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N-NITROSOHYDROXYLAMINES III. REACTION OF N,O-DIBENZYL-N-NITROSOHYDROXYLAMINES WITH ACETIC ANHYDRIDE

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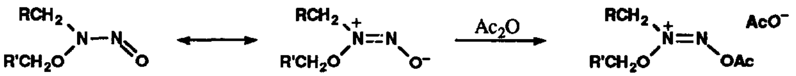
Abstract

The major path of the reaction of N,O-dibenzyl-N-nitrosohydroxylamines (3) with acetic anhydride appears to proceed by initial radical cleavage of the N-N bond with loss of nitric oxide. The formation of the main products (5) may be rationalized by subsequent transformation of the resulting hydroxylamino radicals.

Introduction

The strong contribution of the 1,3-dipolar form to the structure of N,O-disubstituted N-nitrosohydroxylamines (**1**)[1] suggests that as with N-nitrosamines,[2] acylation might occur at the nitroso oxygen to give **2** (*Eq.* 1).

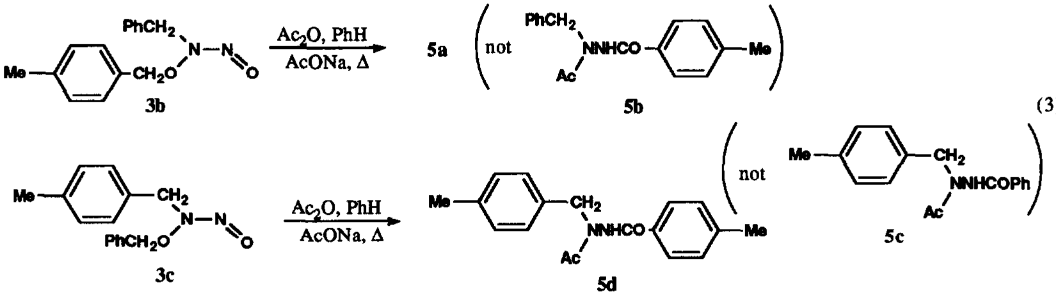


1 **2** (1)

A previous communication briefly described the unusual formation of 1-acetyl-2-benzoylbenzylhydrazine (**5a**) from the reaction of N,O-dibenzyl-N-nitrosohydroxylamine (**3a**) with acetic anhydride.[3] At the outset of this investigation, three assumptions were made in order to ascertain the possible mode for the formation of **5a**. It was first assumed that the *primary* product of that reaction was 2-benzoylbenzylhydrazine (**4**), which would undergo subsequent acetylation to give the isolated product **5a**; thus based on the comparison of the molecular formula of **3a** ($C_{14}H_{14}N_2O_2$) and **4** ($C_{14}H_{14}N_2O$), this reaction appeared to involve a reduction (or more correctly, a "deoxygenation"). Second, since the O-benzyl group already had a C-O bond, it was presumed to have been the source of the benzoyl group of **4**. And finally, it was assumed that *both* nitrogens of **5a** (and of **4**) originated from the *same* molecule of **3a**. Based on these assumptions, several mechanisms for the formation of **5a** were considered and tested. However, there always existed some discrepancies between the experimental results and the possible by-products anticipated from these putative mechanisms.

3a **4** **5a** (2)

Since these mechanistic considerations had suggested that acetate ion might play an important role, the reaction was repeated in the presence of added acetate ion. Indeed, the reaction was completed within half the time required under the original conditions (from 48 hrs to 24 hrs). Once the beneficial effect of the acetate ion and the identity of the major by-products were established, the rearrangement of **3a** with benzoic anhydride was carried out in the presence of sodium benzoate in an attempt to facilitate the work-up procedure and the isolation of the products and in order to examine some of the scope of the rearrangement. As expected, 1,2-dibenzoylbenzylhydrazine was isolated and characterized. Surprisingly however, a similar reaction of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**) also gave *1,2-dibenzoylbenzylhydrazine*. It was soon discovered that the reaction of **3b** and of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**) with acetic anhydride gave **5a** and 1-acetyl-2-(*p*-toluyl)-*p*-methylbenzylhydrazine (**5d**) respectively. These results were in violent contradiction with the assumption that the benzoyl group of **5** originated from the O-benzyl substituents. Had this been true,

