# Employment of Nitriles in the Stereoselective Cycloaddition to Nitrones

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The cycloaddition of the nitrones 8–11 to the geminal dinitriles **12a–d** has been evaluated. Under thermal as well as high-pressure reaction conditions 1,3 dipolar cycloadditions proceed with complete regioselectivity to give the $\Delta^4$-1,2,4-oxadiazolines **13–16**, in high yields. Moreover, complete C(3)→C(1) trans induction in the cycloadducts **13** and **14** is observed.

The 1,3 dipolar cycloaddition of nitrones to dipolarophiles has been studied over the past two decennia.[1] Single-step, concerted four-centered reactions occur with a wide variety of dipolarophiles and have been reported to proceed under thermal[1] as well as high-pressure[2] conditions. Therefore, it is surprising that nitriles have received only scarce attention[3-5] as dipolarophiles in this reaction and that the usefulness of cycloadditions has not been studied at all. Yet there is ample evidence that cyclopropanes add to electron-rich $\pi$ systems (e.g. ketene acetals[6]) as well as to electron-poor $\pi$ systems (e.g. tetracyanoethylene[7]).

Recently we reported[8] that **8**, a nitrone derived from *N*-hydroxytryptophan, adds regio- and stereoselectively to alkenes. We now report that this nitrone **8**, as well as several other nitrones (**9–11**), undergo cycloadditions to geminal dinitriles **12a–d**. The presence of a cyclopropane ring in the dinitrile (**12a,b,e,f**) does not lead to addition of the nitrone to the cyclopropane moiety.

## Synthesis of Nitrones

The nitrones 8–11 were used as 1,3-dipoles in this investigation. Within this series it is possible to study the influence of variation in the nitrone reactivity on the cycloaddition reaction (see Discussion and Conclusions).

Compound **8** was prepared via a known procedure,[8] viz. reaction of the *N*-hydroxytryptophan derivative **6**—prepared by addition of **1** to **3**, followed by reduction of the oxime **4**—with methyl orthoformate (Scheme I).

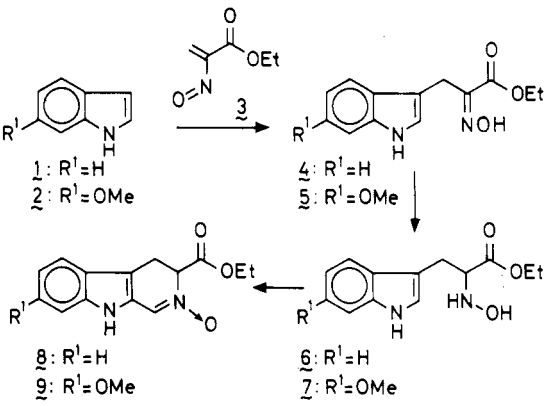
Nitrone **9** was prepared in an analogous fashion. The preparation of this compound is of additional interest as it can be viewed as a precursor of *fumitremorgin C*.[9] Conjugate addition of 6-methoxyindole (**2**)[10] to the transient nitroso olefin **3**[11] gave the oxime **5** in 80% yield. Reduction with the trimethylamine–borohydride complex[12] afforded **7** (88% yield) which was converted into the nitrone **9** (95% yield), again with methyl orthoformate as described[8] for the synthesis of **8**.

The nitrones **10**[13] and **11**[14] were prepared according to known procedures.

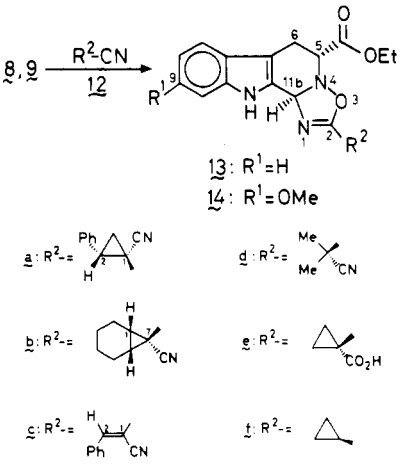
## Cycloadditions

The cycloaddition reaction of the nitrones 8–11 to the cyclopropylnitriles **12e**[15] and **12f**, to the geminal dinitriles **12c** and **12d**, and to the cyclopropyldinitriles **12a** and **12b** were investigated. The reactions are depicted in Schemes II–IV, and the results are listed in Table I. The nitrones **8**, **9**, and **11** react smoothly with the dipolarophiles **12a–d**. These reactions preceed under thermal as well as under high-pressure conditions. When the cyclopropyldinitriles **12a** and **12b** are employed as dipolarophiles, reaction takes

