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Reaction of N-Methoxypyridinium Salt with Nitroalkanes.—Additive Cleavage Reaction of Pyridine Nucleus[1]

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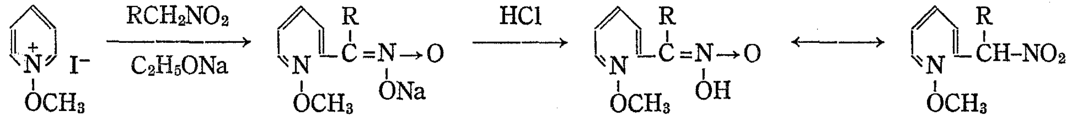
The reactions of N-methoxypyridinium iodide with nitromethane, nitroethane, and 1-nitropropane in the presence of sodium ethoxide in anhydrous ethanol afforded 1-methoxyimino-6-nitrohexa-2,4-diene, 1-methoxyimino-6-aci-nitrohepta-2,4-diene, and 1-methoxyimini-6-aci-nitroocta-2,4-diene, respectively. The spectral behaviors of these products were discussed in relation to the nitro-acinitro prototropy and the assumed reaction mechanism was also offered.

Keywords——N-alkoxypyridinium salt; nitroalkane; base-catalyzed reaction; pyridine ring opening; nitro-acinitro prototropy; conjugated polyene

In the previous paper,[3] it was reported that while the reaction of N-methoxyquinolinium methosulfate with methylketones in aqueous alkali to give quinaldylketones in moderate yields, attempted reactions of N-methoxypyridinium iodide with methylketones under similar conditions resulted in the formation of pyridine *via* liberation of formaldehyde.

In our continued study to explore the new methods for introducing carbon side chain into pyridine nucleus, it was found that N-methoxypyridinium iodide (I) with nitroalkanes in the presence of sodium ethoxide in an absolute ethanol led to the additive cleavage of pyridine nucleus giving the corresponding conjugated nitropolyenes, *e.g.*, 1-methoxymino-6-nitrohexa-2,4-diene (II).

Thus, to the suspension of I in an absolute ethanol was added the equivalent quantity of nitroalkanes and sodium ethoxide at about 5°. After the reaction mixture was kept stirring at room temperature to complete the reaction, the procedure described in the Experimental afforded the corresponding nitropolyenes (II, III, IV) shown in Chart 1.



I

Ⅱ: $R=H$ 61%
Ⅲ: $R=CH_3$ 34%
Ⅳ: $R=C_2H_5$ 5%

Chart 1

Concerning the Structure of Products

Three possible structure (IIa, IIb, IIc)[4] of the product which was obtained from the reaction of I with nitromethane under the above conditions are shown in Chart 2. However the structure–IIa alone satisfies the five data discussed below. i) The infrared (IR) spectrum exhibited $-NO_2$ stretching absorption bands at 1380 and 1555 cm^{-1}. ii) The elementary anal-

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[3] T. Okamoto and H. Takayama, *Chem. Pharm. Bull.* (Tokyo), **11**, 514 (1963).

[4] N.J. Leonard, *J. Am. Chem. Soc.*, **74**, 2110 (1952).

