In each instance the synthesis of the requisite chloropurine nucleoside has been accomplished by introduction of the chlorine into the purine ring prior to attachment of the sugar. The high reactivity of the chlorine atom has led to a number of experimental difficulties. The removal of various blocking groups on the sugar moiety has in certain cases been impossible without concomitant replacement of the chlorine atom.[10,11] Thus, it would be advantageous to be able to introduce the chlorine atom into the purine nucleus at the final stage of synthesis.

This has now been achieved successfully and is the subject of the present communication. The recently reported[12] preparation of 6-chloropurine from 6-methylthiopurine prompted us to investigate the preparation of 6-chloro-9-β-D-ribofuranosylpurine (I) from the readily available 9-β-D-ribofuranosylpurine-6-thiol (II).[13]

Chlorine gas was bubbled slowly into a suspension of five grams of II in methanol at −10°. During the reaction, 9-β-D-ribofuranosylpurine-6-thiol gradually went into solution. Methanolic ammonia then was added carefully to neutralize the excess acid, and 6-chloro-9-β-D-ribofuranosylpurine (I) was isolated from the reaction mixture in above 80% yield. Treatment of 6-methylthio-9-β-D-ribofuranosylpurine (III)[13] (10 g.) in a similar manner gave I in 90% yield.

The present clinical interest in 6-chloropurine in cancer chemotherapy[14] has increased the need for large quantities of 6-chloro-9-β-D-ribofuranosylpurine (I) for preclinical evaluation. This preparation of I was found to be readily adaptable to large-scale synthesis since 125 g. of II gave 60.0 g. of I after recrystallization from methanol–water. This product decomposed at 168–170°[15] and was chromatographically pure. The ultraviolet absorption spectrum was identical with that previously recorded.[11] The product (I) was found to exhibit an infrared spectrum identical with that of an authentic synthetic sample.[15,16] The specific rotation was found to be $[\alpha]^{28}D$ −45.2 (0.796% in water) which is the same as that previously recorded.[11] *Anal.* Calcd. for $C_{10}H_{11}ClN_4O_4$: C, 41.9; H, 3.87; N, 19.5; Cl, 12.4. Found: C, 41.9; H, 3.82; N, 19.5; Cl, 12.4.

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(16) Kindly supplied by Dr. Alexander Hampton of the Sloan-Kettering Institute, New York, N. Y.

The recently reported synthesis of 2-amino-6-chloropurine[17] from 2-amino-6-methylthiopurine suggested the synthesis of the previously unreported 2-amino-6-chloro-9-β-D-ribofuranosylpurine (IV). This synthesis proceeded readily from 2-amino-6-methylthio-9-β-D-ribofuranosylpurine[18] (10 g.) and chlorine gas in methanol at −10°. The product was isolated after carefully adjusting the *p*H to 9 with methanolic ammonia so that the internal temperature was maintained below −10°. After recrystallization first from water and then twice from absolute methanol, IV was obtained in 51% yield. When heated rapidly from room temperature, IV melted with decomposition at 171–172°. 2-Amino-6-chloro-9-β-D-ribofuranosylpurine (IV) in the ultraviolet exhibited: $\lambda_{max}^{pH\ 1}$ 310, 246, 221 mμ, ε 7,450, 7,300, 24,600; $\lambda_{min}^{pH\ 1}$ 267, 236 mμ, ε 1,450, 6,500, $\lambda_{max}^{pH\ 11}$ 308, 246 mμ, ε 7,950, 8,250; $\lambda_{min}^{pH\ 11}$ 267, 235 mμ, ε 1,860, 7,150. The specific rotation was found to be $[\alpha]^{26}D$ −27.7 (0.614% in water). *Anal.* Calcd. for $C_{10}H_{12}ClN_5O_4$: C, 39.9; H, 4.0; N, 23.2; Cl, 11.8. Found: C, 39.7; H, 4.0; N, 23.5; Cl, 11.8.

This relatively mild method of introduction of a halogen atom into a nitrogen heterocyclic system is presently under further investigation.

Acknowledgment.—The author wishes to thank Dr. Howard W. Bond of the Cancer Chemotherapy National Service Center for his suggestion of applying this reaction to the synthesis of 6-chloro-9-β-D-ribofuranosylpurine (I).

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(18) The preparation of 2-amino-6-methylthio-9-β-D-ribofuranosylpurine was accomplished from 2-amino-9-β-D-ribofuranosylpurine-6-thiol[13] and will be reported later.

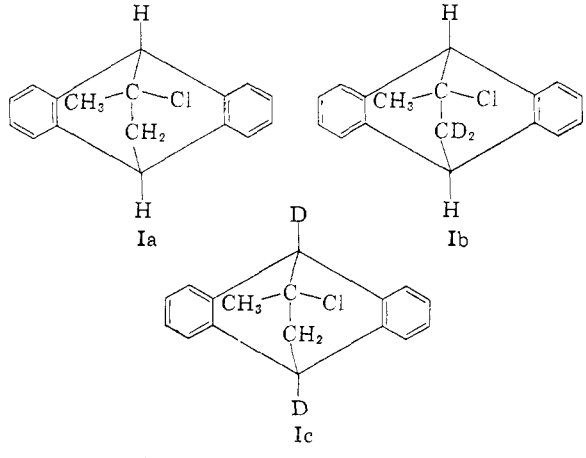
DEPARTMENT OF CHEMISTRY
ARIZONA STATE UNIVERSITY
TEMPE, ARIZONA ROLAND K. ROBINS

RECEIVED MARCH 19, 1960

STERIC INHIBITION OF A SECONDARY DEUTERIUM ISOTOPE EFFECT[1]

Sir:

I would like to report the synthesis and solvolysis rate constants of compounds Ia,b,c.



