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OCTALINE AND DECALONE DERIVATIVES FROM A NEW ANNULATION REACTION IN ENAMINE FIELD

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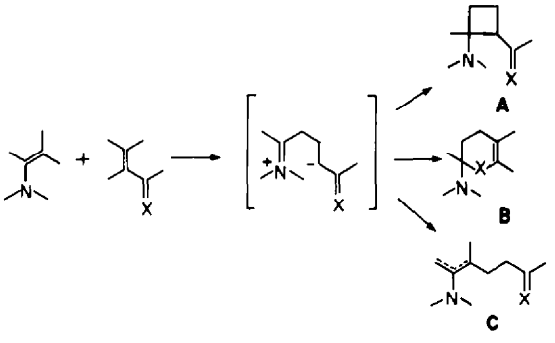
Abstract—An octaline system is obtained from the reaction between 2-cyclohexenyl-1-morpholino-ethene and β-nitrostyrene, carried out under kinetic control. By hydrolysis, it is converted to a 1-decalone derivative, which is also a kinetic control product. The stereochemical aspects of formation and equilibration of the products are examined.

It is well known that enamines react with electrophiles to form cyclobutane adducts (A), heterocyclic adducts (B) and alkylated enamines (C) (Scheme 1).[1]

In the course of our studies concerning the reactivity of substituted amino-ethenes towards various electrophiles,[2] a new cyclization reaction has been found. This reaction has been studied extensively, as formation of an octaline system, "via" enamine and under kinetic control, is unusual.



Scheme 1.

RESULTS AND DISCUSSION

Reaction of β-nitrostyrene with 1 - cyclohexenyl - 1 - morpholino - ethene (**1**) lead to a mixture of an open chain enamine **2**† and of a cyclic compound **3** in ratio 25:75 (Scheme 2).

Enamine **2** could not be isolated but examination of the NMR spectrum of the crude reaction mixture enabled the vinylic proton signal for the cyclohexene ring to be assigned. The presence of **2** was confirmed by hydrolysis of the reaction mixture and successive isolation of the α,β unsaturated ketone **4**, identified by the usual spectroscopic methods.

The octaline **3** was isolated and was assigned the structure 1,2,3,4,4a,5,6,7 - octahydro - 5 - nitro - 8 - morpholino - 6 - phenyl - (4aα,5β,6α) - naphthalene, on the basis of IR and NMR data. The IR spectrum in fact showed the characteristic tetrasubstituted enaminic double bond absorption[3] at 1670 cm^{-1} and the asymmetrical nitro band at 1542 cm^{-1}. The NMR spectrum showed that the proton at C-5, δ5.20, was a doublet of doublets with $J_{5,6}$ = 12.0 Hz and $J_{4a,5}$ = 6.75 Hz. The coupling constant of 12.0 Hz indicated that both C-5 and C-6 hydrogens were axial, while that of 6.75 Hz indicated that the C-4a hydrogen was equatorial.[4]

Acidic hydrolysis of **3**, carried out under kinetic control, lead to the ketone **5**, which was assigned the structure of 4 - nitro - 3 - phenyl - (3α,4β,4aα,8aα) - 1(2H) - octahydro - naphthalenone. The IR spectrum showed carbonyl absorption at 1720 cm^{-1} and the NMR analysis of the ABMX spin-system permitted the configurational assignments to be made (Fig. 1). Therefore the decalone system **5** with the *cis* ring junction derived from the octaline system **3** by the stereoelectronic antiparallel attack of the proton on C-8a of **3**, followed by the attack of H_2O on the immonium salt.

When **5** was refluxed with TsOH in benzene solution, the product of the reaction was a 55:45 mixture of **5** and its stereoisomer **6**, which was isolated. This new decalone system was assigned the structure of 4 - nitro - 3 - phenyl - (3α,4β,4aα,8aβ) - 1(2H) - octahydro - naphthalenone, on the basis of NMR data (Fig. 2).

