Syntheses of Some Highly Substituted Pyridines, 2,7-Naphthyridines and 1*H*-Pyrimido[4,5,6-*i,j*][2,7]naphthyridines

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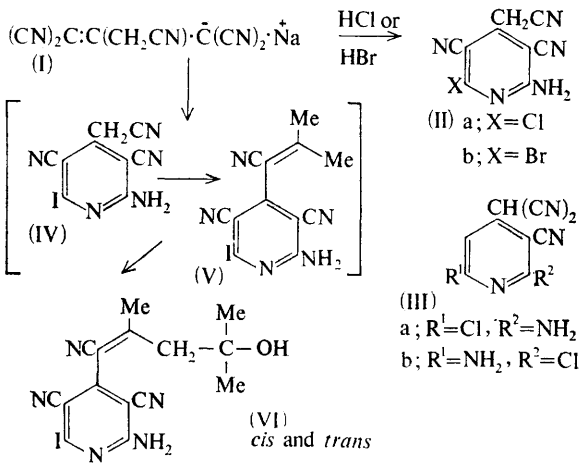
2-Cyanomethyl-1,1,3,3-propenetetracarbonitrile is cyclised by halogen acids in acetone to 2-amino-4-cyanomethyl-6-halogeno-3,5-pyridinedicarbonitrile, although the 6-iodopyridine further reacts with acetone to give 2-amino-4-(1-cyano-4-hydroxy-2,4-dimethylpent-1-en-1-yl)-6-iodo-3,5-pyridinedicarbonitrile. The α-halogen atom of these pyridines has been replaced by a variety of nucleophiles. These 4-cyanomethyl-3,5-pyridinedicarbonitriles cyclise further in the presence of methoxide ion, to produce substituted 2,7-naphthyridine-4-carbonitriles. 2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile on cyclisation gives 1,8-diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile as the sole product, whereas 2-amino-6-*p*-anisidino-4-cyanomethyl-3,5-pyridinedicarbonitrile yields a mixture of 1,8-diamino-3-*p*-anisidino- and 3,8-diamino-1-*p*-anisidino-6-methoxy-2,7-naphthyridine-4-carbonitriles in the ratio 1 : 8. A mechanism to account for these alternative cyclisations is proposed.

1,8-Diamino-2,7-naphthyridines, on reaction with carbonyl derivatives such as orthoesters, aliphatic and aromatic aldehydes, alicyclic ketones, esters, and carboxylic acid anhydrides, yield derivatives of the novel pyrimido-[4,5,6-*i,j*][2,7]naphthyridine system, or, in the case of the reaction with phthalic anhydride, a derivative of the pentacyclic isoindolo[2,1-a]pyrimido[4,5,6-*i,j*][2,7]naphthyridine system.

MALONONITRILE is known to dimerise under either basic [1] or acidic [2] conditions to give 2-amino-1,1,3-propenetricarbonitrile, the biological properties of which have been investigated.[3b] Mendelson and his co-workers [4] observed that solutions of malononitrile showed u.v. absorptions at 270 and 358 mμ of which the former was later shown [2] to be due to the dimer, while, more recently, the longer wavelength absorption has been shown to be due to 2-cyanomethyl-1,1,3,3-propenetetracarbonitrile (I), which was isolated [3a] as a by-product from the base-catalysed dimerisation reaction. Salts of (I) may be prepared, either by treating 2-amino-1,1,3-propenetricarbonitrile with malononitrile in basic media, or directly from malononitrile in aqueous sodium carbonate. The present paper describes various heterocyclic compounds synthesised from 2-cyanomethyl-1,1,3,3-propenetetracarbonitrile, and submitted to biological screening on a speculative basis.

αω-Dinitriles are known to cyclise under aqueous [5] or nonaqueous [6] acidic conditions to α-amino-nitrogen heterocycles. When a solution of the sodium salt of the propene (I) in acetone was treated with concentrated hydrochloric acid, the solution immediately turned bright yellow and a solid separated. This precipitate appeared to be a mixture of a basic product and its hydrochloride, together with sodium chloride; recrystallisation of the mixture from dimethylformamide gave the product as the free base.

The u.v. spectrum of this compound was quite distinct from that of (I), since it had absorption maxima at 281 and 336 mμ, which suggested a cyclic pyridine structure. The cyclisation of (I) with hydrochloric acid could result in the formation of any of the three pyridines (IIa), (IIIa), or (IIIb). The n.m.r. spectrum in deuteriated dimethyl sulphoxide contained two singlets of equal intensity at τ 1·07 and 5·79, which characterised the product as (IIa), rather than (IIIa) or (IIIb), the spectra of which would exhibit three singlets of relative intensities 1 : 1 : 2.



SCHEME 1

The reaction of (I) with 60% hydrobromic acid in acetone similarly gave the corresponding 2-amino-6-bromopyridine (IIb), but in the reaction of (I) with hydriodic acid (*d* 1·7) in acetone, no immediate precipitation occurred; some material separated slowly, however, and after 5 days this was collected. The elementary analysis suggested a molecular formula of $C_{15}H_{14}IN_5O$, that is, the expected 6-iodo-pyridine (IV) plus two molecules of acetone minus one molecule of water. The n.m.r. spectrum showed that no cyanomethyl methylene group analogous to that of (IIa) was present, and the spectrum could be interpreted on the basis of structure (VI) for

[1] U.S.P. 2,719,861/1955.
[2] R. A. Carboni, D. D. Coffman, and E. G. Howard, *J. Amer. Chem. Soc.*, 1958, **80**, 2838.
[3] (*a*) R. B. Kelly, G. Slomp, and E. L. Caron, *J. Org. Chem.*, 1965, **30**, 1036; (*b*) *ibid.*, footnote 2.
[4] J. Mendelson, J. H. Mendelson, B. J. Fax, and R. G. Grenell, *Science*, 1954, **120**, 266.
[5] S. Ruhemann and K. G. Browning, *J. Chem. Soc.*, 1898, **73**, 280.
[6] E. L. Little, W. J. Middleton, D. D. Coffman, V. A. Engelhardt, and G. N. Sausen, *J. Amer. Chem. Soc.*, 1958, **80**, 2832; F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.*, 1965, **2**, 26.

the product. A six-proton singlet at τ 8·82 was assigned to the *gem*-dimethyl groups, a three proton singlet at τ 7·85 to the methyl group on the double-bond, a two proton singlet at τ 7·20 to the allylic methylene group, a one proton doublet at τ 5·08 and 5·17 to the hydroxy-groups of the two geometrical isomers, and a broad singlet at τ 1·75 to the pyridine amino-group.

