# 2-ALKYLISOXAZOLIDINE-3,3-DICARBOXYLIC ACID DERIVATIVES

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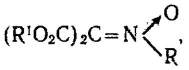
1,3-Dipolar cycloaddition of α,α-bis(alkoxycarbonyl)-N-alkylnitrones to olefins gave 2-alkylisoxazolidine-3,3-dicarboxylic acid esters, the yields of which are determined by the steric conditions and are virtually independent of the electronic effect of the substituents attached to the C=C bond of the dipolarophiles. The structures of the compounds obtained were established by analysis of the PMR spectra. The retention of the cis configuration of the substituents in the isoxazolidines obtained from maleic acid esters constitutes evidence for a one-step, four-center, concerted cycloaddition mechanism. The energy parameters for inversion of the nitrogen atom of dimethyl 2,5,5-trimethylisoxazolidine-5,5-dicarboxylate were measured.

We recently reported the predominant N-alkylation of isonitrosocyanoacetic and isonitrosomalonic esters with diazoalkanes [1, 2]. Because of the presence of two electronegative C-substituents, the resulting nitrones should be more electrophilic than ordinary trialkyl(aryl)nitrones, and the properties of the nitrones should consequently differ.



$$(R^1O_2C)_2C{=}N\begin{smallmatrix}\nearrow O\\ \searrow R\end{smallmatrix},\ \text{I } R{=}R^1{=}CH_3;\ \text{II } R{=}CH_3,\ R^1{=}C_2H_5;\ \text{III } R{=}C_2H_5,\ R^1{=}CH_3$$

The synthesized α,α-bis(alkoxycarbonyl)-N-alkylnitrones (I-III) have high thermal stabilities. For example, III undergoes complete vacuum distillation without any changes when it is heated (150-160°C) for 1 h (as monitored by PMR). However, α-ethoxycarbonyl-α-cyano-N-methylnitrone (IV) is unstable and undergoes polymerization even when it is stored for a month at 20°C. In contrast to C-alkyl(aryl)nitrones, nitrones I-IV decompose rapidly under the influence of nucleophiles [$CH_3ONa$ or $CH_3NH_2$ in $CH_3OH$ at 20°C; $(C_6H_5)_3P$ in $C_6H_6$ at 80°C].

