1,8-*diol* (**16**). See text for NMR data. M.P. 84.3–86.5° (Lit.[17] 80–81°). IR (KBr), ν_{max} 3300, 3000, 2940, 1380, 1360, 1175, 1152, 1122, 1028, 1000, 972, 942, 905, 834, 809 cm^{-1}. MS: *m/e* (relative abundance) 152(3), 134(10), 119(16), 109(15), 95(10), 94(100), 93(27), 92(10), 79(80), 77(27), 59(100+), 43(43).

cis-p-*Menth*-2-*ene*-1,8-*diol* (**18**). NMR ($DCCl_3$), δ 1.16 (3H, S), 1.21 (3H, S), 1.26 (3H, S), 2.5 (2H, S), 5.76 (2H, S) IR (KBr), ν_{max} 3300, 2900, 1668, 1370, 1360, 1150, 1118, 1100, 1058, 1012, 978, 950, 848, 793, 788 cm^{-1}. MS: *m/e* (relative abundance) 152(5), 134(6), 119(10), 109(25), 94(98), 93(25), 91(25), 79(77), 59(100), 43(38).

Reduction of cis- *and* trans-p-*menth*-2-ene-1,8-*diols* (**16**, **18**). A 3:2 mixture of 200 mg (**16**, **18**) was quantitatively reduced by the previously described method of Henbest[16] to a 3:2 mixture of *trans*-1,8-terpin (confirmed by glc peak enrichment and IR comparison with authentic material) and *cis*-1,8-terpin; m.p. 154–156° (Lit. 153.5°,[13] 157–158°[14]). IR of isolated *cis*-1,8-terpin was identical to IR of authentic material.

p-*Menth*-1-*ene*-3,8-*diol* (cis?) (**19**). See text for NMR details. IR (KBr) ν_{max} 3280, 2950, 2860, 2805, 1675, 1435, 1472, 1380, 1366, 1309, 1260, 1181, 1131, 1030, 1018, 1006, 995, 985, 930, 916, 900, 882, 823 cm^{-1}. MS: *m/e* (relative abundance) 152(3), 134(44), 119(75), 117(10), 109(22), 94(100), 93(40), 91(68), 80(10), 79(99), 77(40), 65(14), 59(100+), 51(11).

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