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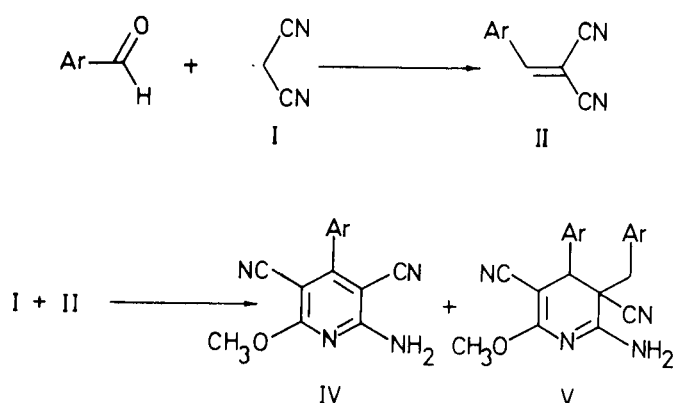
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A synthesis of 2-amino-3-benzyl-3,5-dicyano-6-methoxy-4-phenyl-3,4-dihydropyridines from benzylmalononitriles and benzylidenemalononitrile is described. The structures of the new compounds have been elucidated on the basis of spectral data (ir, nmr, ms), and in two cases (Vb and Ve) by chemical degradation.

J. Heterocyclic Chem., **16**, 273 (1979).

Aryl substituted 2-amino-3,5-dicyano-6-methoxypyridines IV, have been prepared by the reaction, in a methanol-methoxide system, between malononitrile and



II, IV, V:

a, Ar = Phenyl

c, Ar = *p*-Methoxyphenyl

b, Ar = *p*-(*N,N*-Dimethylamino)phenyl

d, Ar = *p*-Chlorophenyl

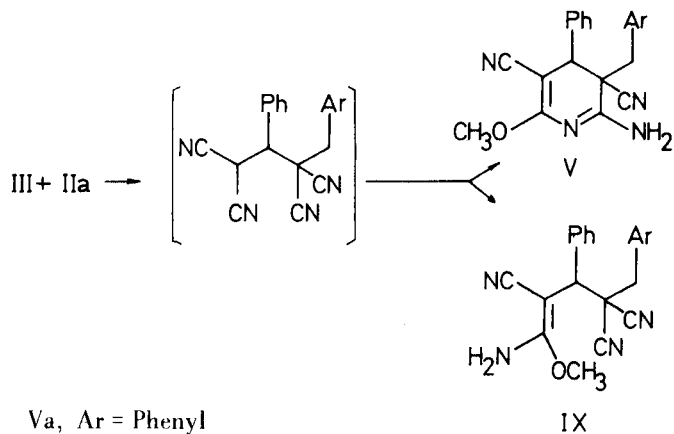
an aldehyde (1) or an alkylidene compound (2). In some cases (3) dihydropyridines V have been isolated as side products, although the relative positions of the amino and methoxy groups have not been determined.

To confirm the structure, a synthesis of type V dihydropyridines with a phenyl group in the four position (Va and Ve-i) has been developed and is described in this paper. Carbon-13 nmr data for Va are indicated as well as the results of the degradation of Vb and Ve.

The synthetic procedure consists of the reaction between benzylmalononitriles (III) and benzylidenemalononitrile in methanol-sodium methoxide.

Benzylmalononitrile (IIIa) can be obtained in three steps from benzaldehyde following the P. B. Russel procedure (4). Benzylmalononitriles IIIb-h can be prepared by either the Neumann method (5,6) or by that reported by Bargain (7), using zinc-potassium borohydride as a reducing agent. We followed the latter procedure, but using sodium borohydride as a reducing agent. The

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Va, Ar = Phenyl

Ve, Ar = *p*-(*N,N*-dimethylamino)phenyl

Vf, Ar = *p*-Chlorophenyl

Vg, Ar = *p*-Methoxyphenyl

Vh, Ar = 2,4-Dimethoxyphenyl

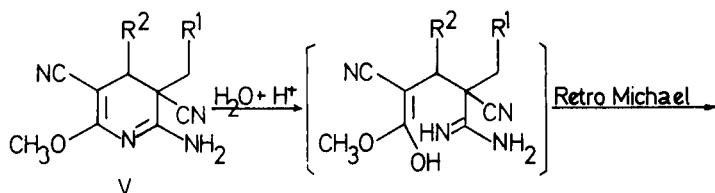
Vi, Ar = *m*-Nitrophenyl

results are outlined in Table 1.

