

The Composition of Iso E Super

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Iso E Super, one of the most successful synthetic aroma chemicals in the history of perfumery, was originally introduced in the mid 1970s by International Flavors and Fragrances Inc.¹ Iso E Super possesses a woody-amber odor and is used globally in many fragrance applications. Among these are fine perfumes and detergents.² Iso E Super is obtained according to Figure 1,¹ which includes a condensation reaction between acetaldehyde and methylethyl ketone, a Diels-Alder reaction between methyl pentenone (MPO) and myrcene, and an acid catalyzed cyclization of the Diels-Alder adduct (DAA). All reactions involved are not very selective, and the cyclization is accompanied by secondary isomerizations, so the final product is a complex mixture of isomeric ketones.

A typical GLC profile for Iso E Super is given in Figure 2. Peaks with greater than 1 percent concentration are labeled with letters A to H. In commercial versions, these isomers are usually present in the following concentrations: A, 3-6 percent; B, 40-60 percent; C, 4-9 percent; D, 11-18 percent; E, 1-2 percent (unreacted DAA, minor isomer, and also a coeluting peak E^o - a product of double bond isomerization of DAA); F, 2-4 percent (unreacted DAA, major isomer); G, 2-4 percent; and H, 9-14 percent.

Surprisingly, until now the structures of only two constituents of Iso E Super have been established: the major isomer (peak B)^{1,3} and one of the minor isomers G.^{2,4,5} The absence of adequate data regarding other isomers may have been due to the difficulties in their separation and purification. Givaudan researchers^{4,5} have found that the predominant isomer B has a weak odor with a threshold of about 500 ng/l of air, and, most interestingly, that the amber odor note of the product is imparted primarily by the minor isomer G, which has a very low odor threshold value of approximately 5 pg/l of air. In other words, the odor of ketone G is a hundred thousand times stronger than that of B. In this connection, it became a very interesting and challenging problem to isolate and evaluate other components of Iso E Super.

In the present study, we have separated, purified to at least 97 percent and fully characterized all the components of Iso E Super which are present in higher than 1 percent concentration. We have also rigorously established their structures as shown in Figure 3, and evaluated their odors. In addition, we have studied the dependence of the composition of the product on the conditions of the cyclization reaction and developed a method that allows one to obtain

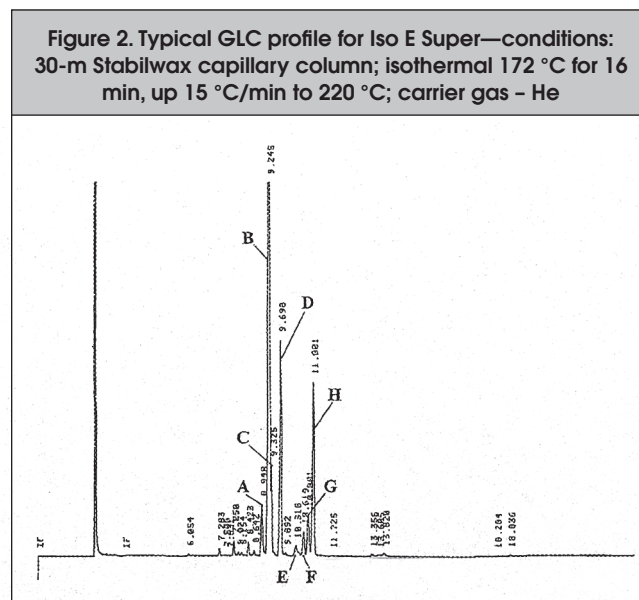
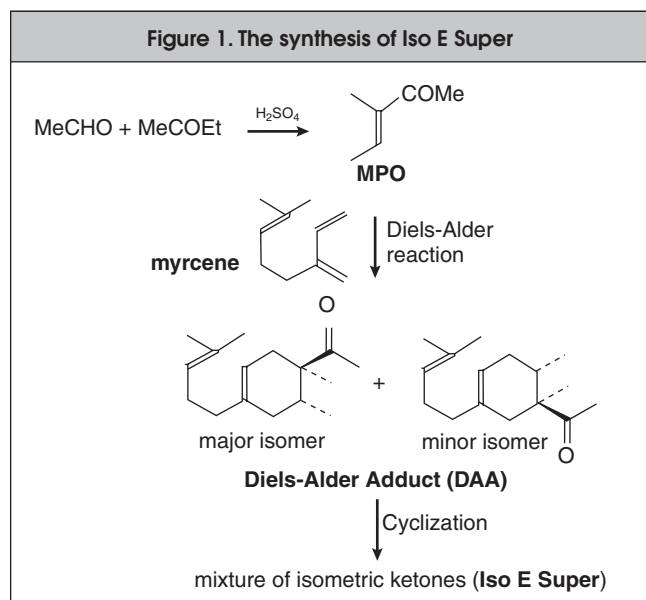


