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# Chemical Behaviors of 1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine toward Organic Hydrogen Acceptors

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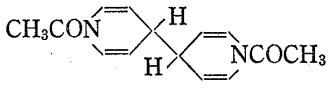
Chemical behaviors of 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine toward organic hydrogen acceptors such as nitrosobenzene, *p*-benzoquinone, dibenzoyldiimide, and 5-benzylidene-1,3-dimethylbarbituric acid were examined to demonstrate its ability in donating hydride and acetylium ion. Reduction processes of these substrates are described and, with the latter two, reductive acetylations of a new fashion are disclosed.

**Keywords**——N-acyldihydropyridine; oxidation; reduction; hydrogen donor; reductive acetylation

Dihydropyridines are known to be readily convertible to pyridines,[2] and the hydride-transfer mechanism of these dehydrogenations has been disclosed[3] in relation to their important role in the biological hydrogen transfer systems such as reduced nicotinamide adenine dinucleotide–nicotinamide adenine dinucleotide (NADH–NAD).[4] Furthermore, the dehydrogenations with a concomitant loss of N-acyl substituent have been reported with certain N-acyl-1,4-dihydropyridines.[5-8] In view of these facts it occurred to us that N-acyldihydropyridines might be used as the reagents which affect a reductive acylation donating both hydrogen and acyl group to the substrates. The present paper deals with successful examples of the reductive acetylation reaction using 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (DTB) which we selected as a model reagent.



DTB

DTB is known to be easily prepared[5,9-11] by the reduction of pyridine with zinc dust in acetic anhydride or in acetic anhydride-ethyl acetate. Its easy oxidations with air, oxygen, iodine, bromine and lead tetraacetate have been reported[5,6,10] describing the formation of 4,4′-bipyridine and pyridine without any indication on the liberated N-acetyl. In order to determine fate of the liberated acetyl preliminary oxidation reactions of DTB were carried out with oxygen bubbled at 45—50° in the presence of butylamine. With an

1) Location: *2-2-1 Oshika, Shizuoka, 422, Japan.*
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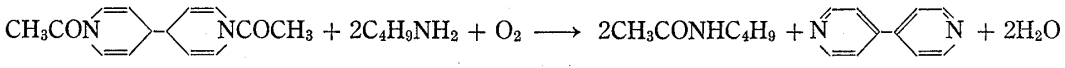
Table I. Oxidation of DTB with Oxygen in the Presence of Butylamine[a]



| Run No. | Solvent | ml | Reaction time (hr) | Yield (%) N-Butyl-acetamide | Yield (%) 4,4'-Bipyridine |
|---|---|---|---|---|---|
| 1 | butylamine | 150 | 8.9 | 89 | 42 |
| 2[b] | chloroform | 20 | 8.7 | 22 | 74 |
| 3 | dioxane | 130 | 5.0 | 17 | 71 |
| 4 | N,N-dimethylformamide | 10 | 5.0 | 59 | 67 |
| 5 | pyridine | 20 | 4.1 | 44 | 67 |
| 6 | dimethyl sulfoxide | 30 | 5.0 | 28 | 26 |

*a*) reaction conditions: DTB 0.02 mole; butylamine 0.048 mole; reaction temperature 45—50°.
*b*) The reaction was carried out at room temperature.

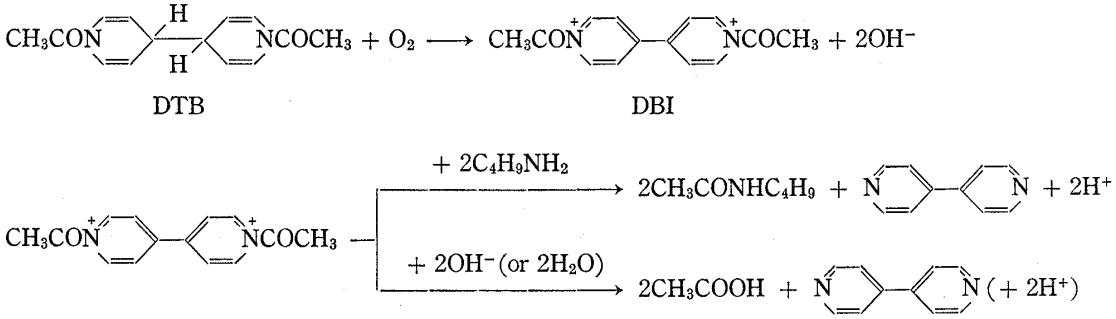


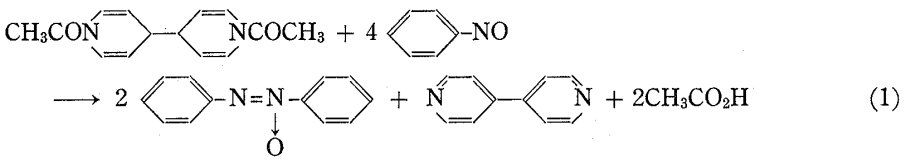

Chart 1

uptake of oxygen the reaction proceeded to give N-butylacetamide and 4,4'-bipyridine with a side formation of pyridine and acetic acid. Effects of several solvents are shown in Table I.

