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# The Reaction of α-Substituted Ketones with *N*-Alkylhydroxylamines

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*N*-Methyl- and *N*-benzylhydroxylamine reacted smoothly with ethyl acetoacetate to afford the pyrroline compounds **1** and **2**, respectively. On the other hand, the reaction of *N*-cyclohexylhydroxylamine gave the nitrone compound **3**.

Other active methylene compounds, *i.e.*, diethyl acetonedicarboxylate, benzoylacetone and nitroacetone, reacted with methylhydroxylamine to give the *N*-methylpyrrole **6**, the nitrone **7** and the isoxazoline **8**, respectively.

**Keywords**——cyclization; *N*-alkylhydroxylamine; active methylene compounds; nitrone; isoxazoline; pyrrole; pyrroline

Saeki *et al.*[1] have reported that the reaction of ethyl acetoacetate with *N*-arylhydroxylamines led to the indole as well as the pyrrole derivatives, as shown in Chart 1. In order to investigate whether *N*-alkylhydroxylamines undergo the same reaction or not, we have examined the reaction of R–NHOH(R=Me, benzyl, cyclohexyl) with ethyl acetoacetate.

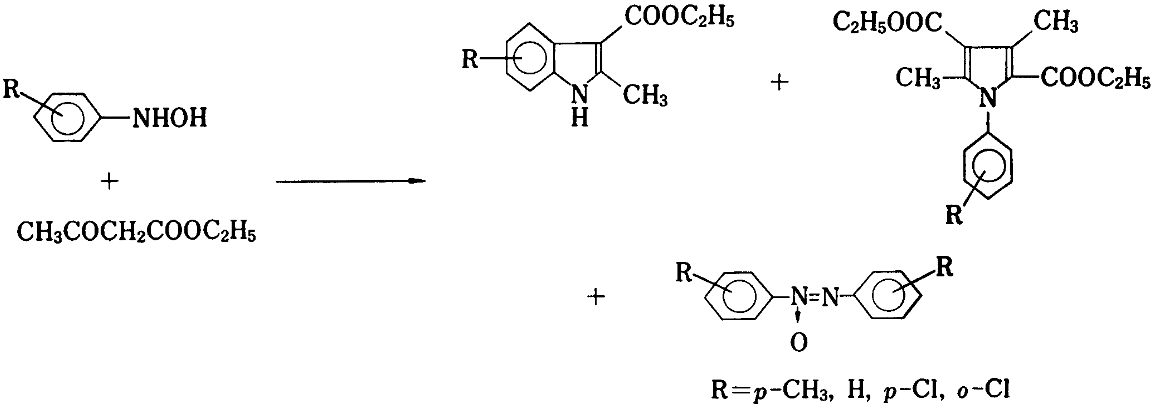


Chart 1

A solution of *N*-methylhydroxylamine (1 mol eq) and ethyl acetoacetate (2 mol eq) in anhydrous ether was refluxed for 4 h, then stirred overnight at room temperature. Purification by chromatography on a silica gel column afforded a colorless oil (**1**), bp 115—117°C (0.4 mmHg), in 58% yield. Its analytical values were consistent with the molecular formula $C_{13}H_{21}NO_5$. In the nuclear magnetic resonance (NMR) spectrum, two peaks due to the methyl group appeared at $\delta$ 1.50 and 2.18. The former, a singlet, can be ascribed to an aliphatic tertiary *C*-methyl group. On the other hand, the latter can be assigned to the methyl group attached to the ethylenic double bond. These data suggest that compound **1** has the pyrroline ring structure.

For proof of the structure, dehydration of **1** under reflux in acetic anhydride was carried out; this gave the known pyrrole derivative **4**. Its melting point, mp 113°C, coincided well with that of 3,5-bis(ethoxycarbonyl)-1,2,4-trimethylpyrrole reported by Corwin.[2] In view of these data, compound **1** was identified as 3,5-bis(ethoxycarbonyl)-4-hydroxy-1,2,4-trimethyl-2-pyrroline.