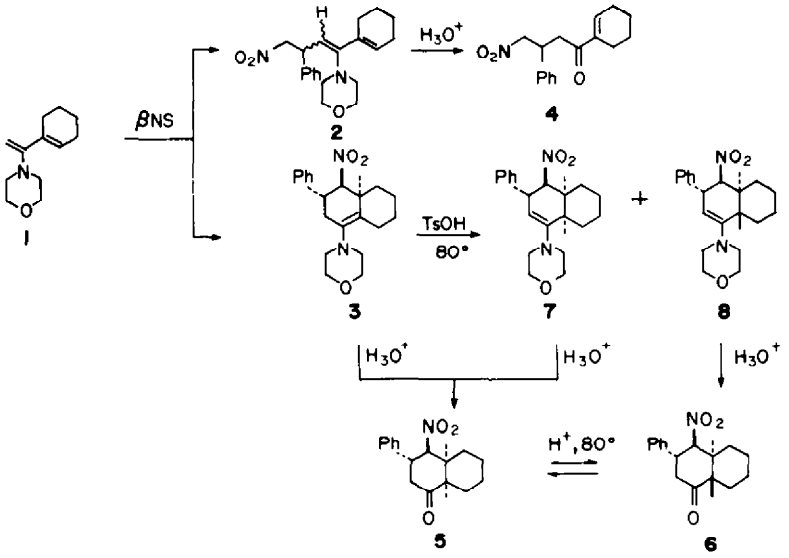
The relative instability of **6** is of interest. Though the ring junction is *trans*, which is regarded as 10–20 times more stable than the *cis* in decalone systems,[5] both groups are axial. The position of the equilibrium **5** ⇌ **6** is determined probably by a counterbalance of conformational and configurational factors.

When **3** was refluxed with TsOH in benzene,‡ a conversion of **3** to the trisubstituted enamines **7** and **8** was accomplished in ratio 65:35. Enamine **7** was identified as 1,2,3,4,4a,5,6,8a - octahydro - 8 - morpholino - 5 - nitro - 6 - phenyl - (4aα,5β,6α,8aα) - naphthalene. Its IR spectrum showed the trisubstituted enaminic absorption at 1632 cm^{-1},[3] and its NMR spectrum confirmed the structure though a complete analysis could not be performed, because of its complexity.§ In agreement with this attribution however, enamine **7** upon hydrolysis yielded the ketone **5**. Since no asymmetric centre is involved in the protonation, the same configurational feature as in **5** was assigned to **7**.

†The NMR spectrum of the crude reaction mixture showed the presence of two cyclohexene vinylic protons in the ratio 1:1, attributed to the E–Z isomers of **2**.

‡The reaction was found to take place also in the absence of TsOH. The equilibration however was acid-catalyzed, since the presence of a strong base inhibited it.[6]

§The nitromethine proton signal in fact was concealed beneath the resonance of the vinylic proton. The spectrum could not simplified by exchange of the nitromethine hydrogen with deuterium, as it had already done in other cases.[7]



Scheme 2.

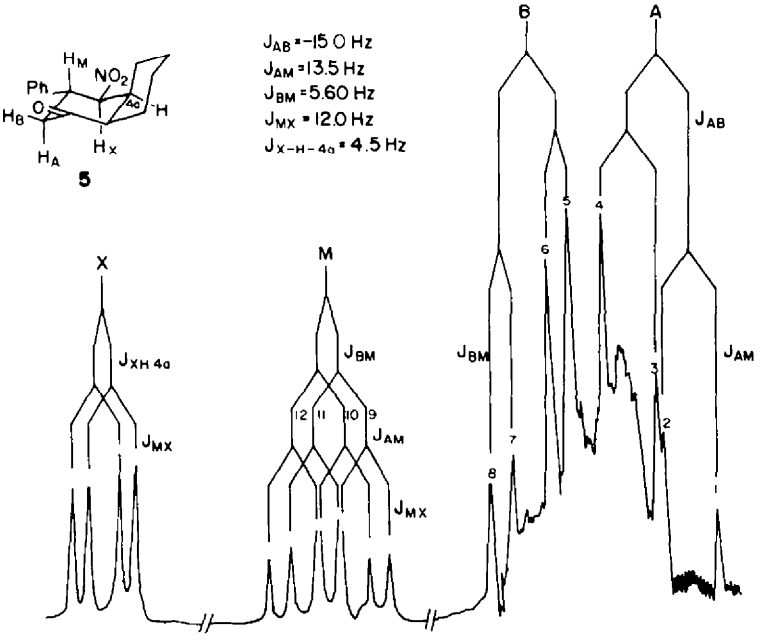


Fig. 1. Partial NMR spectrum of **5** measured at 60 MHz in C_6D_6 + Eu(thd)$_3$.

