TABLE I

KINETICS OF THE CONVERSION OF α-N-ACETYL-L-TYROSINHYDRAZIDE TO 1-ACETYL-2-(L-TYROSYL)-HYDRAZINE AT 96°

Time (min.)	Potentiometric titration [S]$_t$[a]	ln [S]$_t$	Enzyme assay [S]$_t$[a]	ln [S]$_t$	v_0[c]
0	(5.08)	−2.98	(5.08)	−2.98	...
8	3.73	−3.29	3.85	−3.26	0.276
15	3.09	−3.48	3.13	−3.46	.191
30	2.09	−3.87	2.23	−3.80	.141
45	1.32	−4.33	1.74	−4.05	.123
60	0.89	−4.72	1.85	−3.99	.126
75	0.67	−5.01	1.60	−4.14	.119
90	..	....	1.54	−4.17	.117
105	0.34	−5.68	..	....	.116
122	.11	−6.81	1.13	−4.48	.106
150	.06	−7.42	..	....	.119
180	.00	....	..	....	.104
	k = 0.028 min.$^{-1}$ (0-98% conv).		k = 0.025 min.$^{-1}$ (0-66% conv.)		

[a] Concn. of α-N-acetyl-L-tyrosinhydrazide. Units of 10^{-2} M. [c] Units of 10^{-4} M/min.

solution in a flask equipped with reflux condenser was placed in a steam-bath (t, 95°) for 4 hr., then cooled in an ice-bath. An aliquot (0.4 ml.) of the crude reaction mixture was assayed for inhibitor as described previously. The estimate of the concentration of inhibitor was made in an approximate manner by assuming that L-tyrosinhydrazide functioned as a competitive inhibitor in this system. A value of v_0 = 0.653 × 10^{-4} M min.$^{-1}$ was obtained, from which K_S' = 0.148 M. The assumption of a value for K_I = 8.3 × 10^{-5} M gave [I] = 0.113 × 10^{-3} M, equal to a maximum conversion of 5.6% since the sum of the concentrations of L-tyrosinhydrazide and inhibitor equaled 0.002 M in the system being assayed.

Attempted Reaction of L-Tyrosine with Acethydrazide and α-Chymotrypsin.—Incubation of L-tyrosine with enzyme and acethydrazide at 25° for 1 hr. at pH 5.8 and at pH 7.9 did not result in the appearance of a species of low K_I, *i.e.*, 1-acetyl-2-(L-tyrosyl)-hydrazine.

Evaluation of 1-Acetyl-2-(L-tyrosyl)-hydrazine as an Inhibitor of the α-Chymotrypsin Catalyzed Hydrolysis of Methyl Acetyl-L-valinate.—The kinetic constants K_S' = $K_S(1 + [I]/K_I)$ and k_3' were determined in aqueous solutions at 25.0°, pH 7.90 and 0.10 M in sodium chloride with [E] = 0.1464 mg. protein-nitrogen per ml., [I] = 0.227 and 0.454 × 10^{-3} M and $[S]_0$ = 15 to 140 × 10^{-3} M. The inhibition was not totally competitive but was of a mixed type. The data were evaluated by a procedure to be described in a separate communication to give a value of $K_I = 7.4 \pm 0.3 \times 10^{-5}$ M.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF WISCONSIN, MADISON 6, WISC., AND CHEMISCHES LABORATORIUM DER UNIVERSITÄT, FREIBURG I. BREISGAU, GERMANY]

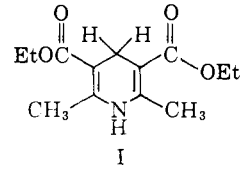
The Effect of Solvent on Spectra. VII. The "Methyl Effect" in the Spectra of Dihydropyridines

BY DIETER HOFMANN, EDWARD M. KOSOWER[1a] AND KURT WALLENFELS

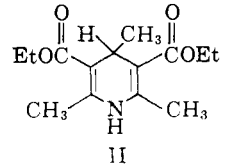
RECEIVED SEPTEMBER 6, 1960

The puzzling difference in ultraviolet maximum between the "Hantzsch compounds," 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (λ_{max} 3690 Å.) and 2,4,6-trimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (λ_{max} 3490 Å.) is now explained as resulting from the relative increase in non-bonded repulsion between the carbethoxy group and the 4-methyl group in the excited state as compared with the compound lacking the 4-methyl group. The explanation is supported by the decrease in the effect when the carbethoxy groups are replaced by cyano groups in which the charge increment in the excited state is farther away from the 4-methyl group. The validity of the comparisons between the carbethoxy and cyano-substituted dihydropyridines is established by the parallelism in solvent effects upon the observed transitions. Data for the model compounds ethyl β-aminocrotonate and β-aminocrotononitrile are also reported.

The spectra of dihydropyridines are of considerable interest and importance because of the necessity for understanding in great detail the spectroscopic behavior of reduced diphosphopyridine nucleotide (DPNH).[1b] It was puzzling to find that replacement of one of the hydrogens at the 4-position in the "Hantzsch compound" 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (I) with a methyl group (II) resulted in a shift of the absorption maximum to *shorter* wave lengths by 200 Å.[2] Since the methyl group is not attached directly to the conjugated system, the displacement of the maximum should have been small, all alkyl groups being approximately equivalent in their intrinsic electron-donating ability.[3,4] Examination of models of I and II indicated little serious steric hindrance in the ground state, but suggested the possibility that acquisition of charge by the oxygen in the carbethoxy group of the excited state (I* and II*) might be opposed by the methyl group on the 4-position.



