CROATICA CHEMICA ACTA CCACAA 59 (1) 165—170 (1986)

YU ISSN 0011-1643
CCA—1634 UDC 547.313
Original Scientific Paper

1,2-Oxazine *N*-Oxide Derivatives from 1-Hetera-4-Cyclohexanone Enamines and Nitroolefins. Ring-chain Tautomerism[1]

Patricia Nitti, Giuliana Pitacco, Vera Rinaldi, and Ennio Valentin

Dipartimento di Scienze Chimiche, Università, 34127 Trieste, Italy

Received June 6, 1985

1,2-Oxazine *N*-oxide condensed heterocycles have been prepared from (*E*)-1-phenyl-2-nitropropene and enamines derived from 1-methyl-4-piperidone, 4H-tetrahydro-pyran-4-one and 4H--tetrahydro-thiapyran-4-one. They are more stable than the analogous systems derived from cyclohexanone enamines and just like them they are in equilibrium with their open-chain isomers.

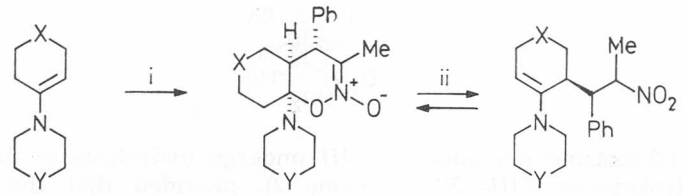
INTRODUCTION

1,2-Oxazine *N*-oxide systems are obtained by formal $|4 + 2|$ cycloaddition reaction between an enamine and a nitroolefin. Several studies have been performed on these condensed heterocycles in order to relate their stability various functionalizations of the rings.[2,3] We are reporting now on the formation of this type of heterocycles from enamines derived from 1-hetera-4--cyclohexanone[4] and (*E*)-1-phenyl-2-nitro-propene.

RESULTS AND DISCUSSION

Enamines *I*—*IV* (Scheme 1) have been synthesized from the appropriate secondary amine and 1-methyl-4-piperidone,[5] 4H-tetrahydro-pyran-4-one and 4H-tetrahydro-thiapyran-4-one,[6] respectively.

Scheme 1



X	Y			
NMe	O	I	V†	IX
NMe	CH_2	II	VI	X
O	CH_2	III	VII	XI
S	CH_2	IV	VIII	XII

i) $PhCH{=}CMeNO_2$, ether, 0 °C; ii) $CHCl_3$, r. t.
† The systems are racemic modifications.

All the four enamines react with (*E*)-1-phenyl-1-nitro-propane at 0 °C to give the corresponding 1,2-oxazine *N*-oxide derivatives *V—VIII*, in good yields. They are stable in the crystalline state and can be stored at 0 °C for a long time. However, an equilibrium is settled in solution between the heterocycles *V—VIII* and the corresponding nitroalkylated enamines *IX—XII*.[7] The isomer distribution is listed in the Table.

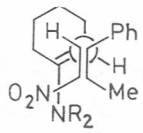
The existence of the equilibrium was proved for compound *V*, isolating both the heterocycle *V* and the corresponding enamine *IX* and by dissolving them in chloroform. Separation of the enamine *IX* was accomplished by treating the 1,2-oxazine *N*-oxide derivative with methanol and subsequently with ether which dissolved only the former system.

TABLE

Ring Form	*Open-Chain Form*	*Ratio*
V	*IX*	75/25
VI	*X*	65/35
VII	*XI*	50/50
VIII	*XII*	85/15

Enamine *IX* shows a particular behaviour, never found before for the enamines derived from 2-substituted-cycloalkanones.[8,9] In the solid state and at room temperature, it reverted spontaneously and completely into its cyclic isomer *V*, in one week. On the contrary, enamine *IX* cyclized only partially in chloroform, to give the already mentioned equilibrium mixture.

