Synthesis of 4-Dimethoxymethyl-6-hydroxy-2-methoxynicotinonitrile: A suggested Mechanism Revision

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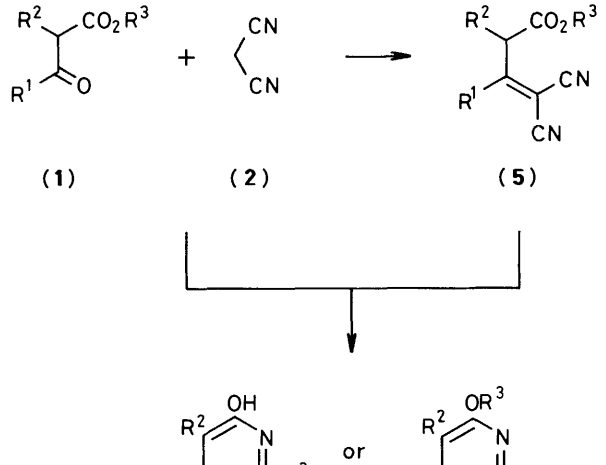
Methyl 4,4-dimethoxy-3-oxobutyrate (**1**) condenses with malonodinitrile (**2**) in methanolic sodium methoxide to form 4-dimethoxymethyl-2-methoxypyridine-3-carbonitrile (**3a**). A previously proposed interpretation of this reaction is shown to be only one of several which allow the formation of one isomer or another [6-alkoxy-2-hydroxy- (**4**) or 2-alkoxy-6-hydroxy-3-cyano-pyridines] depending on the pH of the medium.

The Knoevenagel reaction between β-keto esters and malonic acid derivatives has been widely used for the synthesis of pyridine-2,6-diols.[1] Specifically, the use of malonodinitrile under Cope–Knoevenagel reaction conditions[2] yields the corresponding alkoxypyridones in alcoholic benzene solution.[3] In the absence of alcohol, a simple Knoevenagel adduct is obtained, which may be converted into the alkoxypyridone under the above stated conditions.

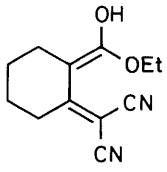
During a general study of the reactivity of methyl 4,4-dimethoxy-3-oxobutyrate (**1**) with malonic compounds,[4] compound (**1**) and malonodinitrile (**2**) were allowed to condense in methanolic sodium methoxide. The spectral data, molecular weight, and elemental analyses of the product were compatible with one of the positional isomers (**3a**) or (**4a**) (Scheme 1).



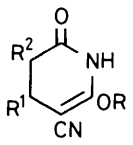
Scheme. 1

Furthermore, when the open-chain Knoevenagel adduct (**5a**) was treated under identical reaction conditions, the same compound was obtained.

The available information, concerning the structures of such cyclization products, is scarce and, perhaps, not entirely relevant to our results because of the different reaction conditions employed. Thus Van der Baan and Bickelhaupt[5] studied the reaction between ethyl 2-oxocyclohexanecarboxylate (**1b**) and (**2**) in the presence of the Cope catalyst (NH_4OAc–AcOH) and obtained a product the structure of which was assigned as (**6**). However, this was reassigned as (**4b**) in a subsequent paper by the same authors.[6] This structure was confirmed by Kasturi and Sharma[7] by means of an unequivocal synthesis.



(**6**)



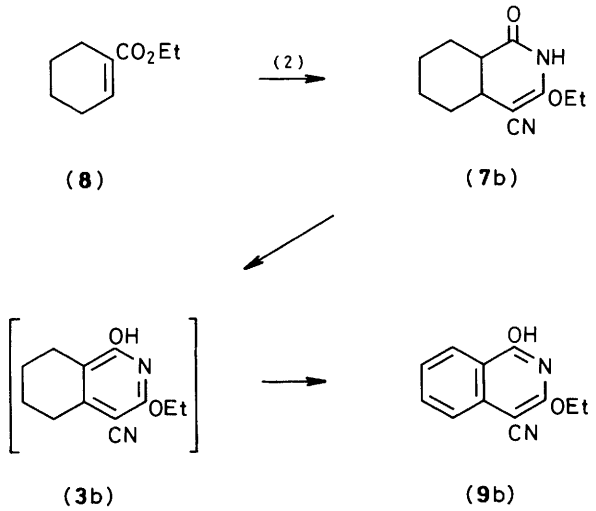
(**7**)