This product presumably arises by initial cyclisation of (I) with hydriodic acid to the pyridine (IV), the hydriodide salt of which is not precipitated from the reaction mixture, as are the salts of the analogous chloro- and bromo-compounds; in solution the hydriodide undergoes two successive acid-catalysed Knoevenagel condensations with acetone, firstly at the active methylene group of (IV), and secondly on one of the methyl groups, activated by the αβ-unsaturated nitrile, of the intermediate (V). The product (VI) thus formed is, apparently, not dehydrated under the conditions of the reaction.

If the reaction of (I) with hydriodic acid was allowed to proceed for only a short time, the product which was isolated, although clearly mainly (IV), contained amidic impurities as evidenced by a peak at 1650 cm.$^{-1}$ in the i.r. spectrum, and also by its mass spectrum; repeated crystallisations from aqueous dimethylformamide, the only suitable solvent system, failed to remove these impurities.

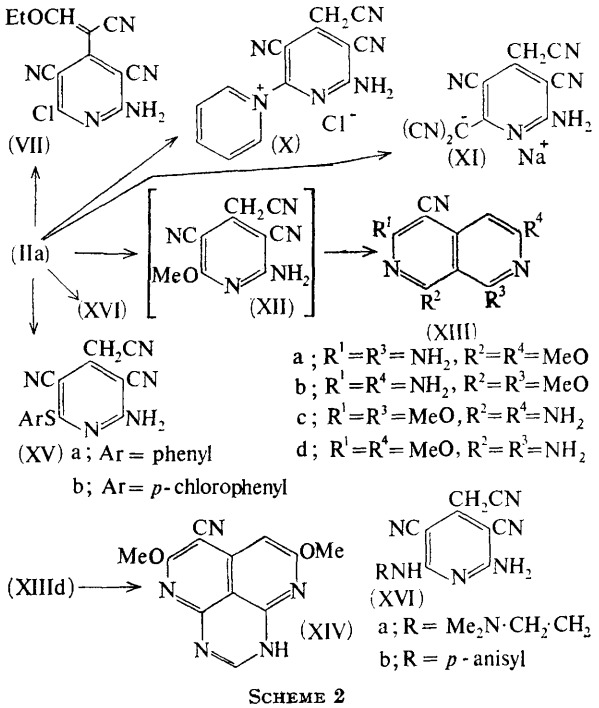
No cyclic products were obtained from (I) with reagents such as sodio-diethyl malonate, and benzene-sulphinic acid and, although αβ-unsaturated nitriles which contain a γ-hydrogen are reported [7] to react with sulphur to form 2-aminothiophens (I) the present compound failed to do so.

The 2-amino-6-chloro-pyridine (IIa) offers the possibility of further chemical exploitation in several ways, for example, by reduction or hydrolysis of the nitrile groups, by condensations on the active methylene group, cyclisation reactions involving the *o*-aminonitrile or 1,3-dinitrile systems, and nucleophilic displacement of the 6-chlorine atom.

The insolubility of (IIa) in suitable solvents restricted attempts to reduce the nitrile groups with lithium aluminium hydride although partial success was achieved on extraction of the compound in a Soxhlet apparatus with dioxan; the extracted material remained in solution for only a short time, however, and the product which was isolated still showed a strong nitrile band in the i.r. spectrum. No reduced material was identified.

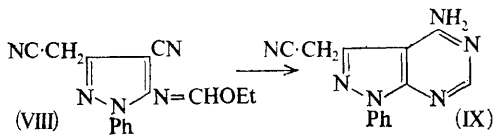
Attempts to hydrolyse (IIa) under a variety of both acidic and basic conditions gave mixtures of products, as shown by t.l.c.; no hydrolysis product of (IIa) has been isolated.

The reaction of triethyl orthoformate with (IIa) resulted in the incorporation of only one ethoxymethylene group; the n.m.r. spectrum of the product showed the presence of the amino-protons, and the absence of methylene protons, as compared with (IIa). This characterised the product as the pyridine (VII), rather than the alternative compound resulting from condensation on the primary amino-group.



SCHEME 2

This compound might reasonably be expected to cyclise by reaction with ammonia or amines, in the same way that (VIII) with ammonia gives (IX).[8] Treatment of



(VII) with ammonia, however, even under very mild conditions, in dilute ethanolic solution at 0°, resulted in a smooth retro-Knoevenagel reaction, and the regeneration of the pyridine (IIa).

An attempted carboxylation of the active methylene group in the pyridine (IIa) with carbon dioxide in the presence of sodium phenoxide in dimethylformamide [9] was unsuccessful and no transformation product was detected by t.l.c., even after prolonged passage of carbon dioxide.

The *o*-amino-nitrile system of (IIa) appears to be remarkably unreactive as shown by the preferred addition of triethyl orthoformate to the active methylene rather than to the amino-group; further, an attempted reaction with phenyl isocyanate to give an aza-analogue of 2-cyanocarbanilide, prior to sodium methoxide cyclisation to give a pyrido-pyrimidine,[10] was also unsuccessful.

[7] K. Gewald and E. Schinke, *Chem. Ber.*, 1966, **99**, 2712.
[8] E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.*, 1959, **81**, 2456.
[9] G. Bottaccio and G. P. Chiusoli, *Chem. Comm.*, 1966, 618.
[10] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, 1962, **27**, 2622.