(1) National Science Foundation Senior Postdoctoral Fellow and Alfred P. Sloan Research Fellow.

The Diels–Alder adduct of anthracene and vinyl acetate[2] was hydrolyzed to the secondary alcohol, oxidized to the ketone[3] and converted with methylmagnesium iodide to the tertiary alcohol, m.p. 134–5°. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.46; H, 6.84. This with thionyl chloride gave Ia, m.p. 92–93°. Calcd. for $C_{17}H_{15}Cl$: C, 80.14; H, 5.93. Found: C, 80.15; H, 6.27. Ib was obtained via exchange of some of the ketonic precursor of Ia with deuterium oxide in boiling dioxane. Ic was made by the same route from anthracene-9,10-d_2, 1.79 atoms D per molecule, from reduction of anthrone.[4] N.m.r. spectra of Ia, Ib and the corresponding ketones were entirely consistent with these formulations and showed the deuterium compounds to be *ca.* 90% isotopically pure. Solvolysis of Ia in 60% aqueous dioxane produced olefin and unrearranged tertiary alcohol. The solvolysis rate constants measured conductometrically are given in the table.

TABLE

FIRST ORDER RATE CONSTANTS (10^{-5} SEC.$^{-1}$) FOR SOLVOLYSIS IN "60%" AQ. ETHANOL AT 45.00°

Each constant given is the average for one experiment of a number of integrated rate constants calculated for points taken over about three half lives. The point by point values drifted downward 1% or less during any run.

Compound	k				k_H/k_D
Ia	9.05	8.98	8.99[a]	9.14[a,b]	
Ib	7.80	7.88	7.92[a]		1.14 ± 0.01
Ic	9.12	9.29[a,b]			0.986 ± 0.01

[a] Taken after one additional recrystallization of previously used material. [b] Run in a second solvent batch.

These figures show that occurrence of the β-deuterium isotope effect depends not only on the position but also on the *orientation* of the isotopic bond. *This result is strikingly consistent with the previous suggestion that hyperconjugative intramolecular transmission of electronic charge is an essential factor in causing β-deuterium substituted compounds to give slower carbonium ion type reactions than their protium analogs.*[5] Theory predicts that hyperconjugation between the bridgehead deuterium atom in Ic and the carbonium ion center resulting from solvolytic loss of the chloride ion would be largely sterically prevented. In molecular orbital terms this is because the two orbitals which must overlap for hyperconjugation are mutually perpendicular. In valence-bond terms this is because contributing forms having double bonds at the bridgehead carbon atom would be too unstable to contribute significantly (Bredt's rule). Thus with Ic the normal isotope rate effect, observed with Ib and other β-deuterio tertiary chlorides,[5] is not found. Instead a very small "inverse" isotope effect, apparently due to an inductive interaction between the reaction center and the isotopic bond, appears. *It would seem that for the first time the inductive and hyperconjugative contributions to β-deuterium secondary isotope rate effects on a carbonium ion solvolysis reaction have been isolated for quantitative comparison.*

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CONTRIBUTION NO. 927
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RECEIVED MARCH 11, 1960

A NEW SYNTHESIS OF ALIPHATIC AND AROMATIC THIOAMIDES FROM NITRILES

Sir:

Previously available methods for the preparation of thioamides from nitriles involve heating the nitrile in alcoholic solution in the presence of an alkali-metal hydrogen sulfide[1] or an ammonium[2] or substituted ammonium[1] sulfide. The formation of aliphatic thioamides under these conditions requires the use of high pressures in an autoclave,[3] and the method is facile only with aromatic nitriles containing electron-withdrawing substituents.[1] However, reduction can take place even under mild conditions, and the formation of *p*-aminothiobenzamide from *p*-nitrobenzonitrile is illustrative.[4,5] The use of a mixture of triethylamine and pyridine as a catalyst for the direct addition of hydrogen sulfide to nitriles is useful only for aromatic nitriles and has little value for the preparation of aliphatic thioamides.[6] Thioacids have found limited application as a source of hydrogen sulfide for this conversion.[7,8]

We wish to report a new and general synthesis of thioamides from nitriles which utilizes thioacetamide as a source of hydrogen sulfide under acidic conditions. The thioamides are formed in good yield in a high state of purity, and the method is equally applicable to aliphatic nitriles, and aromatic nitriles containing either electron-releasing, electron-withdrawing or potentially reducible substituents. One equivalent of the nitrile is heated on a steam-bath for 15–30 minutes with two equivalents of thioacetamide in dimethyl-

Nitrile	Thioamide	Yield, %	M.p., °C.	Ref.
p-$O_2NC_6H_4CN$	*p*-$O_2NC_6H_4CSNH_2$	83	158.5–159.5	7
p-$CH_3OC_6H_4CN$	*p*-$CH_3OC_6H_4CSNH_2$	87	148.5–149.5	6,9
$CH_2(CN)_2$	$CH_2(CSNH_2)_2$	63	211–212 d.	10
$NC(CH_2)_4CN$	$H_2NCS(CH_2)_4CSNH_2$	78	178.5–179.5 d.	3,11,12

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