TABLE 1. Characteristics of the Isoxazolidines

| Compound | mp, °C | $n_D^{20}$ | IR spectrum, $\nu_{C=O}$, cm$^{-1}$ | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | C | H | N | |
| V | — | 1,4558 | 1720* | 51,97 | 7,44 | 6,11 | $C_{10}H_{17}NO_5$ | 51,94 | 7,41 | 6,06 | 77,7 |
| VI | 43 | — | 1730, 1749 | 47,96 | 6,30 | 5,21 | $C_{11}H_{17}NO_7$ | 48,00 | 6,23 | 5,09 | 85,1 |
| VII | 79—80 | — | 1728, 1740 | 49,43 | 5,43 | 11,53 | $C_{10}H_{14}N_2O_5$ | 49,59 | 5,41 | 11,56 | 90,1 |
| VIII | — | 1,4548 | 1750* | 48,38 | 6,17 | 3,99 | $C_{14}H_{21}NO_9$ | 48,42 | 6,09 | 4,04 | 92,0 |
| IX | 65—66 | — | 1730, 1749 | 60,19 | 6,32 | 5,14 | $C_{14}H_{17}NO_5$ | 60,21 | 6,14 | 5,02 | 85,7 |
| X | — | 1,4615 | 1730, 1744* | 45,95 | 5,82 | 5,31 | $C_{10}H_{15}NO_7$ | 45,98 | 5,79 | 5,36 | 90,9 |
| XI | 62—63 | — | 1728, 1752 | 47,44 | 5,42 | 12,23 | $C_9H_{12}N_2O_5$ | 47,37 | 5,30 | 12,28 | 97,4 |
| XII | 69—70 | — | 1720, 1753 | 48,04 | 6,28 | 5,30 | $C_{11}H_{17}NO_7$ | 48,00 | 6,23 | 5,09 | 77,6 |
| XIII | 84 | — | 1720, 1756 | 56,87 | 5,60 | 4,13 | $C_{16}H_{19}NO_7$ | 56,99 | 5,68 | 4,15 | 91,5 |
| XIV | 61—63 | — | 1718, 1739 | 45,18 | 5,39 | 4,29 | $C_{12}H_{17}NO_9$ | 45,15 | 5,37 | 4,39 | 92,1 |
| XV | 52—53 | — | 1714, 1758 | 45,18 | 5,34 | 4,35 | $C_{12}H_{17}NO_9$ | 45,15 | 5,37 | 4,39 | 93,2 |
| XVI | 53—54 | — | 1722, 1758 | 48,36 | 6,11 | 3,93 | $C_{14}H_{21}NO_9$ | 48,41 | 6,09 | 4,03 | 92,3 |
| XVII | 73 | — | 1721, 1762 | 51,27 | 6,73 | 3,77 | $C_{16}H_{25}NO_9$ | 51,20 | 6,71 | 3,73 | 50,0 |
| XVIII | 48—49 | — | 1716, 1758 | 46,88 | 5,86 | 4,25 | $C_{13}H_{19}NO_9$ | 46,85 | 5,75 | 4,20 | 96,5 |
| XIX | 57 | — | 1717, 1740 | 46,80 | 5,73 | 4,29 | $C_{13}H_{19}NO_9$ | 46,85 | 5,75 | 4,20 | 80,0 |
| XX | — | 1,4580 | 1738* | 51,63 | 6,37 | 11,05 | $C_{11}H_{16}N_2O_5$ | 51,55 | 6,29 | 10,93 | 66,7 |

*Molecular layer.

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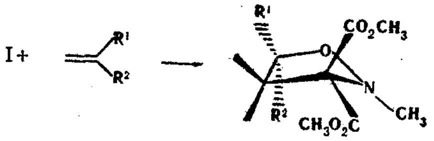
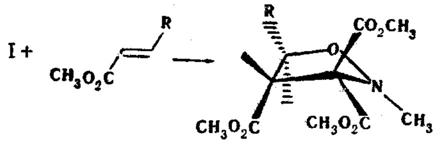
The 1,3-dipolar cycloaddition reactions of nitrones I-IV, which open up a route to new heterocyclic systems, are of interest. Attempts to accomplish the cycloaddition of the I molecule to the carbonyl group of acetone, benzaldehyde, and mesoxalic acid ester (at 20°C for 3 months) were, as expected, unsuccessful. However, the lack of a reaction of I under similar conditions with phenyl isocyanate and phenyl isothiocyanate was unexpected, since C-alkyl(aryl)nitrones react exothermally with them to give 1,2,4-oxadiazoline-5-ones and 1,2,4-oxadiazoline-5-thiones [3].



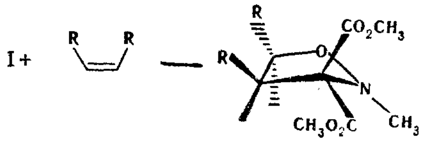
V–XI

(1)



XII–XIV

(2)



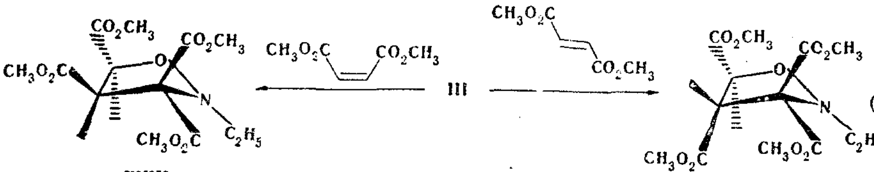
XV–XVII

(3)

