Amphetamine. Specific Labeling and Solution Conformation

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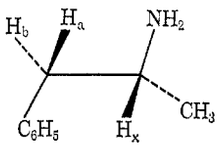
In connection with other work[1] it became necessary to determine the solution conformation of amphetamine (**1**). The conformation population analysis of **1** required



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specific deuterium labeling of H_a and H_b of the ABX (methyl decoupled) spin system, affording previously unreported specifically deuterated amphetamine which is of potential utility in biochemical mechanistic investigations.

The identities of H_a and H_b were established as indicated in Chart I. The previously assigned configuration of 2-methylcinnamic acid (**2**)[2] was confirmed by europium-induced shift studies[3] of the diastereomeric ethyl 2-methylcinnamates. Conversion of **2** to the corresponding ester with subsequent photochemical isomerization[4] afforded the mixture of esters (*E*)- and (*Z*)-**3**. Granted that the most basic site in the ester is the carbonyl oxygen and that coordination of Eu(fod)$_3$ will occur at the carbonyl oxygen, it should be expected that the vinylic hydrogen of (*E*)-**3** should suffer the greater paramagnetic shift of the pair of diastereomers.[5] The ester prepared directly from **2** exhibited a slope of shift *vs.* mol Eu(fod)$_3$/mol ester 2.1 times that exhibited by the photochemical isomerization product. Thus, the ester produced directly from **2** is (*E*)-**3** and the configuration of **2** is firmly[2] established as *E*.

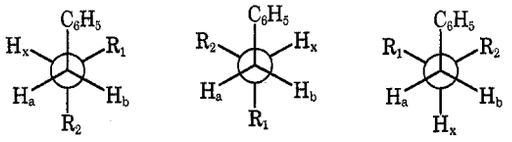
Exchange of the acidic proton of (*E*)-**2** with subsequent catalytic deuteration afforded the enantiomers (2*R*,3*S*)- and (2*S*,3*R*)-2,3-dideuterio-2-methylcinnamic acid (**4a** and **4b**, respectively). Nonspecific deuteration of (*E*)-**2** would produce the 2*R*,3*R* and 2*S*,3*S* diastereomers of **4** in addition to the predicted 2*R*,3*S* and 2*S*,3*R* enantiomers produced by cis deuteration of **2**. The production of diastereomers, resulting from nonspecific (cis and trans) deuteration, is not experimentally observed; **4** exhibits a single-proton resonance in the ABX region of the spectrum, not the doubled resonances (H_a and H_b) expected from a mixture of diastereomers.[6]

Hoffmann rearrangement of the amides of **4a** and **4b** produces (1*R*,2*R*)- and (1*S*,2*S*)-1,2-dideuterio-1-phenyl-2-propylamine (**5a** and **5b**, respectively), *i.e.*, with retention of configuration at C-2.[7] Thus, the single-proton resonance observed in the ABX region of the nmr spectrum of **5** is identified as H_b in **1**.

The coupling constants and conformer populations of amphetamine are reported in Table I. The conformer

TABLE I

NMR PARAMETERS AND POPULATIONS[a]



					Mole fraction[b]		
R_1	R_2	Solvent	J_{ax}	J_{bx}	n_a	n_b	n_c
CH_3	NH_2	$CDCl_3$	8.31	5.84	0.29	0.52	0.19
CO_2^-	NH_3^+	D_2O	8.02[c]	5.10	0.23	0.50	0.27
CO_2^-	NH_2	D_2O	7.52[c]	5.43	0.25	0.47	0.28

[a] 0.5 *M* solution in the given solvent, temperature 18°. [b] Calculated assuming $J_t = 13.6$ and $J_g = 2.6$ Hz (see text). [c] Reference 9.

populations were calculated from the equations

$$J_{ax} = n_a J_g + n_b J_t + n_c J_g$$

$$J_{bx} = n_a J_t + n_b J_g + n_c J_g$$

$$1 = n_a + n_b + n_c$$

assuming $J_t = 13.6$ and $J_g = 2.6$ Hz. These values have been employed in the determination of the conformer populations of amino acids and have both theoretical[8] and experimental[9] support. Granted that a large electronegativity correction on J_g and J_t does not result upon changing a single group (CO_2H in amino acids to CH_3 in amphetamine), these values appear reasonable for amphetamine as well.[10,11]

Granted also that the values of J_t and J_g for amphetamine and phenylalanine are approximately equal,[12] the conformer population of **1** should closely parallel that previously observed[9] for phenylalanine (Table I). In all cases that conformer is preferred in which phenyl and methyl or carboxyl are anti and phenyl and amino are gauche. On the basis of steric interactions alone it should be expected that conformer

(1) J. Jacobus, *Biochemistry*, **10**, 161 (1971).