Mechanistically, oxidation with oxygen may generate 1,1'-diacetyl-4,4'-bipyridinium ion (DBI) from DTB as shown in Chart 1. The formations of N-butylacetamide and acetic acid may be brought on competitively by action of DBI on butylamine and hydroxide or water, respectively, donating acetylium ion. In the use of butylamine as a solvent (run 1 in Table I) N-butylacetamide was obtained in the highest yield (89%). No formation of N-butylacetamide from acetic acid in butylamine under the same condition ruled out a possibility of the formation from the liberated acetic acid in place of DBI.

After the above oxidation with oxygen, we were tempted to examine reductions of organic compounds with DTB.

Nitrosobenzene was submitted to the reaction with DTB in chloroform at room temperature in a stream of nitrogen, whereupon azoxybenzene and 4,4'-bipyridine were obtained in 85% and 79% yield, respectively. The reaction is represented by the following equation (Eq. 1).



(1)

A plausible path of the reaction may be illustrated as in Chart 2, where nitrosobenzene first undergoes the reaction with DTB in the mode of accepting both hydride and acetylium ion from DTB to form O-acetyl-N-phenylhydroxylamine, which is converted into azoxybenzene

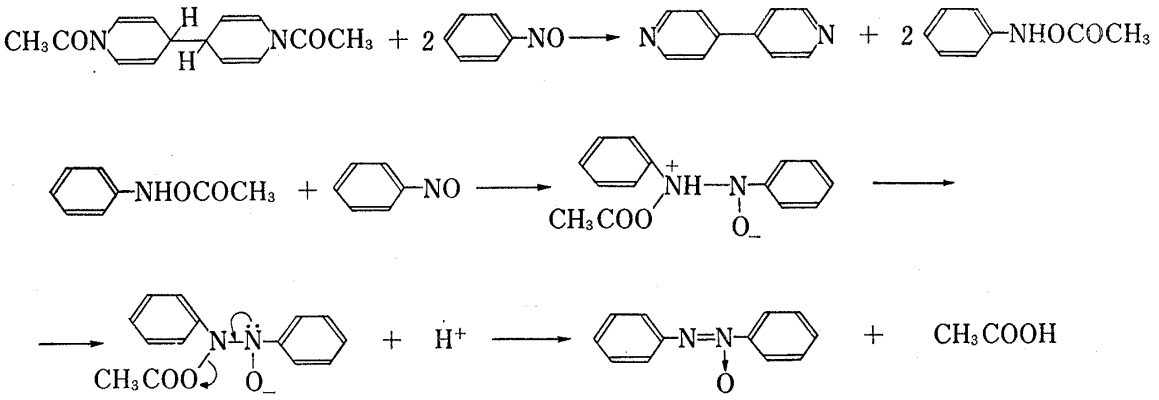
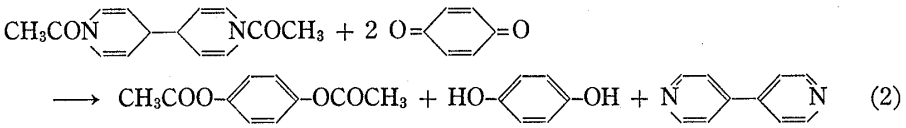


Chart 2

by the reaction with nitrosobenzene as known previously.[12]

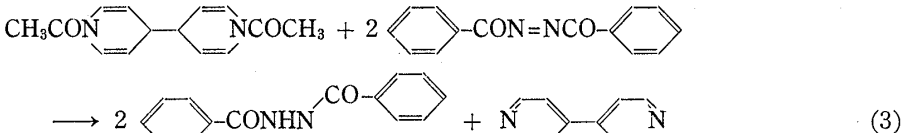
Secondly, *p*-benzoquinone was allowed to react with DTB in chloroform at room temperature. From the reaction solution hydroquinone diacetate, quinhydrone, and prisms, mp 170—171°, were obtained. The last product was identified as a molecular compound consisting of 4,4′-bipyridine and hydroquinone in 2 : 1 molar proportion by nuclear magnetic resonance (NMR) and microanalytical data and further by comparison with an authentic specimen.[13] The reaction can be written by the following equation (Eq. 2), when the molecular compounds are represented by their constituents.



