TABLE I

Rate Constants for the Pinacol Rearrangement as a Function of Sulfuric Acid Concentration

H_2SO_4, %	$k \times 10^6$ (Sec.$^{-1}$)	$\frac{d \log k}{d \% H_2SO_4}$	$\frac{-d H_0}{d \% H_2SO_4}$
38.71	1.75	0.083	0.081
43.98	4.92	.089	.093
51.37	22.6	.105	.108
54.01	45.6	.108	.110
60.25	205	.110	.110
64.36	511	.110	.115
69.09	2010	.115	.121
74.37	8450	.125	.127

$-dH_0$ and $-dC_0$. The symbols H_0 and C_0 refer to the Hammett acidity function based on base-protonated base equilibria and an acidity function (C_0) based on alcohol-carbonium ion equilibria.

The precision of the relation $d \log k = -d H_0$ (Table I) is interpreted to mean that the transition state is of type I as concluded by Duncan and Lynn. Also there is a relatively small amount of stretching of the C—O bond and relatively little delocalization of the positive charge in this transition state. These conclusions apply strictly to the case under study, pinacol to pinacolone. When R is phenyl for example, the reaction path should more closely approach path II if not actually proceeding through the free carbonium ion, II.

EXPERIMENTAL

The rate of conversion of pinacol (2,3-dimethyl-2,3-butanediol) to pinacolone (3,3-dimethyl-2-butanone) has been studied from 39–75% sulfuric acid. The progress of the reaction was followed by calculating the concentration of pinacolone from the optical density at 270 mμ.

The rate constants calculated from the general relation for first-order reaction, $\log c/c_0 = kt$, were remarkably constant from 0% to over 90% completion. Deviations from the average values were rarely greater than 2%. Duplicate runs also generally agreed within 2%. The final optical density was within 5% of that calculated for complete conversion of pinacol to pinacolone based on the extinction coefficients of pure pinacolone and the initial concentration of pinacol employed.

The completeness of the reaction and freedom from side reactions was checked in another way. The 2,4-dinitrophenylhydrazone of pinacolone was isolated in yields of 99% and 91% from the kinetic runs in 53% and 61% sulfuric acid, respectively.

The extinction coefficients of pinacolone varied with the percent sulfuric acid. For example, at 270 mμ the value ranged from 28.0 at 22% sulfuric acid to 41.1 at 69% acid. The extinction coefficients from 220 to 280 mμ and from 22% to 70% sulfuric acid as well as other experimental details have been published in a thesis.[5]

College of Chemistry and Physics
Pennsylvania State University
University Park, Pa.

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(5) Ph.D. Thesis of C. Perizzolo, Pennsylvania State Univ., 1957.

3-(*N*,*N*-Dialkylcarboxamido)piperidinoalkanes[1]

Andrew Lasslo and Pauline D. Waller

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As reported earlier,[2] we have undertaken the synthesis of a series of pyridine- and piperidinecarboxylic acid derivatives in connection with an investigation directed toward the elucidation of the pharmacodynamic characteristics of this group of compounds. The compounds reported in this and the preceding[2] communications were planned as to permit the pharmacological evaluation of gradual changes in chemical structure. We anticipate that such correlation will contribute toward a better understanding of the fundamental principles governing relationships between molecular constitution and biological response, and allow a better insight into the chemotherapeutic potentialities of pyridine- and piperidinecarboxamides.

EXPERIMENTAL

The compounds listed in Table 1 were prepared by the following procedures.

Procedure A1: 1,1-Bis[3-(N,N-diethylcarboxamido)pyridinium]methane dibromide (IV). Reaction mixtures consisting of 53.5 g. (0.300 mole) of pyridine-3-(*N*,*N*-diethylcarboxamide) (I) and 26.1 g. (0.150 mole) of dibromomethane in 200 ml. of anhydrous benzene, or multiples thereof, were refluxed for a total of 51–94 hr. The crystalline reaction product was filtered off and recrystallized from ethanol-ethyl acetate.

Procedure A2: 1-Decyl-3-(N,N-diethylcarboxamido)pyridinium bromide (XI). An excess (106.8 g., 0.483 mole) of 1-bromodecane and 36.0 g. (0.202 mole) of I were heated at 93–95° or refluxed in anhydrous benzene (200 ml.) for a total of 34–35 hr. The excess alkyl halide and the solvent were decanted or removed under reduced pressure, the residue was washed with anhydrous ethyl ether, and recrystallized from ethanol-ethyl acetate.