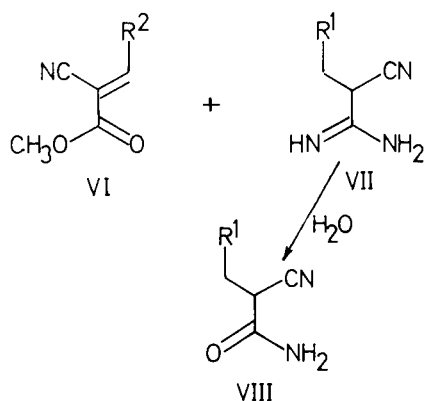
The ¹³C nmr spectrum of Va shows evidence of two cyano groups (see Experimental). Therefore, the possibility of a type IX structure (ring opened with three cyano groups) was discarded.

The degradation of the dihydropyridines was achieved in acid media in the two cases tested. The degradation of Vb which was obtained as a by-product in the preparation of the corresponding pyridine of type IV was achieved with trifluoroacetic acid in wet DMSO, and that of Ve by reaction in ethanol-water with trichloroacetic acid.

The degradative process of the type V compound can be depicted as follows:



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VI

a, R² = *p*-(*N,N*-Dimethylamino)phenyl.b, R² = Phenyl

Chemical degradation of Vb yields methyl *p*-(*N,N*-dimethylamino)benzylidenecyanacetate (VIa). From Ve, methylbenzylidenecyanacetate (VIb) and *p*-(*N,N*-dimethylamino)benzylcyanacetamide (VIII) were isolated.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer or Pye-Unicam Sp 1000 spectrometer. ¹H nmr spectra were recorded on a Varian T-60.A apparatus; ¹³C nmr spectra were recorded on a Bruker HX-90E spectrometer. Mass spectral data were obtained on a Varian Mat mass spectrometer.

Synthesis of Benzylmalononitriles (IIIa-h). General procedure.

To 75 ml. of absolute ethanol, 0.14 g. (3.7 mmoles) of

sodiumborohydride and 0.01 mole of the alkylidene compound were added. The reaction mixture was stirred at 0° for 1 hour, then poured on water and filtered (in some cases the precipitate was formed before the addition of water). The crude products were purified as outlined in Table I. The melting points of the benzylmalononitriles IIIa-f were identical with those reported in the literature; IIIg and IIIh have not been described previously.

2,4-Dimethoxybenzylmalononitrile (IIIg).

This compound had the following data; ir: ν max 3090, 3050, 3020, 2970, 2950, 2920, 2840, 2260, 1615, 1590, 1510, 1475, 1450, 1440, 1425, 1340, 1295, 1285, 1270, 1215, 1190, 1160, 1125, 1045, 1030, 940, 920, 845, 830, 800, 730, 720 cm⁻¹.

Anal. Calcd. for C₁₂H₁₂N₂O₂: C, 66.66; H, 5.59; N, 12.95. Found: C, 66.80; H, 5.34; N, 12.66.

3,4,5-Trimethoxybenzylmalononitrile (IIIh).

This compound had the following data; ir: ν max 3010, 2990, 2960, 2930, 2900, 2250, 1590, 1500, 1465, 1455, 1440, 1420, 1340, 1320, 1245, 1225, 1150, 1120, 1000, 970, 850, 840, 805, 780, 665 cm⁻¹.

Anal. Calcd. for C₁₃H₁₄N₂O₃: C, 63.41; H, 5.73; N, 11.37. Found: C, 63.48; H, 5.69; N, 11.25.

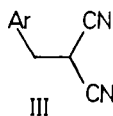
Synthesis of 3-Substituted 2-Amino-3,5-dicyano-6-methoxy-4-phenyl-3,4-dihydropyridines (Va and Ve-i). General procedure.