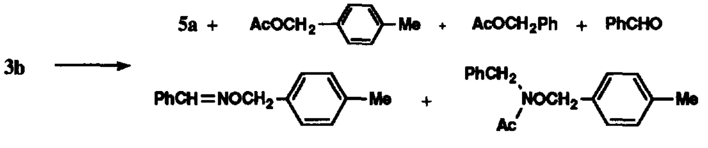


3b 5b 3c 5d 5c (3)

the product of the reaction of **3b** and **3c** should have been 1-acetyl-2-(*p*-toluyl)benzylhydrazine (**5b**) and 1-acetyl-2-benzoyl-(*p*-methylbenzyl)hydrazine (**5c**) respectively.

Results and Discussion

In addition to trace amounts of benzaldehyde, the reaction of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**, 4.9 mmol) with acetic anhydride (5 mmol) in the presence of sodium acetate in benzene at reflux gave 1-acetyl-2-benzoylbenzylhydrazine (**5a**, 1.3 mmol), *p*-methylbenzyl acetate (2.3 mmol), benzyl acetate (0.01 mmol), O-(*p*-methylbenzyl)benzaldoxime (**6**, 0.7 mmol) and N-acetyl-N-benzyl-O-(*p*-methylbenzyl)hydroxylamine (**7**, 0.7 mmol); similar results were obtained from the reaction of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**). The reaction of

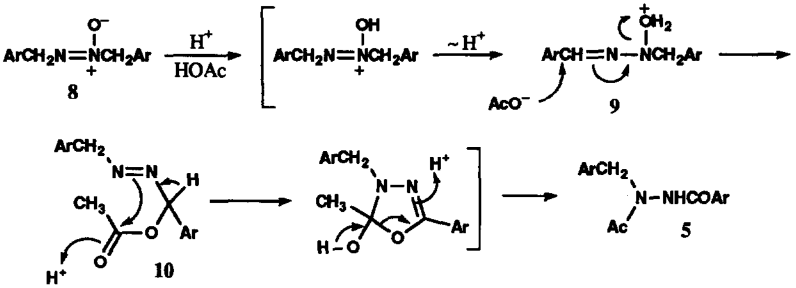


6 7 (4)

(^{15}N)N-nitroso-N-(*p*-methylbenzyl)-O-benzylhydroxylamine (^{15}N **3c**) with acetic anhydride was carried out under the same conditions and gave the same results as in the case of the reaction of unlabelled of **3c**. The mass spectrum of 1-acetyl-2-(*p*-toluoyl)-*p*-methylbenzylhydrazine (**5d**), obtained from this reaction agreed with that of the authentic *unlabelled* hydrazine.

