

TABLE I

RATIOS OF VALUES OF RATE CONSTANTS^a FOR BASE-CATALYZED DEUTERIUM-HYDROGEN EXCHANGE (k_e) AND RACEMIZATION (k_α) OF 2-PHENYLBUTYRONITRILE (I) AND 2-N,N-DIMETHYLAMIDO-9-METHYL-7-NITROFLUORENE (II)

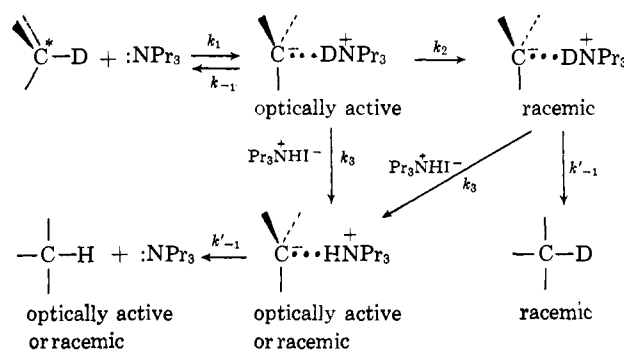
Run no.	Substrate		Base		Solvent	T, °C	Time, hr.	% exch. ^b	% rac. ^c	k_e/k_α
	Nature	Concn., M	Nature	Concn., M						
1	(+)-Id ^d	0.10	NH ₃	0.50	(CH ₃) ₃ COH	145	14	72	57	1.5
2	(+)-Id ^d	0.07	NH ₃	0.30	CH ₃ OH	50	3	41	42	1.0
3	(+)-Id ^d	0.06	NH ₃	0.20	(CH ₃) ₂ SO	25	3	44	43	1.0
4	(+)-Id ^d	0.40	(<i>n</i> -C ₃ H ₇) ₃ N	0.30	CH ₃ OH	50	4.5	32	37	0.84
5	(+)-Id ^d	0.20	(<i>n</i> -C ₃ H ₇) ₃ N	0.50	(CH ₃) ₃ COH	145	14	20	70	0.19
6	(-)-Ih ^e	0.30	(<i>n</i> -C ₃ H ₇) ₃ N	0.50	(CH ₃) ₃ COD ^f	145	7	12	48	0.20
7	(+)-Id ^d	0.07	(<i>n</i> -C ₃ H ₇) ₃ N	0.60	(CH ₂) ₄ O-(CH ₃) ₃ COH ^g	160	28	6	74	0.05
8	(+)-Id ^d	0.07	(<i>n</i> -C ₃ H ₇) ₃ N	0.60	(CH ₂) ₄ O-(CH ₃) ₃ COH ^{g,h}	160	23	11	74	0.09
9	(+)-Id ^d	0.07	(<i>n</i> -C ₃ H ₇) ₃ N	0.60	(CH ₂) ₄ O-(CH ₃) ₃ COH ^{g,i}	160	23	25	79	0.19
10	(+)-IIId ^j	0.05	<i>p</i> -CH ₃ C ₆ H ₄ NH ₂	0.50	(CH ₂) ₄ O	131	1	50	10	6
11	(+)-IIId ^j	0.01	<i>n</i> -C ₃ H ₇ NH ₂	0.10	(CH ₂) ₄ O	-22	0.5	10	11	1
12	(+)-IIh ^k	0.07	(<i>n</i> -C ₃ H ₇) ₃ N	0.60	(CH ₂) ₄ O-(CH ₃) ₃ COD ^{f,g}	75	2	48	99	0.1
13	(+)-IIId ^j	0.07	(<i>n</i> -C ₃ H ₇) ₃ N	0.60	(CH ₂) ₄ O-(CH ₃) ₃ COH ^g	75	2	35	100	<0.1
14	(+)-IIh ^k	0.014	(<i>n</i> -C ₃ H ₇) ₃ N	0.30	(CH ₂) ₄ O-(CH ₃) ₃ COD ^{f,g,l}	40	2	25	93	0.1
15	(+)-IIId ^j	0.014	(<i>n</i> -C ₃ H ₇) ₃ N	0.30	(CH ₂) ₄ O-(CH ₃) ₃ COH ^{g,m}	40	2	10	72	0.1

^a One point. ^b Measured by infrared analysis. ^c Smallest observed rotation was 1° except in runs 12–14, which were carried close to complete racemization. ^d 0.97 atom of deuterium per molecule by combustion and falling drop method, $[\alpha]_{25}^{25.6}$ 24.6°, neat, $l = 1$ dm. ^e $[\alpha]_{25}^{25.6}$ -27.4°, neat, $l = 1$ dm. ^f 0.99 atom of deuterium per molecule. ^g 1.5 M in *t*-butyl alcohol. ^h 0.10 M in (*n*-C₄H₉)₄NI. ⁱ 0.10 M in (*n*-C₃H₇)₃NHI. ^j 0.96 atom of deuterium per molecule by combustion and falling drop method, $[\alpha]_{25}^{25.6}$ 40.5° (*c* 7.6, dioxane). ^k $[\alpha]_{25}^{25.6}$ 38.4° (*c* 7.2, dioxane). ^l 0.0001 M in (*n*-C₄H₉)₄NI; 0.001 M (*n*-C₄H₉)₃NI gave $k_e/k_\alpha = 0.4$, and 0.03 M gave $k_e/k_\alpha = 1$. ^m 0.0001 M in (*n*-C₃H₇)₃NHI. Rate of exchange of (*n*-C₃H₇)₃NDI with (CH₃)₃COH in the presence of (*n*-C₃H₇)₃N was undoubtedly fast enough to prevent accumulation of deuterated salt.