Enamine **8** was identified as 1,2,3,4,4a,5,6,8a - octahydro - 8 - morpholino - 5 - nitro - 6 - phenyl - (4aα,5β,6α,8aβ) - naphthalene. The enamine absorption band appeared at 1642 cm^{-1},[3] while the NMR spectrum showed the nitromethine proton signal at δ4.75 with W_H = 8.25 Hz, and the benzylic proton signal at δ4.1 with W_H = 9.0 Hz. Both values accounted for the equatorial orientations attributed to the protons.[4] The nature of the ring junction and the configurational assignments made for **8** were further confirmed by acidic hydrolysis of **8** itself which yielded the above mentioned ketone **6**.

It is interesting to note that the quantitative conversion of a tetrasubstituted morpholino enamine, such as **3**, into a trisubstituted enamine mixture is unusual.[3] Moreover, in the simple octaline systems the situation is completely opposite. The $\Delta^{8,8a}$ octaline in fact is thermodynamically more stable than the $\Delta^{7,8}$ regardless of the type of ring junction.[8,9]

When the ketone **5** was treated with sodium hydroxide in absolute ethanol, a mixture of **5** and **9** was isolated in ratio 50:50, after addition of acetic acid (pH 6–7) (Scheme 4).

The compound **9** was assigned the structure of 4 - nitro - 3 - phenyl - (3α,4α,4aα,8aα) - 1(2H) - octahydro - naphthalenone, on the basis of NMR analysis. The NMR spectrum showed that the nitromethine proton, δ4.95, was a doublet of doublets with coupling constants of 3.0 Hz and 2.25 Hz, which indicated *trans*-equatorial relation of H-4 and H-4a. The signal of the benzylic proton was poorly resolved with about 13.5 Hz half-height width. This value is smaller than that indicated by Garbisch[10] for an axial benzylic proton, but larger than

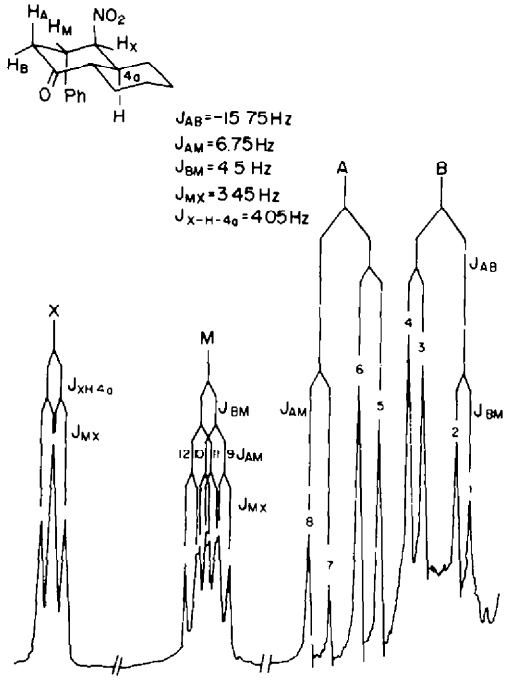
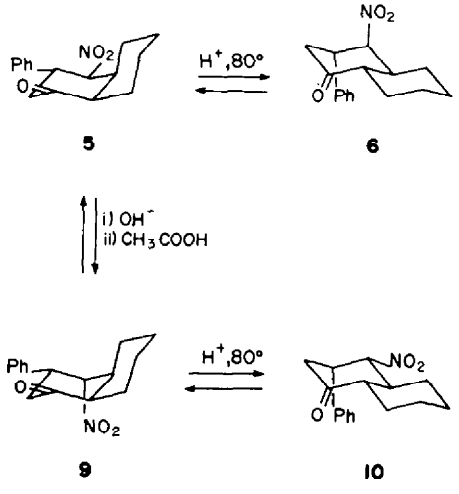


Fig. 2. Partial NMR spectrum of **9** measured at 60 MHz in $CDCl_3$.