V–VII $R^1=CH_3$; V $R^2=CH_3$; VI $R^2=CO_2CH_3$; VII $R^2=NC$; VIII $R^1=R^2=C_2H_5O_2C$;
IX–XI $R^2=H$; IX $R^1=C_6H_5$; X $R^1=CO_2CH_3$; XI $R^1=NC$ (1)
XII $R=CH_3$; XIII $R=C_6H_5$; XIV $R=CO_2CH_3$ (2)
XV $R=CO_2CH_3$; XVI $R=CO_2C_2H_5$; XVII $R=i\text{-}C_3H_7O_2C$ (3)

We made a detailed study of the reaction of readily accessible I with various olefins — from the relatively nucleophilic isobutylene to the electrophilic methylenemalonic ester (Schemes 1-3). It was found that the yields of the corresponding isoxazolidines (Table 1) obtained under identical conditions are virtually independent of the electronic effect of the substituents attached to the C=C bond of the dipolarophiles. At the same time, the I molecule does not react with ethoxymethylene- and isopropylidenemalonic esters. Cycloaddition probably does not occur in these cases because of considerable steric hindrance.

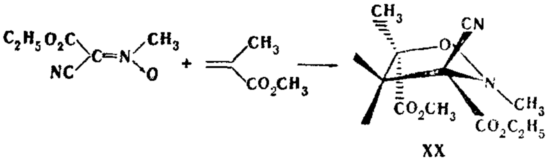
Like I, nitrones III and IV readily undergo cycloaddition (Schemes 4 and 5):



XVIII

XIX

(4)



XX

(5)

The formation of only one isomer was recorded in the PMR spectra in all cases, i.e., the 1,3-dipolar cycloaddition of nitrones is stereospecific and extremely sensitive to steric factors.

In all of the known cases of the reaction of nitrones with monosubstituted olefins the substituents of the latter are directed only to the 5 position of the isoxazolidine ring [4],

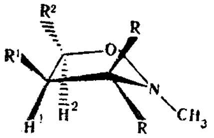


TABLE 2. Parameters of the PMR Spectra[a] and ASIS (Aromatic Solvent-Induced Shift) Effect[b] [6] of Isoxazolidines