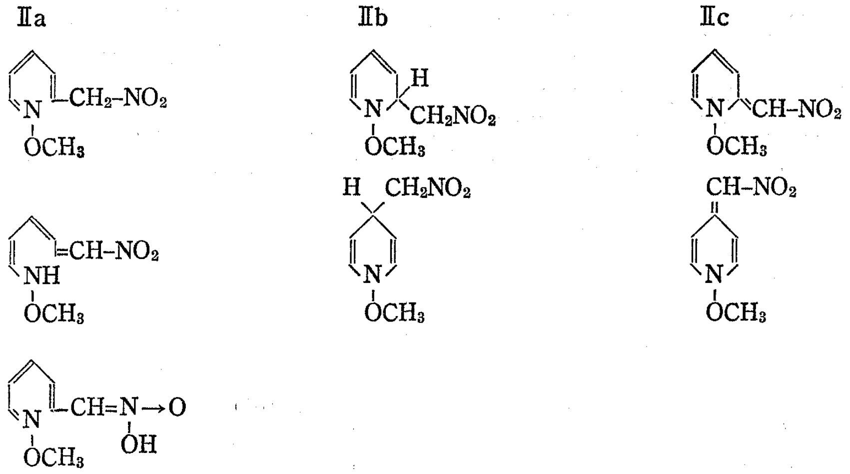

Chart 2

ysis was in good agreement with the calculated value for $C_7H_{10}N_2O_3$. iii) The fact that the ultraviolet (UV) absorption maximum at 276 nm in chloroform shifted dramatically to 354 nm in aq. 1N NaOH solution indicates that II should have two functional groups (conjugated polyene and nitro), which conjugate each other (through nitro–acinitro prototropy) only in an alkaline medium (*cf.* Fig. 1 and Fig. 2). iv) Hydrogenation of II with platinium catalyst in methanol afforded hexamethylenediamine, whose diacetate mp 127°, dibenzoate mp 158—159°, and dihydrochloride mp 240° (dec.) were identified with the respective authentic specimen by mixed melting point determination and IR comparisons. v) The NMR spectrum in $CDCl_3$ showed that II should have ten protons and is good agreement with the structure–IIa: a singlet at 6.15 τ (=N–OC$\underline{H}_3$), a doublet at 5.06 τ (=CH–C$\underline{H}_2$–NO$_2$ J=6.5 Hz), a multiplet at around 3.64τ (4 vinyl protons) and a quartet at around 2.32 τ (–C$\underline{H}$=N–OCH$_3$).

From these considerations, it is reasonable to eliminate the structures-IIb and -IIc for the product. At present, however, an exact geometrical structure (*cis* or *trans*) for IIa has not been determined. The structures of III and IV resulted from the reaction of I with nitroethane and 1-nitropropane respectively, were also deduced to be as indicated from the comparison of their spectra whose chracteristics will be given below, with those of II.

Before to discuss the mechanism of these reactions, it seems worthy to discuss the IR and UV spectra of II, III, and IV, in order to confirm respective structural assignments.

Concerning the IR and UV Spectra of Products

The characteristic IR absorptions of II, III, and IV are listed in Table I. In contrast with the IR spectra of II having the strong characteristic absorption bands of a nitro group both in solid and in chloroform solution, the IR spectra of III and IV showed the absorptions

Table I. Assignment of IR Spectra of Products

R	Polyene δ(CH)			–CH(R)–NO$_2$ ν(NO$_2$)		$\mathrm{C(R){=}\underset{OH}{N}{\rightarrow}O}$ ν(C=N)	ν(OH)
H (II)	901	995	1045	1380	1555	—	—
	(902)	(997)	(1046)	(1378)	(1560)	(—)	(—)
CH_3 (III)	901	990	1047	—	—	1635	2200—3100 (broad)
C_2H_5 (IV)	906$^{a)}$	995	1045	—	—	1645	2200—3050
	(905)$^{b)}$	(993)	(1045)	(1370)	(1555)	(—)	(—)

a) Determined in Tab. KBr (cm^{-1}).
b) Determined in $CHCl_3$ (cm^{-1}).

due to a nitro group only in solution, and in solid state showed the characteristic bands due to acinitro group instead. These facts suggests that nitro-acinitro prototropy in these compounds also depends upon a state change.

The UV spectra of II, III, and IV in chloroform and aq. 1 N-NaOH solution are shown in Fig. 1 and Fig. 2. The figures of the spectra and the spectral changes in both media of these

