The Kinetics of Deuteration of Pyrazole[1a]

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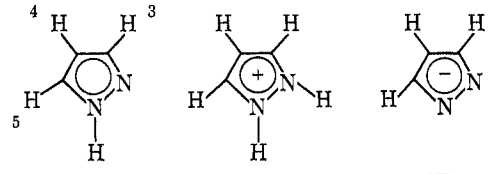
The kinetics of deuteration of the 4 position and the 3(5) position in pyrazole was studied in sealed tubes at 200° and higher temperatures. The mechanism proposed for 4-position deuteration involved general acid catalyzed formation of σ intermediates from the molecular and conjugate-base forms of pyrazole. The rate of deuteration of the 3(5) position exhibited neither buffer catalysis nor pD dependence. This behavior is consistent with formation of an ylide intermediate from attack of the conjugate acid of pyrazole by OD^- ions.

Pyrazole exhibits both weakly basic and very weakly acidic properties in aqueous solution ($pK_b = 11.53$ and $pK_a \cong 14$).[2] Therefore, the molecule I, the conjugate acid II, and the conjugate base III may be subject to electrophilic attack in aqueous media. Thus, the conjugate acid undergoes nitration in the 4 position in stongly acidic media,[3] whereas iodination in media



I II III

ranging from pH 6.0 to 8.0 appears to involve the conjugate base in the 4 position.[4,5] Prior to the research reported in this paper, there has been no report of kinetic studies of the deuteration of unsubstituted pyrazole. However, Olofson, Thompson, and Michelman[6] observed that the 3(5) position but not the 4 position in 1,2-dimethylpyrazolium cation undergoes hydrogen exchange at 31°. Accordingly, it is of interest to study the kinetics of deuteration of pyrazole in heavy aqueous solution to ascertain the relative reactivities of the 4 and equivalent 3 and 5 positions, to determine the rate laws for deuteration of these positions, to propose mechanisms compatible with these rate laws, and to interpret the reactivities of ring positions theoretically and mechanistically.

Experimental Section

Materials.—Pyrazole from Aldrich Chemical Co. was recrystallized three times from cyclohexane, mp 68.5°. D_2O (99.5%), DCl (38% in D_2O), ND_4OD (26% in D_2O), and pyridine-d_5 obtained from Merck Sharp and Dohme of Canada Ltd., were used without further purification. Reagent grade NaCl was also used without further purification.

Kinetic Runs.—The details of the kinetic procedure are given in the preceding paper of this series.[7] The ionic strength was adjusted to 1.00 M by NaCl in all runs. Runs were made with ammonia-d_3, ammonium-d_4 buffer, pyridine-d_5, pyridinium-d_6 buffer, and with no added buffer. Deuterations were carried out in heavy water solutions in sealed heavy-wall borosilicate glass ampoules at temperatures ranging from 200 to 250°. Temperatures were reproducible to within ±1° and rate constants to within ±10%. Uncertainties in concentrations of reagents arising from thermal changes in volume are discussed in the proceding paper.[7]

pD values were measured at room temperature with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long (pD = pH (meter reading) + 0.4).[8]

Results and Discussion

Rate constants for the deuteration of the 4 position and the equivalent 3 and 5 positions are recorded in Tables I and II, respectively. These rate constants are pseudo first order in pyrazole, since D_2O was in

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DEUTERATION OF THE 4 POSITION IN PYRAZOLE

Base concentration[a]	Buffer ratio[b,c]	pD[c]	Temp, °C	$k_4^{obsd} \times 10^4$ sec^{-1}
	ND_3, ND_4^+ Buffer			
1.92	3.75	10.56	200	7.68
0.96				4.43
0.48				2.45
0.24				1.78
0.12				1.35
1.09	8.50	10.92	200	4.68
0.70	1.375	10.13	200	3.53
	Pyridine-d_5, Pyridinium-d_6 Buffer			
0.70	1.34	6.15	200	21.9
0.35				17.8
0.17				15.8
0.09				14.6
0.67	2.08	6.34	200	16.2
0.34				13.1
0.17				12.3
0.085				11.8
0.78	6.03	6.80	200	8.16
0.39				6.15
0.20				5.47
0.10				5.00
0.068	12.7	7.13	200	5.23
0.034				3.98
0.017				3.10
0.0085				2.78
	No Added Buffer			
0.0		7.50	200	0.82
			215	1.61
			230	3.12
			238	4.13
			245	6.48
			245	6.53

[a] Mole/liter. [b] [base]/[acid]. [c] Room-temperature value.

