A Convenient Synthetic Route to 5,5'-Disubstituted 2,2'-Bipyridines

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Syntheses are described for a number of 5,5'-disubstituted 2,2'-bipyridines. In particular the benzidine analogue, [2,2'-bipyridine]-5,5'-diamine and some of its derivatives have been prepared.

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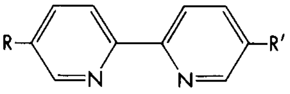
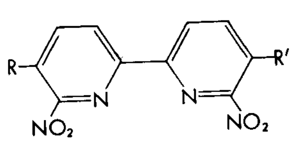
Synthetic and naturally occurring derivatives of 2,2'-bipyridine are of interest for the variety of biological activities which they exhibit (2-5). For many derivatives, biological activity (4), redox potential (4) or chelating ability (6) has been shown to be related to the ability of the biaryl ring to adopt a coplanar configuration. Thus, substituents which offer steric hindrance to coplanarity (4,7) are known to cause a loss of or reduction of biological activity (4) or chelating ability (6). This is particularly true for the bipyridinium herbicides diquat and paraquat, where partially reduced planar free radical structures have been proposed for the biologically active species (4). In connection with a study of the biological activity of 2,2'-bipyridines we required a range of 5,5'-disubstituted derivatives. In these compounds the substituents are *para* to the biaryl bond and might be expected to influence trans annular conjugation and subsequently the stability of planar free radicals generated from the quaternary salts.



1 R = R' = CH_3
2 R = R' = CO_2H
3 R = R' = $CO_2CH_2CH_3$
4 R = R' = CH_2OH
5 R = R' = $CONH_2$
6 R = $CO_2CH_2CH_3$, R' = $CONH_2$
7 R = R' = $CONHNH_2$
8 R = R' = CN
9 R = R' = NH_2
10 R = R' = CON_3
11 R = R' = $NHCO_2CH_2CH_3$
12 R = R' = $NHCOCH_3$
13 R = R' = $N(CH_3)_2$
14 R = R' = Br



15 R = R' = $NHCO_2CH_2CH_3$
16 R = R' = NH_2

Although many substituted 2,2'-bipyridines have been described, those bearing β substituents are usually less readily obtained, and few simple 5,5'-disubstituted 2,2'-bipyridines have been reported. 2,2'-Bipyridines substituted in the α and γ positions of the pyridine ring are easily prepared from 2,2'-bipyridine itself. For example, 2,2'-bipyridine can be *N*-oxidised and nitrated to obtain intermediates from which many 4-substituted (8) and 4,4'-disubstituted derivatives (9,10) can be synthesised. 6-Substituted (11,12) and 6,6'-disubstituted 2,2'-bipyridines (11,13-15) can be prepared by direct substitution of the 2,2'-bipyridine ring system. However, the β positions of 2,2'-bipyridine are unreactive toward electrophilic attack and while sulfonation (16) and bromination (17) have been shown to proceed under vigorous conditions nitration has been reported as unsuccessful (15). Ullmann reactions with 5-substituted 2-halopyridines have been used to synthesise several 5,5'-disubstituted 2,2'-bipyridines (18-20) but the yields are usually poor and the 2-halopyridines are often not readily obtained. Fortunately 5,5'-dialkyl-2,2'-bipyridines can be obtained in high yield by the reaction of β-alkylpyridines in the presence of a degassed Raney nickel catalyst (21,22) and thus 5,5'-dimethyl-2,2'-bipyridine (**1**), prepared from the readily obtainable β-picoline, is a convenient starting material for the preparation of other 5,5'-disubstituted derivatives.