I



II

The s-*trans* arrangement indicated in I and II (and I* and II*) is thought to be the most likely on the basis of the examination of models since there is appreciably more interference between the 2-

(1) (a) To whom requests for reprints should be addressed at Department of Chemistry, State University of New York, Long Island Center, Oyster Bay, N. Y. (b) The authors wish to acknowledge the generous support of the National Institutes of Allergy and Infectious Diseases through grant E-1608.

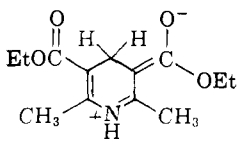
(2) This circumstance was called to our attention some years ago by Professor F. H. Westheimer, Harvard University.

(3) E. M. Kosower and J. A. Skorcz, *J. Am. Chem. Soc.*, **82**, 2195 (1960).

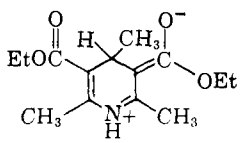
(4) A penetrating inquiry into the "Baker–Nathan order" for hyperconjugation, in which p-methyl groups on benzyl chloride systems are more effective than p-t-butyl groups in raising the rate over that for the unsubstituted system has been carried out by R. A. Clement, J. N. Naghizadeh and M. R. Rice, *ibid.*, **82**, 2449 (1960). Their results indicate that solvation of the solvolyzing molecule may differ sufficiently from the p-methyl case to the p-t-butyl that the observed rate in solution may indeed be slightly augmented for the former. However, approximate "intrinsic reactivities" (*i.e.*, corrected for solvation) are very close to being the same and, thus, intrinsic electron-supply by alkyl groups varies very little with the nature of the alkyl group, a conclusion in complete accord with that found for the effect of alkyl groups upon the position of the pyridinium iodide charge-transfer band.[5]

(and 6)-methyl and the carbonyl oxygen than between these methyls and the ether oxygen of the ester group. To test the hypothesis, we replaced the carbethoxy group with another group of a different geometry, such that the charge generated in the excited state would be localized on an atom further away from the methyl group. The group which best fitted our requirements was the cyano group.

In the present instance, we utilized the effect of solvent on the spectra of the compounds under study to ensure that similar transitions were involved. In the qualitative manner desired, it was hoped that solvent effects would be parallel for compounds with and without the 4-methyl group, allowing us to concentrate our attention on the matter of most significance, the difference in transition energies.



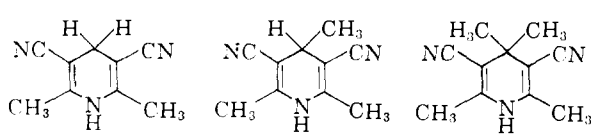
I*



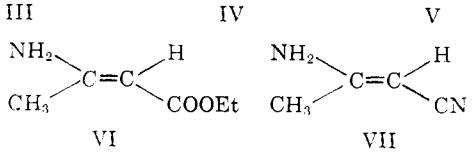
II*

Results

In addition to the dicyano-dihydropyridines III, IV and V, the simple analogs of the two series involved, VI and VII, were also prepared and examined spectroscopically in a number of solvents. The spectra of I, II and V were measured in acetonitrile and methanol, while those of III and IV were taken in water as well as these two solvents. The greater range of solubility of ethyl β-aminocrotonate (VI) and β-aminocrotononitrile (VII) permitted as well the use of isoöctane in the former case and 2,2,3,3-tetrafluoropropanol (TFP) in the latter case as spectroscopic solvents. The



III IV V



VI VII

data obtained for the longest wave length band are collected in Table I and plotted against **Z**[5] in Figs. 1 (I, II, III, IV) and 2 (VI and VII). It may be noted by referring to Table I that V, 4,4-dimethyl-3,5-dicyano-1,4-dihydropyridine, has almost the same spectroscopic properties as the 4-methyl derivative IV so that it is not included in the data shown in Fig. 1.

All 1,4-dihydropyridines reported here possess a second maximum in the region of 2200 Å. Data for these maxima (which are less sensitive to the solvent than the long wave length band) are given in Table II.

(5) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958).

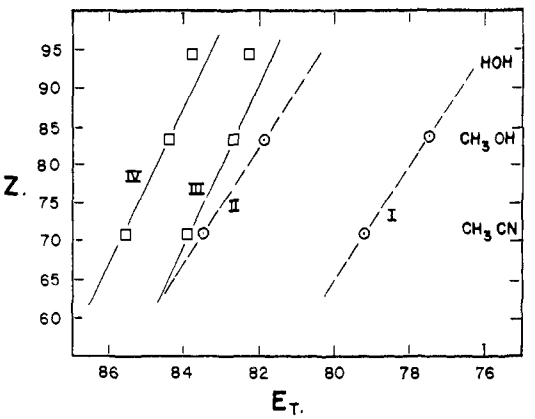
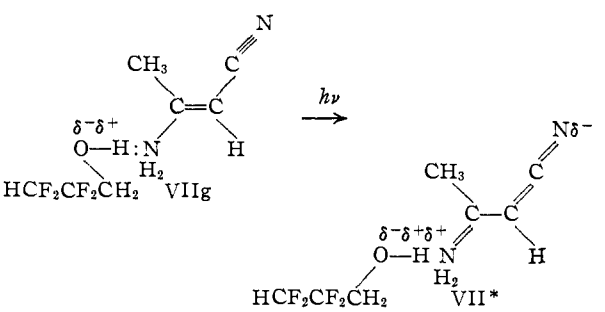


