Chemistry of 6*H*-Pyrido[3,4-*b*]carbazoles. Part 6.[1] The Structure of Some Dihydropyridines derived from the Addition of Cyanide Ion to 1-(*N*-Methylacetamido)pyridinium Salts and Their Further Reactions

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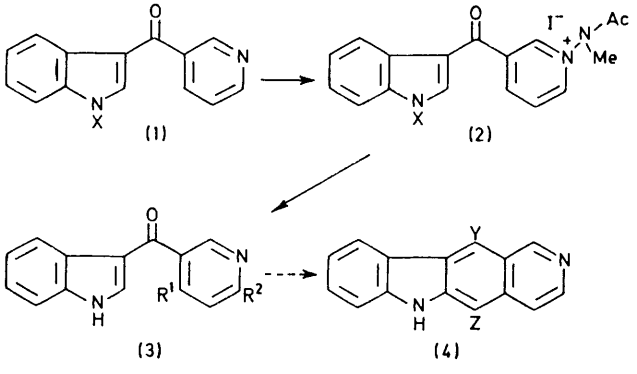
Cyanide ion reacts with certain 3-(indol-3-ylformyl)-pyridinium salts to give 4-cyano-1,4-dihydro-adducts or ring-opened products depending upon the conditions. The former are easily aromatised to the corresponding 4-cyanopyridines and the reaction may be modified so that 2-cyanopyridines are formed, although in this case the intermediate adducts have not been identified. 3-(Indol-3-ylmethyl)pyridine-4-carbonitrile, when treated with dilute hydrochloric acid, gives 10*H*-pyrido[3',4':4,5]cyclopent[1,2-*b*]indole.

SYNTHETIC work directed towards ellipticine (4; Y = Z = Me) and its derivatives substituted at position 9 has received much attention lately,[2] stimulated no doubt by the high anticancer activity of 9-hydroxyellipticine and its metho-salts against experimental tumours,[3] but despite this little has been published on the preparation of pyrido[4,3-*b*]carbazoles substituted at other positions around the tetracycle.

A route to the ellipticine system pioneered in this laboratory [1] appears ideal for this purpose and we chose it in an attempt to prepare 5,11-dihydroxy-6*H*-pyrido-[4,3-*b*]carbazole (4; Y = Z = OH) by the sequence outlined in the Scheme. The starting compound (1;

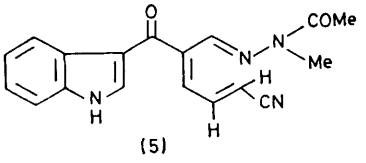


SCHEME

X = H) [4a,b] was easily prepared by the reaction of indolylmagnesium bromide and nicotinoyl chloride at low temperature,† and it reacted with acetic anhydride to afford the *N*-acetyl derivative (1; X = Ac). This was treated with *O*-mesitylsulphonylhydroxylamine, further acetylated with acetic anhydride, and finally combined with methyl iodide to yield the pyridinium salt (2; X = Ac).

The salt was dissolved in chloroform and treated with an aqueous solution of potassium cyanide and ammonium chloride to give a yellow product which was taken up in methanol and irradiated with u.v. light from a medium-pressure source to yield the 2-cyanopyridine (3; R^1 = H, R^2 = CN). Previously [1] we have only isolated 4-cyanopyridines from reactions of this type and we were interested to determine, if possible, the structure of the intermediate dihydro-2-cyano-adduct. Accordingly, the process was now repeated omitting the irradiation step and protecting the contents of the reaction vessel from light throughout. This afforded a pale yellow solid which exhibits i.r. bands at $\nu_{max.}$ 3 200 (NH), 2 220 (CN), and 1 695 (CO) cm^{-1}, and has an exchangeable one-proton peak at δ 12.4 in the ^1H n.m.r. spectrum. Two methyl proton resonances at δ 3.2 and 2.1 may be assigned to the *N*-methyl and *N*-acetyl units of an *N*-methylacetamido-group, but the interpretation of the remainder of the spectrum is more difficult. For example, a one-proton doublet at δ 7.9 (*J* 9 Hz) is coupled to a one-proton double doublet centred at δ 6.7 (*J* 16.5 and 9 Hz). The larger spin–spin interaction results from coupling with a proton the resonance of which is partly obscured by other signals at δ 7.6.