In the present work oxidation of **1** with potassium permanganate, followed by esterification of the diacid **2** with ethanol and sulfuric acid, as described by Case (18), provided diethyl [2,2'-bipyridine]-5,5'-dicarboxylate (**3**) in good yield. This compound can also be prepared directly from ethyl nicotinate (21,22), nevertheless for large scale preparations (20-60 g.), the method of Case (18) is superior. The diester **3** was reduced with lithium aluminum hydride to obtain the 5,5′-bis(hydroxymethyl) derivative **4** and reaction of **3** with amines provided amides. For example [2,2′-bipyridine]-5,5′-dicarboxamide (**5**) is readily prepared from **3** by reaction with ammonia in a mixture of ethylene glycol and ethanol in a sealed tube. The use of ethanol alone as a solvent for this reaction resulted in the formation of the half amide **6**, an unsymmetrically substituted 2,2′-bipyridine. On the other hand, a reaction with hydrazine hydrate proceeded smoothly in ethanol to give the 5,5′-dicarbohydrazide **7**.

Although the dicarboxamide **5** and the dicarbohydrazide **7** proved to be relatively inert (probably because of the low solubilities of these materials) the diamide could be converted to the dicyano compound, [2,2′-bipyridine]-5,5′-dicarbonitrile (**8**) in fair yield. An attempted synthesis of [2,2′-bipyridine]-5,5′-diamine (**9**) by a Hofmann reaction on the diamide was unsuccessful. In 1931 Räth (23) unsuccessfully attempted the preparation of **9** by a benzidine rearrangement of 3,3′-hydrazopyridine. Although 2,2′-hydrazopyridine also failed to undergo a benzidine rearrangement, Beyer found that the rearrangement of 2-phenylhydrazinopyridine to 2-amino-5-[*p*-aminophenyl]-pyridine could be accomplished in poor yield (24). The latter result prompted a re-examination of the earlier work by Räth and with a similar lack of success. More recently **9** has been synthesised by reduction of 5,5′-dinitro-2,2′-bipyridine (19), however, the latter compound was obtained in poor yield and the overall yield of the diamine **9** was less than 9%. In the present work the diamine was successfully synthesised in 62% yield from the 5,5′-dicarbohydrazide **7** by a Curtius reaction. The preparation of the intermediate 5,5′-dicarbazide **10** was not possible under the conditions usually employed for such reactions (25) due to the insolubility of the starting material. The reaction was successful when the 5,5′-dicarbohydrazide was suspended in concentrated hydrochloric acid and treated with sodium nitrite solution. The 5,5′-dicarbazide **10**, soluble in concentrated hydrochloric acid, was precipitated as the free base by dilution with water. Conversion of the diazide to 5,5′-di(ethoxycarbonylamino)-2,2′-bipyridine (**11**) proceeded readily and subsequent hydrolysis of the diurethane with sodium hydroxide or hydrochloric acid afforded [2,2′-bipyridine]-5,5′-diamine (**9**) as the free base or the dihydrochloride respectively. The overall yield of diamine from the diester **3** was 61%. Acetylation of the diamine provided the diacetyl derivative **12** and methylation with formic acid/formaldehyde afforded the bis(dimethylamino) compound **13**. A Sandmeyer reaction gave 5,5′-dibromo-2,2′-bipyridine (**14**). In these respects the diamine behaved normally although diazotisation and hydrolysis failed to provide the 5,5′-dihydroxy compound described by Sadykov, *et al.*, (16).

The diurethane **11** proved to be a useful intermediate for the further substitution of the 2,2′-bipyridine system. Nitration of the diurethane with fuming nitric acid provided a good yield of the dinitro derivative, 5,5′-di(ethoxycarbonylamino)-6,6′-dinitro-2,2′-bipyridine (**15**). By analogy, substitution in the 2-position has been shown to occur in the nitration of 3-ethoxycarbonylaminopyridine (26). Hydrolysis of **15** gave 6,6′-dinitro-[2,2′-bipyridine]-5,5′-diamine (**16**).