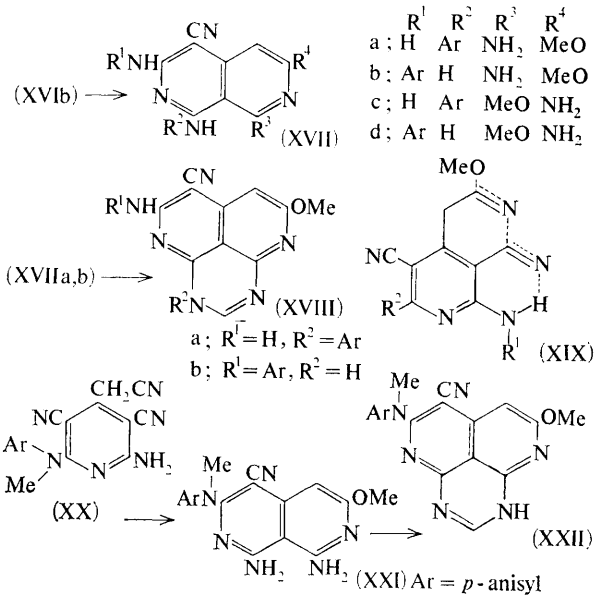
An *o*-amino-nitrile with carbon disulphide in pyridine is reported [11] to yield a fused pyrimidine-2,4-dithione by base-catalysed rearrangement of the initially-formed thiazine; the reaction of the pyridine (IIa) with carbon disulphide in pyridine, however, produced a small amount of brown, amorphous material which contained no sulphur. The reaction was repeated without the carbon disulphide, to give the same compound in moderate yield. This product was difficult to purify, but was identified by its n.m.r. and mass spectrum as the pyridyl-pyridinium chloride (X), formed by nucleophilic displacement of the α-chlorine by pyridine.

The α-chlorine of (IIa) is readily replaced by carbanions, alkoxides, thiophenols, and amines. The reaction of (IIa) with the carbanion, sodio-malononitrile yielded a bright yellow sodium salt, which was too unstable to purify and characterise, but which from the multiplicity of nitrile bands in the i.r. spectrum [2260 (weak shoulder, aliphatic), 2230 and 2200 (aromatic), and 2160 cm.$^{-1}$ (dicyanomethyl)], was assumed to be (XI). All attempts to cyclise this salt to a pyrido-pyrimidine with hydrochloric acid, however, resulted only in the regeneration of (IIa).

The product isolated from the reaction of (IIa) with sodium methoxide was not the presumed, initially formed 2-amino-6-methoxy-pyridine (XII) but a 2,7-naphthyridine (XIII) resulting from the further cyclisation of (XII). The gross structure (XIII) was deduced from the elemental analysis and the n.m.r. spectrum which showed two methoxy-groups and a one proton singlet at τ 3·56 which was assigned to the ring proton; these results shed no light upon which of the four possible isomeric 2,7-naphthyridines were present. N.m.r. spectral evidence and the results of t.l.c. in a number of different solvent systems pointed to the presence of one isomer only. This naphthyridine reacted with triethyl orthoformate in acetic anhydride to give a compound, the n.m.r. spectrum of which indicated the absence of an ethyl group but showed a new, one-proton singlet at τ 0·7. The absence of ethyl groups suggested the incorporation of a one-carbon fragment between the vicinal amino-groups to give the tricycle (XIV), derived from the 1,8-diamino-2,7-naphthyridine (XIIId); the τ 0·70 peak was assigned to the proton of the ·N:CH·N: system of (XIV). Although a satisfactory elemental analysis of (XIV) was not obtained, because of the difficulty of removing traces of dimethylformamide, the only suitable recrystallisation solvent, without initiating decomposition, subsequent reactions of the 2,7-naphthyridine with carbonyl compounds and full identification of the products, confirmed that the cyclisation of (IIa) with methoxide yielded only one naphthyridine, the isomer (XIIId).

The reaction of (IIa) with thiophenols gave the arylthiopyridines (XV) rapidly and cleanly. The cyclisation of (XVb) with methoxide resulted also in the elimination of the thiophenol moiety, and the product isolated was dimethoxynaphthyridine (XIIId).

Aliphatic or aromatic amines also readily displaced the chlorine of (IIa), to give 2-amino-6-(substituted-amino) pyridines (XVI), but the reactions were not as clean as those with thiophenols; in particular, the difunctional compounds *o*-phenylenediamine and *o*-aminothiophenol produced mixtures from which no pure compounds were isolated.



SCHEME 3

The conditions for the methoxide cyclisation of the *p*-anisidino-pyridine (XVIb) to a naphthyridine are critical. The reaction (see Experimental section) was cooled after 1 hr., to precipitate a solid product free from starting material, some of which was still present in the reaction mixture. Longer reaction times resulted in the progressive formation of tarry material, from which it was difficult to isolate any solid products. The concentration of the reaction mixture needed to be such that the precipitation occurred efficiently when the reaction was stopped, as it was not possible to free the required product from starting material by recrystallisation of the total reaction product.

T.l.c. showed that the solid material which separated from the reaction under these conditions was a mixture of two compounds. These were easily separated, as one was soluble, and the other insoluble, in chloroform. Each of these compounds was shown by elemental analysis, and n.m.r. and i.r. spectroscopy, to be a 2,7-naphthyridine, of which there are four isomers (XVIIa—d).

Each naphthyridine (XVII) was treated with triethyl orthoformate in acetic anhydride to give products, the n.m.r. spectra of which in trifluoroacetic acid showed that no ethyl groups had been incorporated; each spectrum contained, however, an additional one-proton singlet typical of the ·N:CH·N: proton.

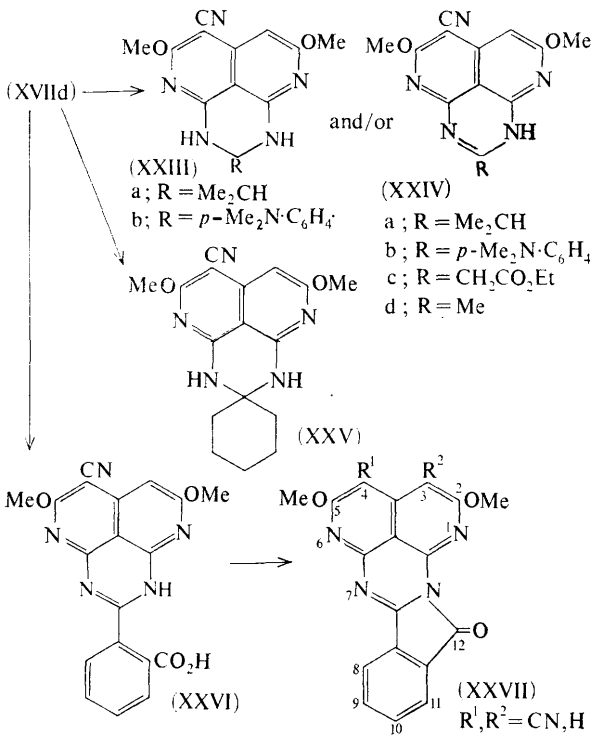
[11] E. C. Taylor, R. N. Warrener, and A. McKillop, *Angew. Chem. Internat. Edn.*, 1966, **5**, 309.