(1) (a) Department of Chemistry, Contribution No. 7-69, supported in part by Atomic Energy Commission Grant AT(11-1)-1620. (b) Addressee for reprints.

(2) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963.

(3) M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1051 (1965).

(4) J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Amer. Chem. Soc.*, **86**, 2857 (1964).

(5) J. D. Vaughan, G. L. Jewett, and V. L. Vaughan, *ibid.*, **89**, 6218 (1967).

(6) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *ibid.*, **86**, 1856 (1964).

(7) J. D. Vaughan, Z. Mughrabi, and E. C. Wu, *J. Org. Chem.*, **35**, 1141 (1970).

(8) P. K. Glaskoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

TABLE II
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DEUTERATION OF THE 3(5) POSITION IN PYRAZOLE

Base concentration[a]	Buffer ratio[b,c]	pD[c]	Temp, °C	$k_{3(5)}^{obsd} \times 10^5$ sec^{-1}
		ND_3, ND_4^+ Buffer		
1.92	3.75	10.56	230	3.95
1.92				3.27
0.96				4.03
1.85	3.44	10.53	230	4.17
0.79	1.1	10.03	230	2.95
		Pyridine-d_5, Pyridinium-d_6 Buffer		
1.90	3.69	6.60	230	2.28
0.95				2.08
0.47				2.27
0.24				2.28
0.70	1.34	6.15	230	2.08
0.35				2.58
0.17				2.88
0.088				2.88
0.044				2.85
0.022				2.58
		No Adder Buffer		
0.00		7.50	220	1.65
			230	3.05
			240	8.55
			250	14.5

[a-c] See footnotes to Table I.

great excess. The rate data for the 4 position conforms to general acid catalyzed deuteration (eq 1–4).

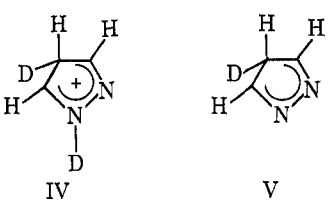
$$SH + D_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Q^+ + D_2O \xrightarrow{k_3} SD + HD_2O^+ \quad (1)$$

$$SH + BD^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Q^+ + B \xrightarrow{k_4} SD + BH^+ \quad (2)$$

$$SH^- + D_3O^+ \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} Q + D_2O \xrightarrow{k_3'} SD^- + HD_2O^+ \quad (3)$$

$$SH^- + BD^+ \underset{k_{-2}'}{\overset{k_2'}{\rightleftharpoons}} Q + B \xrightarrow{k_4'} SD^- + BH^+ \quad (4)$$

Here SH refers to pyrazole (I), SD to pyrazole-4*d*, SH^- and SD^- to the conjugate bases of SH and SD, respectively, BD^+ and BH^+ to general acids, and Q^+ and Q to Wheland intermediates IV and V, respectively.



IV V

This mechanism is similar to that proposed by Kresge and Chiang[9] for acid-catalyzed hydrogen exchange in 1,3,5-trimethoxylbenzene, complicated by the presence of added buffer and by the appearance of two rather than one substrate. The kinetic analysis that follows is an extension of that reported by Kresge and Chiang. We assume that

$$k_1 < k_{-1} \sim k_3$$
$$k_2 < k_{-2} \sim k_4$$
$$k_1' < k_{-1}' \sim k_3'$$
$$k_2' < k_{-2}' \sim k_4'$$

(9) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **89**, 4411 (1967).

