HETEROCYCLIC ANALOGS OF PLEIADIENE XXXI.* STUDY OF THE RATE OF BASIC DEUTERIUM EXCHANGE AND THE BEHAVIOR OF PERIMIDINES AND NAPHTHIMIDAZOLES WITH RESPECT TO BUTYLLITHIUM

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The behavior of N-methyl derivatives of perimidine (I), aceperimidine (VI), aceperimidylene (VII), naphth[2,3-d]imidazole (V), benzimidazole (II), and 1H- and 3H-naphth[1,2-d]imidazoles (III, IV) with respect to n-butyllithium was studied. Compounds I and V-VII add n-butyllithium to the C = N bond to give 2-n-butyl-2,3-dihydro derivatives, whereas II-IV are metallated to give 2-lithio derivatives. The different reactivities of I, V-VII, and II-IV are explained by the reduced aromatic character and high polarization of the C = N bond in I and V-VII. The investigated compounds are arranged in the following order with respect to the ease of undergoing basic deuterium exchange at the C_{μ} -H bond: V > II > III > IV > VII > I > VI. There is no correlation between the rate of deuterium exchange and the behavior of I-VII with respect to butyllithium.

It has previously been shown that 1-methylperimidine (1) adds organometallic compounds at the C = N bond to give 2-substituted 1-methyl-2,3-dihydroperimidines [2]. The formation of 2-lithio-1-methylperimidine in 8% yield has been established in only one case (in the reaction of perimidine I with $n-C_4H_9Li$) [2]. This sort of behavior sharply distinguishes perimidine I from 1-methylbenzimidazole (II) (which also has a 1,3-diazole ring), which is readily metallated by various organometallic reagents at the μ -carbon atom [3].

The aim of the present research was to study the behavior of the 1-methyl derivatives of all of the isomeric naphthimidazoles (III-V) and aceperimidine (VI) and aceperimidylene (VII) – systems that are closely related to heterocycles I and II – with respect to organometallic reagents. We also studied the kinetics of basic deuterium exchange of I-VII. It is known [4, 5] that this reaction may serve as a model for the metallation reaction, since in the absence of side phenomena, the rates of both processes are determined by the ease of formation and stability of the carbanion that is formed in the first step. In the case of azoles the hydrogen attached to the μ -carbon atom is exchanged during basic deuterium exchange [5]:



It was found that the investigated compounds behave either like perimidine I or like imidazole II with respect to butyllithium. Thus both N-methyl derivatives of angular naphthimidazole (III, IV) are metallated by n-butyllithium in ether to give 2-lithio derivatives VIII and X in high yields. The presence of the latter in the reaction mixture is indicated by the fact of the formation from them of carboxylic acids IX and XI under the influence of carbon dioxide.

On the other hand, 1-methyl derivatives of linear naphthimidazole V, aceperimidine VI, and aceperimidylene VII add n-C₄H₉Li to the C = N bond to give 2,3-dihydro derivatives XII, XIV, and XVI. Their structure is confirmed, in particular, by the presence in their IR spectra of $v_{\rm NH}$ bands at 3450 cm⁻¹. Compounds XII, XIV,

*See [1] for communication XXX.

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Com- pound	<i>t</i> , ℃	k - 10⁵, sec -1	E _a , kcal/mole	lg A	-1g k ₅₀	q⁺ ₍₄ ,	REPE (ß)
1	80 70 60	12,0 4,1 1,3	26,0	12,2	5,3	+0,256	0,040
V	50 40	12,0 3,0	(27,8)	(14,9)	3,9	+0,186	0,046
VI	70 180	3.3 1,9†		_	(5,4) (11,0) †	+0,246	0,040
VII	80 70	12,0 5,0	(21,0)	(9,0)	5,2	+0,263	0,038
II	55 45	11,0 2,8	25,7	13,2	4,1	+0,170	0,050
Ш	70 60	15,0 6,5	(19,0)	(8,3)	4,6	+0,152	0,048
IV	65 50	13,0 2,3	(24,0)	(11,5)	4,7	+0,151	0,048

TABLE 1. Results of the Kinetic Study of Basic H-D Exchange, π -Electron Charges on the μ -Carbon Atom, and Indexes of Aromaticity and REPE Values of the Investigated Compounds*

*The rate constants and activation parameters (E_a and log A) presented in parentheses are approximate values.

