REACTIONS OF NITRONES WITH DI- AND TETRAHYDROPYRANS

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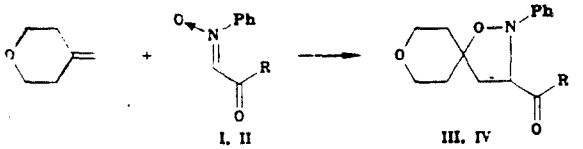
N-(Benzylidene)- and N-(2-phenylamino-2-oxoethylidene)aniline N-oxides add stereospecifically to the double bond in 4-methylene- and 4-acryloylamino-4-methyltetrahydropyrans to give substituted isoxazolidines. The use of 4-methyl-5-arylamino- and 4-arylaminomethyl-5,6-dihydro-2H-pyrans for the synthesis of novel N-oxides has given tricyclic adducts resulting from intramolecular cyclization of the required compounds.

1,3-Dipolar cycloaddition of nitrones to the double bond is well known as a classical method for the preparation of isoxazolidines. A wide variety of alkenes have been employed in this reaction [1], but there have been few reports of the use of unsaturated cyclic ethers other than 2,3-dihydropyran [2].

We have now examined the intra- and intermolecular reactions of nitrones with ethers, namely di- and tetrahydropyrans containing endo- and exocyclic double bonds.

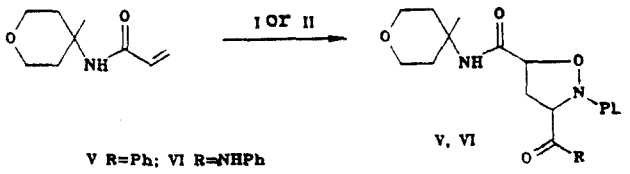
The reaction between nitrones and trisubstituted olefins is known to be difficult. For example, 1-methylcyclohexene fails to react with N-benzylideneaniline N-oxide (I) even on heating [2]. Its heterocyclic analog, 4-methyl-5,6-dihydro-2H-pyran reacts with the nitrone (I) and N-(2-phenylamino-2-oxoethylidene)aniline N-oxide (II) to give only traces of the expected adducts. The spiro-compound 9-methyl-6-oxospiro[4,5]non-9-ene likewise reacts with difficulty with the nitrone (II). The ether 4-methylenetetrahydropyran, which has an exocyclic double bond, reacts much more readily, and with nitrones (I) and (II) the spiroisoxazolidines (III) and (IV) are obtained in yields of 60 and 90%, respectively.



I, II III, IV

I, III R=Ph; II, IV R=NHPh

Indeed, when the double bond is conjugated with an amido-group, as in 4-acryloylamino-4-methyltetrahydropyran, the reaction with nitrones (I) and (II) is exothermic, giving (V) and (VI).



V R=Ph; VI R=NHPh

The PMR spectra of the adducts (III-VI) contain multiplets for the methine protons of the isoxazolidine ring at 2.3-4.7 ppm (Table 1). This shows that the reaction of the nitrones (I) and (II) with cyclic ethers is regiospecific, the oxygen of the nitrone adding to the more highly substituted carbon atom of the double bond. Otherwise, the spectra of the adducts (III) and (IV) would show a singlet for the CH group, and the spectra of (V) and (VI) a doublet.

Arylaminodihydropyrans such as (VIIa-c), being polyfunctional compounds with a reactive NH group, can be used to obtain a variety of heterocycles. For example, they should react as in the preparation of amidonitrones [3, 4] to give novel N-oxides. However, successive treatment of the 4-arylaminomethyl-5,6-dihydro-2H-pyrans (VIIa-c) with chloroacetyl chloride, pyridine, and nitrobenzene gave (IXa-c), which are the intramolecular cyclization products of the expected nitrones (VIIIa-c).

