drous ether was then added over a 5-min period with stirring. The solution was maintained at −70° for 30 min and was poured into saturated ammonium chloride solution. The aqueous layer was separated and extracted with fresh ether. The organic phases were combined, dried over magnesium sulfate, and stripped at reduced pressure to a crystalline solid, 1.80 g. This material was purified by sublimation (60°, 1 mm) to yield 1.55 g (91%) of 4-*tert*-butyl-1-methylcyclohexanol, mp 62-65° (lit.[19] 70.5-71° for the pure axial alcohol).

In conclusion, MeLi–Me_2CuLi is a highly effective reagent for the equatorial methylation of unhindered, conformationally biased cyclohexanones. Further work will include studies of this reagent with other substrates and the stereochemical behavior of a variety of mixed cuprates and other transition metal ate complexes.

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References and Notes

(1) Examples include the reagents of: H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc. C*, 785 (1970); H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94,** 7159 (1972); and J. Hooz et al., *ibid.*, **96,** 274 (1974).

(2) To the best of our knowledge, the most stereoselective addition of an organometallic methylating agent to 4-*tert*-butylcyclohexanone utilizes trimethylaluminum and gives 90% axial attack: (a) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37,** 1918 (1972); (b) T. Suzuki, T. Kobayashi, Y. Takegami, and Y. Kawasaki, *Bull. Chem. Soc. Jpn*, **47,** 1971 (1974). The previous record for equatorial methylation is 86% with *n*-propyloxydimethylaluminum at 10% conversion and was recently reported by E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **40,** 1469 (1975). An alternate approach to this type of conversion involves stereospecific epoxidation followed by reduction: E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87,** 1353 (1965); C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *ibid.*, **95,** 7424 (1973).

(3) For recent reviews of organocopper chemistry, see G. H. Posner, *Org. React.*, **19,** 1 (1972); J. F. Normant, *Synthesis*, 63 (1972); A. E. Jukes, *Adv. Organomet. Chem.*, **12,** 215 (1974).

(4) (a) W. J. Houlihan, *J. Org. Chem.*, **27,** 3860 (1962); (b) E. C. Ashby, L.-C. Chao, and J. Laemmle, *ibid.*, **39,** 3258 (1974).

(5) The addition of dialkylcuprates to saturated ketones appears to be a very slow process based on starting material recovery ((a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31,** 3128 (1966); (b) G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Am. Chem. Soc.*, **94,** 5106 (1972); (c) L. T. Scott and W. D. Cotton, *J. Chem. Soc., Chem. Commun.*, 320 (1973); and (d) H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40,** 1460 (1975)), although a fast, reversible oxidative addition to yield an alkoxy copper(III) species cannot be ruled out. In contrast, D. J. Goldsmith and I. Sakano (*Tetrahedron Lett.*, 2857 (1974)) have reported one example of lithium dimethylcuprate addition to a saturated ketone at low temperature.

(6) The reaction of lithium dimethylcuprate with a conformationally fixed acylalkylidine cyclohexane proceeds by greater than 95% equatorial attack: ref 5a; S. Wolff and W. C. Agosta, *J. Org. Chem.*, **38,** 1694 (1973); H. O. House, J. Lubinkowski, and J. J. Good, *ibid.*, **40,** 86 (1975).

(7) The reaction of a saturated ketone with MeLi–Me_2CuLi has been previously reported by House et al. (ref 5a).

(8) The effect of exact stoichiometry has not been thoroughly investigated, but a full equivalent of Me_2CuLi and MeLi seems to be required.

(9) Proportions of the epimeric methyl carbinols were determined by VPC (6-ft Carbowax 20M column) and were confirmed by integration of the appropriate methyl signals in the NMR. In the case of the products from 4-*tert*-butylcyclohexanone, $Eu(fod)_3$ in carbon tetrachloride was used to resolve the epimers.

(10) For comparison, cholestanone gives 57% equatorial attack with methyl magnesium iodide at 0°: D. H. R. Barton, A. S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(11) J. Ficini and A. Maujean, *Bull. Soc. Chim. Fr.*, 219 (1971).