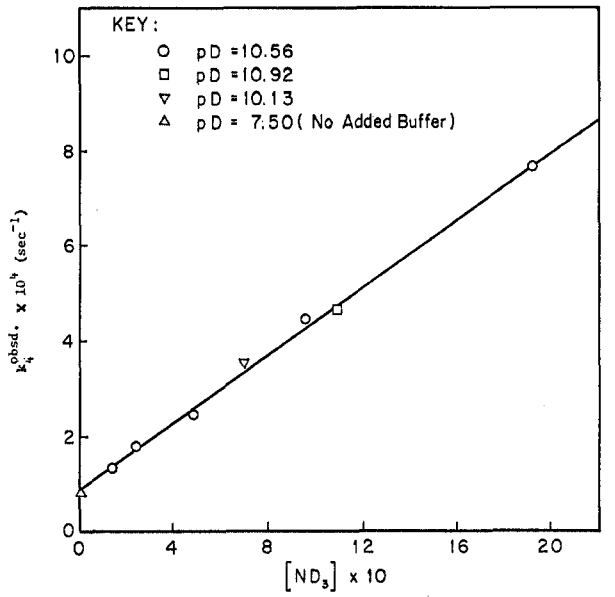


Figure 1.—Rate of deuteration of the 4 position of pyrazole at 200° in ammonia buffer.

where the pairs on the right of the inequality (*e.g.*, k_{-1}, k_3, etc.) differ only because of the primary isotope effect. Therefore

$$\text{rate (4 position)} = k_1[SH][D_3O^+] - k_{-1}[Q^+][D_2O] + k_2[SH][BD^+] - k_{-2}[Q^+][B] + k_1'[SH^-][D_3O^+] - k_{-1}'[Q][D_2O] + k_2[SH^-][BD^+] - k_{-2}[Q][B]$$

Using the steady-state approximation to eliminate $[Q^+]$ and [Q], together with the relations

$$K_a = [SH^-][D_3O^+]/[SH]$$
$$K_b = [BD^+]K_w/[B][D_3O^+]$$

to eliminate $[SH^-]$ and $[BD^+]$, we derive the pseudo-first-order rate constant for 4-position deuteration to be

$$k_4^{obsd} = \{k_1X[D_3O^+] + k_1'K_aX'\} + \{(k_2K_bX/K_w)[D_3O^+] + (k_2'K_aK_bX'/K_w)\}[B] \quad (5)$$

where

$$X = \frac{k_3[D_2O] + k_4[B]}{(k_{-1} + k_3)[D_2O] + (k_{-2} + k_4)[B]}$$

$$X' = \frac{k_3'[D_2O] + k_4'[B]}{(k_{-1}' + k_3')[D_2O] + (k_{-2}' + k_{-4}')[B]}$$

and $K_w = [D_3O^+][OD^-]$. If no buffer is present and if the reacting medium is strongly acidic, then [SH] $\gg$ $[SH^-]$, $[BD^+]$ = [B] = 0, and eq 5 reduces to the Kresge and Chiange rate equation[9]

$$k_4^{obsd} = \left(\frac{k_1}{1 + k_{-1}/k_3}\right)[D_3O^+] \quad (6)$$

In the general case (eq 5), X and X' each are functions of B, so that k_4^{obsd} contains terms in the second degree. However, Figures 1 and 2 exhibit first-order dependence upon [B] for the ammonia-d_3 and pyridine-d_5 buffers, respectively. This behavior is consistent with eq 5 provided that X and X' are constant, irrespective of [B]; the conditions for constancy of X and X' are that

$$\frac{k_3}{k_{-1} + k_3} = \frac{k_4}{k_{-2} + k_4} \quad (7)$$

$$\frac{k_3'}{k_{-1}' + k_3'} = \frac{k_4'}{k_{-2}' + k_4'} \quad (8)$$

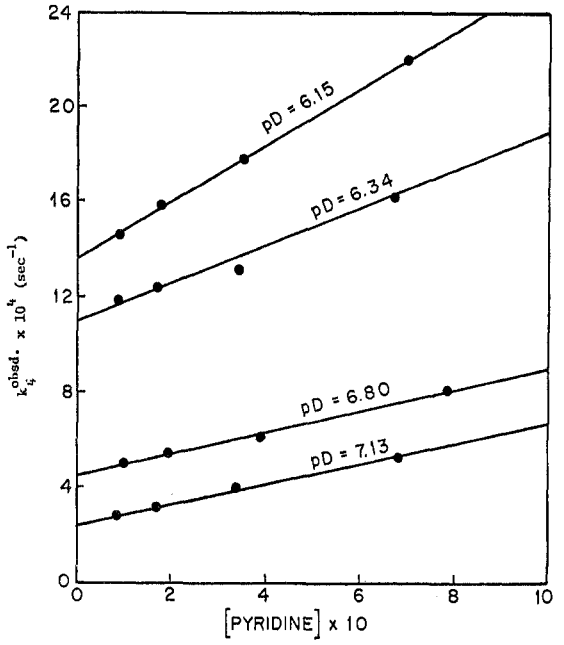


Figure 2.—Rate of deuteration of the 4 position of pyrazole at 200° in pyridine buffer.

