TABLE I

RESULTS FROM PREPARATIONS OF SEVERAL DEUTERATED COMPOUNDS USING A ZN-DUST TECHNIQUE

Compound to be deuterated	Moles taken/ gram-atom of Zn	Reaction medium	Reaction time	Reaction product	Yield, mg. and (%)
2-Bromopyridine[1]	0.0085/0.05	25 ml. of 2 *N* D_2SO_4	100 min.	2D-Pyridine	400 (59)
3-Bromopyridine[1]	0.0085/0.05		100 min.	3D-Pyridine	350 (51)
4-Chloropyridine[1]	0.0085/0.05		100 min.	4D-Pyridine	500 (74)
3-Iodothiophene[2]	0.048/0.107	0.138 mole CH_3COOD + 1.18 moles D_2O	75 min.	3D-Thiophene	2700 (66)
3,4-Diiodothiophene[2]	0.036/0.107		75 min.	3,4 D_2-Thiophene	2000 (64)
2,4,6-Tribromofluorobenzene[3]	0.012/0.246		24 hours	2,4,6 D_3-Fluorobenzene	500 (42)
Tetraiodothiophene[2]	0.034/0.246	0.278 mole CH_3COOD + 1.11 moles D_2O	20 hours	Tetradeuterothiophene	1100 (37)
Methylene iodide	0.039/0.462	0.400 mole CH_3COOD + 1.05 moles D_2O	Instantaneous	Dideuteromethane	300 (43)
Methyl iodide	0.22/1.25	1.10 mole CH_3COOD + 3.20 moles D_2O	Instantaneous	Monodeuteromethane	3540 (93)
1,4-Diiodobenzene	0.076/0.246	0.278 mole CH_3COOD + 2.22 moles D_2O	20 hours	1,4 D_2-benzene	3800 (57)

the solution of CH_2COOD in D_2O [prepared *in situ* from $(CH_3CO)_2O$ and D_2O] at room temperature in a 100-ml. flask fitted with a reflux condenser. The mixture was boiled for the period given in Table I. The deuterated pyridines were isolated *via* complex compounds but the remaining species were distilled-off *in vacuo* with some D_2O and CH_3COOD. Most of the water could then be removed with a syringe. After treating the organic compounds with anhydrous soda they were finally dried over P_2O_5 and distilled. Their identity and the fact that no undesired exchange had taken place was established by investigation of the infrared and microwave spectra of the parent compounds and the deuterated species of Table I.[1,2,3,4]

Because of the vigorous reaction methylene iodide and methyl iodide had to be introduced dropwise. The deuterated methanes obtained were not contaminated by isotopic methanes.

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Preparation and Derivatives of 2-Cyanotetrahydropyran

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This study of 2-cyanotetrahydropyran followed closely to that for cyano-1,4-dioxane.[1] Two differences in experimental procedure were observed: (1) the 2-cyanotetrahydropyran was prepared in better yields using an ether medium rather than toluene, and (2) the reaction between the 2-cyanotetrahydropyran and phenylmagnesium bromide to yield 2-benzoyltetrahydropyran behaved normally. The derivatives of tetrahydropyran were less soluble in the solvents employed than were the corresponding derivatives of 1,4-dioxane and could be worked up more easily.

The hydrolysis of 2-cyanotetrahydropyran produced the corresponding carboxylic acid, which had been prepared previously from acrolein dimer.[2]

N-(2-Tetrahydropyranylmethyl)-4-aminobenzenesulfonamide, produced by the reaction between 2-aminomethyltetrahydropyran and *p*-acetamidobenzenesulfonyl chloride, was tested by Sharp and Dohme, Inc., Philadelphia for physiological activity. It was found to be inactive *in vitro* toward *Proteus vulgaris* and *in vivo* toward a strain of hemolytic streptococcus. Trimethyl(2-tetrahydropyranylmethyl)ammonium iodide, prepared from 2-aminomethyltetrahydropyran and methyl iodide, will be submitted for a physiological activity study.