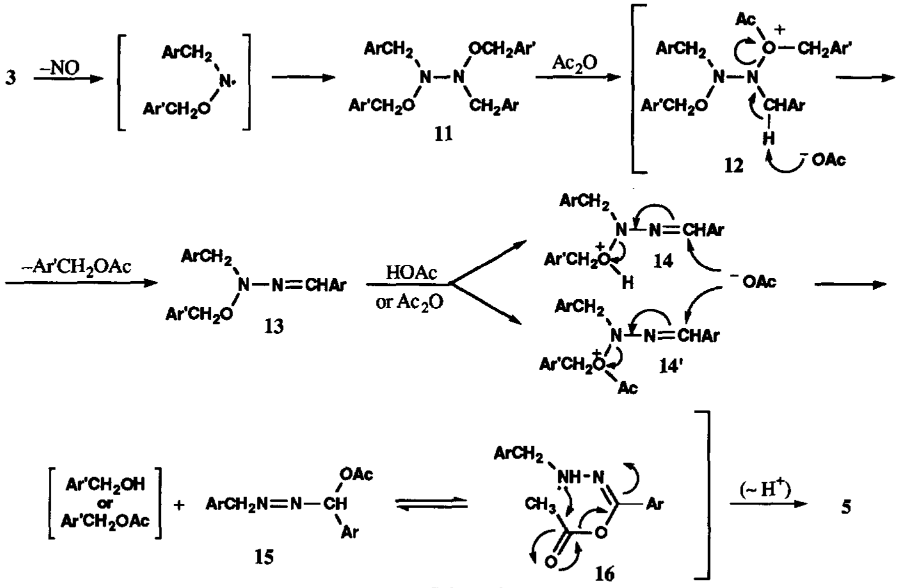
Concurrent with this investigation, we carried out a study of the thermal decomposition of **3** and characterized ω,ω'-azoxytoluenes (**8**) as one of the products.[4] Thus the ω,ω'-azoxytoluenes seemed to fit the requirements of the first of our initial assumptions (*vide supra*) and as such were good candidates to explain the formation of **5**; indeed Gillis and Shimmel[5] had reported the rearrangement of azoxy compounds to the corresponding 2-acyl-1-alkylhydrazines *under acidic conditions*. Although ω,ω'-azoxytoluene (**8**, Ar = Ph) did provide **5a** in acetic acid at reflux, its treatment with acetic anhydride under conditions similar to our reaction conditions afforded only trace amounts of **5a**, detected by tlc. In a further control reaction, the reaction of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**) and acetic anhydride was carried out in the presence of ω,ω'-azoxytoluene (**8**) under the same conditions; 1-acetyl-2-benzoylbenzylhydrazine (**5a**), the expected product of the rearrangement of **8**, was *not* formed and only the usual products (*vide supra*) were obtained, in addition to recovered **8**. The mechanism for the formation of 1-acetyl-2-benzoylbenzylhydrazine (**5a**) from ω,ω'-azoxytoluene (**8**) under acidic conditions[5,6] may be rationalized as depicted in *Scheme* 1. Protonation of the negative oxygen of **8** followed by proton transfer from C to O would lead to **9**. Attack of acetate ion on the aldehydic carbon of **9** and subsequent loss of water would then afford azo intermediate **10**; intramolecular transacylation will finally lead to 1-acetyl-2-benzoylbenzylhydrazine (**5a**) (*Scheme* 1).

The failure of the ω,ω'-azoxytoluenes **8** to account for the formation of the acylhydrazines (e. g. **5a**) prompted us to consider the dialkoxyhydrazines (**11**)[4] as possible sources of the rearranged products (*Scheme* 2). We have previously provided presumptive evidence for their participation in the thermal decomposition of 3.[4a] Indeed, O-acetylation of **11** followed



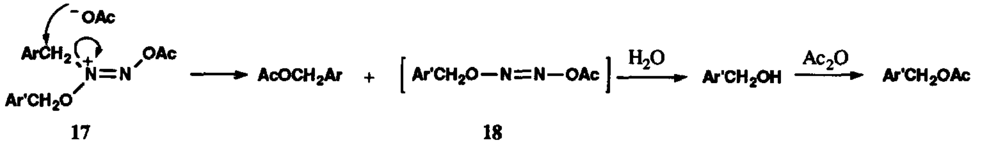
Scheme 1

by loss of benzyl acetate, could lead to **13**. Protonation (or acetylation) of the oxygen of **13** followed by the addition of acetate ion to the aldehydic carbon of **14** (**14'**) will afford azo intermediate **15** with concurrent loss of the benzyl alcohol (or benzyl acetate). Tautomerization of **15** to **16** and subsequent intramolecular transacetylation of **16** followed by proton transfer



Scheme 2

would provide **5**. The direct acetylation of N,O-dibenzylhydroxylamine (from the denitrosation of **3a**)[6] or of **3a** itself[7] accounts for the formation of the N-acetyl-N,O-dibenzylhydroxylamine.[8] The formation of the minor products such as the benzyl acetate (from the N-benzyl portion) may be viewed as arising *via* direct displacement on O-acetyl-N,O-dibenzyl-N-nitrosohydroxylaminium ion (**17**) as shown in *Eq*. 5.