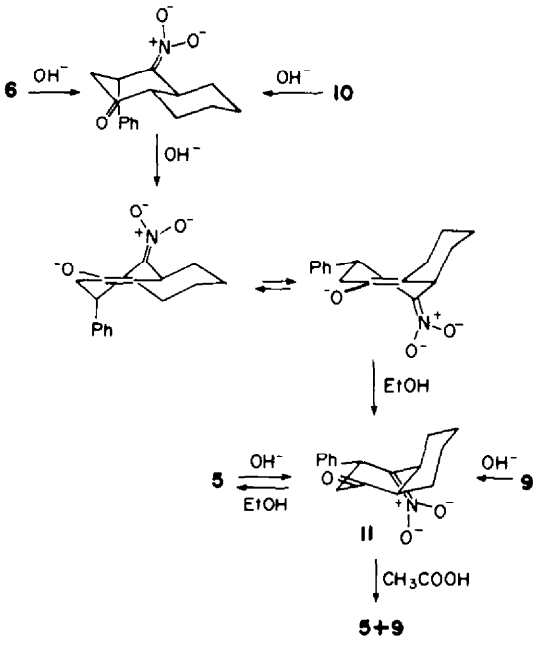


Scheme 3.

that of an equatorial one. The hydrogen therefore was assigned the axial conformation.

When the ketone **9** was refluxed with TsOH in benzene, a mixture of **9** and **10** in ratio 30:70 was obtained. The ketone **10** was isolated and identified as 4 - nitro - 3 - phenyl - (3α,4α,4aα,8aβ) - 1(2H) - octahydro - naphthalenone, on the basis of its NMR spectrum (Fig. 3), which was consistent with the proposed structure.

Surprisingly, also ketones **6**, **9** and **10** when subjected to the same basic treatment yielded the same mixture of **5** and **9** in ratio 50:50, if the solutions were neutralized with acetic acid or diluted hydrochloric acid. If the solutions were allowed to stand for at least 72 hr, the only ketone **5** was obtained. Unlike the former protonation, the latter case was an example of stereospecific protonation, in which the solvent itself worked as a weak acid. Since all the decalones behaved the same way



Scheme 4.

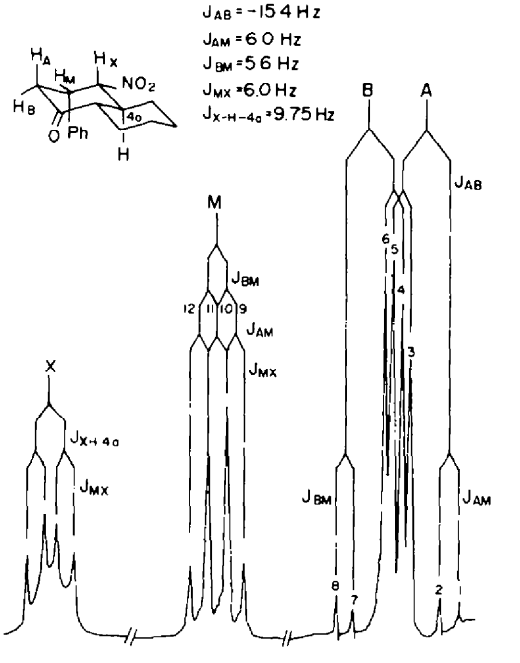


Fig. 3. Partial NMR spectrum of **10** measured at 60 MHz in $CDCl_3$.

towards basic treatment, it seemed reasonable to postulate the same intermediate for all of them. The situation could be rationalized as depicted in Scheme 4.

Actually a nitronate salt was isolated despite its instability and was attributed the structure **11**. Its IR spectrum showed two strong bands at 1620 cm^{-1},[11] and 1720 cm^{-1}. UV spectrum showed that the strong band at 234 nm ($\epsilon \sim 8000$), characteristic of a nitronate group,[11] moved to 225 nm ($\epsilon \sim 8000$), by conversion to the corresponding nitronic acid (pH ~ 2). Ethanol approached from the less hindered side of **11** to yield the single ketone **5**, whereas a stronger acid attacked the molecule from both sides in equal amounts.

