Synthesis and Chiroptical Properties of Some Piperidin-2-ones

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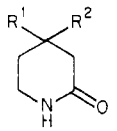
The synthesis of optically pure (*R*)-(+)-4-isopropylpiperidin-2-one, (*R*)-(+)-4-isopropyl-4-methylpiperidin-2-one, and (*R*)-(+)-5-methylpiperidin-2-one in high yields from monocyclic terpene percursors are described. The CD spectra of these compounds are reported, and the chiroptical properties of δ-lactams are examined in terms of current theories for the amide chromophore. It is concluded that slight, conformationally induced nonplanarity of the amide chromophore is responsible for the signs of the longest wavelength bands in the CD spectra of these and related compounds.

Piperidin-2-ones **1** substituted in the 4-position belong to a large group of structurally related compounds which include the barbiturates and glutarimides (e.g., bemegride) and which, depending on the nature of the substituents, exhibit a stimulant or depressant action on the central nervous system.[2] In these systems there is usually observed a progressive change from excitatory and convulsant activity to sedative and anticonvulsant activity with increasing size of alkyl substituents in a manner which correlates well with the lipid solubilities of the drugs. Although it has been speculated[3] that the action of these drugs results from nonspecific binding to the outer protein layers of synaptic membranes, accompanied by modification of their permeability, several observations indicate a much more specific drug–receptor interaction. For example, the (+) enantiomers of *N*-methyl-5-propyl-5-phenyl- and 5-(1,3-dimethylbutyl)-5-ethylbarbituric acids (**2a,b**)



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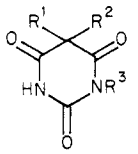
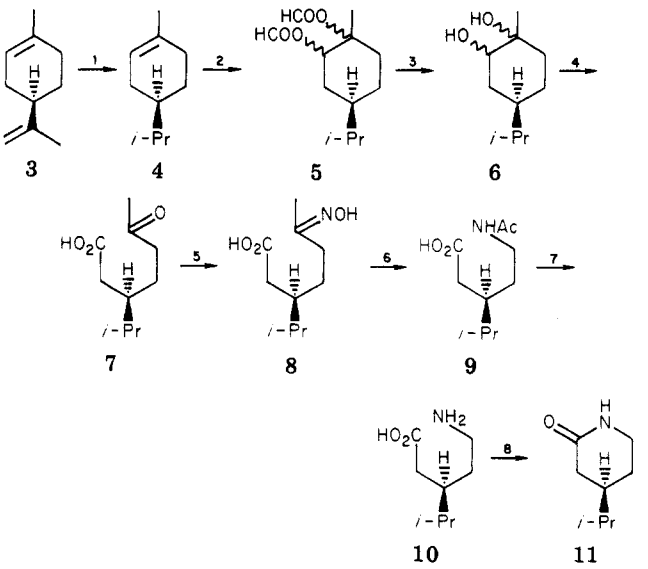


2a, $R^1 = CH_3CH(CH_3)CH_2CH(CH_3)$; $R^2 = CH_3CH_2$; $R^3 = H$
b, $R^1 = Ph$; $R^2 = CH_3CH_2$; $R^3 = CH_3$

are convulsants whereas the (−) enantiomers are hypnotics and antagonists of convulsant activity.[4,5] Furthermore, there are a number of barbiturates for which it has been shown[6] that the (*S*)-(−) enantiomers are more potent hypnotics than the (*R*)-(+) enantiomers. Piperidin-2-ones include compounds (e.g., **1**, $R^1 = CH_3$, $R^2 = n$-Pr; **1**, $R^1 = CH_3$, $R^2 = i$-Pr) which exhibit both stimulant and depressant action depending on dose level[2b] and therefore constitute an interesting series for further studies of the relation of absolute enantiomeric configuration to CNS activity. We have therefore undertaken the synthesis of some optically active members of this series.

Scheme I. Synthesis of (*R*)-(+)-4-Isopropylpiperidin-2-one[a]



[a] (1) Ni/H_2, (2) HCOOH, (3) OH^-/H_2O, (4) CrO_3/HOAC, (5) NH_2OH, (6) polyphosphoric acid, (7) OH^-/H_2O, (8) 130 °C/h.

Since pharmacological studies of the action of piperidin-2-ones require substantial quantities of at least one enantiomer of known absolute configuration and preferably high optical purity, routes involving optical resolution are not attractive. We have therefore developed syntheses which utilize ready available monoterpenes as starting materials, an approach which has the additional advantage that it does yield enantiomers of known optical configuration.

In addition to providing compounds for pharmacological studies, the present work also affords an opportunity for a further investigation of the chiroptical properties of lactams. Studies of β-,[7] γ-,[8-10] δ-,[8,10-13] and ε-lactams[14-17]

(1) (a) Smith, Kline, and French Laboratories, Philadelphia, PA 19101. (b) CSIRO Division of Applied Organic Chemistry, Fisherman's Bend, Victoria, Australia.
(2) G. M. Laycock and A. Shulman, *Nature (London)*, **200**, 849 (1963); (b) A. Shulman and G. M. Laycock, private communication.
(3) A. Shulman, G. M. Laycock, and A. S. Buchanan in "Physico-Chemical Aspects of Drug Action", E. J. Ariens, Ed., Pergamon, Oxford, 1968, pp 355–375.
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(7) (a) R. Busson, E. Roets, and H. Vanderhaeghe, *J. Org. Chem.*, **43**, 4434 (1978); (b) R. Busson and H. Vanderhaeghe, *ibid.*, **43**, 4438, (1978); (c) D. B. Boyd, J. P. Riehl, and F. S. Richardson, *Tetrahedron*, **35**, 1499 (1979).
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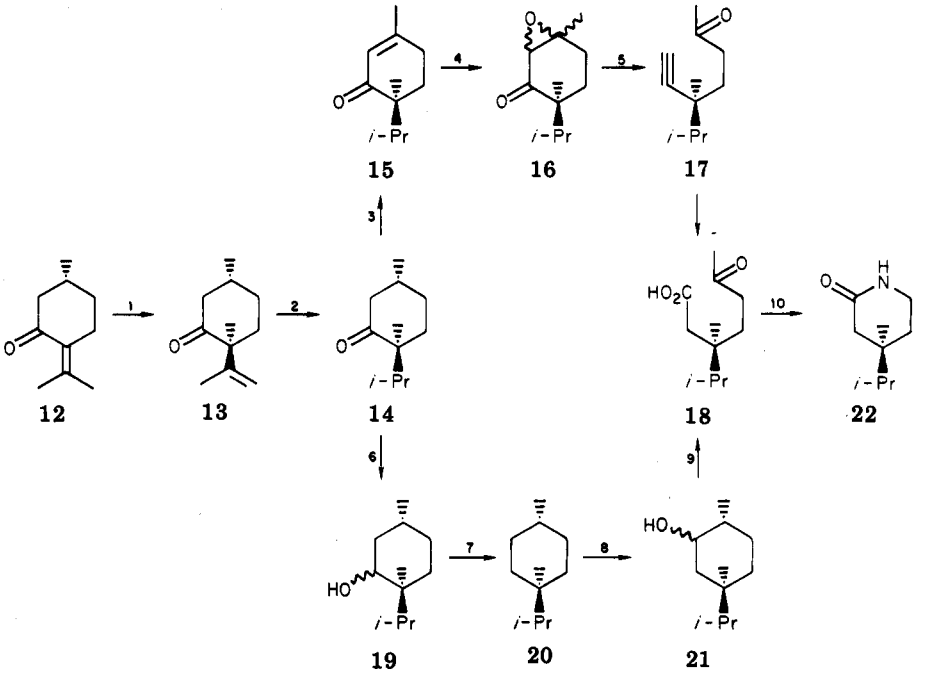
Scheme II. Synthesis of (*R*)-(+)-4-Isopropyl-4-methylpiperidin-2-one



[a] (1) $C_5H_{11}O^-/CH_3I$; (2) Pd(C)/H_2; (3) Br_2, Li_2CO_3/LiBr; (4) *m*-chloroperbenzoic acid; (5) tosylhydrazine; (6) $LiAlH_4$; (7) $CS_2/NaNH_2/CH_3I$, 375 °C; (8) B_2H_6, H_2O_2; (9) CrO_3/HOAc; (1) as in Scheme I.

have been reported as well as several theoretical investigations[16,18-20] leading to symmetry rules analogous to the well-known octant rule for ketones. We take this opportunity to assess the efficacy of CD data for determining the absolute configurations of δ-lactams.

