over magnesium sulfate. The resulting solution was passed through a column of neutral alumina (1 × 5 cm.) to give 0.5 g. of white crystalline material. Further recrystallization gave white granules, m.p. 149–150°.[18]

Bis-2-phenyl-1-cyclohexenyl Sulfide.—To 2.63 g. (1.53 mmoles) of 2-phenylcyclohexanone (prepared by oxidation of the 2-phenylcyclohexanol[19]) in 30 ml. of absolute methanol at 0–5° were added hydrogen sulfide and hydrogen chloride gases with stirring. Within 10 min. the solution turned pink, then became cloudy. After 6 hr. the gases were stopped and the flask stoppered and refrigerated for 2 days. The solution was evaporated to dryness at the aspirator under nitrogen, 20 ml. benzene added, and the solution again evaporated to leave 2.6 g. of a waxy white solid. This material was chromatographed on a column of 90 g. of 100-mesh silicic acid made up in *n*-hexane and eluted with cyclohexane–5% ether. The purified product, 1.6 g. (61%) melted at 91–92°, λ_{max} 280 mμ (log ε 3.97).

Anal. Calcd. for $C_{24}H_{26}S$: C, 83.18; H, 7.56; S, 9.25; mol. wt., 346.5. Found: C, 83.18; H, 7.64; S, 9.20; mol. wt. ($CHCl_3$), 346.

Trithiocycloheptanone.—Hydrogen sulfide and hydrogen chloride were passed into a solution of 11.2 g. (0.1 mole) of cycloheptanone in 40 ml. of absolute methanol at 0–5° in a salt–ice bath. The solution began to turn peach colored in a few moments, then clouded. After 3 hr. the gases were stopped, and the flask was stoppered and refrigerated overnight. The resulting white granular solid was collected on a fritted glass funnel, washed with cold methanol, and dried in a vacuum desiccator over sodium hydroxide, yielding 12 g. (94%) of trithiocycloheptanone, m.p. 73–75°. A sample recrystallized for analysis from *n*-hexane melted at 75–76°.

Anal. Calcd. for $(C_7H_{12}S)_3$: C, 65.56; H, 9.44; S, 25.00; mol. wt., 385. Found: C, 65.54; H, 9.35; S, 25.24; mol. wt. ($CHCl_3$), 385.

1,3-Di-*p*-nitrophenyl-2-propanone.—1,3-Diphenyl-2-propanone was nitrated by the method of Manchot and Zahn[11] to give 11 g. of a product melting at 105–110°. This material was dissolved in benzene and chromatographed on a column of 300 g. of alumina in cyclohexane. Elution with benzene returned about half of the material in fractions melting between 120 and 140°. The alumina turned brown on contact with the nitro compound. A fraction melting at 137–139°, 2.4 g., was refractionated on 100 g. of Woelm Grade 1 Neutral alumina. The brown color appeared again when the nitro compound contacted the alumina. Benzene elution gave fractions totaling 1 g. A center fraction melted at 140–141° after three recrystallizations from ethanol.

Anal. Calcd. for $C_{15}H_{12}O_5N_2$: N, 9.33. Found: N, 9.36.

The oxime of this ketone was prepared and found to melt at 155–156° (lit., m.p. 133°).[10]

Anal. Calcd. for $C_{15}H_{13}O_5N_3$: N, 13.33. Found: N, 13.20.

Oxidation with dichromate, permanganate, chromic oxide, and nitric acid gave varying yields of *p*-nitrobenzoic acid plus, in some runs, a lower melting nitro acid which was shown by comparison of its infrared spectrum with that of an authentic sample, and further oxidation to *p*-nitrobenzoic acid, to be *p*-nitrophenylacetic acid. No other isomeric nitro acids were detected among the oxidation products by infrared examination.

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[18] H. Hauptmann and B. Wladislow, *J. Am. Chem. Soc.*, **72**, 707 (1950), report this compound to melt at 149–150.5°.

[19] A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960).

The Synthesis and Properties of Some Simple 1,4-Dihydropyridines

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A simple analogue of the dihydropyridine system present in the coenzyme DPNH, 1,4,4-trimethyl-1,4-dihydropyridine, has been synthesized by the reaction of β,β-dimethylglutaraldehyde and methylamine and characterized by elemental analysis, reduction to a known compound, and n.m.r., infrared, and ultraviolet [$\lambda\lambda_{max}$ 2708 (ε 3200); 2305 (ε 7500) in isooctane] spectra. Its basicity, measured by the method of Hall, was appreciably lower than that expected (pK_a 7.4 *vs.* 10.45 for the corresponding tetrahydropyridine), implying a stabilization energy of *ca.* 4 kcal./mole for the 1,4-dihydropyridine system and suggesting that the 1,4-dihydropyridine ring system is flat. Thus, the stereochemical preference for side A or side B in enzymatic reactions of carbonyl compounds with DPNH must be due to asymmetry of the transition state permitted by the "active sites" of the enzymes concerned. A few reactions of the 1,4,4-trimethyl-1,4-dihydropyridine were studied and some 1-aryl-1,4-dihydropyridines were prepared and characterized.

The dihydropyridine ring system is of considerable interest because of its presence in the coenzyme, diphosphopyridine nucleotide (DPNH). The coenzyme has been firmly established as a 1,4-dihydropyridine.[2–4] Very little reliable information is available on the properties of unsubstituted (or alkyl-substituted) 1,4- or 1,2-dihydropyridines. In this paper, we report the synthesis and properties of 1,4,4-trimethyl-1,4-dihydropyridine as well as a series of 1-aryl-1,4-dihydropyridines. The 4,4-dimethyl grouping prevents facile isomerization to the isomeric 1,2-dihydropyridine.[5]

Results

Synthesis.—The lithium aluminum hydride reduction of the bis-*N*-methylanilide of β,β-dimethylglutaric acid according to Weygand and coworkers[6] yielded a solution of β,β-dimethyl-

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[1] (a) To whom requests for reprints should be addressed at the Department of Chemistry, State University of New York, Long Island Center, Stony Brook, N. Y.; (b) support of the National Institute of Arthritis and Metabolic Diseases through Grant E-1608 is gratefully acknowledged; (c) based on a portion of the Ph.D. thesis of T. S. Sorensen, 1960.

[2] M. Pullman, A. San Pietro, and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954).

[3] (a) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955); (b) R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958).