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Pmr spectra were recorded with a Varian A60 spectrometer (TMS as internal standard). Infra red spectra were obtained on a Perkin-Elmer Model 457 Spectrometer. Mass spectra were measured using an MS-902 Mass Spectrometer with an 'on-line' Raytheon 706 computer. Microanalyses were carried out by the Australian Microanalytical Service, CSIRO, Melbourne.

Diethyl [2,2′-Bipyridine]-5,5′-dicarboxylate (**3**).

5,5′-Dimethyl-2,2′-bipyridine (22) (20 g.) was oxidised with potassium permanganate (110 g.) by the method of Case (18). The crude acid **2** was precipitated from the filtered reaction mixture by addition of hydrochloric acid, separated from the aqueous phase by centrifugation and dried in a desiccator. The [2,2′-bipyridine]-5,5′-dicarboxylic acid (*ca.*, 25 g.), ethanol (380 ml.) and concentrated sulfuric acid (95 g.) were heated under reflux for 18 hours. The reaction mixture was poured into water (1000 ml.) and the precipitate removed by filtration. The product was recrystallised from ethanol to obtain 20.8 g. (62%) of **3**, m.p. 145-146° (lit. (21), 148-149°), identical with a sample prepared from ethyl nicotinate (22).

5,5′-Bis(hydroxymethyl)-2,2′-bipyridine (**4**).

A mixture of **3** (0.5 g.), lithium aluminum hydride (0.2 g.) and anhydrous ether (25 ml.) was stirred for 12 hours at room temperature. Water (50 ml.) was added cautiously to the reaction mixture, which was then filtered and continuously extracted with ether for 6 hours. The colorless crystalline material obtained from the dried ethereal extract was recrystallised from acetone/light petroleum to obtain 0.2 g. (56%) of **4**, m.p. 158-161°. Further purification by sublimation (0.2 mm/175°) provided a sample m.p. 160-162°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.6; N, 13.0. Found: C, 66.9; H, 5.8; N, 12.5.

[2,2′-Bipyridine]-5,5′-dicarboxamide (**5**).

A mixture of **3** (0.5 g.), ethanol (25 ml.) and ethylene glycol (25 ml.) was saturated with ammonia and heated in a sealed tube at 90° for 40 hours. The insoluble product was collected and washed with boiling ethanol followed by hot ethylene glycol. The diamide **5** was obtained as fine colorless crystals (0.4 g., 100%), m.p. $>$ 310°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.5; H, 4.2; N, 23.1. Found: C, 59.2; H, 4.3; N, 22.9.

Ethyl 5′-Carbamoyl-[2,2′-bipyridine]-5-carboxylate (**6**).

A mixture of **3** (0.5 g.) and ethanol saturated with ammonia (10 ml.) was heated at 90° in a sealed tube for 65 hours. The solvent was removed by evaporation and the residue was recrystallised several times from ethylene glycol to obtain 0.25 g. (55%) of **6** as colorless fine crystals, m.p. 264-266°.

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 62.0; H, 4.8; N, 15.5. Found: C, 61.7; H, 4.8; N, 15.4.

[2,2'-Bipyridine]-5,5'-dicarbonitrile (**8**).

An intimate mixture of **5** (0.1 g.) and phosphorus pentoxide (0.25 g.) was heated in a sublimator at 300° *in vacuo* until sublimation had ceased. The product was purified by resublimation to obtain colorless [2,2'-bipyridine]-5,5'-dicarbonitrile (**8**), (0.05 g., 59%) as colorless crystals, m.p. 269-271° (lit. (16), 272-273°); ir (Nujol): 2240 cm^{-1} (C≡N); ms: m/e (M$^{+\cdot}$), Calcd. for $C_{12}H_6N_4$: 206.05925. Found: 206.05999.

5,5'-Di(ethoxycarbonylamino)-2,2'-bipyridine (**11**).