Synthesis of Optically Active Piperidin-2-ones

(*R*)-(+)-4-Isopropylpiperidin-2-one (11). The starting point for this synthesis (Scheme I) is commercially available (*R*)-(+)-limonene (3) which, based on the best available data for the pure enantiomer,[21] is 98% optically pure. Its conversion to *p*-menthane-1,2-diol (6), and thence to the keto acid 7, has been reported by Meerwein,[22] who selectively epoxidized the trisubstituted double bond and then hydrogenated the isopropenyl group. We found it more convenient to reverse the order of these operations. Although a pure diol, identical with that reported by Meerwein, could be obtained, the mixed epimers were carried forward without purification.

Oxidation of the diol to (*R*)-(+)-3-isopropyl-6-oxoheptanoic acid (7) was effected in 70% yield by chromium trioxide in aqueous acetic acid. Initially, we used glacial acetic acid, but under these conditions a stable, purple complex was obtained. This crystalline material appears to be an oligomeric chromate ester having a molecular weight of 1380 and four chromium atoms per molecule.

The Beckmann rearrangement of the oxime of 8 occurs regiospecifically in good yield to afford the acetamide 9 which on alkaline hydrolysis followed by heating at 130 °C gave the desired (*R*)-(+)-4-isopropylpiperidin-2-one (11). Under somewhat different conditions the lactam could be isolated directly from the polyphosphoric acid reaction. The (*S*)-(−) enantiomer was also prepared by the same route, but in this case the commercially available (*S*)-(−)-limonene was only 72% optically pure. The overall yield of the piperidinones from the corresponding limonenes is 25%.

(*R*)-(+)-4-Isopropyl-4-methylpiperidin-2-one (22). The starting material for the synthesis of this compound was (*R*)-(+)-pulegone (12). Methylation of its enolate ion by methyl iodide has been shown[23] to give a 83:17 mixture of the epimeric 4-methyl analogue from which a pure (−)-4-methylisopulegone can be isolated by fractional crystallization of the semicarbazone of the mixed ketones followed by hydrolysis. This product has been established as having the 2*R*,5*R* configuration, 13. Although this is a rather low-yield (10%) process, it can be performed quite cheaply and on a large scale and affords an optically pure product. Hydrogenation gives the corresponding saturated ketone 14 in high yield.

Our first approach to the cleavage of the 5,6-bond of 4 to obtain the keto acid 18 is shown in the upper sequence in Scheme II, in which the key reaction is the well-documented fragmentation of an α,β-epoxy ketone to an ace-

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(13) M. Tichý, P. Maloň, I. Frič, and K. Bláha, *Collect. Czech. Chem. Commun.*, **42**, 3591 (1977).
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(17) W. Klyne, D. N. Kirk, and J. Tilley, *Tetrahedron*, **36**, 543 (1980).
(18) (a) H. Ogura, H. Takayanagi, K. Kubo, and K. Furuhata, *J. Am. Chem. Soc.*, **95**, 8056 (1973); (b) H. Ogura, H. Takayanagi, and K. Furuhata, *Chem. Lett.*, 387 (1973); (c) H. Ogura, H. Takayanagi, and K. Furuhata, *J. Chem. Soc. Perkin Trans. 1*, 665 (1976).
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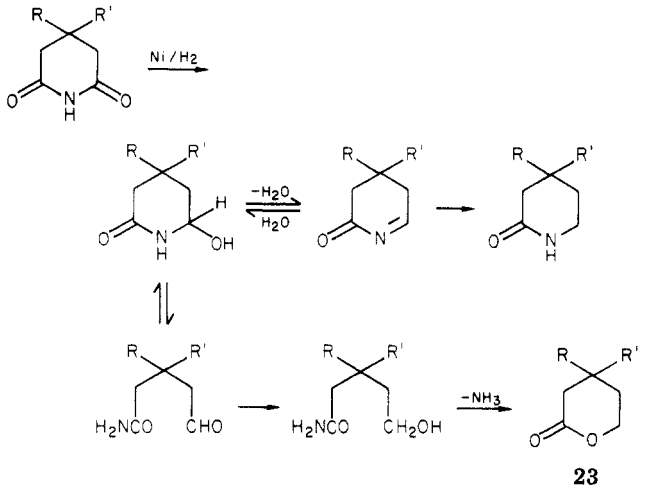
(23) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 4433 (1961).
(24) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

Scheme III. Hydrogenation of Glutarimides



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tylenic ketone.[25] Although the epoxy ketone **16** was obtained in excellent yields, it unfortunately did not undergo conversion to **17**, presumably because it is too sterically hindered to give the intermediate tosylhydrazone. We were, unable, in fact, to form the oxime, semicarbazone, or other hydrazones of this ketone.

The second approach is shown in the lower pathway in Scheme II. Reduction of the ketone with lithium aluminum hydride gave a 1:1 mixture of the epimeric alcohols **19**. Pyrolysis of the corresponding mixture of acetates at 510° gave a mixture from which the desired cycloalkene **20** could be obtained by careful fractional distillation in low yield. The pyrolysis of the corresponding mixture of xanthates (Chugaev reaction) proved much more effective. It is noteworthy that whereas the xanthates of (−)-menthol[25] and (+)-neomenthol[27] undergo the Chugaev reaction at 145–155 and 180–220 °C, respectively, the present mixture of xanthates can be distilled at 300 °C without decomposition. However, when the mixture was passed through a column of glass beads at 375 °C under nitrogen, a smooth elimination occurred, affording the olefin **20** in 70% yield. Evidently, in this system, it is difficult to set up the six-membered cyclic transition state involved in the Chugaev reaction.

Hydroboration of **21** gave an oil which analyzed for $C_{11}H_{22}O_2$ and which appears to be the epimeric alcohols **21** corresponding to attack at the 1-position since oxidation with chromium trioxide in aqueous acetic acid at 60 °C gave the keto acid **18** in 61% yield. It is not surprising that hydroboration occurs at the considerably less hindered position. Beckmann rearrangement of the oxime of **18** followed by hydrolysis and ring closure gave the desired piperidin-2-one. The overall yield from the pure alkylation product **13** is 13%.

(±)-4-Isopropyl-4-methylpiperidin-2-one was also required for pharmacological studies. The corresponding β-isopropyl-β-methylglutarimide was prepared from β-isopropyl-β-methylglutaric acid[28] by fusion with urea. The imide was not reduced by hydrogen over Adam's platinum catalyst or under Clemmensen conditions, whereas lithium aluminum hydride or hydrogenation over copper chromite gave the piperidine. Hydrogenation over Raney nickel catalyst gave an 11:9 mixture of the desired piperidin-2-one and the corresponding valerolactone **23** (R = CH_3; R′ = *i*-Pr). Scheme III suggests the probable course of this reaction and is consistent with the observation that addition of water to the reaction mixture increases the proportion of lactone in the product.