Thus, since the products are tricyclic compounds (XVIII) analogous to (XIV), each of the naphthyridines (XVII) must contain a 1,8-diamino-system. Of the four isomers (XVIIa—d), the two which are isolated therefore are (XVIIa) and (XVIIb) in which R^3 is an amino and R^4 is a methoxy group.

The tricyclic compounds (XVIII) are very insoluble and a useful n.m.r. spectrum in a non-exchanging solvent was only obtained for the compound (XVIII), derived from the chloroform-insoluble naphthyridine, in dimethyl sulphoxide at 120° on a 100 Mc. instrument. This spectrum contained no signal in the region near τ 1·4, the position of the anisidino NH proton in (XVII), but, in addition to signals corresponding to those of the trifluoroacetic acid spectrum, it contained a broadened two-proton singlet at τ 3·33, which was assigned to the primary amino-group of the isomer (XVIIIa). Thus, the chloroform-insoluble naphthyridine was assigned the structure (XVIIa) and the chloroform-soluble isomer, the structure (XVIIb).

The formation of the two isomers (XVIIa) and (XVIIb) in the ratio *ca.* 8 : 1 can be explained by postulating that methoxide ion adds first to the aliphatic nitrile, rather than to one of the hindered, *ortho*-disubstituted ring-nitrile groups, leading to a transition state (XIX) in which an amino-proton is involved. In the cyclisation of (IIa) there is only one amino-group, so the only transition state possible is (XIX; R^1 = H, R^2 = MeO) which leads to the observed product (XIIId). In the cyclisation of (XVIb) the proton involved in the transition state could be either the anisidino-proton (XIX; R^1 = *p*-anisyl, R^2 = NH_2) or a proton from the primary amino-group (XIX; R^1 = H, R^2 = *p*-anisidino). The relative abundance of the two transition-states should be dependent upon the availability, that is, the acidity, of the amino-proton involved, and hence, the transition state involving the less basic anisidino-proton should be favoured, and the naphthyridine derived therefrom, (XVIIa), should predominate; this is, in fact, observed.

In order to test this hypothesis, the cyclisation of the *N*-methyl-anisidino-pyridine (XX) analogous to (XVIb) was examined. In this case, only one naphthyridine the 1,8-diamino-isomer, should be formed, there being only the protons of the primary amino-group available for participation in a transition state (XIX; R^1 = H, R^2 = *N*-methyl-*p*-anisidino). *N*-Methyl-*p*-anisidine was condensed with the chloro-pyridine (IIa) to give the *N*-methyl analogue (XX) which upon cyclisation with methoxide gave one product (XXI) only, as judged by t.l.c., in a wide variety of solvent systems on both alumina and silica gel, and n.m.r. spectroscopy. Upon heating this naphthyridine with triethyl orthoformate a tricyclic compound was formed, which was shown to be (XXII) by mass spectrometry and its n.m.r. spectrum; the latter spectrum contained the characteristic signal for a C-2 proton, in addition to the other expected signals. Thus, *N*-methylation of the anisidino-group of (XVIb) results in cyclisation exclusively to the 1,8-diamino-isomer. This result would appear to confirm that a proton from one of the α-substituents of the pyridine ring is involved in the cyclisation to a 2,7-naphthyridine.



SCHEME 4

Further cyclisation reactions of the dimethoxy-naphthyridine (XIIId) with aldehydes, ketones, α-dicarbonyl compounds, esters, and acid anhydrides, were investigated. The reaction of (XIIId) with isobutyraldehyde or with *p*-dimethylaminobenzaldehyde, either in the presence or the absence of air, gave both the saturated (XXIII) and unsaturated (XXIV) tricyclic derivatives. In the reaction with isobutyraldehyde, when air was drawn through the reaction mixture, the product was predominantly the unsaturated compound (XXIVa), which was obtained pure after recrystallisation from dimethoxyethane–methanol. Under nitrogen, the reaction gave mainly the saturated compound (XXIIIa), together with some of the unsaturated compound (XXIVa), which was removed by recrystallisation; a further product present was not removed by recrystallisation. The n.m.r. spectrum in deuteriochloroform contained a broad singlet at τ 4·25 and a broadened doublet at 5·10 which, on the addition of D_2O, became sharp, while the 4·25 signal disappeared; these signals were assigned to the system ·NH·CH($CHMe_2$)·NH· of (XXIIIa). In addition, the spectrum also contained, at a lower intensity, a sharp singlet at τ 2·56 and additional isopropyl methyl signals, downfield of the main isopropyl peaks, which were attributed to the unidentified impurity.

The reaction of (XIIId) with *p*-dimethylaminobenzaldehyde always produced the two products (XXIIIb)

and (XXIVb), irrespective of whether the reaction was performed under nitrogen or not. Even with rigorous exclusion of air, the product contained a significant proportion of the unsaturated product, and recrystallisation, even under nitrogen, appeared only to increase the proportion of this product. Compound (XXIIIb) was eventually obtained pure, as shown by t.l.c., by the dropwise addition of water to the reaction mixture as the dimethylformamide was distilled off under nitrogen; a subsequent attempt to repeat this procedure failed to produce pure material. Repeated attempts to obtain the unsaturated compound (XXIVb) by crystallisation of the mixed products were completely unsuccessful.