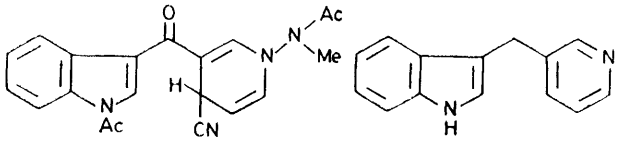
Since this product cannot be a dihydropyridine the most likely structure is the ring-opened isomer (5) which has a *trans*-arrangement of hydrogen atoms on the terminal double bond. When heated above the melting point this compound is partly converted into the 2-cyanopyridine (3; R^1 = H, R^2 = CN), but photolysis has no effect. It is clear that the triene (5) is not the immediate precursor of the cyanopyridine but despite a claim by Japanese workers [5] to have isolated 2-cyano-1,2-dihydropyridines in related experiments we were unable to obtain any other products from our reaction procedure.



Rather than adding potassium cyanide to the pyridinium salt in chloroform we now reverted to our normal practice of employing totally aqueous solutions and in this case, prior to irradiation, we obtained the 1,4-dihydro-4-cyano-adduct (6) as the sole isolated product (86%), and were able to convert this into the corresponding 4-cyanopyridine (3; R^1 = CN, R^2 = H) very easily by photolysis or by gentle heating. Sammes and

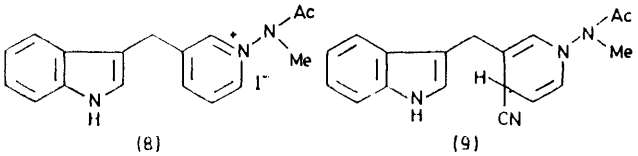
† Above 0 °C this product is contaminated with the dinicotinoyl compound (1; X = nicotinoyl).

Katritzky [6] report that the concentration of cyanide ion in contact with the pyridinium cation is of paramount importance in determining the position of nucleophilic attack. High concentrations favour 2-substitution, while low concentrations allow preferential 4-attack. It is likely that the variations in products that we observe simply reflect this phenomenon, although at the moment our evidence, circumstantial as it is, seems to point to the opposite conclusion. Unfortunately the conditions required to effect hydrolysis of the 4-cyanopyridine (3; R^1 = CN, R^2 = H) are so severe that the substrate is decomposed and in consequence an approach to the pyrido[4,3-*b*]carbazole system *via* this compound was abandoned.

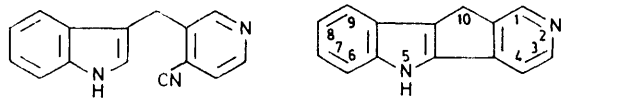


(6) (7)

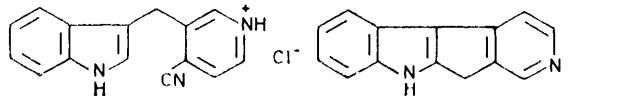
Formerly [4b] we have prepared the β-picoline derivative (7) by sodium borohydride reduction of the carbonyl compound (1; X = H); however, Wolff–Kishner conditions [7] are more efficient and using the product of this reaction we now sought to complete the projected synthesis (Scheme) forming 5-hydroxy-6*H*-pyrido[4,3*b*]-carbazole (4; Y = H, Z = OH) rather than the original target, the 5,11-dihydroxylated analogue (4; Y = Z = OH). The required pyridinium salt (8) was



(8) (9)



(10) (11)



(12) (13)

prepared and treated with potassium cyanide in aqueous solution to give the 1,4-dihydro-4-cyano-adduct (9). Photolysis of this afforded the related 4-cyanopyridine (10) in excellent yield. Again alkaline conditions of hydrolysis were unsuccessful in effecting conversion into the corresponding acid, but heating with aqueous hydrochloric acid gave a colourless crystalline product which has a molecular mass two units less than that of the starting 3-alkylpyridine (7). The ^{1}H n.m.r. spectrum does not show a signal characteristic of an α-indolic hydrogen atom but there is a two-proton resonance at δ 3.7 which indicates a bridging methylene group between the indole and pyridine units.