(*R*)-(+)-5-Methylpiperidin-2-one (24). Since (*R*)-(+)-3-methylcyclopentanone is commercially available or can be obtained in two steps from (*R*)-(+)-pulegone, we investigated the possibility of obtaining (*R*)-(+)-4-methylpiperidin-2-one by the Beckmann rearrangement of its oxime. However, the reaction gives mainly the 3-isomer. This is in contrast to the *tert*-butyl analogue for which the ratio of 4- to 3-isomer is 3:2.[13] (*R*)-(+)-5-Methylpiperidin-2-one (**24**) prepared in this way is identical with the (*R*)-(+) enantiomer derived from (*R*)-(+)-citronellal.[30]

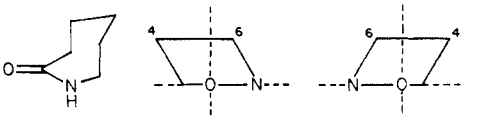
Circular Dichroism of δ-Lactams. The development of sector rules for the sign of the circular dichroism (CD) associated with the longest wavelength transition (n → π*; 220–235 nm) of amides and lactams has received considerable attention in the last two decades, but it is fair to say that no one set of rules can completely accommodate the available body of experimental data. This may be in part due to the fact that the incorporation of the amide function in a ring system introduces uncertainty regarding the conformation of the ring. It must also be added that, whereas the successful theoretical treatment of the rotational strength of a simple carbonyl group is aided by its C_{2v} symmetry, the lower symmetry of the amide chromophore requires sector rules to be based on the numerical results of quantum mechanical calculations, although early approaches[31] to the problem did assume effective C_{2v} symmetry for the carbonyl group in amides.

Two empirical models have met with good success for specific classes of amides and lactams. The first of these[11] uses "ring chirality" for the prediction of the sign of the CD of the longest wavelength transition and has been mainly applied to δ-lactams. This rule simply states that the conformations **25a,b** are positive and negative, re-

25a (+) **25b** (−)

spectively. In this model, the role of substituents is to define the conformation, although it has been recognized[12] that substituents in the 3- or 6-positions might also make a direct contribution to the rotational strength of the chromophore. This model is clearly only applicable to half-chair conformations.

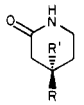
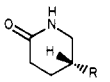
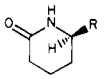
The second model was proposed by Ogura and his coworkers,[18b] who applied it specifically to ε-lactams which are generally believed to populate the quasi-chair conformation **26a** in which the amide group is essentially



26a **26b** (−) **26c** (+)

(25) (a) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); (b) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schute-Elte, E. Sundt, G. Ohloff, J. Kalvoda, H. Kaufmann, P. Wieland, and G. Anner, *ibid.*, **50**, 2101 (1967); (c) M. Tanabe, D. F. Crowe, and R. L. Dehn, *Tetrahedron Lett.*, 3943 (1967); (d) M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detne, *ibid.*, 3739 (1967).
(26) H. R. Nace *Org. React.*, **12**, 57 (1962).
(27) W. Hückel, W. Tappe, and G. Legutke, *Justus Liebigs Ann. Chem.*, **543**, 191 (1960).
(28) S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).
(29) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).
(30) O. Jeger, V. Prelog, E. Sundt, and R. B. Woodward, *Helv. Chim. Acta*, **37**, 2302 (1954).
(31) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).

Table I. Longest Wavelength Absorptions and Their Molecular Ellipticities for Some (+)-δ-Lactams

structure	R	R′	config	H_2O λ_{max}, nm	H_2O $10^{-3}[\theta]$	methanol λ_{max}, nm	methanol $10^{-3}[\theta]$	ref
	$(CH_3)_2CH$	H	*R*	222	2.2			*a*
	$(CH_3)_2CH$	CH_3	*R*	218	1.9	220	1.3	*a*
	$(CH_3)_3C$	H	*R*	219	1.8	218	2.8	13
	CH_3		*R*	230	1.9			*a*
	$(CH_3)_3C$		*S*	221	1.3	227	0.9	13
	CH_3		*S*			222	4.7	8
	CH_2CO_2H		*R*			220	3.9	10

[a] This work.

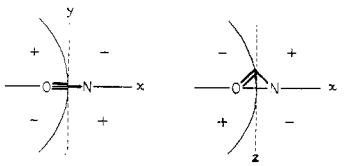


Figure 1. Octant rule for the formate ion and the amide group. The signs refer to the octants with $-z$ (left-hand diagram) and $-y$ (right-hand diagram). The octants for the formate ion are bounded by the cartesian planes. For the amide group, the yz plane is spherically distorted as shown. In addition, it is believed that there is a small clockwise rotation (not shown) about the z axis.

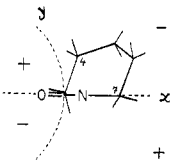


Figure 2. Amide octant rule for amides applied to ϵ-lactams. The possibility of a small rotation of axes about the z axis is not shown.

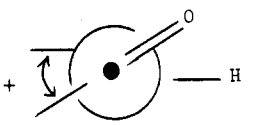


Figure 3. Proposed skewing of the amide chromophore in δ-lactams.

planar. The rule is expressed in terms of the conformations **26b,c** in which the atoms C(4), C(5), and C(6) are behind and above the plane of the amide system. Extensive studies by Klyne and his co-workers[17] have shown that this model gives a reasonably good account of the CD's of some 30 ϵ-lactams.

The Ogura "lactam rule" is consistent with the modified octant rule developed by Ong, Cusachs, and Weigang. These workers treated the amide chromophore as a perturbed formate ion. The corresponding octant diagram for the unperturbed ion is shown in Figure 1. Perturbation calculations using an extended Hückel basis set for the formate ion showed that, for the amide, the x and y coordinates will be rotated slightly clockwise about the z axis and the yz nodal surface will be spherically distorted as indicated in Figure 1. The atoms C(4), C(5), and C(6) in **26a** will therefore all lie in the right, rear, upper octant, and the sign of the CD will be negative (Figure 2). Ogura and his co-workers reached a similar conclusion using a CNDO/2 basis set for the calculation of rotational strength. They further concluded that C(4) was the principal perturbing influence contributing to the CD in ϵ-lactams. Ogura has also presented data for β-lactams which are accommodated by the octant rule provided it is assumed that C(3) substituents extend into the upper, left-hand, rear octants.

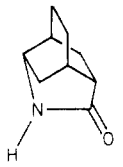
The "ring chirality rule" is consistent with neither Ogura's "lactam rule" or the octant rule. For example, the piperidin-2-one system represented by **25a** should have C(4) in a position very similar to C(4) in the (−)-ϵ-lactam (Figure 2), i.e., in a negative octant. C(4) is supposed to provide the largest perturbation, so that even though C(5) is in a positive octant the overall CD should be negative.

The compounds **11**, **22**, and **24** in the previous section, together with some further compounds described in the literature, provide a series of simple alkyl-substituted, monocyclic δ-lactams suitable for discussing the above models. The molecular ellipticities of this series are presented in Table I.

First, it can be concluded from the data for the 4- and 5-substituted piperidin-2-ones that the substituents extend their effect by controlling the conformations of the molecules since the substituents are well removed from the chromophore and since their effect on its rotational strength is independent of their nature and position. Substituents in the 6-position may make an additional direct contribution. These observations suggest that the 4-, 5-, and probably the 6-substituted derivatives have the same conformation. The X-ray structure of 4-*tert*-butylpiperidin-2-one[32] shows that this is the half-chair conformation, at least in the solid state. This is probably also true for solutions in solvents which prevent the formation of hydrogen bonded oligomers. If indeed boat conformations prevailed, Ogura's "lactam rule" would be applicable, and this predicts the wrong sign for the longest wavelength CD in the 4-substituted series (Table I).