The reaction of the naphthyridine (XIIId) with ketones was expected to be less complex than the reactions with aldehydes, in that only one product should be formed. The spiro-product (XXV), obtained from the reaction of the naphthyridine with cyclohexanone, was, however, rapidly oxidised in solution in organic solvents. Such solutions were noticeably pink in colour after a few minutes, and the colour progressively intensified. When the reaction was worked up, and the product was crystallised, under nitrogen, the pure spiro-compound (XXV) was obtained, which, on t.l.c., was free from the impurities present in chromatograms of the pink solutions.

Compound (XIIId) failed to condense with isatin after being heated for extended periods in glacial acetic acid or dimethylformamide, although isatin is known [12] to react readily with *o*-phenylenediamine.

The reaction of diethyl malonate with the naphthyridine (XIIId) proceeded smoothly to give the tricyclic acetic ester (XXIVc), contaminated with a small amount of the decarboxylated derivative, the methyl compound (XXIVd), which could not be removed, either by crystallisation or chromatography.

Phthalic anhydride reacted with (XIIId) at 130° to give the tricyclic intermediate (XXVI), which was not purified, but was cyclised directly to the orange-red pentacyclic compound (XXVII) which was presumed to be an equal mixture of the two isomers. The cyclisation of (XXVI) with acetic anhydride [13] was unsatisfactory, but with phosphorus oxychloride, the reaction, although heterogeneous, proceeded much more cleanly and in good yield.

Compound (XIIId) failed to undergo either basic or acidic hydrolysis under a wide variety of conditions and, further, the action of concentrated sulphuric acid and ethanol, in an attempt to obtain the ethyl ester of the corresponding acid, failed to give any useful product; attempts to form a triazino-naphthyridine by diazotisation of the 1,8-diaminonaphthyridine were also unsuccessful.

2-Cyanomethyl-1,1,3,3-propenetetracarbonitrile can thus be utilised for the synthesis of a variety of monocyclic, bicyclic, tricyclic, and pentacyclic nitrogen heterocycles of unusual substitution patterns.

[12] L. Marchlewski, *Roczniki Chem.*, 1938, **18**, 698 (*Chem. Abs.*, 1939, **33**, 4593).
[13] A. Bistrzycki and A. Lecco, *Helv. Chim. Acta*, 1921, **4**, 425.

EXPERIMENTAL

I.r. maxima are for Nujol mulls, and u.v. maxima are for methanol solutions. Melting points are corrected.

2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (IIa).—The sodium salt of 2-cyanomethyl-1,1,3,3-propenetetracarbonitrile (52·0 g.) was dissolved in AnalaR acetone (260 ml.) and concentrated hydrochloric acid (260 ml.) was added portionwise with stirring to give a bright yellow solution. A precipitate formed at once, and the mixture was heated on a steam-bath for 20 min. The mixture was cooled in ice, and the precipitate was filtered off and washed with AnalaR acetone. The crude product (57·2 g.) was suspended in water to give a thin slurry, which was heated to boiling point; dimethylformamide was then added slowly to the boiling mixture until complete solution was achieved. The bright yellow solution was treated with carbon and filtered, and, on being cooled, gave *2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile* (31·8 g., 57%), m.p. 257—259° (Found: C, 49·7; H, 2·1; N, 32·5. $C_9H_4ClN_5$ requires C, 49·65; H, 1·85; N, 32·2%), $\nu_{max.}$ 3350, 3160, 2235, 2205, and 1645 cm.$^{-1}$; τ 1·07 (s, NH_2) 5·79 (s, methylene) in deuteriated dimethyl sulphoxide, $\lambda_{max.}$ 218, 281, and 336 mμ (log ε 4·28, 4·29, and 4·02).

2-Amino-6-bromo-4-cyanomethyl-3,5-pyridinedicarbonitrile (IIb).—Hydrobromic acid (60%; 5·0 ml.) was added with stirring to a solution of the sodium salt of 2-cyanomethyl-1,1,3,3-propenetetracarbonitrile (0·5 g.) in AnalaR acetone (5·0 ml.). An exothermic reaction occurred, and a white solid immediately separated. After 1 hr. the solid was filtered off (0·6 g.) and was recrystallised from aqueous dimethylformamide as described above, to give *2-amino-6-bromo-4-cyanomethyl-3,5-pyridinedicarbonitrile*, m.p. 256—258° (decomp.) (Found: C, 41·15; H, 1·65; Br, 30·1; N, 26·5. $C_9H_4BrN_5$ requires C, 41·2; H, 1·55; Br, 30·5; N, 26·7%), τ 1·13 (s, NH_2) and 5·81 (s, CH_2) in deuteriated dimethyl sulphoxide.

2-Amino-4-(1-cyano-4-hydroxy-2,4-dimethylpent-1-en-1-yl)-6-iodo-3,5-pyridinedicarbonitrile (VI).—Hydriodic acid (*d* 1·7), (25 ml.) was added to a solution of the sodium salt of 2-cyanomethyl-1,1,3,3-propenetetracarbonitrile (2·5 g.) in AnalaR acetone (25 ml.) and the mixture was left at room temperature for 5 days. The solid material was filtered off, and crystallised from aqueous dimethylformamide or glacial acetic acid to give the *product* (1·2 g., 24%), m.p. 238—240° (Found: C, 44·05; H, 3·45; I, 31·4; N, 17·2. $C_{15}H_{14}IN_5O$ requires C, 44·25; H, 3·45; I, 31·2, N, 17·2%), $\nu_{max.}$ 3350, 3250, 3140, 2200, and 1690 cm.$^{-1}$, τ 1·75 (s, NH_2), 5·08, 5·17 (d, isomeric OH), 7·20 (s, CH_2), 7·85 (s, C:CMe), and 8·82 (s, *gem*-dimethyl), in deuteriated dimethyl sulphoxide.