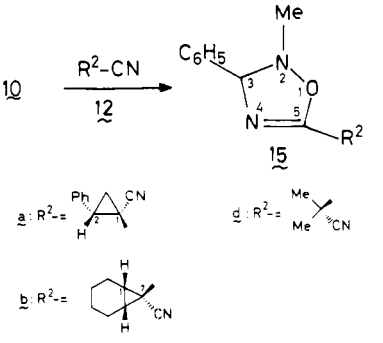
**Scheme I**




**Scheme II**




**Scheme III**

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**Scheme IV**

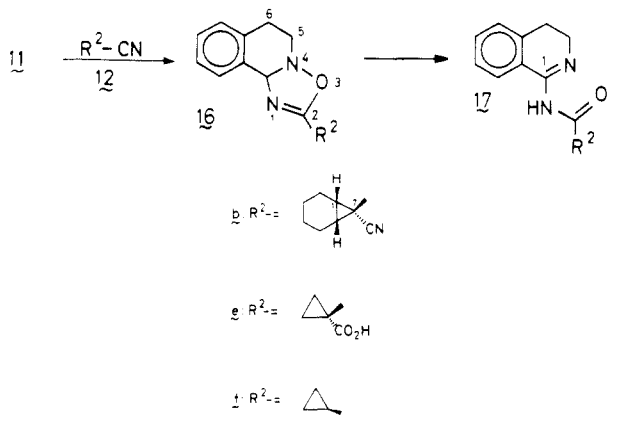


**Table I**

| entry | nitrone | nitrile | reaction conditions | product (% yield) |
|---|---|---|---|---|
| A | 8 | **12a** | 100 °C, 2 days | **13a**[a] (74%) |
| B | 8 | **12a** | 12 kBar, 2 days | **13a**[a] (90%) |
| C | 8 | **12b** | 12 kBar, 5 days | **13b** (92%) |
| D | 8 | **12c** | 80 °C, 3 days | **13c** (78%) |
| E | 8 | **12d** | 80 °C, 1 h | **13d** (100%) |
| F | 8 | **12e, 12f** | 12 kbar, 7 days | no reaction |
| G | 9 | **12c** | 60 °C, 7 h | **14c** (95%) |
| H | 10 | **12a, 12b** | 12 kBar, 7 days | no reaction |
| J | 10 | **12d** | 110 °C, 10 days | **15d** (85%) |
| K | 11 | **12b** | 12 kbar, 7 days | **16b** (86%) |
| L | 11 | **12b** | 110 °C, 2 days | **17b** (78%) |
| M | 11 | **12e, 12f** | 12 kBar, 7 days | no reaction |

[a] Mixture of two diastereomers found in a 1/1 ratio.

place selectively with a nitrile function and not with the cyclopropylring (Table I, entries A–C, K, and L). Cycloaddition reactions with the nitrile function take place only when a second nitrile function is present in the $\alpha$ position. Even under high-pressure conditions for 7 days no reaction

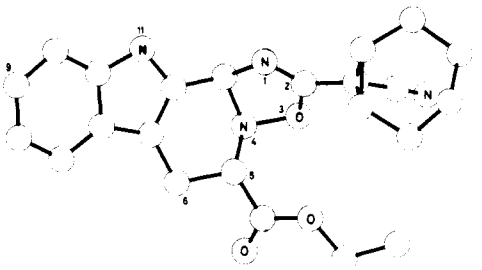
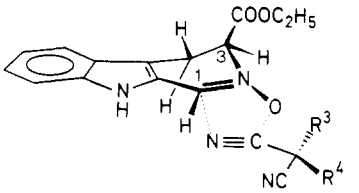
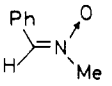


**Figure 1.** PLUTO drawing of **13b**.

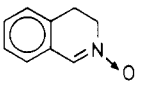
**Chart I**



takes place when the nitriles **12e** or **12f** were allowed to react with **8** or **11** (entries F and M).



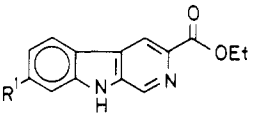
**10**



**11**

Yields are higher when high-pressure conditions are employed (viz., entries A and B). Under thermal conditions the cycloadducts **13–16** have a tendency to rearrange. This is examplified in entry L; treatment of the nitrone **11** with the nitrile **12b** at 110 °C for 2 days resulted in complete conversion of the initially formed cycloadduct **16b** into the rearranged product **17b**. Having observed this, the thermal reactions—being monitored by TLC—were interrupted as soon as the starting material had disappeared.

Another side product that could be identified is **18**.[8] This $\beta$-carboline is formed in up to 10% yield when the nitrones **8** and **9** were subjected to cycloaddition reactions under thermal conditions.



**18**

Nitrone **10** did not react with the nitriles **12a,b**; under thermal as well as high-pressure conditions, only the starting materials were isolated. However, cycloaddition of this nitrone **10** with nitrile **12d** (Scheme III) gave **15d** (entry J), although the reaction proceeds very sluggishly.

Unequivocal evidence for the structure of **13b** was derived from a single-crystal X-ray analysis[16] (see Figure 1). The structures of the other new products could be assigned—by $^1$H NMR spectroscopy. The critical chemical shifts for the C(5), C(6), and C(11b) protons compare favorably with the chemical shifts of the corresponding protons in **13b**.