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EXPERIMENTAL

2-Cyanotetrahydropyran. 2-Chlorotetrahydropyran was prepared at −10° by passing 9.1 g. (0.25 mole) of dry hydrogen chloride into 21.0 g. (0.25 mole) of dihydropyran at a rate to prevent discoloring. Chlorotetrahydropyran was added dropwise to a vigorously stirred suspension of 33.3

(1) Nelson, Minsek, Simon, and Underwood, *J. Am. Chem. Soc.*, **77**, 1965 (1955).

(2) Whetstone and Ballard, *J. Am. Chem. Soc.*, **73**, 5281 (1951).

g. (0.25 mole) of silver cyanide in 125 ml. of refluxing anhydrous ether. After refluxing for three hours, the silver salts were removed by filtration, the ether was distilled off, and the residue was fractionated under reduced pressure. The yield was 8.4 g. (38%) of a colorless liquid, b.p.$_{22}$ 81.5°,[3] n_D^{20} 1.4425, d_4^{20} 1.0128.

Anal.[4] Calc'd for C_6H_9NO: C, 64.86; H, 8.11; N, 12.61; MR, 29.01. Found: C, 65.03; H, 8.32; N, 12.40; MR, 29.02.

Tetrahydropyran-2-carboxylic acid. 2-Cyanotetrahydropyran (6.1 g.; 0.055 mole) was refluxed for five hours with 5.0 g. (0.12 mole) of sodium hydroxide in 45 ml. of water. The solution was acidified with 15 ml. of 6 *N* sulfuric acid, extracted with several 35-ml. portions of ether, and the ether solution was dried over sodium sulfate. After removal of the ether, the residue was fractionated under reduced pressure to yield 4.8 g. (67%) of a clear viscous liquid, b.p.$_{24}$ 144–147°, n_D^{20} 1.4661, d_4^{20} 1.161.

Anal. Calc'd for $C_6H_{10}O_3$: C, 55.38; H, 7.75; MR, 30.75; Neut. equiv. 130.1. Found: C, 55.30; H, 7.85; MR, 31.01; Neut. equiv. 130.2.

An approximate ionization constant is 1.3×10^{-4} at 25° based upon the Beckman *p*H values of 0.1 to 0.2 *M* solutions of the acid.

2-Benzoyltetrahydropyran. 2-Cyanotetrahydropyran (6.1 g.; 0.055 mole) in 40 ml. of dry ether was added dropwise with stirring to a 0.1 mole solution of phenylmagnesium bromide in 75 ml. of ether. After standing for eight hours, the mixture was poured over 75 g. of crushed ice and 10 ml. of concentrated sulfuric acid. The ether layer was separated, the water layer extracted with three 20-ml. portions of ether, and the combined ether solutions were dried over sodium sulfate. Removal of the ether, followed by fractionation of the residue under reduced pressure yielded 7.0 g. (67%) of a very slightly yellow, viscous liquid, b.p.$_{26}$ 170–171°, n_D^{20} 1.5445, d_4^{20} 1.102.

Anal.[4] Calc'd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.33; MR, 53.36. Found: C, 75.59; H, 7.47; MR, 54.51.

The *2,4-dinitrophenylhydrazone* of the 2-benzoyltetrahydropyran melted at 171–173°.

Anal.[4] Calc'd for $C_{18}H_{18}O_5N_4$: N, 15.14. Found: N, 14.90.

2-Aminomethyltetrahydropyran. A modified procedure of Amundsen and Nelson[5] was employed. Lithium aluminum hydride (7.6 g., 0.2 mole) was crushed under dry ether and then was refluxed with stirring in 400 ml. of dry ether for two hours. After cooling to 0°, 22.2 g. (0.2 mole) of 2-cyanotetrahydropyran in 40 ml. of dry ether was added dropwise over a period of 0.5 hour. The reaction was allowed to continue for an additional 0.5 hour, when 8 ml. of water was added, followed by 6 ml. of 6 *N* sodium hydroxide and then 28 ml. of water. The ether layer was decanted through a fluted filter and the residual salts were refluxed for ten minutes with two successive 100-ml. portions of ether. The combined ether decantates were dried with sodium sulfate. The ether was removed and the residue was fractionated under reduced pressure to yield 15.3 g. (66%) of a colorless, partly water-soluble liquid having a strong ammonia odor, b.p.$_{21}$ 64–66°, n_D^{20} 1.4598, d_4^{20} 0.9635.