On the basis of these results, the condensation product between (**1a**) and (**2**) should correspond to the isomer (**4a**). However, the differences between our reaction conditions and those used by the aforementioned authors and their mechanistic implications led us to a detailed reappraisal of the foregoing structures and a reinterpretation of the results obtained.

Results and Discussion

In connection with a new synthesis of pyrido[2,3-*d*]pyrimidines,[8] we have developed an unequivocal general synthesis of 6-alkoxy-5-cyano-3,4-dihydropyridin-2(1*H*)-ones (**7**) with a wide range of possible substituents. By dehydrogenation of [**7a**; $R^1 = CH(OMe)_2$, $R^2 = H$, $R^3 = Me$] with activated MnO_2 on charcoal,[9] the hydroxynicotinonitrile (**3a**) was obtained. The identity of this product and the one obtained in the reaction between (**1a**) and (**2**) was established by comparing their physical constants, t.l.c. and undepressed mixed m.p., and spectroscopic data. That is to say, instead of the 6-alkoxy-2-hydroxypyridine (**4a**) expected according to Van der Baan and Bickelhaupt results, the 2-alkoxy-6-hydroxy isomer (**3a**) was obtained. In order to check the relative positions of the substituents in the Knoevenagel adducts, the literature results have been reviewed.

First of all, (**7b**) has been synthesized by a Michael reaction between ethyl cyclohexanecarboxylate (**8**) and (**2**). By dehydrogenation of (**7b**) the isoquinoline (**9b**) was obtained, the partial oxidation system (**3b**) (Scheme 2) not being isolable. In parallel, the Knoevenagel reaction between ethyl 2-oxocyclohexanecarboxylate (**1b**) and (**2**) was carried out under two different sets of reaction conditions: first by using those described by Van der Baan and Bickelhaupt[6,10] and second using sodium ethoxide as



Scheme 2.

a catalyst. Each procedure gave a different positional isomer, (**4a**) or (**3b**), with non-identical physical constants although similar spectral data.

In order to establish the nature of each isomer, the dehydrogenation of the one obtained in the presence of sodium ethoxide was carried out: (**9b**) was obtained and its structure unambiguously established by comparison with identical material obtained from the unequivocal aromatization of (**7b**). Consequently, the method described by Van der Baan and Bickelhaupt leads to the 6-alkoxy-2-hydroxynicotinonitrile (**4**), while our method leads to the 2-alkoxy-6-hydroxy isomer (**3**).

In order to validate both methods, the synthesis of (**4a**), using NH_4OAc/AcOH as a catalyst was attempted. Unfortunately, only multicomponent systems were obtained. Surprisingly, by heating the 'normal' Knoevenagel adduct (**5a**) in methanol, the desired 2-hydroxy-6-methoxypyridine (**4a**) was obtained.

The differences in the results, which depend on the nature of the catalyst employed, allowed us to obtain valuable information about the mechanism of the reaction. This subject has been the centre of controversy. Thus, Kasturi *et al.*[11] reported a route through ketenimine intermediates, a mechanism which was immediately rejected by Van der Baan and Bickelhaupt,[12] who showed that the u.v. absorptions on which it was based were caused by the anion of the 'normal' Knoevenagel product (**5**) instead of the presence of keteneimines. A satisfactory mechanism for this reaction (Route I, Scheme 3) was subsequently reported by Gunter and Ducker.[13]

Although this interpretation seems to be clearly supported by the studies of Van der Baan and Bickelhaupt, it is only one of the possible routes of a more general mechanism. Thus, the pH of the medium seems to be the driving force which leads to the 6-alkoxy-2-hydroxypyridine (**4**), in an acid or neutral medium, or the 2-alkoxy-6-hydroxypyridine (**3**), with a basic catalyst (Scheme 3).

