a complex mixture of products is formed and the desired dihydro-1,2,4,5-tetrazine is difficult to separate from the mixtures. In our variation of this procedure the reaction is carried out under anhydrous conditions in a mixture of methanol and triethylamine. The dihydrotetrazine precipitates from this reaction mixture, the reaction time is shortened, and the overall yields are improved to around 50%. Attempts to prepare those diaryltetrazines containing electron attracting substituents and 3,6-dipyridyl-1,2,4,5-tetrazine were unsuccessful by either procedure.

The infrared spectra of these 3,6-diaryl-1,2,4,5-tetrazines show a very strong ring stretching vibration at 1375–1390 cm.$^{-1}$ which appears to be a characteristic of the tetrazine ring since it is absent from the spectra of the corresponding dihydrotetrazines. Another rather unique feature of these spectra is a strong band at 913–925 cm.$^{-1}$. A similar band was found in the spectrum of azobenzene at 920 cm.$^{-1}$ but was absent from the spectrum of both freshly recrystallized hydrazobenzene and the dihydro derivative of 3,6-di-*p*-biphenylyl-1,2,4,5-tetrazine. Although this would seem to indicate a connection between this frequency and the azo linkage, data for additional compounds is needed to establish this definitely. When examined by previously described techniques[5,6] none of these compounds showed relative pulse heights in excess of 0.12.

EXPERIMENTAL

Details are given for the preparation of a typical dihydrotetrazine and tetrazine. Similar procedures were used in the preparation of 3,6-diphenyl-1,2,4,5-tetrazine, m.p. 195° (reported,[1] 192°), yield 55%, and 3,6-di-*m*-tolyl-1,2,4,5-tetrazine, m.p. 151° (reported,[2] 150–52°), yield 53%.

1,2-Dihydro-3,6-di-p-biphenyl-1,2,4,5-tetrazine. Dry hydrogen chloride gas was bubbled for 12 hr. into a solution of 10 g. (0.058 mole) *p*-biphenylcarbonitrile in 200 ml. of anhydrous methanol. At the end of this time the methanol solution was kept at 0° for 4 hr. to cause precipitation of the crystalline methyl *p*-biphenylimidate hydrochloride. This slurry of the imido ester hydrochloride in methanol was added very slowly and cautiously to a solution of 5 g. 95% hydrazine in 200 ml. anhydrous methanol and 100 g. triethylamine. After the addition was complete the mixture was heated on a steam bath until precipitation of the yellow-orange dihydrotetrazine was complete. The precipitate was immediately filtered and washed with distilled water. Recrystallization from toluene yielded 6 g. (53.5%) of yellow-orange plates melting at 160° with resolidification. No attempt was made to obtain analytical data on this compound since it is so readily oxidized by air.

3,6-Di-p-biphenyl-1,2,4,5-tetrazine. To a solution of 5 g. of isoamyl nitrite in 100 ml. 95% ethanol was added 6 g. of 1,2-dihydro-3,6-di-*p*-biphenyl-1,2,4,5-tetrazine. This mixture was refluxed for 4 hr., cooled to room temperature, and filtered. The product was recrystallized from toluene to yield 5 g. (83.5%) of fuchsia needles, m.p. 297° (corr.).

Anal. Calcd. for $C_{26}H_{18}N_4$: C, 80.80; H, 4.70; N, 14.50. Found: C, 80.56; H, 4.56; N, 14.55.

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The Pinacol Rearrangement[1]

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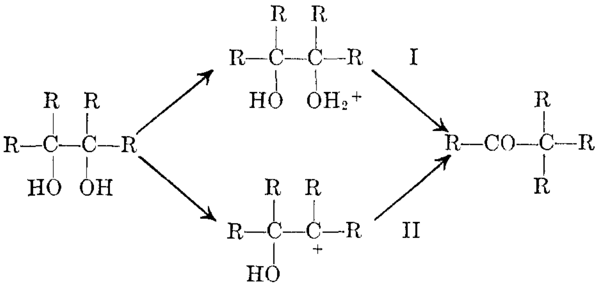
The pinacol rearrangement is acid-catalyzed and could conceivably proceed through an intermediate protonated glycol (I) or the free alkyl cation (II). Duncan and Lynn[3] concluded that for pinacol itself (2,3-dimethyl-2,3-butanediol) the reaction proceeded *via* I. This conclusion was based on the observation that $d \log k = -d\, H_0$. However, the comparison was made using values of H_0 measured at 25° with values of log k measured at 70–150°.



We have now measured the rate of conversion of pinacol to pinacolone from 39–75% sulfuric acid at 25 ± 0.01°. The data, which are summarized in Table I, show that the relation $d \log k = -dH_0$ is precisely followed.

The conclusions of Duncan and Lynn can be extended as follows. The hypothesis has been developed[4] that if the transition state were of type I with the positive charge residing principally on the OH_2 group, d log k would equal $-d\, H_0$. For transition states of type II, d log k would equal $-d\, C_0$. For transition states intermediate between I and II, d log k would have values intermediate between

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[1] Grateful acknowledgment is made of the support of this research by a grant from the Petroleum Research Fund of the AMERICAN CHEMICAL SOCIETY.

[2] Recipient of the Carbide and Carbon Fellowship for 1956–57.

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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]

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[5] Ph.D. Thesis of C. Perizzolo, Pennsylvania State Univ., 1957.

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

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Received January 14, 1957

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.

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