magnesium sulfate, and evaporated. The resulting oil appeared to be a mixture of desired acid and ester. The oil was dissolved in chloroform and extracted with sodium carbonate solution. The basic layer was acidified and the resulting oil collected in ether. The ether extracts were combined, dried, and evaporated. Recrystallization of the residue from benzene–Skelly B afforded 1.5 g of **16** (8%), mp 93–95°.

Anal. Calcd for $C_{15}H_{17}NO_5S$: C, 55.71; H, 5.30; N, 4.33. Found: C, 55.96; H, 5.46; N, 4.28.

4,5,6,7-Tetrahydro-2,5-dimethyl-4-oxo-6-benzenesulfonylfuro[2,3-*c*]pyridine (17).—The sodium salt of **16** (8.0 g, 0.025 mole) was prepared as described for **6b**. Treatment of the salt with 19.0 g (0.15 mole) of oxalyl chloride and 13.0 g (0.05 mole) of stannic chloride in 100 ml of benzene under conditions described for the preparation of **7b** gave three layers on work-up. The benzene layer was separated, washed with water, and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silicic acid although tlc indicated only one major component. From Skelly B–ethyl acetate (85:15) was obtained a solid which characterized as the ketone **17** (2.6 g, 34%), mp 127–128° (ethanol). No rearrangement products were isolated.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.72; H, 5.05; N, 5.00.

Ethylenedithioketal of 7b (19).—To a slurry of 9.2 g (0.032 mole) of **7b** in 100 ml of methanol was slowly added 5.2 g (4.7 ml, 0.055 mole) of 1,2-ethanedithiol. The mixture was cooled and 2.5 ml of boron trifluoride etherate added. The slurry was stirred for 15 min in the cold then heated until solution was effected. A solid precipitated on cooling and was washed with cold methanol to give 10.3 g (90%) of **19**, mp 149–151°; nmr ($CDCl_3$) peaks appeared at 2.22 (3 H, 2-CH_3, singlet), 3.62 (2 H, CH_2–N, singlet), 4.11 (2 H, C=C–CH_2–N, singlet), 3.44 (4 H, S–CH_2–CH_2–S, singlet), 6.13 (1 H, 3-H, singlet), and 7.5–8.0 (5 H, aromatic, multiplet).

Anal. Calcd for $C_{16}H_{17}NO_3S_3$: C, 52.29; H, 4.66; N, 3.81; S, 26.18. Found: C, 52.37; H, 4.84; N, 3.81; S, 25.75, 25.89.

Desulfurization of 19. Preparation of 20 and 21.—To a suspension of 50 g of W-4 Raney nickel in 250 ml of dioxane was added a solution of 5.0 g (0.135 mole) of **19** in 50 ml of dioxane. The suspension was refluxed with stirring for 12 hr and the catalyst removed by filtration over Filter Cel. The catalyst was washed with hot dioxane and the filtrate evaporated under reduced pressure. The residue was shown by tlc to consist of two major components and was chromatographed on a silicic acid column. Skelly B–ethyl acetate (9:1) gave 0.384 g of a solid which was shown to be 4,5,6,7-tetrahydro-2-methyl-6-benzenesulfonylfuro[2,3-*c*]pyridine (**20**), mp 103–104° (Skelly B).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.36; H, 5.63; N, 5.04.

Skelly B–ethyl acetate (4:1) eluted 0.275 g of a solid which was shown to be 2-methyl-6-benzenesulfonylperhydrofuro[2,3-*c*]pyridine (**21**), mp 97–98° (Skelly B).

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 60.09; H, 6.76; N, 4.99; S, 11.48.

2-Methyl-4-hydroxyfuro[2,3-*c*]pyridine (22).—Potassium hydroxide (1.0 g, 0.02 mole), **7b** (2.0 g, 0.007 mole), and 50 ml of triethylene glycol were combined and shaken until a solution was effected. Hydrazine hydrate (85%, 4.0 g) was added and the mixture refluxed for 2 hr. The temperature of the mixture was elevated to 190° to remove water. Heating was continued at this temperature for 4 hr and the mixture cooled. Water was added and the resulting mixture extracted with ether. The ether extracts were combined, washed with water, and dried over sodium sulfate. Evaporation afforded a white solid which was recrystallized from chloroform–acetone to give a product which was characterized as **22** (0.35 g, 35%), mp 201–202°; nmr (d_6-DMSO) peaks appeared at 2.5 (3 H, 2-CH_3, singlet), 6.8 (1 H, 3-H, singlet), 8.0 and 8.5 (2 H, 5-H and 7-H, singlets), and 4.2–4.9 (N–H, broad absorption).

Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.74; N, 9.39. Found: C, 64.43; H, 4.74; N, 9.24.

N-Methyl-N-(5-methyl-2-furfuryl)-2-bromoacetamide (23).—A mixture of **8** (5.85 g, 0.047 mole), pyridine (3.7 g, 0.047 mole), and 25 ml of dry benzene was cooled to 5°. Bromoacetyl bromide (9.4 g, 0.047 mole) in 25 ml of dry benzene was added dropwise and the resulting mixture allowed to stir at room temperature for 8 hr. The resulting solid was removed by filtration and washed with benzene. The filtrate was evaporated under reduced pressure and the residue chromatographed on a silicic acid column. Elution with Skelly B–ethyl acetate (85:15) gave a clear yellow oil which resisted efforts at crystallization; nmr ($CDCl_3$) peaks appeared at 2.25 (3 H, 5-CH_3, singlet), 4.43 (Br–CH_2–C=O, singlet), 2.95 (3 H, N–CH_3, chemical-shift doublet), 3.90 (2 H, C=C–CH_2–N, chemical-shift doublet), and 5.90 and 6.10 (2 H, 3-H and 4-H, multiplets).

Anal. Calcd for $C_9H_{12}NO_2Br$: C, 43.92; H, 4.92; N, 5.69; Br, 32.47. Found: C, 44.23; H, 4.91; N, 5.78; Br, 32.16.

Registry No.—**2**, 14668-86-1; **3**, 14668-87-2; N-benzenesulfonyl-N-(5-methyl-2-furfuryl)aminoacetaldehyde diethyl acetal, 14668-88-3; **6b**, 14668-89-4; **7b**, 14668-90-7; **8**, 14668-91-8; **9**, 14668-92-9; methiodide of **11**, 14668-93-0; **12**, 14668-94-1; **15**, 14668-95-2; **16**, 14668-96-3; **17**, 14668-97-4; **19**, 14668-98-5; **20**, 14723-32-1; **21**, 14723-33-2; **22**, 14668-99-6; **23**, 14669-00-2.

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Dimeric Dihydropyridines Derived from 3-Cyanopyridine

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The enamine function of a 3-cyano-1,2-dihydropyridine derivative has been observed to undergo condensation reactions with the isomeric 1,6-dihydropyridine and corresponding pyridinium salt giving the dimeric 3,4′-dihydropyridine derivatives I and II.

Investigations directed toward elucidating the structures and mode of biological action of the coenzymes NAD and NADP have frequently engendered studies on the chemistry of dihydropyridines.[1] On several occasions the facile formation of dimeric reduced pyridines has been encountered in these studies. The various dimers described in the literature have been prepared by reductive dimerization of the corresponding pyridinium salts[2] and by acid-catalyzed dimerization of 1,4-dihydropyridines.[3,4] Sodium borohydride[5] and electrolytic[6] reductions of NAD yield products which are not enzymically reoxidized and it has been suggested

(1) See, for example, papers by (a) K. Wallenfels and coworkers, *Ann.*, **621**, 86, 106, 137, 149, 166, 178, 188, 198, 215 (1959); and (b) P. Karrer and coworkers, *Helv. Chim. Acta*, **19**, 811 (1936); **20**, 72, 418 (1937); **40**, 740, 751 (1957).

(2) (a) K. Wallenfels and M. Gellrich, *Chem. Ber.*, **92**, 1406 (1959); (b) J. N. Burnett and A. L. Underwood, *J. Org. Chem.*, **30**, 1154 (1965).

(3) R. E. Lyle and D. A. Nelson, *ibid.*, **28**, 169 (1963).

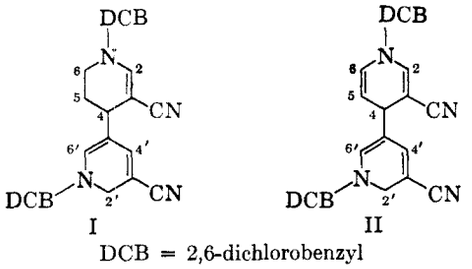
(4) H. L. Ammon and L. H. Jensen, *J. Am. Chem. Soc.*, **88**, 613 (1966).