Consequently, the reaction path becomes pH-dependant after the formation of the pyran (**11**), obtained by cyclization of the 'normal' Knoevenagel adduct (**5**). Thus, when the reaction is carried out in the presence of ammonium acetate–acetic acid mixtures (acid or neutral medium), Route I of Scheme 3 is followed. This is supported by the dependence of the reaction rate on the NH_4OAc–AcOH ratio, observed by Van der Baan and Bickelhaupt.[12]

On the other hand, when the reaction is carried out in a strong basic medium, *e.g.* sodium alkoxides, Route II (Scheme 3) seems to be followed. Thus, after the formation of the pyran (**11**), the high basicity of the medium precludes the 1,6-addition of alcohol that leads to (**12**) *via* Route I. The alkoxide then attacks the imino group and the ring is opened, leading to the intermediate (**16**). The final product (**3**) is then formed by subsequent cyclization.

In conclusion, we have confirmed and complemented the literature results and achieved a methodology that allows the synthesis of both positional isomers by a change of the catalyst (Scheme 3).

Moreover, a detailed study of the u.v. spectra of both families of isomers recorded in ethanolic KOH has shown an interesting difference between them when R^1 and R^2 are alkyl groups. Thus, the 6-alkoxy-2-hydroxypyridines (**4**) show two absorption maxima at 265 ± 1 nm and 299—304 nm, while for the 2-alkoxy-6-hydroxypyridines (**3**) these maxima appeared at 255 ± 1 nm and 315—327 nm. This difference provides an excellent method for an initial assignment of the isomer obtained in such cyclizations.