To a solution of 10 mmoles of sodium in 75 ml. of methanol, 10 mmoles of benzylidenemalononitrile and 10 mmoles of the correspondent benzylmalononitrile were added. The reaction mixture was stirred at 0° for 24 hours, then poured over water or brine. The resulting solid was filtered and washed to neutral pH. Isolation of pure products was performed as follows:

2-Amino-3-benzyl-3,5-dicyano-6-methoxy-4-phenyl-3,4-dihydropyridine (Va).

The reaction mixture was poured on water. The crude product (3.3 g.) was chromatographed on a silica gel column; elution with benzene-ethyl acetate 4:1 gave 1.8 g. (52%) of Va. Recrystallization from methanol afforded pure Va, m.p. 207-208° (3); ¹³C nmr (deuterioacetone): δ 166.2 and 162.3 (C-2 and C-6), 138.7 and 134.4 (C-1 of the two aromatic rings), 131.2,

Table I



Compound	Ar	Formula	M.p. °C	Yield %
IIIa	Ph	C ₁₀ H ₈ N ₂	90 (Ethanol)	79
IIIb	<i>p</i> -(<i>N,N</i> -Dimethylamino)-phenyl	C ₁₂ H ₁₃ N ₃	74-75 (Sublimes)	67
IIIc	<i>p</i> -Methoxyphenyl	C ₁₁ H ₁₀ N ₂	89-90 (Methanol)	49
IIId	<i>p</i> -Chlorophenyl	C ₁₀ H ₇ N ₂ Cl	93 (water)	86
IIIe	<i>p</i> -Nitrophenyl	C ₁₀ H ₇ N ₃ O ₂	153-154 (Ethanol)	87
IIIf	<i>m</i> -Nitrophenyl	C ₁₀ H ₇ N ₃ O ₂	132-133 (Ethanol)	67
IIIg	2,4-Dimethoxyphenyl	C ₁₂ H ₁₂ N ₂ O ₂	102 (Ethanol)	83
IIIh	3,4,6-Trimethoxyphenyl	C ₁₂ H ₁₄ N ₂ O ₃	145-147 (Ethanol)	60

129.4, 129.3 and 128.8 (aromatic carbons), 119.6 and 118.1 (two CN groups), 63.3 and 49.4 (C-5 and C-3), 54.6, 47.3 and 42.3 (CH₃O, C-4 and C₆H₅-CH₂-).

2-Amino-3,5-dicyano-3-*p*-(*N,N*-dimethylaminobenzyl)-6-methoxy-4-phenyl-3,4-dihydropyridine (Ve).

The crude product (3.4 g.) obtained on pouring the reaction mixture on brine was treated with ca 5 ml. of methanol giving a precipitate which weighed 1.4 g. Recrystallization from methanol gave yellow crystals, m.p. 211-212°.

The remaining methanolic solution was concentrated *in vacuo* yielding, after several days, 0.6 g. of crystals of the same product, yield 52%; ir: max 3380, 3240-2500, 2260, 2200, 1670, 1620, 1600, 1570, 1530, 1450, 1435, 1360, 1320, 1295, 1250 1225, 1195, 1150, 1100, 1090, 1060, 1030, 1005, 945, 910, 830, 800, 760, 730, 720, 700, 670 cm⁻¹; nmr (deuterioacetone): δ 2.88 (6H, singlet, N(CH₃)₂), 3.1 and 3.25 (2H, AB system, J = 14 Hz, *p*-(CH₃)₂N-C₆H₄-CH₂), 3.58 (1H, singlet, CH), 3.78 (3H, singlet CH₃O), 6.33-7.33 (10H, aromatics + N-H), 7.33-7.83 (1H, wide band, N-H).

Anal. Calcd. for C₂₃H₂₃N₅O: C, 71.76; H, 6.01; N, 18.17. Found: C, 71.46; H, 6.19; N, 17.91.

2-Amino-3-(*p*-chlorobenzyl)-3,5-dicyano-6-methoxy-4-phenyl-3,4-dihydropyridine (Vf).