As to the stereochemical feature of compounds *V—VIII*, the fusion between the hteerocyclic rings is most probably *cis*, as already found in the chemistry of cycloalkanone derivatives (X = CH_2).[7,10] The two asymmetric carbon atoms C-4 and C-4a are described by the symbolism *like*,† their respective R,R configurations resulting from the Re—Re approach of the reagents.[11]

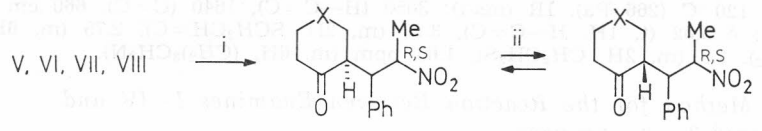


The 1,2-oxazine *N*-oxides *V—VIII* undergo hydrolysis to the corresponding γ-nitroketones *XIII—XV* (Scheme 2), provided that the pH value is maintained between 5 and 6 and the temperature around 0 °C, to avoid the Nef reaction.[10]

The γ-nitroketones *XIII—XV* are a 1 : 1 mixture of diastereoisomers, differing only in the configuration of the β carbon atom. The configuration of the α carbon atom is determined by the type of approach of the nitro-

† The assignement follows from the sequence rule:
C-4: C=N > C_6H_5 > $CH(CH_2)C$
C-4a: CCNO > CH_2X > CHPh.

Scheme 2.



X		
NMe	XIII†	XVI
O	XIV	XVII
S	XV	XVIII

i) $H_2O/CH_3COOH/MeOH$, pH 5—6, 0 °C; ii) bz, TsOH, 80 °C.
† The systems are racemic modifications.

olefin onto the parent enamine[11] and remains unchanged in all the subsequent transformations. These ketones, however, are products of kinetic control, as far as the newly formed C—C bond is concerned. Incidentally, not many examples of highly diastereoselective C—C bond formation through Michael addition are known.[11]

In acidic medium, the γ-nitroketones *XIII—XV* undergo partial epimerization at C-3, to afford mixtures containing about 50% of the corresponding diastereoisomers *XVI—XVIII*.

In conclusion, the presence of a heteroatom in the ring fused to the 1,2-oxazine *N*-oxide ring enhances the stability of the latter ring, both in solution and the solid state, when compared with the analogous systems derived from cyclohexanone enamines.

EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus. The infrared spectra (4000—625 cm^{-1}) were recorded as nujol mulls, unless otherwise indicated, with a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were run either on a Bruker WP-80 spectrometer or on a Jeol-C-60HL spectrometer, for $CDCl_3$ solutions, with tetramethylsilane as internal standard.

Reagents

Enamines *I—IV* were prepared from 1-methyl-4-piperidone (Fluka), 4H-tetrahydro-pyran-4-one (Aldrich) and 4H-tetrahydro-thiapyran-4-one (Aldrich), respectively, by Stork condensation[12] with morpholine and piperidine (Erba).

1-Methyl-4-(4-morpholinyl)-1,2,5,6-tetrahydro-pyridine (I)

B. p. 125 °C (933 Pa). IR (neat): 3060 (H—C=C), 1650 (C=C), 1118 cm^{-1} (C—O—C). ^1H NMR: δ 4.65 (t, 1H, HC=C), 3.75 (m, 4H, CH_2OCH_2), 3.05 (m, 2H, $NCH_2CH=C$), 2.85 (m, 4H, CH_2NCH_2), 2.7—2.2 ppm (m, s, 7H, CH_2CH_2N, CH_3N).

1-Methyl-4-(1-piperidinyl)-1,2,5,6-tetrahydro-pyridine (II)

B. p. 130 °C (133 Pa). IR (neat): 3065 (H—C=C), 1650 cm^{-1} (C=C). ^1H NMR: δ 4.65 (t, 1H, HC=C), 3.05 (m, 2H, NCH_2—CH=C), 2.7—2.1 (m, s, 7H, CH_2CH_2N, CH_3N), 1.6 ppm (m, 6H, $(CH_2)_3CH_2N$).

2H-4-(1-Piperidinyl)-5,6-dihydro-pyran (III)

B. p. 90 °C (266 Pa). IR (neat): 3055 (H—C=C), 1640 (C=C), 1135 cm^{-1} (C—O—C). ^1H NMR: δ 4.75 (t, 1H, HC=C), 4.35 (m, 2H, $OCH_2CH=C$), 3.95 (t, 2H, CH_2O), 2.95 (m, 4H, CH_2NCH_2), 2.3 (m, 2H, CH_2CH_2O), 1.7 ppm (m, 6H, $(CH_2)_3CH_2N$).