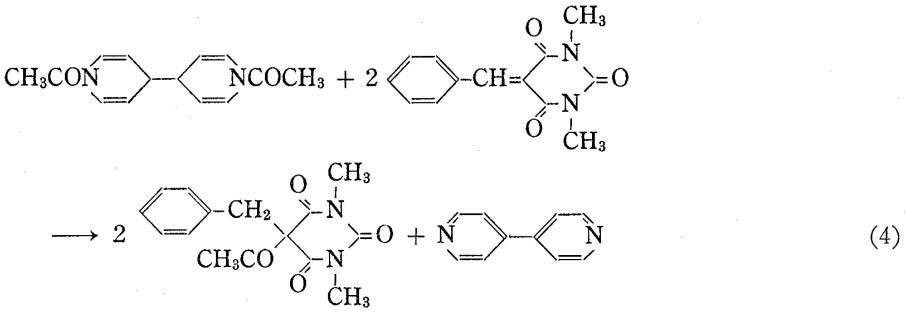
(2)

From the yields of the three products percentages of the conversions into hydroquinone diacetate, hydroquinone and 4,4′-bipyridine can be estimated as 95, 77 and 97, respectively.

We then hoped to search for substrates accepting both hydride and acetylium ion. Demonstrations were made by the use of dibenzoyldiimide and 5-benzylidene-1,3-dimethylbarbituric acid as substrates. When dibenzoyldiimide was allowed to react with DTB in refluxing benzene, 1-acetyl-1,2-dibenzoylhydrazine and 4,4′-bipyridine were obtained in 70% and 100% yield, respectively (see Eq. 3). The former product was identified by converting into 1,2-dibenzoylhydrazine by hydrolysis. 5-Benzylidene-1,3-dimethylbarbituric acid was shown to undergo a reaction with DTB in refluxing chloroform to give 5-acetyl-5-



(3)



(4)

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benzyl-1,3-dimethylbarbituric acid (85%) and 4,4′-bipyridine (71%) (see Eq. 4).

The reaction mode of DTB as demonstrated above with several examples appears to reveal its versatilities as a donor of both hydride and acetylium ion affecting a reductive acetylation.

## Experimental[14]

**Oxidation of DTB with Oxygen in the Presence of Butylamine**——General Procedure: Into a solution of 4.9 g (0.02 mole) of DTB[10] (mp 121—123°) dissolved in an appropriate solvent 3.5 g (0.048 mole) of butylamine was added, and the whole was stirred and warmed at 45—50° while dry oxygen was introduced until oxygen uptake was nearly ceased. The reaction times required and the solvents employed together with their amounts are listed in Table I. The reaction solution was concentrated and the residue was submitted to distillation under reduced pressure to give two main fractions, bp 121—124° (14 mmHg) and bp 108—111° (0.8 mmHg). The former was identified as N-butylacetamide by comparison of its IR spectrum and gas chromatogram with those of authentic specimen. The latter fraction was solidified and identified as 4,4′-bipyridine, needles from water, mp 107—109° (lit.[10] mp 111—112°). NMR ($CDCl_3$) $\delta$: 7.43 (4H, d, $J$=4.8 Hz, $C_{3,3',5,5'}$–H), 8.63 (4H, d, $J$=4.8 Hz, $C_{2,2',6,6'}$–H). *Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.42; H, 5.26; N, 17.71. Yields of the products are listed in Table I. In every run pyridine and acetic acid as the side products were also detected from the reaction solution by gas chromatography.

**Reaction of Nitrosobenzene with DTB**——Into a solution of 3.7 g (0.015 mole) of DTB in 30 ml of $CHCl_3$ 6.4 g (0.06 mole) of nitrosobenzene was gradually added at 20—25°, and the resulting green solution was stirred for 28 hr at room temperature in a stream of nitrogen. The brown reaction solution was concentrated under reduced pressure, and the residue was dissolved into isopropyl ether followed by extraction with 10% HCl. The isopropyl ether solution was washed with 10% $K_2CO_3$ solution and then with water, dried over anhydrous $MgSO_4$, and evaporated. Distillation of the residue under reduced pressure gave 5.0 g of azoxybenzene, bp 129—130° (0.9 mmHg), orange prisms from EtOH, mp 34—35°. Yield, 84%. The foregoing HCl extract was basified and saturated with KOH followed by extraction with benzene, and the resulting benzene solution was dried over anhydrous $MgSO_4$. Concentration of the dried solution followed by distillation under reduced pressure gave 1.8 g of 4,4′-bipyridine. Yield, 78%. Identities of the products were made by comparison of their IR spectra with those of authentic specimens and by mixed melting point test.