Because paths 1 and 2 are quite similar in nature, as are paths 3 and 4, respectively, we conclude that the conditions expressed by eq 7 and 8 are realized, and that X and X' are indeed constant. In the ammonia buffer case, pD is large and $[D_3O^+]$ vanishingly small; therefore, eq 5 predicts that k_4^{obsd} will be independent of pD, as observed in Figure 1. In the pyridine buffer case, where the solutions range from neutral to weakly acidic, $[D_3O^+]$ is 10^3 to 10^4 times larger than in ammonia buffer, so that one might expect the $[D_3O^+]$ terms in eq 5 to become significant. Therefore, in pyridine buffer, eq 5 predicts a family of linear plots of k_4^{obsd} *vs.* [pyridine] for given pD values, as seen in Figure 2. According to eq 5, the intercepts (k^0) and slopes (k^s) observed in Figures 1 and 2 should depend linearly upon $[D_3O^+]$; this behavior is exhibited in Figure 3. In earlier work, electrophilic attack of a free molecule and its conjugate base was proposed by Katritzky and coworkers[10] to account for the deuteration of phenol (2,4,6 positions).

The results of Figures 1 and 3 may be used to estimate the relative electrophilic reactivities of the pyrazole molecule and its conjugate base. In Figure 1, the intercept $k^0 = 0.8 \times 10^{-4}$ sec^{-1} $= k_1'K_aX'$; in Figure 3, $k^0 = 5 \times 10^{-4}$ sec^{-1} at $[D_3O^+] = 2 \times 10^{-7}$. Therefore, since $k^0 = k_1X[D_3O^+] + k_1'K_aX'$ and if we let $K_a = 10^{-14}$ for pyrazole,[2] we find that $k_1X \sim 2 \times 10^3$ sec^{-1} M^{-1} and that $k_1'X' \sim 8 \times 10^9$ sec^{-1} M^{-1}. Accordingly, we estimate that the conjugate base is about 4×10^6 more reactive than the molecule with respect to the D_3O^+ electrophile; the rates of deuteration of the anion and molecule are calculated to be about equal at pD = 7.4 (room-temperature value).[11] By comparative iodinations of pyrazole and 1-methylpyrazole, the reactivity (relative to I_2 or IOH_2^+) of the conjugate base of pyrazole was estimated to be between 10^9 and 10^{13} greater than that of the molecule.[5]

(10) G. P. Bean, *et al.*, *J. Chem. Soc.*, *B*, 1222 (1967).

(11) Compare phenol, where the phenoxide anion is estimated to be 2×10^7 more reactive than the phenol molecule, and the rates of deuteration of the two substrates to be equal at pD = 3.4.[10]

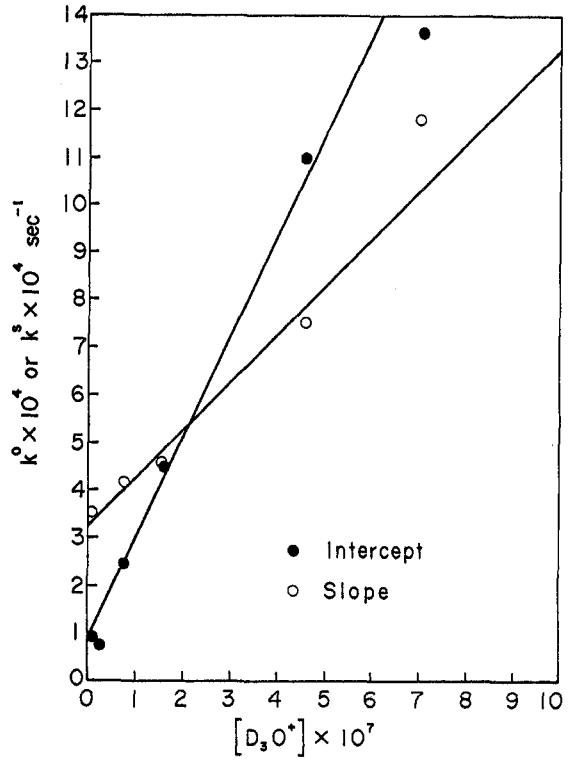
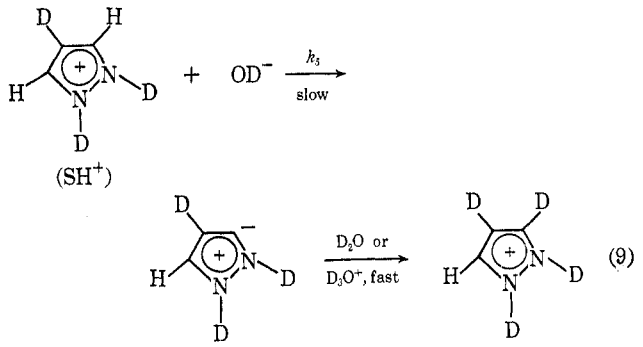