(5) M. B. Mathews and E. E. Conn, *ibid.*, **75**, 5428 (1953).

(6) B. Ke, *ibid.*, **78**, 3649 (1956); *Arch. Biochem. Biophys.*, **60**, 505 (1956).

that these products may constitute further examples of dimeric dihydropyridines.[1a]

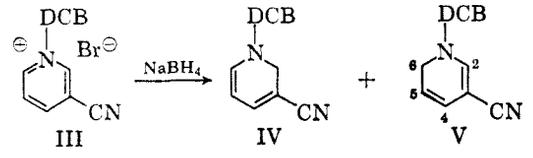
Two members of a new class of dimeric dihydropyridines, based on the 3,4′-bipyridyl system, have recently been prepared in our laboratory. These are compounds I and II, obtained by the condensation of 1-(2,6-dichlorobenzyl)-3-cyano-1,2-dihydropyridine (IV) with its 1,6 isomer V and the pyridinium salt III, respectively. The dihydropyridine precursors of these dimers



I II

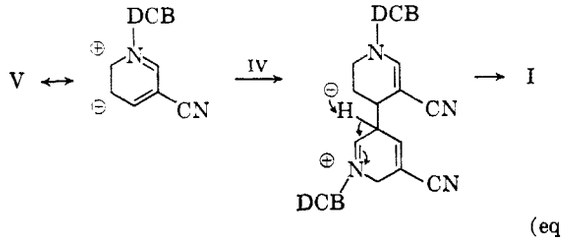
DCB = 2,6-dichlorobenzyl

are obtained by sodium borohydride reduction of the pyridinium bromide III.[1a]



III IV V

The formation of dimer I can be regarded mechanistically as the result of electrophilic attack by (the dipolar form of) dihydropyridine V on the enamine function of dihydropyridine IV (eq 1). The reaction is



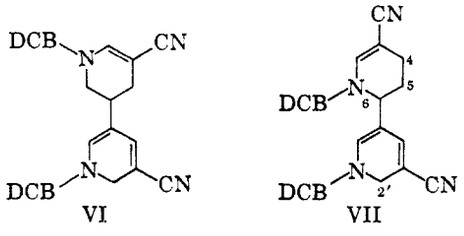
(eq 1)

carried out by prolonged refluxing of a chloroform solution of the two isomers. The intervention of acid catalysis in the dimerization has not been rigorously excluded; however, it was observed that the addition of acetic acid led to a complex mixture of products while the omission of hydroquinone (added to retard oxidation) did not inhibit the formation of the dimer.

This mechanism is essentially identical with that proposed by Schenker and Druey[7] for the base-catalyzed condensation of 1-methyl-3-cyano-1,6-dihydropyridine with phenylacetonitrile.

The structure of dimer I was established primarily by its spectroscopic properties. The mass spectrum shows a molecular ion peak at m/e 528 with the isotope peaks expected for a compound containing four chlorine atoms. The ultraviolet spectrum has absorption maxima at 268 mμ (ε 15,200) and 410 mμ (ε 4000) indicating the presence of vinylogous cyanamide and 3-cyano-1,2-dihydropyridine chromophores (1-methyl-3-cyano-1,4,-5,6-tetrahydropyridine[8] and compound IV have λ_{max} at 278 mμ (ε 18,300) and 403 mμ, respectively). The infrared spectrum establishes the presence of conjugated nitrile (2200 cm^{-1}) and olefin (1630 and 1540 cm^{-1}) groups. The 100-Mc nmr spectrum of the dimer is entirely consistent with structure I although alternative structures are not excluded (*vide infra*). The six aromatic hydrogens appear as a symmetrical A_2B multiplet at 7.27 ppm. A sharp, one-proton singlet at 6.92 is assigned to H_2 and two slightly broader one-proton singlets at 6.41 and 6.27 ppm are assigned to H_4' and H_6'. The two benzylic methylene groups appear as two-proton singlets at 4.48 and 4.36 and the methylene protons H_2' as a two-proton singlet at 3.85 ppm, (the signals at 4.48 and 3.85 show very slight AB splitting attributable to the assymetric center in the molecule). An unresolved three-proton multiplet between 2.8 and 3.0 is assigned to H_4 and H_6 and an unresolved two-proton multiplet between 1.4 and 1.9 ppm to H_5.