These two systems provide stereochemical results that are different from any heretofore obtained. Nitrile I gave k_e/k_α values that ranged from 1.5 to 0.05, nitroamide II provided a range of 6 to 0.1, whereas amide III in the same solvent-base systems gave 148–0.69.² Particularly striking are those results obtained with nitrile I and nitroamide II in tetrahydrofuran 1.5 M in *t*-butyl alcohol with tripropylamine as base. In these runs (7–9 and 12–15), k_e/k_α ranged from 0.05 to 0.2. Of particular importance are the results of run 9 with nitrile Id, and of run 15 with nitroamide IId, which were carried out in the presence of tripropylammonium iodide. The presence of the tripropylammonium ion in the medium had only a minor effect on k_e/k_α with nitrile Id (compare runs 7–9), and no effect with nitroamide IId (compare runs 12–15).

These results indicate that nitrile I and nitroamide II undergo base-catalyzed *intramolecular racemization*. The racemization undoubtedly occurs through tripropylammonium-carbanide ion pair intermediates, which racemize and collapse to covalent product faster than they either dissociate, or react with isotopically labeled tripropylammonium iodide or *t*-butyl alcohol molecules in the medium (see runs 5 and 6). The term "isomerization" is suggested for processes in which racemization occurs without exchange of any of the groups attached to the asymmetric carbon atom involved.⁴

The general mechanism of the isomerization is formulated. In this scheme, a condition for $k_e/k_\alpha < 0.5$ is that k_2 and $k_{-1}' > k_3$. Two more specific mechanisms can be envisioned for the racemization of the ion pair (step governed by k_2). In the first, the carbanion simply rotates 180° (with respect to the tripropylammonium ion) around any axis which passes through the plane of the carbanion, and does this repeatedly. In the second, which might be called a "conducted tour



mechanism," the deuterium attached to carbon becomes hydrogen bonded or even covalently bound to the nitrogen of nitrile I or the oxygen of the nitro group of II. In further stages, the deuterium could be moved by the amine catalyst from the hetero atom back to carbon on the side remote from its original residence. Base-catalyzed intramolecular rearrangements have been observed.⁵

In runs 1–4, nitrile Id exhibits behavior qualitatively similar to that of amide IIIId.² Although exchange occurred with net retention in *t*-butyl alcohol-ammonia in both systems, Id gave $k_e/k_\alpha = 1.5$, whereas IIIId gave >50 . Probably isomerization competes with retention more effectively in nitrile Id than in amide IIIId. Both systems underwent exchange with racemization in methanol-ammonia and dimethyl sulfoxide-ammonia ($k_e/k_\alpha = 1$), and both systems gave net inversion in methanol-triethylamine ($k_e/k_\alpha = 0.84-0.69$).

Nitroamide IId in tetrahydrofuran-*n*-propylamine gave $k_e/k_\alpha = 1$ (run 11), whereas amide IIIId with the same solvent-base gave $k_e/k_\alpha = >56$.² When *p*-toluidine was substituted for *n*-propylamine in run 10,

(5) (a) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **84**, 4358 (1962); (b) S. Bank, C. A. Rowe, Jr., and A. Schriesheim, *ibid.*, **85**, 2115 (1963); (c) W. von E. Doering and P. P. Gaspar, *ibid.*, **85**, 3043 (1963); (d) G. Bergson and A. M. Weidler, *Acta Chem. Scand.*, **17**, 862 (1963).

(4) The authors thank Prof. P. D. Bartlett for suggesting this term.

nitroamide II_d gave $k_e/k_\alpha = 6$. These data highlight the dependence of the stereochemistry of the reaction on the acid-base strength relationships, which relate to the rate of the proton capture by the carbanion.

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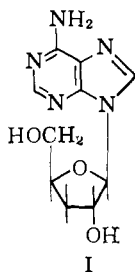
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3'-Deoxynucleosides. I. A Synthesis of 3'-Deoxyadenosine

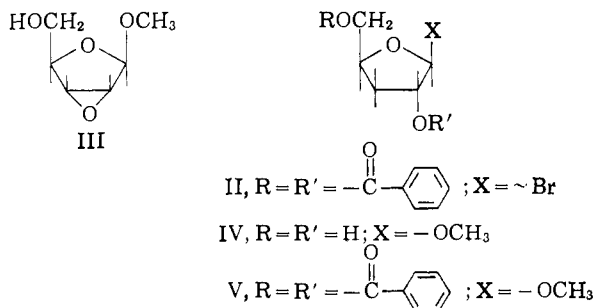
Sir:

The identity of cordycepin with 3'-deoxyadenosine (I) has recently been reported.¹ 3'-Deoxyadenosine has been shown to inhibit the growth of KB cell cul-



tures,² *B. subtilis*,³ an avian tubercle bacillus,³ and Ehrlich ascites carcinoma⁴ in mice, but its effects on other animal tumor systems have not yet been reported. In contrast to the large amount of work, both chemical and biological, carried out on 2'-deoxynucleosides, of the 3'-deoxynucleosides only 3'-deoxyadenosine^{5,6} and 3'-deoxyuridine⁷ appear to have been reported. Consequently, even though 3'-deoxyadenosine has been synthesized^{5,6} previously, we are now reporting its synthesis by a route providing a 3-deoxyribose derivative useful for synthesis of large amounts of 3'-deoxyadenosine, as well as being amenable to synthesis of 3'-deoxyadenosine-8-C¹⁴ and other 3'-deoxynucleosides.

For synthesis of 3'-deoxynucleosides, 2,5-di-*O*-benzoyl-3-deoxy- β -D-ribofuranosyl bromide (II) was chosen as a generally useful intermediate. Preparation of



(1) E. A. Kaczka, N. R. Trenner, B. Arison, R. W. Walker, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 456 (1964).

(2) E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, *ibid.*, **14**, 452 (1964).

(3) K. G. Cunningham, S. A. Hutchinson, W. Manson, and F. S. Spring, *J. Chem. Soc.*, 2299 (1951).

(4) D. V. Jagger, N. M. Kredich, and A. J. Guarino, *Cancer Res.*, **21**, 216 (1961).

(5) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961).

(6) A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3275 (1960).

(7) I. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *ibid.*, 3028 (1958).

this new 3-deoxyribose derivative utilized methyl 2,3-anhydro- β -D-ribofuranoside (III)⁸ as the starting material. Stereospecific reduction of the epoxide function in III by hydrogenation in ethanol over a Raney nickel catalyst at 80° and 40 p.s.i.g. gave almost exclusively the 3-deoxyribose derivative, methyl 3-deoxy- β -D-ribofuranoside (IV), characterized by its infrared spectrum [2.92 (OH), 3.52 (OCH₃), no band at 11.6 μ (epoxide)] and n.m.r. spectrum [60 Mc., in CDCl₃, using a Varian Associates Model 4300B spectrometer: *O*-methyl protons, τ 6.16; C-1 proton, τ 5.22 (singlet)]. Benzoylation of IV with benzoyl chloride and pyridine gave methyl 2,5-di-*O*-benzoyl-3-deoxy- β -D-ribofuranoside (V), m.p. 80–81°, characterized by infrared and n.m.r. spectra and elemental analysis. Direct conversion of this methyl glycoside (V) to 2,5-di-*O*-benzoyl-3-deoxy- β -D-ribofuranosyl bromide (II) was accomplished by reaction with ten parts of a 16% solution of hydrogen bromide in acetic acid at 25° for 20 min. After removal of the solvents, II was obtained as an oil. Its n.m.r. spectrum no longer showed a band characteristic of the methoxyl function and the C-1 proton band was shifted downfield to τ 3.43.

The bromo sugar II was coupled with chloromercuri-6-benzamidopurine⁹ in refluxing xylene (15 min.) to give 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy- β -D-ribofuranosyl)purine, which on treatment with sodium methoxide in methanol gave 3'-deoxyadenosine (I), m.p. 224–225°; its infrared spectrum in Nujol was identical with that of an authentic sample.

Acknowledgment.—We are indebted to Dr. Nelson R. Trenner and Mr. Byron Arison for the n.m.r. spectra and their interpretation.

(8) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).

(9) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 3967 (1959).

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Specific Reaction Rate of the Second-Order Formation of Ar₂⁺

Sir:

The formation of Ar₂⁺ by a bimolecular reaction involving an excited argon atom was first reported by Hornbeck and Molnar.¹ More recently, Fuchs and Kaul² and Dahler, Franklin, Munson, and Field³ reported kinetic studies of this second-order reaction. In neither of these latter mass spectrometric studies^{2,3} (which employed continuous electron beams and ion-repeller fields) could the specific reaction rate be determined explicitly because the reaction time, τ , was not known; the product of specific reaction rate and reaction time, $k\tau$, was reported. Combination of $k\tau$ values with the usual 10⁻⁸ sec. radiative lifetime leads to astonishingly high rate constants.³ Recently, Kaul⁴ has reported that three excited states of argon, with an

(1) J. A. Hornbeck and J. P. Molnar, *Phys. Rev.*, **84**, 621 (1951).

(2) R. Fuchs and W. Kaul, *Z. Naturforsch.*, **15**, 108 (1960).

(3) J. S. Dahler, J. L. Franklin, M. S. B. Munson, and F. H. Field, *J. Chem. Phys.*, **36**, 332 (1962).

(4) W. Kaul, VI International Conference on Ionization Phenomena in Gases, Paris, 1963, p. 169.