Figure 3.—Dependence of buffer-catalyzed (slopes) and uncatalyzed (intercepts) deuteration of the 4 position in pyrazole at 200°.

Numerous other examples of Wheland-intermediate mechanisms have been proposed for hydrogen exchange in aromatic substrates, chiefly in six-member-ring systems.[12]

The deuteration of the 3(5) position of pyrazole at 230° is sensibly independent of both buffer and pD from pD = 6.15 to pD = 10.56 (Table II). This behavior conforms to deuterioxide-catalyzed ylide formation.



(9)

Here rate [3(5) position] $= k_5[SH^+][OD^-]$; noting that $K_a' = [SH][D_3O^+]/[SH^+]$, we derive

$$k_{3(5)}^{obsd} = \frac{k_5K_w}{K_a'} \quad (10)$$

which agrees with experiment. Similar independence of the rate of deuteration upon $[OD^-]$ attributable to the ylide-intermediate mechanism has been reported.[7,13,14] An alternative path for 3(5) deuteration independent of pD could involve attack of the conjugate base III by D_3O^+ to form a Wheland intermediate.

(12) For example, see G. P. Bean, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and A. M. White, *J. Chem. Soc.*, *B*, 1219 (1967).

(13) J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Lett.*, 421 (1968).

(14) T. M. Harris and J. C. Randall, *Chem. Ind.* (London), 1728 (1965).

However, the independence of the rate of ND_4^+ and pyridinium-d_5 casts doubt upon this alternative. Further, the numerous examples of other heteroatomic aromatic substrates[6,15-20] that appear to undergo hydrogen exchange in α positions through ylide intermediates support this mechanism for the 3(5) position in pyrazole. Of particular interest, 1,2-dimethylpyrazolium cation undergoes deuteration in the 3(5) position at 31° in alkaline solution.[6] Here, the much smaller rate of deuteration of the 3(5) position in pyrazole in terms of the ylide path is a consequence of the very weak base strength of pyrazole.[2]

The experimental activation energy for the 4 position is 21.8 ± 1.6 kcal and that for the 3(5) position is 38.8 ± 6.4 kcal. Corresponding pseudo-unimolecular collision factors are 7.6 ± 10^5 sec^{-1} and 2.1 × 10^{12} sec^{-1}, respectively. The activation energy for the 3(5) position is unexpectedly large;[21] the smaller exchange reactivity for the 3(5) position compared to the 4 position is due to the great difference in activation energies of these positions, partially offset by the larger preexponential factor of the 3(5) position.

It is evident that two types of exchange mechanism are operative in aromatic heterocyclic systems. The first type involves base-catalyzed proton removal from the exchange site of the substrate. The second type involves acid-catalyzed Wheland intermediate formation. In general, in neutral, weakly acidic, or weakly alkaline solutions, positions next to nitrogen, oxygen, or sulfur heteroatoms undergo exchange by the first type,[6,7,15-20] whereas positions with carbon neighbors may react through the first[22] or the second type.[10,12,23] The relative reactivities of the conjugate acid, conjugate base, and molecule forms of the substrates differ, depending upon which type mechanism is operative. Thus, for the proton abstraction mechanism, the conjugate acid is most reactive, the molecule next,[7,19] and the conjugate base apparently unreactive. Here protonation of the heteroatom leads to rate enhancement in two ways: first, by increased inductive stabilization of transition states leading to ylide or anion intermediates[6,7,20] and second, by the increased entropy of activation attending reactions between ions of opposite charge. For the Wheland intermediate mechanism, the conjugate base is most reactive, the molecule next, and the conjugate acid least. In the latter case, deprotonation of the heteroatom appears to stabilize transition states leading to the Wheland intermediate, and also to cause the entropy of activation to increase for positively charged electrophiles.