The "ring chirality rule", together with the assumption that all compounds are in the half-chair conformation, correctly predicts the signs for all the molecules listed in Table I. However, as discussed above, this rule is at variance with the modified lactam octant rule. It seems unlikely that the positions of the nodal surfaces would be changed dramatically in δ-lactams compared with those for ϵ- and β-lactams. We believe that a more reasonable explanation is that the adoption of the half-chair conformation causes a significant skewing of the amide chromophore [C(3)–CO–NH–C(6), Figure 3] and that its intrinsic dissymmetry then controls the sign of its longest wavelength CD. Fric, Malon, Tichy, and Blaha[14a] have shown that the dihedral angle (viewed with CO in front of N) of −14.5° in the tricyclic lactam **27** is associated with a molecular ellipticity which is negative and some 20 times

(32) D. Van der Helm and D. J. Ekstrand, *Acta Crystallogr., Sect. B*, **B35**, 3101 (1979).



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greater in absolute value than that found for the 4- and 5-substituted piperidin-2-ones. In the piperidin-2-ones having the absolute configurations shown in Table I, a distortion from a half-chair toward a full-chair conformation develops a positive dihedral angle and therefore makes a positive contribution which must be added to those direct contributions which are governed by the octant rule. The octant rule predicts that, in the half-chair conformation, the positions of C(4) and C(5) are such that they are associated with rotational contributions of opposite sign and, although the effect of C(4) is probably more important, the net contribution of C(4) and C(5) is doubtless small [as indeed are the combined contributions of C(4), C(5), and C(6) in ϵ-lactams in which all three have the same sign]. Thus, even the introduction of nonplanarity of the amide of a few degrees (positive) should be sufficient to account for the small positive molecular ellipticities recorded in Table I. For example, in the solid state, 4-*tert*-butylpiperidin-2-one has a torsional angle of +2.4°.[32]

We conclude, on the basis of the above discussion, that, in the absence of strongly perturbing substituents, the "ring chirality rule" is satisfactory for predicting the sign of the longest wavelength CD in δ-lactams but that this empirical rule has its origin in the intrinsic dissymmetry of the amide chromophore rather than in electronic perturbations governed by the octant rule.

Experimental Section

All solvents are redistilled before use. Absolute methanol and ethanol were obtained by distillation from the corresponding alkoxides. Other anhydrous solvents were obtained by refluxing over and distillation from sodium metal.

All melting points were determined in a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 sodium chloride spectrophotometer; liquid samples were run as films and solids as potassium chloride disks. Ultraviolet spectra were measured on a Cary 14 recording spectrophotometer; methanol solutions were used unless otherwise stated. Mass spectra were obtained with an AEI MS 902 high-resolution mass spectrometer. NMR spectra were obtained with Varian A 60 and HA100 spectrometers and with Bruker WP 200 and WP 360 spectrometers. ORD and CD spectra were obtained by using either Cary 60 or JASCO J-20 spectropolarimeters, and rotations at the sodium D lines were measured with a Perkin-Elmer P 22 spectropolarimeter.

Hydrogenation of (*R*)-(+)-Limonene. (*R*)-(+)-Limonene [190 g, 1.4 mol; $[\alpha]^{18}_D$ + 113° (chloroform)] was shaken with W-4 Raney nickel (12 g) under hydrogen at atmospheric pressure. After hydrogen (31.9 L) had been absorbed, the solution was filtered through fuller's earth to remove the nickel catalyst and transferred to a separatory funnel. After the mixture was washed with 100 mL of ethanol, the lower layer contained ethanol together with some unchanged limonene. The upper layer, which contained essentially pure (*R*)-(+)-carvomenthene (184 g, 96%) was distilled (bp 176–178 °C (735 mm)]: n^{20}_D 1.4574; $[\alpha]^{20}_D$ +101.8° (chloroform) [lit.[33] bp 179 °C (737 mm); n^{20}_D 1.4572; $[\alpha]^{20}_D$ +96° (no solvent given)].

(*S*)-(−)-Limonene [190 g; $[\alpha]^{18}_D$ −51.8° (chloroform)] was treated in an analogous fashion to yield (*S*)-(−)-carvomenthene: 180 g (93%); bp 177 °C (732 mm); n^{20}_D 1.4577; $[\alpha]^{20}_D$ −47.3° (chloroform).

Epoxidation and Formolysis of (*R*)-(+)-Carvomenthene (4). To (*R*)-(+)-carvomenthene (184 g, 1.33 mol) dissolved in 90% formic acid (700 mL) in a 2-L three-necked flask fitted with a thermometer and stirrer was added hydrogen peroxide (30%, 185 g, 1.63 mol) at a rate which maintained the temperature between 30 and 40 °C. The solution was stirred overnight (total reaction time 30 h). The excess formic acid was removed (rotary evaporator) to yield 274 g (90%) of a yellow viscous oil, IR (neat) 1720 cm^{-1}.

Identical treatment of (*S*)-(−)-carvomenthene (180 g, 1.3 mol) yielded the diformyl ester, 269 g (89%).

***p*-Menthane-1,2-diol (6).** (*R*)-(+)-1,2-diformyl-*p*-menthane (274 g, 1.2 mol) was added to 3 M sodium hydroxide (1200 mL, 3.6 mol), and the mixture was refluxed for 6 h. When the mixture cooled, the semisolid diol separated as an oil on top of the reaction mixture. The contents of the flask were transferred to a separatory funnel and extracted with portions (8 × 500 mL) of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and evaporated to yield the crude diol, 174 g (84%). The epimeric diol mixture could be recrystallized from carbon tetrachloride as white needles, mp 88–89 °C (lit.[22] mp 89–89.5 °C). The crude diol mixture was found to be sufficiently pure to be used directly in the next step.

Analogous saponification of the *S* enantiomer (269 g) yielded the *S* diol, 169 g (83%).

(*R*)-(+)-3-Isopropyl-6-oxoheptanoic Acid (7). Chromium trioxide (120 g, 1.2 mol) dissolved in acetic acid was slowly added (4 h) to a solution of (+)-*p*-menthane-1,2-diol (172 g, 1.0 mol) in glacial acetic acid at 60–70 °C. Water (200 mL) was added and the mixture heated at 60 °C for a further 24 h. The mixture was diluted with an equal volume of water, and each portion (1.5 L) was extracted with ether (5 × 300 mL). The ether extracts were washed with water (2 × 500 mL), and the combined ethereal extracts were treated with sodium hydroxide (5 × 250 mL, 10% w/v) and then acidified with HCl to congo red. The acidified aqueous solution was extracted with ether (4 × 250 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated. The viscous liquid remaining was distilled and the main fraction collected: 117 g (70%); bp 137–140 °C (0.2 mm); $[\alpha]^{20}_D$ +2.91° (methanol) [lit.[34] $[\alpha]^{20}_D$ + 2.5° (no solvent given)]. (The yield is corrected for the recovery of 17 g of diol from the ether solution remaining after extraction with sodium hydroxide.)

The keto acid formed a semicarbazone, mp 159–160 °C (lit.[35] mp 162–164 °C).

(*R*)-(+)-3-Isopropyl-6-oximinoheptanoic Acid (8). (*R*)-(+)-3-Isopropyl-6-oxoheptanoic acid (71 g) was dissolved in aqueous dioxane (350 mL, 25% v/v) together with hydroxylamine hydrochloride (30 g). The mixture was refluxed for 4 h and cooled, and the dioxane and water were removed. The residue was taken up in ether (3 × 100 mL), and the ether solution was washed with water (3 × 50 mL). The ether extracts were dried ($MgSO_4$) and evaporated to yield the oxime (70 g, 92%) as an oil which slowly solidified after several days: mp 74–75 °C; $[\alpha]^{20}_D$ +2.13° (methanol); ^1H NMR (CCl_4) δ 9.83 (s, 2 H), 2.4–1.3 (m, 8 H), 1.90 (s, 3 H), 0.92 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.77; H, 9.64; N, 6.74.