Figure 3. Routes of formation and structures of components of Iso E Super

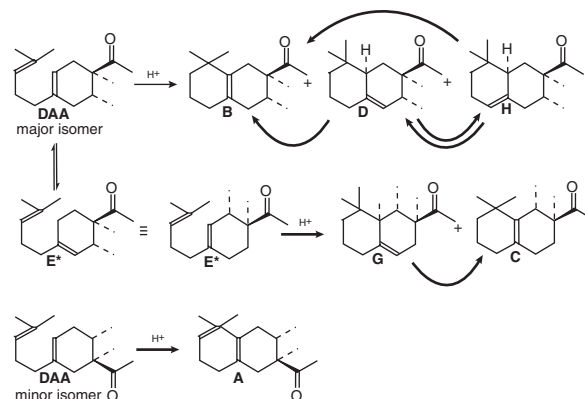
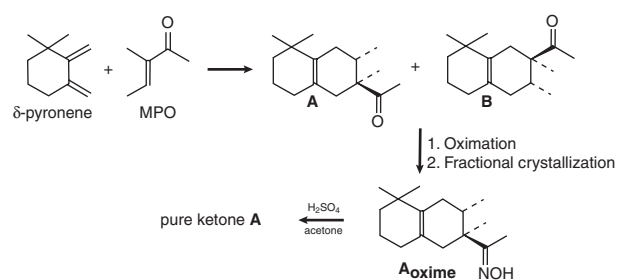


Figure 4. Independent synthesis of ketone A from δ -pyronene



products containing enhanced amounts of G, the most valuable isomer.

Separation and Structure Elucidation

Ketones B, C, and G were isolated by oximation of Iso E Super, followed by fractional crystallization of the oximes and hydrolysis. The oximation was carried out as described in the original patent.¹ The resulting ethanolic solution of oximes was diluted with water several times, giving a number of crystalline oxime fractions. Recrystallization of selected fractions from heptane gave individual oximes B_{oxime}, C_{oxime}, and G_{oxime}. Individual ketones were obtained by hydrolysis of the corresponding oximes in acetone in the presence of sulfuric acid. Crystalline ketones D and H (melting points 67-68°C and 42-43°C, respectively) were isolated by a combination of fractional distillation of Iso E Super and crystallization at reduced temperature. They were further purified by oximation, recrystallization of the oximes, and hydrolysis.

The oxime of ketone A was difficult to isolate from the total oxime mixture, so we obtained a comparison sample of ketone A independently by a thermal Diels-Alder reaction of δ -pyronene with MPO followed by oximation, fractional crystallization, and hydrolysis of A_{oxime} according to Figure 4.

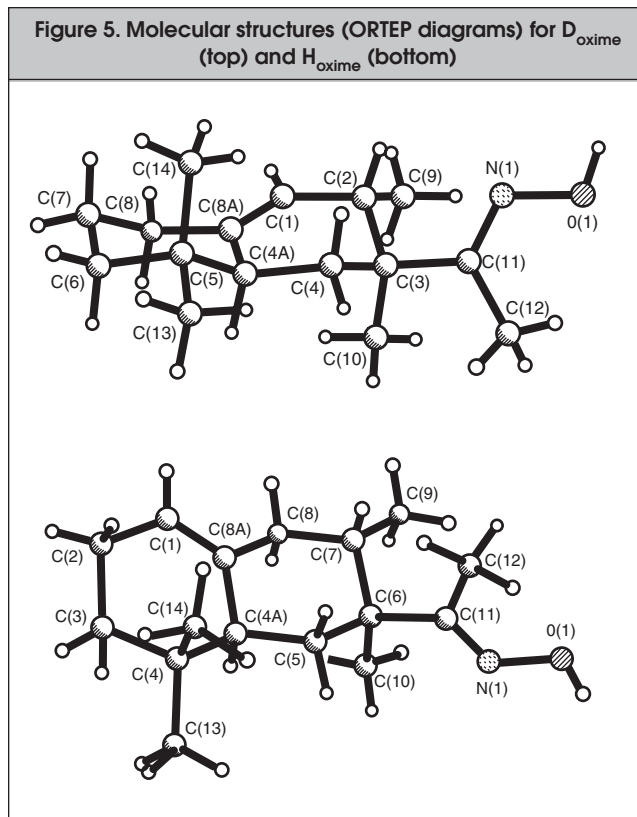
The structures of isomers (Figure 3) and their oximes are consistent with their NMR spectra as given in Tables 1 and

2 (details of homonuclear decoupling experiments are not provided for the sake of brevity). Signals in ^{13}C NMR spectra were assigned on the basis of the DEPT sequence.