†This is the constant that characterizes hydrogen exchange in the CH_2 - CH_2 bridge.

and XVI are extremely unstable and are gradually oxidized in air to give aromatic structures of the XIII and XV type. The latter can also be obtained by oxidation of dihydro derivatives XII, XIV, and XVI with chloranil. It should be noted that dihydro derivatives XIV and XVI are converted to the same product XV by chloranil, i.e., in the case of aceperimidine XIV both the NH bond and the CH_2-CH_2 bridge are dehydrogenated.

It is apparent from the rate constants for basic H-D exchange presented in Table 1 that I-VII differ relatively little with respect to their CH acidities: the difference between the $-\log k_{50}$ values (the logarithms of the rate constants referred to 50 deg C) for the least and most reactive compounds amounts to only 1.5 orders of magnitude. Within the limits of these small differences, the compounds can be arranged in the following order with respect to decreasing reactivity: V > II > III > IV > VII > I > VI.

The absence of any correlation between the kinetic CH acidities of I-VII and their behavior with respect to butyllithium is an important fact. Thus imidazole V, which most readily undergoes H-D exchange, is not metallated but rather adds butyllithium to the C = N bond, whereas heterocycles II-IV, which are metallated, are found in the middle of the series. Judging from the $-\log k_{50}$ and E_a values, the CH acidity of VII is somewhat higher than the CH acidity of perimidine I; however, in contrast to the reaction with perimidine I, not even traces of the 2-lithio derivative were detected in the reaction of VII with n-butyllithium.

On the basis of the material set forth above, it can be concluded that the direction of the reaction of I-VII with organometallic reagents depends most of all on the relative energies of activation of two competitive processes in which the site of initial attack is either the hydrogen atom (protophilic attack) or the C = N bond (nucleophilic addition). Protophilic attack, the probability of which is controlled to a considerable extent by the magnitude of the charge on the μ -hydrogen atom, terminates with cleavage of the C-H bond and can lead to both isotopic exchange and metallation. The simultaneous addition of R^-M^+ to the C = N bond, which is favored by the high π -electron polarization of this bond and the reduced aromatic character of the heteroring, is evidently the chief reason for the disruption of the similar trend in the changes in the relative rates of comparable reactions. The high polarization of the C = N bonds in the I and V-VII molecules follows from the results of quantum-mechanical calculations [6-8], particularly from the effective charges on the μ -carbon atom that are presented in Table 1. Our calculated REPE (resonance energies per π electron) values, which are presently one of the most widely accepted indexes of aromaticity [9-11], also clearly attest to the considerably lower aromatic character of perimidines and aceperimidylene as compared with metallated benzimidazole and angular naphthimidazoles. With respect to its aromatic character, imidazole V occupies an intermediate position, and the above-noted high polarization of the C = N bond may be the decisive factor in its tendency to undergo addition reactions.



EXPERIMENTAL

The quantum-mechanical calculations of the π -electron charges were performed by the Hückel MO method with the Streitwieser parameters by the method in [6]. The REPE indexes were calculated by the method in [10, 11]. The IR spectra were measured with a UR-20 spectrometer. Chromatography was carried out on activity IV (Brockmann classification) aluminum oxide. The method for the study of the exchange reaction was described in [12].

<u>1-Methylnaphth[2,3-d]imidazole (V)</u>. The method described below is substantially better than the method described in [13]. A 4-ml (0.06 mole) sample of methyl iodide was added with stirring in the course of 7-10 min to a solution of 9 g (0.05 mole) of naphth[2,3-d]imidazole and 3.8 g (0.05 mole) of KOH in 50 ml of alcohol, after which the mixture was stirred at room temperature for 2 h and then refluxed for 1 h. The alcohol was removed by distillation, and the residue was extracted with chloroform. The extract was washed with water, dried with calcium chloride, and evaporated. The residue was passed through a column filled with aluminum oxide with elution by chloroform. The barely yellowish fraction with $R_f 0.7$ was collected. Reaction product V was obtained as white needles with mp 158 deg C (from octane), in agreement with [13].