We judge this compound to be the tetracycle (11) formed by direct α-substitution of the indolic nucleus by the pyridinium salt (12) followed by expulsion of hydrogen cyanide. The alternative arrangement (13) cannot be discounted entirely but its formation through attack at the indole β-position, followed by rearrangement, requires the participation of a four-membered spiro-intermediate which seems most unlikely. Finally we tried numerous ways of converting the 4-cyanopyridine (10) into the corresponding aldehyde. Such a compound would undoubtedly cyclise extremely easily affording 6*H*-pyrido[4,3-*b*]carbazole, but so far we have obtained neither compound.

EXPERIMENTAL

U.v. spectra were recorded for solutions in 98% aqueous ethanol, and i.r. spectral data refer to Nujol mulls. ^{1}H N.m.r. spectra were recorded at either 60 or 100 MHz with tetramethylsilane as internal standard. Photochemical experiments were conducted in a Hanovia photochemical reactor.

3-(1-*Acetylindol*-3-*ylformyl*)-1-(N-*methylacetamido*)*pyridinium Iodide* (2; X = Ac).—The indole (1; X = Ac) (10 g) in dichloromethane (100 cm^3) was cooled to 0 °C and *O*-mesitylsulphonylhydroxylamine (8.2 g) in dichloromethane (50 cm^3) added. After several minutes the mixture was treated with diethyl ether (100 cm^3) and stirred for a further 30 min. The solid product was then filtered off, washed with diethyl ether, and air-dried; yield, 16.8 g, 92%; m.p. 198—203 °C; $\nu_{max.}$ 1 730 and 1 640 cm^{-1}; δ[$(CD_3)_2SO$] 9.2 (1 H, s, 2-H), 8.85 (1 H, d, *J* 6 Hz, 6-H), 8.6—8.4 (3 H, m, 2′-H * + NH_2), 8.3—7.9 (4 H, m, 4-, 5-, 4′-, and 7′-H), 7.4—7.2 (2 H, m, 5′- and 6′-H), 6.55 (2 H, s, mesitylate ArH), 2.75 (3 H, s, Ac), 2.5 (6 H, s, 2 × Me), and 2.1 (3 H, s, Me). This compound (20 g) in chloroform (300 cm^3) was stirred vigorously and acetic anhydride (20 cm^3) added. After 60 min the mixture was basified with aqueous sodium hydrogen carbonate solution and the organic phase separated, dried, and evaporated to give needles of 3-(1-acetylindol-3-ylformyl)pyridinium *N*-acetylimide; yield, 10.6 g, 90%; m.p. 179—181 °C; δ($CDCl_3$) 9.4br (1 H, s, 2-H), 8.7—8.2 (5 H, m, 4-, 6-, 2′-, 4′-, and 7′-H), 7.9 (1 H, dd, J_1 8, J_2 6 Hz, 5-H), 7.4 (2 H, m, 5′- and 6′-H), 2.9 (3 H, s, NMe), and 2.1 (3 H, s, $^+$N–N̄Ac); *m/e* 321 (M^+), 306, 279, and 144. If the reaction is carried out in aqueous ethanol or the basification procedure is not carried out very quickly de-*N*-acetylation of the indolic *N*-acetyl group occurs. The monoacetyl derivative (2; X = H) is then obtained as pale yellow prisms, m.p. 244 °C (from Me_2SO); $\nu_{max.}$ 3 100, 1 620, and 1 560 cm^{-1}; δ[$(CD_3)_2SO$] 12.3br (1 H, s, NH), 9.1 (1 H, s, 2-H), 8.85 (1 H, d, *J* 6 Hz, 6-H), 8.5—8.1 (3 H, m, 4-, 2′-, and 4′-H), 7.9 (1 H, dd, J_1 8 Hz, 5-H), 7.5—7.05 (3 H, m, 5′-, 6′-, and 7′-H), and 1.95 (3 H, s, $^+$N–N̄Ac).