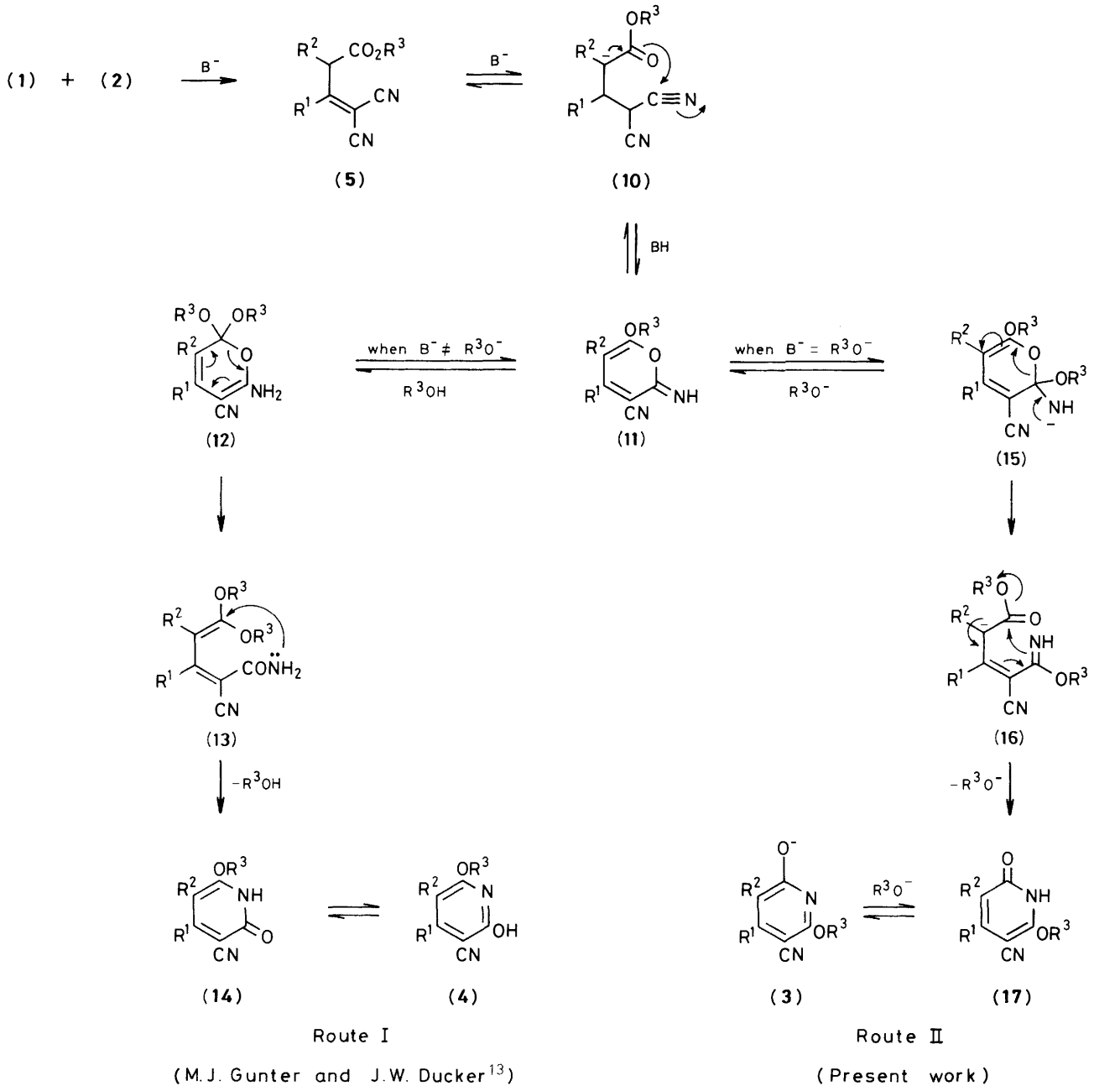
Experimental

All m.p.s and b.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 683 spectrometer as KBr discs (solids) or films (liquids), unless otherwise stated. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R-24 (60 MHz) or on a Varian XL 200/F-19 (200 MHz) spectrometer in Cl_3CD, with tetramethylsilane as internal reference. All OH signals were confirmed by disappearance of their signals after addition of D_2O. U.v. spectra were recorded on a Hewlett-Packard 8450 A spectrophotometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RM-50 (70 eV) or on a Hewlett-Packard 5995 A (70 eV) instruments.

Methyl 4,4-*Dimethoxy*-3-*oxobutyrate* (**1a**).—This compound, b.p. 76—77 °C (5 Torr), was prepared by the method of J. A. Secrist III *et al.*[14] [lit., 76 °C (5 Torr)] on a molar scale (68%); n_D^{25} 1.4266.

Methyl 4,4-*Dicyano*-3-*dimethoxymethylbut*-3-*enoate* (**5a**).—To a solution of the ester (**1a**) (10.4 g, 59 mmol), malonodinitrile (3.9 g, 59 mmol) in methanol (25 ml), was rapidly added a solution of potassium hydroxide (3.31 g, 59 mmol) in methanol. The mixture was refluxed for 1 h, cooled, and allowed to stand at room temperature for 3 h. After distillation of methanol, the residue was dissolved in the minimum volume of water and the solution obtained was cooled at 4 °C. It was then acidified with 6M hydrochloric acid to pH 5, extracted with chloroform, and the extract dried. Evaporation of the latter yielded crude (**5a**) as a red oil (10 g, 76%). This polymerized when distilled to give the product (0.92 g, 7%), b.p. 117—122 °C (0.15 Torr); $\nu_{max.}$ 2 235 (C≡N), 1 745 (C=O), and 1 615 cm^{-1} (C=C); δ(60 MHz) 3.42 [6H, s, $C(OMe)_2$], 3.56 (2 H, s, CH_2), 3.69 (3 H, s, CO_2Me), and 5.11 [1 H, s, $CH(OMe)_2$].