(12) A similar temperature dependence with a methylaluminate complex was recently reported by Ashby et al. (ref 4b).

(13) The latter reagent could arise via equilibration among the dimeric species Me_4Cu_3Li, $Me_4Cu_2Li_2$, and Me_4CuLi_3 and was suggested by Professor H. O. House.

(14) R. Nast and W. Pfab, *Chem. Ber.*, **89,** 415 (1956); the corresponding lithium salts have also been reported: (a) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34,** 3615 (1969); (b) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91,** 4871 (1969).

(15) H. O. House, D. G. Koepsell, and W. J. Campbell, *J. Org. Chem.*, **37,** 1003 (1972).

(16) Reference 14b; C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95,** 7783 (1973).

(17) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94,** 5495 (1972).

(18) Further cooling frequently causes precipitation of the reagent. This occurence must be avoided since addition of the ketone to this suspension results in recovered starting material.

(19) C. H. DePuy and R. W. King, *J. Am. Chem. Soc.*, **83,** 2743 (1961).

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Benzamide Oxygen Exchange Concurrent with Acid Hydrolysis

Sir:

Although it is generally accepted that bimolecular acid-catalyzed amide hydrolysis proceeds via a tetrahedral addition intermediate probably formed from the O-protonated amide,[1] a number of workers recently have found it difficult to rule out the alternate route in which water directly displaces an amine molecule from the N-protonated amide.[2] At the basis of this controversy is the fact that, to date, the occurrence of carbonyl oxygen exchange concurrent with the hydrolysis has not been demonstrated.[2a,b,3] Such exchange is observed during base hydrolysis,[3,4] as well as with carboxylate esters in both acid and base solutions,[1a,5] and is usually taken to imply the presence of tetrahedral intermediates.[1a] We report here that accompanying the acid-catalyzed hydrolysis of benzamide there is a small, but detectable, amount of exchange.

This study was carried out using a sample of the amide enriched with ca. 90% ^{18}O.[6] This was hydrolyzed in 5.9% H_2SO_4 at 85°, and the unreacted amide was recovered[7] at various times and subjected to direct mass spectrometric analysis (Table I). A small, but definite, increase with time is seen in the ratio of the intensities of the peaks at m/e 121 and 123 (molecular ions), indicative of exchange of the benzamide oxygen with solvent oxygen. Conversion[8] of these ratios to per cent ^{18}O shows that there is a decrease of about 0.2% ^{18}O for each half-life of hydrolysis. From the data can be calculated a rate of exchange of 1.28×10^{-5} min^{-1}, $^{1}/_{320}$ the rate of hydrolysis. In control experiments (i) the analysis procedure was shown to be capable of reproducing the small differences in ^{18}O content very accurately (Table II), and (ii) it was demonstrated that the observed decrease in ^{18}O content on hydrolysis cannot have arisen either through the work-up procedure or because of reversibility of the hydrolysis reaction.[9]

The very small amount of exchange found here shows why this was not detected in previous investigations, where a much smaller ^{18}O enrichment was used. For example, in that study with the greatest enrichment (3%),[2a] our result shows that there was a decrease in ^{18}O content of only 0.02% (over three half-lives of hydrolysis), not outside the limit of experimental error. Interestingly Bender and Ginger,[3c] on the basis of the error in their data, placed a lower limit on k_H/k_E of 374 (for benzamide under slightly different acidic conditions).