<u>1-Methyl- (IV)</u> and 3-Methylnaphth[1,2-d]imidazoles (III). An 8.1-ml (0.13 mole) sample of methyl iodide was added with stirring in the course of 7-10 min to a solution of 16.8 g (0.1 mole) of naphth[1,2-d]imidazole and 7.5 g (0.1 mole) of KOH in 100 ml of alcohol, and the mixture was then stirred at room temperature for 3 h and refluxed for 1 h. The alcohol was removed by distillation, and the residue was extracted with chloroform. The extract was dried with calcium chloride and evaporated. The reaction products were separated with a

column filled with 800 g of aluminum oxide [elution with chloroform-petroleum ether-acetone (3:1:0.5)]. Since both substances were colorless and had close R_f values, the eluate was collected in small portions (3-4 ml each) with thin-layer chromatography (TLC) monitoring of the separation. The first compound eluted [8.5 g (47%)] was colorless needles of naphth[1,2-d]imidazole with R_f 0.35 and mp 136 deg C (from octane), in accordance with the data in [14]. The second fraction yielded 2.6 g (14%) of colorless needles of 1-methyl-naphth[1,2-d]imidazole with R_f 0.30 and mp 134-135 deg (from octane). Found: C 79.2; H 5.3; N 15.1%. $C_{12}H_{10}N_2$. Calculated: C 79.1; H 5.5; N 15.4%.

<u>2-Methylnaphth[1,2-d]imidazole-2-carboxylic Acid (IX).</u> A solution of 1.8 g (0.01 mole) of III in 40 ml of absolute toluene was added to a cooled (to -78 deg C) solution of n-butyllithium obtained from 0.56 g (0.08 gatom) of lithium and 5.6 g (0.04 mole) of freshly distilled butyl bromide, in 30 ml of absolute ether. The mixture turned yellow immediately. It was stirred at -78 deg C for 5 h, after which small pieces of dry ice were added. The excess CO₂ was then evaporated, and 40 ml of water was added to the residual viscous mass. The resulting white precipitate of the lithium salt of acid IX was removed by filtration. The yield was 2 g (80%). For isolation of the acid, its salt was dissolved in water, the solution was filtered, and the filtrate was acidified with acetic acid. The resulting white crystals of acid IX were removed by filtration, washed with water, and dried in a vacuum desiccator over calcium chloride. The acid melted with decarboxylation at 92-93 deg C. Found: C 59.5; H 5.5; N 10.7%. C₁₃H₁₀N₂O₂ · 2H₂O. Calculated: C 59.6; H 5.4; N 10.7%. IR spectrum (in petrolatum): 1670 (C=O) and 3380-3490 cm⁻¹ (OH).

<u>1-Methylnaphth[1,2-d]imidazole-2-carboxylic Acid (XI).</u> A solution of 1.8 g (0.01 mole) of IV in 50 ml of absolute toluene was added to a cooled (to -78 deg C) solution of n-butyllithium, obtained from 0.42 g (0.06 g-atom) of lithium and 3 ml (0.03 mole) of butyl bromide, in 30 ml of ether, and the mixture was stirred at -78 deg C for 2 h, after which it was carbonated with dry ice. The excess CO₂ was evaporated, and the residue was treated with 30 ml of water. The resulting precipitate of the lithium salt of acid XI was removed by filtration. The yield was 1.8 g (72%). The salt was dissolved by gentle heating in the minimum amount of water, the mixture was filtered, and the cooled filtrate was neutralized with acetic acid and worked up to give 1.5 g of the dihydrate of the acid in the form of a white powder that melted with decomposition at 89 deg C. The product was purified by reprecipitation from alkaline solution. Found: C 59.4; H 5.3; N 10.5%. C₁₃H₁₀N₂O₂ · 2H₂O. Calculated: C 59.6; H 5.4; N 10.7%. IR spectrum (in petrolatum): 1670 (C=O); and 3370-3490 cm⁻¹ (OH).