Fig. 1.—Transition energies for the long wave length band of 1,4-dihydropyridines plotted against **Z**: I, 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine; II, 2,4,6-trimethyl-3,5-dicarbethoxy-1,4-dihydropyridine; III, 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridine; IV, 2,4,6-trimethyl-3,5-dicyano-1,4-dihydropyridine. The lines indicated are arbitrarily drawn through the methanol and acetonitrile points so that comparison between all compounds is facilitated.

Discussion

The simple analogs β-aminocrotononitrile (VII) and ethyl β-aminocrotonate (VI) present some interesting spectroscopic features. The nitrile group is much less effective than the carbethoxy group in promoting a $\pi \rightarrow \pi^*$-transition, although there is a little doubt that a cyano group is a more effective electron-attractor.[6] With the exception of VII in TFP, it may be seen in Fig. 2 that the solvent sensitivities of the transitions are similar and relatively low (*ca.* −0.10 for *m* in the expression $E_T = mZ + b$, about half of that found for α,β-unsaturated ketones). The anomalous position of the point for TFP is probably due to the acidity of the solvent[7] which can hydrogen bond to the amino group in the ground state so strongly that the transition energy is raised (VIIg → VII*). The geometry of VI and VII are presumed



VIIg VII*

to be *trans*, although there might well be a solvent effect upon the *cis–trans* equilibrium.[8,9]

(6) E. M. Kosower, J. A. Skorcz, W. M. Schwarz, Jr., and J. W. Patton, *ibid.*, **82**, 2188 (1960). The referee has pointed out that σ_R (CN) is only 0.07 while σ_R(COOEt) is 0.20.

(7) pK_a is *ca.* 11.4 ("Fluoroalcohols," Organic Chemicals Department, E. I. du Pont de Nemours and Co., Inc., Wilmington, Del., 1956).

(8) E. M. Kosower and G.-S. Wu, *J. Am. Chem. Soc.*, **83**, 3142 (1961).

(9) E. M. Kosower, G.-S. Wu and T. S. Sorensen, *ibid.*, **83**, 3147 (1961).

TABLE I

SPECTROSCOPIC DATA FOR DIHYDROPYRIDINES

Compound	Solvent (Z): Isoöctane (60.1) λ_{max}, Å. (ϵ_{max})[b]	Acetonitrile (71.3) λ_{max}, Å. (ϵ_{max})[b]	Methanol (83.6) λ_{max}, Å. (ϵ_{max})[b]	Water (94.6) λ_{max}, Å. (ϵ_{max})[b]
I [E_T[c]]		3610 (6800) [79.20]	3690 (6100) [77.48]	
II [E_T[c]]		3425 (8600) [83.47]	3490 (8600) [81.92]	
III [E_T[c]]		3400 (5800) [84.10]	3458 (6300) [82.68]	3475 (6300) [82.27]
IV [E_T[c]]		3341 (6100) [85.57]	3388 (6500) [84.39]	3410 (7100) [83.84]
V [E_T[c]]		3343 (6700) [85.52]	3380 (7100) [84.59]	
VI [E_T[c]]	2658 (15000) [107.56]	2710 (17400) [105.50]	2743 (14400) [104.23]	2762 (14500) [103.50]
VII [E_T[c]]	2540[a] (16500) [112.56]	2545 (16600) [112.34]	2576 (10900) [110.99]	2580 (8800)[d] [110.81]

[a] In 2,2,3,3-tetrafluoropropanol (96.3); Z-value based on cyclohexanone, ref. 8. [b] Maxima between 3000 and 4000 Å. are ±10 Å. while those between 2400 and 2800 Å. are ±5–6 Å., except for β-aminocrotononitrile in water which is ±10 Å. [c] Transition energies in kcal./mole. [d] Optical density decreased with time in water, and the ε given is a minimum value; $t_{1/2}$ *ca.* 7 minutes.

TABLE II

SHORT WAVE LENGTH ABSORPTION BY DIHYDROPYRIDINES

Compound	Solvent (Z): Acetonitrile (71.3) λ_{max}, Å. (ϵ_{max})[a]	Methanol (83.6) λ_{max}, Å. (ϵ_{max})[a]	Water (94.6) λ_{max}, Å. (ϵ_{max})[a]
I [E_T[b]]	2270 (15700) [125.95]	2290 (14000) [124.85]	
II [E_T[b]]	2280 (15700) [125.39]	2325 (18300) [122.97]	
III [E_T[b]]	2145 (24300) [133.30]	2157 (27200) [132.55]	2190 (24400) [130.55]
IV [E_T[b]]	2157 (25100) [132.55]	2163 (26500) [132.21]	2187 (26900) [130.73]
V [E_T[b]]	2178 (24100) [131.27]	2180 (25800) [131.15]	
	2140 (24100) [133.60]	2140 (25800) [133.60]	

[a] All maxima are ±10 Å., except for the maxima for III and IV in water, which are ±15 Å. [b] Transition energies in kcal./mole.