[4] F. A. Loewus, B. Vennesland, and D. L. Harris, *J. Am. Chem. Soc.*, **77**, 3391 (1955).

[5] *Cf.* discussion in Sec. 2.13, E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

[6] F. Weygand, *et al.*, *Angew. Chem.*, **65**, 525 (1953).

TABLE I

1-(4-X-ARYL)-4,4-DIMETHYL-1,4-DIHYDROPYRIDINES

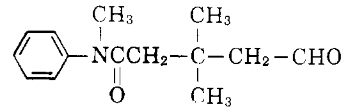
Compound no.	X	Color	M.p., °C.	Theor. H_2 uptake (moles)	% Theor. H_2 absorbed[a]
3	—H	White	35.8–36.7	2	101
4	—Br	White	101–102	3[b]	101
5	—OCH_3	White	62.5–63.3	2	99
6	—NO_2	Or.-red	79.5–80.7	5	99
7	—CN	Pale yel.	78–79	2	94
8	—$N(CH_3)_2$	White	105.8–106.6	2	100

[a] Hydrogenation at atm. press. in 95% ethanol over palladium-charcoal. [b] *p*-Bromoaniline is completely hydrogenolyzed in three minutes over palladium-charcoal in methanol; R. Baltzly and A. P. Phillips, *J. Am. Chem. Soc.*, **68**, 261 (1946).

glutaraldehyde. Reaction of the latter with the appropriate amine produced the desired 1,4-dihydropyridine.

Formation of the diacid dichloride required treatment of the anhydride with phosphorus pentachloride,[7] since thionyl chloride yielded only the anhydride from the acid.

The dialdehyde could not be isolated in pure form and was used as a solution (see Experimental). From one attempt at isolation, a 15% yield of the aldehyde (*1*) was obtained. Its structure rests upon infrared data and the formation of a semicarbazone with the correct analysis.



1

Pure 1,4,4-trimethyl-1,4-dihydropyridine (*2*) has a b.p. 33.5°/8 mm. (133°/740 mm.) and is a colorless liquid with an amine odor. The $n^{25}\mathrm{D}$ 1.4794 and $d_4^{2.35}$ 0.8552 correspond to a molar refraction of 40.82 (calcd. 39.96). In air, *2* is transformed into a red tar but has been stored for several years at 0° under nitrogen.

The properties of the 1-aryl-4,4-dimethyl-1,4-dihydropyridines prepared according to Chart I are summarized in Table I.

The structures of *2* and *3* were proven by hydrogenation to the corresponding piperidines (*9* and *10*). The picrate of 1,4,4-trimethylpiperidine (*9*) produced by hydrogenation was identical to that prepared by the lithium aluminum hydride reduction of *N*-methyl-β,β-dimethylglutarimide.[8] The picrate of the piperidine, 1-phenyl-4,4-dimethylpiperidine (*10*), from *3* was identical to that made from the lower boiling lithium aluminum hydride reduction product of N-phenyl-β,β-dimethylglutarimide.[9] The higher boiling *major* product of reduction was assigned the structure, 5-phenylamino-3,3-dimethylpentanol-1 (*11*), on the basis of elemental analysis, ultraviolet and infrared spectra. Its formation (Chart II) can be rationalized as due to the successful competition of a ring-opening reaction with further attack of hydride on the first product of reduction.

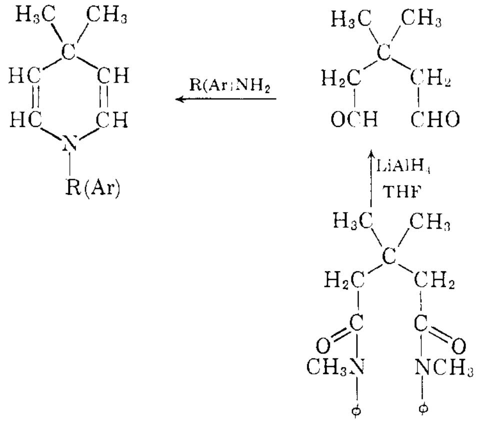


Chart I

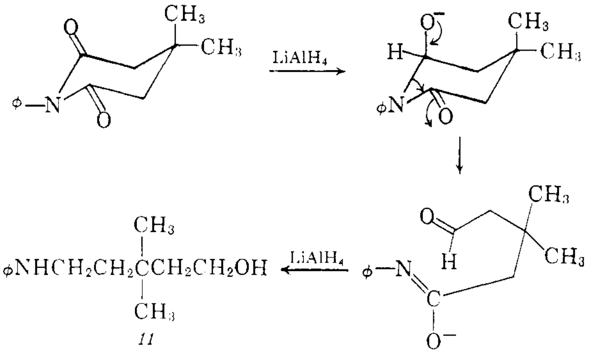


Chart II

The piperidine, (*10*), also was produced on hydrogenation of *4*, while the other piperidines produced by reduction were characterized by elemental analysis, either as the free base or as the picrate.

The use of ammonia in place of methylamine for the last step of Chart I yielded no isolable low boiling product.

Ultraviolet Spectra.—Two maxima are observed in the spectrum of *2*. Addition of excess perchloric acid in acetonitrile to an acetonitrile solution of *2* results in a changed spectrum, ascribable to the formation of the β-protonated species, (*12*).

Spectroscopic data for all of the dihydropyridines are listed in Table II.

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(7) G. Tschudi and H. Schinz, *Helv. Chim. Acta*, **33**, 1865 (1950).

(8) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(9) L. Schmerling and J. P. West, *ibid.*, **74**, 2885 (1952), reported the compound (*10*), but gave no data for solid derivatives.

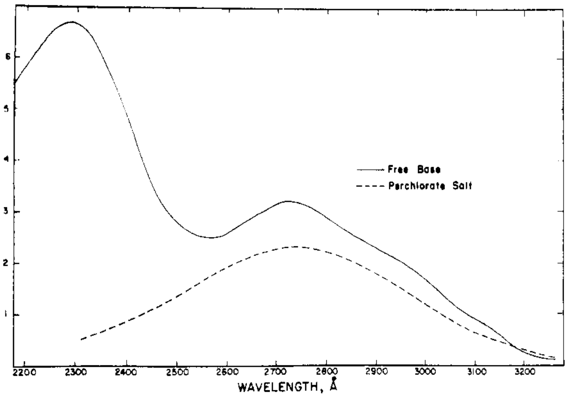
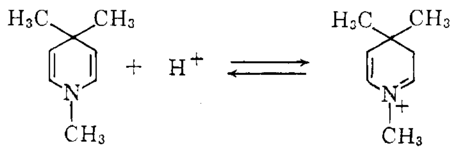


Fig. 1.—The ultraviolet spectrum of 1,4,4-trimethyl-1,4-dihydropyridine (*2*) and its conjugate acid (*12*) in acetonitrile.

