β-AMINOCROTONONITRILE

I. GEOMETRICAL ISOMERISM AND SOME REACTIONS

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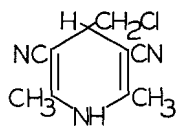
ABSTRACT

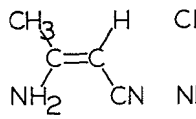
The low-melting form of β-aminocrotononitrile is a mixture of two components, one of which is the high-melting isomer. Isomerization reactions between the high- and low-melting forms occur very easily, reactions in solution being subject to acid–base catalysis. Self-condensation of β-aminocrotononitrile gives 4-amino-1,3-dicyano-2-methylpenta-1,3-diene which readily cyclizes to 2-amino-5-cyano-4,6-lutidine.

Condensation of β-aminocrotononitrile with 1,2-dichloroethyl ethyl ether gives the chloromethyldihydropyridine (I) and other products (1, 2). During attempts to increase the yield of (I) at the expense of by-products we examined the isomeric composition of the nitrile.

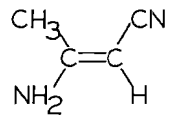
In connection with the nomenclature of the geometrical isomers of the title compound, double bonds carrying four different substituents cannot be described unambiguously by the terms *cis-* and *trans-*, without a definition. Conn and Taurins (3) define (II) as *cis-* and (III) as *trans-β*-aminocrotononitrile, presumably on the reasonable basis that CH_3— and H— are the 'most alike' of the substituents (4).



I



II



III

We wished to compare proton nuclear magnetic resonance (n.m.r.) spectra of the nitrile with those of crotonic acid derivatives, and it is possible to make a definition in terms of the parent nitriles. This leads to the description of (II) as *trans* and (III) as *cis* but is more convenient for the present purpose than the older nomenclature. Thus, in this paper the terms *cis-* and *trans-β*-aminocrotononitrile refer to formulas (III) and (II) respectively and are the reverse of those in ref. 3.

Two forms of β-aminocrotononitrile have been described (5, 6, 7), and recently it was suggested that the high-melting form (m.p. ca. 80°) was the *cis*-compound (III) and the low-melting material (m.p. ca. 50°) has the *trans*-configuration (II) (3).

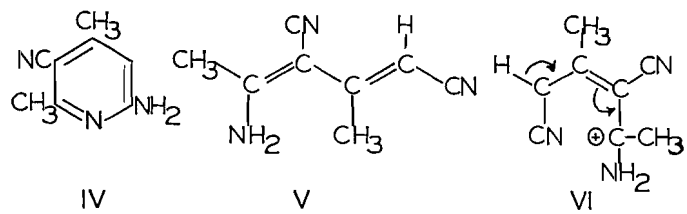
The n.m.r. spectra of the two forms show that the low-melting material is a mixture of two components, one of which is the high-melting form. (The spectra are consistent with the assignment of structure (III) to the high-melting form; see detailed discussion of n.m.r. results.) The composition of the low-melting material is variable and depends on the method of preparation, the solvents used, and even the storage conditions. It has been noted that the melting point of the low-melting material rises on keeping in the solid phase (8) and this change corresponds to an increase in the proportion of the *cis*-isomer.

The high-melting form is isomerized on heating under reflux in benzene (6) or on attempted recrystallization from ethanol (3). The conversion is subject to acid–base

catalysis. Thus, acetic acid (0.1 *M* solution) in benzene accomplishes the change in less than 5 min at room temperature. A similar concentration of piperidine in benzene completes the same reaction in about 6 h. The final composition of the product of the reaction depends on the solvent used, but is insensitive to low concentrations of acid or base. If any β-aminocrotononitrile is allowed to stand in commercial chloroform for 2 days, it achieves a composition (which is somewhat concentration dependent) of about 65% of (II) and closely resembles material isolated by the literature preparation of the low-melting form (3). Melting point is a poor criterion of composition of β-aminocrotononitrile except for the very pure *cis*-form (m.p. 78–80°). In general, a material which melts below about 55° will have a preponderance of the *trans*-compound. Repeated fractional sublimation (40°, 0.1 mm) of the chloroform equilibration mixture gives material, m.p. 41–53°, which is about 90% *trans*-isomer. We have been unable to improve the purity of this isomer any further. This material rapidly equilibrates to the starting mixture when dissolved in chloroform.