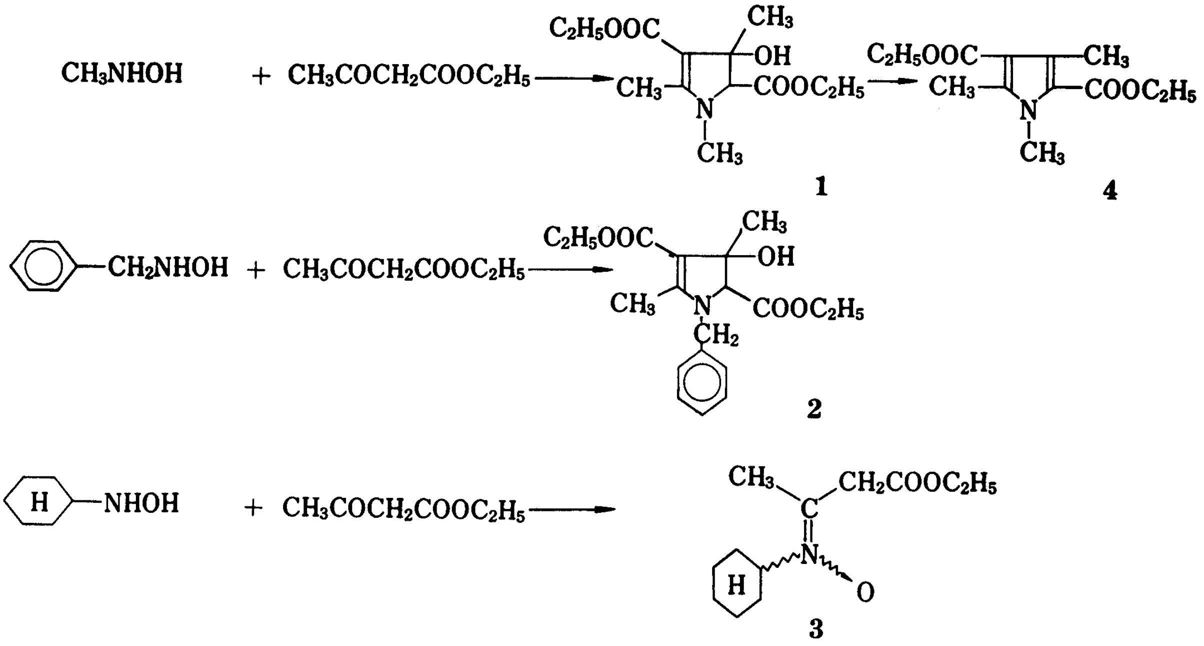
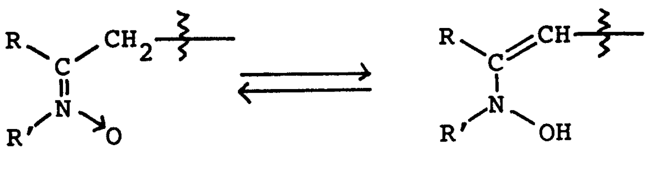


Chart 2

Next, we examined the reaction of *N*-benzylhydroxylamine. A mixture of *N*-benzylhydroxylamine (1 mol eq) and ethyl acetoacetate (2 mol eq) in ether was refluxed, then fractionally distilled. Purification by chromatography on silica gel gave a colorless oil (**2**), bp 180—190°C (0.2 mmHg, bath temp.), in 28.4% yield. The analitical data were consistent with $C_{19}H_{25}NO_5$. The peaks of the NMR spectrum at $\delta$ 1.00 and 2.14 due to two different methyl groups suggested the existence of a pyrroline ring. Thus, the structure of compound **2** was established as 1-benzyl-3,5-bis(ethoxycarbonyl)-4-hydroxy-2,4-dimethyl-2-pyrroline.

Next, *N*-cyclohexylhydroxylamine was chosen as a representative secondary alkylhydroxylamine and its reaction with ethyl acetoacetate was examined. Equimolecular quantities of the two compounds were stirred in EtOH for 6 d at room temperature and usual treatment gave the nitrone **3** as a colorless oil, bp 170°C (0.5 mmHg), in 78% yield. Its molecular formula was established as $C_{12}H_{21}NO_3$ from the elemental analysis. The infrared (IR) and NMR spectral data supported the structure **3**.

It is generally accepted that nitrone and enehydroxylamine tautomers may coexist at equilibrium.



nitrone enehydroxylamine

However, the absorption peak due to the vinylic proton was entirely absent in the NMR spectrum of compound **3**, so it appears that this compound exists exclusively as the nitrone structure. On the other hand, the signal at $\delta$ 3.54 and 3.46 appeared at 82 : 18 relative intensity; these were assigned to the methylene protons located near the $=\overset{|}{N}-O$ group, whereas that at $\delta$ 3.54 was assigned to methylene protons far from the $=\overset{|}{N}-O$ group, by reference to Tori's conclusion[3] for the nitrone structures (A) and (B).[4]

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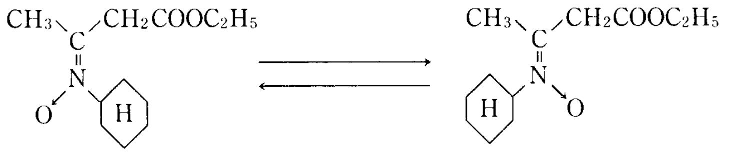
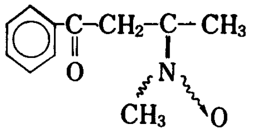
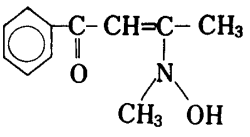


3 *E*-form (82%)   3 *Z*-form (18%)

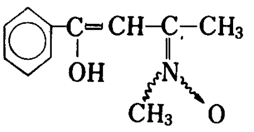
As described above, the reaction of ethyl acetoacetate with several *N*-alkylhydroxylamines led to the pyrroline or the nitrone compound, depending on the structure of the *N*-alkylhydroxylamines. Next, in order to examine the relation between the reactivity and the structure of the $\beta$-ketoester, we reacted several $\alpha$-substituted ketones(diethyl acetonedicarboxylate, benzoylacetone, acetoacetamide and nitroacetone) with *N*-methylhydroxylamine as shown in Chart 3.