| Compound | $CH_3$ | R | | R' | | $H^1$ | $R^2$ | $H^2$ | $J^c$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $CH_3$ | $CH_3$ | $CH_3$ | H | | $CH_3$ | | gem | cis | trans |
| V[d] | 2,83 | 3,30 | — | — | 2,53 | — | 1,28 | — | 9,5[e] | — | — |
| VI | 2,61 | 3,64 | 3,67 | — | 3,13 | 3,06 | 1,39 | 3,61[f] | 6,5 | — | — |
| | (−0,22) | (0,35) | (0,31) | — | (−0,48) | (−0,24) | (0,00) | (0,31) | (7,0) | — | — |
| VII | 2,78 | 3,77 | 3,79 | — | 3,07 | 2,81 | 1,65 | — | 13,5 | — | — |
| | (0,06) | (0,60) | (0,52) | — | (0,17) | (0,25) | (0,38) | — | (13,5) | — | — |
| VIII[d] | 2,85 | 3,30 | — | — | 3,70 | — | 0.83[g] | — | — | — | — |
| IX | 2,95 | 3,63 | 3,66 | — | 2,61 | 3,06 | | 4,90 | 12,7 | 7,7 | 7,7 |
| | (0,08) | (0,44) | (0,38) | — | (−0,08) | (0,05) | 7.27[h] | (−0,06) | (12,7) | (7,7) | (7,7) |
| X | 2,66 | 3,69 | 3,70 | — | 2,78 | 3,01 | 3,66 | 4,41 | 12,5 | 8,5 | 6,0 |
| | (−0,09) | (0,51) | (0,49) | — | (−0,24) | (0,01) | (0,48) | (0,05) | | | |
| XI | 2,79 | 3,73 | 3,76 | — | 2,86 | 3,18 | — | 4,69 | 13,0 | 8,5 | 4,8 |
| | (0,08) | (0,60) | (0,58) | — | (0,20) | (0,49) | — | (0,59) | | | |
| XII | 2,59 | 3,57 | 3,67 | — | 3,54 | 3,56[f] | 1,26 | 4,07 | 6,0[i] | — | 7,0 |
| | (−0,27) | (0,26) | (0,23) | — | (−0,34) | (0,22) | (0,02) | (−0,20) | (6,0) | — | (7,7) |
| XIII | 2,73 | 3,60 | 3,68 | — | 3,97 | 3,53[f] | 7,21 | 5,00 | — | — | 8,0 |
| | (−0,13) | (0,44) | (0,36) | — | (−0,41) | (0,32) | — | (−0,32) | — | — | (7,6) |
| XIV | 2,66 | 3,61 | 3,69 | — | 4,22 | 3,59 | 3,65 | 4,64 | — | — | 5,3 |
| | (−0,13) | (0,39) | (0,41) | — | (−0,49) | (0,37) | (0,38) | (−0,37) | — | — | (5,3) |
| XV | 2,75 | 3,63 | 3,75 | 3,55 | — | 4,31 | 3,63 | 4,67 | — | 9,5 | — |
| | (−0,06) | (0,43) | (0,48) | (0,30) | —[j] | (−0,24) | (0,38) | (−0,05) | — | (10,0) | — |
| XVI | 2,82 | 3,71 | 3,83 | 1,18 | 4,08[j] | 4,40 | 1,21[k] | 4,76 | — | 9,6 | — |
| | (−0,06) | (0,47) | (0,50) | (0,29) | (0,16) | (−0,14) | (0,31) | (0,04) | — | (9,7) | — |
| XVII | 2,77 | 3,67 | 3,79 | 1,16 | 4,86[l] | 4,28 | 1.20[m] | 4,67 | — | 9,7 | — |
| | (−0,12) | (0,40) | (0,43) | (0,17) | (−0,08) | (−0,29) | (0,15) | (−0,11) | — | (10,0) | — |
| XVIII | 1,22[n] | 3,73 | 3,83 | 3,66 | — | 4,46 | 3,72 | 4,82 | — | 10,0 | — |
| | (−0,07) | (0,42) | (0,44) | (0,30) | — | (−0,18) | (0,36) | (0,03) | — | (10,0) | — |
| XIX | 1,44[o] | 3,75 | 3,83 | — | 4,40 | 3.75[f] | 3,80 | 4,88 | — | — | 5,6 |
| | (−0,03) | (0,39) | (0,42) | — | (−0,40) | (0,38) | (0,53) | (−0.27) | — | — | (5,6) |
| XX | 2,77 | 1,29 | 4,26[j] | — | 3,79 | 2,50 | 1,45 | 3.70[f] | 13,5 | — | — |
| | (0,08) | (0,61) | (0,59) | — | (0,14) | (0,28) | (0,31) | (0,50) | (13,5) | — | — |

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[a] For 5 mole% solutions in $CCl_4$ at 80 MHz with δ in parts per million, hexamethyldisiloxane as the standard, and J in hertz.
[b] $\Delta v_{CCl_4}^{C_6H_6} = v_{CCl_4} - v_{C_6H_6}$, for mole% solutions in parts per million, given in parentheses. [c] Absolute values; the values in parentheses are for solutions in $C_6H_6$. [d] In $C_6H_6$. [e] In $CHFCl_2$ at −70°C. [f] $CH_3$. [g] 3.91 ($CH_2$), J = 7.0. [h] $C_6H_5$. [i] $J_{CHCH_3}$. [j] $CH_2$, $J_{CH_2CH_3}$ = 7.2 (7.0). [k] 4.18 (0.26) ($CH_2$), $J_{CH_2CH_3}$ = 7.2 (7.0). [l] CH, $J_{CHCH_3}$ = 6.0. [m] 4.94 (−0.04) (CH), $J_{CHCH_3}$ = 6.0. [n] $C_2H_5-N$, 2.86 (−0.26) ($CH_AH_B$), $\Delta v_{AB}$ = 62 Hz, $J_{AB}$ = 14.0, $J_{CH_2CH_3}$ = 7.0. [o] $C_2H_5-N$, 2.90 (0.17) ($CH_2$), $J_{CH_2CH_3}$ = 7.0.

