REACTION OF CITRAL WITH ACETONE CYANOHYDRIN AND DIETHYLAMINE, AND THERMOLYSIS OF THE RESULTING AMINONITRILE

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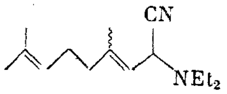
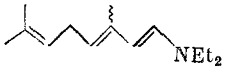
The reactions of citral with acetone cyanohydrin and secondary amines (diethylamine, piperidine, morpholine, and N-methylaniline) to give 2-substituted amino-4,8-dimethyl-3,7-nonadienoic acid nitriles have been examined. Possible pathways for these reactions are discussed. The thermolysis of 2-diethylamino-4,8-dimethyl-3,7-nonadienoic acid nitrile has been examined in solution, to give irreversibly 3-cyano-1-diethylamino-3,7-dimethyl-1,6-octadiene, this reaction proceeding faster in polar than in nonpolar solvents.

α,β-Enals have been known for some time to react with equimolar mixtures of acetone cyanohydrin (ACH) and dialkylamines to give β,γ-unsaturated α-dialkylaminonitriles (DAN) [1-4], but the mechanism of the reaction has not been discussed. The DAN formed tend to undergo secondary reactions, the nature of which depends on the structure of the starting α,β-enal. It is known [3] that the product of the reaction of citral (I) with ACH and Et_2NH, 2-diethylamino-4,8-dimethyl-3,7-nonadienoic acid nitrile (II), is converted even on vacuum distillation or simply on storage for extended periods (12-15 months at 20-25°C) into a difficultly separable mixture of three components, identified as 1-cyano-1-diethylamino-3,7-dimethyl-1,3,6-octatriene (III), 1-cyano-1-diethylamino-3,7-dimethyl-1,6-octadiene (IV), and 3-cyano-1-diethylamino-3,7-dimethyl-1,6-octadiene (V).

The reaction (I) + ACH + Et_2NH → (II), like the conversion of other α,β-enals into the corresponding DAN, is similar to the classic Strecker–Zelinskii–Stadnikov synthesis of amino acids (cf. [5]). Unlike the latter, however, it takes place in anhydrous media, in which the equilibrium between the reaction components is different from that in the system RCHO–NH_3–HCN–H_2O, and therefore the pathway leading to the formation of α-aminonitriles cannot be the same. For example, depending on the ratio of the rates of reaction of Et_2NH with (I), Et_2NH with ACH, and ACH with (I), under the reaction conditions the intermediate products could be citral diethylaminal (VI), citral cyanohydrin (VII), or the dieneamine (III).



(II)



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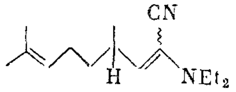

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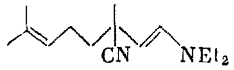

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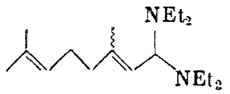

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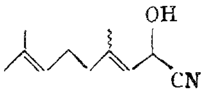

(VII)

In order to establish the mechanism of formation of DAN from α,β-enals, we examined the reaction of (I)* with each of the components of the reaction system separately, and the possible formation of the aminonitrile (II) from the products thus obtained. Treatment of (I) with two equivalents of Et_2NH (in the presence or absence of K_2CO_3) failed to give the diaminal (VI), removal of volatile products under reduced pressure at 20-25°C giving the dienamine (III)

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*The synthetic citral used contained, according to GLC, 65% of the E- and 35% of the Z-isomer.

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TABLE 1. Yields and Properties of Products Obtained