## Regioselectivity

All of the cycloaddition reactions under consideration show complete regioselectivity in the formation of the

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$\Delta^4$-1,2,4-oxadiazoline ring of **13–16**. This selectivity can be rationalized by frontier molecular orbital theory.[17,18] For a given electron-deficient dipolarophile, viz. the nitrile, the regiochemistry of the reaction will depend on a favourable LUMO (dipolarophile)–HOMO (dipole) frontier orbital interaction. Thus, overlap of orbitals with comparable terminal coefficients, i.e. orbitals of the nitrogen and the carbon atoms of the nitrile with the orbitals of the carbon and oxygen atoms of the nitrone, respectively, will lead to the $\Delta^4$-1,2,4-oxadiazoline ring. Alternatively, the regiochemistry can be rationalized by combining the *anionic* terminus of the nitrone, i.e. the oxygen atom, with the electrophilic side of the nitrile group, i.e. the carbon atom.[18]

## Stereochemistry

As far as the relative stereochemistry of the reactions depicted in Scheme III is concerned, it is noteworthy that the C(5) and C(11b) substituents of **13** and **14** are in an *E* orientation. This stereochemistry of the reactions, which proceed in a completely stereocontrolled fashion, is similar to that observed in the cycloadditions of **8** with alkenes.[8] This result may be rationalized as depicted in Chart I, indicating that the nitrile approaches the nitrone exclusively from the side opposite the C(3) substituent.

The diastereoselectivity deserves further attention. When the dinitrile **12b** is employed, only one of the two diastereotopic nitrile functions adds to the 1,3 dipole of **8** (entry C) or **11** (entry K). This selectivity is easily explained by steric hindrance; Figure 1 shows that the less hindered nitrile function —being in the exo position—is involved in these reactions. Cycloadditions involving the alkene **12c** proceed in a similar diastereoselective fashion. Entries D and G show that only one of the two possible diastereomers if formed. This selectivity might also be explained by steric hindrance. Addition to the less hindered nitrile function of **12c** leads to adducts **13c** and **14c** having the *E* geometry in the alkene moiety. A related diastereoselectivity was observed when cyclopropyl dinitrile **12a** was employed (entries A and B). Of the four possible stereoisomers only two are formed, in both experiments, in a 1/1 ratio. On the basis of the abovementioned observations we assume that here too the nitrone reacts with the less hindered nitrile function of **12a**. Due to the chirality of **12a**, two diastereomers of **12a**—epimeric in their cyclopropane moiety—are formed. Assignment of formula **13a** to the cycloadducts is based on these considerations.

## Discussion and Conclusions

The reaction of geminal dinitriles with nitrones gives access to $\Delta^4$-1,2,4-oxadiazolines. This scantly studied class of compounds might be used for the stereoselective construction of 1-amino-$\beta$-carboline derivatives (cf. **16**→**17**), which are structural features of the indole alkaloids evodiamine[19] and ruthecarpine.[19]

Obviously, the success of the reaction depends on the ractivity of the nitrones as well the nitriles. As far as the nitrones are concerned, they have to be sufficiently reactive. Their reactivity appears to be correlated with their electron richness. A measure of the electron richness of conjugated nitrones is the weighted average of the first two ionization potentials. These values for **8**,[8] **11**[20], and **10**[20] are 8.40, 8.46, and 8.58 eV, respectively.[21] In agreement with these data **10** has a very low reactivity; it does not add to **12a** and **12b**; in our experiments it reacts only with the most reactive nitrile, i.e. **12d**, in a very slow reaction. Nitrone **11** is more reactive,[22] and the reactivity of **8** is even slightly better than that of **11**. Of the series studied, nitrone **9** is the most reactive one (compare entries D and G).

As far as the reactivity of the dinitriles is concerned, it appears that the rate of the cycloaddition reaction increases when the nitrile group becomes more electron deficient. Replacement of the cyclopropyl or alkene group in **12a–c** by alkyl groups (**12d**) enhances the rate of reaction (compare entries A–D with entry E). We anticipate that the addition of nitrones to geminal dinitriles will appear of general applicability if the dipolarophile employed is sufficiently electron deficient.

It has been predicted[23] that the double bond of very electron-deficient dipolarophiles like 1,1-dicyanoethene will add to nitrones to give HOMO (nitrone)–LUMO (double bond) controlled 4-substituted isoxazolidines. In the light of our results we anticipate, however, that one of the nitrile functions and not the double bond of 1,1-dicyanoethene will react with nitrones.

## Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model 555. Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as $\delta$ values relative to tetramethylsilane as an internal standard; deuteriochloroform was used as the solvent unless stated otherwise. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, or $Cl_2$–TDM.[24] For high-performance liquid column chromatography (John Yvon) Merck silica gel H (type 60) was used.

**Ethyl α-(Hydroxyimino)-β-(6-methoxyindol-3-yl)-propanoate (5).** A solution of ethyl α-(hydroxyimino)-β-bromopropanoate[12] (3 mmol, 630 mg) in $CH_2Cl_2$ (20 mL) was added dropwise to a stirred solution of **2**[10] (6.8 mmol, 1.0 g) and a suspension of $Na_2CO_3$ (6 mmol, 620 mg) in $CH_2Cl_2$ (20 mL) at room temperature in an argon atmosphere. Stirring was continued at room temperature for 18 h. The mixture was then filtered through a thin layer of silica gel (60) and concentrated to dryness. The residue was subjected to column chromatography (silica gel 60, $CH_2Cl_2$) to yield 670 mg of crystalline **5**, 80%. It was recrystallized from $CH_2Cl_2$/MeOH/*n*-hexane: mp 148–149 °C; $R_f$ 0.29 (MeOH/$CHCl_3$, 4/96, v/v); UV (MeOH) $\lambda_{max}$ 290, 220 nm, $\lambda_{min}$ 250 nm; EIMS (70 eV) *m/e* 276 ($M^+$, 93%), 259 ($[M - OH]^+$, 41%), 186 ($[C_{11}H_{10}N_2O]^+$, 50%), 185 (62%), 160 ($[C_{10}H_{10}NO]^+$, 100%); exact mass for $C_{14}H_{16}N_2O_4$, calcd 276.1110, found 276.1113; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.89 (s br, 1 H, NH), 7.70–6.73 (m, 3 H, indole C(4) H–C(5) H and C(2) H), 6.83 (s, 1 H, indole C(7) H, 4.26 (q, 2 H, $OCH_2CH_3$), 4.07 (s, 2 H, indole C(3) $CH_2$), 3.83 (s, 3 H, $OCH_3$), 1.31 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{14}H_{16}N_2O_4$ (MW 276.192): C, 60.86; H 5.84; N, 10.14. Found: C, 60.92; H, 5.85; N, 10.15.