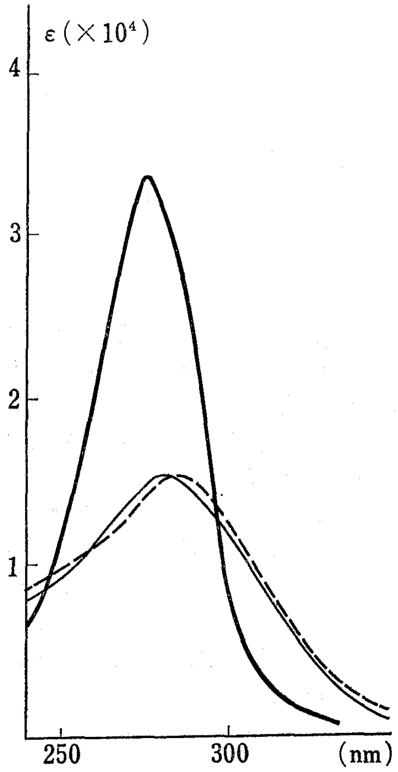

Fig. 1. UV Spectra of II ━━
(in CHCl$_3$) III ----
IV ——

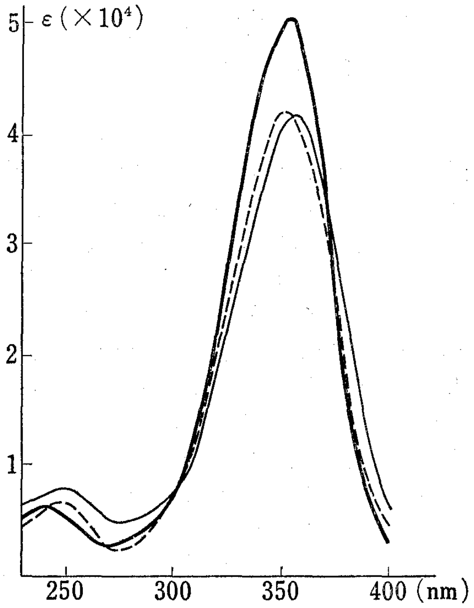

Fig. 2. UV Spectra of II ━━
(in 1N NaOH) III ----
IV ——

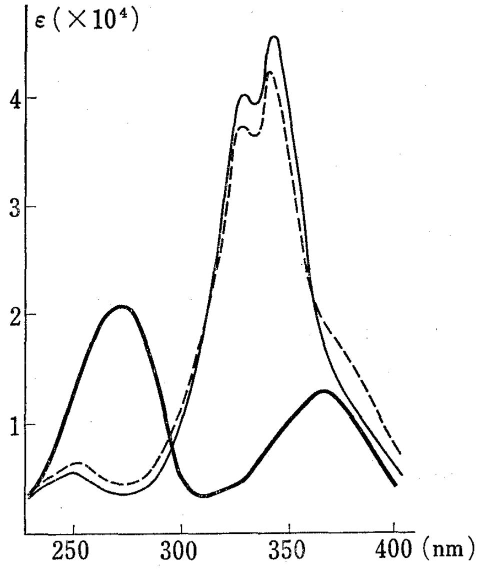

Fig. 3. UV Spectra of II ━━
(in EtOH) III ----
IV ——

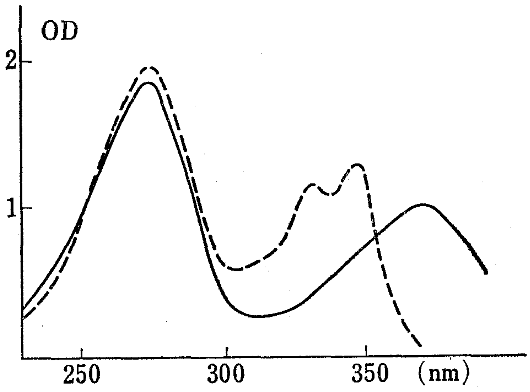

Fig. 4. UV Spectra of II in EtOH ━━ and after Addition of a Drop of 1N HCl ----

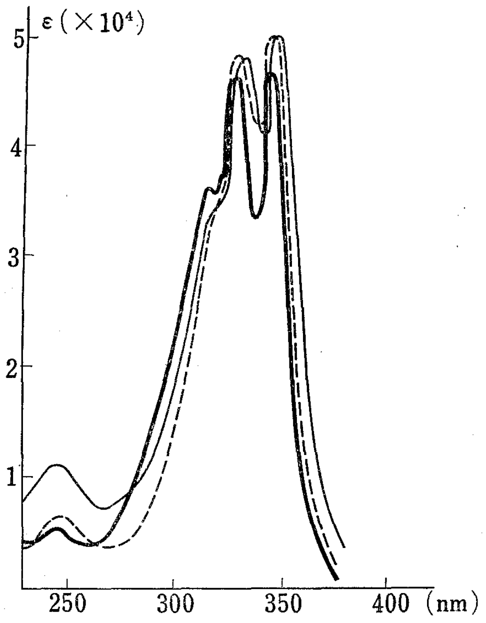

Fig. 5. UV Spectra of Methylnitronate
of II —— (in EtOH)
III ----
IV ——

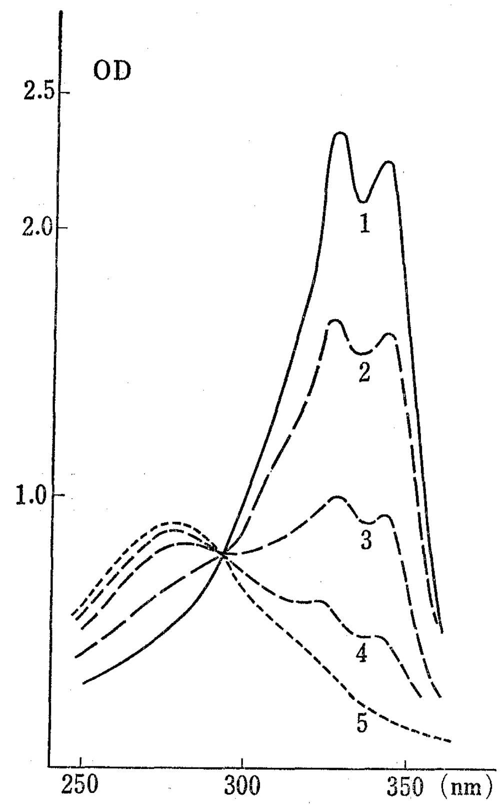

Fig. 6. UV Spectra of III in EtOH during 20 min after Addition of a Drop of 1 N HCl (1--->5)

compounds are quite similar and this fact proved with certainty the presence of the common conjugated system in these compounds.

Furthermore, the absorption maxima of II in ethanol (Fig. 3) showed two peaks at 273 nm (ε=23600) and 367.5 nm (ε=13000), the former corresponded to that in chloroform, the latter to that in aq. 1 N NaOH. Considering from the absorption intensity at the maxima, it seems likely that II in ethanol exists as the equibrium mixture of nitro and acinitro form. On the other hand, the spectra of III and IV in ethanol were quite different from that of II and showed the absorptions only due to acinitro form and were quite similar to those of the methylated compounds (completely fixed as acinitro form) of II, III, and IV in ethanol (Fig. 5) which were derived from the reaction of II, III, and IV with diazomethane.

Moreover, when a drop of dilute HCl was added to the ethanol solution of II, the spectrum was dramatically changed to the pattern similar to that of its methylated compound (Fig. 4). Inversely, when a drop of dilute HCl was added to the ethanol solution of III, the pattern of the spectra was changed gradually to that in chloroform solution with a clear isosbestic point (Fig. 6). These spectral results definitely proved the existance of nitro-acinitro equilibrium in II, III, and IV.

Concerining the Reaction Mechanism

It has been studied[5] that 2- and 4- positions on N-alkoxypridinium ring are very susceptible to nucleophilic attack. In the first step in the present reactions, the nitroalkane anion produced by base, attacks the 2-position on N-methoxypyridinium ring to form 1,2-dihydro

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[5] T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 130, 925, 930 (1959); W.E. Feely and E.M. Beavers, *J. Am. Chem. Soc.*, **81**, 4008 (1959); O. Cerrinka, *Chem. and Ind.*, **1960**, 1482.