(5)

EXPERIMENTAL SECTION

All mps and bps are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137B spectrophotometer (KBr pellets or NaCl plates). Unless otherwise noted, NMR spectra were determined on a Hitachi Perkin-Elmer R-24 (60MHz) and Varian XL 300 in carbon tetrachloride for liquid samples or deuteriochloroform for solid samples using tetramethylsilane as the internal standard. Mass spectra were recorded on a Varian Mat 8200 Mass spectrometer. Elemental analyses were carried out by the Microanalysis Laboratories of the University of Massachusetts at Amherst. Gas liquid chromatographic analyses were performed on a GOW-MAC Instruments Co. Gas Chromatograph, Series 550 Thermal Conductivity Detector with DC-200 column, helium as a carrier gas (5 psi) (column, detector and injection port temperatures 110°, 135° and 120° respectively); the retention times (min.) of compounds under those conditions are benzyl alcohol (11), *p*-methylbenzyl alcohol (20), benzaldehyde (7), *p*-tolualdehyde (15), benzyl acetate (22), *p*-methylbenzyl acetate (47), benzonitrile (12) and *p*-toluonitrile (23). All solvents used for the reaction were dried and kept over molecular sieves (4Å). All products obtained from reactions were compared with authentic samples by tlc, ir and nmr spectra. Physical constants for benzyl alcohol, *p*-methylbenzyl alcohol, *p*-chlorobenzyl alcohol, benzaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, benzyl acetate, *p*-methylbenzyl acetate, *p*-chlorobenzyl acetate, benzonitrile, *p*-toluonitrile were obtained from one of the following sources: "CRC Handbook of Chemistry and Physics", "Merck Index", "Dictionary for Organic Compounds" and Fieser's "Reagents for Organic Synthesis". The hydroxylamines and oximes obtained were characterized previously.[6]

Reaction of N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b) with Benzoic Anhydride.- A mixture of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (2.56 g, 10 mmol),[6] sodium benzoate (1.44 g, 10 mmol) and benzoic anhydride (2.26 g, 10 mmol) in 40 mL of benzene was heated at reflux for 24 hrs under a nitrogen atmosphere. After removal of the solid by filtration, the benzene solution was washed with water, saturated aqueous $NaHCO_3$ and dried over $MgSO_4$; the solvent was then evaporated to yield 3.51 g of an oil, which upon addition of carbon tetrachloride and pet. ether and standing provided 0.36 g (1.1 mmol) of 1,2-dibenzoylbenzylhydrazine, mp. 149-150°, lit.[3] 153-154°. The mother liquor was concentrated to an oil which was then chromatographed on SiO_2 (50 g) using benzene as eluent to give 2.52 g of a mixture of O-(*p*-methylbenzyl) benzaldoxime, *p*-methylbenzyl benzoate, benzyl benzoate and *p*-tolualdehyde. When the eluent was changed to methanol, 0.44 g (1.3 mmol) of N-benzoyl-N-benzyl-O-(*p*-methylbenzyl)hydroxylamine, mp. 71.5-72.5°, was obtained whose mass spectrum (chemical ionization) gave M+1 at 332.

Reaction of N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b) with Acetic Anhydride.- A mixture of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**, 1.26 g, 4.9 mmol),[6] acetic anhydride (0.51 g, 5 mmol) and sodium acetate (0.43 g, 5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. The benzene solution was washed with water and saturated $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the benzene left 1.35 g of an oil which was dissolved in a mixture of carbon tetrachloride (5 mL) and pet. ether (3 mL); upon cooling 1-acetyl-2-benzoylbenzylhydrazine (0.29 g, 1.1 mmol) crystallized, mp. 119-120.5°.[9] The filtrate was concentrated and the residual oil was chromatographed on silica gel (50 g) using benzene as eluent to yield an additional 0.2 mmol of 1-acetyl-2-benzoylbenzylhydrazine, O-(*p*-methylbenzyl)benzaldoxime (0.7 mmol), *p*-methylbenzyl acetate (2.3 mmol), benzyl acetate (0.01 mmol), N-acetyl-N-benzyl-O-(*p*-methylbenzyl)hydroxylamine (0.7 mmol) and trace amounts of benzaldehyde.