TABLE II
ULTRAVIOLET MAXIMA FOR 1-R (OR Ar-)-4,4-DIMETHYL-1,4-DIHYDROPYRIDINES

Compound	Solvent	λ_{max} (ϵ_{max})	λ_{max} (ϵ_{max})
2	Isoöctane	2708 (3200)	2305 (7500)
	CH_3CN	2732 (3200)	2289 (6700)
	CH_3OH	2703 (3000)	2295 (6700)
3	Isoöctane	2865 (23800)[a]	
	95% EtOH	2855 (22700)	
4	Isoöctane	2970 (28100)	
	95% EtOH	2960 (26400)	
5	Cyclohexane	2815 (24400)[b]	
	95% EtOH	2780 (22900)	
6	Cyclohexane	3930 (24600)	2470 (15600)
	95% EtOH	4135 (20700)	2530 (14600)
7	Isoöctane	3325 (28500)	2450 (5000)[c]
	95% EtOH	3350 (30500)	2450 (5000)[c]
8	Cyclohexane	2900 (30400)	
	95% EtOH	2875 (28000)	

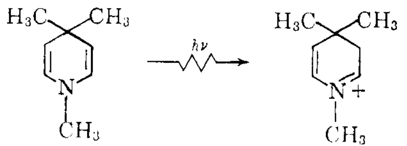
[a] 1-Phenyl-1,4-dihydropyridine has λ_{max} 2860 (ϵ 22,000) (R. D. Kallen, unpublished results) (Karrer, *et al.*, reports the same max, ϵ 100,000). [b] 1-(4-Methoxyphenyl)-1,4-dihydropyridine has λ_{max} 2800 (ϵ 100,000) [P. Karrer, G. Schwarzenbach, and G. E. Utzinger, *Helv. Chim. Acta*, **20**, 72 (1937)]. [c] A third maximum is present at 2250 Å. (ϵ 10,000) in both isoöctane and 95% EtOH.



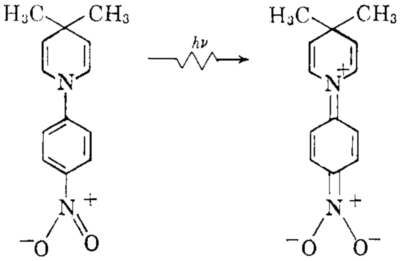
2 *12* (1)

The effect of conjugation on the 1,4-dihydropyridine system is similar to the effect on enamines, expressed as Δ E_T (kcal./mole), the change in transition energy for the longest wave length maximum. In diethyl ether, 1-butenylpiperidine has λ_{max} 2280 (ϵ 7500)[10] while 1-diethylamino-1-hexen-3-one in ethanol has λ_{max} 3070 (ϵ 28,000),[11] corresponding to a Δ E_T of 32.3 kcal./mole. The Δ E_T derived from the spectra of (*2*) and 1-benzyl-3-acetyl-1,4-dihydropyridine in ethanol [λ_{max} 3710 (ϵ 10,400)][12] is 28.5 kcal./mole.

The lack of solvent effect on the spectrum of *2* indicates that the excited state is not appreciably more polar than the ground state, although some charge rearrangement (equation 2) probably occurs. The effect of the *p*-nitro group on the position and solvent sensitivity of the long wave length band of a 1-phenyldihydropyridine suggests that the transition be described as in equation 3.



2 (2)



6 (3)

N,N-Divinylaniline (*13*) possesses an ultraviolet maximum at 2550 Å (ϵ 15,000)[13] with a shoulder at 2800 Å. (ϵ 6000). Interference between the vinyl groups clearly results in a displacement of the maximum to shorter wave lengths than found for the 1,4-dihydropyridine (*3*).

Infrared Spectra.—All of the 1,4-dihydropyridines possess a strong band at 1662-1668 cm.$^{-1}$, lacking in *13*.[13] The spectrum of a thin film of the simple symmetrical compound (*2*) is shown in Fig. 2.

N.m.r. Spectrum of *2*.—The spectrum of *2* is completely consistent with its structure and has peaks centered at 9.11 τ[14] (CH_3—C), 7.36 τ (CH_3—N), *ca.* 5.89 τ (3—CH), and *ca.* 4.49 τ (2—CH). The latter two peaks are complex and fit the pattern expected for an A_2X_2 spectrum[15] (Fig. 3). Data for *2* may be compared with that for 1-methyl-3-carbamido-1,4-dihydropyridine[3b]: 7.22 τ (CH_3—N), *ca.* 5.48 τ (5—CH), *ca.* 4.30 τ (6—CH), and 3.12 τ (2—CH).

Basicity of *2*.—The pK_a of *2* was determined by titration in acetonitrile with perchloric acid according to the method of Hall.[16] Data for the corresponding tetrahydropyridine (*14*) (equation 4)

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(10) N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955).

(11) K. Bowden, E. A. Braude, E. R. H. Jones, and B. Weedon, *J. Chem. Soc.*, 45 (1946).

(12) A. C. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

(13) E. Y. C. Chang and C. C. Price, *ibid.*, **83**, 4650 (1961).

(14) Peaks were measured for the pure liquid at 40 Mc. using a benzene capillary reference and converted to τ-units by the addition of 2.74.

(15) *Cf.* J. D. Roberts, "An Introduction to Spin-Spin Splitting in High Resolution Nuclear Magnetic Resonance," W. A. Benjamin, Inc., New York, N. Y., 1961, p. 100.

(16) H. K. Hall, *J. Phys. Chem.*, **60**, 63 (1956).