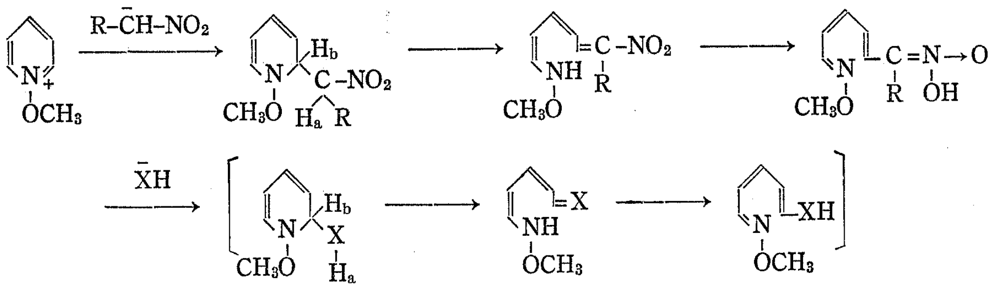

Chart 3

intermediate. The active methylene or methine hydrogen (H_a) neighboring to the nitro group is then eliminated by base to afford the final product by the N-C bond scission. The loss of aromatic system (pyridinium ring) in this process would partly be compensated by the gain of longer conjugated system present in the product. Furthermore, the resulting product is stabilized by the formation of a sodium salt and precipitated out from the reaction mixture. Thus the whole reactions proceeded smoothly to give the final product. This would clearly be consistent with the facts that both the reaction of I with 2-nitropropane and the reaction of N-methoxyquinolinium methosulfate with nitromethane failed to give the N-C bond cleavage product, but merely afforded the parent bases (pyridine and quinoline). In the former case, the failure may be due to the bulkiness of crowded dimethyl-nitromethane anion[$(CH_3)_2$-$\bar{C}$-NO_2] which prevented the attack at 2-position of pyridine ring or more probably due to the fact that if the dihydro-intermediate is formed, it has no active hydrogen (H_a) to be eliminated, thus could not undergo the N-C bond scission. In the latter case, the failure might be due to the difficulty in forming the sodium salt of the corresponding acinitro form in the final stage which requires the unstable quinoid structure due to the loss of benzene system of the quinoline ring.

While systematic studies on the additive cleavage reactions of pyridine nucleus have never been undertaken, scrutinizing our reactions coupled with some analogous reactions,[6] it seems likely to conclude that there could be some necessary conditions to effect the cleavage of pyridine nucleus; These are, i) anionic nucleophiles ($\bar{X}H$) such as $-\bar{C}H-$, $\bar{O}H$,– $\bar{N}H$, must have a hydrogen (H_a) which is more susceptible than that of allylic hydrogen (H_b) to be eliminated by base when 1,2-dihydro intermediate is formed, ii) after scission of N-C bond, the resulting intermediate, if unstable, must be transferred to the more stablized form by a further prototropy.

Experimental

Reaction of N-Methoxypyridinium Iodide (I) with Nitromethane——To a suspension of 32.2 g (0.136 mol) of I in 300 ml of anhydrous ethanol, 8.3 g (0.136 mol) of nitromethane was added and sodium ethoxide solution, prepared from 3.2 g (0.136 atom) of sodium dissolved in 100 ml of anhydrous ethanol, was added dropwise during 1 hr at about 5°. The suspended I gradually dissolved and a pale yellow precipitate began to produce. The mixture was stirred for 3 hr at room temperature, cooled, and the precipitate was collected by filtration. The dried yellow filter cake weighed 15 g. The filtrate was evaporated to dryness under a reduced pressure and 7.3 g of brownish yellow solid was obtained. Both these solids were dissolved in a small quantity of water and cautiously neutralized with 2 N HCl after addition of cracked ice. The precipitate there by formed was extracted with ether, the ethereal solution was washed with cold water, dried over anhyd. Na_2SO_4, and ether was evaporated, leaving 14.08 g (61%) of crude crystals (mp 88—91° (dec.)) of 1-methoxyimino-6-nitrohexa-2,4-diene (II). Recrystallization from methanol gave pale yellow needles, mp 91—92°

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[6] T.H. Anderson, *Ann.*, **105**, 339 (1858); von Th Zinke, *Ann.*, **330**, 361 (1904); **333**, 296 (1904); **341**, 365 (1905); H.T. Bucherer and J. Schenkel, *Chem. Ber.*, **41**, 1346 (1908); E. Koenig and H. Greiner, *Chem. Ber.*, **64**, 1045 (1931); F.W. Bergstrom, *Chem. Rev.*, **35**, 77 (1935); F. Kröhnke, *Ann.*, **597**, 87 (1955); Dobeneck, *Chem. Ber.*, **95**, 1484 (1962).

(dec.). *Anal.* Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.32; H, 5.60; N, 16.12. UV $\lambda_{max}^{1N\ NaOH}$ nm (ε): 244 (6200), 354 (51300); λ_{max}^{EtOH} nm (ε): 273 (23600), 367—368 (13000); $\lambda_{max}^{CHCl_3}$ nm (ε): 276 (33700). IR cm^{-1}: ν_{NO_2} 1380, 1555 (KBr); δ_{C-H} 901, 995, 1045 (KBr); ν_{NO_2} 1378, 1560 ($CHCl_3$); δ_{C-H} 910, 997, 1046 ($CHCl_3$). NMR ($CDCl_3$): δ 6.15 (3H, singlet), 5.06 (2H, doublet, J=6.5 Hz), 3.64 (4H, multiplet), 2.32 (1H, quartet).