2H-4-(1-Piperidinyl)-5,6-dihydro-triapyran (IV)

B. p. 120 °C (266 Pa). IR (neat): 3050 (H—C=C), 1640 (C=C), 660 cm^{-1} (C—S). ^1H NMR: δ 5.02 (t, 1H, H—C=C), 3.36 (m, 2H, $SCH_2CH=C$), 2.75 (m, 6H, CH_2S, CH_2NCH_2), 2.5 (m, 2H, CH_2CH_2S), 1.65 ppm (m, 6H, $(CH_2)_3CH_2N$).

General Method for the Reaction Between Enamines I—IV and (E)-1-Phenyl-2-nitro-propene

The nitroolefin (13 mmoles) in dry ether (25 ml) is added dropwise to a solution of the appropriate enamine (13 mmoles) in the same solvent (25 ml), at 0 °C. The mixture is kept in the refrigerator for 24 hrs. The precipitate formed is then filtered off.

4H-4a,5,6,7,8,8a-Hexahydro-3,6-dimethyl-8a-(4-morpholinyl)-4-phenyl--pyrido | 3,4-e | 1,2-oxazine N-*oxide | 4a,4aα,8aα | (V)*

85% yield. M. p. 113—5 °C. IR: 1610 (C=N), 1600, 1495, 710 (Ph), 1118 cm^{-1} (C—O—C). ^1H NMR: δ 7.45 (m, 5H, Ph), 4.0—3.7 (m, 5H, CH_2OCH_2, CHPh), 2.4 (s, 3H, CH_3N), 1.95 ppm (d, J = 1.5 Hz, 3H, $CH_3C=N$).

Anal. $C_{19}H_{27}N_3O_3$ (345.4) calc'd: C 66.06; H 7.85; N 12.40%
found: C 66.20; H 7.88; N 12.16%

4H-4a,5,6,7,8,8a-Hexahydro-3,6-dimethyl-4-phenyl-8a-(1-piperidinyl)--pyrido | 3,4-e | -1,2-oxazine N-*oxide | 4a,4aα,8aα | (VI)*

85% yield. M. p. 103—5 °C. IR: 1610 (C=N), 1495, 710 (Ph). ^1H NMR†: δ 7.6—7.0 (m, 5H, Ph), 5.4 (dq, J_1 = 6.75 Hz, J_2 = 10.5 Hz, 0.35H, $CHNO_2$), 4.9 (t, 0.35H, H—C=C), 4.35 (m, 0.35H, CHPh), 2.4 (s, 1.9H, CH_3N), 2.25 (s, 1.1H, CH_3N), 1.95 (d, J = 1.5 Hz, 1.9H, $CH_3C=N$), 1.60, 1.45 (2d, J = 6.75 Hz, CH_3CHNO_2), 1.5 ppm (m, 6H, $(CH_2)_3CH_2N$).

Anal. $C_{20}H_{29}N_3O_2$ (343.5) calc'd: C 69.94; H 8.51; N 12.23%
found: C 70.10; H 8.31; N 12.40%

4H,5H-3-Methyl-4-phenyl-8a-(1-piperidinyl)-4a,7,8,8a-tetrahydro--pyran | 3,4-e | -1,2-oxazine N-*oxide | 4a,4aα,8aα | (VII)*

80% yield. M. p. 76—8 °C. IR 1615 (C=N), 1495, 700 (Ph), 1100 cm^{-1} (C—O—C). ^1H NMR†: δ 7.35 (m, 5H, Ph), 5.5—5.3 (dq, 0.5H, $CHNO_2$), 4.70 (t, 0.5H, H—C=C), 4.2 (m, 1.5H, CHPh, $CH_2OCH=C$), 4.1—3.9 (m, 3.5H, CHPh$CHNO_2$, CH_2O, CH_2OCH_2), 1.95 (d, J = 1.5 Hz, $CH_3C=N$), 1.75 (m, 6H, $(CH_2)_3CH_2N$), 1.6, 1.5 ppm (2d, J = 6.75 Hz, CH_3CHNO_2).