Anal.[4] Calc'd for $C_6H_{13}NO$: C, 62.61; H, 11.30; N, 12.17; MR, 32.65. Found: C, 62.24; H, 11.40; N, 12.27; MR, 32.68.

N-(2-Tetrahydropyranylmethyl)-4-aminobenzenesulfonamide. *p*-Acetamidobenzenesulfonyl chloride (31.6 g., 0.13 mole) was added cautiously to a solution of 15.0 g. (0.13 mole) of 2-aminoethyltetrahydropyran in 20.8 g. (0.26 mole) of anhydrous pyridine. The reaction mixture was heated for 45 minutes at 100° and then was poured into 130 ml. of water acidified with hydrochloric acid. The solidified product was crushed with a stirring rod, filtered, and washed with 25 ml. of ice-water. The yield was 30.0 g., m.p. 131.5–133.5°, after recrystallization from water. The crude product was refluxed with 200 ml. of 2 *N* sodium hydroxide for one hour, filtered, and the filtrate was neutralized with concentrated hydrochloric acid. An oily substance, which solidified upon standing and cooling, was separated and recrystallized from 1600 ml. of hot water. The product, separating in fine white flakes, weighed 16.2 g. (46%), m.p. 95–97°.

Anal.[4] Calc'd for $C_{12}H_{18}N_2O_3S$: C, 53.32; H, 6.71; S, 11.87. Found: C, 52.50; H, 6.74; S, 11.91.

Trimethyl(2-tetrahydropyranylmethyl)ammonium iodide. A mixture of 1.2 g. (0.01 mole) of 2-aminoethyltetrahydropyran and 2.3 g. (0.04 mole) of potassium hydroxide in 25 ml. of ethyl alcohol was treated gradually with 14.0 g. (0.1 mole) of methyl iodide to maintain a gentle refluxing of the alcohol. After heating for 0.5 hour, the mixture was cooled, filtered, and the solids were washed with 20–25 ml. of warm ethyl alcohol. The filtrate was evaporated to expel unused methyl iodide and was cooled in ice and salt. The crude product was recrystallized from ethyl alcohol to yield 1.2 g. (40%) of granular, white crystals, m.p. 188–190°.

Anal. Calc'd for $C_9H_{20}INO$: I, 44.52. Found: I, 44.83, 44.76.

Replacing 2-aminomethyltetrahydropyran with aminomethyl-1,4-dioxane[1] yielded trimethyl(dioxanylmethyl)ammonium iodide (51%), m.p. 214–215°.

Anal. Calc'd for $C_8H_{18}INO_2$: I, 44.22. Found: I, 44.20.

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(3) Reported b.p. 80° (12 mm.). Office of the Publications Board, PB 823, Office of Technical Services, U. S. Dept. of Commerce, Washington, D. C.

(4) Analysis by Micro-Tech Laboratories, Skokie, Ill.

(5) Amundsen and Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

Partial Hydrogenation of Benzhydrylpyridines[1]

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In an attempt to evaluate differences in the pharmacological action of identically substituted pyridines and piperidines, we have reduced the 4-amyl and the 4-methyl substituted 1-(diphenylmethyl)pyridines to the corresponding piperidine moieties.

EXPERIMENTAL

(All melting points uncorrected. Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.)

1-(Diphenylmethyl)-4-amylpiperidine hydrobromide (I). 1-(Diphenylmethyl)-4-amylpyridinium bromide[2] (50 g., 0.126 mole) was dissolved in 180 ml. of aqueous 66% ethanol and hydrogenated in the presence of 1.0 g. Adams' platinum oxide catalyst ("Parr" hydrogenation apparatus, max. pressure 50 lbs./inch^2). Hydrogen absorption ceased after 15–18 hours. The platinum oxide was filtered off and the solvents were removed under reduced pressure (max. pot temp. 50°). The residue was dissolved in anhydrous benzene and crystallization was induced by adding anhydrous

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(2) Courtesy Bristol Laboratories, Syracuse, New York.