To unambiguously determine the position of the double bond and the geometry at the bridgehead carbon atom in D and H, the corresponding oximes were additionally analyzed by the single crystal X-ray diffraction method. Their molecular structures (ORTEP diagrams) are shown in Figure 5. The length of the double bond between carbon atoms C(1) and C(8a) in D_{oxime} is 1.319 Å, and in H_{oxime} 1.321 Å. In both structures, the hydrogen atom at bridgehead carbon C(4a) is in the *trans* position with respect to the acetyl group. The oxime N-OH group has the *anti* configuration with respect to the bulkier octalin moiety.

Composition of the Product and Cyclization Conditions

The Iso E Super mixture results from a tricky and fragile balance between different cyclization and isomerization reactions of the Diels-Alder Adduct. Initially formed ketones B, C, D, G and H undergo further mutual transformations (Figure 3). These secondary transformations play an important role in the process. A separate study using pure ketones D and H showed that they can readily, and practically irreversibly, isomerize under the cyclization conditions into their thermodynamically stable β -isomer B. Similarly,



ketone G irreversibly gives the corresponding β -isomer C. In general, higher temperature, acid strength, and reaction time result in larger amounts of B and C due to the secondary isomerizations. These secondary isomerizations are shown in Figure 3 with the curved arrows. Products with isomer concentrations within the standard ranges are usually obtained with dilute aqueous sulfuric or phosphoric acid at moderate temperatures and reaction times.

Obviously, the small concentration of the most valuable isomer G in the products is due to a faster rate of cyclization of DAA into ketones B, D, and H, compared to the rate of its double bond isomerization into E.⁹ We have found that when the reaction is carried out in the presence of methanol or other lower alcohols, the cyclization slows down. The resulting concentration of ketone G increases up to 7 percent. This increase can be explained through the reversible formation of intermediate ketone I, in which the side chain double bond is temporarily “blocked” with a

methoxy group, and is thus unavailable for the cyclization (Figure 6). This allows more time for the remaining endocyclic double bond to isomerize into I,⁹ which consequently produces more G and C.

To further confirm this hypothesis, we obtained pure methoxylated ketone I by a reaction of DAA with methanol

Figure 6. Formation of increased amounts of ketone G from DAA in the presence of methanol

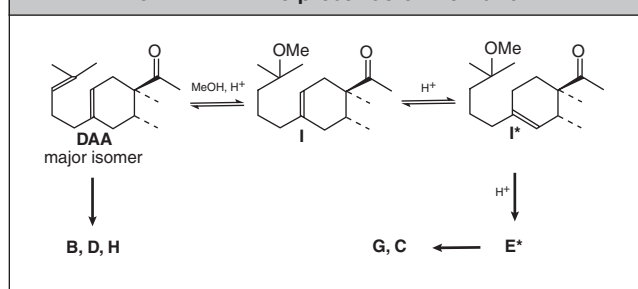


Table 1. ¹H NMR spectra of ketones A-D, G, and H and their oximes in CDCl₃

Compound	Chemical shift, δ ppm			
	MeC _{quat} (s)	MeCH (d; J~7 Hz)	MeC=O or MeC=N (s)	=CH(m)
A	0.93, 0.93, 0.96	0.78	2.11	-
A _{oxime}	0.94, 0.95, 0.96	0.76	1.83	-
B	0.91, 0.92, 0.95	0.75	2.12	-
B _{oxime}	0.90, 0.92, 0.94	0.72	1.87	-
C	0.98, 1.00, 1.06	1.00	2.06	-
C _{oxime}	0.91, 1.01, 1.04	1.00	1.77	-
D	0.68, 0.83, 0.87	0.68	2.06	5.00
D _{oxime}	0.74, 0.87, 0.91	0.76	1.84	5.07
G	0.82, 0.99, 1.02	0.87	2.12	5.41
G _{oxime}	0.83, 1.00, 1.03	0.90	1.88	5.42
H	0.75, 0.88, 1.07	0.68	2.10	5.35
H _{oxime}	0.75, 0.87, 1.11	0.70	1.83	5.34