Anal. $C_{19}H_{26}N_3O_2$ 330.4) calc'd: C 69.06; H 7.93; N 8.48%
found: C 68.56; H 8.09; N 8.20%

4H,5H-3-Methyl-4-phenyl-8a-(1-piperidinyl)-4a,7,8,8a-tetrahydro--thiapyran | 3,4-e | -1,2-oxazine N-*oxide | 4a,4aα,8aα | (VIII)*

80% yield. M. p. 128—30 °C. IR: 1608 (C=N), 1600, 1492, 710 (Ph), 660 cm^{-1} (C—S). ^1H NMR: δ 7.55 (m, 5H, Ph), 4.65 (dd, J_1 = 1.5 Hz, J_2 = 11.0 Hz, 1H, CHPh), 1.92 (d, J = 1.5 Hz, 3H, $CH_3C=N$), 1.62 ppm (m, 6H, CH_2N).

Anal. $C_{19}H_{26}N_2O_2S$ (346.4) calc'd.: C 65.88; H 7.56; N 8.09%
found: C 67.67; H 7.11; N 8.29%

1-Methyl-4-(4-morpholinyl)-3-(α-phenyl-β-nitro)propyl-1,2,5,6-tetrahydro--pyridine (IX)

M. p. 104—6 °C. IR: 1650 (N—C=C), 1600, 1490, 775, 700 (Ph), 1540 cm^{-1} (NO_2). ^1H NMR: δ 7.3 (m, 5H, Ph), 5.4 (m, 1H, $CHNO_2$), 4.9 (t, 1H, H—C=C), 4.2—3.4 (m, 5H, CHPh, CH_2OCH_2), 3.4—2.0 (m, s, 12H, 2 CH_2NCH_2, CH_3N, CH=C—CH), 2.2 (s, CH_3N), 1.4 ppm (d, J = 6.75 Hz, 3H, CH_3CHNO_2).

† In mixture with its open-chain isomer.

Anal. $C_{19}H_{27}N_3O_3$ (354.4) calc'd.: C 66.06; H 7.85; N 12.40%
found: C 65.85; H 7.60; N 12.23%

General Procedure for the Hydrolysis of the Systems V—VIII

The heterocycles *V—VIII* (15 mmoles) in methanol-water are treated with acetic acid (15 mmols) at 0 °C. After elimination of methanol the mixture is extracted with benzene, washed with $NaHCO_3$ and dried on anhydrous Na_2SO_4.

1-Methyl-3-(α-phenyl-β-nitro)propyl-4-piperidone (XIII)

Oil. IR (neat): 1710 (C=O), 1600, 1495, 700 (Ph), 1545 cm^{-1} (NO_2). ^1H NMR: δ 7.5—6.9 (m, 5H, Ph), 5.2 (dq, $J_1 = 6.75$ Hz, $J_2 = 4.8$ Hz, $CHNO_2$), 5.0 (dq, $J_1 = J_2 =$ = 6.75 Hz, $CHNO_2$), 4.1 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.75$ Hz, O.6H, *CH*Ph), 3.65 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.0$ Hz, O.4H, *CH*Ph), 2.2 (s, 3H, CH_3N), 1.32, 1.31 ppm (2d, $J = 6.75$ Hz, 3H, CH_3CHNO_2).

Equilibration of the diasteroisomeric pair *XIII* in refluxing benzene for 2 hrs, with TsOH as catalyst, leads to a 1 : 1 mixture of *XIII* and *XVI*. The latter compound, which could not be separated, is also a diastereoisomeric pair. ^1H NMR π: δ 5.70 (dq, $J_1 = 10.0$ Hz, $J_2 = 6.75$ Hz, $CHNO_2$), 5.65 (dq, $J_1 = 9.0$ Hz, $J_2 = 6.75$ Hz, $CHNO_2$), 3.3 (m, *CH*Ph), 1.5, 1.30 ppm (2d, $J = 6.75$ Hz, CH_3CHNO_2).

4H-3-(α-Phenyl-β-nitro)propyl-tetrahydro-pyran-4-one (XIV)

M. p. 80—3 °C, from light petroleum. IR: 1710 (C=O), 1600, 1590, 700 (Ph), 1540 cm^{-1} (NO_2). ^1H NMR: δ 7.6—7.0 (m, 5H, Ph), 5.15, 5.0 (2 dq, 1H, $CHNO_2$), 4.6—2.85 (m, 6H, CH_2OCH_2CH, *CH*Ph), 2.7 (t, 2H, CH_2CO), 1.40 1.38 (2d, $J = 6.75$ Hz, 3H, CH_3CHNO_2).