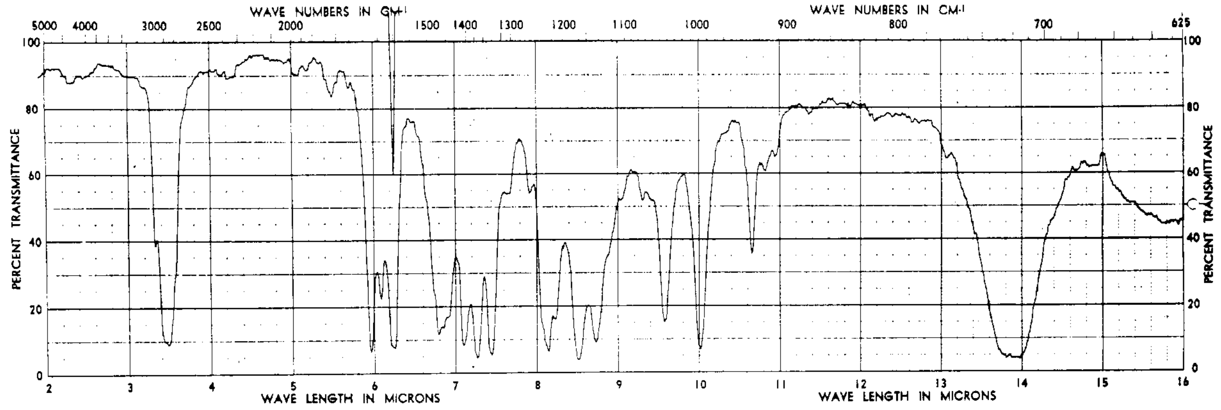


Fig. 2.—The infrared spectrum of *2*.

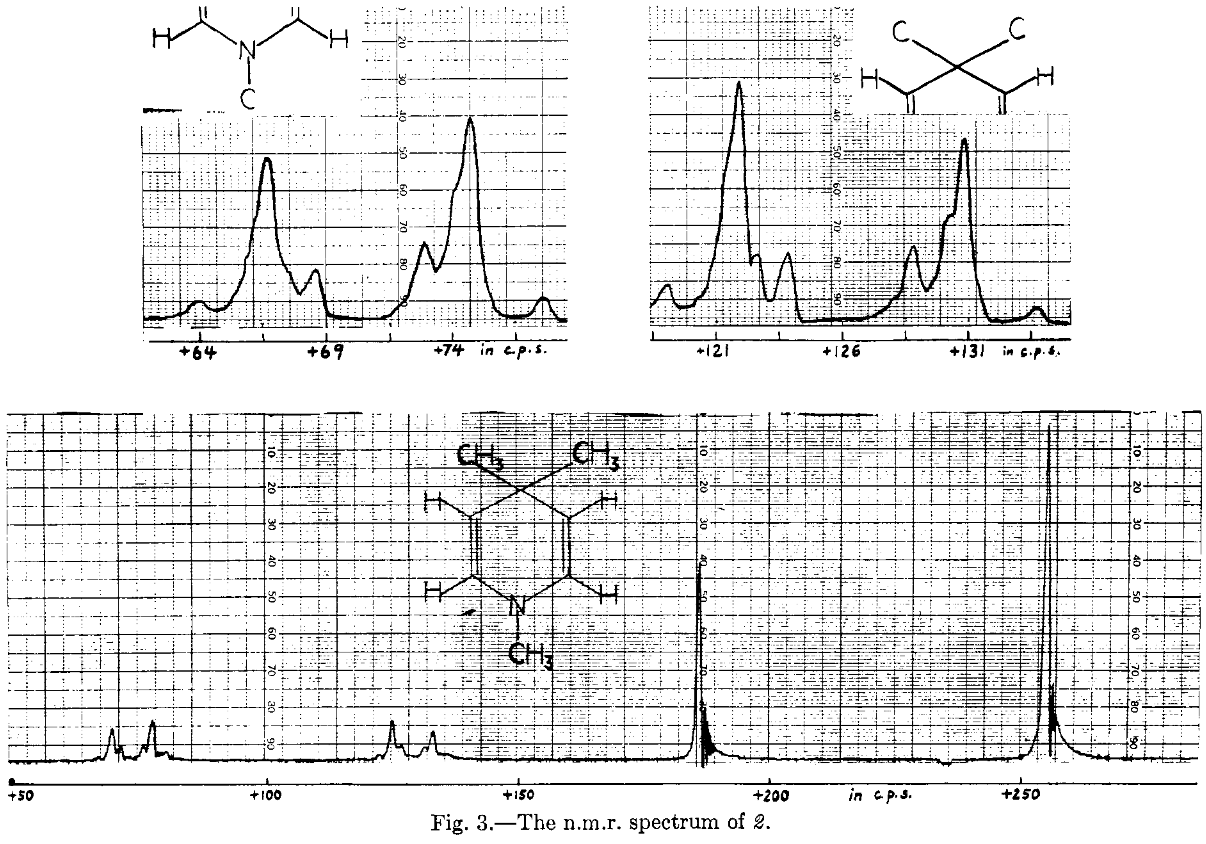
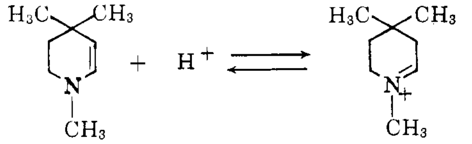


Fig. 3.—The n.m.r. spectrum of *2*.



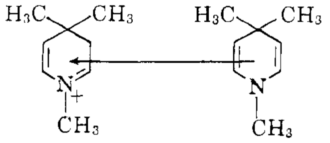
14 *15* (4)

and piperidine (*9*) were also obtained. The reversibility of the protonation of *2* to *12* could readily be demonstrated spectroscopically by the addition of *t*-butylamine to the solution.

The pK_a values found are: (*2*) 7.4, (*14*) 10.45, and (*9*) 10.3.

Complex Formation.—The compounds *2* and *9* interact with maleic anhydride in acetonitrile solution, as shown by the rapid development of long wave length light absorption. Slower subsequent changes indicate chemical changes more complicated than complex formation. For the system *2*–maleic anhydride (each at 0.05 *M*), a distinct new band (D = 1.0) is immediately observed at 3570 Å. It is likely that this new absorption is due to charge-transfer, with the dihydropyridine as donor and maleic anhydride as acceptor.

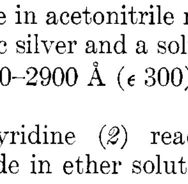
During the titration of *2* with perchloric acid in acetonitrile, a yellow color was noted which reached maximum apparent intensity at the half-equivalence point and disappeared upon complete conversion of *2* into *12*. The complex (*16*) is proposed to explain this observation.