The diacetyl product (10 g) was heated with methyl

* Primed numbers refer to the indolyl unit and unprimed numbers to the pyridyl unit throughout.

iodide (20 cm³) in acetone (100 cm³) at reflux for 1 h. On cooling, the *iodide* (2; X = Ac) was obtained as yellow needles; yield 12.8 g, 88.7%; m.p. 236 °C (decomp.); $\nu_{max.}$ 1 720, 1 690, and 1 650 cm^{-1}; δ[$(CD_3)_2SO$] 10.1 (1 H, s, 2-H), 9.7 (1 H, d, *J* 6 Hz, 6-H), 9.35 (1 H, d, *J* 8 Hz, 4-H), 8.8—8.2 (4 H, m, 5-, 2′-, 4′-, and 7′-H), 7.7—7.5 (2 H, m, 5′- and 6′-H), 3.9 (3 H, s, NAc), 2.85 (3 H, s, $^+$N–NMe), and 2.3 (3 H, s, $^+$N–NAc) (Found: C, 49.4; H, 4.0; N, 9.0. $C_{19}H_{18}IN_3O_3$ requires C, 49.3; H, 3.9; N, 9.1%).

6-Cyanopyridin-3-yl Indol-3-yl Ketone (3; R^1 = H, R^2 = CN).—The metho-salt (2; X = Ac) (1.25 g) dispersed in chloroform (100 cm³) was stirred vigorously as ammonium chloride (0.5 g) in water (20 cm³) was added and then as potassium cyanide (0.23 g) in water (20 cm³) was introduced. The aqueous phase was then removed and extracted with chloroform (2 × 20 cm³) and the combined chloroform layer and extracts were washed with water (3 × 25 cm³), dried, and evaporated to give a non-crystalline solid. This was dissolved in methanol (100 cm³) and irradiated with u.v. light (medium-pressure Hg lamp) for 2 h. Finally the solvent was removed to afford the *ketone* (3; R^1 = H, R^2 = CN) as pale yellow prisms; yield 0.28 g, 42%; m.p. 260 °C (from Me_2SO); $\lambda_{max.}$ 244, 272, and 335 nm; $\nu_{max.}$ 3 200, 2 200, and 1 620 cm^{-1}; δ[$(CD_3)_2SO$] 12.3br (1 H, s, NH), 9.1 (1 H, d, *J* 2 Hz, 2-H), 8.2 (4 H, m, 4-, 5-, 2′-, and 4′-H), 7.4 (1 H, m, 7′-H), and 7.15 (2 H, m, 5′- and 6′-H); *m/e* 247 (M^+) (Found: C, 72.6; H, 3.9; N, 17.1. $C_{15}H_9N_3O$ requires C, 72.9; N, 3.7; N, 17.0%).

1-(N-Acetyl-N-methylhydrazonomethyl)buta-1,3-dienyl Indol-3-yl Ketone (5).—When the foregoing reaction was repeated but with protection of the reactants from light a yellow solid was obtained, which formed prisms of the *ketone* (5) from ethanol; yield 69.6%; m.p. 246—250 °C (decomp.) (from $CHCl_3$); $\lambda_{max.}$ 245, 263, and 322 nm; *m/e* 320 (M^+) and 248 (100%); $\nu_{max.}$ 3 200, 2 220, 1 695, and 1 600 cm^{-1}; δ[$(CD_3)_2SO$] 12.4br (1 H, s, NH), 8.3 (1 H, m, 4-H), 8.25 (1 H, s, 1-H), 7.9 (1 H, d, *J* 9 Hz, 3-H), 7.6 (1 H, m, 7′-H), 7.25 (3 H, m, 5-, 5′-, and 6-H), 6.7 (1 H, dd, J_1 16.5, J_2 9 Hz, 4-H), 6.15 (1 H, s, 2′-H), 3.2 (3 H, s, NMe), and 2.1 (3 H, s, NAc) (Found: C, 67.6; H, 5.1; N, 17.3. $C_{18}H_{16}N_4O_2$ requires C, 67.5; H, 5.0; N, 17.5%). This compound was unchanged after irradiation with u.v. light but when heated at its m.p. it was partially converted into the 2-cyanopyridine (3; R^1 = H, R^2 = CN).