(*S*)-(−)-5-(Acetylamino)-3-isopropylpentanoic Acid (9, Enantiomer). The (*S*)-(−) oxime (2.0 g, 10 mmol) was heated to 140 °C with polyphosphoric acid (prepared by dissolving 70 g of P_2O_5 in 60 mL of 86% orthophosphoric acid), and the mixture was stirred at this temperature for 20 min. On cooling, the mixture was diluted with an equal volume of water and partially neutralized with sodium hydroxide. The faintly acidic solution was then extracted with chloroform (4 × 50 mL). The chloroform extracts were combined, dried, and evaporated to yield the oily

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amido acid, 1.5 g (75%). The amido acid was purified by column chromatography using silica with chloroform as the eluent: $[\alpha]^{23}_D$ −1.47° (methanol); IR (neat) ν_{max} 3330, 1710, 1665 cm^{-1}; ^{1}H NMR (CCl_4) δ 10.03 (s, 1 H), 8.25 (br s, 1 H), 3.28 (m, 2 H), 2.5–1.1 (m, 6 H), 1.94 (s, 3 H), 0.90 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.43; H, 9.71; N, 6.86.

(*S*)-(−)-4-Isopropylpiperidin-2-one (11, Enantiomer). (*S*)-(−)-5-(Acetylamino)-3-isopropylvaleric acid (1.3 g, 6.5 mmol) was refluxed for 3 h with 3 M sodium hydroxide (30 mL). The solution was cooled, neutralized to pH 6 with concentrated HCl, and evaporated to dryness. The residue was heated at 130 °C for 3 h and then extracted with petroleum ether (12 × 25 mL). Dry HCl gas was bubbled through the cooled petroleum ether extract, precipitating the white, flocculent lactam hydrochloride. The hydrochloride was recrystallized from ethyl acetate to give colorless crystals: 0.9 g (70%); mp 132–134 °C; $[\alpha]^{23}_D$ −32.7° (water); ^{1}H NMR (D_2O) δ 3.3 (m, 2 H), 2.4 (m, 2 H), 2.1–1.1 (m, 4 H), 0.90 (d, J = 6 Hz, 6 H) [identical with the spectrum of (±)-4-isopropylpiperidin-2-one].

(*R*)-(+)-4-Isopropylpiperidin-2-one (11). (*R*)-(+)-3-Isopropyl-6-oxoheptanoic acid oxime (20 g, 0.1 mol) was dissolved in orthophosphoric acid (120 mL) containing P_2O_5 (120 g). The mixture was heated at 140 °C for 0.5 h with vigorous stirring, diluted with one equal volume of water, and heated at 100 °C for 3 h. On cooling, the solution was further diluted to 4 times its volume with cold water and extracted with chloroform (10 × 200 mL). No further lactam could then be detected in the aqueous layer. The chloroform extracts were combined, dried ($MgSO_4$), and evaporated to yield a yellowish liquid. The liquid was treated with an equal volume of benzene and evaporated again. After three such treatments with benzene, the liquid was dissolved in petroleum ether/ethyl acetate (80:20), and the addition of dry HCl gas precipitated the piperidin-2-one hydrochloride: 9 g (51%); mp 120–124 °C. Recrystallization from ethyl acetate raised the melting point to 123–125 °C; $[\alpha]^{23}_D$ +71° (H_2O).

The free base was obtained by treatment with aqueous sodium bicarbonate. (*R*)-(+)-4-Isopropylpiperidin-2-one has the following: mp 56–57 °C; $[\alpha]^{23}_D$ +76° (H_2O); ^{1}H NMR (CCl_4) δ 8.5 (br s, 1 H), 3.3 (m, 2 H), 2.5–1.1 (m, 6 H), 0.91 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.94; H, 10.76; N, 9.80.

(*S*)-(−)-4-Isopropylpiperidin-2-one: mp 69–70 °C; $[\alpha]^{23}_D$ −35.0° (H_2O). The NMR and IR spectra were identical with those of the (*R*)-(+) enantiomer and the racemate prepared by hydrogenation of the corresponding glutarimide. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.25; H, 10.61; N, 9.71.

(2*R*)-(−)-2,5-Dimethyl-2-isopropenylcyclohexanol (13). Methylation of (+)-pulegone (n^{25}_D 1.4822) was effected by the method of Djerassi et al.[23] The pure (*R*)-(−) isomer [bp 38–39 °C (0.30 mm); n^{20}_D 1.4719; $[\alpha]^{26}_D$ −107.7°; α^{26}_D −122.3° (lit.[23] α_D −122.6°)] was obtained by recrystallization of the semicarbazone of the crude alkylation product. Five crystallizations from 2-propanol followed by two from ethanol were required to give the pure (2*R*)-(−) semicarbazone: mp 213–215 °C; $[\alpha]^{26}_D$ −131.6° (methanol).

(2*R*)-(+)-2,5-Dimethyl-2-isopropylcyclohexanone (14). A solution of the optically pure (2*R*)-(−)-methylisopulegone (66 g, 0.4 mol) in ethanol (100 mL) was hydrogenated at room temperature under atmospheric pressure in the presence of 10% palladium charcoal (2 g). Hydrogen (9.35 L) was absorbed (theory requires 8.96 L). The mixture was filtered through fuller's earth. The clear ethanolic solution was evaporated and the residue distilled at reduced pressure. A colorless liquid was obtained: 60 g (90% yield); bp 46–48 °C (0.55 mm); n^{20}_D 1.4582; $[\alpha]^{28}_D$ +0.38° (methanol). The ketone yielded the semicarbazone, mp 205–207 °C (lit.[23] 188–189 °C).

(6*R*)-(−)-3,6-Dimethyl-6-isopropyl-2-cyclohexenone (15). Bromine (31 g, 0.39 mol) was added dropwise to a stirred mixture of (2*R*)-(+)-2,5-dimethyl-2-isopropylcyclohexanone (29.2 g, 0.174 mol) in water (100 mL) over a period of 5 h. The mixture was stirred overnight and then extracted with ether. The ether extract was washed three times with water and dried ($MgSO_4$). On evaporation of the ether, a pale yellow liquid was obtained, which solidified on standing and was recrystallized once from *n*-pentane. The bromo ketone (42.4 g, 99% yield) was obtained as colorless crystals, mp 78.5–80 °C.

A mixture of the once-recrystallized bromo ketone (13.2 g, 0.054 mol), anhydrous lithium carbonate (10 g), anhydrous lithium bromide (11 g), and freshly distilled dimethylformamide (115 mL) was heated on a steam bath for 28 h under a nitrogen atmosphere. After the mixture cooled water was added, and the mixture was steam distilled. The distillate was saturated with sodium chloride and extracted with ether. The ether extract was washed once with water and dried ($MgSO_4$). The ether was evaporated and the residue distilled at reduced pressure. (6*R*)-(−)-3,6-Dimethyl-6-isopropyl-2-cyclohexenone was obtained as a colorless oil: 8 g (90%); bp 48–49 °C (0.15 mm); n^{25}_D 1.4861; $[\alpha]^{25}_D$ −55.3° (hexane); UV (methanol) λ_{max} 234 nm (ε 15 600), 321 (77); IR (neat) ν_{max} 1665, 1640 cm^{-1}; ^{1}H NMR δ 5.74 (q, J = 1.5 Hz, 1 H), 2.38–1.52 (m, 5 H), 1.92 (d, J = 1.5 Hz, 3 H), 0.96 (s, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 3 H). Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91; O, 9.62. Found: C, 79.23; H, 10.72.

(6*R*)-3,6-Dimethyl-2,3-epoxy-6-isopropylcyclohexenone (16). A solution of (6*R*)-(−)-3,6-dimethyl-6-isopropyl-2-cyclohexenone (10.9 g) in methanol (75 mL) was cooled to 15 °C. Hydrogen peroxide (30%, 20 mL) was added at once, and the stirred mixture was kept at 15–20 °C. A solution of sodium hydroxide (1.55 g) in water (12 mL) and methanol (15 mL) was added dropwise over a period of 45 min. After the addition was complete, the mixture was kept at 25–30 °C for 3 h. Water was then added, and the mixture was extracted with ether. The ether extract was washed twice with water and dried ($MgSO_4$). The solvent was evaporated, and the light yellow residue was distilled at reduced pressure.