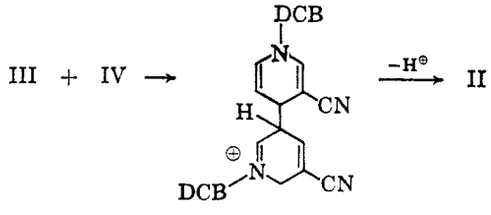
There are two other bipyridyl skeleta capable of incorporating vinylogous cyanamide and 3-cyano-1,2-dihydropyridine chromophores into structures whose nmr spectra can be expected to have three vinyl singlets, namely those of VI and VII. Whereas these structures



VI VII

are less attractive on mechanistic grounds, they are not excluded by the properties of the dimer.

Consideration of the mechanism proposed for the formation of dimer I led to the preparation of a new dimer (II), an alternative synthesis of dimer I, and data permitting the selection of I as its correct structure. If dimer I does in fact arise from electrophilic attack by dihydropyridine V on the enamine function of dihydropyridine IV, then other electrophilic species, such as pyridinium salt III, can reasonably be expected to undergo a similar mode of condensation. This expectation was realized when treatment of a methanolic solution of the dihydropyridine with an aqueous solution of pyridinium salt III afforded a second dimer with structure II, *i.e.*



On catalytic hydrogenation, dimer II was transformed into dimer I, establishing the identity of their skeletons. Its molecular weight was shown by its mass spectrum to be 526. The ultraviolet spectrum has an absorption maximum at 412 mμ and a shoulder at 335 mμ demonstrating the presence of the 3-cyano-1,2-dihydropyridine and 3-cyano-1,4,-dihydropyridine[1a] chromophores, respectively. Conjugated olefinic and nitrile groups are indicated by the infrared spectrum. The characteristic absorptions of the 3-cyano-1,6-dihydropyridine system (λ_{max} 235 and 350 mμ and ν_{max} 1590 and 1650 cm^{-1}) were absent in the spectra of this dimer.

(7) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 2571 (1959).
(8) K. Schenker and J. Druey, *ibid.*, **42**, 1960 (1959).

The nmr spectrum of dimer II shows no absorptions above 3 ppm but has signals for two new vinylic protons. This excludes alternative structure VI for dimer I since it is impossible to generate two new vinylic protons by introducing one new double bond. A C_4–C_5 double bond in structure VII gives two new vinylic protons but in a 3-cyano-1,6-dihydropyridine system. This system is incompatible with the infrared and ultraviolet spectra and with the absence of new nmr signals near 4.7 and 5.0 ppm—the chemical shifts of the protons H_4 and H_5 in compound V.

The spectrum of II again shows a six-proton A_2B system at 7.26 (aromatic) and two-proton singlets at 4.54 (benzylic), 4.35 (benzylic), and 3.87 ppm (H_2'). The protons H_4' and H_6' appear at 6.52 and 6.30 ppm and are coupled with $J \simeq 0.6$ cps. The remaining four protons (H_2, H_4, H_5, and H_6) give well-separated signals but with extensive coupling. The following assignments were unequivocally proven by spin-decoupling experiments. H_2 appears as a doublet at 6.63 ($J_{26} \simeq 0.8$ cps), H_6 as a pair of quartets at 5.94 ($J_{65} = 4.0$, $J_{64} \simeq 0.5$, and $J_{62} \simeq 0.8$ cps), H_5 as a pair of doublets at 4.48 ($J_{56} = 4.0$ and $J_{54} = 2.2$ cps), and, finally, H_4 as a pair of doublets at 3.50 ppm ($J_{45} = 2.2$ and $J_{46} \simeq 0.5$ cps). The chemical shift of H_4 offers further evidence against structure VII (for dimer I) since, if assigned to the methine proton H_5 in the Δ^4 compound, it would be higher than the chemical shift of the methylene protons H_2' (3.87 ppm).