A mixture of **3** (10 g.), hydrazine hydrate (51 ml.) and ethanol (51 ml.) was heated under reflux on an oil bath at 115° for 3 hours. The creamy insoluble product was removed by filtration and washed with boiling ethanol to obtain 9.0 g. (98%) of [2,2'-bipyridine]-5,5'-dicarbohydrazide (**7**), m.p. > 360°, insoluble in acid, base and organic solvents. The finely powdered dihydrazide **7** (9.0 g.) was suspended in concentrated hydrochloric acid (180 ml.) and the mixture was cooled to 0°. A cold solution of sodium nitrite (5.34 g.) in water (40 ml.) was added dropwise with stirring, keeping the temperature below 10°. The suspended hydrazide slowly reacted and dissolved. The clear or slightly cloudy solution was diluted with water to precipitate the diazide **10**, which was collected and washed with water and hot ethanol. [2,2'-Bipyridine]-5,5'-dicarbazide (8.5 g., 88%), m.p. > 360°, was obtained as a colorless powder, soluble in concentrated hydrochloric acid and insoluble in dilute acid and organic solvents. The infra red spectrum (Nujol) showed absorption in the region 2140-2180 cm^{-1} ($-N_3$).

The diazide **10** (8.5 g.) was suspended in a mixture of ethanol (250 ml.) and xylene (250 ml.) and heated under reflux. After 6 hours the suspended material had all dissolved. After 9 hours the solution was allowed to cool and the crystalline product was collected and recrystallised from ethanol to give 9.0 g. (95.5%) of 5,5'-di(ethoxycarbonylamino)-2,2'-bipyridine (**11**) as colorless crystals, m.p. > 300°; uv λ max in nm (ethanol): (log ε) 275 (4.3), 315 (4.43) and 271 infl. (4.3); uv λ max in nm (*p*H 1.15): 287 and 347.6; uv λ max in nm (*p*H 10.8): 267.5 and 311; ir (Nujol): 3302 cm^{-1} (NH), 1735 cm^{-1} and 1706 cm^{-1} (C=O); H^1 nmr (d_6-DMSO): 1.25 δ (CH_3, t), 4.11 δ (CH_2, q), 7.97 δ (ArH, m), 8.57 δ (ArH, d), 9.75 δ (NH, s); ms: m/e (M$^{+\cdot}$) 330.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.2; H, 5.5; N, 17.0; O, 19.4. Found: C, 58.4; H, 5.4; N, 17.0; O, 19.6.

[2,2'-Bipyridine]-5,5'-diamine (**9**).

a. By Alkaline Hydrolysis of **11**.

A mixture of **11** (1.0 g.), ethanol (15 ml.) and 2.5 *N* sodium hydroxide solution (15 ml.) was stirred at 70-80° for 24 hours. The mixture was cooled and the product was collected and recrystallised from water containing a few drops of concentrated ammonium hydroxide. [2,2'-Bipyridine]-5,5'-diamine (**9**)(0.5 g., 74%) was obtained as a dihydrate, colorless needles, m.p. 205-206° (with evolution of water at about 100°). After drying at 150°/25mm the product was obtained as an off-white powder, m.p. 205-206° (lit. (19), 208-210°); ms: m/e (M$^{+\cdot}$) 186; uv λ max in nm (ethanol): (log ε) 287 (4.30) and 328 (4.33); uv λ max in nm (*p*H 1): (log ε) 292 (4.21) and 361 (4.20); uv λ max in nm (*p*H 11): (log ε) 278 (4.24) and 318 (4.29); uv λ max in nm (*p*H 3.7): (log ε) 301 (4.30) and 370.5 (4.17). The p*K*a (measured potentiometrically) for the monoprotonated base was 5.85. The second p*K*a was found to be below 2.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.2; H, 5.4; N, 29.9.

b. Dihydrochloride of **9** by Acid Hydrolysis of **11**.