**7**
**nitrone**



**7′**
**enehydroxylamine**



**7″**
**enol**

First, we attempted the reaction with diethyl acetonedicarboxylate. A mixture of *N*-methylhydroxylamine (1 mol eq) and diethyl acetonedicarboxylate (2 mol eq) in anhydrous ether was stirred overnight at room temperature. Chromatographic purification afforded a colorless oil (**6**), bp 170—185°C (0.4 mmHg, bath temp.), in 9.8% yield and a colorless oil (**5**), bp 160—170°C (0.4 mmHg, bath temp.), in 66.8% yield. The molecular formula of **6** was established as $C_{19}H_{27}NO_8$ by the high-resolution MS. Further, from the spectral data, **6** was identified as 2,4-bis(ethoxycarbonylmethyl)-3,5-bis(ethoxycarbonyl)-1-methylpyrrole.

The analytical values of **5** corresponded well with the formula $C_8H_{11}NO_4$ and the IR and NMR spectral data were consistent with the proposed structure of **5**, 3-ethoxycarbonylmethyl-2-methyl-3-isoxazolin-5-one.

Next, the reaction of *N*-methylhydroxylamine with benzoylacetone was attempted. A solution of the former (1 mol eq) in ether was added into a similar solution of the latter (2 mol eq) and the mixture was stirred at room temperature for 48 h. The precipitate of (**7**) was separated as colorless needles, mp 113°C, in 73.9% yield. The analytical values were consistent with the empirical formula $C_{11}H_{13}NO_2$.

Two nitrones may be formed in the reaction of benzoylacetone, but the observation of the fragment peak *m/e*: 105, characterized as $PhCO^+$, in the mass spectrum of **7** revealed that *N*-methylhydroxylamine reacts exclusively at the acetyl carbonyl group of benzoylacetone. In view of the IR, NMR and mass spectral (MS) data, the structure of **7** was assigned as *N*-methyl-*C*-phenacylnitrone.

Based on the fact that its NMR spectrum showed the signal of a vinylic proton at $\delta$ 5.49 which has an integrated intensity of 0.8H, it is evident that compound **7** exists predominantly in the enehydroxylamine form, and the ratio of **7′** and **7** should be four to one.

Although the enol form **7″** can also be postulated in place of **7′** on the basis of the presence of a vinylic proton in the NMR spectrum, the enehydroxylamine structure **7′** is more likely