(2) On the basis of ultraviolet[3] and equilibration[4] data the assignment of configuration *E* to the 81° melting isomer would appear to be correct.

(3) A. Mangini and F. Montanari, *Gazz. Chim. Ital.*, **88**, 1081 (1958).

(4) C. Sandris, *Tetrahedron*, **24**, 3569 (1968).

(5) The utilization of shift reagents has recently been reviewed: see R. von Ammon and R. D. Fischer, *Angew. Chem.*, **84**, 737 (1972).

(6) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(7) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939).

(8) K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963); **20**, 581 (1964).

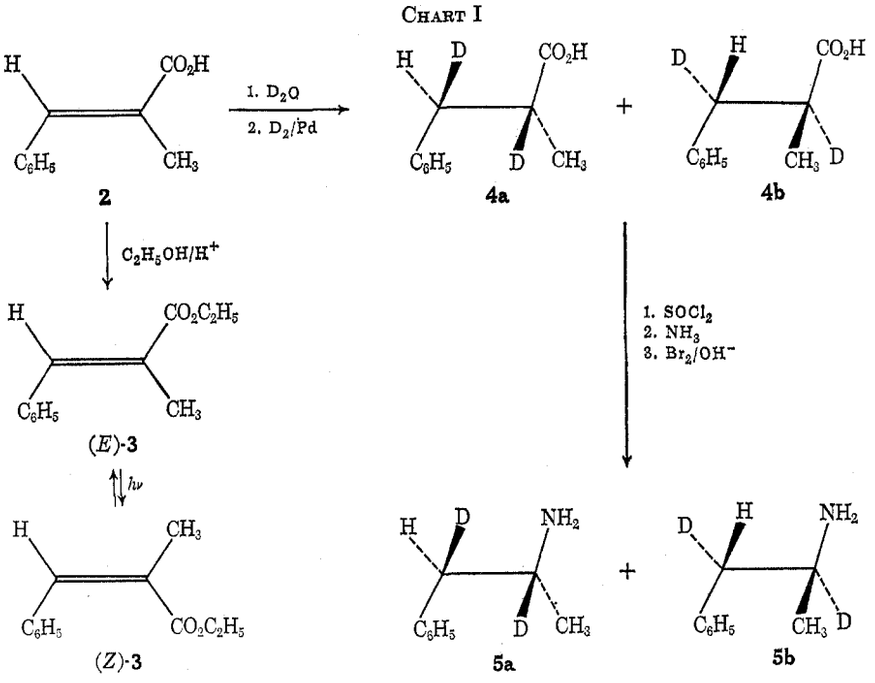
(9) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **89**, 1558 (1967); **90**, 4533 (1968).

(10) The group electronegativities of CH_3 and CO_2H are 2.30 and 2.85, respectively (P. R. Wells, "Progress in Physical Organic Chemistry," Vol. 6, Interscience, New York, N. Y., 1968, p 111 ff). This change should amount to a *ca.* 0.04 Hz change in J_t and J_g.[11]

(11) *Cf.* A. A. Bothner-By, "Advances in Magnetic Resonance," Vol. 1, Academic Press, New York, N. Y., 1965, p 195 ff.

(12) It is appreciated that the assumptions inherent in this analysis are gross simplifications, *i.e.*, J_t in conformer a *cannot* equal J_t in conformer b and J_g in a *cannot* equal J_g in b or J_g in c on the basis of simple symmetry arguments [K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967)]. However, granted the assumed coupling constants and other approximations [*cf.*, *inter alia*, R. L. Lichter and J. D. Roberts, *J. Org. Chem.*, **35**, 2806 (1970)] we feel that within this series of compounds, although the experimental data cannot unambiguously define the conformations of the compounds in question, the conformer populations are essentially identical.

CHART I



c (Table I) should be the least populated, as is the case for amphetamine.[12a]

Experimental Section

Nmr spectra were recorded at 60 and 90 MHz as 0.5 *M* solutions in the indicated solvents. Coupling constants were determined from calculated spectra (LAOCN3).