16

Chemical Reactions of *2*.—The 4,4-dimethyl grouping prevents facile oxidation to a pyridine. Silver perchlorate in acetonitrile reacts slowly with *2* to yield metallic silver and a solution having only a shoulder at 2800–2900 Å (ϵ 300) in its ultraviolet spectrum.

The dihydropyridine (*2*) reacts quite slowly with methyl iodide in ether solution at room temperature. After two years, only 28% of an insoluble red powder had separated. An ultraviolet spectrum in acetonitrile revealed the presence of ionic iodide [λ_{max} 2470 Å. (ϵ 9200)].[17] However, the low absorption at 2800 Å. (shoulder, ϵ 600) indicated that only a small proportion of the expected product (*17*) might be present. All attempts to purify the product failed.



17

An immediate reaction occurred between *2* and acetyl perchlorate but the oil isolated was not a 3-acetyl-1,4-dihydropyridine (no ultraviolet absorption past 3100 Å.) and was not further investigated.

Discussion

Simple dihydropyridines constitute a class of compounds which has scarcely been investigated. Only thirteen entries occur in a recent tabulation[18] and it is quite probable that many of these are not dihydropyridines.[19–24]

Bohlmann[25] has described a reactive compound derived from the reaction of lithium aluminum hydride and pyridine in ether, but could only demonstrate that it was readily oxidized. In view of the importance of the dihydropyridine ring system, further work in this area would be desirable.

Stabilization of Dihydropyridine Ring.—The dihydropyridine (*2*) is considerably less basic than might have been expected, after making appropriate corrections for the nature of the substituents attached to nitrogen. From a consideration of the basicity data, it may be estimated that the 1,4-dihydropyridine ring is stabilized *ca.* 4 kcal./mole more than an unstabilized 1,4,5,6-tetrahydropyridine. The size of the stabilization suggests that the 1,4-dihydropyridine ring is *planar*.

The stabilization energy is estimated as follows for a comparison of equations 1 and 4: The conjugate acid of the dihydropyridine (*12*) and the tetrahydropyridine (*14*) are assumed to have stabilization energies equivalent to that of 1,3-cyclohexadiene (1.8 kcal./mole or 1.3 pK_a units).[26,27] The additional bond to an sp^2-orbital present in *2* should reduce basicity by 2.7 pK_a units[28] in comparison with *14*. Thus, *2* should differ in pK_a from *14* by -2.7 units (additional double bond) plus 1.3 units (stabilization of *12* plus 1.3 units (loss of stabilization of *14*, *i.e.*, by about -0.1 pK_a units). The experimental difference in pK_a is 3.05 units, corresponding to the stabilization of *2* by *ca.* 4 kcal./mole. The second double bond present in the 1,4-dihydropyridine has roughly the effect estimated for the double bond of the tetrahydropyridine. The arrangement of six π-electrons present in the 1,4-dihydropyridine thus does not lead to unusual stabilization of the system.

Biochemical Significance.—The small, but appreciable, stabilization energy found for 1,4-dihydropyridines implies a planar structure for the ring, provided that maximum overlap of p-orbitals is responsible for the stabilization. The high absorption coefficients observed for the long wave length bands of many dihydropyridines[5] also suggest a planar arrangement of the ring atoms. We may thus conclude that the preference exhibited by many enzymatic reactions for one side or the other of the dihydropyridine ring in DPNH[29] is *not* the consequence of a non-planar ring[30] but rather a result which demonstrates that only one of two possible transition-state arrangements of enzyme, DPNH, and carbonyl compound actually occurs.

The low basicity found for simple 1,4-dihydro-

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[17] E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3261 (1958), reported λ_{max} 2461 A. (ϵ 12,500) for lithium iodide in acetonitrile.

[18] R. A. Barnes, "Pyridine and Its Derivatives," E. Klingsberg, ed., Interscience Publishers, Inc., New York, N. Y., 1960, Chap. 1, pp. 89–90.

[19] Several "1,2-dihydropyridines," prepared by the distillation of 1-alkylpyridinium iodides with potassium hydroxide, attacked mucous membranes and failed to give identifiable derivatives.[20] The acetone–ammonia condensation product of Hancox[21] probably is 2,4,6,6-tetramethyl-5,6-dihydropyridine.[22] On the basis of its ultraviolet spectrum, a reported 1-phenyl-1,4-dihydropyridine[23] cannot be 1,4-, but might be 1,2 [λ_{max} 3400 (ϵ 12,500)]. No ultraviolet spectroscopic data are mentioned for the 1-benzyldihydropyridine claimed by Patrick[24] which forms a picrate, m.p. 122° (no analysis given; picric acid, m.p. 122°) and is said to yield a pyridine carboxylic acid on oxidation by the red color produced by ferrous sulfate in one fraction of the product.

[20] A. W. Hofmann, *Ber.*, **14**, 1498 (1881).

[21] N. C. Hancox, *Australian J. Chem.*, **6**, 143 (1953).

[22] T. S. Sorensen, unpublished results.

[23] D. Craig, L. Schaefgen, and W. P. Tyler, *J. Am. Chem. Soc.*, **70**, 1624 (1948).

[24] T. M. Patrick, Jr., *ibid.*, **74**, 2984 (1952).

[25] F. Bohlmann, *Chem. Ber.*, **85**, 390 (1952).

[26] G. Wheland, "Resonance in Organic Chemistry," J. Wiley & Sons, Inc., New York, N. Y., 1955, p. 80.

[27] M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, **5**, 166 (1959).

[28] P. Schickedantz and H. Schecter, American Chemical Society Abstracts, Cleveland, Ohio, April, 1960, p. 23–O.

[29] B. Vennesland, *Discussions Faraday Soc.*, **20**, 240 (1955).

[30] B. Vennesland and H. R. Levy, *J. Biol. Chem.*, **228**, 85 (1957).