Reaction of I with Nitroethane——To a suspension of 23.7 g (0.1 mol) of I and 7.5 g (0.1 mol) of nitroethane in 230 ml of anhyd. ethanol, was added dropwise, sodium ethoxide solution prepared from 2.3 g (0.1 atom) of sodium dissolved in 100 ml anhyd. ethanol. The reaction mixture was treated according to the same procedure mentioned above. The crude sodium salts (20.5 g) of product were neutralized with 2 N HCl solution. The precipitate was extracted with ether, the ether solution was washed with cold water, dried over anhyd. Na_2SO_4, and the ether was evaporated leaving 6.18 g (34%) of crude crystals of 1-methoxyimino-6-aci-nitrohepta-2,4-diene (III). Recrystallization from ether gave pale yellow needles, mp 112—113° (dec.). *Anal.* Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.28; H, 6.55; N, 15.30. UV λ_{max}^{EtOH} nm (ε): 251 (6600), 330 (37000), 343 (42500); $\lambda_{max}^{1N\ NaOH}$ nm (ε): 250 (6700), 353 (42300); $\lambda_{max}^{CHCl_3}$ nm (ε): 283 (15400). IR cm^{-1}: ν_{O-H} 2200, 3100 (broad) (KBr); $\nu_{+N=C}$ 1635 (KBr); δ_{C-H} 901, 990, 1045 (KBr).

Reaction of I with 1-Nitropropane——To a suspension of 5.24 g (0.022 mol) of I and 1.96 g (0.022 mol) of 1-nitropropane in 50 ml of anhyd. ethanol, was added dropwise, sodium ethoxide solution prepared from 0.510 g (0.022 atom) of sodium dissolved in 20 ml of anhyd. ethanol, during 15 minutes at about 5°. After the reaction mixture was stirred for 1 hr, the resulting dark yellow solution was concentrated to dryness under a reduced pressure. The solid thus obtained, was dissolved in cold water and cautiously neutralized with 2 N HCl. The precipitate was collected by filtration, washed with water and a small quantity of cold ethanol, and recrystallization from ether gave 0.222 g (5.1%) of pale yellow needles, mp 110—112° (dec.) of 1-methoxyimino-6-aci-nitroocta-2,4-diene (IV). *Anal.* Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.31; H, 7.09; N, 13.95. UV λ_{max}^{EtOH} nm (ε): 247—248 (5600), 330 (40000), 345 (45300); $\lambda_{max}^{1N\ NaOH}$ nm (ε) 252 (8300), 356 (41800); $\lambda_{max}^{CHCl_3}$ nm (ε): 282 (15500). IR cm^{-1}: ν_{O-H} 2200—3050 (KBr), $\nu_{+N=C}$ 1645 (KBr), ν_{NO_2} 1370, 1555 ($CHCl_3$), δ_{C-H} 906, 995, 1045 (KBr).

Catalytic Hydrogenation of II——A mixture of 1.70 g (0.01 mol) of II and platinum black (500 mg of PtO_2) in 60 ml of methanol, was shaken under hydrogen atmosphere under an ordinary pressure. After the reaction was completed in absorbing 0.065 mol of hydrogen, the catalyst and methanol were removed. The remained oil was dissolved in acetic anhydride and heated on steam bath for 1 hr. The acetic anhydride was removed under a reduced pressure, the residue was poured into a small quantity of water, neutralized with $NaHCO_3$, and extracted with chloroform. The chloroform solution dried over anhyd. Na_2SO_4, was evaporated to give viscous oil, which was chromatographed on alumina column. The colorless crystals thereby purified were recrystallized from acetone to afford hexamethylenediamine diacetate, colorless needles, mp 127° (360 mg). *Anal.* Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.73; H, 9.46; N, 13.72. A solution of 50 mg of the crystals (mp 127°) obtained above in 1 ml of dil. HCl was heated and evaporated to dryness. The resulted solid was recrystallized from ethanol–ether to afford 35 mg of hexamethylenediamine dihydrochloride, mp 240° (dec.). An aqueous solution of the hydrochloride was neutralized with K_2CO_3 and extracted with ether. The ethereal solution was concentrated to give an oil, which was treated with benzoyl chloride in pyridine affording colorless needles, mp 158—159°, of hexamethylenediamine dibenzoate. These derivatives of the hydrogenation product were identified with those of hexamethylenediamine by IR comparison and admixture with those of authentic sample derived from commercial hexamethylenediamine.

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