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**Ethyl α-(Hydroxyamino)-β-(6-methoxyindol-3-yl)-propanoate (7).** A solution of HCl in ethanol (20 mL of a 7 N solution) was added dropwise to a stirred solution of **5** (11.7 mmol, 3.25 g) and $(CH_3)_3N{\cdot}BH_3$ (Aldrich Chemical Co.; 12.9 mmol, 940 mg) in EtOH (50 mL) at room temperature and in an argon atmosphere. Stirring was continued for 5 h. The mixture was then concentrated to dryness. The residue was dissolved in $CH_2Cl_2$. This solution was neutralized with $NaHCO_3$ and filtered. The filtrate was washed with 0.1 N HCl and dried over $Na_2SO_4$. Evaporation of the solvent in vacuo and HPLC ($MeOH/CH_2Cl_2$, 2/98, v/v) gave 2.85 g of **7** (88%), which was recrystallized from $CH_2Cl_2$/*n*-hexane: mp 64–67 °C; $R_f$ 0.25 ($MeOH/CHCl_3$, 4/96, v/v); UV (MeOH) $\lambda_{max}$ 295 (sh), 288, 277, 230 nm, $\lambda_{min}$ 280, 252 nm; EIMS (70 eV) *m/e* 278 ($M^+$, 17%), 160 ($[C_{10}H_{10}NO]^+$, 100%); exact mass for $C_{14}H_{18}N_2O_4$ calcd 278.1267, found 278.1272; $^1H$ NMR (90 MHz, $CDCl_3$) δ 7.95 (s br, 1 H, NH), 7.52–6.72 (m, 3 H, indole C(4) H–C(5) H and C(2) H), 6.85 (s, 1 H, indole C(7) H, 5.53 (s br, 2 H, NHOH), 4.19 (q, 2 H, $OCH_2CH_3$), 3.96 (X part of ABX spectrum, 1 H, indole C(3) $CH_2CH$), 3.84 (s, 1 H, $OCH_3$), 3.15 and 3.03 (AB part of ABX spectrum, 2 H, $^3J$ = 4.5 Hz, $^3J$ = 9.0 Hz, $^2J$ = 11.4 Hz, indole C(3) $CH_2CH$), 1.23 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{14}H_{18}N_2O_4$ (MW 278.308): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.29; H, 6.51; N, 10.05.

**2-Oxo-3-(ethoxycarbonyl)-7-methoxy-3,4-dihydro-β-carboline (9).** Trifluoroacetic acid (1 mL) was added to a stirred solution of **7** (7.65 mmol, 2.13 g) in $HC(OMe)_3$ (30 mL at room temperature and in an argon atmosphere. Stirring was continued for 1 h. The mixture was then concentrated to near dryness, dissolved in $CH_2Cl_2$, and concentrated again. The residue was dissolved in $CH_2Cl_2$, and the resulting solution was washed with 0.1 N $NaHCO_3$ and water and dried over $Na_2SO_4$. Evaporation of the solvent gave crystalline **9**, which was recrystallized ($MeOH/CH_2Cl_2$): yield 2.1 g (95%); mp 161–164 °C; $R_f$ 0.39 ($MeOH/CHCl_3$, 7/97, v/v); UV (MeOH) $\lambda_{max}$ 404, 392, 275, 249 (sh), 231 (sh), 225 nm, $\lambda_{min}$ 389, 301, 258 nm; EIMS (70 eV) *m/e* 288 ($[M]^+$, 6%), 270 ($[M-OH]_2^+$, 22%), 200 (73%), 198 ($[C_{12}H_{10}N_2O]^+$, 100%), 173 (48%); exact mass for $C_{15}H_{16}N_2O_4$, calcd 288.1110, found 228.1116; $^1H$ NMR (90 MHz, $CDCl_3$) δ 9.32 (s br, 1 H, NH), 7.96 (s, 1 H, C(1) H), 7.56–6.78 (m, 2 H, C(5)–C(6) H), 6.87 (s, 1 H, C(8) H), 4.92 (X part of ABX spectrum, 1 H, (C(3) H–C(4) $H_2$, 4.25 (q, 2 H, $OCH_2CH_3$), 3.85 (s, 1 H, $OCH_3$), 3.63–3.53 (AB part of ABX spectrum, 2 H, C(4)$H_2$–C(3) H), 1.23 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (MW 288.303): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.54; H, 5.58; N, 9.73.