Procedure B: 1,10-Bis[3-(N,N-diethylcarboxamido)piperidino]decane dihydrobromide (XIII). The quaternary derivative was obtained by Procedure A1. The crude 1,10-bis[3-(*N*,*N*-diethylcarboxamido)pyridinium]decane dibromide, obtained from 45.0 g. (0.150 mole) of 1,10-dibromodecane and 53.5 g. (0.300 mole) of I, was washed with anhydrous ethyl ether, and dissolved in 100–200 ml. of warm water. The aqueous solution was washed with two 50 ml. portions of benzene, treated with charcoal, and filtered through Celite (Johns-Manville filter-aid). The filtrate was subjected to hydrogenation at room temperature, in the presence of platinum oxide (Adams' catalyst), at maximum pressures of 50–55 p.s.i. Hydrogen absorption ceased after about 9 hr. The platinum oxide was filtered off, and the water was removed under reduced pressure (max. pot temp. 50°). The residual moisture was removed from the reaction product by azeotropic distillation under reduced pressure with about 800 ml. of anhydrous benzene. The crystalline residue was recrystallized from ethanol-ethyl acetate.

Procedure C: 1-Cyclopentyl-3-(N,N-diethylcarboxamido)-

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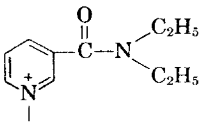
(1) This investigation is supported by grants from the Geschickter Foundation for Medical Research.

(2) A. Lasslo, W. M. Marine, and P. D. Waller, *J. Org. Chem.*, 21, 958 (1956).

TABLE I

Compound No.	Alkane	Substitution	Method of Preparation	Yield, %[a]	B.P., °C., at Mm. Hg	n_D, °C.	Analyses[c]											
							Salt	M.P., °C.[b]	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Br, % Calcd.	Br, % Found	Cl, % Calcd.	Cl, % Found	N, % Calcd.	N, % Found
III	Methane	1-(R''')	D	48.8	96–8 0.10–0.15	26.5 1.5021	HCl	158.5–159.5	52.80	52.49	8.37	8.43	—	—	17.32	17.2	13.69	13.7
IV	Methane	1,1-Bis(R')	A1	60.5	—	—	2Br⁻	214.0–215.0	47.56	47.39	5.70	5.74	30.14	30.20	—	—	10.56	10.30
V	Ethane	1-(R'')	B	95	—	—	HBr	135.5–136.0	49.14	49.02	8.59	8.54	27.25	27.2	—	—	9.55	9.26
VI	Ethane	1,2-Bis(R'')	B	51.1	—	—	2HBr	273.0–274.0	47.48	47.24	7.97	8.02	28.73	28.6	—	—	10.07	10.1
VII	Cyclopentane	1-(R'')	C	74.5	141–2 0.35–0.37	26 1.4950	HCl	161.5–162.0	62.36	62.35	10.12	10.25	—	—	12.27	12.35	9.70	9.6
VIII	Cyclohexane	1-(R'')	C	13.5	152 0.50–0.52	27 1.4971	—	—	72.13	72.04	11.35	11.27	—	—	—	—	10.52	10.40
IX	Hexane	1-(R'')	B	97.7	—	—	HBr	175.0–176.0	55.00	55.16	9.52	9.47	22.88	22.9	—	—	8.02	8.0
X	Hexane	1,6-Bis(R'')	B	64.7	—	—	2HBr	253.5–254.5	50.98	50.97	8.56	8.58	26.09	26.3	—	—	9.15	8.80
XI	Decane	1-(R')	A2	95	—	—	Br⁻	91.0–92.0	60.14	60.30	8.83	8.75	20.01	20.0	—	—	7.01	7.00
XII	Decane	1-(R'')	B	66.3	—	—	HBr	157.5–158.0	59.24	59.11	10.19	10.16	19.71	19.90	—	—	6.91	6.90
XIII	Decane	1,10-Bis(R'')	B	97.7	—	—	2HBr	223.0–224.0	53.89	53.86	9.05	9.05	23.90	23.8	—	—	8.38	8.35

R'


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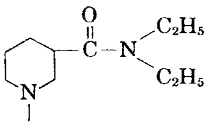

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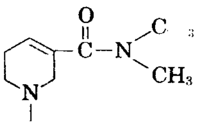

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[a] Crude yield. [b] Melting points uncorrected. [c] Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

piperidine hydrochloride (VII). A reaction mixture consisting of 60.0 g. (0.402 mole) of bromocyclopentane, 61.6 g. (0.335 mole) of piperidine-3-(*N*,*N*-diethylcarboxamide) (II),[2] 62.0 g. (0.449 mole) of anhydrous potassium carbonate, and 150 ml. of anhydrous benzene was heated at reflux temperature, with mechanical agitation, for a total of 124 hr. Upon cooling, the solid constituents of the reaction mixture were filtered off, the filtrate was washed with aqueous 40% potassium hydroxide, and dried over anhydrous magnesium sulfate. The dry benzene solution was filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