TABLE III

PROPERTIES OF PIPERIDINES AND PIPERIDINE PICRATES

Hydrogenated compound from	Form	Analyzed as	M.p., °C. anal. sample	Calcd.		Found	
				C	H	C	H
3	Liquid	Picrate	142–143.5	54.54	5.30	54.30	5.41
4	Liquid	Picrate	141–142.5	. . .[a]			
5	Solid	Free base	45–46[b]	76.67	9.65	77.21	10.09
6	Low melting solid	Picrate	134–136.5 (dec.)	52.72	5.35	53.07	5.59
7	Solid	Free base[c]	121–122	78.46	8.46	78.84	8.48
8	Low melting solid	Picrate	173.5–175.5 (dec.)	54.65	5.90	54.94	6.04

[a] Picrate identical to that from *3*. [b] Recrystallized from 80% methanol–water. [c] Recrystallized from petroleum ether (b.p. 60–68°).

pyridines does not lend credence to enzymatic mechanisms (for DPNH) which require the dihydropyridine ring to serve as a base in the oxidation of alcohols to carbonyl compounds.[31]

Experimental

β,β-Dimethylglutaric Anhydride.—Treatment of the diacid *prepared from 5,5-dimethyl-1,3-cyclohexanedione*[32] with an excess of boiling thionyl chloride led to a good yield of anhydride. The latter could also be purchased from the Aldrich Chemical Company, Milwaukee.

β,β-Dimethylglutaric Acid Di-N-methylanilide.—The anhydride was converted into the diacid chloride in 91% yield by heating with equimolar phosphorus pentachloride for 2 hr. at 105°. The chloride distilled at 94–97°/25 mm. (Reported[7] 93–95°/11 mm.) Conversion to the dianilide was effected by reaction with the theoretical quantity of N-methylaniline (4 moles/mole dichloride) in chloroform solution. The resulting solution was washed with 2 *N* hydrochloric acid and 10% sodium bicarbonate, then dried and evaporated to yield 93% crude anilide (recrystallized from ethanol–water), m.p. 104–106°.

Anal. Calcd. for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.75. Found: C, 74.33; H, 7.70.

β,β-Dimethylglutardialdehyde.—Dry dianilide (50 g., 0.148 mole) was dissolved in purified tetrahydrofuran (400 ml., allowed to stand over potassium hydroxide distilled from lithium aluminum hydride) and the solution was cooled to 5°. To this solution was added a solution of lithium aluminum hydride (6.05 g., 0.159 mole) in diethyl ether (120 ml.) with stirring over a period of 1.25 hr. The course of the reaction was followed by preparation of the 2,4-dinitrophenylhydrazone derivative. Yields after 75 min. (start of addition = t_0) were about 20% and rose to 40% after 225 min. The reaction mixture was stirred for 8 hr., followed by *cautious* addition of 80 ml. of concentrated hydrochloric acid (to avoid basic conditions). The two layers were separated. The aqueous portion was saturated with sodium chloride and extracted with three 100-ml. portions of diethyl ether. The combined ether–tetrahydrofuran layers were washed twice with two 200-ml. portions of 3 *N* hydrochloric acid and the acid was extracted with five 100-ml. portions of diethyl ether. All organic extracts were combined and evaporated to a small volume on the steam bath. The residual oil was steam distilled, collecting about 800 ml. of water. The steam distillate was saturated with sodium chloride and extracted with four 300-ml. portions of diethyl ether. This ether solution was utilized in most experiments requiring the dialdehyde since attempts at isolation only yielded polymer. The yields, as measured with the 2,4-dinitrophenylhydrazone derivative in a number of preparations, were: 32–40% undecomposed reaction mixture; 23–27% ether extract before steam distillation; and 13–16% ether solution after steam distillation. The 2,4-dinitrophenylhydrazone derivative was recrystallized several times from dioxane, m.p. 222–223°.

Anal. Calcd. for $C_{19}H_{20}N_8O_8$: C, 46.72; H, 4.13. Found: C, 46.91; H, 4.34. Ultraviolet spectrum in chloroform $\lambda\lambda_{max}$ 3545 Å. (ϵ 38,000), 2580 (ϵ 27000).

From a reaction mixture (0.1 mole of dianilide) worked up by addition of methanol and water, then chloroform extraction, distillation (at 8 mm.) of the residual oil yielded two major fractions, b.p. 97–106° (1.1 g., impure dialdehyde, polymerized shortly after collection) and b.p. 170–187°, 3.5 g. The latter was redistilled, b.p. 175–176°/8 mm., $n^{25}\text{D}$ 1.5218. The infrared spectrum had useful bands at 2756 cm.$^{-1}$ (*weak*) (aldehyde C—H), 1718 cm.$^{-1}$ (*strong*) (aldehyde carbonyl), 1648 cm.$^{-1}$ (*strong*) (aromatic amide carbonyl). The compound yielded a semicarbazone (recrystallized from ethanol–water), m.p. 194–195.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_2$: C, 62.05; H, 7.64. Found: C, 62.41; H, 7.88. The liquid was assigned the structure *1*, the N-methylanilide of 3,3-dimethyl-4-formylbutanoic acid.

1,4,4-Trimethyl-1,4-dihydropyridine (*2*).—Although the dihydropyridine could be prepared from the dialdehyde solution in ether by reaction with methylamine, higher yields of the compound could be obtained by working up the reduction mixture with methylamine. The reduction mixture from 25 g. of dianilide was treated with 4 g. of methylamine in 50 ml. of diethyl ether, followed immediately by 10 ml. of 25% aqueous methylamine. The inorganic precipitate was filtered off and discarded after thorough washing with ether. The combined ether solutions were stirred vigorously for 1.5 hr. with 15 g. anhydrous potassium carbonate. After standing overnight, the solution was filtered, the solvent evaporated, and the residue steam-distilled (600 ml. of water collected). The distillate was saturated with sodium chloride and extracted with three 150-ml. portions of diethyl ether. After drying over magnesium sulfate, the ether was evaporated to yield an oil which was distilled at 8 mm. to give two fractions: (*2*), b.p. 33.5°, 1.85 g. (20%) and N-methylaniline, b.p. 69°, 8.3 g. (53%). Another run gave a 28% yield of *2*. The dihydropyridine was redistilled through a micro helices-packed column under nitrogen to yield pure 1,4,4-trimethyl-1,4-dihydropyridine, b.p. 77°/84 mm., $n^{25}\text{D}$ 1.4794, $d_4^{23.5}$ 0.8552. The compound must be stored under nitrogen in the refrigerator.

Hydrogenation of a sample of *2* in ethanol (0.103 g.) over palladium-charcoal was complete in 20 min. After filtering off the catalyst, an ethanol solution of picric acid yielded 54% (158 mg.) of 1,4,4-trimethylpiperidine picrate, recrystallized from 95% ethanol, m.p. 226–228°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.20; H, 5.66; Found: C, 46.93; H, 5.26.