Compound	Yield, %	Reaction time, h	n_D^{20}	IR spectrum, ν, cm^{-1}	Mass spectrum $[MH^+]$	UV spectrum EtOH, $\lambda_{max}(\varepsilon)$	PMR spectrum (CCl_4, δ, ppm, J, Hz)
(II)	90–95	4–5	1,4700	2235 (CN) 1665 (C=C)	235	238 (5630)	1,10 m (6H, NCH_2CH_3); 1,58 s and 1,67 s (9H, allyl CH_3); 2,03–2,1 m (4H, H_2 at C^4, C^5); 2,4–2,8 m (4H, NCH_2CH_3); 4,20 d and 4.32 d (total 1 H, H at C^1); 5,10–5,20 m (2H, H at C^2 and C^6);
(IIa)	85	0,5	1,4890	2230 (CN) 1665 (C=C)	247	238 (1270) *	1,50–1,77 m, 1,57 s, 1,68 s (15H, allyl CH_3 + 3 ring, CH_2) 2.07 m (4H, H_2 at C^4 and C^5); 2.49 m (4H, CH_2NCH_2); 4,03 d (1H, H at C^1, J=8); 5,15 m (2H, H at C^2 and C^6)
(IIb)	81	0,5	1,4912	2230 (CN) 1665 (C=C)	249	238 (800) *	1,56–1,78 m 1,58 s, 1,67 s (9H, allyl CH_3); 2.10 m (4H, H_2 at C^4 and C^5); 2,55 m (4H, CH_2NCH_2); 3,62 t (4H, CH_2OCH_2, J=4,5); 4,05 d (1H, H at C^1, J=8); 5,01 m (2H, H at C^2 and C^6
(IIc)	75–80	4	1,5442	2230 (CN) 1660 (C=C)	269	288 (21 600)	1,52–1,78 m, 1,55 s, 1,69 s (9H, allyl CH_3), 2.05 m (4H, H_2 at C^4, and C^5); 2,80 s (3H, NCH_3); 4.88–5.40 m (3H, H at C^1, C^2, and C^6); 6.35–7,33 m (5H, C_6H_5)
(III)	65–70	4	1,5220	1645 1630 1610 930	208		1,20 t, 1,23 t (6H, NCH_2CH_3, J=7); 1.60–1,70 m (9H, allyl) CH_3); 2.50-2.80 m (2H, H_2 at C^5); 3,00 q, 3,05 q (4H, NCH_2CH_3, J=7); 4,65 d, 4,79 d (1H, H at C^2, J=13.5); 5,10 m (2H, H at C^4 and C^6) 5.92 d 6.06 d (1H, H at C^1, J=13,5)
(VII)	45–50	6	1.4805	2250 (CN) 3440 (OH) 3040 (C–CH)	180		1,58 s (3H); 1,66 s (3H); 1,72 d and 1.78 d (total 3H, CH_3 at C^3, J=1,5); 2,07 m (4H, H_2 at C^4 and C^5); 4.10 br. s (1H, OH); 4,83–5,40 m (3H, H at C^1, C^2 and C^6).

*From the absorption at λ_{pl} 288 nm (ε ~ 450-500), the sample contained ~5% of the dienamine (IIIa, b) as impurity.

as the sole product. Although the (III) was homogeneous according to GLC, the PMR spectrum showed it to be a mixture of the 1E,3E- and 1E,3Z-isomers in a ratio of ~2:1 (cf. [6]). The reaction of (III) with ACH at 20°C gave the aminonitrile (II), in accordance with the 1,4-addition of HCN to the dienamine. The yield of (II) obtained after 4-5 h was 55-60%, whereas in the three-component system (I) + ACH + Et_2NH the yield after the same time was 90-95% (GLC).

The third likely intermediate, the cyanohydrin (VII), was obtained by treating a solution of (I) in ether with HCN at 0°C. The addition of HCN to (I) under these conditions is reversible, the equilibrium mixture of (I):(VII) ≈ 30:70 being established rapidly, and remaining unchanged after 48 hours. The mixture obtained could not be separated by vacuum distillation, but preparative TLC on silica gel gave a yield of 45-50% (65-71% allowing for the citral reacted) of homogeneous product, identified by its spectral properties as the cyanohydrin (VII) (Table 1).*