Reaction of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3c) with Acetic Anhydride.- A mixture of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**, 1.26 g, 9 mmol),[6] acetic anhydride (1.51 g, 5 mmol) and sodium acetate (0.43 g, 5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. Work-up as previously described afforded 1.27 g of an oil to which carbon tetrachloride and pet. ether were added. Upon standing overnight, 0.35 g (1.2 mmol) of 1-acetyl-2-(*p*-toluyl)-*p*-(methylbenzyl)hydrazine, mp. 132.5-134°, crystallized as a white solid, whose nmr and ir spectra were superimposable upon those of an authentic sample, mp. 137-138°, prepared from the acetylation of *p*-methylbenzylhydrazine with acetyl chloride (2:1) in ether followed by treatment with *p*-toluyl chloride and triethylamine in ether by the procedure described by Aylward *et al.*[9]

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.02; H, 6.69; N, 9.52

The filtrate was concentrated to give 0.9 g of an oil, which was then chromatographed on SiO_2 (50 g) using benzene as an eluent to give O-benzyl *p*-tolualdoxime (0.4 mmol), *p*-methylbenzyl acetate (0.9 mmol), benzyl acetate (2.6 mmol), benzaldehyde (0.1 mmol) and N-acetyl-N-(*p*-methylbenzyl)-O-benzylhydroxylamine (0.7 mmol).

Reaction of N,O-Dibenzyl-N-nitrosohydroxylamine (3a) with Acetic Anhydride. 1:1 Ratio.- A mixture of N,O-dibenzyl-N-nitrosohydroxylamine (**3a**, 1.21 g, 5 mmol), acetic anhydride (0.51 g, 5 mmol) and sodium acetate (0.41 g, 5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. The benzene solution was washed with water and saturated $NaHCO_3$, dried over $MgSO_4$ and the benzene was evaporated *in vacuo* to give 1.09 g of an oil. Carbon tetrachloride and pet. ether were added to the oil and the mixture was allowed to stand overnight to yield 0.27 g (1.0 mmol) of 1-acetyl-2-benzoylbenzylhydrazine, mp. 119-120°, lit.[9] 124°. The filtrate was concentrated *in vacuo* to give 0.83 g of an oil, which was chromatographed on silica gel (50 g); in addition to trace amounts of benzaldehyde, elution with chloroform afforded benzyl acetate (3.0 mmol) and O-benzylbenzaldoxime (1.0 mmol) in the first fraction and N-acetyl-N,O-dibenzylhydroxylamine[9] (0.6 mmol) and benzyl alcohol (0.1 mmol) in the second fraction; the yields were estimated by nmr.

1:2 Ratio.- A mixture of N,O-dibenzyl-N-nitrosohydroxylamine (**3a**, 1.21 g, 5 mmol), acetic anhydride (1.02 g, 10 mmol) and sodium acetate (0.82 g, 10 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. After work-up as described in the previous procedure, the benzene was evaporated *in vacuo* to give 1.22 g of an oil, to which carbon tetrachloride and pet. ether were added; 1-acetyl-2-benzoylbenzylhydrazine (0.32 g, 1.2 mmol), mp. 120-121°, was obtained upon standing. The filtrate was concentrated to give an oil (0.87 g), which contained O-benzylbenzaldoxime (3.4 mmol), benzyl acetate (0.9 mmol) and N-acetyl-N,O-dibenzylhydroxylamine (0.7 mmol); the yields were estimated by nmr.