Workup of the organic layer of the filtrate remaining after separation of the lithium salt of the acid made it possible to obtain ~ 0.12 g (8%) of starting IV.

<u>1-Methyl-2-n-butyl-2,3-dihydronaphth[2,3-d]imidazole (XII) and 1-Methyl-2-n-butylnaphth[2,3-d]imidazole</u> (XIII). A solution of 1.8 g (0.01 mole) of V in 40 ml of absolute toluene was added to a cooled (to -78 deg C) solution of n-butyllithium in 30 ml of absolute ether [obtained from 0.56 g (0.08 g-atom) lithium and 5.6 g (0.04 mole) of butyl bromide]. The mixture turned yellow. It was stirred at -78 deg C for 5 h, after which it was carbonated with dry ice. The excess CO₂ was evaporated, and the mixture was treated with 30-40 ml of water. The layers were separated, and the organic layer was worked up to give 1.8 g (75%) of XII in the form of a yellow oil. Found: N 11.8%. C₁₆H₂₀N₂. Calculated: N 11.6%. IR spectrum (in chloroform): 3460 cm⁻¹ (NH). The product decomposed rapidly during storage; it was therefore converted to XIII by oxidation with an equimolar amount of chloranil in benzene solution by the method in [2]. The yield was 1.5 g (63%). Compound XIII was obtained as yellowish needles with mp 95 deg C (from octane). Its IR spectrum did not contain bands of stretching vibrations of N-H bonds. Found: C 80.7; H 8.2; N 11.8%. C₁₆H₁₈N₂. Calculated: C 80.6; H 7.6; N 11.8%.

<u>1-Methyl-2-n-butyl-2,3-dihydroaceperimidylene (XVI) and 1-Methyl-2-n-butylaceperimidylene (XV).</u> A solution of 1.06 g (5 mmole) of VII in 50 ml of toluene was added to a cooled (to -78 deg C) solution of butyl-lithium in 30 ml of absolute ether, obtained from 0.28 g (0.04 g-atom) of lithium and 2.7 g (0.02 mole) of butyl bromide, during which the mixture became red. It was stirred at -78 deg C for 2 h, after which it was carbonated with dry ice. The excess CO_2 was evaporated, 20 ml of water was added to the orange residue, and the layers were separated. Evaporation of the solvent from the organic layer gave 1.1 g (83%) of XVI in the form of orange-red crystals. IR spectrum (in chloroform): 3450 cm^{-1} (NH). The product underwent oxidation rapidly; if the residue remaining after evaporation of the CO_2 is not worked up immediately but rather 24 h afterwards, it no longer contains an N-H group according to the IR spectral data. In view of the instability of XVI, it was not subjected to elementary analysis but was converted to XV by refluxing with an equimolar amount of chloranil in benzene solution. The yield of yellow crystals of XV, with mp 144 deg C (from octane), was 0.9 g (71%). Found: C 81.5; H 6.6; N 10.7%. C₁₈H₁₈N₂. Calculated: C 82.4; H 6.9; N 10.7%.

Action of n-Butyllithium on Perimidine VI. A solution of 1.04 g (5 mmole) of VI in 20 ml of toluene was added to a cooled (to -78 deg C) solution of butyllithium in 30 ml of absolute ether, obtained from 0.28 g (0.04 g-atom) of lithium and 2.7 g (0.02 mole) of butyl bromide, during which the mixture became dark-brown. It was stirred at -78 deg C for 3 h, after which it was carbonated. The excess CO₂ was removed, 20 ml of water was added, and the layers were separated. The organic layer was evaporated to dryness, and the residue was dissolved in the minimum amount of benzene and purified with a column filled with aluminum oxide (elution with benzene). The first fraction was collected and worked up to give 1.1 g (82%) of XIV in the form of an orange oil. IR spectrum (in chloroform): 3450 cm⁻¹ (NH). Found: N 10.2%. C₁₈H₂₂N₂. Calculated: N 10.5%. Compound XV, which was identical with respect to its IR spectrum and melting point to the substance formed by oxidation of XVI, was obtained by refluxing XIV with two equivalents of chloranil in benzene solution.

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