The recorded solubility data for the nitrile (3) suggest that the *cis*-compound (III) is about 2.5 times more soluble in benzene in the presence of the *trans*-isomer than when it is pure. This fact, plus the marked sensitivity of the n.m.r. peak positions to concentration and the reasonably well-defined melting point of the equilibrated material, suggests that strong intermolecular complexing occurs when the two isomers are present in the same solution. Cryoscopic molecular weight determinations in benzene were limited by solubility, but even in 0.15 *M* solution, the molecular weight of the low-melting form is about 30% high. Infrared comparisons were limited (by solubility difficulties) to chloroform solutions and mulls. The only differences between the solution spectra of the high- and low-melting forms were in intensities of certain bands. The relative absorbances of these particular absorptions are noted in the Experimental section.

Clarification of the mechanism of the isomerization reactions in the solution and solid phases is being sought through rate studies.



IV V VI

The main by-product from the preparation of (I) is a white, crystalline solid, $C_8H_9N_3$, which shows two intense nitrile absorptions in the infrared spectrum. The n.m.r. spectrum (partially shown in Fig. 1) indicates the presence of two methyl groups, one of which is coupled ($J \sim 0.9$ c.p.s.) to an olefinic proton. The compound yields 2-amino-5-cyano-4,6-lutidine (IV) (6) under a variety of conditions and is thus formulated as the pentadiene derivative (V). (This formula is not intended to imply a proved stereochemistry.) In pyridine solution (9) the n.m.r. absorptions are more complex (Fig. 1) and strongly suggest that the compound is a mixture of conformational (or, less likely, geometric or tautomeric) isomers. The NH region of the infrared spectrum (in chloroform) also supports this idea, though the melting point is very sharp. Recovery of the compound from pyridine solution gives a substance which is identical in all respects with starting material. Compounds with similar melting characteristics to those of (V) have been reported previously (10, 11) from reactions involving β-aminocrotononitrile and may be identical with our material. A

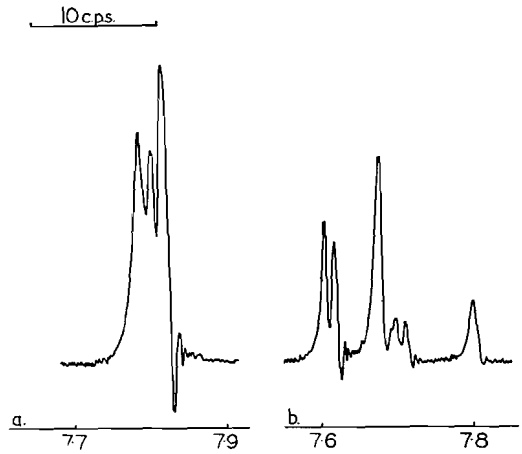


FIG. 1. Partial nuclear magnetic resonance spectra of (V): (*a*) in d_6-dimethylsulfoxide, (*b*) in pyridine.

mechanism for the self-condensation of β-aminocrotononitrile (to pyridine derivatives) has been proposed (12), and involves the formation of a carbonium ion intermediate (VI). Loss of a proton from this intermediate would give (V). This product contrasts with that from the acid-catalyzed dimerization of diphenylacetaldimine, $(C_6H_5)_2$—CH—CH=NH (or tautomer), in which attack of the enamine on the imine form gives a divinylamine $[(C_6H_5)_2C{=}CH]_2NH$ (13).

The use of pure *cis*-β-aminocrotononitrile in the preparation of (I) causes a marked decrease in the reaction rate (cf. ref. 8), but does not materially affect the composition of the product. Since formation of both (I) and (V) occurs with elimination (of the elements of ammonia) there may be a steric factor in the reaction which requires the presence of both isomers. Thus the rate of formation of products from pure *cis*-isomer would be slow and dependent largely on the rate of isomerization. A modified technique for the preparation of (I) using water as a moderator (14) gives a good yield of the desired product.

EXPERIMENTAL

Melting points (uncorrected) were determined in capillaries (for β-aminocrotononitrile samples) or on a Kofler block. Nuclear magnetic reso nance spectra were recorded on a Varian A-60 analytical spectrometer and peak positions are given on the τ-scale. Infrared spectra were recorded on a Perkin–Elmer Model 237B spectrometer.