Authentic picrate had m.p. 228–230° (reported[8] 231–232°)

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(31) *Cf.*, for example, M. Dixon and T. C. Webb, "The Enzymes," Longmans, London, 1958.

(32) W. T. Smith and G. L. McLeod, *Org. Syn.*, **31**, 40 (1951).

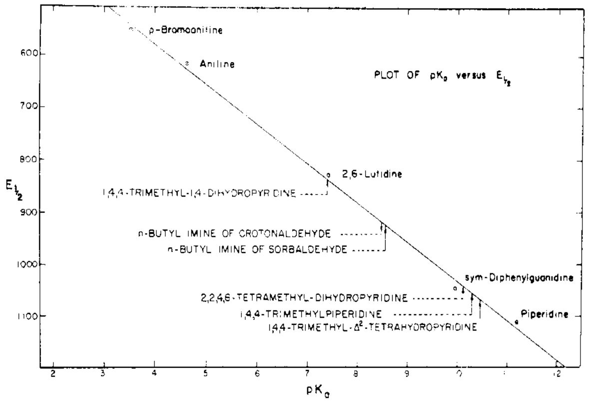

Fig. 4.—A plot of $E_{1/2}$ values (millivolt readings at half-neutralization) for a series of bases of known pK_a. The positions of bases of unknown pK_a are indicated.

TABLE IV
$E_{1/2}$ VALUES FOR BASES

Compound	$E_{1/2}$	pK_a reported[16]
1,4,4-Trimethylpiperidine (*9*)	1065, 1067, 1072	
2	842, 830, 834	
14	1068, 1068	
2,4,6,6-Tetramethyl-5,6-dihydropyridine[21],[a]	1045, 1042	
n-Butylimine of crotonaldehyde	924, 923	
n-Butylimine of sorbaldehyde	918, 918	
p-Bromoaniline	546, 550	3.91
Aniline	612, 613	4.60
2,6-Lutidine	827, 826	7.42
sym-Diphenylguanidine	1050, 1046	10.00
Piperidine	1115, 1110	11.20

[a] Structure assigned on the basis of basicity and ultraviolet spectrum (ref. 22).

and gave no m.p. depression with picrate derived from the hydrogenation product of *2*.

1-Aryl-1,4-dihydropyridines.—A typical procedure for the case in which 1-aryl is 1-(4-methoxyphenyl)- is described. Freshly distilled *p*-anisidine (0.97 g., 0.0079 mole, m.p. 60–63°) in 50 ml. of diethyl ether was added to a suspension of 5 g. of anhydrous potassium carbonate in a solution of β,β-dimethylgutardialdehyde (*ca.* 1.01 g., 0.0078 mole) in diethyl ether. After stirring for 2.4 hr. and standing overnight, the solution had only the ultraviolet absorption expected for *p*-anisidine. The solution was filtered and evaporated to a viscous oil (λ_{max} 2710 Å., EtOH–not the dihydropyridine). The oil was taken up in benzene and refluxed for 2 hr., the benzene evaporated, and the semisolid residue taken up in petroleum ether (b.p. 60–68°) and chromatographed on 50 g. of Woelm neutral alumina, activity grade 1. Elution with petroleum ether (b.p. 60–68°) gave 1.03 g. of white solid, with 20% benzene–petroleum ether 0.15 g. of white solid, and with 50% benzene–petroleum ether 0.03 g. of white solid. Benzene and diethyl ether eluted small quantities of yellow oil while methanol eluted 1.06 g. of dark brown tar. The white solids were combined (73% yield), sublimed twice, and recrystallized from pentane to yield white plates of *5*, m.p. 62.5–63.3°.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.96; Found: C, 77.83; H, 7.82.

The other aryldihydropyridines were purified as follows (yield): *3* (67%), sublimed three times.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16. Found: C, 84.30; H, 7.97.

4 (73%), sublimed at 0.15 mm. and 50°, recrystallized several times from pentane.

Anal. Calcd. for $C_{13}H_{14}NBr$: C, 59.10; H, 5.34. Found: C, 59.28; H, 5.50.

6 (83%), recrystallized from petroleum ether (60–68°).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 67.81; H, 6.13. Found: C, 68.10; H, 6.10.

7 (96%), sublimed at 0.1 mm. and 60°, then recrystallized five times from pentane.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71, Found: C, 80.33, H, 6.85.

8 (> 95%), recrystallized four times from pentane.

Hydrogenation of the dihydropyridines to piperidines (see Results) was carried out with 10% palladium on carbon. The piperidines were analyzed as the free base or as picrates.

β,β-Dimethyl-N-phenylglutarimide.—Aniline (33.52 g., 0.36 mole) was added to a solution of β,β-dimethylglutaric anhydride (50 g., 0.35 mole) in 200 ml. of dry benzene. The solution became hot, was allowed to stand for 6 hr., and the solvent evaporated under reduced pressure to yield β,β-dimethylglutaranilic acid, 80 g. (97%), m.p. 127–132.5° (recrystallized from acetone to a pure sample, m.p. 134.5–136.5°).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.40; H, 7.33. The acid was slowly heated in a 100-ml. flask to 250°, and 5 ml. of water (0.27 mole) was collected. The product was flash-distilled at 10 mm. to yield 62.5 g. (85%) of greenish-yellow solid, m.p. 157–159°. A portion was recrystallized several times from benzene to give long white needles of the imide, m.p. 160–161°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 71.94, H, 7.04.