4-*Dimethoxymethyl*-6-*hydroxy*-2-*methoxynicotinonitrile* (**3a**).—(*a*) *From* 4,4-*dimethoxy*-3-*oxobutyrate* (**1a**). To a solution of sodium (0.15 g, 6.5 mmol) in methanol (5 ml), malonodinitrile (0.4 g, 6 mmol) and the ester (**1a**) (1 g, 5.7 mmol) were added. The mixture was refluxed for 1 h, cooled, and stirred at room temperature for 1 h. After the methanol had been distilled off, the residue was dissolved in the minimum volume of water, acidified with 6M hydrochloric acid to pH 5, extracted with chloroform, and the extract dried. The latter was evaporated under reduced pressure to give an oil which was recrystallised from heptane (0.78 g, 61%), m.p. 108—109 °C (Found: C, 53.55; H, 5.4; N, 12.3%; M^+, 224. $C_{10}H_{12}N_2O_4$ requires C, 53.57; H, 5.39; N, 12.49%; *M*, 224); $\nu_{max.}$ 3 120 (OH), 2 235 (C≡N), 1 610, 1 580, and 1 480 (C=C and C=N), and 1 240 cm^{-1} (C–O); δ(200 MHz) 3.436 [6 H, s, $C(OMe)_2$], 4.000 (3 H, s, ArOMe), 5.453 [1 H, s, $CH(OMe)_2$], and 6.627 (1 H, s, 5-H); $\lambda_{max.}$(EtOH + 1%



Scheme 3.

KOH) 264 (ε 13 100 dm^3 mol^{-1} cm^{-1}), and 307 nm (12 100); *m/z* 224 (M^+, 11%) and 75 (100).

(b) *From methyl* 4,4-*dicyano*-3-*dimethoxymethylbut*-3-*enoate* (**5a**). To a solution of sodium (0.15 g, 6.5 mmol) in methanol (5 ml), the adduct (**5a**) (1.26 g, 5.57 mmol) was added and the solution refluxed for 1 h. Work-up as above gave the product (0.81 g, 65%), the spectral and analytical data of which were identical with those stated above.

(c) *From* 5-*cyano*-4-*dimethoxymethyl*-3,4-*dihydro*-6-*methoxypyridin*-2(1H)-*one* (**7a**). A mixture of 5-cyano-4-dimethoxymethyl-3,4-dihydro-6-methoxypyridin-2-(1*H*)-one (**7a**) (1 g, 4.4 mmol), activated MnO_2 on charcoal (10 g) prepared by a literature method[8] and dry toluene (100 ml) was stirred and refluxed for 48 h. The mixture was cooled, filtered, and the filtrate continuously extracted with methanol for 48 h. The solvent was then distilled off and the residue dissolved in 1M NaOH solution. After acidification with 6M hydrochloric acid the solution was extracted with chloroform and the extract dried. Evaporation of the extract gave crude material which was purified by column chromatography (SiO_2, $CHCl_3$) (0.30 g, 30%). The spectral and analytical data for the compound were identical with those of a pure sample obtained by procedure (a).

4-*Cyano*-3-*ethoxy*-4a,5,6,7,8,8a-*hexahydroisoquinolin*-1(2H)-*one* (**7b**).—To a solution of sodium (6.58 g, 0.29 mmol) in methanol (180 ml), malonodinitrile (15.71 g, 0.24 mol) in methanol (90 ml) was added. Ethyl cyclohex-1-enecarboxylate (**8**) (26 g, 0.2 mol) in methanol (90 ml) was then added dropwise and the mixture refluxed for 90 min. After cooling of the mixture methanol was distilled off and the residue dissolved in water (180 ml) and neutralized with 6M hydrochloric acid. The resulting precipitate was filtered off, washed with cold water (20