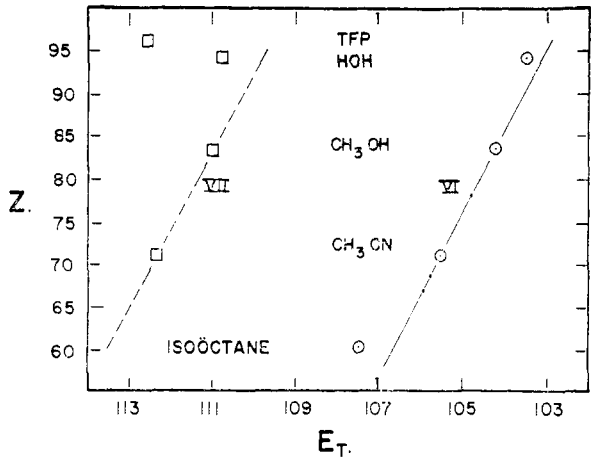


Fig. 2.—Transition energies against Z for VI ethyl β-aminocrotonate and VII β-aminocrotononitrile. As in Fig. 1, the lines are drawn *arbitrarily* through the points for the solvents, acetonitrile and methanol.

The effect of solvent on the spectra of the dicarbethoxy-dihydropyridines was the same for the compound with the methyl group in the 4-position (II) as for the compound lacking the methyl group (I). Solvent change produced a somewhat smaller change in the spectra of the dicyanodihydropyridines (III, IV and V) but the parallelism between the plots against Z was a clear indication that the same electronic transition was being observed in all cases and that the methyl group (or groups) at the 4-position made no qualitative change in that transition. The similarity in oscillator strengths, f_0, also served to show that the same electronic transition was involved.

In two solvents, the "methyl effect" on the dicarbethoxy derivatives I and II is 4.4 ± 0.2 kcal./mole; that is, the methyl group at the 4-position raises the transition energy by that amount. In contrast, the "methyl effect" in the dicyano series is only 1.6 ± 0.2 kcal./mole, with the excited states III* and IV* resulting from the transition. The sharp reduction in the "methyl effect" by the replacement of carbethoxy groups with cyano groups constitutes support for the hypothesis proposed in the Introduction.

Before the nature of the "methyl effect" can be considered, it is necessary to point out that the 1,4-dihydropyridine ring is probably planar. A nonplanar arrangement has been suggested to explain the selectivity of hydrogen transfer from DPNH in enzymatic reactions,[10] but this seems most unlikely on two grounds. First, the occurrence of an intense long wave length transition in 1,4-dihydropyridines at much longer wave lengths than the longest wave length transition in conjugated tetrahydropyridines implies full conjugation of the additional double bond with the nitrogen and the double bond already present. Second, the considerably reduced basicity of 1,4-dihydropyridines in comparison with tetrahydropyridines and piperidines suggests appreciable stabilization energy for the 1,4-dihydropyridines, again implying that the two double bonds and the p-orbital of the nitrogen are in conjugation.[11]

The factors which give rise to the "methyl effect" will be present in many molecules; it is instructive to examine appropriate models closely in *both ground and excited states*. The dicarbethoxy

(10) B. Vennesland and H. R. Levy, *J. Biol. Chem.*, **228**, 85 (1957); *cf.* also F. A. Loewus, H. R. Levy and B. Vennesland, *ibid.*, **223**, 589 (1956).

(11) T. S. Sorensen, unpublished results on 1,4,4-trimethyl-1,4-dihydropyridine and related compounds, in which the considerably decreased basicity is shown to be far more than one could expect for the attachment of sp^2-orbitals to the nitrogen.