(6*R*)-3,6-Dimethyl-2,3-epoxy-6-isopropylcyclohexanone was obtained as a colorless liquid: 9.2 g (83%); bp 53–55 °C (0.11 mm); n^{22}_D 1.4663; UV (methanol) λ_{max} 202 nm (ε 3875), 307 (54); IR (neat) 3000 (s), 1710 (s) cm^{-1}; ^{1}H NMR δ 3.08 (s, 0.8 H), 3.02 (s, 0.2 H), 3.32–1.70 (m, 4 H), 1.42 (s, 3 H), 1.26–1.02 (m, 1 H), 0.98 (s, 0.8 H), 0.94 (s, 0.2 H), 0.82 (q, J = 6.5 Hz, 0.8 H), 0.79 (q, J = 6.5 Hz, 0.2 H). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.36; H, 9.81.

Reaction of *p*-Toluenesulfonylhydrazine and Epoxy Ketone (16). A solution of the epoxy ketone (1.081 g, 6 mmol) in methylene chloride (10 mL) was added dropwise to a stirred, ice-cooled solution of *p*-toluenesulfonylhydrazine (1.23 g, 6 mmol) in dry methylene chloride (10 mL) and acetic acid (10 mL). The mixture was stirred at 0 °C for 0.5 h and kept in a refrigerator for 24 h. *p*-Toluenesulfonic acid (1.35 g) was then added, and the mixture was stirred at room temperature for 1 h. The methylene chloride was evaporated. Water was added to the residue. The mixture was made alkaline with saturated sodium bicarbonate solution and extracted with ether. The ether extract was washed three times with cold HCl (5% v/v) and twice with water, dried ($MgSO_4$), and evaporated. A yellow brown viscous liquid (1.48 g) was obtained. Its IR spectrum shows a very weak absorption at 2100 cm^{-1}. The ^{1}H NMR spectrum shows no acetylenic proton absorption. However, aromatic proton absorptions in the region δ 7.9–7.2 are present.

(2*R*)-2,5-Dimethyl-2-isopropylcyclohexanol (19). A mixture of lithium aluminum hydride (12 g, 0.315 mol) and dry ether (200 mL) was refluxed under anhydrous conditions and a nitrogen atmosphere. A solution of (2*R*)-(+)-2,5-dimethyl-2-isopropylcyclohexanone (49.5 g, 0.294 mol) in dry ether (100 mL) was added dropwise, at a rate just sufficient to maintain gentle refluxing. The mixture was stirred throughout the addition. After the addition was complete, the mixture was refluxed for a further 42 h, and after it cooled, ethyl acetate (125 mL) was added slowly at a rate which maintained gentle reflux. The reaction mixture was then decomposed with a solution of aqueous hydrochloric acid (90% v/v, 550 mL). The aqueous layer was separated and extracted four times with ether. The ether extracts were combined, washed twice with water, and dried ($MgSO_4$). The solvent was evaporated and the residue distilled at reduced pressure. Distillation of the residue gave a partially solid alcohol: 48.4 g (97%); bp 52–53 °C (0.10 mm); IR (neat) ν_{max} 3500 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02; O, 9.40. Found: C, 77.53; H, 12.85; O, 9.69.

Refluxing the alcohol with a large excess of acetic anhydride yields the acetate: bp 64–50 °C (0.15 mm); n^{24}_D 1.4536; ^{1}H NMR

δ 2.04 (s, 1.5 H), 2.02 (s, 1.5 H).

Pyrolysis of (2*R*)-2,5-Dimethyl-2-isopropylcyclohexyl Acetate. (2*R*)-2,5-Dimethyl-2-isopropylcyclohexyl acetate (20.8 g, 0.098 mol) was passed dropwise through a Pyrex column packed with glass beads maintained at 520 ± 10 °C under a gentle flow of dry nitrogen. The effluent was collected in a flask maintained at −15 °C. The yellow liquid thus collected was dissolved in ether and washed three times with saturated sodium bicarbonate solution and once with water, dried ($MgSO_4$), evaporated, and distilled to give a crude product: 5.5 g; bp 28–65 °C (25 mm). A fraction collected at >70 °C (25 mm) was found to be the unchanged acetate (8.2 g).

The crude product was fractionated through a spinning-band column to give the (3*R*)-(+)-3,6-dimethyl-3-isopropylcyclohexene as a pale yellow liquid: 2.2 g (17.4%); bp 93–96 °C (80 mm). NMR and GLC analysis showed that the cycloalkene was contaminated with various aromatic compounds.

(3*R*)-(+)-3,6-Dimethyl-3-isopropylcyclohexene (20). A mixture of ferric nitrate (0.5 g), sodium metal (1 g), and liquid ammonia (25 mL) was stirred until the blue color disappeared and a black precipitate formed. To the resulting mixture was added liquid ammonia (350 mL). Sodium metal (25 g) was then added in portions over a period of 30 min. The resulting blue mixture was stirred at room temperature under anhydrous conditions until all the liquid ammonia evaporated, and the remaining residue was then dried by suction under anhydrous conditions. A solution of (2*R*)-2,5-dimethyl-2-isopropylcyclohexanol (57 g, 0.335 mol) in dry toluene (150 mL) was added slowly, and the resulting mixture was warmed on a steam bath under anhydrous conditions for 1 h and then refluxed for 14 h. After cooling, the mixture was filtered. Dry ether (300 mL) was added to the filtrate followed by carbon disulfide (120 g). The mixture was refluxed for 1.5 h and cooled, a solution of methyl iodide (135 g) in ether (100 mL) was added, and the mixture was refluxed for 3 h. After cooling, water was added, the organic layer was separated, and the aqueous layer was extracted with ether. The ether extracts were combined with the organic layer, and the mixture was washed twice with water and dried ($MgSO_4$). Removal of the solvent afforded a viscous orange liquid which was distilled, giving the xanthate as a yellow liquid: 69 g (80% yield); bp 103–108 °C (0.25 mm); IR (neat) ν_{max} 1200 (s, C=S) cm^{-1}.

The xanthate (69 g, 0.265 mol) was passed dropwise through a column packed with glass beads and maintained at a temperature of 375 ± 5 °C under a gentle flow of nitrogen. The effluent was collected in a flask maintained at −15 °C. The resulting yellow liquid was distilled several times over sodium metal at reduced pressure until no more odor of the xanthate could be detected. The distillate was finally fractionated at reduced pressure through a Widmer column equipped with a total-reflux variable takeoff head to give (3*R*)-(+)-3,6-dimethyl-3-isopropylcyclohexene: 28 g (70%); bp 75–77 °C (25 mm); n^{20}_D 1.4565; $[\alpha]^{25}_D$ +41.7° (methanol); IR (neat) ν_{max} 1650 cm^{-1}; ^1H NMR δ 5.4 (s, 2 H), 2.84–2.10 (m, 6 H), 0.93 (s, 3 H), 0.96 (d, J = 7 Hz, 6 H), 0.8 (m, 3 H). Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H 13.24. Found: C, 87.13; H, 13.20.