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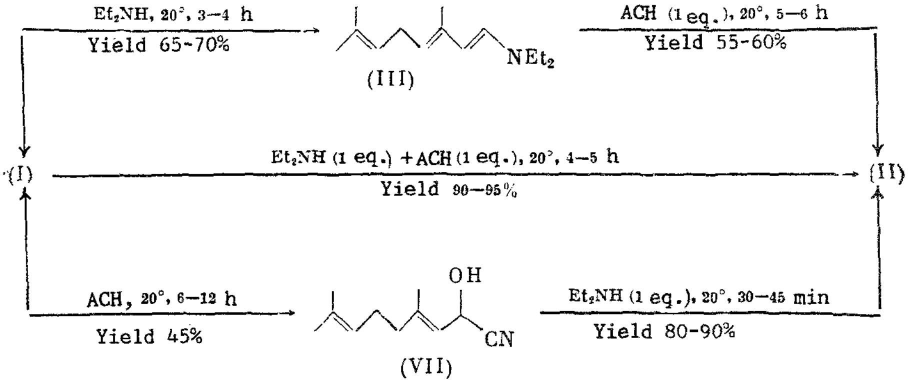
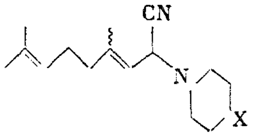
*Although the cyanohydrin (VII) is mentioned in [7], we here describe its preparation and properties for the first time.

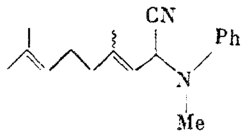
Reaction of (I) with ACH at 20°C (both in the presence and absence of K_2CO_3) resulted in the formation of (VII) at a much lower rate than in the reaction of (I) with HCN. However, addition of an equivalent amount of Et_2NH to the pure cyanohydrin (VII) at 20°C resulted in a rapid, exothermic reaction, to give after 30-45 min 80-90% yields of the aminonitrile (II). The results of these experiments are shown in the scheme. From these findings, it follows that (II) may be formed by any of the three routes shown, but the reaction is best carried out in the three-component system (I) + ACH + Et_2NH, which leads to the rapid formation of high yields of (II).



The general features of the reaction of citral with ACH and secondary amines to give analogs of the aminonitrile (II) are seen in the reactions of (I) with ACH and piperidine, morpholine, and N-methylaniline. The yields of the piperidine (IIa) and morpholine (IIb) compounds reach 80% after only 30 min, whereas with N-methylaniline the yield of the DAN (IIc) reaches 75-80% after four hours. The aminonitriles (IIa-d) were unstable, and were characterized only by their spectra (Table 1).

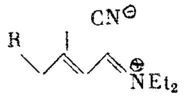


(IIa, b)
$X=CH_2$ (a), O (b).



(IIc)

The aminonitriles (II), (IIa-c) show characteristic strong UV absorption at λ 238 nm, indicating the possible existence of a resonance structure or ion pair (A).



(A)

In view of the fact that of the three products formed on distillation or prolonged storage of the aminonitrile (II), only the 3-cyano-substituted enamines (V) have been isolated [3] in 50-75% yields and reliably identified, we examined the thermal reactions of (II) under more controlled conditions. Prolonged heating of a solution of (II) in toluene (48 h at 100-105°C) resulted in complete conversion of (II) into the isomer (V). Heating (II) in toluene with one equivalent of NEt_3 shortened the time required to convert (II) into (V) to 16-18 h, but the dienamine (III) was not formed (according to the PMR and UV spectra, cf. [3]). The isomeric α,β-unsaturated aminonitrile (IV), the presence of which in the thermolyzate could have been detected from the presence of a doublet for the CH_3 group at C^3 at $\delta \sim 1.0$ ppm in the PMR spectrum, was not found in any of the thermolysis experiments. When both of the reactions were followed by GLC, however, a further product was shown to be present in small amounts during thermolysis, which disappeared as the (V) accumulated in the thermolyzate. Attempts to obtain (IV) by passing a solution of (II) in ether through a column of alumina (as in [2]) failed to result in any change.