(*E*)-2-Methylcinnamic acid (2) was prepared by silver oxide oxidation of 2-methylcinnamaldehyde (Aldrich) in 70% yield: mp 81–83° (lit.[4] mp 81°); nmr ($CDCl_3$) δ 2.04 (CH_3, d, J = 2.0 Hz), 7.59 (vinylic H, q, J = 2.0 Hz).

2,3-Dideuterio-2-methylcinnamic acid (4a and 4b) was prepared by exchanging the acidic proton of 15.0 g (0.093 mol) of **2** in 90 ml of ethyl acetate with three 15-ml portions of D_2O, with subsequent catalytic reduction (200 mg of 5% Pd on carbon) of **2**-d_1 in a deuterium atmosphere at 45 psi. Removal of catalyst and solvent afforded 12.3 g (80%) of **4**: mp 35–36°; bp 142° (2 mm)[13] [lit.[14] bp 174–176° (20 mm)]; nmr ($CDCl_3$) δ 1.10 (2-methyl, s), 2.55 (H_b, s).

2,3-Dideuterio-2-methylcinnamamide was prepared by the previously described sequence for the conversion of dihydro-2-methylcinnamic acid to dihydro-2-methylcinnamamide.[15] The product amide exhibited mp 108–110° (lit. mp 108°,[14] 110°[13]); nmr (DMSO-d_6) δ 0.97 (2-methyl, s), 2.44 (H_b, s).

(1*R*,2*R*)- and (1*S*,2*S*)-1,2-Dideuterio-1-phenyl-2-propylamine (5a and 5b) (dideuterioamphetamine) was prepared in a manner analogous to that described for the nondeuterated analog.[15] The product amine exhibited bp 200–201° (lit.[16] bp 205°); nmr ($CDCl_3$) δ 0.97 (2-methyl, s), 2.69 (H_b, s). Amphetamine (Aldrich) had nmr ($CDCl_3$) δ 0.97 (2-methyl, d, J = 6.0 Hz), 2.52 (H_a), 2.69 (H_b), 3.17 (H_x); J_{ab} = −14.29, J_{ax} = 8.31, J_{bx} = 5.84 Hz.

Registry No.—**1**, 300-62-9; **2**, 1895-97-2; **4**, 39949-56-9; **5**, 39949-57-0.

(12a) NOTE ADDED IN PROOF.—The assignments of protons H_A and H_B of amphetamine have recently been made [G. E. Wright, *Tetrahedron Lett.*, 1097 (1973)]; although the assignments are correct by comparison with this work, the claim that the assignments confirm the work of Bailey, *et al.* [K. Bailey, A. W. By, K. C. Graham, and D. Verner, *Can. J. Chem.*, **49**, 3143 (1971)] is incorrect since the assignments of conformer population by Wright are reversed.

(13) I. Shahak, *J. Chem. Soc.*, 3160 (1961).

(14) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 199 (1957).

(15) E. S. Wallis and S. C. Nagel, *J. Amer. Chem. Soc.*, **53**, 2787 (1931).

(16) D. H. Hey, *J. Chem. Soc.*, 18 (1930).

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Preparation of Methyl and Ethyl *N*-Monochlorocarbamates by Disproportionation[1]

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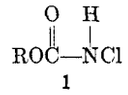
N-Monochlorocarbamate esters (**1**) are versatile pseudohalogens. They add predominantly in cis fashion to olefins in the presence of ultraviolet to yield vicinal chlorocarbamates,[3] they react rapidly with thioethers to form iminosulfonium salts,[4] and they form interesting isolable salts on reaction with base.[5,6]



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(1) Pseudohalogens. XIX. Paper XVIII: *J. Org. Chem.*, **37**, 3004 (1972). Work supported in part by U. S. Public Health Service Grants CA-12227 and CA-07803 of the National Cancer Institute, and the Samuel S. Fels Fund.

(2) Participants in the Chemistry Honors Undergraduate Research Program, Temple University.

(3) K. Schrage, *Tetrahedron Lett.*, 5795 (1966); *Tetrahedron*, **23**, 3033, 3039 (1967).

(4) G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *Tetrahedron Lett.*, 3543 (1970).

(5) D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968).

(6) P. Chabrier, *Ann. Chim. (Paris)*, **17**, 353 (1942), and references therein to older literature.