The crude product (3.12 g.) obtained on pouring the reaction mixture on brine was treated with toluene to give a crystalline product. Recrystallization from toluene yielded yellow crystals, m.p. 211-212° (65%); ir: ν max 3440, 3360-3320, 3250, 3080-3030, 2950, 2850, 2240, 2200, 1640, 1590, 1545, 1495 1460, 1445, 1410, 1350, 1335, 1300, 1280, 1205, 1160, 1115, 1095, 1030, 1020, 980, 880, 840, 825, 800, 770, 755, 750, 730, 720, 705 cm⁻¹; nmr (deuterioacetone): δ 3.24 and 3.40 (2H, AB system, J = 13 Hz, Cl-C₆H₄-CH₂), 3.65 (1H, singlet, -CH), 3.78 (3H, singlet, CH₃O-), 6.56-7.33 (10H, aromatics + N-H), 7.33-8 (1H, wide band, N-H); ms: m/e 376 (23%, M⁺), 361 (7%, M⁺-CH₃), 251 (88%), 212 (11%), 155 (24%), 125 (100%, *p*-Cl-C₆H₅-CH₂⁺).

Anal. Calcd. for C₂₁H₁₇ClN₄O: C, 66.95; H, 4.51; N, 14.87; Cl, 9.40. Found: C, 66.72; H, 4.33; N, 14.67; Cl, 9.75.

2-Amino-3,5-dicyano-3-(*p*-methoxybenzyl)-6-methoxy-4-phenyl-3,4-dihydropyridine (Vg).

The crude product (3.34 g.) obtained on pouring the reaction mixture on brine was crystallized from methanol to give yellow crystals, m.p. 194-195° (48%); ir: ν max 3410, 3340, 3240, 2970, 2950, 2940, 2840, 2250, 2200, 1660, 1615, 1595, 1555, 1515, 1455, 1350, 1320, 1290, 1250, 1235, 1205, 1185, 1160, 1125, 1025, 1015, 990, 930, 890, 850, 840, 820, 810, 780, 760, 740, 725, 710 cm⁻¹; nmr (deuterioacetone): δ 3.14 and 3.30 (2H, AB system, J = 13 Hz, *p*-CH₃O-C₆H₄-CH₂), 3.56 (1H, singlet, -CH), 3.68 and 3.76 (6H, singlets, two CH₃O-), 6.56-7.33 (10H, aromatics + NH), 7.33-7.83 (1H, wide band, NH); ms: m/e 372 (7%, M⁺), 156 (5%), 121 (100%, *p*-CH₃O-C₆H₄-CH₂⁺), 91 (6%), 77 (7%, C₆H₅⁺).

Anal. Calcd. for C₂₂H₂₀N₄O₂: C, 70.96; H, 5.37; N, 15.05. Found: C, 70.93; H, 5.43; N, 14.74.

2-Amino-3,5-dicyano-3-(2,4-dimethoxybenzyl)-6-methoxy-4-phenyl-3,4-dihydropyridine (Vh).

The crude product (3.3 g.) obtained on pouring the reaction mixture on brine was crystallized from methanol to give 1.4 g. of pure product, m.p. 224-226° (34%); ir: ν max 3440, 3340, 3260, 3000, 2940, 2840, 2250, 2200, 1645, 1610, 1590, 1550, 1505, 1450, 1345, 1325, 1285, 1205, 1165, 1155, 1120,

1025, 980, 935, 875, 835, 810, 780, 750, 730, 710, 700 cm⁻¹; nmr (deuterioacetone): δ 3.28 (2H, singlet, benzylic protons), 3.61 (1H, singlet, -CH), 3.75, 3.76 and 3.80 (9H, CH₃O-), 6.48 and 6.65-7.31 (9H, aromatics + NH), 7.31-7.85 (1H, wide band, NH); ms: m/e 402 (6%, M⁺), 151 (100%, (CH₃O)₂-C₆H₃-CH₂⁺), 91 (11%), 77 (8%, C₆H₅⁺).

Anal. Calcd. for C₂₃H₂₂N₄O₃: C, 68.63; H, 5.51; N, 13.91. Found: C, 68.52; H, 5.52; N, 13.91.

2-Amino-3,5-dicyano-3-(*m*-nitrobenzyl)-6-methoxy-4-phenyl-3,4-dihydropyridine (Vi).