Hence, in solution the aminonitrile (II) does not show any tendency to lose HCN on treatment with bases (NEt_3, Al_2O_3). The sole stable product on heating in toluene at 100-105°C is the isomer (V). The accelerating effect of NEt_3 on the conversion of (II) into (V) may be due to the increase in the polarity of the medium. In fact, on heating (II) in toluene (ε 2.38) at 100-105°C, or on boiling (II) in dioxane (bp 102°C, ε 2.21), the rearrangement (II) → (V) proceeds at similar rates, and is complete in 48 and 40 h respectively. However, on boiling (II) in acetonitrile (bp 82°C, ε 36.2), the conversion to (V) is complete in 13-14 h. In addition, the isomerization of (II) to (V) in ethanol (ε 24.3) in the cell of a UV spectrometer is 75% complete within 18-19 h at room temperature (from the UV absorption at λ 238 nm, and GLC), the formation of the dienamine (III) not being detected. Irradiation of a solution of (II) in a quartz cell with light of $\lambda \geq 200$ nm for 1 h had no effect on the rate of conversion (II) → (V). The reverse formation of (V) into (II), like that of (V) into (III) and/or (IV), failed to occur on heating (V) in toluene for 48 h in the presence of one equivalent of NEt_3.

From these results, it may therefore be concluded that the anionotropic rearrangement (II) → (V) probably involves the intermediate formation of the species (A), formation of which is facilitated by the polarity of the medium.

EXPERIMENTAL

The products and reaction mixtures were analyzed on an LKhM-8MD-5 chromatograph with a flame ionization detector and a glass column (1.4 × 0.003 m, 5% SE-30 on Chromatone N-AW-DMCS, carrier gas nitrogen) and on Silufol 254 plates. PMR spectra were obtained in CCl_4 with TMS as standard on a Tesla BS-467 (operating frequency 60 MHz), IR spectra in CCl_4 or $CHCl_3$ on a UR-20 instrument, and UV spectra in ethanol on a Specord UV-VIS. Mass spectra were obtained on a Varian MAT-112 GC-MS with chemical ionization (working gas – isobutane). The products were purified chromatographically using silica gel L (Czech SSR), particle size 40-100 µm.

Preparation of Aminonitriles (IIa)-(IIc). General Method. To a mixture of 3.04 g (0.02 mole) of citral and 1.74 g (0.02 mole) of freshly distilled ACH was added at 20°C with rapid stirring over five minutes 0.02 mole of pure piperidine (1.70 g), morpholine (1.74 g) or N-methylaniline (2.14 g). The reactions with piperidine and morpholine were exothermic (to 30-35°C), and were largely complete within 30 min (GLC and TLC), but N-methyaniline required 4 h. The mixture was cooled to 20°C, diluted with 30 ml of ether, dried over $MgSO_4$, the drying agent removed, and the filtrate passed through a small funnel containing 5 g of SiO_2. The eluate was evaporated under reduced pressure, and the residue, a clear, bright yellow oil, was dried for 3 h at 20-25°C in vacuo (1-2 mm). The properties of (IIa)-(IIc) are given in Table 1.

Dienamine (III). To 1.52 g (0.01 mole) of freshly distilled citral was added at 20°C with rapid stirring 1.46 g (0.02 mole) of Et_2NH, and the mixture stirred for 4 h. When the reaction was complete (GLC and TLC), the mixture was diluted with 5 ml of ether, the water which separated removed, and the ether layer dried over $MgSO_4$ and evaporated. Vacuum distillation of the residue gave the pure dienamine (III) as a mixture of the 3E- and 3Z-isomers (pale yellow oil), bp, 90-92°C (0.2 mm). Its properties are given in Table 1.

1-Hydroxy-1-cyano-3,7-dimethyl-2,6-octadiene (VII). To a mixture of 1.52 g (0.01 mole) of citral (I) and 0.74 g (0.015 mole) of NaCN in 5 ml of ether was added with stirring and cooling at 0°C over a few minutes 0.8 ml of conc. HCl. The mixture was stirred for 0.5 h at 0°C, then for 6 h at 20°C. It was then filtered, the solid washed with ether (3 × 3 ml), and the combined ethereal solutions dried over $MgSO_4$. After removal of the ether under reduced pressure, the residue consisted according to TLC and the PMR spectrum of a mixture of (I) and (VII) in a ratio of 3:7, which on attempted distillation in vacuo was completely converted into (I). Chromatography of the residue on plates with an unbound layer of silica gel (24 × 22 × 0.2 cm) in the system chloroform:methanol = 49:1 (by volume), followed by elution of the lower zone with ether, filtration of the eluate through a fine-pore filter, removal of the ether, and keeping the residue under vacuum (3 h at 20-25°C and 1-2 mm) gave 0.8-0.9 g of the pure cyanohydrin (VII) as a colorless oil. Found: C 73.14; H 9.75; N 8.43%. $C_{11}H_{17}ON$. Calculated: C 73.70; H 9.56; N 7.81%. For properties, see Table 1. Reaction of 10 mmoles of (I) with 10 mmoles of pure ACH at 20°C for seven hours gave a reaction mixture containing (by PMR and UV spectroscopy) (I):(VII) = 55-60:45-40.