**2-(1-Cyano-2-phenylcyclopropyl)-5-(ethoxycarbonyl)-4,5,6,11b-tetrahydro-Δ⁴-1,2,4-oxadiazolino[3,2-*a*]-β-carboline (13a). Thermal Reaction Conditions.** A solution of the nitrone **8**[8] (0.5 mmol, 120 mg) and the nitrile **12a**[25] (0.55 mmol, 77 mg) in dry toluene (10 mL) was kept at 100 °C for 36 h. The reaction was monitored by TLC ($MeOH/CH_2Cl_2$, 1/99, v/v). Evaporation of the solvent and flash column chromatography of the residue gave a mixture of two diastereomers **13a** in a 1/1 ratio [188 mg (74%)] and 12 mg of **18**[8] (10%). The diasteromers were separated by HPLC to yield the pure compounds.

**High-Pressure Reaction Conditions.** The nitrone **8**[8] (0.25 mmol, 65 mg) and the nitrile **12a**[25] (0.275 mmol, 46 mg) were dissolved in 1.5 mL of $EtOH/CH_2Cl_2$ (50/50, v/v) and brought into a Teflon high-pressure vessel, which was placed in a high-pressure apparatus. After 18 h at 12 kbar all starting material had been converted. Evaporation of the solvents and flash column chromatography of the residue gave a mixture (1/1) of two diastereomers **13a** [96 mg (90% yield)], which were identical with the cycloadducts from the thermal cycloaddition reaction.

**Compound 13a₁:** $R_f$ 0.42 ($MeOH/CH_2Cl_2$, 1/99, v/v); mp 126–128 °C ($CH_2Cl_2$/*n*-hexane); UV (MeOH) $\lambda_{max}$ 289 (sh), 279 (sh), 272, 221 nm; $\lambda_{min}$ 248 nm; IR (KBr) ν(C≡N) 2255, ν(C=O) 1730, ν(C=N) 1665 $cm^{-1}$; EIMS (70 eV) *m/e* 426 ($M^+$, 3%), 258 ($[M - C_{11}H_8N_2]^+$, 8%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 9%); 185 ($[C_{11}H_9N_2O]^+$, 20%), 168 ($[C_{11}H_8N_2]^+$, 100%); exact mass for $C_{25}H_{22}N_4O_3$, calcd 426.1699, found 426.1692; $^1H$ NMR (90 MHz, $CDCl_3$) δ 8.48 (s br, 1 H, N(11) H), 7.54–7.06 (m, 9 H, C(7)–C(10) H, $C_6H_5$), 6.28 (s, 1 H, C(11b) H), 4.33 (q, 2 H, $OCH_2CH_3$), 3.85 (X part of ABX spectrum, $^3J_{AX}$ = 4.7 Hz, $^3J_{BX}$ = 9.7 Hz, 1 H), 3.29 (X' part of A'B'X' spectrum, $^3J_{A'X'} = {}^3J_{B'X}$ = 9.1 Hz, $C_6H_5CH$) 3.28 and 3.00 (AB part of ABX spectrum, $^3J_{AX}$ = 4.7 Hz, $^3J_{BX}$ = 9.7 Hz, $^2J_{AB}$ = 16 Hz, C(6) $H_2$), 2.30–2.00 (A'B' part of A'B'X spectrum, 2 H, $C_6H_5CHCH_2$), 1.35 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{25}H_{22}N_4O_3$ (MW 426.471): C, 70.41; H, 5.20; N, 13.14. Found: C, 70.10; H, 5.15; N, 13.01.

**Compound 13a₂:** $R_f$ 0.34 ($MeOH/CH_2Cl_2$, 1/99, v/v); mp 169–172 °C ($CH_2Cl_2$/*n*-hexane); UV (MeOH) $\lambda_{max}$ 289 (sh), 280 (sh), 273, 221 nm, $\lambda_{min}$ 250 nm; IR (KBr) ν(C≡N) 2255, ν(C=O) 1730, ν(C=N) 1665 $cm^{-1}$; EIMS (70 eV) *m/e* 426 ($[M^+]$, 3%), 258 ($[M - C_{11}H_8N_2]^+$, 6%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 8%), 185 ($[C_{11}H_9N_2O]^+$, 168 ($[C_{11}H_8N_2]^+$, 100%); exact mass for $C_{25}H_{22}N_4O_3$, calcd 426.1699, found 426.1692; H NMR (90 MHz, $CDCl_3$) δ 8.52 (s br, 1 H, N(11) H), 7.54–7.00 (m, 9 H, C(7)–C(10) H, $C_6H_5$), 6.30 (s, 1 H, C(11b) H), 4.35 (q, 2 H, $OCH_2CH_3$), 3.85 (X part of ABX, $^3J_{AX}$ = 5.0 Hz, $^3J_{BX}$ = 9.5 Hz, 1 H, C(5) H), 3.35–2.85 (m, 3 H, C(6) $H_2$ and $C_6H_5CH$), 2.35–2.00 (A'B' part of A'B'X, 2 H, $C_6H_5CHCH_2$), 1.35 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{25}H_{22}N_4O_3$ (MW 426.476): C, 70.41; H, 5.20; N, 13.14. Found: C, 69.98; H, 5.18; N, 13.10.