A mixture of **11** (1.0 g.) and concentrated hydrochloric acid (75 ml.) was gently heated under reflux for 24 hours. During this time the diurethane **11** dissolved and a bright yellow solution was obtained. The solution was allowed to cool and 0.75 g. (95.6%) of the dihydrochloride of **9** separated as golden crystals, m.p. 290-293°. This product was identical with that obtained by treating the diamine with concentrated hydrochloric acid.

Anal. Calcd. for $C_{10}H_{10}N_4 \cdot 2HCl$: Cl, 27.4. Found: Cl, 27.2.

5,5'-Di(acetamido)-2,2'-bipyridine (**12**).

The diamine **9** (0.55 g.) was treated with acetic anhydride (2 ml.). An immediate exothermic reaction occurred. Excess acetic anhydride was removed and the product (0.65 g., 97%) was washed with benzene-petroleum ether. A small sample was purified by sublimation to obtain **12** as colorless crystals, m.p. 326-327° (lit. (19), 331-333°); ms: m/e (M$^{+\cdot}$), Calcd. for $C_{14}H_{14}N_4O_2$: 270.11168. Found: 270.11245.

5,5'-Bis(*N*,*N*-dimethylamino)-2,2'-bipyridine (**13**).

A mixture of **9** (0.5 g.), formic acid (5 ml., 90%) and formaldehyde (15 ml., 36%) was heated under reflux for 20 hours. Excess formaldehyde was removed by steam distillation and the reaction mixture was then basified with 10% sodium hydroxide solution. The product was removed by filtration and purified by sublimation. 5,5'-Bis(*N*,*N*-dimethylamino)-2,2'-bipyridine (**13**) (0.5 g., 92%) was obtained as yellow crystals, m.p. 228-230°.

Anal. Calcd. for $C_{14}H_{18}N_4$: C, 69.4; H, 7.5; N, 23.1. Found: C, 69.3; H, 7.4; N, 22.8.

5,5'-Dibromo-2,2'-bipyridine (**14**).

A stirred solution of **9** (0.22 g.) in hydrobromic acid (5 ml., 48%) was cooled below -10° and treated dropwise with a cold solution of sodium nitrite (0.14 g.) in water (2 ml.) keeping the temperature below -10°. The cold reaction mixture was poured into a solution of freshly prepared cuprous bromide (0.29 g.) in hydrobromic acid (10 ml., 48%) and warmed with stirring to 40° for 15 minutes. After this time effervescence had ceased and 0.880 ammonium hydroxide was added slowly to obtain a deep blue basic solution which was extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated to obtain a crystalline residue. This material was recrystallised from ethanol to obtain 5,5'-dibromo-2,2'-bipyridine (**14**) (0.07 g., 22%) as colorless crystals, m.p. 222-224° (lit. (17,18) 224-225°); ms: m/e (M$^{+\cdot}$), Calcd. for $C_{10}H_6Br_2N_2$: 311.88976. Found: 311.88932.

5,5'-Di(ethoxycarbonylamino)-6,6'-dinitro-2,2'-bipyridine (**15**).

The diurethane **11** (0.5 g.) was treated with a mixture of concentrated sulfuric acid (1.0 ml.) and fuming nitric acid (1.0 ml.) for 15 minutes on a steam bath. An exothermic reaction occurred. The dark orange viscous reaction mixture was poured onto ice and the yellow insoluble product was collected and washed with water followed by ethanol. 5,5'-Di(ethoxycarbonylamino)-6,6'-dinitro-2,2'-bipyridine (**15**) (0.5 g., 79%) was obtained pure as a yellow powder, m.p. 277-279°, sparingly soluble in

DMSO, insoluble in most other solvents, soluble in 2.5 *N* sodium hydroxide/DMSO to give a red solution.

Anal. Calcd. for $C_{16}H_{16}N_6O_8$: C, 45.7; H, 3.8; N, 20.0. Found: C, 45.4; H, 3.7; N, 20.0.

6,6′-Dinitro-[2,2′-bipyridine]-5,5′-diamine (**16**).