2-Amino-6-chloro-4-(1-cyano-2-ethoxyvinyl)-3,5-pyridinedicarbonitrile (VII).— 2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (1·0 g.), triethyl orthoformate (14·8 g.), and acetic anhydride (10·2 g.) were stirred and heated on a water-bath to 70° over 1 hr. and then maintained at 70° for a further 1 hr.; the mixture was then cooled and the solvents were distilled off under reduced pressure. The residue was extracted with ether and the ether extract was treated with charcoal and filtered; on concentration prisms of *2-amino-6-chloro-4-(1-cyano-2-ethoxyvinyl)-3,5-pyridinedicarbonitrile* (0·4 g.) were obtained, m.p. 193—195°

(Found: C, 52·4; H, 2·85; N, 25·6. $C_{12}H_8ClN_5O$ requires C, 52·65; H, 2·95; N, 25·6), $\nu_{max.}$ 3330, 3160, 2205, and 1650 cm.$^{-1}$, τ 2·31 (s, olefinic CH), 3·5 (br, s, NH_2), 5·57 and 8·52 (ethyl), in trifluoroacetic acid.

Reaction of 2-*Amino*-6-*chloro*-4-(1-*cyano*-2-*ethoxyvinyl*)-3,5-*pyridinedicarbonitrile with Ammonia*.—2-Amino-6-chloro-4-(1-cyano-2-ethoxyvinyl)-3,5-pyridinedicarbonitrile (0·1 g.) was dissolved in absolute ethanol (15 ml.) cooled to 0°, and ethanol saturated with ammonia at 0° (1·0 ml.) was added. The solution immediately became bright yellow, and after being stirred for 2 hr., the precipitate was filtered off; it was identified as 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (IIa) from its n.m.r. spectrum in deuteriated dimethyl sulphoxide, which showed singlets of equal integral area at τ 1·08 (NH_2) and 5·80 (CH_2).

1,8-*Diamino*-3,6-*dimethoxy*-2,7-*naphthyridine*-4-*carbonitrile* (XIIId).— 2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (27·0 g.) was added to a solution of sodium (17·5 g.) in AnalaR methanol (1250 ml.) and heated under reflux for 20 hr. The mixture was cooled to 0°, and the solid product was filtered off and crystallised from glacial acetic acid, to give the *naphthyridinecarbonitrile* (XIIId) (23·3 g., 77%), m.p. 258—260° (Found: C, 53·9; H, 4·5; N, 29·0. $C_{11}H_{11}N_5O_2$ requires C, 53·9; H, 4·5; N, 28·6%), τ 3·56 (s, naphthyridine ring proton), 5·75 (s, MeO), 5·82 (s, MeO) in trifluoroacetic acid.

Reactions of 2-*Amino*-6-*chloro*-4-*cyanomethyl*-3,5-*pyridinedicarbonitrile with Thiols*.—(a) *With thiophenol*. Thiophenol (0·55 g.) was added to a solution of 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (1·1 g.) and triethylamine (1·1 g.) in dimethylformamide (20 ml.). After a few minutes, triethylamine hydrochloride started to separate, and after 1 hr. this was filtered off. The filtrate was poured into water and extracted with ethyl acetate. The extract was dried, the solvent was evaporated under reduced pressure, and the residue solidified on being scratched with water containing a few drops of methanol. Crystallisation from chloroform gave 2-*amino*-4-*cyanomethyl*-6-(*phenylthio*)-3,5-*pyridinedicarbonitrile* (XVa) (0·7 g., 47%), m.p. 193—195° (Found: C, 61·9; H, 3·2; N, 24·15. $C_{15}H_9N_5S$ requires C, 61·8; H, 3·1; N, 24·0%), τ 2·47 (aromatic), 3·64 (br, s, NH_2), 6·04 (s, CH_2) in acetonitrile.

(b) *With* p-*chlorothiophenol*. In a similar manner, the pyridine (IIa), (6·5 g.), triethylamine (3·3 g.), and *p*-chlorothiophenol (4·3 g.) gave 2-*amino*-6-(p-*chlorophenylthio*)-4-*cyanomethyl*-3,5-*pyridinedicarbonitrile* (XVb), (4·2 g., 43%), m.p. 224—226° (decomp.) from ethyl acetate (Found: C, 55·45; H, 2·65; N, 21·5. $C_{15}H_8ClN_5S$ requires C, 55·3; H, 2·5; N, 21·5%).

Reactions of 2-*Amino*-6-*chloro*-4-*cyanomethyl*-3,5-*pyridinedicarbonitrile with Amines*.—(a) *With pyridine*. A solution of 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (0·75 g.) in pyridine (5·0 ml.) was warmed to 60° for a few minutes, filtered, and then maintained at 50° for 2 hr. The solution was cooled and the red-brown precipitate was filtered off and crystallised from methanol to give orange plates (0·25 g.), m.p. 182—184° (decomp.), of 6-*amino*-3,5-*dicyano*-4-*cyanomethylpyrid*-2-*ylpyridinium chloride* (X) from a mass spectral molecular formula of $C_{14}H_9N_6$ for the cation, and n.m.r. spectrum, τ 0·5—1·7 (complex, 5 pyridine protons), 2·7 (vbr,s, NH_2), 5·66 (s, CH_2), in trifluoroacetic acid.

(b) *With* 2-*dimethylaminoethylamine*. 2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (3·3 g.) and triethylamine (1·65 g.) in dimethylformamide (70 ml.) was mixed with 2-dimethylaminoethylamine (1·32 g.) in the same solvent; the mixture was then heated on a steam-bath for 1·5 hr., cooled, poured into water, and extracted with ethyl acetate. The extract was dried, the solvent was evaporated under reduced pressure, and the residue was crystallised from dimethylformamide to give 2-*amino*-4-*cyanomethyl*-6-(2-*dimethylaminoethylamino*)-3,5-*pyridinedicarbonitrile* (XVIa) (1·8 g., 44%), m.p. 230—232° (Found: C, 57·8; H, 5·6; N, 36·4. $C_{13}H_{15}N_7$ requires C, 57·95; H, 5·6; N, 36·4%), τ 2·55 (s, NH_2), 5·95—6·85 (complex, three CH_2), and 7·84 (s, NMe_2) in deuteriated dimethyl sulphoxide.

(c) *With* p-*anisidine*. In a similar manner the pyridine (IIa) (7·95 g.), triethylamine (4·05 g.), and *p*-anisidine (4·5 g.) gave 2-*amino*-6-p-*anisidino*-4-*cyanomethyl*-3,5-*pyridinedicarbonitrile* (XVIb) (3·35 g., 30%), m.p. 224—226° from ethyl acetate (Found: C, 63·3; H, 3·8; N, 27·8. $C_{16}H_{12}N_6O$ requires C, 63·15; H, 3·95; N, 27·65%).