**2-(1-Cyanonorcaran-7-yl)-5-(ethoxycarbonyl)-4,5,6,11b-tetrahydro-Δ⁴-1,2,4-oxadiazolino[3,2-*a*]-β-carboline (13b).** The nitrone **8**[8] (0.25 mmol, 120 mg) and the nitrile **12b**[26] (0.55 mmol, 80 mg) were dissolved in 1.5 mL of $EtOH/CH_2Cl_2$ (50/50, v/v). This solution was brought into a Teflon high-pressure vessel, which was placed in a high-pressure apparatus. A pressure of 12 kbar was applied for 5 days to convert all of **8**. Evaporation of the solvent and flash column chromatography of the residue using $CH_2Cl_2$ as an eluent gave **13b** in 92% yield (186 mg): $R_f$ 0.5 ($MeOH/CH_2Cl_2$, 1/99, v/v); mp 161–164 °C (methyl ethyl ketone); UV (MeOH) $\lambda_{max}$ 289 (sh), 280 (sh), 272, 220 nm, $\lambda_{min}$ 253 nm; IR (KBr) ν(C≡N) 2245, ν(C=O) 1730, ν(C=N) 1670 $cm^{-1}$; EIMS (70 eV) *m/e* 404 ($[M]^+$, 1%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 5%), 168 ($[C_{11}H_8N_2]^+$, 41%); exact mass for $C_{23}H_{24}N_4O_3$, calcd 404.1850, found 404.1860; $^1H$ NMR (90 MHz, $CDCl_3$) δ 8.45 (s br, 1 H, N(11) H), 7.60–7.05 (m, 4 H, C(7)–C(10) H), 6.21 (s, 1 H, C(11b) H), 4.47 (q, 2 H, $OCH_2CH_3$), 3.83 (X part of ABX spectrum, $J_{AX}$ = 5.0 Hz, $J_{BX}$ = 9.6 Hz, 1 H, C(5) H), 3.20 and 3.05 (AB part of ABX spectrum, $^3J_{AX}$ = 5.0 Hz, $^3J_{BX}$ = 9.6 Hz, $^2J_{AB}$ = 15.5 Hz, 2 H, C(6) $H_2$), 1.4–2.4 (m, 10 H, cyclohexyl H), 1.47 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{23}H_{24}N_4O_3$ (MW 404.47): C, 68.30; H, 5.98; N, 13.85. Found: C, 68.09; H, 5.98; N, 13.74. The structure has been secured by single-crystal x-ray crystallography.[16]

**2-(1-Cyano-2-phenylvinyl)-5-(ethoxycarbonyl)-4,5,6,11b-tetrahydro-Δ⁴-1,2,4-oxadiazolino[3,2-*a*]-β-carboline (13c).** A solution of the nitrone **8** (1 mmol, 260 mg) and the nitrile **12c**[28] (1.25 mmol, 190 mg) in dry toluene (10 mL) was kept at 80 °C for 36 h. Evaporation of the solvent and flash column chromatography of the residue (EtOAc/*n*-hexane, 25/75, v/v) gave 320 mg of **13c**, 78%. Recrystallization (EtOAc/*n*-hexane) gave yellow crystals: mp 164–166 °C; $R_f$ 0.25 (EtOAc/*n*-hexane, 25/75, v/v); UV (MeOH) $\lambda_{max}$ 304, 290, 283, 220 nm; IR (KBr) ν(C≡N) 2235, ν(C=O) 1730, ν(C=N) 1640 $cm^{-1}$; EIMS (70 eV) *m/e* 472 ($[M]^+$, 1%), 185 ($[C_{11}H_9N_2O]^+$, 69%), 154 ($[C_{10}H_6N_2]^+$, 100%); exact mass for $C_{24}H_{20}N_4O_3$, calcd 412.1535, found 412.1537; $^1H$ NMR (90 MHz, $CDCl_3$) δ 8.60 (s br, 1 H, N(11) H), 8.05–7.15 (m, 10 H, C(7)–C(10) H, C=$CHC_6H_5$), 6.50 (s, 1 H, C(11b) H), 4.45 (q, 2 H, $OCH_2CH_3$), 3.95 (X part of ABX spectrum, $^3J_{AX}$ = 4.5 Hz, $^3J_{BX}$ = 9.8 Hz, 1 H, C(5) H), 3.30 and 3.05 (AB part of ABX spectrum, $^3J_{AX}$ = 4.8 Hz, $^3J_{BX}$ = 9.8 Hz, $^2J_{AB}$ = 15.5 Hz, 2 H, C(6) $H_2$), 1.45 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{24}H_{20}N_4O_3$ (MW 412.447): C, 69.89; H, 4.89; N, 13.58. Found: C, 69.78; H, 4.88; N, 13.63.