Experimental Section[9]

Dihydropyridines IV and V.[1a]—1-(2,6-Dichlorobenzyl)-3-cyanopyridinium bromide[10] (7.00 g, 0.02 mole) in 160 ml of water was cooled in ice and treated dropwise while stirring with a solution of sodium borohydride (0.80 g, 0.021 mole) and sodium bicarbonate (6 g) in 100 ml of water. The orange precipitate was filtered out, washed with water, and dried giving 5.40 g (100%) of orange powder. This material showed two spots on silica gel thin layer chromatography. The yellow spot, due to the 1,2 isomer IV, showed a λ_{max} at 403 mμ when transferred to an ultraviolet cell and shaken with ethanol. The colorless spot is due to the 1,6 isomer V. The compounds were not amenable to large-scale chromatographic separation but crystals of pure, nearly colorless V were obtained by five recrystallizations of the mixture from ethanol. Pure V has mp 146–152° dec; ultraviolet bands are at λ_{max}^{EtOH} 235 mμ (ε 6600) and 350 mμ (ε 6300); infrared bands are at ν_{max}^{Nujol} 2200, 1650 and 1590 cm^{-1}; nmr signals (60 Mc) are at 4.07 (2 H, quartet, H_6), 4.42 (2 H, singlet, benzylic H), 4.70 (1 H, multiplet, H_4), 5.0 (1 H, multiplet, H_5), 6.76 (1 H, singlet, H_2), and 7.30 ppm (3 H, multiplet, aromatic H).

Dimer I.—The crude dihydropyridine mixture (1.50 g) was refluxed in 10 ml of absolute chloroform with a trace of hydroquinone under nitrogen for 4 days. The solution was chromatographed on alumina (30 g) packed in hexane. The yellow band was eluted with chloroform–ethyl acetate (10:1) and recrystallized from ethanol to give 0.65 g (44%) of fine yellow needles: mp 175–183° dec; $\lambda_{max}^{CH_2Cl_2}$ 268 mμ (ε 15,200) and 410 mμ (ε 4000); ν_{max}^{Nujol} 2200, 1630, and 1540 cm^{-1}; mol wt 528 (mass spectrum). The product was homogeneous on silica gel thin layer chromatography.

Anal. Calcd for $C_{26}H_{20}N_4Cl_4$: C, 58.88; H, 3.80; N, 10.57; Cl, 26.71. Found: C, 58.72; H, 3.92; N, 10.70; Cl, 26.76.

Dimer II.—A hot solution of the dihydropyridine mixture (260 mg, 1 mmole) in 6 ml of methanol was added all at once to a hot solution of the pyridinium salt III (340 mg, 1 mmole) and sodium bicarbonate (100 mg) in 5 ml of water. The resulting solution was kept at 50° for 1 hr, then cooled. The crude product (140 mg, 27%) was filtered out and recrystallized from methylene chloride–ethanol to give 90 mg of fine yellow needles: mp 165–180° dec; $\lambda_{max}^{CH_2Cl_2}$ 300 mμ (ε 7200), 335 (shoulder, 5000), and 412 (6450); ν_{max}^{Nujol} 2200, 1675, 1645, 1600, and 1545 cm^{-1}; mol wt 526 (mass spectrum). This product was also homogeneous on silica gel thin layer chromatography. The R_f value is different (higher) from that of dimer I.

Anal. Calcd for $C_{26}H_{18}N_4Cl_4$: C, 59.11; H, 3.43; N, 10.61; Cl, 26.84. Found: C, 59.13; H, 3.39; N, 10.47; Cl, 27.01.

Dimer I from Dimer II.—A solution of dimer II (100 mg) and 1 drop of acetic acid in 20 ml of tetrahydrofuran was stirred with platinum oxide (50 mg) under hydrogen for 24 hr. The catalyst was filtered out and the solvent evaporated. The crude product was filtered through alumina with chloroform and recrystallized from ethanol to give a sample of dimer I, identical in all respects (melting point, infrared spectroscopy, tlc) with that obtained previously.

Registry No.—I, 15042-73-6; II, 15042-74-7; IV, 15042-75-8; V, 15042-76-9.

Acknowledgments.—The author wishes to thank Dr. Richard Newmark for the 100-Mc nmr spin-decoupling experiments.

(9) Melting points are uncorrected. Nmr spectra were recorded on Varian HA-100 and A-60 instruments using deuteriochloroform as solvent and tetramethylsilane as internal standard. Infrared, ultraviolet, and mass spectra were measured on Perkin-Elmer 137, Cary 14, and CEC 21-103 instruments, respectively. Analyses were carried out by Galbraith Laboratories Inc., Knoxville, Tenn.

(10) F. Krohnke, K. Ellegast, and E. Bertram, *Ann.*, **600**, 176 (1956).