(d) *With* N-*methyl*-p-*anisidine*. In a similar manner the pyridine (IIa) (7·2 g.), triethylamine (4 g.), and *N*-methyl-*p*-anisidine (4·5 g.) gave 2-*amino*-4-*cyanomethyl*-6-(N-*methyl*-p-*anisidino*)3,5-*pyridinedicarbonitrile* (XX), (2·1 g., 20%), m.p. 208—211° from ethyl acetate (Found: C, 64·5; H, 4·55; N, 26·2. $C_{17}H_{14}N_6O$ requires C, 64·15; H, 4·4; N, 26·4%), τ 2·4—2·9 (A_2, B_2, aromatic), 5·78 (s, CH_2), 5·98, 6·10 (singlets, OMe and NMe) in trifluoroacetic acid.

The Reaction of 2-*Amino*-6-p-*anisidino*-4-*cyanomethyl*-3,5-*pyridinedicarbonitrile with Sodium Methoxide*.—2-Amino-6-*p*-anisidino-4-cyanomethyl-3,5-pyridinedicarbonitrile (10·6 g.) was added to a solution of sodium (7·2 g.) in AnalaR methanol (300 ml.) and the mixture was heated under reflux for 1 hr. The solution was allowed to cool and the solid which crystallised was filtered off and extracted with boiling chloroform (2 × 50 ml.).

(a) The chloroform-insoluble material was crystallised from ethanol to give 3,8-*diamino*-1-p-*anisidino*-6-*methoxy*-2,7-*naphthyridine*-4-*carbonitrile* (XVIIa), (6·3 g., 54%), m.p. 214—217° (Found: C, 60·95; H, 4·8; N, 24·85. $C_{17}H_{16}N_6O_2$ requires C, 60·7; H, 4·8; N, 25·0%), τ 2·5—2·85 (A_2B_2, aromatic), 3·49 (s, 5-H), 5·71, 6·01 (singlets, 2 MeO), in trifluoroacetic acid.

(b) The chloroform extract was evaporated to dryness, and the residue was recrystallised from glacial acetic acid to give 1,8-*diamino*-3-p-*anisidino*-6-*methoxy*-2,7-*naphthyridine*-4-*carbonitrile* (XVIIb), (0·8 g., 7%), m.p. 213—215° (Found: C, 60·65; H, 4·9; N, 24·8. $C_{17}H_{16}N_6O_2$ requires C, 60·7; H, 4·8; N, 25·0%), τ 2·5—2·85 (A_2B_2, aromatic), 3·51 (s, 5-H), 5·72, 5·98 (singlets, 2 MeO), in trifluoroacetic acid.

On t.l.c. on silica gel, run in ethyl acetate–methanol (9 : 1), (XVIIa) had R_F 0·68, and (XVIIb) had R_F 0·74.

The Reaction of 2-*Amino*-4-*cyanomethyl*-6-(N-*methyl*-p-*anisidino*)3,5-*pyridinedicarbonitrile with Sodium Methoxide*. The pyridine (XX) (1·4 g.) was added to a solution of sodium 0·3 g.) in AnalaR methanol (20 ml.) and the mixture was heated on a steam-bath for 1 hr. The solution was cooled and the solid was filtered off and recrystallised from acetone to give 1,8-*diamino*-6-*methoxy*-3-(N-*methyl*-p-*anisidino*)2,7-*naphthyridine*-4-*carbonitrile* (XXI) (0·62 g., 41%), m.p. 236—239° (Found: C, 61·8; H, 5·2; N, 23·85. $C_{18}H_{18}N_6O_2$ requires C, 61·7; H, 5·2; N, 24·0%), τ 2·6—3·1 (complex, aromatic), 3·72 (s, 5-H), 5·90, 6·11, 6·25 (singlets, NMe and 2 MeO) in trifluoroacetic acid; R_F 0·69 on silica gel in ethyl acetate–methanol (9 : 1).

Reactions of Naphthyridines with Triethyl Orthoformate.—(a) 3,8-*Diamino*-1-p-*anisidino*-6-*methoxy*-2,7-*naphthyridine*-4-*carbonitrile*. The naphthyridine (XVIIa) (100 mg.) in triethyl orthoformate–acetic anhydride (1·0 ml. of an equimolar mixture) was heated on a steam-bath for 2 hr.; the mixture was cooled, and the solid was filtered off and crystallised from dimethylformamide, m.p. >300°. The mass spectrum showed a molecular ion at *m/e* 346, which, on accurate measurement, gave the molecular formula $C_{18}H_{14}N_6O_2$ as required for 5-*amino*-3-p-*anisyl*-8-*methoxy*-3H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-6-*carbonitrile* (XVIIIa), τ 1·64 (s, 2-H), 2·4—2·85 (A_2B_2, aromatic), 3·33 (br, s, NH_2), 3·72 (s, 7-H), 5·98, 6·08 (singlets, 2 MeO) in dimethyl sulphoxide at 120° on a Varian A100 instrument; R_F = 0·81 on silica-gel in ethyl acetate–methanol (9 : 1).

(b) 1,8-*Diamino*-3-p-*anisidino*-6-*methoxy*-2,7-*naphthyridine*-4-*carbonitrile*. In a similar manner, the naphthyridine (XVIIb) gave 5-p-*anisidino*-8-*methoxy*-3H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-6-*carbonitrile* (XVIIIb), m.p. 260—262°, identified by accurate mass measurement of the mass spectrum molecular ion at *m/e* 346 as $C_{18}H_{14}N_6O_2$, τ 0·73 (s, 2-H), 2·4—2·95 (aromatic), 3·28 (s, 7-H), 5·70, 5·98 (singlets,[3] 2 MeO) in trifluoroacetic acid; R_F 0·48, for system as above.