(15) H. S. Staub, *Tetrahedron Lett.*, 845 (1964).
(16) P. Beak and J. Bonham, *J. Amer. Chem. Soc.*, **87**, 3365 (1965).
(17) P. Haake and W. B. Miller, *ibid.*, **85**, 4044 (1963).
(18) R. Breslow, *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962).
(19) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966).
(20) P. Haake, L. S. Bauscher, and W. B. Miller, *ibid.*, **91**, 1113 (1969).
(21) For example, the activation energy for exchange in the 4(5) position in imidazole is about 22 kcal.[7]
(22) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).
(23) The β position in 4-aminopyridines exhibits mechanism type 1 in alkaline solution and type 2 in acid solution. See ref 13.

Registry No.—Pyrazole, 288-13-1.

The Azodiformate Adduct of Indene and the Stereochemistry of Some 1,2-Disubstituted Indans[1]

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It has been shown by chemical degradations that the structure of the adduct of indene and diethyl azodiformate is correctly formulated as an oxadiazine. The stereochemical structure assigned to a 2-amino-1-indanol by interpretation of nmr data has been shown to be erroneous. The generalizations proposed to deduce the stereochemistry of 1,2-disubstituted indan on the basis of nmr spectra have been shown to be an oversimplification.

A recent study on Diels–Alder reactions of indene[3] presented physical data on whose basis the long-known adduct of indene and diethyl azodiformate[4] was formulated as diazetidine **1**. Chemical evidence now, however, shows this substance to be represented properly by the oxadiazine structure.[5] In this connection it is noteworthy that reaction of indene with sterically restricted phthalazine-1,4-dione leads to 1,2 addition and hence to the formation of an authentic diazetidine **2**,[6] while reactions of azodiformates with other olefins have been shown recently to yield both 1,2 and 1,4 adducts.[7]

Structure **1** became untenable when a hydrazino alcohol was obtained upon its reduction by lithium aluminum hydride. Proof of the nature of the reduction product and formulation of its structure as **4** emerged from the following observations. Its nmr spectrum showed the presence of two replaceable hydrogens and two N-methyl groups. Acetylation gave an O,N-diacetyl derivative. Hydrogenation of **4** over platinum oxide in acetic acid gave an amino alcohol

(1) Delay in publication of this paper was the responsibility of the editor. Since acceptance of this paper for publication the correct structures for **1** and **7** have been proposed by others: (a) H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 556 (1969); (b) H. Rimek, T. Yupraphat, and F. Zymalkowski, *Justus Liebigs Ann. Chem.*, **725**, 116 (1969); (c) H. Rimek, T. Yupraphat, and F. Zymalkowski, *ibid.*, **726**, 25 (1969).
(2) (a) CIBA Pharmaceutical Co.; (b) Indiana University.
(3) C. F. Huebner, P. L. Strachan, E. M. Donoghue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32**, 1126 (1967).
(4) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **450**, 237 (1926).
(5) Dr. E. Koerner von Gustorf also concluded that this new structure is the correct one (private communication). He has since then completed his evidence for this structure: E. K. von Gustorf, D. White, B. Kim, D. Hess and J. Leitich, *J. Org. Chem.*, **35**, (155 197). His earlier paper, E. K. von Gustorf and B. Kim, *Angew. Chem.*, **76**, 592 (1964), proposing the diazetidine structure, was neither abstracted nor indexed by *Chemical Abstracts*.
(6) O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31**, 3862 (1966).
(7) J. J. Tufariello, T. F. Mich, and P. S. Miller, *Tetrahedron Lett.*, 2293 (1966); G. Ahlgren and B. Akermark, *Acta Chem. Scand.*, **21**, 2910 (1967).