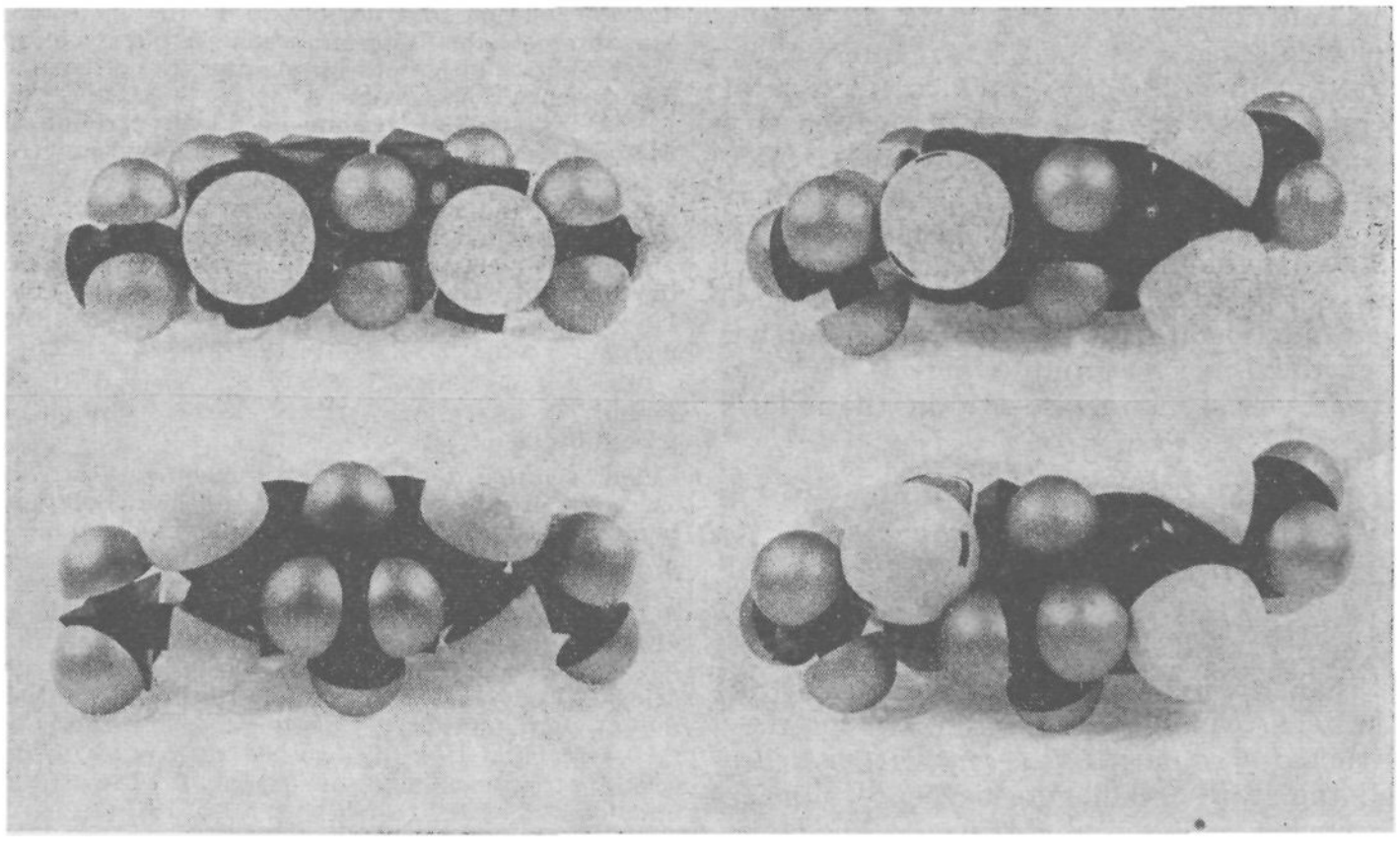


Fig. 3.—The states are indicated for I and II; (a) upper left, ground state of I; (b) upper right, excited state of I; (c) lower left, ground state of II; (d) lower right, excited state of II.