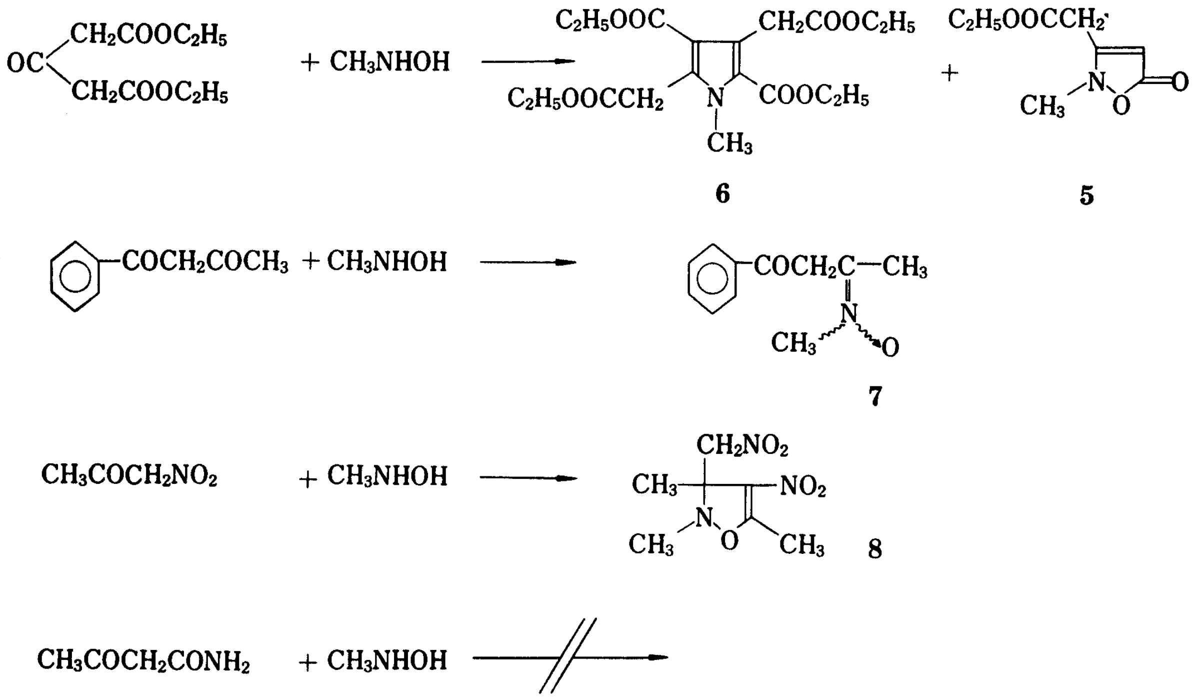


Chart 3

than the enol structure **7″**, in view of the fact that the MS showed a fragment peak at *m/e*: 174 ($M^+-OH$), considered to be generated *via* the removal of the hydroxyl group from the enehydroxylamine **7′**.

Finally, we attempted the reaction of *N*-methylhydroxylamine with nitroacetone, which is more acidic. A solution of nitroacetone (2 mol eq) and *N*-methylhydroxylamine (1 mol eq) was stirred for 40 h at room temperature. After the usual work-up, compound **8** was obtained as yellow needles, mp 130°C, in 39.5% yield. Its molecular formula was established as $C_7H_{11}N_3O_5$ by the analytical values, and its MS exhibited the parent peak at *m/e*: 217. This dinitro compound was assigned as 4-nitro-3-nitromethyl-2,3,5-trimethyl-4-isoxazoline. The IR and NMR spectral data also supported this structure.

The reaction of acetoacetamide with *N*-methylhydroxylamine did not proceed. This unreactivity may be a result of the weak acidity.

Now we have to consider the mechanism of the reaction of α-substituted ketones with *N*-methylhydroxylamine. Previously, Winterfeld *et al.*[5] reported that the reaction of the nitrone **9** with methyl propiolate yielded two pyrrole compounds, **10** and **11**, and suggested the mechanism shown in chart 4. That is to say, 1,3-dipolar cycloaddition of the nitrone **9** with methyl propiolate proceeded to give the intermediate **12**. Following bond cleavage of this intermediate through route (a), Cope rearrangement afforded the pyrrole compound **10**. The other pyrrole **11** was formed by ring cleavage of the aziridine intermediate followed by ring closure *via* the alternative route (b).

In the case of the present reactions, reference to Winterfeld's report indicates that the reaction might take place through route (a), (b) or (c), as depicted in Chart 5. The first route (a) involves condensation of ethyl acetoacetate with the enehydroxylamine (**14′**) generated *via* prototropy of the nitrone (**14**), and subsequent ring closure to form the pyrroline **1**. Route (b) involves addition of ethyl acetoacetate to the –C=N– group of the nitrone **14**, followed by dehydrating ring closure to lead to the isoxazoline (**13**) with several further reaction processes through an azirizine intermediate to form the pyrroline **1**. The last route (c) involves 1,3-dipolar cycloaddition of the nitrone **14** with the enehydroxylamine **14′** to give the isoxazolidine