(c) 1,8-*Diamino*-6-*methoxy*-3-(N-*methyl*-p-*anisidino*)2,7-*naphthyridine*-4-*carbonitrile*. The naphthyridine (XXI) similarly gave 8-*methoxy*-5-(N-*methyl*-p-*anisidino*)-3H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-6-*carbonitrile* (XXII), m.p. >300°, identified by accurate mass measurement of the mass spectrum molecular ion at *m/e* 360 as $C_{19}H_{16}N_6O_2$; τ 1·70 (s, 2-H), 2·55—3·15 (aromatic), 4·08 (s, 7-H), 6·13, 6·19, and 6·57 (singlets, 2 MeO and NMe) in deuteriated dimethylsulphoxide; R_F 0·42, in system as above.

Reactions of 1,8-*Diamino*-3,6-*dimethoxy*-2,7-*naphthyridine*-4-*carbonitrile with Carbonyl Derivatives.*—(a) *With triethyl orthoformate.* 1,8-Diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile (1·0 g.), triethyl orthoformate (6·0 ml.) and acetic anhydride (4·1 ml.) were stirred and heated on a steam-bath. Complete dissolution was obtained after *ca.* 0·5 hr., and, almost at once, the product started to separate. After a further 1·5 hr. the mixture was cooled, the product was filtered off and crystallised from dimethylformamide to give 5,8-*dimethoxy*-1H-*pyrimido*[4,5,6-i,j]-[2,7]*naphthyridine*-6-*carbonitrile* (XIV) (0·4 g.); m.p. >300° (Found: C, 55·9; H, 3·8; N, 27·0. $C_{12}H_9N_5O_2$ requires C, 56·45; H, 3·55; N, 27·45%), τ 0·70 (s, 2-H), 3·22 (s, 7-H), 5·69 (s, 2 OMe) in trifluoroacetic acid.

(b) *With isobutyraldehyde.* Isobutyraldehyde (0·45 g.) was added to 1,8-diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile (1·2 g.) in dimethylformamide (8·0 ml.), and a stream of air was drawn through the solution, which was heated on a steam-bath for 12 hr. The reaction mixture was poured into water, and the product was extracted with ethyl acetate. After evaporation of the solvent, the residue was crystallised from glacial acetic acid, or methanol–dimethoxyethane, to give 2-*isopropyl*-5,8-*dimethoxy*-1H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-6-*carbonitrile* (XXIVa) (0·4 g.), decomposes *ca.* 290° (Found: C, 60·4; H, 5·15; N, 23·5. $C_{15}H_{15}N_5O_2$ requires C, 60·6; H, 5·05; N, 23·55%), τ 3·31 (s, 7-H), 5·72 (s, 2 MeO), 6·75 (vbr, $-CHMe_2$), 8·41, 8·52 (isopropyl Me groups), in trifluoroacetic acid.

(c) *With* p-*dimethylaminobenzaldehyde.* 1,8-Diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile (10·0 g.) and *p*-dimethylaminobenzaldehyde (7·5 g.) in dimethylformamide (50 ml.) were heated under nitrogen on a steam-bath for 6 hr. The solvent was removed by the dropwise addition of water, and distillation of the azeotrope until the internal temperature had fallen to 100°. The solid which was thus precipitated was filtered off and washed with acetone, to give 2-p-*dimethylaminophenyl*-2,3-*dihydro*-5,8-*dimethoxy*-1H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-6-*carbonitrile* (XXIIIb) (5·5 g., 36%), m.p. 218—222° (Found: C, 63·9; H, 5·25; N, 22·5. $C_{20}H_{20}N_6O_2$ requires C, 63·85; H, 5·3; N, 22·35%), τ 2·06, 2·26 (A_2, B_2, aromatic), 3·38, 3·64 (singlets, 2-H and 7-H), 5·79, 5·82 (singlets, 2 MeO), and 6·51 (s, NMe_2) in trifluoroacetic acid.

(d) *With cyclohexanone.* Cyclohexanone (6·0 ml.) was added to a solution of 1,8-diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile (3·6 g.) in dimethylformamide (40 ml.) and was stirred under a nitrogen atmosphere, which was maintained until the crystalline product was obtained. The reaction flask was heated on a steam-bath for 15 hr., and was then transferred to an electric heating-mantle; water was added dropwise to the reaction mixture, while an azeotrope of water and dimethylformamide was distilled off. When the internal temperature of the mixture had fallen to 100°, the yellow oil adhering to the flask wall was dissolved by the dropwise addition of ethanol; the solution was then left to crystallise, still under nitrogen. 6-*Cyano*-2,3-*dihydro*-5,8-*dimethoxy*-1H-*pyrimido*[4,5,6-i,j][2,7]*naphthyridine*-2-*spirocyclohexane* (XXV) (2·0 g., 42%) was thus obtained as off-white needles, m.p. 194—198°, with no indication on t.l.c. of the pink oxidation product (Found: C, 62·7; H, 6·0; N, 21·45. $C_{17}H_{19}N_5O_2$ requires C, 62·75; H, 5·85; N, 21·55%), τ 3·86 (s, 7-H), 4·16 (br, s, NH), 6·02, 6·11 (singlets, 2 MeO) and 7·9—8·6 (multiplets, cyclohexane), in deuteriochloroform.

(e) *With phthalic anhydride.* 1,8-Diamino-3,6-dimethoxy-2,7-naphthyridine-4-carbonitrile (9·5 g.) and phthalic anhydride (5·75 g.) were mixed and heated to 130° in an oil-bath, until no more water was evolved (2 hr.). The reaction product was triturated with acetone, filtered, and washed well with acetone. The crude product (13·4 g.) was suspended in phosphorus oxychloride (100 ml.), stirred, heated under reflux for 3 hr., and then allowed to cool. The suspension was filtered off, and crystallised from dimethylformamide to give a mixture of 2,5-dimethoxy-12-oxo-12*H*-isoindolo[2,1-*a*]pyrimido[4,5,6-*i*,*j*][2,7]naphthyridine 3-, and 4-carbonitriles (XXVII), (10·8 g., 78%), m.p. 296—300° (decomp.) (Found: C, 63·7; H, 3·6; N, 19·8. $C_{19}H_{11}N_5O_3$ requires C, 63·85; H, 3·1; N, 19·6%), τ 1·6—2·1 (m, aromatic), 3·10 (s, 3-H or 4-H) 5·58, 5·70 (singlets, 2 MeO), in trifluoroacetic acid.

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