**Reaction of *p*-Benzoquinone with DTB**——A solution of 4.3 g (0.04 mole) of *p*-benzoquinone in 25 ml of $CHCl_3$ was dropwise added into a stirred solution of 4.9 g (0.02 mole) of DTB in 25 ml of $CHCl_3$ in a stream of nitrogen at room temperature, and the resulting red solution was stirred for further 4.5 hr. The green crystals with metallic luster deposited in the reaction mixture was collected by filtration and identified as quinhydrone, mp 169—170°, weighing 1.1 g. The filtrate was concentrated under reduced pressure, and the residue was extracted with ether. From the ether solution 3.8 g of hydroquinone diacetate was obtained, plates from EtOH, mp 120—122° (lit.[15] mp 120.5—121°). Identities of the above two products were made by comparison of their IR and NMR spectra with those of authentic specimens and by mixed melting point test. The foregoing ether insoluble residue, weighing 4.1 g, was identified as a molecular compound consisting of 4,4′-bipyridine and hydroquinone in 2: 1 molar proportion. Prisms from EtOH, mp 170—171° (lit.[13] mp 173°). NMR (DMSO-$d_6$) $\delta$: 6.51 (4H, s, $C_6H_4$), 7.69 (8H, d, $J$=4.2 Hz, 4,4′-bipyridine $C_{3,3',5,5'}$–H), 8.52 (2H, s, OH), 8.60 (8H, d, $J$=4.2 Hz, 4,4′-bipyridine $C_{2,2',6,6'}$–H). *Anal.* Calcd. for $C_{26}H_{22}O_2N_4$ ($2C_{10}H_8N_2+C_6H_6O_2$): C, 73.91; H, 5.25; N, 13.26. Found: C, 73.38; H, 5.19; N, 13.32. Identity of this product was also established by comparison of its IR spectrum with that of an authentic specimen and by mixed melting point test.

**Reaction of Dibenzoyldiimide with DTB**——A mixture of 2.5 g (0.01 mole) of DTB and 50 ml of dry benzene was stirred and refluxed in a stream of nitrogen, and the resulting red solution was dropwise added with 4.8 g (0.02 mole) of dibenzoyldiimide[16] (mp 118—120° (decomp.)) dissolved in 50 ml of dry benzene. Rapid fading of the red color of the solution was noted upon addition of dibenzoyldiimide. Heating and stirring were continued for 3 hr in a stream of nitrogen. After cooling, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was extracted with isopropyl ether. From the isopropyl ether extract 1.5 g of 4,4′-bipyridine was obtained. Yield, 100%. The isopropyl

14) All melting and boiling points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi EPI-G2 spectrophotometer. NMR spectra were taken at 60 MHz with a Hitachi R-24 spectrometer using tetramethylsilane as internal standard. Signal multiplicities are represented by s (singlet), d (doublet), and m (multiplet). Gas chromatographies were carried out with a Perkin-Elmer F-11.

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ether insoluble residue, weighing 3.9 g, was identified as 1-acetyl-1,2-dibenzoylhydrazine, prisms from EtOH, mp 165—166° (lit.[17] mp 169—170°). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3196, 1721, 1709, 1658, 1651, 1627. NMR (DMSO-$d_6$) $\delta$: 2.44 (3H, s, $CH_3$), 7.80—7.05 (10H, m, aromatic protons), 11.10 (1H, s, NH). *Anal.* Calcd. for $C_{10}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.32; H, 5.06; N, 9.26. Yield, 70%. Hydrolysis with ethanolic HCl by the usual manner gave 1,2-dibenzoylhydrazine, mp 232—234° (lit.[18] mp 234—238°), identified by comparison of its IR spectrum with that of an authentic specimen and by mixed melting point test.

**Reaction of 5-Benzylidene-1,3-dimethylbarbituric Acid with DTB**——A solution of 2.4 g (0.01 mole) of DTB and 4.9 g (0.02 mole) of 5-benzylidene-1,3-dimethylbarbituric acid[19] (mp 159—160°) in 50 ml of $CHCl_3$ was stirred and refluxed for 7 hr in a stream of nitrogen. After cooling, the reaction mixture was filtered and the filtrate was extracted with 10% HCl. The $CHCl_3$ solution was washed with 10% $K_2CO_3$ and water, dried over anhydrous $MgSO_4$ and evaporated. From the evaporation residue 4.9 g (85%) of 5-acetyl-5-benzyl-1,3-dimethylbarbituric acid was obtained, needles from EtOH, mp 157—159°. NMR ($CDCl_3$) $\delta$: 2.22 (3H, s, $CH_3CO$), 3.05 (6H, s, $CH_3N$), 3.54 (2H, s, $CH_2$), 7.25—6.74 (5H, m, aromatic protons). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.17; H, 5.66; N, 9.45. The foregoing HCl extract was treated in the same manner as described before in the reaction of nitrosobenzene, and 1.1 g (71%) of 4,4′-bipyridine was obtained.

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