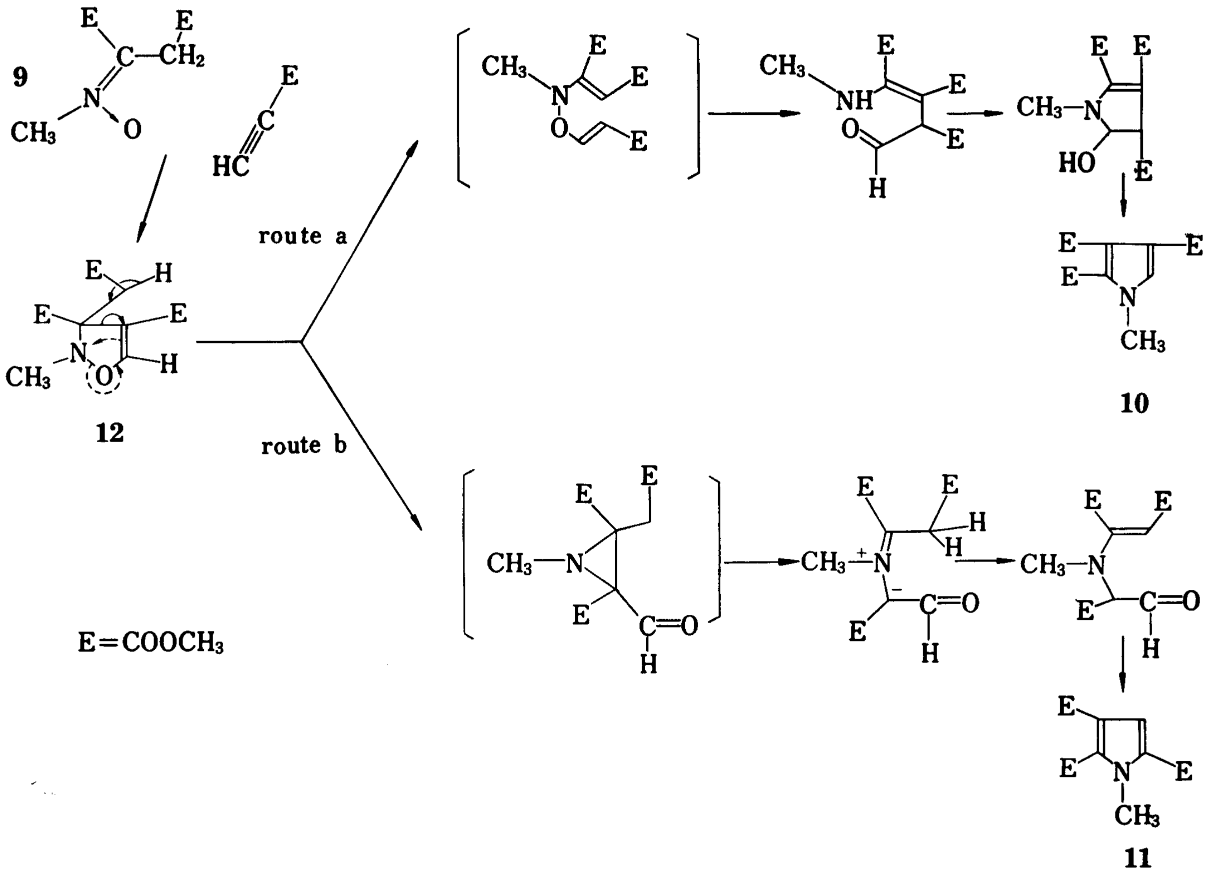


Chart 4

compound, followed by bond cleavage with elimination of methylhydroxylamine, 1,3-sigmatropic rearrangement on the nitrogen atom and a final ring closure step to form **1**. Route (c) also involves elimination of methylhydroxylamine from the isoxaline compound to afford the compound **13** and subsequent steps *via* an aziridine intermediate to lead to **1**.

The reaction process through route (b) could be ruled out in view of the evidence that the reaction of the nitrone **15** with ethyl acetoacetate in ether did not proceed and the starting material was recovered. Thus, it seems likely that the reaction proceeds through route (a) or (c). Finally, the mechanism of the reaction of nitroacetone with *N*-methylhydroxylamine may involve 1,3-dipolar cycloaddition of the nitrone **16** and enehydroxylamine **16′**, which was generated *via* tautomerization from the nitrone by analogy with route (c) in Chart 5, followed by elimination of *N*-methylhydroxylamine to afford the nitro compound **8** (Chart 6).

## Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal reference. MS were obtained on a JMS 01SG spectrometer.

**3,5-Bis(ethoxycarbonyl)-4-hydroxy-1,2,4-trimethyl-2-pyrroline (1)**——A mixture of 2.4 g (1 mol eq) of *N*-methylhydroxylamine and 13.2 g (2 mol eq) of ethyl acetoacetate in 100 ml of anhydrous ether was refluxed for 4 h, then stirred overnight at room temperature. After evaporation of the solvent, the residue was purified on a silica gel column. Elution with hexane–$CH_2Cl_2$ (1 : 1) gave 8 g (58%) of **1** as a colorless oil, bp 115—117°C (0.4 mmHg). IR $\nu_{\max}^{\text{neat}}$ $cm^{-1}$: 1730, 1695 (C=O), 3400 (OH). $^1H$-NMR ($CDCl_3$) $\delta$: 1.23 (3H, t, $J=6.0$ Hz, $-COOCH_2C\underline{H}_3$), 1.31 (3H, t, $J=7.0$ Hz, $-COOCH_2C\underline{H}_3$), 1.50 (3H, s, $C_4-C\underline{H}_3$), 2.18 (3H, s, $C_2-CH_3$), 2.71 (1H, s, C–H), 2.73 (3H, s, $N-CH_3$), 4.01 (2H, q, $J=7.0$ Hz, $-COOC\underline{H}_2CH_3$), 4.22 (2H, q, $J=6.0$ Hz, $-COOC\underline{H}_2CH_3$). Ultraviolet (UV) $\lambda_{\max}^{\text{ethanol}}$ nm (log $\varepsilon$): 271 (4.16). MS *m/e*: 271 ($M^+$), 256 ($M^+-CH_3$), 253 ($M^+-H_2O$). *Anal.* Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 56.99; H, 7.83; N 5.09. Further elution with the same solvent gave 500 mg of unidentified material.