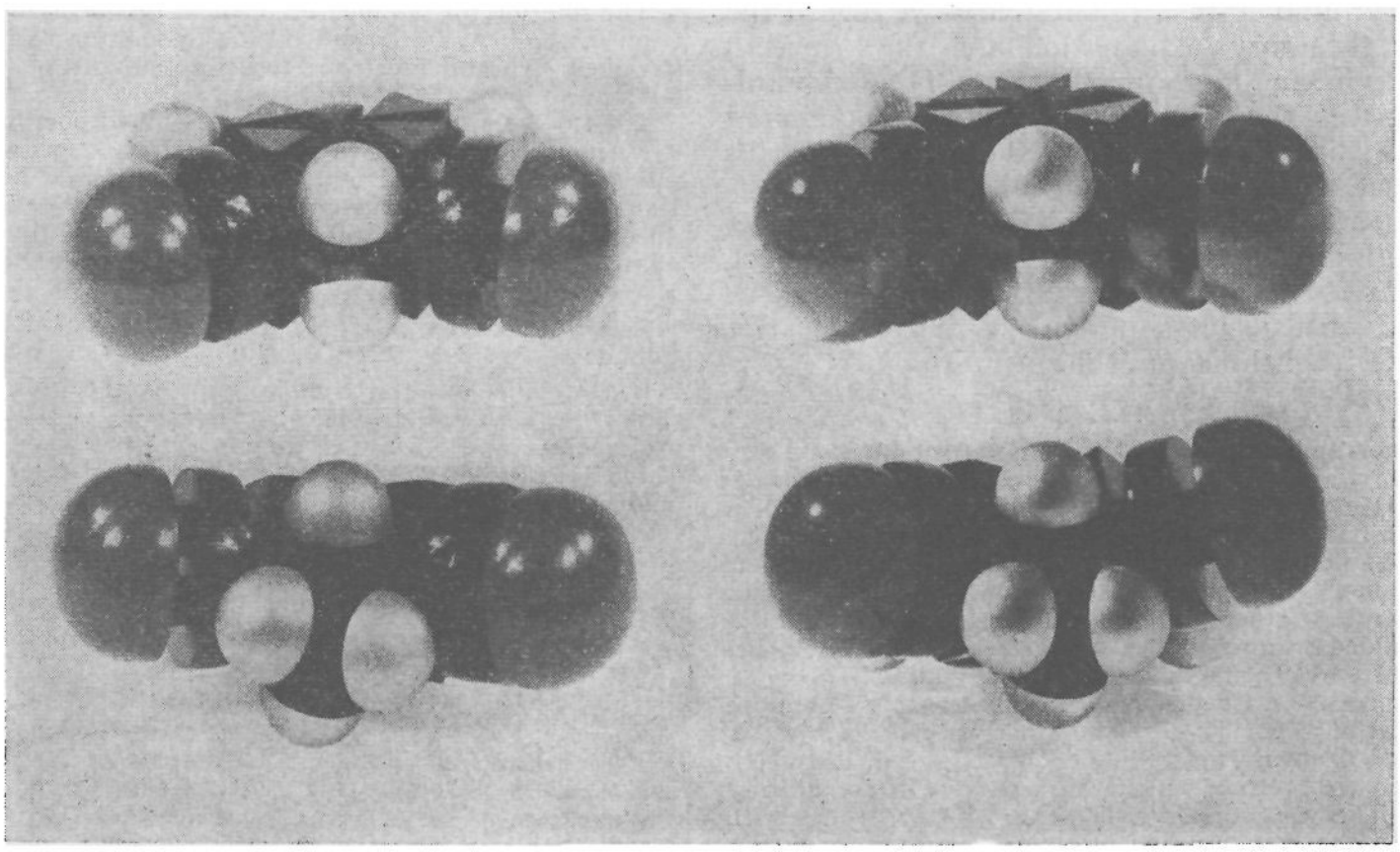


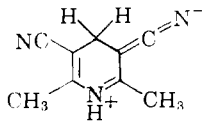
Fig. 4.—The states are shown for III and IV: (a) upper left, ground state of III; (b) upper right, excited state of III; (c) lower left, ground state of IV; (d) lower right, excited state of IV.

ground and excited states are illustrated for the 4-H_2 (Fig. 3a,b) and the 4-CH_3, H molecules (Fig. 3c,d), while the corresponding states for the dicyano compounds (III, IV) are shown in Fig. 4a–d. All of the molecules are constructed of Courtauld models and are viewed along the axis piercing the 4-carbon and 1-nitrogen of the ring. *In no case is there any serious steric strain*, although the methyl derivatives are subject to restrictions in free rotation. Enhancement of the "methyl effect" by buttressing from the 2- and 6-methyl groups may well be responsible for the magnitude of the effect found for the present cases. The "methyl effect," then, does not belong in the category of steric effects so elegantly set forth by Heilbronner and Gerdil[12] in which interference between adjacent groups on a ring system led to a twisting of the substituent, which, however, could result in a positive, null or negative change in transition energy depending on the relative effects upon the ground and excited states. According to Coulson and Stocker,[13] there is reason to believe that nonbonded van der Waals repulsion between neighbor-

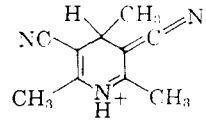
(12) E. Heilbronner and R. Gerdil, *Helv. Chim. Acta*, **39**, 1996 (1956).

(13) C. A. Coulson and D. Stocker, *Mol. Phys.*, **2**, 397 (1959).

ing atoms contributes substantially to the energy of a molecule, although there is at present no satisfactory method for the exact calculation of such energies. The augmentation of the negative charge on oxygen in the excited state of II (II*) should produce an increment in the van der Waals repulsion which is more than that produced in the excited state for the molecule without the 4-methyl (I*). In contrast, the negative charge introduced into the excited state nitrile nitrogen is farther away from the 4-methyl group (compare III* and IV*). In a sense, it is unwise to take the models



III*



IV*

as more than approximate representations of the excited state in which we are interested for they are constructed to conform to the *equilibrium excited state*, and the state actually formed on excitation is the "Franck–Condon excited state." The latter atomic arrangement presumably has bond distances and angles which are closer to those of the original ground state. In summary, we regard the most satisfactory explanation for the "methyl effect" as being due to increased non-bonded repulsion between the 4-substituent and the augmented negative charge on oxygen in the excited state as compared with the case in which there is no 4-substituent. The evidence which we have described indicates that placing the atom which functions as charge acceptor farther away from the 4-substituent results in substantial (but not complete) abolishment of the effect.[14]

Experimental

β-Aminocrotononitrile (VII).—β-Aminocrotononitrile was prepared by a modification of the procedure of Holzwart.[15] Sodium (10 g.) was melted in 100 ml. of xylene and then shaken in order to form small globules of the metal. The xylene was poured off and the residue washed with ether. The sodium was then poured into a two-necked flask together with 250 ml. of ether. To this suspension acetonitrile (28 g.) was added dropwise with stirring over a period of 1 hour. The mixture was then refluxed for 3 more hours. The white solid formed was washed several times with ether to remove excess acetonitrile. Then to the ethereal suspension water was added dropwise until all solid material had dissolved. Two layers were formed which were separated in a separatory funnel. The water layer was extracted three times with ether and the combined ether solutions were dried with sodium sulfate overnight. The ether was evaporated and after some time the oily residue crystallized; yield 13 g. (72%) calculated on the basis of sodium used, m.p. of the crude material 46–52°; recrystallized twice from benzene, m.p. 50–52°. When stored in a desiccator the melting point changed within 2 days to 50–72° and after several days to 70–78° and the compound was found to have lost much of its reactivity. In ethereal solution over sodium sulfate the β-aminocrotononitrile is stable for weeks.