A solution of **15** (0.1 g.) in 2.5 *N* sodium hydroxide solution (2 ml.) and DMSO (1 ml.) was allowed to stand at 45-50° for 24 hours. Water (10 ml.) was added to the reaction mixture and the orange product collected by filtration and recrystallised from ethylene glycol/ethanol. 6,6′-Dinitro-[2,2′-bipyridine]-5,5′-diamine (**16**) (0.05 g., 76%) was obtained as fine orange crystals, m.p. > 300°; ms: m/e ($M^{+\bullet}$), Calcd. for $C_{10}H_8N_6O_4$: 276.0607. Found: 276.0610.

REFERENCES AND NOTES

(1) Present address: Division of Entomology, CSIRO, Canberra, A. C. T. 2601, Australia.

(2) A. Funk and P. V. Divekar, *Can. J. Microbiol.*, 5, 317 (1959); P. V. Divekar, G. Read and L. C. Vining, *Can. J. Chem.*, 45, 1215 (1967).

(3) K. V. Rao, K. Biemann and R. B. Woodward, *J. Am. Chem. Soc.*, **85**, 2532 (1963).

(4) A. Calderbank in "Advances in Pest Control Research," Vol. 8, R. L. Metcalf, Ed., John Wiley and Sons, Inc., New York, N. Y., 1968, p. 127.

(5) The Australian National University, British Patent 956,242; *Chem. Abstr.*, **61**, 10541 (1964); Belgium Patent 617,989; *Chem. Abstr.*, 59, 11531 (1963); British Patent 958,132; *Chem. Abstr.*, 61, 8141 (1964).

(6) W. W. Brandt, F. P. Dwyer and E. C. Gyarfas, *Chem. Rev.*, **54**, 959 (1954).

(7) D. Aziz and J. G. Breckenridge, *Can. J. Res.*, **28**, 26 (1950).

(8) R. A. Jones, B. D. Roney, W. H. F. Sasse and K. O. Wade, *J. Chem. Soc. (B)*, 106 (1967).

(9) J. Haginiwa, *J. Pharm. Soc. Japan*, **75**, 731 (1955).

(10) G. Maerker and F. H. Case, *J. Am. Chem. Soc.*, **80**, 2745 (1958).

(11) F. H. Burstall, *J. Chem. Soc.*, 1662 (1938).

(12) F. H. Case, *J. Org. Chem.*, **31**, 2398 (1966).

(13) T. A. Geissman, M. J. Schlatter, I. D. Webb and J. D. Roberts, *ibid.*, **11**, 741 (1946).

(14) I. Murase, *Nippon Kagaku Zasshi*, **77**, 682 (1956).

(15) H. D. T. Willink and J. P. Wibaut, *Rec. Trav. Chim.*, **54**, 275 (1935).

(16) O. S. Otroshchenko, Yu. V. Kurbatov and A. S. Sadykov, *Nauchn. Tr., Tashk. Gos. Univ.*, **263**, 27 (1964); *ibid.*, **263**, 36 (1964).

(17) Yu. V. Kurbatov, V. K. Kiryukhin, O. S. Otroshchenko and A. S. Sadykov, *ibid.*, **286**, 92 (1966).

(18) F. H. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).

(19) K. Kurita and R. L. Williams, *J. Polym. Sci., Polym. Chem. Ed.*, **11**, 3125 (1973).

(20) Z. Talik and E. Plażek, *Rocz. Chem.*, **34**, 165 (1960).

(21) G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, 616 (1956).

(22) W. H. F. Sasse and C. P. Whittle, *ibid.*, 1347 (1961).

(23) A. Binz and C. Räth, *Ann. Chem.*, **486**, 95 (1931).

(24) H. Beyer, H-J. Haase and W. Wildgrube, *Chem. Ber.*, **91**, 247 (1958).

(25) P. A. S. Smith in "Organic Reactions," Vol. 3, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337.

(26) J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 442 (1957).