Procedure D: 1-Methyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarboxamido)pyridine hydrochloride (III). 1-Methyl-1,2,-5,6-tetrahydropyridine-3-carboxylic acid was prepared from arecoline according to Jahns' procedure.[3] To 30.0 g. (0.213 mole) of the acid, 245.7 g. (2.065 moles) of thionyl chloride was added, the mixture was heated gradually to reflux temperature, and the resulting solution was refluxed for 16 min. The excess thionyl chloride was removed under reduced pressure (max. pot temp. 40°). The residual thionyl chloride was removed from the reaction product by azeotropic distillation under reduced pressure with two 400 ml. portions of anhydrous benzene. Then 200 ml. of anhydrous benzene was introduced into the reaction vessel, and the solid acid chloride was finely dispersed with mechanical agitation. To this dispersion, a solution of 100 g. (2.219 moles) of dimethylamine in 200 ml. of anhydrous benzene was added gradually, while the reaction mixture was maintained at room temperature. After the addition, the mixture was stirred an additional 2 hr. at room temperature and an additional 5 hr. at 50–55°. The resulting slurry was treated with aqueous 40% sodium hydroxide and the base extracted with benzene. The combined benzene extracts were dried over anhydrous sodium sulfate, filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

The following monoalkylcarboxamido derivatives were prepared by Procedure D: *1-Methyl-3-(N-methylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride* (*XIV*). The base distilled at 129–131°/0.5 mm. Hg; n_D^{27} 1.5197 (yield 41.0%). The compound melted at 184.0–185.0°.

Anal. Calcd. for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; Cl, 18.60; N, 14.70. Found: C, 50.40; H, 8.00; Cl, 18.55; N, 14.70.

1-Methyl-3-(N-ethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (*XV*). The base distilled at 128–132°/0.09 mm. Hg; n_D^{27} 1.5107 (yield 42.2%). The compound melted at 163.0–164.0°,

Anal. Calcd. for $C_9H_{17}ClN_2O$: C, 52.80; H, 8.37; Cl, 17.32; N, 13.69. Found: C, 52.96; H, 8.39; Cl, 17.3; N, 13.8.

In tests on blood pressure and upon the autonomic nervous system as defined by changes in response to acetylcholine, epinephrine, tetramethylammonium bromide, and carotid occlusion (in chloralose anesthetized dogs), several compounds induced ganglionic blockade, some adrenergic blockade, and some effected hypotension of an as yet undetermined nature. The pharmacological evaluation is not complete at the time of this writing.

DEPARTMENT OF PHARMACOLOGY
DIVISION OF BASIC HEALTH SCIENCES
EMORY UNIVERSITY, GA.

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[3] E. Jahns, *Arch. Pharm.*, **229**, 680 (1891).

Nitriles in Nuclear Heterocyclic Syntheses. I. Dihydro-1,3-oxazines[1]

EMMA-JUNE TILLMANNS WITH JOHN J. RITTER

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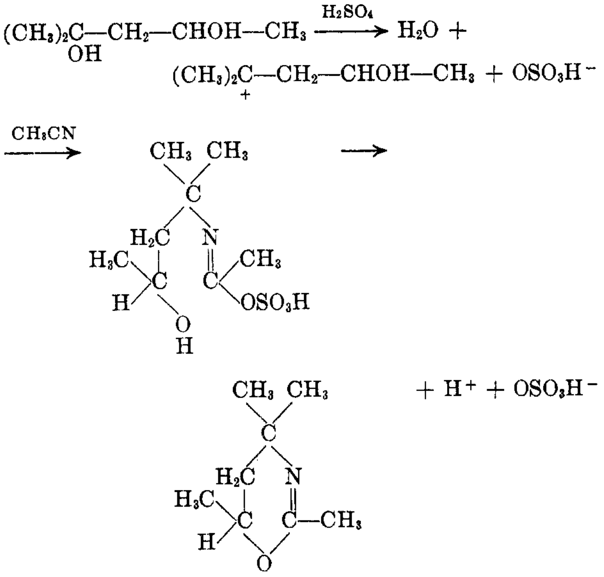
The acid-catalyzed reaction of secondary and tertiary alcohols with nitriles has been shown to result in formation of a variety of *N*-substituted amides.[2] Interaction of 2-methyl-2,4-pentanediol with acetonitrile has now been found to yield a dihydro oxazine instead of the expected diamide. It is suggested that primary reaction of a tertiary carbonium ion with the nitrile in the ordinary manner is followed by cyclization with displacement of —OSO_3H as follows:



$$(CH_3)_2\underset{OH}{C}—CH_2—CHOH—CH_3 \xrightarrow{H_2SO_4} H_2O + (CH_3)_2\underset{+}{C}—CH_2—CHOH—CH_3 + OSO_3H^-$$

Confirmation of the identity of the product was obtained by comparison with authentic 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine.[3] Further proof consisted in comparison of the caprylate of the amine resulting from alkaline cleavage of this dihydro oxazine with that of an authentic specimen of 4-amino-4-methyl-2-pentanol.

Two additional dihydro oxazines, 4,4,6-trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine and 4,4,6-trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine were prepared in the same manner by substituting benzo-

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[1] Abstracted from part of a thesis submitted by Emma-June Tillmanns to the Graduate Faculty of New York University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, February 1954.

[2] J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948); F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949); L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949); H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951).

[3] M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, **60**, 407 (1938).