Ethyl β-aminocrotonate (VI) was prepared by the method of Collie.[16] The addition of 10 λ of 0.5 *N* perchloric acid–dioxane solution to 3 ml. of a 5×10^{-5} *M* ester solution caused immediate disappearance of the ultraviolet spectrum. After addition of 5 λ of *t*-butylamine, the original spectrum was once again observed.

2,6-Dimethyl-3,5-dicyano-1,4-dihydropyridine (III).—β-Aminocrotononitrile (4 g.) and hexamethylenetetramine (4 g.) were dissolved in glacial acetic acid (30 ml.). The temperature of the solution rose spontaneously to 75°. After the solution had cooled to room temperature, scratching produced a yellow precipitate. After standing overnight, the precipitate was filtered off and washed with ether; yield 1.5 g. (39%). The solid was recrystallized five times from methanol, m.p. 225–228° (reported[17a,b] 222°, 225°).

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.09; H, 5.92; N, 26.05 (see result of altered procedure below).

The solution for the measurement of the ultraviolet spectrum in water was prepared by the dissolution of 2.61 mg. (weighed on Cahn Electrobalance) in 1000 ml. of water at 80°.

2,4,6-Trimethyl-3,5-dicyano-1,4-dihydropyridine (IV).—β-Aminocrotononitrile (13 g.) and acetaldehyde-ammonia (13 g.) were dissolved in hot water (160 ml.) and the solution heated to 100°. Without further heating, 2 *N* hydrochloric acid (100 ml.) was added slowly until precipitation of the dihydropyridine occurred. After 2 hours, the yellow crystals were filtered off and washed with ether; yield 11 g. (80%). The compound was recrystallized seven times from ethanol–water (3:5) and had m.p. 184–185° (reported[16] 170°).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.57; H, 6.56; N, 24.15.

The solution for the measurement of the ultraviolet spectrum in water was prepared by the dissolution of 1.19 mg. (weighed on Cahn Electrobalance) in 1000 ml. of water at 50°.

2,4,4,6-Tetramethyl-3,5-dicyano-1,4-dihydropyridine (V).—β-Aminocrotononitrile (4 g.) and acetone (2 g.) were dissolved in glacial acetic acid (30 ml.) and slowly heated to 100°. After cooling to room temperature, scratching produced crystals, which were recrystallized five times from methanol; m.p. 235.5–239° dec. (strongly fluorescent), yield 1.8 g. (40%).

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.58; H, 7.00; N, 22.45. Found: C, 70.77; H, 7.09; N, 22.05.

In the course of an attempt to improve the "Meyer synthesis,"[17a] a new tetrahydropyridine was isolated. The experiments and yields of dihydropyridine are given in Table III, while a procedure which formed a substantial quantity of the new compound is given in detail below.

TABLE III

VARIATIONS IN PROCEDURE FOR DICYANODIHYDROPYRIDINES

Aldehyde	β-Aminocrotononitrile, g.	Solvent	Temp., °C.	Yield, %
3 g. formaldehyde, 40%	4	Glacial AcOH	60	15
6 g. formaldehyde, 40%	8	Glacial AcOH	60	15.3
8 g. formaldehyde, 40%	11	Glacial AcOH	70	14.4
3 g. formaldehyde, 40%	3	Acetic anhydride	70	10
3 g. HMTA[a]	3	Acetic anhydride	88	0
4 g. HMTA	4	Glacial AcOH	60–75	36
8 g. HMTA	8	Glacial AcOH	48	22.8
3 g. HMTA	3	Glacial AcOH	100	50
10 g. acetaldehyde–ammonia	10	Glacial AcOH	100	22
13 g. acetaldehyde–ammonia	13	1, H_2O; 2, 2 *N* HCl	100	80

[a] Hexamethylenetetramine.

Tetrahydropyridine (VIII).—Hexamethylenetetramine (3 g.) and β-aminocrotononitrile (3 g.) were mixed and then dissolved in a mixture of 15 ml. of glacial acetic acid and 15 ml. of water and the solution heated to 100°. Hydrochloric acid (40 ml., 2 *N*) was then added and the reaction mixture

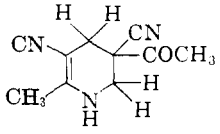
(14) 1-Phenyl-1,4-dihydropyridine and 1-phenyl-4,4-dimethyl-1,4-dihydropyridine have almost precisely the same ultraviolet maxima: λ_{max} 2860 Å. (methanol) is found for the former and λ_{max} 2855 Å. (95% ethanol) for the latter; T. S. Sorensen, Ph.D. Thesis, University of Wisconsin, 1960. No "methyl effect" is expected in the spectra of these molecules and *none is found*.

(15) R. Holzwart, *J. prakt. Chem.*, [2] **39**, 230 (1889).

(16) J. N. Collie, *Ann.*, **226**, 294 (1884).