1-Acetylindol-3-yl 1-(N-Ethylacetamido)-4-cyano-1,4-dihydropyridin-3-yl Ketone (6).—A dispersion of the metho-salt (2; X = Ac) (2.0 g) in water (200 cm³) was stirred at room temperature and ammonium chloride (0.68 g) and potassium cyanide (0.33 g) in water (25 cm³) were added. After 1 h, dichloromethane (75 cm³) was introduced and the mixture stirred for a further 10 min. The aqueous phase was washed with dichloromethane (2 × 50 cm³) and the combined organic phase and extracts were washed with water and dried. Removal of the solvent at room temperature afforded a yellow gum which rapidly turned green. This was dissolved in the minimum of warm ethanol and allowed to cool whereupon yellow prisms of the *ketone* (6) separated; yield 0.92 g, 86%; m.p. 154—155 °C (decomp.) (from MeOH); $\nu_{max.}$ 2 230, 1 720, 1 690, 1 600, and 1 200 cm^{-1}; δ[$(CD_3)_2SO$] 8.3 (2 H, m, 4′- and 7′-H), 7.9 (2 H, m, 2- and 2′-H), 7.35 (2 H, m, 5′- and 6′-H), 6.6 (1 H, m, 6-H), 5.2 (1 H, m, 5-H), 4.75 (1 H, m, 4-H), 3.15 (3 H, 2 × s, NMe), 2.7 (3 H, s, NAc), and 2.0 (3 H, 2 × s, N–NAc) (Found: C, 67.4; H, 5.2; N, 17.3. $C_{18}H_{16}N_4O_2$ requires C, 67.5; H, 5.0; N, 17.5%).

4-Cyanopyridin-3-yl Indol-3-yl Ketone (3; R^1 = CN, R^2 = H). The 1,4-dihydropyridine (6) just described may be converted into the corresponding pyridine by heating gently in organic solvents, or by irradiation with u.v. light to give the *ketone* (3; R^1 = CN, R^2 = H) as a yellow solid, m.p. 256—258 °C (from Me_2SO); $\nu_{max.}$ 3 200 and 1 620 cm^{-1}; δ[$(CD_3)_2SO$] 12.2br (1 H, s, NH), 9.15 (1 H, s, 2-H), 9.05 (1 H, d, *J* 5 Hz, 6-H), 8.3 (1 H, m, 4′-H), 8.15 (1 H, s, 2′-H), 8.05 (1 H, d, *J* 5 Hz, 5-H), and 7.4 (3 H, m, 5′-, 6′-, and 7′-H) (Found: C, 72.8; H, 3.8; N, 16.8%; M^+, 247.074 2. $C_{15}N_9N_3O$ requires C, 72.9; H, 3.7; N, 17.0%; M^+, 247.074 6).

3-(Indol-3-ylmethyl)pyridine-4-carbonitrile (10).—3-(Indol-3-ylmethyl)pyridine (7) (3 g) in dichloromethane (150 cm³) was cooled to 0 °C and treated with a solution of *O*-mesitylsulphonylhydroxylamine (3.2 g) in the same solvent (50 cm³). The pale straw-coloured oil which separated was collected, washed with diethyl ether, dissolved in 50% aqueous ethanol (60 cm³), and treated with acetic anhydride (10 cm³) during 1 h. The solution was made basic with 2N sodium hydrogen carbonate solution and evaporated at reduced pressure to low bulk. The residue was extracted with chloroform to afford an oil which was treated with methyl iodide (20 cm³) in boiling acetone (30 cm³).

The yellow crystalline product was dissolved in water (250 cm³) containing ammonium chloride (1.0 g) and treated with potassium cyanide (0.6 g) in water (25 cm³). After stirring for 2 h, chloroform (100 cm³) was added and the organic phase separated, dried, and evaporated under reduced pressure at room temperature to give an almost colourless oil. This was washed with diethyl ether and crystallised from ethanol simply by dissolution in the solvent and allowing the excess to evaporate. The product, which has an indefinite m.p., shows $\nu_{max.}$ 3 210, 2 240, 1 725, 1 620, 1 610, and 1 600 cm^{-1}; δ($CDCl_3$) 8.5br (1 H, s removed by addition of D_2O), 7.7—7.0 (5 H, m, H-2′, 2′-, 4′-, 5′-, 6′-, and 7′-H), 6.0 (1 H, m, 6-H), 5.95br (1 H, 2 × s, 2-H), 4.7 (1 H, 6-line m, 5-H), 4.1br (1 H, 2 × d, 4-H), 3.65br (2 H, s, CH_2), 3.0 (3 H, 2 × s, NMe), and 2.05 (3 H, 2 × s, NAc). This spectrum, which clearly shows evidence of the diastereoisomeric nature of the 4-cyano-1,4-dihydropyridine (9) produced, is considerably simplified when the sample is warmed. The multiple peaks at, for example, δ 4.7 and 4.1 merge into more easily defined spin–spin interaction patterns and the resonances at δ 3.65, 3.0, and 2.05 become singlet peaks. At >50 °C, or if the n.m.r. tube is left exposed to sunlight, the spectrum now becomes that of the 4-carbonitrile (10) with additional signals due to the resonances of the protons of *N*-methylacetamide superimposed upon it.