The observation here of the exchange process establishes that a tetrahedral intermediate is formed during the acid-catalyzed hydrolysis of benzamide. Although this species is not necessarily on the hydrolysis pathway, it is difficult to imagine that this is not the case. In particular the small amount of return to amide relative to break-up to products (a factor of 160 assuming rapid proton transfer) is precisely what is expected for such a tetrahedral intermediate formed under acid conditions.[1] In such solutions it will exist pre-

Table I. Oxygen Exchange during Benzamide Hydrolysis in 5.9% H_2SO_4 at 85.0°

Run 1			Run 2		
Time, min^a	121/123^b	% ^{18}O^c	Time, min^a	121/123^b	% ^{18}O^c
0	0.1005	90.87	0	0.1013	90.80
153	0.1030	90.66	150	0.1033	90.64
304	0.1049	90.51	312	0.1057	90.44
470	0.1071	90.33	478	0.1082	90.24
$k_E{}^d = 1.25 \times 10^{-5}$ min^{-1}			$k_E{}^d = 1.30 \times 10^{-5}$ min^{-1}		

[a] For hydrolysis, $k_H = 4.09 \times 10^{-3}$ min^{-1}, $t_{1/2} = 169$ min (C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, 93, 6578 (1971). [b] Ratio of peak intensities at *m/e* 121 and 123, measured on an AEI MS-902, equipped with a Vacuumetrics ratiometer. These values are the average of 30–40 determinations; standard deviations range from 0.00025 to 0.00035. [c] $(1/r)/(1 + (1/r))$,[8] $r = 121/123$. [d] Slope of the plot of ln (% ^{18}O – 0.2) *vs.* time.

Table II. Control Experiment Demonstrating Reproducibility of Mass Spectral Analysis

% labeled benzamide^a	121/123^b	% ^{18}O^c	% labeled benzamide, calcd
100	0.1010	90.83	(100)
99.86	0.1030	90.66	99.81
99.73	0.1041	90.57	99.71
99.45	0.1069	90.34	99.46

[a] Samples of ^{18}O enriched benzamide diluted with small amounts of unlabeled material. [b, c] See footnotes *b* and *c* in Table I.

dominantly in an N-protonated form, so that the best leaving group will be amine and not water. In addition an analogy exists with the hydrolysis of imidate esters where a similar tetrahedral intermediate is formed and also decomposes in acid mainly by expulsion of amine.[10]

In conclusion the results obtained here provide compelling evidence for the intermediacy of tetrahedral species in the acid-catalyzed hydrolysis of benzamide, and there appears to be no reason to assign this reaction to a mechanistic category different from that of other hydrolysis reactions of carboxylic acid derivatives.

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References and Notes

(1) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) B. C. Challis and J. A. Challis, "Chemistry of the Amides", J. Zabicky, Ed., Oxford University Press, London, 1971; (c) C. J. O'Connor, *Q. Rev., Chem. Soc.*, **24**, 553 (1971).

(2) (a) C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, **94**, 8811 (1972); (b) C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J. Chem. Soc., Perkin Trans. 2*, 1869 (1972); (c) M. Liler, *ibid.*, 816 (1972); 71 (1974); (d) "Reaction Mechanisms in Sulphuric Acid", Academic Press, London, 1971, pp 189–202; (e) B. C. Challis and S. P. Jones, *J. Chem. Soc., Perkin Trans. 2*, 153 (1975).

(3) (a) C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. Ind. (London)*, 1154 (1954); (b) M. L. Bender, R. D. Ginger, and K. C. Kemp, *J. Am. Chem. Soc.*, **76**, 3350 (1954); (c) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955); (d) H. Ladenheim and M. L. Bender, *ibid.*, **82**, 1895 (1960).

(4) C. A. Bunton, B. Nayak, and C. J. O'Connor, *J. Org. Chem.*, **33**, 572 (1968).

(5) (a) S. A. Shain and J. F. Kirsch, *J. Am. Chem. Soc.*, **90**, 5848 (1968); (b) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *ibid.*, **90**, 6492 (1968).

(6) (a) This was prepared by the reaction of trimethyl orthobenzoate with 90% ^{18}O water (Miles) in the presence of a small amount of HCl,[6b] followed by treatment of the methyl benzoate so obtained with $NaNH_2$ in liquid NH_3; (b) C. B. Sawyer, *J. Org. Chem.*, **37**, 4225 (1972).