(17) (a) E. v. Meyer, *J. prakt. Chem.*, [2] **78**, 497 (1908); (b) The compound was analyzed because the absorption maximum disagreed with that of F. Bohlmann and M. Bohlmann, *Ber.*, **86**, 1419 (1953), who gave λ_{max} 3625 Å. in methanol.

again heated to 70°. After cooling and scratching, a yellow precipitate was formed, which was filtered off after dilution with water (200 ml.). The solid was washed with ether; yield 1.8 g. (52%), m.p. 188.5–190° following five recrystallizations from methanol. The substance when pure was *colorless*, had ultraviolet maxima at 2588 Å. (ϵ_{max} 14900) in acetonitrile, 2613 Å. (ϵ_{max} 15600) in methanol, and infrared absorption which indicated a double bond, a cyano group and a *saturated carbonyl* group. Finally, the analysis fit the empirical formula $C_{10}H_{11}N_3O$. Calcd.: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.58, 63.43; H, 6.19, 5.85; N, 21.67, 22.18. The compound was assigned the structure VIII.



VIII

2,6-Dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (I) was prepared by the method of Hantzsch[18] and 2,4,6-trimethyl-3,5-dicarbethoxy-1,4-dihydropyridine by a similar method.[19]

Spectra.—All spectra were measured with a Cary recording spectrophotometer, model 11 or 14, using 10-cm., 5-cm., 2-cm., 1-cm., 0.2-cm., 0.1-cm., and 0.01-cm. quartz cells. The maxima were rerun three to five times at lowest speed. All solvents were of Spectrograde quality or were correspondingly purified.

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(18) A. Singer and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 215.

(19) W. Traber and P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958).

[CONTRIBUTION FROM THE LABORATORY OF THE ALDRICH CHEMICAL CO., MILWAUKEE 10, WIS.]

Indoles. II.[1a,1b] The Acid-catalyzed Rearrangement of N-2-Alkenylanilines

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The acid-catalyzed rearrangement of N-2-alkenylanilines provides a convenient and simple method for the preparation of many indoles and indolines.

In studying the reactions of N-alkenylanilines, the observation was made[1b] that N-crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindoline and 2,3-dimethylindole. Further work has shown that this proton-catalyzed Claisen-type rearrangement of N-crotylaniline is but one instance of a general reaction not limited either to polyphosphoric acid or to N-crotylaniline.

In the simplest case, N-allylaniline reacts with hydrochloric acid at 180° to yield 2-methylindoline and 2-methylindole, and as N-allylaniline can be made almost quantitatively by heating aniline with allyl chloride,[2] 2-methylindoline and 2-methylindole become easily accessible. Under the conditions used, N-allylaniline is in stoichiometric excess over hydrochloric acid, and the ratio of amine salt to free amine is approximately 2:1. The rearrangement of N-crotylaniline to yield 2,3-dimethylindoline and 2,3-dimethylindole proceeds so smoothly that refluxing of a mixture of excess aniline with crotyl chloride or bromide suffices. The rearrangement is quite exothermic, and an inert solvent such as 2-methylnaphthalene is helpful in controlling the reaction.

At least two competing reactions tend to reduce the yields of the simple indolines and indoles. Firstly, N-alkenylanilines are thermally unstable; thus while N-allylaniline can be distilled at atmospheric pressure, N-crotylaniline cannot, and in the reactions of N-allylaniline, N-crotylaniline and N-allyl-N-methylaniline with hydrochloric acid, some aniline is formed. Secondly, the disproportionation which yields aniline also liberates allyl moieties which alkylate the indoles further. Thus, in the simplest case, 2-methylindole is accompanied by 2-methyl-3-propylindole[3]: presumably the intermediate 2-methyl-3-allylindole is hydrogenated by the considerable quantities of hydrogen evolved. The identity of the 2-methyl-3-propylindole was proved by comparison with a sample prepared by the lithium aluminum hydride reduction of 2-methyl-3-propionylindole.

2-Methylindoline is converted slowly to 2-methylindole by the action of hydrochloric acid at 240°, and larger amounts of indoline and smaller of indole are isolated when the reaction mixture is not allowed to reflux after the initial exothermic reaction has subsided. Actually, even when the indoles rather than the indolines are wanted, it is easier to isolate the indolines, which are colorless, stable liquids, distilling without decomposition at atmospheric pressure, and then to dehydrogenate them. The simplest, quantitative mode of dehydrogenation is to heat the indoline with palladium-on-charcoal at 200° for 15–20 minutes.

The indolines can be characterized by solid derivatives such as arylsulfonamides and the high melting, easily purified diketolilolidines, formed in the reaction of indolines with diethyl malonate.[4] The easiest characterization of indolines is, however, their dehydrogenation to the crystalline indoles.

The rearrangement also can be applied to many ring-substituted anilines. Thus N-allyl-*o*-toluidine and N-allyl-*p*-toluidine yield 2,7- and 2,5-dimethylindole and 2,7- and 2,5-dimethylindoline, respectively, and the reaction of *o*-toluidine with crotyl chloride yields 2,3,7-trimethylindoline and 2,3,7-trimethylindole. The rearrangement is not confined to N-alkenylanilines monosubstituted on nitrogen; N-allyl-N-methylaniline rearranges easily

(1) (a) Presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960. (b) For Paper I, see J. E. Hyre and A. R. Bader, *J. Am. Chem. Soc.*, **80**, 437 (1958).

(2) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).

(3) A. E. Arbuzov, I. A. Zaitzev and A. I. Razumov, *Ber.*, **68B**, 1792 (1935); B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933).

(4) E. Bamberger and H. Sternitzki, *Ber.*, **26**, 1300 (1895).