When the product is irradiated in ethanol solution and the solution evaporated to low bulk, *3-(indol-3-ylmethyl)-pyridine-4-carbonitrile* (10), m.p. 145 °C, separates; total yield 1.46 g, 43%; δ[$(CD_3)_2SO$] 10.5br (1 H, s, NH), 8.8 (1 H, s, 2-H), 8.6 (1 H, d, *J* 6 Hz, 6-H), 7.65 (1 H, d, *J* 6 Hz, 5-H), 7.55—6.95 (5 H, m, 2′-, 4′-, 5′-, 6′-, and 7′-H), and 4.35 (2 H, s, CH_2) (Found: C, 77.25; H, 4.7; N, 18.0. $C_{15}H_{11}N_3$ requires C, 77.2; H, 4.7; N, 18.0%).

Some of this product was converted into the known [1] and fully characterized indole-*N*-acetyl derivative, m.p. and mixed m.p. 157—158 °C.*

10H-Pyrido[3′,4′:4,5]cyclopent[1,2-b]indole (11).—3-(Indol-3-ylmethyl)pyridine-4-carbonitrile (10) (0.2 g) was

* This compound was previously described incorrectly as an ethyl derivative.[1]

boiled with 2N-hydrochloric acid (25 cm^3) for 1 h, and the resulting red solution then basified with dilute ammonium hydroxide. Extraction with chloroform afforded the *tetracycle* (11) as a yellow amorphous solid, 0.17 g (93%), m.p. 225 °C (decomp.); *m/e* 206 (M^+; 100%); $\lambda_{max.}$ 225 (infl.) 245, 256, and 330 nm; $\nu_{max.}$ 3 400 and 1 600 cm^{-1}; δ[$(CD_3)_2$SO] 10.8 (1 H, s, NH), 8.7 (1 H, s, 1-H), 8.6 (1 H, d, *J* 9 Hz, 3-H), *ca.* 7.6 (3 H, m), *ca.* 7.2 (2 H, m), and 3.7 (2 H, s, 10-H_2); δ(DCl), 8.8 (1 H, s, 1-H), 8.75 (1 H, d, *J* 9 Hz, 3-H), 7.9 (1 H, d, *J* 9 Hz, 4-H), 7.6—7.0 (4 H, m, 6-, 7-, 8-, and 9-H), and 3.8 (2 H, s, 10-H_2) (Found: C, 81.4; H, 5.0; N, 13.8. $C_{14}H_{10}N_2$ requires C, 81.5; H, 4.9; N, 13.6%); hydrochloride salt: yellow needles (from EtOH), m.p. >275 °C (Found: C, 69.3; H, 4.5; N, 11.55. $C_{14}H_{11}ClN_2$ requires C, 69.0; H, 4.5; N, 11.4%).

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REFERENCES

[1] Part 5, M. Sainsbury and R. F. Schinazi, *J.C.S. Perkin I*, 1976, 1155.

[2] M. Sainsbury, *Synthesis*, 1977, **7**, 437, and references cited therein.

[3] J.-B. Le Pecq, C. Gosse, N. Dat Xuong, and C. Paoletti, *Cancer Res.*, 1976, **36**, 3067, and references cited therein.

[4] (*a*) J. I. De Graw, J. G. Kennedy, and W. A. Skinner, *J. Heterocyclic Chem.*, 1966, **3**, 67; (*b*) K. N. Kilminster and M. Sainsbury, *J. Chem. Soc.*, 1972, 2264.

[5] A. Ohsawa, M. Hirobe, and T. Okamoto, *J. Pharm. Soc, Japan*, 1972, **92**, 73.

[6] C. W. F. Leung, M. P. Sammes, and A. R. Katritzky, *J.C.S. Perkin I*, 1979, 1698.

[7] R. J. Sundberg, *J. Org. Chem.*, 1968, **33**, 487.