Finally, something must be said about the mechanism of formation of **3**. It is our opinion that the reaction proceeds through a zwitterionic intermediate, as already postulated in other cases.[1] The presence of the open-chain enamine **2** in fact seems a proof sufficient to support the two-step mechanism, as enamine **2** must be derived from a dipolar intermediate. Formation of **3** through a different mechanism, such as a synchronous attack of the olefine on the substrate, seems quite unlikely.

EXPERIMENTAL

M.ps were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded as mull (Nujol) on a Perkin-Elmer 257 spectrometer. UV spectra were recorded on a Perkin-Elmer 124 spectrophotometer. NMR spectra were recorded on a JNM-60-HL Jeol spectrometer in $CDCl_3$ solns, unless otherwise stated, using TMS as internal standard. The nomenclature followed the rules indicated by Chemical Abstracts.

Reaction of **1** *with β-nitrostyrene.* β-Nitrostyrene (4.83 g, 34.6 mmol) was added to **1**[2] (6.7 g, 34.6 mmol) in dry ether, at 5°. After 72 hr, removal of the solvent left an oily residue, which showed δ: 2.6 (CH_2NCH_2, m); 3.6 (CH_2OCH_2, m); 4.5 (CH_2NO_2, m); 5.2 ($CHNO_2$, dd); 5.6, 5.8 (C=CH). The oil was crystallized from benzene–ligroin. **3** was obtained (5.0 g, 43.5%), m.p. 142° (Found: C, 70.5; H, 7.83; N, 7.97. Calc. for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18%). NMR, δ 2.60 (CH_2NCH_2, 4H, m); 3.35 ($CHPh$, 1H, m); 3.70 (CH_2OCH_2, 4H, m); 5.20 ($CHNO_2$, 1H, dd, $J_{5,6} = 12.0$ Hz, $J_{4a,5} = 6.75$ Hz); 7.30 (Ph, 5H); ν_{max} (cm^{-1}) 1670 (C=C–N); 1600, 1490, 695 (Ph); 1542, 1372 (NO_2). The mother liquors, which contained enamines **2** and **3**, were hydrolysed and extracted. Evaporation of the solvent gave an oily residue which was chromatographed on SiO_2. Elution with benzene gave 1.9 g (24%) of **4**, m.p. 73–4°, from benzene–light petroleum (Found: C, 70.3; H, 7.12; N, 5.25. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%). NMR, δ3.45 (CH_2CO, 2H); 4.00 ($CHPh$, 1H, m); 4.60 (CH_2NO_2, 2H, dd); 6.80 (C=CH, 1H); 7.20 (Ph, 5H). ν_{max} (cm^{-1}) 1665 (CO); 1635 (C=C); 1600, 1490, 758, 694 (Ph); 1545 (NO_2). 4.0 g of a mixture of **5** and **6** were also separated. The total yield was 87% and the ratio open-chain ketone: cyclic ketones was 25:75.

Equilibration of **3**. A soln of **3** (3.0 g, 8.75 mmol) in dry benzene was heated at reflux under N_2 for 4 hr. Evaporation of the solvent gave a yellow oil which could be crystallized from an ether-petroleum ether mixture to afford **8** (1.0 g, 33%), m.p. 141–3° (Found: C, 70.2; H, 7.77; N, 8.29. Calc. for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18%). NMR, δ 2.75 (CH_2NCH_2, 4H, m); 3.75 (CH_2OCH_2, 4H, m); 4.10 ($CHPh$, 1H, $W_H = 9.0$ Hz); 4.50 (C=CH, 1H); 4.75 ($CHNO_2$, 1H, $W_H = 8.25$ Hz); 7.30 (Ph, 5H). ν_{max} (cm^{-1}) 1642 (C=C–N); 1595, 1485, 710, 695 (Ph); 1535, 1365 (NO_2). The mother liquors contained the isomer **7** (1.8 g, 66%), m.p. 152–3° (Found: C, 69.7; H, 7.49; N, 8.20. Calc. for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18%). NMR, δ 2.70 (CH_2NCH_2, 4H, m); 3.75 (CH_2OCH_2, 4H, m); 4.45 ($CHNO_2$, C=CH, $CHPh$, 3H, m); 7.30 (Ph, 5H). ν_{max} (cm^{-1}) 1632 (C=C–N); 1600, 1485, 765, 700 (Ph); 1540, 1360 (NO_2). The ratio **7**:**8** was 65:35.