2:1 Ratio.- A mixture of 1.21 g (5 mmol) of N,O-dibenzyl-N-nitrosohydroxylamine (**3a**), acetic anhydride (0.25 g, 2.5 mmol) and sodium acetate (0.21 g, 2.5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. After work-up as described in the previous procedure, 1.12 g of a viscous liquid was obtained, from which 0.25 g (0.9 mmol) of 1-acetyl-2-benzoylbenzylhydrazine, mp. 119-120.5°, crystallized upon addition of carbon tetrachloride and pet. ether. The filtrate was concentrated to give 0.83 g of an oil which was then separated by chromatography on SiO_2 (50 g) using chloroform as an eluent; in addition to 1.1 mmol of benzyl alcohol, benzyl acetate (1.9 mmol), O-benzylbenzaldoxime (0.9 mmol), N-acetyl-N,O-dibenzylhydroxylamine (0.8 mmol) and additional amounts of 1-acetyl-2-benzoylbenzylhydrazine (0.1 mmol, total yield of 1.1 mmol isolated); the yields were estimated by nmr. Trace amounts of benzaldehyde were detected by nmr.

Control Reaction of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3c) with Acetic Anhydride (2:1).- A mixture of 1.26 g (4.9 mmol) of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**), acetic anhydride (0.26 g, 2.5 mmol) and sodium acetate (0.22 g, 2.5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under a nitrogen atmosphere. After the same work-up as described previously, carbon tetrachloride and pet. ether were added to the oil (1.22 g) obtained; upon standing in the refrigerator overnight, 0.11 g (0.04 mmol) of 1-acetyl-2-(*p*-toluyl)-(*p*-methylbenzyl)hydrazine was obtained. The filtrate was concentrated to give an oil (1.10 g) which was chromatographed on silica gel (50 g) and pet ether/benzene, benzene, $CHCl_3$ and MeOH were used as eluents in this order and gave benzyl alcohol (1.1 mmol), benzyl acetate (1.7 mmol) *p*-methylbenzyl acetate (0.3 mmol), O-benzyl *p*-tolualdoxime (0.7 mmol), benzaldehyde (0.1 mmol), N-acetyl-N-(*p*-methylbenzyl)-O-benzylhydroxylamine (0.6 mmol), trace amounts of *p*-tolualdehyde and 1-acetyl-2-(*p*-toluoyl)-*p*-methylbenzylhydrazine (total yield: 1.2 mmol); the yields were estimated by nmr and vpc.

Reaction of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine [^{15}NO (3d)] with Acetic Anhydride.- A mixture of the labeled N-nitrosohydroxylamine (**3d**, 1.29 g, 5 mmol), acetic anhydride (0.51 g, 5 mmol) and sodium acetate (0.42 g, 5 mmol) in benzene (20 mL) was heated to reflux for 24 hrs under nitrogen. After work-up as described in the previous procedure, 1.30 g of an oil was obtained and carbon tetrachloride (5 mL) and pet. ether (27 mL) were added to the oil and upon standing gave 0.23 g of a white solid, mp. 121.5-140° which was recrystallized from ether to afford white crystals, mp. 137-138°. The nmr and ir spectra were superimposable on those of authentic 1-acetyl-2-benzoylbenzylhydrazine and its mass spectrum demonstrated the absence of the label, M^+ 296.

Reaction of ω,ω'-Azoxytoluene in Acetic Acid.- A mixture of ω,ω'-azoxytoluene (0.45 g, 2mmol)[10] in acetic acid (10 mL) was heated to reflux for 20 hrs. The cooled reaction mixture was poured into 30 g of ice-water and the products were extracted into 30 mL of ether. The ethereal layer was washed with water, saturated $NaHCO_3$ and water, dried over $MgSO_4$ and the ether was evaporated *in vacuo* to an oil (0.38 g). Its nmr spectrum and tlc showed the presence of benzyl acetate, benzalazine, benzaldehyde as minor products and 1-acetyl-2-benzoylbenzylhydrazine as the major product, and the yields were estimated to be 0.1 mmol, 0.2 mmol, 0.4 mmol and 1.3 mmol respectively by nmr; some of the 1-acetyl-2-benzoylbenzylhydrazine (0.13 g, 0.5 mmol), mp. 120-121°, was isolated from the mixture.

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† Taken from the Ph. D. Thesis of K. Kano, University of Massachusetts at Amherst, May 1986. For part II, see ref. 4a.

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