Table I. Deuteration of Amino Acids at the α Position

Amino acid	α-Deuteration, % One exchange	Two exchanges	Registry no.
Isoleucine	77	>95[a]	62076-83-9
Leucine	83	91	62076-84-0
Methionine	79	>95[a]	62076-85-1
Valine	81	>95[a]	62076-86-2
Alanine	82	92	5046-58-2
Tyrosine	80	95	62076-87-3
S-Benzylcysteine	67	89	57866-79-2
Proline	73	86	62076-88-4

[a] No measurable α protons were detected by ^{1}H NMR.

problem of stereoisomer resolution. The resolution scheme for the four stereoisomers of isoleucine, for example, is quite lengthy. Third, this process directly yields *N*-acetyl-α-labeled amino acids which are the starting compounds for enzymatic resolution using hog renal acylase, carboxypeptidase, or other enzymes capable of selective cleavage of an acetyl group from one stereoisomer without a significant cleavage of the enantiomeric compound. Fourth, if the D isomer is not desired, it can be recycled. Fifth, the exchange efficiency is related to the proportional excess of available deuterons to protons. To achieve high levels of exchange, a high ^{2}H/^{1}H ratio is required. This condition can be approached in several ways: (a) a high molar excess of acetic acid-*d* relative to the amino acid can be used; (b) labile hydrogens of the amino acid can be subjected to prior exchange; (c) the exchange reaction can be repeated.

With the methods we have used thus far, one treatment generally leads to 70–80% exchange. A second treatment raises the level of exchange to 90–100% in most cases studied (Table I).

Experimental Section

Synthesis of *N*-Acetyl-DL-[α-^{2}H$_1$]alanine. The following procedure exemplifies the experimental procedure used. All-protio alanine (0.89 g, 0.01 mol) was shaken with 3.7 mL of D_2O to exchange labile protons. The mixture was frozen and lyophilized to dryness. Immediately, 21.7 mL of Ac_2O and 2.5 mL of D_2O were added to the resulting powder and the flask was placed in a 170 °C bath. The solution was refluxed for 2 min, then cooled (drying tube) and 2 mL of D_2O was added to destroy the remaining Ac_2O and convert any azlactone **2** back to the *N*-acetyl amino acid. The solvents were removed by rotary evaporation. Crystals appeared as the evaporation neared completion. The residue was recrystallized from ethyl acetate. The crystals were filtered, washed with ether, and dried in vacuo over KOH: yield 1.17 g (89%); mp 127–128 °C; NMR (Me_2SO-d_6) δ 1.55 (s, 3 H), 2.15 (s, 1.1 H), 2.80 (Me_2SO), 4.4–4.6 (α-CH, 0.18 H). After the reaction was repeated, 0.08 α hydrogens were detectable by proton nuclear magetic resonance spectroscopy, yield 1.06 g (80%). Similar procedures were used for other amino acids and the results are summarized in Table I.

There was exchange of deuterium into the acetyl methyl groups. This fact effectively decreases the ^{2}H/^{1}H ratio and is undoubtedly responsible for some, if not most, of the nondeuteration at the α carbon. Clearly, this method could also be used for the exchange of tritium into the α position.

Registry No.—DL-Isoleucine, 443-79-8; DL-leucine, 328-39-2; DL-methionine, 59-51-8; DL-valine, 516-06-3; DL-alanine, 302-72-7; DL-tyrosine, 556-03-6; DL-*S*-benzylcysteine, 5680-65-9; DL-proline, 609-36-9.

References and Notes

(1) (a) Financial support from the National Science Foundation, the U.S. Public Health Service (AM 17420), and the Lubrizol Foundation is gratefully acknowledged. (b) Taken in part from the Ph.D. Thesis of Donald A. Upson, University of Arizona, 1975.
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Conformational Analysis. 127. Force Field Calculations on the Dodecahydrophenanthrenes[1,2]

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In an earlier paper the structures and relative stabilities of the isomeric octahydronaphthalenes were discussed.[3] It was felt that the relative energies of the various isomers could be accurately calculated, and simultaneous but independent experimental work showed that this was indeed so.[4] In the course of continuing studies on the isomers of perhydrophenanthrene,[5] various synthetic sequences were projected which involved a dodecahydrophenanthrene with a trans,syn,trans backbone as an intermediate. Because of the possibility of rearrangement, it was desirable to know something about the relative stabilities of some of these compounds. The previously used calculational methods (molecular mechanics) were expected to yield reliable predictions here, so the calculations were carried out (1973 force field[6]) and the results are reported herein.

There are 25 isomers of dodecahydrophenanthrene which were considered in this work. They are shown in Table I. The calculated heat of formation (H_f, gas, 25 °C) is −29.60 kcal/mol for the most stable compound (**7**). The values of $\Delta H_f°$ are given for each conformation. Also, the values of ΔH for each *compound* (conformational mixture) relative to the most stable isomer are shown, together with the relative entropies if nonzero, calculated by taking into account symmetry numbers and entropies of mixing. The relative free energies (80 °C) are also shown for isomers within 4 kcal/mol of the most stable one.