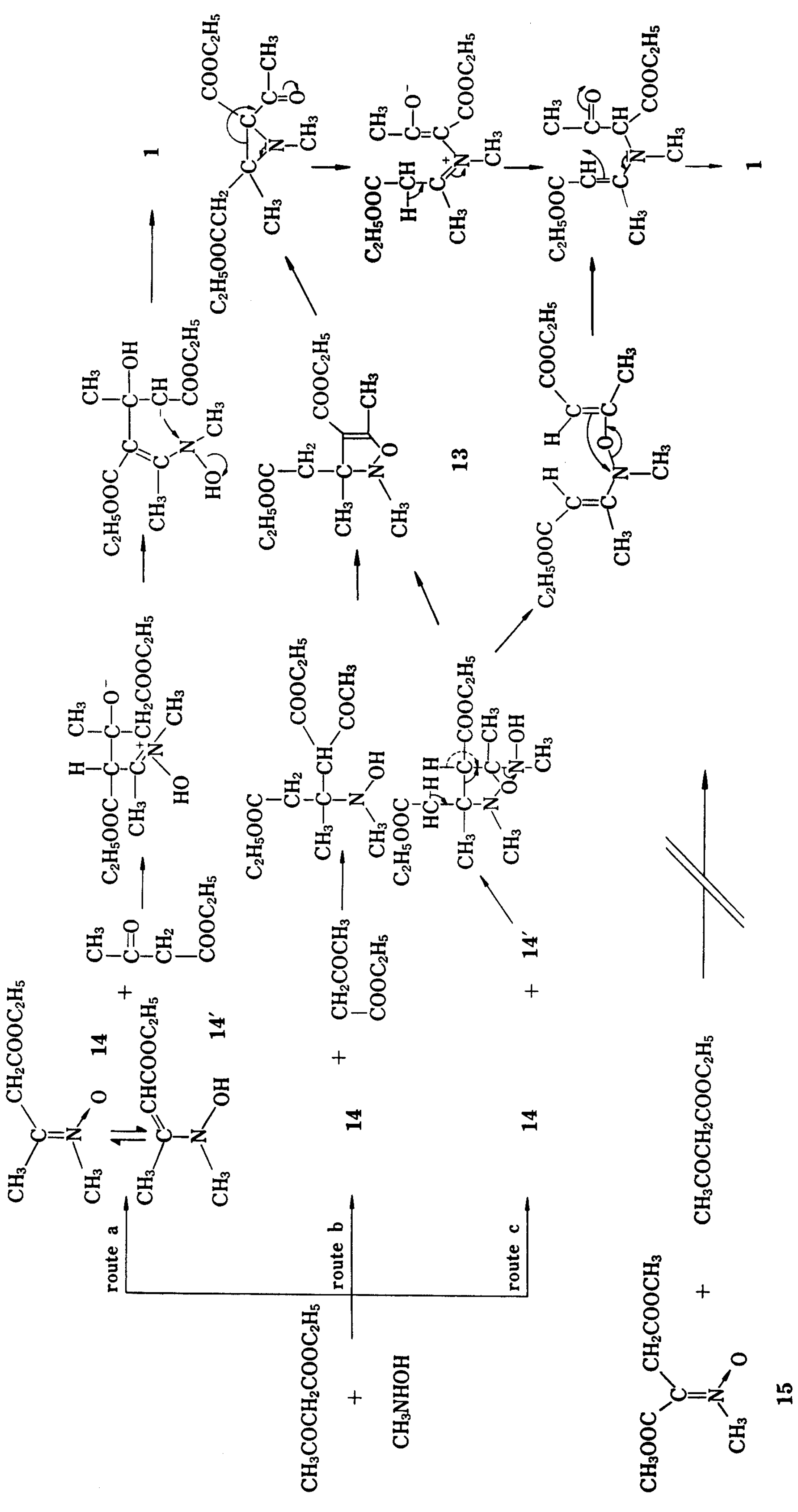
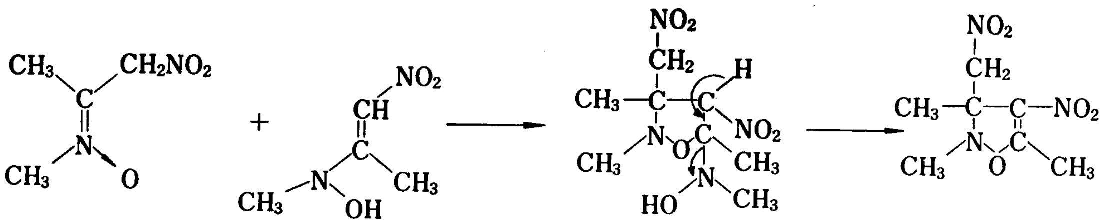

route a
route b
route c
14
14'
13
1
15
CH3COCH2COOC2H5
CH3NHOH
CH3COCH2COOC2H5
CH3OOC
CH2COOCH3