and a similar structure was therefore assumed for V-XI and XX. This a priori conclusion was confirmed by an analysis of the PMR spectra of the synthesized isoxazolidines.

Thus the most deshielded proton of the carbon atom bonded directly to the ring oxygen atom (5-C) should be found at weakest field as compared with the other protons of the isoxazolidine ring. Since in the case of IX-XI this proton (δ = 4.40-4.90 ppm) is vicinal with respect to the remaining ring protons [see the spin—spin coupling constants (SSCC) in Table 2], the substituent that enters with the olefin — $C_6H_5$, $CO_2CH_3$, and NC groups, respectively — should be found attached to the carbon atom bearing it. However, the absence of signals of ring protons with chemical shifts greater than 4 ppm in the PMR spectra of osoxazolidines V-VIII and XX (Table 2) undoubtedly indicates the presence of two substituents in the 5 position of the ring.

The structures of isoxazolidines XII and XIII and, correspondingly, the stereospecificity of the cycloaddition of I to the methyl esters of transcrotonic and cinnamic acids are determined either from the observed spin—spin coupling of the weak-field proton with the geminal $CH_3$ group (XII, Fig. 1, and Table 2) or from the broadening of the signals of this proton because of a nonbonded interaction with the geminal $C_6H_5$ group (XIII, Fig. 1).

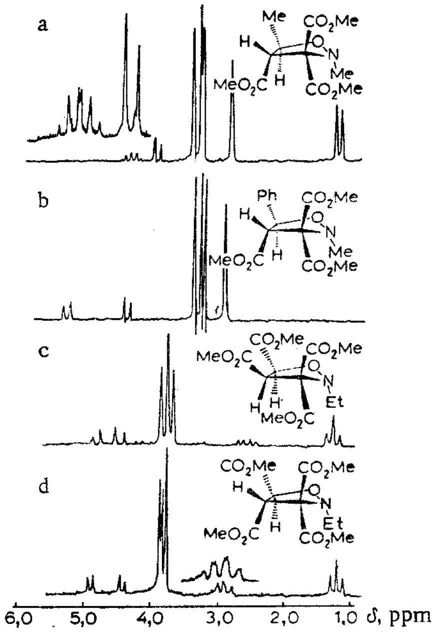

Fig. 1. PMR spectra of isoxazolidines (80 MHz, 5% molar solutions): a) XII in $C_6H_6$; b) XIII in $C_6H_6$; c) XVIII in $CCl_4$; d) XIX in $CCl_4$.

The vicinal SSCC of the ring protons of isoxazolidines XII-XIX (Table 2) indicate retention of the configuration of the starting olefins in the cyclization products. The retention of the cis configuration of the substituents in isoxazolidines obtained from maleic acid esters (XV-XVIII) undoubtedly constitutes evidence for a one-step, four-center, concerted mechanism for the addition of nitrones to olefins.

The nonequivalence of the geminal $CH_2$ protons of the Et—N group observed for XVIII in contrast to XIX (Fig. 1 and Table 2) is evidently due to realization of the configurationally stable chiral nitrogen center as a consequence of considerable steric hindrance. However, the presence of remote 4-C and 5-C asymmetric centers probably does not affect the geminal nonequivalence of the prochiral substituent attached to the nitrogen atom.