Hydrolysis of **3**. Acetic acid (or dil HCl) and enamine **3** in equal amounts were mixed up in acetone–water. After 2 hr **5** was filtered off, m.p. 152–53°, from benzene–ligroin. (Found: C, 69.8; H, 7.25; N, 5.40. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%). ν_{max} (cm^{-1}) 1720 (CO); 1600, 1585, 770, 695 (Ph); 1548, 1350 (NO_2). NMR, δ (C_6D_6 + Eu(thd)$_3$) 1.90, 2.40 (H-2, two pseudo-AB quartets, $J_{AB} = -15.0$ Hz, $J_{AM} = 13.5$ Hz, $J_{BM} = 5.60$ Hz); 3.57 ($CHPh$, 1H, $J_{AM} = 13.5$ Hz, $J_{BM} = 5.60$ Hz, $J_{MX} = 12.0$ Hz); 4.90 ($CHNO_2$, 1H, dd, $J_{MX} = 12.0$ Hz, $J_{X\text{-}H\text{-}4a} = 4.5$ Hz); 7.30 (Ph, 5H).

Equilibration of **5**. Ketone **5** was refluxed with TsOH in benzene for 4 hr. A 55:45 mixture of **5** and **6** was obtained. **6** was isolated by crystallization, m.p. 70–1°, from benzene–ligroin (Found: C, 69.8; H, 7.04; N, 5.11. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%) ν_{max} (cm^{-1}) 1710 (CO); 1600, 1580, 1494, 760, 695 (Ph); 1552 (NO_2). NMR, δ 2.80, 3.30 (H-2, two pseudo-AB quartets, $J_{AB} = -15.75$ Hz, $J_{AM} = 6.75$ Hz, $J_{BM} = 4.5$ Hz); 4.04 ($CHPh$, 1H, m, $J_{AM} = 6.75$ Hz, $J_{BM} = 4.5$ Hz, $J_{MX} = 3.45$ Hz); 4.86 ($CHNO_2$, 1H, dd, $J_{MX} = 3.45$ Hz, $J_{X\text{-}H\text{-}4a} = 4.05$ Hz); 7.35 (Ph, 5H).

Basic treatment of **5**. Ketone **5** in abs. EtOH was added to NaOH. After 24 hr the soln was neutralized by addition of dil. HCl (or CH_3COOH). By adding some more water, a solid formed rapidly. It consisted of a mixture of **5** and **9** in ratio 50:50. Ketone **9** was separated by crystallization from petroleum ether–ether, m.p. 176° (Found: C, 70.7; H, 7.32; N, 5.27. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%). ν_{max} (cm^{-1}) 1706 (CO); 1600, 1580, 1492, 785, 745, 695 (Ph); 1542 (NO_2). NMR, δ3.25 ($CHPh$, 1H, $W_H = 13.5$ Hz); 3.65 (H-2, 2H); 4.95 ($CHNO_2$, 1H, dd, $J = 3.0$ Hz, $J = 2.25$ Hz, $W_H = 6.75$ Hz); 7.25 (Ph, 5H).

Equilibration of **9**. Ketone **9** was treated with TsOH in refluxing benzene for 13 hr. A 30:70 mixture of **9** and **10** was obtained. **10** was isolated from the mixture by crystallization from petroleum ether–ether, m.p. 124° (Found: C, 70.0; H, 6.95; N, 5.27. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%). ν_{max} (cm^{-1}) 1707 (CO); 1600, 1580, 1495, 757, 690 (Ph); 1550 (NO_2). NMR, δ 2.75, 3.05 (H-2, two pseudo-AB quartets, $J_{AB} = -15.4$ Hz, $J_{AM} = 6.0$ Hz, $J_{BM} = 5.6$ Hz); 3.85 ($CHPh$, 1H, $J_{AM} = 6.0$ Hz, $J_{BM} = 5.6$ Hz, $J_{MX} = 6.0$ Hz); 4.95 ($CHNO_2$, 1H, dd, $J_{MX} = 6.0$ Hz, $J_{X\text{-}H\text{-}4a} = 9.75$ Hz); 7.10 (Ph, 5H).

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