Nuclear Magnetic Resonance Results

Nuclear magnetic resonance studies of *cis-/trans*-isomers of β-substituted crotonic acid derivatives (bibliography in ref. 15) have led to the generalization that the methyl signal of a *trans*-compound will occur to high field of the methyl signal of the corresponding *cis*-isomer. The position of the signal is relatively unaffected by the substituent on C-3. Further, olefinic protons of $CH_3.CX{=}CH.COOR$ (R = H, Me, etc.) isomers show the reverse order, i.e. the *trans*-olefinic proton occurs to low field of the corresponding *cis*-proton. This holds for a number of derivatives (15) but the position of the olefinic proton signal is very sensitive to the nature of X. In particular, the *trans*-proton appears to be more affected by electron-donating substituents on C-3 than does the *cis*-proton, through in no case is the difference large enough to reverse the generalization. The n.m.r. spectra of crotononitrile isomers have been analzyed (16) and the above generalizations still hold. In this example, however, the *cis*-2-proton is only 0.05 p.p.m. to high field of the corresponding *trans*-proton. (The corresponding difference in the methyl crotonates is 0.63 p.p.m. (17).) Table I shows that the resonance signals for the two forms of β-aminocrotononitrile do not follow the generalization for the esters since the isomer with the high field methyl signal also has the high field olefinic proton. Since chemical evidence favors (III) for the high-melting isomer (3), the n.m.r. results will be consistent with known effects if it is postulated that the primary amino-group reverses the expected order for the olefinic protons.

TABLE I

Compound	Solvent	Olefinic H	Methyl H	NH	J (c.p.s.)
cis-β-Aminocrotononitrile (III) (saturated solution)	Benzene	6.36	8.50	Not observed	$H/CH_3 = 0$
Equilibrium mixture (dilute solution)	Benzene				
(*a*) *cis* (III)		6.37	8.50	Not observed	$H/CH_3 = 0.8$
(*b*) *trans* (II)		6.64	8.97		
Equilibrium mixture (saturated solution)	Benzene				
(*a*) *cis* (III)		6.02	8.22	Broad, 5.35	$H/CH_3 = 0.8$
(*b*) *trans* (II)		6.51	8.68		
Compound (V) (see Fig. 1)	d_6-Dimethyl sulfoxide	4.70	(*a*) 7.80 (*b*) 7.82	Broad, 2.45	$H/CH_3(a) = 0.9$
Compound (V)	Pyridine				
(*a*) major component		4.30	(*a*) 7.60 (*b*) 7.65	Not observed	$H/CH_3(a) = 0.9$
(*b*) minor component		4.71	(*a*) 7.70 (*b*) 7.76		$H/CH_3(a) = 0.9$

The olefinic proton absorptions are about 1.5 p.p.m. to high field of the corresponding unsubstituted crotononitrile (16) and similar effects have been noted in vinyl ethers (18) and other enamines (19).

Molecular Weight of β-Aminocrotononitrile

The molecular weight of the low-melting form was determined cryoscopically in benzene. The variation of molecular weight with concentration is shown below.

Concentration (g/l)	Molecular weight
3.393	87.1
6.619	94.7
10.293	109.0
Theory	82.108

cis-β-Aminocrotononitrile (III)

The sodium salt was prepared by the method of Adkins and Whitman (20). The salt was decomposed with water at 0° and the product taken into ether which was washed twice with a small volume of water and dried (magnesium sulfate). The solvent was removed *in vacuo* at room temperature. It is important that all stages after decomposition of the salt are performed rapidly. The aminonitrile should not be left in solution over extended periods. The residue after removal of the majority of the ether (it is difficult to remove the ether completely) was cooled and the residual liquid decanted from the crystalline product. The solid was allowed to stand overnight at room temperature in a stoppered vessel and then recrystallized five times from benzene to give a white, crystalline solid, m.p. 78–80° (with preliminary softening above about 72°), which was homogenous (by n.m.r. spectrum in benzene).