(7) By extraction with methylene chloride, followed by washing with Na_2CO_3, evaporation of the solvent and recrystallization (chloroform–petroleum ether).

(8) The formula employed neglects contributions from the isotopes of the other elements. Although this means that the ^{18}O values are slightly in error, their trend remains the same and the error introduced in k_E is very small.

(9) In this experiment, unlabeled benzoic acid (1.0 g) and ammonium sulfate (0.5 g) were dissolved in 5.9% H_2SO_4, and the solution was heated at 85° overnight. Upon cooling, labeled benzamide (0.02 g) was added and a sample of benzamide recovered by the usual procedure.[7] This showed no difference in the 121/123 ratio from that of the original benzamide (0.1011 and 0.1010).

(10) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965); G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968); R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968); T. C. Pletcher, S. Koehler, and E. H. Cordes, *ibid.*, **90**, 7072 (1968).

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The Pyridine Route to Optically Active Estrone and 19-Norsteroids

Sir:

The use of the bis annelating agent **1** has been previously described.[1-3] System **2** may be elaborated after reaction of **1** with a nucleophilic equivalent of R. Such systems are convertable by reductive hydrolytic cyclization into cyclohexenones such as **3**. Alternatively, compound **4** may be employed as a tris annelating agent.[4a] For instance, reaction of **4** with **5**[5a] under acidic catalysis gives racemic hydrindenedione (**6a**). Of course, the use of **6a** in a total synthesis of estrone would require recourse to resolution if optically active product is to be produced.[5b]

Alternatively compound **7**[4a] can be produced in high yield[4b] from the reaction of **4** and **5** in ethyl acetate containing triethylamine. The prochiral nature of **7** lends itself to the possibility of asymmetrically induced aldolization under the influence of L-amino acids. This highly original concept had been demonstrated and used with great success by Hajos[6a,b] and Eder[7] in the synthesis of the parent hydrindenedione **9** (R = H) from the oxobutyl system **8** (R = H). In pursuing this approach, we were not unmindful of previous reports,[7] which indicated a sharp deterioration of asymmetric specificity in the transformation of **8** → **9**, as R becomes alkyl.

We report the total synthesis of optically active estrone and the commercially important 19-norsteroids involving, as a key step, the conversion of prochiral **7** → *optically active* **6** *with high asymmetric specificity via an aromatic amino acid.*

The sign and value of $[\alpha]$D for the pure 13*S* antipode, **6b**, were obtained as follows. Reduction of the pure 13*S* enantiomer, **9**,[6,7] with sodium borohydride gave **10**. The latter was converted to **11** $[\alpha]$D +94.6° (benzene, *c* 1%) according to Hajos.[8] Picolyethylation of **11** (1 equiv of enone **1**; 1 equiv of potassium *tert*-amyl oxide–*tert*-amyl alcohol; 2 equiv of **1**; reflux 12 hr) followed by cleavage of the *tert*-butyl ether (HCl-EtOH-H_2O; reflux 45 min) gave **12b** $[\alpha]$D +28.4° (benzene, *c* 1%), in 36% yield. Jones oxidation of **12b** gave optically pure **6b** $[\alpha]$D +202.0° (benzene, *c* 1%).

Attempted cyclization of **7** under the influence of L-proline using the conditions of either Hajos[6] or Eder[7] gave disappointing results in terms of optical specificity. Fortunately, it was found that reaction of **7** with L-phenylalanine under conditions similar to those of Eder[7] (1 equiv of trione; 1.2 equiv of amino acid; 0.5 equiv of $HClO_4$ in acetonitrile 2.7 ml/mmol of trione; reflux 40 hr) gave **6c** $[\alpha]$D +173.6° (i.e., 86% optical purity) in 82% chemical yield from **4**.[9] We now describe the conversion of **6c** into estrone and 19-norsteroids. Separations of the c series (86% optically pure) into the optically pure (b compounds) and largely racemic (a compounds) was achieved with nearly perfect efficiency in one recrystallization at the tetracyclic stages (vide infra).