Table 2. ¹³C NMR spectra of ketones A-D, G, and H and their oximes in CDCl₃

Compound	Chemical shift, δ ppm					
	Me groups	CH ₂ groups	CH	C _{quat}	C=O or C=N	C=C
A	15.1, 15.9, 24.8, 27.2, 27.7	19.0, 29.6, 30.9, 39.3, 39.8	32.8	33.1, 50.1	213.5	124.2, 132.9
A _{oxime}	9.8, 15.5, 16.1, 27.4, 28.2	19.3, 30.0, 31.1, 39.5, 41.1	33.1	33.4, 42.6	163.4	125.0, 133.0
B	15.0, 16.1, 25.2, 27.0, 27.8	19.1, 30.7, 34.0, 36.7, 39.5	32.4	33.3, 50.7	213.8	125.7, 131.9
B _{oxime}	9.8, 14.2, 16.2, 27.0, 28.1	19.3, 30.7, 35.7, 37.0, 39.8	32.5	33.5, 43.2	163.7	125.8, 132.6
C	16.7, 23.5, 24.5, 28.1, 29.7	18.7, 25.4, 28.5, 30.7, 40.4	33.8	34.0, 51.2	212.5	127.4, 139.1
C _{oxime}	10.8, 17.0, 25.5, 28.9, 30.0	19.3, 26.7, 28.7, 31.2, 41.0	34.9	34.2, 43.4	162.7	127.3, 138.1
D	13.7, 16.5, 20.4, 25.4, 29.3	22.3, 34.2, 34.6, 42.3	34.3, 43.9	34.5, 51.0	214.0	125.6, 136.2
D _{oxime}	9.8, 14.4, 16.1, 20.6, 29.4	22.5, 34.7, 34.8, 42.5	34.3, 44.3	34.6, 43.4	163.9	125.7, 136.5
G	15.5, 19.7, 20.0, 25.1, 31.4	23.8, 35.1, 35.9, 43.0	33.2, 53.3	37.3, 52.1	213.7	116.4, 140.4
G _{oxime}	10.1, 16.5, 19.2, 20.5, 31.8	24.1, 35.7, 36.3, 43.4	33.2, 53.6	37.6, 44.9	164.0	117.5, 139.9
H	13.1, 16.9, 23.1, 24.9, 28.6	22.3, 35.7, 37.5, 39.5	36.7, 41.6	30.9, 52.2	213.1	118.8, 137.9
H _{oxime}	9.7, 14.4, 16.6, 23.3, 28.8	22.5, 35.8, 38.2, 39.6	31.1, 36.9,	42.0, 44.6	163.5	118.7, 138.5

in the presence of boron trifluoride etherate and subjected it to the cyclization conditions. This two-step version of the cyclization gave a product containing up to 9.2 percent of ketone G. Other isomers were present in the following concentrations: A, 2.8 percent; B, 39.0 percent; C, 6.6 percent; D, 16.9 percent, E and E*, 2.8 percent; F, 3.6 percent; and H, 11.3 percent.

Numerous examples illustrating the dependence of the composition of Iso E Super type products on the cyclization conditions can be found in the patent to Millennium Specialty Chemicals.⁶

Odor Properties

The odors of individual components of Iso E Super are as follows:

- Ketone A has a woody (cedar) odor with an amber note, slightly fruity acetic.
- Major isomer B: amber-woody, cedar.
- Ketone C: woody (cedar), cedryl ketone-like, with an amber note, slightly solventy and slightly acetic.
- Ketone D has a woody, incense, leather, amber odor, slightly animalic, with a very slight sweet burnt sugar note.
- Ketone G: ambery (much stronger than B), woody, cedary, vetiver acetate-like, wood sap.
- Ketone H has a sweet woody resinous note, slightly leathery, smoky.

Having individual components of Iso E Super on hand, we were tempted to reconstitute the product from these components and to compare the odors of the reconstituted and the standard mixtures. One of the goals was also to determine whether the remaining dozen smaller unidentified peaks seen on the GLC (Figure 2) were important for the odor of the product. The reconstituted mixture contained the components in the following concentrations, which were selected within the above given commercial range: A, 4.41 percent; B, 54.25 percent; C, 6.45 percent; D, 15.27 percent; E, 1.07 percent; F, 1.86 percent; G, 3.80 percent; and H, 12.89 percent. The odor of the reconstituted mixture was very similar to that of the standard product, though less ambery and more woody (cedar). It also had slight musky and incense notes. The standard Iso E Super was smoother, more "round." Apparently, the remaining 12 or more minor unidentified peaks play some role in the odor pattern of Iso E Super. Their identification, although technically much more difficult, could be an interesting topic for future studies. ■

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