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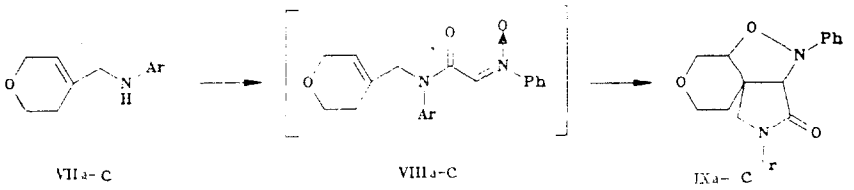
TABLE 1. Properties of Compounds Obtained

Compound	Empirical formula	T_{mp} °C	R_f	PMR spectrum (δ, ppm)	Yield, %
III	$C_{20}H_{21}NO_3$	128...129	0,51	1,25...1,75 (4H, m, 6-CH_2, 10-CH_2); 2,3 (m, 4-CH_2); 3,0...3,75 (4H, m, CH_2OCH_2); 4,25...4,55 (1H, m, 3-CH); 6,75...8,9 (10H, m $2C_6H_5$)	60
IV	$C_{20}H_{22}N_2O_3$	146...147	0,64	1,24...1,76 (4H, m, 6-CH_2, 10-CH_2); 2,3 (2H, m, 4-CH_2); 3,15...3,75 (4H, m, CH_2OCH_2); 4,35 (1H, m, 3-CH); 6,75...8,89 (10H, m, $2C_6H_5$); 9,95 (1H, s, NHCO)	90
V	$C_{23}H_{25}N_2O_4$	143...145	0,63	1,25 (3H, s, CH_3); 1,5...2,0 (2H, m CH_2); 2,5...3,1 (2H, m, 4-CH_2); 3,2...3,80 (4H, m CH_2OCH_2); 4,25...4,75 (2H, m, 3-CH, 5-CH); 6,1 (1H, c, NHCO); 6,75...7,8 (10H, m, $2C_6H_5$)	35
VI	$C_{23}H_{26}N_3O_4$	172...174	0,29	1,26 (3H, s, CH_3); 1,5...2,25 (2H, m, CH_2); 3,5...4,0 (4H, m CH_2OCH_2); 2,61...3,0 (2H, m, 4-CH_2); 4,5...4,75 (1H, m 3-CH); 6,5 (1H, s, NHCO); 6,8...8,25 (10H, m, $2C_6H_5$); 9,21 (1H, s, NHCO)	59
IXa*	$C_{20}H_{20}N_2O_3$	198...199	0,41	0,9...1,9 (2H, m, 5-CH_2); 2,8...4,3 (8H, m, CH_2OCH_2, N—CH_2, 1-CH, 9-CH); 6,5...7,5 (10H, m, $2C_6H_5$)	24
IXb	$C_{21}H_{22}N_2O_4$	210...211	0,43	0,9...2,0 (2H, 5-CH_2); 2,3 (3H, s, CH_3Ph); 3,4...4,1 (8H, m, CH_2OCH_2, 6-CH_2, 1-CH, 9-CH); 6,9...7,5 (9H, m, C_6H_4, C_6H_5)	26
IXc	$C_{21}H_{22}N_2O_3$	178...180	0,47	0,9...1,8 (2H, 5-CH_2); 2,3 (3H, s, CH_3Ph); 3,4...4,2 (8H, m, CH_2OCH_2, 6-CH_2, 1-CH, 9-CH); 6,5...7,5 (9H, m, C_6H_4, C_6H_5)	30
XIIa	$C_{20}H_{20}N_2O_3$	238...239	0,37	1,38 (3H, s, CH_3); 3,57...4,06 (4H, m, CH_2OCH_2); 4,28...4,42 (2H, m, 1-CH, 5-CH); 4,6 (1H, s 8-CH); 6,5...7,8 (9H, m C_6H_4, C_6H_5)	40
XIIb	$C_{21}H_{22}N_2O_3$	230...231	0,48	1,4 (3H, s, CH_3); 3,2...3,85 (7H, m CH_3OPh, CH_2OCH_2); 3,9...4,45 (2H, m, 1-CH, 5-CH); 4,6 (1H, s, 8-CH); 6,5...7,65 (9H, m, C_6H_4, C_6H_5)	43
XIIc	$C_{21}H_{22}N_2O_3$	195...197	0,45	1,35 (3H, s CH_3); 2,0 (3H, s, CH_3Ph); 3,4...4,1 (6H, m, CH_2OCH_2, 1-CH, 5-CH); 4,5 (1H, c, 8-CH); 6,5...7,8 (9H, m, C_6H_4, C_6H_5)	23
XIId	$C_{21}H_{22}N_2O_3$	198...199	0,39	1,38 (3H, s, CH_3); 3,0...4,5 (8H, m, CH_2OCH_2, > N—CH_2Ph, 1-CH, 5-CH); 5,1 (1H, s, 8-CH); 6,7...7,8 (10H, m, $2C_6H_5$)	35
XIIe**	$C_{21}H_{22}N_2O_4$	190...192	0,42	1,37 (3H, s, CH_3); 3,4...4,1 (9H, m, CH_2OCH_2, CH_3OPh, 1-CH, 5-CH); 4,5 (1H, s, 8-CH); 6,5...7,8 (9H, m, C_6H_4, C_6H_5)	45