(5*R*)-2,5-Dimethyl-5-isopropylcyclohexanol (21). A solution of (3*R*)-(+)-3,6-dimethyl-3-isopropylcyclohexane (48 g, 0.316 mol) in dry diglyme (50 mL) was added dropwise over a period of 45 min to a cooled, stirred mixture containing freshly resublimed anhydrous aluminum chloride (26 g, 0.195 mol), potassium borohydride (26 g, 0.482 mol), and dry diglyme (300 mL). The reaction mixture was kept under anhydrous conditions, and a gentle flow of nitrogen was maintained. After the addition was complete, the reaction mixture was stirred at room temperature for 5 h. It was then warmed on a steam bath for 30 min. After the mixture cooled, water (50 mL) was added slowly (hydrogen was evolved), followed by 3 N sodium hydroxide solution (300 mL). Hydrogen peroxide (30%, 250 g) was then added at a rate just sufficient to maintain a gentle refluxing. After the addition of hydrogen peroxide was complete, the mixture was stirred at room temperature for 1.5 h. It was then cooled in an ice bath, and water (400 mL) was added. The organic layer was separated and the aqueous layer extracted with ether. The ethereal extract was combined with the organic layer, washed twice with water, and dried ($MgSO_4$). The ether was evaporated and the residue distilled at reduced pressure to give (5*R*)-2,5-dimethyl-5-isopropylcyclohexanol as a colorless liquid: 45.4 g (84.5%); bp 64.5–65 °C (0.2 mm); n^{20}_D 1.4682; IR (neat) ν_{max} 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (br, 1 H), 1.95–1.0 (m, 9 H), 1.06 (s, 2.4 H), 1.01 (s, 0.6 H), 0.86 (d, J = 6 Hz, 2.4 H), 0.81 (d, J = 6 Hz, 0.6 H), 0.77 (d, J = 5.5 Hz, 3 H). Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02; O, 9.40. Found: C, 77.75; H, 12.87; O, 9.57.

(3*R*)-(+)-3-Isopropyl-3-methyl-6-oxoheptanoic Acid (18). A solution of chromium trioxide (100 g, 1.0 mol) in acetic acid (350 mL) and water (111 mL) was added dropwise to a solution of (5*R*)-2,5-dimethyl-5-isopropylcyclohexanol (42 g, 0.247 mol) in acetic acid (150 mL) maintained at 60 ± 5 °C at a rate such that the temperature of the reaction mixture did not exceed this value. The mixture was stirred throughout the addition. After the addition was complete, the mixture was kept at 50–60 °C for 3 h and then at room temperature overnight. Water (1 L) was then added, and the mixture was reextracted with ether. The ether extract was washed three times with water and then extracted with 10% sodium hydroxide solution. The sodium hydroxide extract was acidified with dilute HCl and extracted with ether. This ether extract was washed twice with water and then extracted with saturated sodium bicarbonate solution. The sodium bicarbonate extract was cooled, acidified with cold dilute HCl, and extracted with ether. This ether extract was washed twice with water and dried ($MgSO_4$). On removal of the ether, a yellow viscous liquid (30 g, 61% yield) was obtained. This acid could not be crystallized or distilled. However, the methyl ester obtained by reaction with diazomethane showed a single peak on GLC, indicating that the crude material was essentially pure keto acid: bp 76.5 °C (0.16 mm); n^{20}_D 1.4524; $[\alpha]^{27}_D$ +6.88° (methanol); UV (methanol) λ_{max} 275 nm (ε 311); IR (neat) ν_{max} 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64 (s, 3 H), 2.22 (s, 2 H), 2.14 (s, 3 H), 2.55–1.45 (m, 5 H), 0.91 (s, 3 H), 0.85 (d, J = 6.5 Hz, 6 H).

(4*R*)-(+)-4-Isopropyl-4-methylpiperidin-2-one (22). A solution of hydroxylamine hydrochloride (105 g, 1.5 mol) and sodium hydroxide (60 g) in water (350 mL) was mixed with a solution of (3*R*)-(+)-3-methyl-3-isopropyl-6-oxoheptanoic acid (24 g, 0.12 mol) and sodium hydroxide (10 g) in water. The mixture was heated on a steam bath for 30 min and was left at room temperature for 5 h. It was cooled in an ice bath and acidified with dilute HCl to pH 6 and extracted with ether. The ethereal extract was washed twice with water, dried ($MgSO_4$), and evaporated. A light brown viscous liquid (24 g, 93%) was obtained. This liquid could not be readily crystallized but was sufficiently pure for use in the next step. A sample of the oxime partially crystallized after being allowed to stand over several months. The crystalline material was separated by trituration with petroleum ether (bp 40–60 °C), mp 91–92.5 °C. A mixture of the oxime (580 mg), orthophosphoric acid (4 mL), and phosphorus pentoxide (4 g) was kept at 135–140 °C under anhydrous conditions with vigorous stirring for 15 min. After the mixture cooled, water (10 mL) was added, and the mixture was refluxed for 30 min. It was cooled, diluted with water (50 mL), neutralized with saturated sodium bicarbonate solution, and extracted twice with ether, three times with chloroform, and finally again with ether. The extracts were combined, washed once with saturated sodium bicarbonate solution and once with water, and dried ($MgSO_4$). The solvent was evaporated, leaving a yellow crystalline residue. This was recrystallized from ethyl acetate to give (4*R*)-(+)-4-methyl-4-isopropylpiperidin-2-one as colorless prisms: 230 mg (55%); mp 131.5–132.5 °C; $[\alpha]^{25}_D$ +18.7° (methanol); UV (methanol) λ_{max} 197 (ε 7830) nm; IR (KCl) ν_{max} 3480 (w), 3300 (m), 1670 (s), 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (br, 1 H), 3.33 (t, J = 7 Hz, 2 H), 2.15 (s, 2 H), 1.58 (t, 7 Hz, 2 H), 1.49 (q, 1 H), 0.88 (d, J = 6.5 Hz, 6 H), 0.89 (s, 3 H). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; O, 10.31. Found: C, 69.80; H, 11.05; N, 8.95; O, 10.47.

The corresponding hydrochloride after recrystallization from ethyl acetate had the following: mp 132–133 °C; $[\alpha]^{25}_D$ +18.8° (water).

(+)-4-Isopropyl-4-methylpiperidin-2-one. β-Isopropyl-β-methylglutaric acid (mp 97–98 °C) prepared by the method of Bruice and Bradbury[44] was converted to the corresponding glu-

(44) T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, 87, 4838 (1965).

tarimide, [mp 162-164 °C (lit.[45] mp 165-166 °C)] by fusion with urea.

A solution of β-isopropyl-β-methylglutarimide (34 g, 0.2 mol) in ethanol (500 mL) was shaken with hydrogen and Raney nickel catalyst (15 g) at 110 °C with a starting pressure of 1800 psi for 20 h. The resulting solution was filtered and evaporated, leaving a yellow oily residue which solidified on standing. This material was digested with dilute HCl and washed three times with ether. The aqueous acidic solution was neutralized and extracted five times with ether. The ethereal extract was washed once with water, dried ($MgSO_4$), and evaporated to leave a crystalline residue which was recrystallized from a mixture of ethyl acetate and petroleum ether (bp 40-60 °C). (±)-4-Isopropyl-4-methylpiperidin-2-one was obtained as colorless plates: 16.8 g (55%); mp 112.5-113.5. Anal. Calcd for $C_9H_{17}O$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.72; H, 10.87; N, 8.98; O, 10.44.

The ethereal solution of the acid-insoluble material was washed with water and dried ($MgSO_4$). The ether was removed and the residue distilled to give (±)-4-isopropyl-4-methylvalerolactone: 12 g (88%); bp 65 °C (0.10 mm); n^{24}_D 1.4628; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.35 (t, J = 5.5 Hz, 2 H), 2.34 (d, J = 2.0 Hz, 2 H), 1.76 (t, J = 5.5 Hz, 2 H), 1.42 (q, J = 6.5 Hz, 1 H) 1.01 (s, 3 H), 0.92 (d, J = 6.5 Hz, 6 H). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32; O, 20.48. Found: C, 69.02; H, 10.30; O, 20.11.