Low-Melting β-Aminocrotononitrile

Decomposition of the above sodium salt at 30° yields material of m.p. 38–44° before crystallization and m.p. 44–46° after crystallization from a small volume of benzene (3). Alternatively, the pure *cis*-compound (above) may be kept in chloroform (10 mg/ml) for 64 h, after which removal of the solvent gives a clean, low-melting product which contains 65.4% *trans*-isomer (mean of nine integrations of n.m.r. spectrum; spread of values ±0.4%). Infrared spectrum of pure *cis*-compound (freshly prepared solution 8.1 mg per ml of chloroform) showed peaks at 3 516 (0.35), 3 417 (0.71), 3 357, 3 250, 3 219, 3 199, 2 918, 2 201, 1 637, 1 605, 1 434, 1 409, 1 365, (0.23) 1 298 (0.38) 1 123, and 1 020 cm^{-1}. After 3.5 days at room temperature, intensity changes occurred for the following bands 3 516 (0.44), 3 417 (0.54), 1 365 (0.30), 1 305 (0.16) cm^{-1}. Pure *cis*-compound (Nujol mull) showed peaks at 3 433, 3 339, 3 247, 3 219, 3 054, 2 180, 1 646, 1 594, 1 523, 1 311, 1 122, 1 023, 841, 760, and 719 cm^{-1}. The low-melting form (Nujol mull) showed peaks at 3 427, 3 332, 3 233, 3 207, 3 047, 2 172, 1 648, 1 591, 1 523, 1 309, 1 122, 1 026, 844, 764, and 722 cm^{-1}.

4-Amino-1,3-dicyano-2-methylpenta-1,3-diene (V)

(i) β-Aminocrotononitrile (29 g, 0.28 moles mixed isomers) was dissolved in benzene (30 ml) and cooled in ice, while 1,2-dichloroethyl ethyl ether (25 ml, 0.2 moles) was added. A vigorous exothermic reaction occurred. The mixture was kept for 2 h when the precipitated yellow solid (19.5 g) was separated, washed with ether and then water, and fractionally crystallized from aqueous ethanol. The more soluble product, m.p. 178–180°,

was 4-chloromethyl-3,5-dicyano-1,4-dihydro-2,6-lutidine (I:2). The less soluble compound (which was the major product) had m.p. 166–166.5° and resolidified at 167°, remelting with sublimation at 220–225°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55; molecular weight, 147. Found: C, 65.10; H, 6.01; N, 28.60; molecular weight (Rast), 178.

Light absorption (ethanol); λ_{max} at 219, 254, and 328 mμ; ϵ_{max} 11 300, 7 080, and 17 500 respectively. The infrared spectrum showed main maxima at 3 540, 3 511, 3 440, 3 405, 3 344, 3 244, 2 210, 2 196, 1 630, 1 598, 1 557, and 1 040 cm^{-1}.

(ii) The above reaction was repeated using pure *cis*-β-aminocrotononitrile. There was no exothermic reaction on removal of the mixture from the ice bath and development of a yellow precipitate required approximately 12 h. The same products were isolated.

4-Chloromethyl-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (I)

β-Aminocrotononitrile (5 g, mixed isomers) was melted and then cooled almost to crystallization. 1,2-Dichloroethyl ethyl ether (5.04 g) was added and followed immediately by water (30 ml). After the reaction had subsided, the mixture was warmed on the steam bath for 5 min, cooled, and filtered. The solid was crystallized twice from aqueous ethanol to give the dihydropyridine, 3.0 g (47%), identical with that from (i) above.

2-Amino-5-cyano-4,6-lutidine (IV)

(i) The foregoing dinitrile (V) was heated to 170° and the product crystallized from ethanol to yield colorless needles, m.p. 227–228° (with sublimation).

(ii) A mixture of the dinitrile (100 mg) and potassium hydroxide (40 mg) in ethanol (5 ml) was heated under reflux for 20 min when the ethanol was removed and the residue treated with water. The crystalline solid thus obtained was crystallized from aqueous ethanol giving the product in almost quantitative yield as colorless needles, m.p. 227–228°.

(iii) The dinitrile (2.6 mg) was dissolved in ethanol (25 ml) and the solution was divided into two parts. The first was kept in the dark and the ultraviolet absorption spectrum was shown to be unchanged after 17 h. The second fraction was irradiated under an ultraviolet lamp and after 17 h, the light absorption showed maxima at 210, 271, and 295 mμ; ϵ_{max} 11 250, 17 300, and 7 470 respectively. Evaporation of the solvent gave colorless needles, m.p. 227–228°.

The same product (melting point and spectra) was obtained from all three reactions. (Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.00; H, 5.97; N, 28.40.) The infrared spectrum showed main maxima at 3 519, 3 415, 2 212, 1 615, 1 555, 1 472, 1 448, 1 378, 1 357, 1 173, and 846 cm^{-1}. Reaction of this product with sodium nitrite in dilute sulfuric acid gave 5-cyano-4,6-lutid-2-one (6, 7), m.p. 305–307° (sealed tube) with darkening ca. 280°. This was identical (melting point and spectra) with the product obtained from β-aminocrotononitrile with boiling water.

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