A few experimental investigations of the relative stabilities of some of the isomers of dodecahydrophenanthrene have appeared in the literature, together with suggestions regarding possible bond migrations in the course of a synthesis of a perhydrophenanthrene[7]. Christol and co-workers, in a series of papers,[8] carried out some equilibration studies, and isolated what they believed to be the isomers indicated, in the yields

Table I. Relative Enthalpies, Energies, Entropies, and Free Energies of the Conformations of the Dodecahydrophenanthrenes[a,b] 1–25

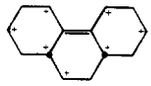
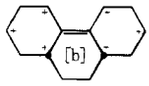
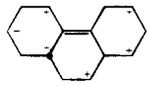
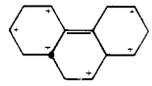
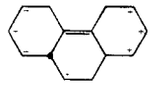
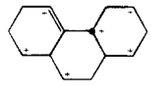
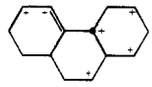
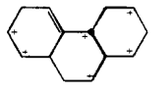
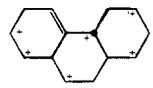
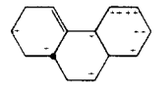
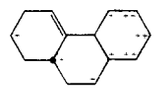
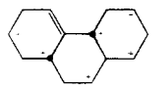
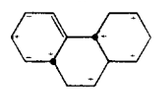
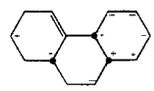
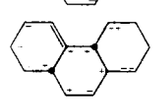
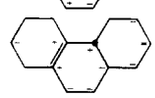
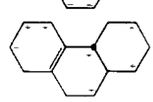
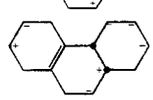
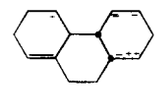
No.	Structure	Position of double bond	ΔH_f° (25 °C)	ΔH	ΔS	ΔG (80 °C)
1		4a,4b	3.17	3.17	−1.38	3.66
1		4a,4b	13.21			
2		4a,4b	5.82	3.12	−0.43	3.27
2		4a,4b	3.81			
2		4a,4b	2.94			
3		4,4a	7.23	7.18		
3		4,4a	7.14			
3		4,4a	14.49			
3		4,4a	12.43			
4		4,4a	2.98	2.98		2.98
4		4,4a	9.23			
5		4,4a	3.04	3.07	+1.37	2.59
5		4,4a	3.09			
6		4,4a	7.02	7.07		
6		4,4a	9.18			
7		4,10a	6.27	0.00	0	0.00
7		4,10a	0.00			
8		4,10a	1.61	1.28	+1.19	0.86
8		4,10a	1.13			
9		1,10a	3.97	4.03		
9		1,10a	7.52			

Table I
(*Continued*)

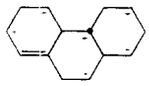
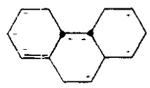
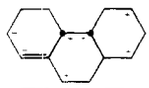
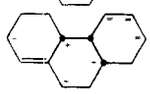
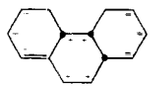
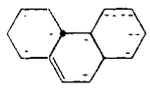
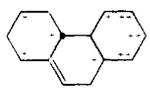
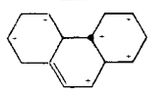
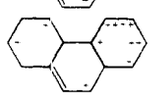
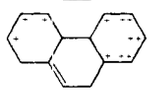
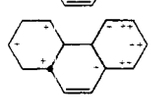
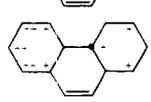
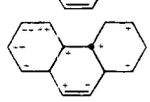
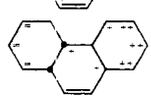
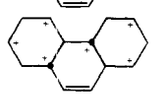
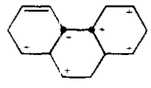
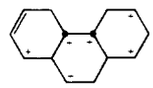
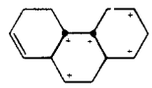
No.	Structure	Position of double bond	ΔH_f° (25 °C)	ΔH	ΔS	ΔG (80 °C)
10		1,10a	1.64	1.64	0	1.64
11		1,10a	9.13	7.00		
11		1,10a	6.98			
12		1,10a	5.37	5.37		
12		1,10a	11.93			
13		10,10a	3.34	3.31	+1.37	2.83
13		10,10a	3.24			
14		10,10a	1.36	1.36	0	1.36
15		10,10a	2.42	2.42	0	2.42
16		10,10a	4.98	4.99		
16		10,10a	8.15			
17		9,10	5.28	5.28		
17		9,10	14.50			
18		9,10	5.00	5.00		
18		9,10	12.98			
19		9,10	6.31	6.41		
19		9,10	7.87			
20		9,10	11.38	11.38		
21		9,10	4.00	4.00		
22		9,10	9.96	9.96		
23		3,4	11.94	11.94		