Preparation of Aminonitrile (II) from Postulated Intermediates (III) and (VII). a) To 2.07 g (10 mmoles) of freshly distilled dienamine (III) was added at 20°C with stirring over five minutes 0.87 g (10 mmoles) of ACH, and stirring continued for 4 h. The mixture was diluted with 5 ml of ether, the water which separated removed, and the ether layer dried over $MgSO_4$ and evaporated. The product was separated as described above for (IIa)-(IIc). The resulting aminonitrile (II) ws identical to that described previously [3] (PMR spectrum, MH^+, UV spectrum).

b) To 0.89 g (5 mmoles) of the cyanohydrin (VII) was added at 20°C with stirring over five minutes 0.37 g (5 mmoles) of diethylamine. The temperature of the mixture rose to 35-40°C, and after 30-45 min the mixture contained (II) alone (GLC and TLC). The product was separated as described above, the (II) obtained being identical to that previously described [3].

Purification of a small amount (1.46 g) of the aminonitrile (II) by vacuum distillation at 112.5-114°C (0.35 mm) over 15-20 min afforded a pure sample of (II), n_D^{20} 1.5012 (cf. [3]) containing no thermal reaction products and identical with the material obtained above according to the IR and PMR spectra.

Isomerization of (II) to (V). A solution of 1.17 g (5 mmoles) of (II) in 3 ml of acetonitrile (or toluene, or dioxane) was heated for a given length of time, completion of the reaction of (II) being followed by TLC and GLC. The solvent was evaporated, and the residue distilled in vacuo to give pure (V) as a pale yellow oil, bp 108-110°C (0.3 mm). UV spectrum: λ_{max} 245 (ε 7400) and λ_{pl} 300 nm (ε 670). IR spectrum, CCl_4, ν, cm^{-1}: 2240 (CN) and 1655 (C=C). PMR spectrum (δ, ppm, J, Hz): 1.05 t (6H, $NCH_2C\underline{H}_3$), 1.32 s (3H, Me^3), 1.57 s and 1.62 s (6H, Me^7 and Me^8), 1.80-2.15 m (4H, $C\underline{H}_2C\underline{H}_2$), 2.92 q (4H, $NC\underline{H}_2CH_3$), 3.65 d (1H, $\underline{H}^2$, J_{AB} = 14), 4.94 m (1H, $\underline{H}^6$), 5.97 d (1H, $\underline{H}^1$, J_{AB} = 14), in agreement with the data reported in [3].

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BENZOYLATION OF 1,4-DIAZA-1,3-BUTADIENES: SYNTHESIS OF REPRESENTATIVES OF A NEW CHEMICAL CLASS – 1,2-DIAMINO-1-CHLOROETHYLENES

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and G. A. Stashina

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Trans-N,N'-dialkyl-N,N'-dibenzoyl-1,2-diamino-1-chloroethylenes – the first representatives of a new chemical class – and N,N'-dialkyl-N,N'-dibenzoyl-1,2-diaminoethylenes were obtained by benzoylation of N,N'-dialkyl-1,4-diaza-1,3-butadienes. On increase in pressure to 10,000 atm, the yields of the N,N'-dibenzoylated 1,2-diamino-1-chloroethylenes increase, and those of the N,N'-dibenzoylated 1,2-diaminoethylenes decrease.

The acylation of conjugated bis-amines has not been investigated whatsoever. The benzoylation of 1,4-diazabutadienes (I), undertaken in the present work, proceeds stereospecifically and results in the formation of new functional derivatives of ethylene

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