The energy parameters for the inversion of the nitrogen atom of V were measured from the coalescence temperatures of the $Me_2C$ ($T_C = -48°C$, $\Delta\nu = 11$ Hz) and $H_2C$ ($T_C = -54°C$, $\Delta\nu = 20.95$ Hz, $J_{AB} = 9.5$ Hz) groups of the isoxazolidine ring. The rate constants for inversion of the nitrogen atom are, respectively, 24.4 and 69.5 $sec^{-1}$, and the changes in the free energy of activation of inversion $\Delta G^{\neq}_{T_c}$ are 11.6 and 10.8 kcal/mole (calculated by the method in [7]).

## EXPERIMENTAL

The PMR spectra of the compounds were measured with a Tesla BS-487c spectrometer (80 MHz). The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer.

Nitrones I-IV were synthesized by the method in [2].

General Method for the Synthesis of Isoxazolidines. A solution of the nitrone in $C_6H_5$ was maintained in contact with an equimolar amount of high-boiling olefin or in excess low-boiling olefin in a sealed ampul at 20°C for 1 month, after which the solvent was removed by distillation, the residue was chromatographed with a column (L 100/160μ silica gel, elution with $CHCl_3$), and the solid isoxazolidines were recrystallized from n-hexane, petroleum ether, or a mixture of these solvents.

The low yield of XVII is due to the loss during crystallization, and the low yield of XX is due to its instability.

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# SYNTHESIS AND PROPERTIES OF AZOMETHINES OF THE PYRAN SERIES

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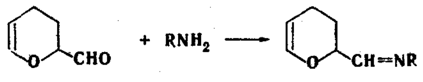
2-Formyl-$\Delta^5$-dihydropyran reacts with amines to give azomethines. $\Delta^2$-Triazolines are formed in the reaction of azomethines containing aromatic substituents with diazomethane. The structures of the compounds obtained were proved by means of UV and PMR spectroscopy.

Continuing our research on pyran compounds [1, 2], we studied the reactions of 2-formyl-$\Delta^5$-dihydropyran I with amines. Azomethines II-IV (Table 1) are formed as a result of the reaction of I with allylamine, aniline, and p-bromoaniline. When azomethines III and IV are allowed to stand, they are converted to dimers V and VI. Azomethine II is stable during storage. Compound I reacts immediately with p-nitroaniline and anthranilic acid to give dimers VII and VIII.



I

II-IV

II $R=CH_2=CH-CH_2$; III $R=C_6H_5$; IV $R=p\text{-}BrC_6H_4$

The data from the PMR and UV spectra (Table 2) are in agreement with the proposed structures of the compounds obtained. The UV spectra of I and II provide evidence for the transparency of the groupings entering into them in the near-UV region. The weak absorption at 346 nm in the spectrum of azomethine II, which in all likelihood is associated with the $n \rightarrow \pi^*$ transition of the C=N bond, cannot be used for identification purposes in view of the very low intensity of the band. On the basis of this, the absorption observed in the spectra of the azomethine derivatives should be associated with the aryl fragment of the molecule, while the absorption bands of III at $\lambda_{max}$ 242 and 285 nm can be regarded as the K and B bands of benzene ($\pi \rightarrow \pi^*$). The sensitivity of the bands to para substitution in the benzene ring (IV, VI, and VII) constitutes evidence in favor of this interpretation. The considerable bathochromic shift of the K and B bands of III as compared with benzene ($\Delta\lambda$ = 38 and 31 nm, respectively) and the smoothing out of the fine vibrational structure of the B band of benzene provide evidence for significant conjugation of the phenyl ring with the free electron pair of the nitrogen atom.

As expected, the intensities of the bands in the UV spectra of dimers V and VI are approximately doubled, while $\lambda_{max}$ changes only slightly (2-6 nm).

It is well known that azomethines add diazomethane upon prolonged standing in the presence of water or methanol [4-6]. We carried out the addition of diazomethane to III and IV

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