Table I
(Continued)

No.	Structure	Position of double bond	ΔH_f° (25 °C)	ΔH	ΔS	ΔG (80 °C)
24		2,3	8.49	8.49		
25		1,2	11.25	11.25		

[a] The values for ΔH_f° are the relative (to 7) values for the individual conformations. The values for ΔS allow for symmetry and mixing, and together with ΔG, these are for *compounds* rather than *conformations*. All for the gas phase. [b] The symbol (+) [or (−)] means that the carbon indicated is above (or below) the general place of the molecule. The symbols (++) and (−−) mean the same thing to a greater degree.

shown: **8**, 40%; **7**, 30%; **3**, 30%. They obtained the same mixture in several different ways, and hence concluded that it represented equilibrium. Their identification of the isomers was by gas phase chromatography, and structure determination with the aid of infrared, NMR (proton only), and Raman sepctroscopy.

Our calculations are in moderate agreement with the experimental work of the French workers. We agree that isomers **7** and **8** are the most stable, but find that isomer **3** is quite unstable, and therefore not likely to contribute significantly to the equilibrium mixture. We believe that isomer **10** or isomer **14**, or possibly a mixture of the two, was the third component which they obtained in the mixture. An unambiguous distinction between isomers **10**, **14**, and **3** does not seem possible on the basis of only infrared, Raman spectra, and ^1H NMR.

The starting coordinates were generated in each case from Fieser models by projection onto graph paper. About 3–6 min of computer time (IBM 360/65) was required for each calculation.

Registry No.—**1**, 16041-60-4; **2**, 17002-05-0; **3**, 20480-70-0; **4**, 62076-17-9; **5**, 62075-58-5; **6**, 62075-59-6; **7**, 20480-69-7; **8**, 20480-68-6; **9**, 62046-20-2; **10**, 62046-21-3; **11**, 62406-22-4; **12**, 62046-23-5; **13**, 62046-24-6; **14**, 39142-79-5; **15**, 62046-25-7; **16**, 62046-26-8; **17**, 62046-27-9; **18**, 62046-28-0; **19**, 62046-29-1; **20**, 62046-30-4; **21**, 62046-31-5; **22**, 62046-32-6; **23**, 62046-33-7; **24**, 62046-34-8; **25**, 62046-35-9.

References and Notes

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Phthalide Components of Celery Essential Oil

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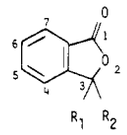
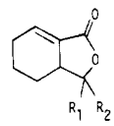
The characteristic odor of celery essential oil is due to a series of phthalide derivatives, of which 3-*n*-butyl phthalide (**1**) and sedanolide (**4**)[1,2] are reported to be the major odor components. Several other phthalides (**2**, **3**, **6**–**8**)[2–4] occur in





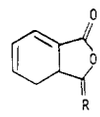
1 R_1 = H, R_2 = $CH_2CH_2CH_2CH_3$

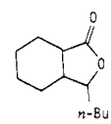
2 R_1, R_2 = $CHCH(CH_3)_2$

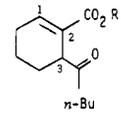
3 R_1, R_2 = $CHCH_2CH(CH_3)_2$

4 R_1 = H, R_2 = *n*-Bu

5 R_1, R_2 = $CH(CH_2)_2CH_3$







6 R = $CHCH(CH_3)_2$

7 R = $CHCH_2$-$CH(CH_3)_2$

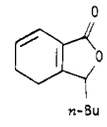
8

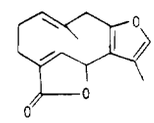
9 R = H

10 R = Me

trace quantities along with an additional major component which on base hydrolysis yields sedanonic acid (**9**). The suggested identity of this secondary component, sedanonic anhydride (**5**), was proposed by Ciamician and Silber[1] based on their classical work with celery constituents. More recent reports continue to suggest that sedanonic anhydride is a major odor component of celery and other oils.[5–7]

Our work with certain biologically active components of celery oil[8] has resulted in the isolation of the two major phthalide compounds: the well-characterized 3-*n*-butyl phthalide (**1**) and a second material which yields sedanonic acid on treatment with aqueous base. We wish to report the results of our work, which indicate that this secondary material is not sedanonic anhydride, but an unreported compound, 3-*n*-butyl 4,5-dihydrophthalide (sedanenolide) (**11**).





11 12

Chromatographic separation of the essential oil components of celery seed led to the isolation of 3-*n*-butyl phthalide (**1**) and sedanenolide in approximately equal quantities. Sedanenolide (**11**), $C_{12}H_{16}O_2$ (high-resolution mass spectrum), $[\alpha]^{24}_D$ −43.2°, shows absorption at λ_{max} 280 nm (ϵ 3790) in agreement with the cross-conjugated 3,4-dihydrophthalide system.[9] The