**2-(1-Cyano-1-methylethyl)-5-(ethoxycarbonyl)-4,5,6,11b-tetrahydro-Δ⁴-1,2,4-oxadiazolino[3,2-*a*]-β-carboline (13d).** A solution of the nitrone **8** (1 mmol, 260 mg) and the nitrile **12d**[28] (10 mmol, 940 mg) in dry toluene (10 mL) was kept at 80 °C for 1 h. Evaporation of the solvent and flash column chromatography of the residue ($MeOH/CH_2Cl_2$, 0.5/99.5, v/v) gave **13d** quantitatively. Recrystallization from dimethyl ether gave white crystals: mp 145–148 °C; $R_f$ 0.75 ($MeOH/CH_2Cl_2$, 7/93, v/v); UV (MeOH)

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$\lambda_{max}$ 288, 278, 270, 228, 220 nm; IR (KBr) $\nu$(C≡N) 2250, $\nu$(C=O) 1740, $\nu$C=N) 1668 cm$^{-1}$; EIMS (70 eV) $m/e$ 352 ([M]$^+$, 15%), 284 (33%), 258 (31%), 252 (49%), 210 (28%), 185 ([$C_{11}H_9N_2O$]$^+$, 100%), 169 (74%), 168 ([$C_{11}H_8N_2$]$^+$, 84%; exact mass for $C_{19}H_{20}N_4O_3$, calcd 352.1535, found 352.1543; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 8.35 (s br, 1 H, N(11) H), 7.55–7.05 (m, 4 H, C(7)–C(10) H), 6.20 (s, 1 H, C(11b) H), 4.35 and 4.32 (2 q, 2 H, $OCH_2CH_3$), 3.80 (X part of ABX spectrum, $^3J_{AX}$ = 10.0 Hz, $^3J_{BX}$ = 5.0 Hz, 1 H, C(5) H), 3.15 and 3.05 (AB part of ABX spectrum, $^3J_{AX}$ = 10.0 Hz, $^3J_{BX}$ = 5.0 Hz, $^2J_{AB}$ = 12.5 Hz, 2 H, C(6) $H_2$), 1.70 (s, 6 H, $C(CH_3)_2$), 1.35 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{19}H_{20}N_4O_3$ (MW 352.394): C, 64.76;, H, 5.72; N, 15.90. Found: C, 64.74; H, 5.73; N, 15.70.

**2-(1-Cyano-2-phenylvinyl)-5-(ethoxycarbonyl)-9-methoxy-4,5,6,11b-tetrahydro-Δ$^4$-1,2,4-oxadiazolino[3,2-*a*]-β-carboline (14c).** A solution of the nitrone **9** (1mmol, 288 mg) and the nitrile **12c**[27] (2.16 mmol, 330 mg) dissolved in toluene (15 mL) was kept at 65 °C for 7 h. The reaction was monitored by TLC (MeOH/$CHCl_3$, 7/93, v/v). Evaporation of the solvent, flash column chromatography of the residue (MeOH/$CH_2Cl_2$, 0.8/99.2, v/v, and recrystallization gave 400 mg of **14c**: 95%; mp 188–190 °C; $R_f$ 0.60 ($CH_2Cl_2$/*n*-hexane); UV (MeOH) $\lambda_{max}$ 307 (sh), 299, 228 nm; $\lambda_{min}$ 251 nm; IR (KBr) $\nu$(C≡N) 2200, $\nu$(C=O) 1725, $\nu$(C=N) 1642 cm$^{-1}$; EIMS (70 eV) $m/e$ 442 ([M]$^+$, 42%), 369 ([$C_{22}H_{17}N_4O_2$]$^+$, 20%), 314 ([$C_{16}H_{16}N_3O_4$]$^+$, 10%), 198 ([$C_{12}H_{10}N_2O$]$^+$, 100%); exact mass for $C_{25}H_{22}N_4O_4$, calcd 442.1641, found 442.1635; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 8.27 (s br, 1 H, NH), 7.97–6.71 (m, 9 H, C(7)–C(8) H, C(10) H, $C_6H_5$, C=CH), 6.34 (s, 1 H, C(11b) H), 4.35 (q, 2 H, $OCH_2CH_3$), 3.90 (X part of ABX spectrum, 1 H, C(5) H–C(6) $H_2$), 3.83 (s, 1 H, $OCH_3$), 3.18 and 3.04 (AB part of ABX spectrum, 2 H, $^3J$ = 3.3 Hz, $^3J$ = 11.7 Hz, $^2J$ = 12.6 Hz, C(6) $H_2$–C(5) H), 1.35 (t, 3 H, $OCH_2CH_3$). Anal. Calcd for $C_{25}H_{22}N_4O_4$ (MW 442.476): C, 67,86; H, 5.01; N, 12.66. Found: C, 67.56; H, 4.85; N, 12.50.

**2-Methyl-3-phenyl-5-(1-cyano-1-methylethyl)-Δ$^4$-1,2,4-oxadiazoline (15d).** A solution of the nitrone **10**[19] (0.8 mmol, 108 mg) and the nitrile **12d** (0.81 mmol, 76 mg) in dry toluene (5 mL) was kept at 110 °C for 10 days. evaporation of the solvent and flash column chromatography of the residue (MeOH/$CH_2Cl_2$, 0.5/99.5 v/v) gave 156 mg of **15d** (85%) as an oil, which was homogeneous on TLC: $R_f$ 0.35 (MeOH/$CDCl_3$, 7/93); CIMS (100 eV) $m/e$ 230 ([M + 1), 28%), 161 ([$C_9H_9N_2O$], 100%); exact mass for $C_{13}H_{15}N_3O$, calcd 229.1215, found 229.1211; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 7.23 (s, 5 H, $C_6H_5$), 5.61 (s, 1 H, C(3) H), 2.89 (s, 3 H, N(2) $CH_3$), 1.71 (s, 6H, C(1) $(CH_3)_2CN$).