4,4-Dimethyl-1-phenylpiperidine (*10*) **and 3,3-Dimethyl-5-phenylaminopentanol-1** (*11*).—A solution of the imide (25 g., 0.115 mole) in 160 ml. of tetrahydrofuran was added over 1.5 hr. to a solution of 12.2 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran. After addition, the reaction mixture was refluxed for 12 hr. with stirring. After removal of 250 ml. of tetrahydrofuran by distillation, 10% methanol-diethyl ether (250 ml.) was cautiously added to decompose unchanged hydride, 200 ml. of diethyl ether and 1000 ml. of water were added, the whole was shaken and the ether separated. The aqueous layer was extracted with 200 ml. of diethyl ether, and the combined ether extracts were extracted with two 200-ml. portions of 3 *N* hydrochloric acid. The combined acid layers were made basic with solid potassium hydroxide and extracted with two 200-ml. portions of diethyl ether. After drying over potassium carbonate, the ether was evaporated and the residue was distilled at 0.3 mm., yielding four fractions: (1) 90–95°, 0.89 g.; (2) 95–105°, 2.66 g.; (3) 105–150°, 2.30 g.; and (4) 150–154°, 13.43 g. The first two fractions were redistilled to yield pure 1-phenyl-4,4-dimethylpiperidine (*10*), b.p. 106°/0.8 mm., $n^{25}D$ 1.5402 (reported[9] b.p. 117–118°/3 mm., $n^{25}D$ 1.5434). The highest boiling fraction was redistilled to give 3,3-dimethyl-5-phenylaminopentanol-1 (*11*), b.p. 140–142.5°/0.1 mm., $n^{25}D$ 1.5432.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21. Found: C, 74.99, 75.21; H, 9.95, 10.22. Compound *10* formed a picrate, m.p. 144°. Compound *11* has no carbonyl band in the infrared, but has a band at 3279 cm.$^{-1}$ (N—H or O—H). The ultraviolet spectrum in methanol had $\lambda\lambda_{max}$ 2470 (ϵ13,900) and 2980 Å. (ϵ 1900) which may be compared withthat of N-methylaniline, $\lambda\lambda_{max}$ 2440 Å. (ϵ 12,000) and 2950 Å, (ϵ 2000). Attempts to prepare a solid derivative with 3,5-dinitrobenzoyl chloride led only to oily products.

1,4,4-Trimethyl-1,4,5,6-tetrahydropyridine (*14*).—Prepared by the method of Leonard and Hauck,[8] b.p. 137–140°/740 mm., $n^{27.5}D$ 1.4510.

1,4,4-Trimethylpiperidine (*9*).—Prepared by the method of Leorard and Hauck,[8] b.p. 137–140°/738 mm. from the N-methylanilide of β,β-dimethylglutaric acid, m.p. 59–61°.[8]

Basicity measurements.—The method developed by Hall[16] was used. Acetonitrile was refluxed over phosphorus pentoxide and distilled. Perchloric acid (60%, 8.42 g.) was made up to 100 ml. with dioxane purified by distillation and passage through an alumina column (concn. *ca.* 0.5 *M*). The acid was standardized against pure 1,4,4-trimethylpiperidine. Titrations were carried out in a 5-cm.-diameter vessel (height *ca.* 5 cm.), capacity, 75 ml., and fitted with a Teflon cover. Titrations were followed with a Beckman Zeromatic pH meter with a glass electrode (no. 41263). Solutions were stirred with a Teflon covered magnet and acid was added from a 1-ml. Gilmont microburet.

Procedure.—About 0.0005 mole of amine was dissolved in 50 ml. of acetonitrile and titrated with perchloric acid, using electrodes standardized against buffer, pH 7 (then rinsed and dried) and using 1000 mv. as the starting point. Stirring was maintained but did not affect the readings. Readings were taken every 0.005 ml. near the end point. The millivolt readings were plotted against the volume of acid and the $E_{1/2}$ values recorded. ($E_{1/2}$ was the millivolt reading at half-neutralization.) The $E_{1/2}$ values were then plotted against known pK_a values. The new pK_a values were read from the plot. The $E_{1/2}$ values are recorded in Table IV.

Nucleophilic Reactions of Morpholine with the Benzoyl Halides. The Presence of an Element Effect[1]

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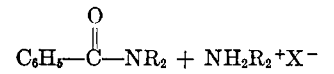
The rate constants for the reactions of morpholine with benzoyl fluoride, chloride, bromide, and iodide have been determined in cyclohexane solution by spectrophotometric means. All the reactions obey second-order kinetics. The kinetic constants for these four reactions differ widely, that for benzoyl iodide being about 10^5 times faster than that for benzoyl fluoride. These results are compared to those for aromatic nucleophilic substitution reactions of aryl halides with amines in which it is found that the halogen atom has relatively little effect on the rate. It is concluded that differences in resonance stabilization of the reactant acid halides and differences in the partitioning of the tetrahedral addition intermediate account for the large differences in rate found here.

Acid chlorides may react with nucleophiles either through an S_N1 reaction with the intermediacy of an acylium ion or *via* a reaction which can be described either as an S_N2 reaction or a carbonyl addition reaction. In highly polar solvents and in the absence of strong nucleophiles, the first mechanism predominates, whereas in nonpolar solvents and in the presence of strong nucleophiles the latter mechanism predominates. The present study is directed to the elucidation of some of the details of the latter (bimolecular) process.

Examination of the bimolecular reaction of benzoyl halides with various nucleophiles has established many of the characteristics of these reactions. The relative rates of solvolysis of various *para*-substituted benzoyl chlorides in 40% ethanol–60% diethyl ether show that electron-attracting groups accelerate the reaction.[3,4] Furthermore, the bimolecular reactions of a series of substituted benzoyl chlorides with aniline in benzene also shows the same substituent effect (Hammett rho = 1.2).[5-7] The relative rates of reaction of a series of substituted anilines with benzoyl chloride in benzene solution show that the reaction is also proportional to the basicity of the amine[5,8] [Hammett rho = 2.73[6] (3.12)[7]]. Furthermore, the rate of this reaction is dependent on the polarity of the solvent in benzene–nitrobenzene mixtures, indicating that the transition state of the amine–acid chloride reaction is more polar than the reactants.[9,10] Thus the kinetic importance of nucleophilic attack on the carbonyl carbon atom is established for this reaction.

Presumably, the bimolecular reaction of an amine with an acid chloride proceeds through a mechanism similar to that proposed for the saponification of an ester, that is, the addition of the amine to the carbonyl group of the acid chloride leading to a tetrahedral intermediate which can either decompose to products or revert to reactants. The most pertinent evidence concerning such a mechanism is the observation that benzoyl chloride and *p*-toluyl chloride undergo isotopic oxygen exchange concur-



$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}{-}X + R_2NH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_6H_5{-}\underset{\underset{\displaystyle +NHR_2}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}{-}X \xrightarrow[NHR_2]{k_3} C_6H_5{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NR_2 + NH_2R_2{}^+X^- \quad (1)$$

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[4] In 50% water–50% acetone, both electron-attracting and electron-withdrawing groups accelerate the reaction, indicating that bond-breaking is starting to assume importance. Therefore, the present experiments were carried out in the nonpolar solvent cyclohexane.

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