The crude product (2.4 g.) obtained on pouring the reaction mixture on water was chromatographed on a alumina column, benzene elution and crystallization from methanol give 2.2 g. (57%) of pure product, m.p. 195-6°; ir: ν max 3480, 3300, 3160, 2200 1645, 1585, 1535, 1485, 1465, 1355, 1335, 1210, 1155, 1100, 1075, 1040, 1030, 975, 940, 905, 825, 810, 780, 765, 745, 720, 700, 680 cm⁻¹. nmr (deuterioacetone): δ 3.55 (2H, *m*-NO₂-C₆H₄-CH₂), 3.75 (1H, -CH), 3.81 (3H, CH₃O), three signals centered at 7.08, 7.58 and 8.08 (11H, aromatics + NH₂).

Anal. Calcd. for C₂₁H₁₇O₃N₅: C, 65.10; H, 4.42; N, 18.08. Found: C, 65.19; H, 4.28; N, 18.29.

2-Amino-3,5-dicyano-3-(*p*-*N,N*-dimethylaminobenzyl)-4-(*p*-*N,N*-dimethylaminophenyl)-6-methoxy-3,4-dihydropyridine (Vb).

This compound was obtained as a side product in the synthesis of 2-amino-3,4-dicyano-4-(*N,N*-dimethylaminophenyl)-6-methoxy-pyridine (IVb) (3).

Degradation of Vb.

A sample of 0.1 g. of Vb was dissolved in 1 ml. of DMSO and two drops of trifluoroacetic acid were added. After two days at room temperature, orange crystals were formed and identified as methyl *p*-(*N,N*-dimethylamino)benzylidene cyanacetate (VIa), m.p. 119-120°, by comparison with a pure sample; ir: ν max 2960-2760, 2220, 1705, 1610, 1570, 1525, 1440 1405, 1375, 1325, 1275, 1225, 1190, 1145, 1095, 1055, 1000, 940 810, 760 cm⁻¹; ms: m/e 230 (100%, M⁺), 199 (35%, M⁺ - CH₃O), 171 (18%, M⁺ - CO₂CH₃).

Degradation of Ve.

a) Methylbenzylidene cyanacetate (VIb).

To a 40 ml. mixture of water-ethanol, 0.96 g. (2.5 mmoles) of Ve and 1 g. (6.0 mmoles) of trifluoroacetic acid were added. The reaction mixture was stirred at 0° for four days and a crystalline precipitate was then formed. Crystallization from benzene yields 0.3 g. of yellowish-white scales identified as VIb, m.p. 90-91°; ir: ν max 3050, 2960, 2240, 1735, 1610, 1575, 1505, 1455, 1435, 1330, 1275, 1210, 1095, 1005, 970, 845, 790, 770, 690 cm⁻¹.

Anal. Calcd. for C₁₁H₉NO₂: C, 70.59; H, 4.81; N, 7.48. Found: C, 71.08; H, 4.77; N, 7.37.

b) *p*-(*N,N*-Dimethylamino)benzylcyanacetamide (VIII).

The filtrate was basified with 30% sodium hydroxide, extracted with ether and concentrated *in vacuo*. The residue was chromatographed on a silica gel column; elution with benzene-ethyl acetate 7:3 gave the crude product (0.16 g.). Recrystallization from benzene gave the pure product, m.p. 123° identified as VIII; ir: ν max 3430, 3320, 3200, 2920, 2810, 2260, 1670, 1620, 1570, 1530, 1480, 1450, 1415, 1355, 1290, 1225, 1195, 1165, 1130, 1100, 1060, 1030, 950, 820, 780, 750, 715 cm⁻¹; nmr (deuterioacetone): δ 2.83 (6H, N(CH₃)₂), 3.01 and 3.05 (2H, 2 doublet, J_{ab} = 9 Hz and J_{ac} = 6 Hz, diastereotopic protons Hb and Hc), 3.76 (1H, quartet, J_{ab} = 9 Hz and J_{ac} = 6 Hz, hydrogen

Ha), 6.33-7.33 (6H, AB system of the aromatic protons, and protons of group NH₂).

Anal. Calcd. for C₁₂H₁₅N₃O: C, 66.36; H, 6.91; N, 19.35.
Found: C, 66.76; H, 6.74; N, 18.88.

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