**2-(7-Cyanonorcaran-7-yl)-4,5,6,10b-tetrahydro-Δ$^4$-1,2,4-oxadiazolino[3,2-*a*]isoquinoline (16b).** The nitrone **11**[14] (0.5 mmol, 74 mg) and the nitrile **12b**[27] (0.55 mmol, 80 mg) were dissolved in $CH_2Cl_2$ (1.5 mL). The solution was placed in a high-pressure vessel, which was placed in a high-pressure apparatus (12 kbar) for 7 days. After evaporation of the solvent and flash column chromatography (MeOH/$CH_2Cl_2$, 1/99, v/v) **16b** was obtained as an oil in 86% yield: 126 mg; $R_f$ 0.30 (MeOH/$CH_2Cl_2$, 1/99, v/v); EIMS (70 eV) $m/e$ 293 ([M]$^+$, 6%), 147 ([$C_9H_9NO$]$^+$, 100%); exact mass for $C_{18}H_{19}N_3O$, calcd 293.1528, found 293.1517; $^1$ H NMR (90 MHz, $CDCl_3$) $\delta$ 7.60–7.00 (m, 4 H, C(77)–C(10) H), 5.95 (s, 1 H, C(10b) H), 3.70–2.50 (m, 4 H, C(5) $H_2$–C(6) $H_2$, 2.40–1.10 (m, 10 H, cyclohexyl H).

**1-[[(7-Cyanonorcaran-7-yl)carbonyl]amino]-3,4-dihydroisoquinoline (17b).** The nitrone **11**[14] (0.5 mmol, 74 mg) and the nitrile **12b**[27] (0.55 mmol, 80 mg) were dissolved in toluene and heated (110 °C) for 2 days. Evaporation of the solvent and flash column chromatography of the residue (MeOH/$CH_2Cl_2$, 2/98, v/v) gave **17b** [115 mg (78%)], which was recrystallized from $CH_2Cl_2$/*n*-hexane: $R_f$ 0.7 (MeOH/$CH_2Cl_2$, 1/99, v/v); mp 128–130 °C; UV (MeOH) $\lambda_{max}$ 282, 210 nm; $\lambda_{mi}$( 230 nm; IR (KBr) $\nu$(C≡N) 2218 cm$^{-1}$; EIMS (70 eV) $m/e$ 293 ([M]$^+$, 37%), 173 ([$C_{10}H_9N_2O$]$^+$, 100%), 130 ([$C_9H_8N$]$^+$, 18%); exact mass for $C_{18}H_{19}N_3O$, calcd 293.1528, found 293.1524; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 11.10 (s br, 1 H, CONH), 8.50–7.10 (m, 4 H, C75)–C(8) H), 3.60 (dt, 2 H, C(3) $H_2$), 2.95 (t, 2 H, C(4) H), 2.20–1.10 (m, 10 H, cyclohexyl H). Anal. Calcd for $C_{18}H_{19}N_3O$ (MW 293.370): C, 73.69; H, 6.53; N, 14.32. Found: C, 73.50; H, 6.54; N, 14.32.

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**Registry No.** **2**, 3189-13-7; **5**, 106544-16-5; **7**, 106544-17-6; **8**, 106544-20-1; **9**, 106544-18-7; **10**, 3376-23-6; **11**, 24423-87-8; **12a**, 6904-17-2; **12b**, 29782-28-3; **12c**, 2700-22-3; **12d**, 7321-55-3; **12e**, 6914-79-0; **12f**, 5500-21-0; **13a** (isomer 1), 106544-19-8; **13a** (isomer 2), 106622-86-0; **13b**, 106544-21-2; **13c**, 106544-22-3; **13d**, 106544-23-4; **14c**, 106544-24-5; **15d**, 106544-25-6; **16b**, 106568-14-3; **17b**, 106544-26-7; **18**, 74214-62-3; $BrCH_2C(=NOH)CO_2Et$, 73472-94-3.

# Anthracyclinones. 2. Isosaccharinic Acid as Chiral Template for the Synthesis of (+)-4-Demethoxy-9-deacetyl-9-(hydroxymethyl)daunomycinone and (−)-4-Deoxy-γ-rhodomycinone[1]

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Chiral aldehyde derivatives **12**, **19**, and **22** were prepared in few steps from α-D-isosaccharino-1,4 lactone (**1a**). These derivative precursors of ring A of the title anthracyclinones were condensed with leucoquinizarin (**28**), the component of the BCD rings. Aldolization reactions afforded alkylanthraquinones **29**, **33**, and **34**, respectively. After suitable transformations of **29** and ring closure, the protected anthracyclinone **27** was obtained. Acetal cleavage of **27** led to the (+)-4-demethoxy-9-deacetyl-9-(hydroxymethyl)daunomycinone (**5**). Similarly suitable transformations of **33** or **34** followed by ring closure gave the (−)-4-deoxy-γ-rhodomycinone (**30**).

Rearrangement of hexoses by prolonged treatment with aqueous alkali leads primarily to the formation of "saccharinic acids" or deoxyaldonic acids, usually isolated as their crystalline lactones which are isomeric with the parent monosaccharides.[2]

In this way, for instance, α-D-isosaccharino-1,4-lactones **1a,b** and α-D-glucosaccharino-1,4-lactone (**2**) were prepared in high yield from lactose,[3] xylobiose or xylotriose,[4] and fructose,[5] respectively.

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