ml), and dissolved in chloroform (2 × 100 ml). The combined extracts were dried and evaporated to yield the desired product (28.60 g, 65%), m.p. 129—130 °C (from hexane–benzene, 1:5) (Found: C, 65.35; H, 7.35; N, 12.75%; M^+, 220. $C_{12}H_{18}N_2O_2$ requires C, 65.43; H, 7.32; N, 12.72%; M^+, 220); $\nu_{max.}$ 3 200 and 3 100 (NH), 2 195 (C≡N), 1 690 (C=O), 1 620 (C=C), and 1 255 cm^{-1} (C–O); δ(60 MHz) 1.38 (3 H, t, *J* 7 Hz, CH_3CH_2O), 1.43 [8 H, m, $(CH_2)_4$], 2.63 (2 H, m, 4a-H and 8a-H), 4.41 (2 H, q, *J* 7 Hz, CH_3CH_2O), and 7.92 (1 H, br s, NH); *m/z* 220 (M^+, 21) and 150 (100).

3-*Ethoxy*-1-*hydroxyisoquinoline*-1-*carbonitrile* (**9b**).—(a) *From* 4-*cyano*-2-*ethoxy*-4a,5,6,7,8,8a-*hexahydroisoquinolin*-1(2H)-*one* (**7b**). A mixture of (**7b**) (1 g, 4.5 mmol), activated MnO_2 on charcoal (10 g)[8] and dry toluene was stirred and refluxed for 48 h. Work-up as for compound (**9**) gave the desired product (0.42 g, 43%), m.p. 221—222 °C (decomp.); $\nu_{max.}$ 2 930 (NH), 2 215 (C≡N), 1 660 (C=O), 1 615, 1 560, and 1 510 cm^{-1}; δ(60 MHz, [$^2H_6$]-DMSO) 1.40 (3 H, t, *J* 7 Hz, CH_3CH_2O), 4.56 (2 H, q, *J* 7 Hz, CH_3CH_2O), 7.59, and 8.16 (4 H, m, ArH); *m/z* 214 (M^+, 26%) and 185 (100).

(b) *From* 3-*ethoxy*-5,6,7,8-*tetrahydro*-1-*hydroxyisoquinoline*-1-*carbonitrile* (**3b**). The same procedure as described above starting with (**3b**) (1 g, 4.6 mmol) gave the product (0.44 g, 45%), the spectral data for which were identical with those of a pure sample obtained by procedure (a).

3-*Ethoxy*-5,6,7,8-*tetrahydro*-1-*hydroxyisoquinoline*-4-*carbonitrile* (**3b**).—To a solution of sodium (0.8 g, 35 mmol) in ethanol (100 ml), malonodinitrile (2 g, 33 mmol) and ethyl 2-oxocyclohexanecarboxylate (**1b**) (Fluka ref. 29161) (4.87 g, 33 mmol) were added. The resultant solution was refluxed for 3 h, cooled, and allowed to stand at room temperature for 12 h. Work-up as described above for (**3a**) yielded the desired product (6.90 g, 96%), m.p. 180 °C (from hexane–benzene) (lit.,[5] 176—177 °C) (Found: C, 65.9; H, 6.7; N, 12.8%; M^+, 218. $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.84%; *M* 218); $\nu_{max.}$ 3 120 (OH), 2 225 (C≡N), and 1 600 cm^{-1}; δ(60 MHz) 1.43 (3 H, t, *J* 7 Hz, CH_3CH_2O), 1.63—2.03 (4 H, m), 2.27—2.67 (2 H, m), and 4.48 (2 H, q, *J* 7 Hz, CH_3CH_2O); $\lambda_{max.}$(EtOH + 1% KOH) 265 (ε 12 600 dm^3 mol^{-1} cm^{-1}) and 304 nm (16 600); *m/z* 218 (M^+, 42%) and 175 (100).