Chart 5



16 16′ 8

Chart 6

**3,5-Bis(ethoxycarbonyl)-1,2,4-trimethylpyrrole** (4)——A solution of 90 mg of **2** in 5 ml of acetic anhydride was refluxed for 3 h. Ethanol was added to the reaction mixture in order to decompose the remaining acetic anhydride. After evaporation of the solvent, recrystallization of the residue from hexane afforded 15 mg of **4** as colorless rhombic crystals, mp 113°C (lit.,2) mp 113—114°C). $^1$H-NMR ($CDCl_3$) $\delta$: 1.37 (3H, t, $J$=6.8 Hz, $-COOCH_2C\underline{H}_3$), 1.39 (3H, t, $J$=6.8 Hz, $-COOCH_2C\underline{H}_3$), 2.51 (3H, s, $C-CH_3$), 2.55 (3H, s, $C-CH_3$), 3.79 (3H, s, $N-CH_3$), 4.30 (2H, q, $J$=6.8 Hz, $-COOC\underline{H}_2CH_3$), 4.32 (2H, q, $J$=6.8 Hz, $-COOC\underline{H}_2CH_3$). MS *m/e*: 253 ($M^+$). *Anal.* Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.81; H, 7.49; N, 5.80.

**1-Benzyl-3,5-bis(ethoxycarbonyl)-4-hydroxy-2,4-dimethyl-2-pyrroline** (2)——A mixture of 400 mg (1 mol eq) of *N*-benzylhydroxylamine and 850 mg (2 mol eq) of ethyl acetoacetate in 30 ml of anhydrous ether was refluxed for 9 h. After evaporation of the solvent, the residue was fractionally distilled; 390 mg of ethyl acetoacetate was recovered from the first fraction and 400 mg of the crude **2** was obtained from the second fraction, bp 180—190°C (0.2 mmHg, bath temp.). Further chromatographic purification of the crude **2** on silica gel with hexane–AcOEt (9 : 1) gave 320 mg (28.4%) of **2** as a colorless oil. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1695, 1730 (C=O), 3400 (OH). $^1$H-NMR ($CDCl_3$) $\delta$: 1.24 (3H, t, $J$=6.8 Hz, $-COOCH_2C\underline{H}_3$), 1.32 (3H, t, $J$=6.5 Hz, $-COOCH_2C\underline{H}_3$), 1.00 (3H, s, $C_4-CH_3$), 2.14 (3H, s, $C_2-CH_3$), 2.67 (1H, d, $J$=13.5 Hz, $-\underset{|}{N}-\underset{H}{\overset{\underline{H}}{C}}-$), 3.07 (1H, d, $J$=13.5 Hz, $-\underset{|}{N}-\underset{\underline{H}}{\overset{H}{C}}-$, 4.14 (2H, q, $J$=6.8 Hz, $-COOC\underline{H}_2CH_3$), 4.24 (2H, q, $J$=6.5 Hz, $-COOC\underline{H}_2CH_3$), 7.20—7.40 (5H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.51; H, 6.91; N, 4.01.

**Reaction of *N*-Cyclohexylhydroxylamine with Ethyl Acetoacetate**——A solution of 150 mg (1 mol eq) of *N*-cyclohexylhydroxylamine and 170 mg (1 mol eq) of ethyl acetoacetate in 10 ml of EtOH was stirred for 7 dat room temperature. After evaporation of the solvent, chromatography on silica gel with $CH_2Cl_2$–MeOH (9 : 1) afforded crude **3**, and further purification by distillation gave 230 mg (78%) of **3** as a colorless oil, bp 170°C (0.5 mmHg, bath temp.). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1730 (C=O), 1645 (C=C), 1582 (C=N). $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (t, $J$=6.0 Hz, $-COOCH_2C\underline{H}_3$), 1.25 (t, 6.0 Hz, $-COOCH_2C\underline{H}_3$), 3.46 (0.36H, s, $-CH_2-COO$), 3.54 (1.64H, s, $-CH_2-COO$), 4.18 (q, $J$=6.0 Hz, $-COOC\underline{H}_2CH_3$), 4.20 (q, $J$=6.0 Hz, $-COOC\underline{H}_2CH_3$), 2.20 (3H, s, $=C-CH_3$). *Anal.* Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.12; H, 9.22; N, 5.96.