*^{13}C NMR spectrum, δ, ppm: 64.17 (t, $C_{(2)}$); 76.70 (d, $C_{(1)}$); 46.60 (s, $C_{(6)}$); 55.09 (t, $C_{(7)}$); 169.59 (s, C=O); 77.02 (d, $C_{(10)}$); 120.17 d, 122.07 d, 128.79 d, 129.05 d, 138.58 s, 151.44 s ($2C_6H_5$).

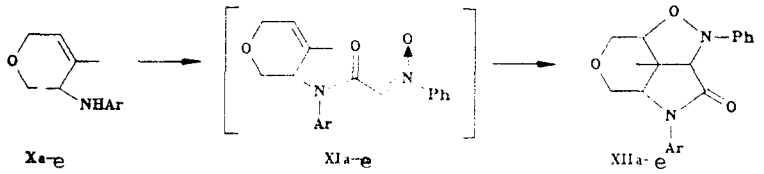
**^{13}C NMR spectrum, δ, ppm: 78.53 (d, $C_{(1)}$), 63.38 (t, $C_{(2)}$); 60.25 (d, $C_{(5)}$); 170.57 (s, C=O); 76.51 (d, $C_{(8)}$); 45.17 (s, $C_{(11)}$); 23.24 (q, CH_3); 55.55 (q, CH_3OPh); 114.56 d, 114.76 d, 122.39 d, 127.35 d, 128.79 s, 129.18 d, 149.22 s, 158.62 s ($2C_6H_5$).



VII—IX a Ar=C_6H_5; b Ar=*p*-$OCH_3C_6H_4$; c Ar=*m*-$CH_3C_6H_4$

This was confirmed by their PMR spectra, in which no signals were present for olefinic protons (at 5.4-5.6 ppm) or the imine oxide group (~9 ppm), but signals for the protons of the isoxazolidine ring were seen (3.9-4.6 ppm).

Intramolecular cycloaddition of the intermediate nitrones (XIa-e) also occurs in similar syntheses of the branched arylaminodihydropyrans (Xa-e). In these cases, the tricycloundecanones (XIIa-e) were isolated in yields of 29-40%.



X—XII a Ar=C_6H_5; b Ar=*o*-$CH_3C_6H_4$; c Ar=*m*-$CH_3C_6H_4$; r Ar=Bz; e Ar=*p*-$CH_3OC_6H_4$

These results show that the endocyclic double bond is quite reactive toward intramolecular cycloaddition. However, intermolecular reactions, which would be expected to occur even more readily, fail to occur even on prolonged heating. This was shown in the case of 1-{2-[N-(4-methyl-5,6-dihydro-2H-pyran-5-yl)-N-phenylamino]-2-oxoethyl}pyridinium chloride and the highly reactive nitrone N-[2-(m-tolylamino)-2-oxoethylidene]aniline N-oxide. It appears that the intramolecular cycloaddition of the nitrones (VIII) and (XI) is due to the favorable mutual orientation of the imine oxide and ethylene groups in the molecule.

The PMR spectra of (XIIa-e) show multiplet signals for the protons of the methylene groups of the tetrahydropyran ring (at 3.6-4.1 and 4.3-4.4 ppm), a singlet for the methine proton (4.6 ppm) of the isoxazolidine ring, and signals for the methyl protons (1.4 ppm) and the aromatic ring protons (7.2-7.9 ppm). A more complex situation is seen in the case of (IXa-d) as a result of the superimposition of the methine protons (3.2-4.2 ppm) of the isoxazolidine and tetrahydropyran rings. For this reason, the ^{13}C NMR spectra of these compounds were used for their identification. These showed separate signals for the carbon atoms, appearing as doublets at 77.02 (C_{10}) and 76.70 ppm ($C_{(1)}$). The spectrum of (XIIa) was similar (Table 1).

According to these observations, intramolecular cycloaddition of the intermediate nitrones (VIII) and (XI) proceeds in such a way that the oxygen is directed toward the less-substituted terminus of the double bond. In all likelihood, this is due to the more favored orientation of the reacting groups, since the intermolecular reaction regiospecifically affords the 5-substituted isoxazolidines (III-VI).