Anal. $C_{14}H_{17}NO_4$ (263.3) calc'd.: C 63.87; H 6.51; N 5.32%
found: C 63.76; H 6.38; N 5.47%

Equilibration of ketones *XIV* leads to a 1 : 1 mixture of *XIV* and *XVII*. The latter compound is also a diastereoisomeric pair. ^1H NMR π: δ 5.75, 5.70 (2 dq, 0.5 H, $CHNO_2$), 1.6, 1.42 (2d, $J = 6.75$ Hz, CH_3CHNO_2).

4H-3-(α-Phenyl-β-nitro)propyl-tetrahydro-thiapyran-4-one (XV)

Oil. IR ($CHCl_3$): 1700 (C=O), 1600, 1490, 700 (Ph), 1545 cm^{-1} (NO_2). ^1H NMR: δ 7.6—6.9 (m, 5H, Ph), 4.9, 4.8 (2 dq, 1H, $CHNO_2$), 4.2, 3.8 (2 dd, 1H, *CH*Ph), 1.30, 1.25 ppm (2d, $J = 6.75$ Hz, CH_3CHNO_2).

Equilibration of compounds *XV* leads to a mixture of diastereoisomers *XV* and *XVIII*. ^1H NMR π: δ 5.70, 5.65 (2 dq, 0.5 H, $CHNO_2$), 1.5, 1.34 (2 d, $J = 6.75$ Hz, CH_3CHNO_2).

π Signals of the NMR spectrum of the mixture attributable to the ketones of thermodynamic formation.

Acknowledgement. — The authors thank the Ministry of Education (Rome) for financial support.

REFERENCES

1. Part of this paper was presented at the *2nd Graz—Ljubljana—Trieste Symposium on Organic Chemistry* (TRISOC II), Bled, Yugoslavia, April 11—13, 1985.
2. A. Mezzetti, P. Nitti, G. Pitacco, and E. Valentin, *Tetrahedron* **41** (1985) 1415.
3. G. Barbarella, S. Brückner, G. Pitacco, and E. Valentin, *Tetrahedron* **40** (1984) 2441, and references therein cited.
4. J. A. Hirsch and E. Havinga, *J. Org. Chem.* **41** (1976) 455.
5. R. Fusco, G. Bianchetti, and S. Rossi, *Gazz. Chim. Ital.* **90** (1961) 825.
6. D. N. Reinhoudt and C. G. Houwenhoven, *Tetrahedron Lett.* (1973) 3751.
7. G. Pitacco and E. Valentin, *Tetrahedron Lett.* (1978) 2339.
8. P. W. Hickmott, *Tetrahedron* **38** (1982) 1975, 3363.

9. G. Pitacco and E. Valentin, *Enamines and Ynamines*, in: S. Patai (Ed.), *The Chemistry of Functional Groups*, Supplement F, John Wiley & Sons, 1982.
10. S. Daneo, G. Pitacco, A. Risaliti, and E. Valentin, *Tetrahedron* **38** (1982) 1499.
11. D. Seebach and J. Goliński, *Helv. Chim. Acta* **64** (1981) 1413.
12. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Amer. Chem. Soc.* **85** (1963) 207.

POVZETEK

Derivati 1,2-oksazin-*N*-oksidov pripravljenih iz 1-hetera-4-cikloheksanon enaminov in nitroolefinov

Tavtomerija obroč-veriga

P. Nitti, G. Pitacco, V. Rinaldi in E. Valentin

1,2-Oksazin *N*-oksidi so bili pripravljeni iz 1-fenil-2-nitropropena in enaminov kot derivatov 1-metil-4-piperidona, 4H-tetrahidropiran-4-ona in 4H-tetrahidrotiapiran-4-ona. Ti sistemi, ki so stabilnejši od analognih sistemov pripravljenih iz cikloheksanon enaminov, so prav tako v ravnotežju z odprtimi oblikami.