(*R*)-(+)-β-Methyladipic Acid. To redistilled pulegone [120 g, 0.79 mol; bp 104-106 °C (14 mm); $[\alpha]^{20}_D$ +24° (neat)] suspended in water (1.2 L) was added potassium permanganate (150 g), and the mixture was shaken for 36 h. The precipitated MnO_2 was removed, and the clear solution was acidified to congo red with concentrated HCl, saturated with salt, and continuously extracted with ether for 12 h to yield a waxy acid: 60 g (50%); mp 75-80 °C. Recrystallization from benzene gave the pure acid: mp 79-81 °C (lit.[36,37] mp 84.5, 78-83 °C); $[\alpha]^{21}_D$ +8.3° (water) [lit. $[\alpha]^{22}_D$ 8.6° (water),[38] +8.42° (water)[37]]. The diethyl ester was prepared by refluxing the acid in an excess of absolute ethanol with a trace of sulfuric acid. The distilled product was obtained: 88% yield; bp 130-135 °C (16-20 mm); n^{14}_D 1.4328 [cf. lit. bp 126.5 °C (10 mm) and n^{18}_D 1.4335,[37] bp 138-144 °C (16-17 mm[39])].

The preparation of (*R*)-(+)-3-methylcyclopentanone was carried out according to the method of Dieckmann.[40] The final product had the following: bp 142-144 °C (732 mm); n^{20}_D 1.4331 (cf. lit.[41] n^{19}_D 1.4340, n^{28}_D 1.4300); $[\alpha]_D^{18}$ +148° (methanol) (lit. $[\alpha]^{20}_D$ +152.8°,[42] $[\alpha]^{12}_D$ +133°[43]); $[\alpha]^{250}$ -2450°, $[\alpha]^{311}$ +4450°, and $[\alpha]^{272}$ -4250° (methanol) (cf. lit.[33] -3062, +4450, -4250, respectively).

(*R*)-(+)-3-Methylcyclopentanone Oxime. To the ketone (5 g, 0.05 mol) in 30% (w/v) aqueous sodium acetate (30 mL) was added hydroxylamine hydrochloride (4 g, 0.058 mol), and the mixture was stirred for 2 h at 50 °C. When the mixture was allowed to stand overnight, colorless needlelike crystals formed. Recrystallization from petroleum ether (bp 60-80 °C) afforded the oxime: 5.1 g (83%); mp 78-79 °C (lit.[43] mp 86 °C).

(*R*)-(+)-5-Methylpiperidin-2-one (24). The oxime (2 g, 0.018 mol) was heated at 150 °C for 15 min with polyphosphoric acid [60 mL, prepared by dissolving phosphorus pentoxide (70 g) in orthophosphoric acid (60 mL)]. On cooling, the mixture was diluted with an equal volume of water and neutralized to pH 6 with 3 M sodium hydroxide.

The solution was then extracted with chloroform (4 × 50 mL). The chloroform extracts were combined, dried ($MgSO_4$), and evaporated to yield a yellowish liquid. The liquid showed an IR spectrum similar to, but not identical with, that of racemic 4-methylpiperidin-2-one. On treatment with dry HCl, a hexane solution of the liquid yielded a colorless white crystalline hydrochloride: 1.8 g (70%); mp 155-160 °C. After recrystallization from ethyl acetate the product melted at 169-171 °C. The ^1H NMR spectrum of the hydrochloride was quite different from that of 4-methylpiperidin-2-one. The free base was regenerated with $NaHCO_3$ and the viscous liquid obtained slowly solidified on cooling at 0 °C: mp 38 °C [lit.[30] mp 40 °C (for (*R*)-(+)-5-methylpiperidin-2-one)]; $[\alpha]^{20}_D$ +89.2° (water) [cf. lit.[30] $[\alpha]^{22}_D$ +82° (ethanol)]. The sample gave only one spot on thin-layer chromatography with a variety of solvents and conditions and only one peak on GLC (SE-30). An IR spectrum of the sample was identical in all respects with that reported[30] for (*R*)-(+)-5-methylpiperidin-2-one. The ^1H NMR spectrum was compatible with this structure and distinctly different from that of a sample of racemic 4-methylpiperidin-2-one prepared by hydrogenation of the glutarimide.

Registry No. (+)-(*R*)-**3**, 5989-27-5; (-)-(*S*)-**3**, 5989-54-8; (+)-(*R*)-**4**, 1195-31-9; (-)-(*S*)-**4**, 499-94-5; **5**, 80845-80-3; **6**, 33669-76-0; (+)-(*R*)-**7**, 80845-81-4; (+)-(*R*)-**7** semicarbazone, 80845-82-5; (+)-(*R*)-**8**, 80845-83-6; (-)-(*S*)-**8**, 80845-84-7; (-)-(*S*)-**9**, 80845-85-8; (-)-(*S*)-**11**, 80845-86-9; (-)-(*S*)-**11**·HCl, 80865-84-5; (+)-(*R*)-**11**, 80845-87-0; (+)-(*R*)-**11**·HCl, 80845-88-1; (+)-**12**, 89-82-7; (-)-(2*R*)-**13**, 5298-65-7; (-)-(2*R*)-**13** semicarbazone, 43060-33-9; (+)-(2*S*)-**14**, 15815-65-3; (+)-(2*S*)-**14** semicarbazone, 80845-89-2; (+)-(2*S*)-**14** bromo ketone, 15815-66-4; (-)-(6*S*)-**15**, 15815-67-5; **16**, 80845-90-5; (+)-(3*R*)-**18**, 80845-91-6; (+)-(3*R*)-**18** methyl ester, 80845-92-7; (+)-(3*R*)-**18** oxime, 80845-93-8; (2*S*)-**19** (isomer I), 80865-85-6; **19** acetate, 80845-94-9; **19** xanthate, 80845-95-0; (+)-(3*R*)-**20**, 80845-96-1; **21**, 80845-97-2; (+)-(4*R*)-**22**, 80845-98-3; (+)-(4*R*)-**22**·HCl, 80845-99-4; (+)-**23** (R = *i*-Pr; R′ = Me), 80846-00-0; (+)-(*R*)-**24**, 1121-71-7; (+)-(*R*)-**24**·HCl, 80846-01-1; (2*S*)-**19** (isomer II), 80846-02-2; *p*-toluenesulfonylhydrazine, 1576-35-8; (+)-4-isopropyl-4-methylpiperidin-2-one, 80876-86-4; β-isopropyl-β-methylglutarimide, 80846-03-3; (+)-(*R*)-β-methylodipic acid, 623-82-5; (+)-(*R*)-diethyl β-methyladipate, 80846-04-4; (+)-(*R*)-3-methylcyclopentanone, 6672-30-6; (+)-(*R*)-3-methylcyclopentanone oxime, 80846-05-5; (*S*)-5-*tert*-butylpiperidin-2-one, 80876-87-5.

(45) G. J. Handley, E. R. Nelson, and T. C. Somers, *Aust. J. Chem.*, **13**, 129 (1960).

Codeine Analogues. Synthesis of 4a-(2,3-Dimethoxyphenyl)decahydroisoquinolines and Octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines

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Extension of our methods for the synthesis of phenyl- and (*m*-methoxyphenyl)decahydroisoquinolines to the 2,3-dimethoxyphenyl series is presented. Surprisingly, direct extrapolation of the previous methodology was frequently not possible, as the dimethoxyphenyl system presented unique problems in a number of steps. Detailed studies are reported for selective amide reduction in the presence of an ester, allylic oxidation of α-methylene lactams, and solvolysis of tertiary allylic/benzylic alcohols. Finally, selective ether cleavages in the 4a-aryldecahydroisoquinoline ring system allow elaboration to the new 6,2′-oxygen-bridged 4a-aryldecahydroisoquinolines, the benzopyrano[4,3,2-*ef*]isoquinolines.

The 4a-aryldecahydroisoquinolines 1 (Chart I), representing the A, C, and N (nitrogen) rings of codeine (**2a**), have evoked considerable interest as a class of analgesics.[1] Earlier papers from this laboratory have described the

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