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on a Tesla BS-487 C (80 MHz) in $CDCl_3$, and ^{13}C NMR spectra on a Jeol FX-90 (22.5 MHz) in CCl_4, internal standard HMDS and TMS. The R_f values were measured on Brockman grade II alumina, eluent benzene–alcohol (10:1).

The properties of the compounds obtained are given in Table 1. The elemental analyses of the products for C, H, and N were in agreement with the calculated values.

2-Phenyl-3-benzoyl-5-[N-(4-methyl-4-tetrahydropyranyl)carbamino]isoxazolidine (VI). A solution of 0.81 g (1.9 mmoles) of N-benzylideneaniline N-oxide (I) and 0.52 g (3 mmoles) of 4-acryloylamino-4-methyltetrahydropyran in 2 ml of toluene was kept for 48 h at 20°C. The solid which separated was filtered off and washed with CCl_4. Compounds (III), (IV), and (VI) were obtained similarly.

11-Methyl-6,9-diphenyl-6,9-diaza-3,10-dioxatricyclo[5,3,$1^{1,5}$,$0^{8,11}$]undecan-7-one (XIIa). To a mixture of 2.36 g (11.9 mmoles) of the amine (Xa) and 1.75 g of anhydrous K_2CO_3 in 10 ml of toluene was added gradually 1.41 g (12.4 mmoles) of chloroacetyl chloride with vigorous stirring. When gas evolution had ceased and the reaction mixture cooled, the solid was filtered off and washed with ether. The ether was removed from the filtrate, and the residue treated with 1.7 g (21.5 mmoles) of dry pyridine and heated until boiling commenced. Forty minutes after heating was interrupted, the solidified reaction mixture was dissolved in 3 ml of water, and combined with a solution of 1.07 g (10 mmoles) of nitrobenzene

in 10 ml of alcohol. To the resulting clear solution was added with vigorous stirring and cooling a solution of 0.4 g (10 mmoles) of NaOH in 1 ml of water. The solid which separated was filtered off and washed with 2 ml of alcohol.

Compounds (IXa-c) and (XIIb-e) were obtained similarly.

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ELECTRON IMPACT MASS SPECTRA OF 2-HYDRAZONO-1,3-THIAZOLIDIN-4-ONE DERIVATIVES

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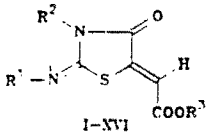
Mass fragmentation of 2-hydrazono-1,3-thiazolidin-4-ones is dominated by two processes, namely cleavage of the hydrazone fragment with accompanying proton transfer from the latter to the thiazolidine ring, and cleavage of a hydrazone imide residue.

The reaction of thiourea with dimethyl acetylenedicarboxylate is known to result in the formation of 1,3-thiazine derivatives [1, 2]. The structures of these products have been established based on analysis of their high-resolution mass spectra [2]. It was later demonstrated [3, 4] that the compounds consist of 2-imino-1,3-thiazolidin-4-ones. In the present paper we have studied the mass spectra of newly synthesized 2-hydrazono-1,3-thiazolidin-4-ones I-XVI [5].



I-XVI

I—IX $R^1=Me_2N$, X, XI $R^1=PhNH$, XII, XIII $R^1=PhEtN$, XIV—XVI $R^1=(CH_2)_5N$; I, II $R^2=H$, III, IV, X, XII—XV $R^2=Me$, V $R^2=t$-Bu, VI, XI, XVI $R^2=CH_2CH=CH_2$, VII, VIII $R^2=Ph$, IX $R^2=CH_2Ph$; I, III, V—VII, IX, XII, XIV $R^3=H$, II, IV, VIII, X, XI, XIII, XV, XVI $R^3=Me$

Formation of the highly conjugated system involving three exocyclic double bonds in the thiazolidine ring in compounds I-XVI increases the stability of these molecules with respect to electron impact and hinders their fragmentation via ring decomposition. The maximum intensity peaks in the mass spectra of most of these compounds are their respective molecular ion peaks (Table 1). Ring decay or decomposition occurs via the formation of fragments A and B (pathway *a* in scheme), whose corresponding peaks have either medium or low intensity. This type of fragmentation (cleavage of fragment A) accompanied by formation of a $[C_5H_4O_3S]^+$ ion is characteristic of all 2-imino-5-methoxycarbonylmethylene-1,3-thiazolidin-4-

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