1-*Ethoxy*-5,6,7,8-*tetrahydro*-3-*hydroxyisoquinoline*-4-*carbonitrile* (**4b**).—This compound, m.p. 196—197 °C (from benzene), was prepared by the method of Van der Baan and Bickelhaupt[8,10] (lit., 196—197 °C) (6.10 g, 85%); $\nu_{max.}$ 3 160 (OH), 2 235 (C≡N), 1 605, and 1 580 cm^{-1}; δ(60 MHz) 1.33 (3 H, t, *J* 7 Hz, CH_3CH_2O), 1.80 (4 H, m), 2.45 (2 H, m), and 4.38 (2 H, q, *J* 7 Hz, CH_3CH_2O); $\lambda_{max.}$(EtOH + 1% KOH) 255 (ε 19 300 dm^3 mol^{-1} cm^{-1}) and 325 nm (22 200).

4-*Dimethoxymethyl*-2-*hydroxy*-6-*methoxynicotinonitrile* (**4a**). —A solution of the adduct (**5a**) (14 g, 66 mmol) in methanol (250 ml) was refluxed for 14 h, and then cooled, and evaporated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, Cl_3CH) to afford the desired product (8.60 g, 58%), m.p. 175—176 °C; $\nu_{max.}$ 2 920 (OH), 2 215 (C≡N), 1 595, and 1 555 cm^{-1}; δ(200 MHz, [$^2H_6$]-DMSO) 3.475 [6 H, s, $C(OMe)_2$], 4.006 (3 H, s, ArOMe), 5.412 [1 H, s, $CH(OMe)_2$], and 6.118 (1 H, s, 5-H); $\lambda_{max.}$(EtOH + 1% KOH) 254 (ε 14 600 dm^3 mol^{-1} cm^{-1}), and 327 nm (14 400); *m/z* 224 (M^+, 10%) and 75 (100).

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References

1 (*a*) J. R. Stevens, R. H. Beutel, and E. Chamberlain, *J. Am. Chem. Soc.*, 1942, **64**, 1093; (*b*) J. R. Stevens and R. H. Beutel, *ibid.*, 1943, **65**, 449; (*c*) B. M. Ferrier and N. Campbell, *J. Chem. Soc.*, 1960, 3513; (*d*) J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 1960, **25**, 560.
2 A. C. Cope, *J. Am. Chem. Soc.*, 1937, **59**, 2327.
3 (*a*) T. R. Kasturi and L. Krishnan, *Tetrahedron Lett.*, 1980, **21**, 865; (*b*) T. R. Kasturi, L. Krishnan, and R. S. Prasad, *J. Chem. Soc., Perkin Trans. 1*, 1982, 63.
4 J. Sempere, Ph.D. Thesis. Instituto Quimico de Sarriá, 1983.
5 J. L. Van der Baan and F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.*, 1968, 1661.
6 J. L. Van der Baan and F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.*, 1970, 326.
7 T. R. Kasturi and V. K. Sharma, *Tetrahedron*, 1975, **31**, 1545.
8 (*a*) P. Victory and J. Diago, *Afinidad*, 1978, **35**, 161; (*b*) P. Victory, A. Crespo, and R. Nomen, *J. Heterocycl. Chem.*, 1988, **25**, 245, and the references therein; (*c*) P. Victory, A. Crespo, R. Nomen, and J. I. Borrell, *Afinidad*, 1989, **46**, 107.
9 L. A. Carpino, *J. Org. Chem.*, 1970, **35**, 3971.
10 J. L. Van der Baan and F. Bickelhaupt, *Tetrahedron*, 1974, **30**, 2447.
11 T. R. Kasturi, V. K. Sharma, and A. Srinivasan, *Tetrahedron*, 1973, **29**, 4103.
12 J. L. Van der Baan and F. Bickelhaupt, *Tetrahedron*, 1975, **31**, 1545.
13 J. W. Ducker and M. J. Gunter, *Aust. J. Chem.*, 1975, **28**, 581.
14 J. A. Secrist III, C. J. Mickey, and R. E. Norris, *J. Org. Chem.*, 1977, **42**, 525.

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