**Reaction of *N*-Methylhydroxylamine with Diethyl Acetonedicarboxylate**——A mixture of 0.35 g (1 mol eq) of *N*-methylhydroxylamine and 3.0 g (2 mol eq) of diethylacetonedicarboxylate in 30 ml of anhydrous ether was stirred overnight at room temperature. After evaporation of the solvent, the residue was subjected to distillation, bp 160—185°C (0.4 mmHg, bath temp.). Chromatography of the distillate on silica gel with $CH_2Cl_2$ afforded 290 mg (9.8%) of 2,4-bis(ethoxycarbonylmethyl)-3,5-bis(ethoxycarbonyl)-1-methylpyrrole **6** as a yellow oil, bp 170—185°C (0.4 mmHg, bath temp.). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1740, 1700 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.18—1.36 (12H, 4 × $-COOCH_2C\underline{H}_3$), 3.38 (3H, s, $N-CH_3$), 3.48 (2H, s, $C_2-$ or $C_4-C\underline{H}_2-COOC_2H_5$), 3.56 (2H, s, $C_2-$ or $C_4-C\underline{H}_2COOC_2H_5$), 4.05—4.32 (8H, 4 × $-COOC\underline{H}_2CH_3$). High-res. MS *m/e*: Calcd for $C_{19}H_{27}NO_8$: 397.174. Found: 397.172. Further elution with $CH_2Cl_2$–MeOH (9 : 1) afforded 920 mg (66.8%) of 3-ethoxycarbonylmethyl-2-methyl-3-isoxazolin-5-one **5** as a colorless oil, bp 160—170°C (0.4 mmHg, bath temp.). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1730, 1760 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.28 (3H, t, $J$=7.0 Hz, $-COOCH_2C\underline{H}_3$), 3.42 (3H, s, $N-CH_3$), 3.57 (2H, s, $-CH_2-$), 4.24 (2H, q, $J$=7.0 Hz, $-COOC\underline{H}_2CH_3$), 5.16 (1H, s, $-C=C-H$). MS *m/e*: 185 ($M^+$). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.62; H, 6.19; N, 7.82.

***N*-Methyl-*C*-methyl-*C*-phenacylnitrone(*N*-(3-benzoyl-2-propylidene)-methylamine*N*-oxide)** (7)——A solution of 50 mg (1 mol eq) of *N*-methylhydroxylamine in 1 ml of anhydrous ether was added to a solution of 324 mg (2 mol eq) of benzoylacetone in 10 ml of anhydrous ether under ice cooling. Stirring was continued for 48 h, and white crystals separated out. Recrystallization from $CH_2Cl_2$–hexane afforded 150 mg (73.9%) of **7** as white needles, mp 113°C. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1675(C=O), 1620 (C=N or C=C), 1575 (nitrone). $^1$H-NMR

(CDCl$_3$) δ: 2.14 (3H, s, $=\overset{|}{C}-CH_3$), 3.60 (2.4H, s, $-N-CH_3$), 3.74 (0.4H, s, $-CH_2-$), 4.25 (0.6H, s, $=N-CH_3$), 5.49 (0.8H, s, $-C=C-H$), 7.24—8.10 (5H, m, aromatic protons). MS *m/e*: 191 (M$^+$), 174 (M$^+$$-$OH), 105 (PhCO$^+$). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 19.15. Found: C, 69.10; H, 6.80; N, 19.12.

**4-Nitro-3-nitromethyl-2,3,5-trimethyl-4-isoxazoline (8)**——A solution of 300 mg (1 mol eq) of *N*-methylhydroxylamine in 2 ml of anhydrous ether was added to a solution of 600 mg (1 mol eq) of nitroacetone in 30 ml of anhydrous ether under ice cooling. Stirring was continued for 40 h at room temperature, then the solvent was evaporated off and the residue obtained was purified on a silica gel column. Elution with $CH_2Cl_2$ gave crude **8**. Recrystallization from $CH_2Cl_2$–isopropylether afforded 250 mg (39.5%) of **8** as a yellow needles, mp 130°C. IR $\nu_{\max}^{\text{Neat}}$ cm$^{-1}$: 1558, 1363 ($NO_2$). $^1$H-NMR (CDCl$_3$)δ: 1.79 (3H, s, $C_3-CH_3$), 2.46 (3H, s, $C_5-CH_3$), 3.25 (3H, s, $-N-CH_3$), 4.60 (1H, d, $J=12.0$ Hz, $-\underset{H}{\overset{H}{\underset{|}{\overset{|}{C}}}}-NO_2$, 5.20 (1H, d, $J=12.0$ Hz, $-\underset{H}{\overset{H}{\underset{|}{\overset{|}{C}}}}-NO_2$. MS *m/e*: 217 (M$^+$). *Anal.* Calcd for $C_7H_{11}NO_5$: C, 38.71; H, 5.11; N, 19.35. Found: C, 38.71; H, 5.32; N, 19.19.

## References and Notes

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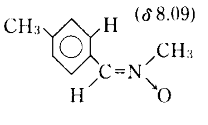
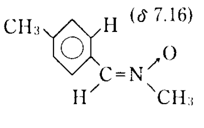
2) A.H. Corwin and Wm. M. Quattlebaum, Jr., *J. Am. Chem. Soc.*, **58**, 1081 (1936).
3) Y. Yoshimura, Y. Mori and K. Tori, *Chem. Lett.*, **1972**, 181.
4) Tori *et al.*[3] have reported two nitrones having the stereostructures (A) and (B) in a study of the configurational assignment of nitrones by the use of a lanthanide shift reagent. A comparison of the chemical shifts of the benzene ring $C_2$-protons makes it evident that the signal (δ 7.16) due to the proton located near the oxygen atom of the N–O group is shifted markedly to higher field than the other (δ 8.09).



(A)



(B)

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