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# A NEW SYNTHESIS OF 4,4'-DIHYDROXYDIPHENYL(2-PYRIDYL)METHANE

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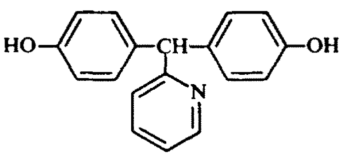
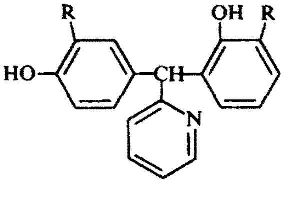
**Abstract**—Condensing phenol with pyridine-2-aldehyde has been shown to give 4,4'-dihydroxydiphenyl(2-pyridyl)methane (I) together with 24–29% of its isomer 2,4'-dihydroxydiphenyl(2-pyridyl)methane (II). Repeated crystallizations of the mixture, required to obtain I free from II, caused the yield of I to fall to scarcely 25%, based on pyridine-2-aldehyde. To prevent or reduce formation of *ortho* condensation products, pyridine-2-aldehyde was made to react with phenols halo substituted in both or in a single *ortho* position. Reductive dehalogenation of the compounds thus obtained gave I in 65–70% yield.

4,4'-DIHYDROXYDIPHENYL(2-PYRIDYL)METHANE (I) is known as an important intermediate in preparing laxatives like 4,4'-diacetoxydiphenyl(2-pyridyl)methane (bisacodyl),[1] and 4,4'-(2-picolylidene)-bis-phenylsulphuric acid disodium salt (sodium picosulphate).[2] Although the literature reports many methods for the synthesis of I,[3] the majority are clearly unsatisfactory, except for the one which involves condensing phenol with pyridine-2-aldehyde.[3a]

On repeating this last reaction, we found that two isomers always form in unequal amounts, and may be separated and obtained pure (Experimental). These compounds were identified as I and 2,4'-dihydroxydiphenyl(2-pyridyl)methane (II).



I



II: R = H
IX: R = Cl
X: R = Br

The more abundant isomer has properties similar to those reported for I. Furthermore, its consistency with structure I was confirmed by IR and PMR spectra (Fig. 1). A strong absorption band occurs around 830 cm$^{-1}$ which should be attributed to the out-of-plane deformations of the four groups of two adjacent hydrogens on *para* substituted benzenes, while a band appears at 763 cm$^{-1}$ which is due to the four adjacent hydrogens on the α-substituted pyridine ring. The PMR spectrum furnished critical structural evidence: a sharp singlet occurs at 5·45 δ which should be ascribed to the methine hydrogen, while the aromatic proton resonances appear as two doublets centered at 6·71 and 7·01 δ, thus clearly confirming the *para* substitution of both benzene rings.

The less abundant isomer shows a lower m.p. and a higher thin layer $R_f$ value. Two bands can be observed in its IR spectrum at 835 and 804 $cm^{-1}$ which, for their position and intensity, are indicative of a *para* substituted benzene, while another absorption band attributable to an *ortho* substituted benzene occurs at 756 $cm^{-1}$, very close to the absorption of the pyridine hydrogens (764 $cm^{-1}$). The PMR spectrum (Fig. 2) shows that the methine proton is deshielded to 5·75 δ, thus suggesting the presence of an *ortho* OH group. The aromatic pattern is rather complex, but the occurrence of two doublets centered at 6·70 and 7·02 δ can be observed, and these are also consistent with a *para* substituted benzene. A complex absorption with maximum peak at 6·87 δ is superimposed on these signals, and this does not contrast with an *ortho* substituted benzene.

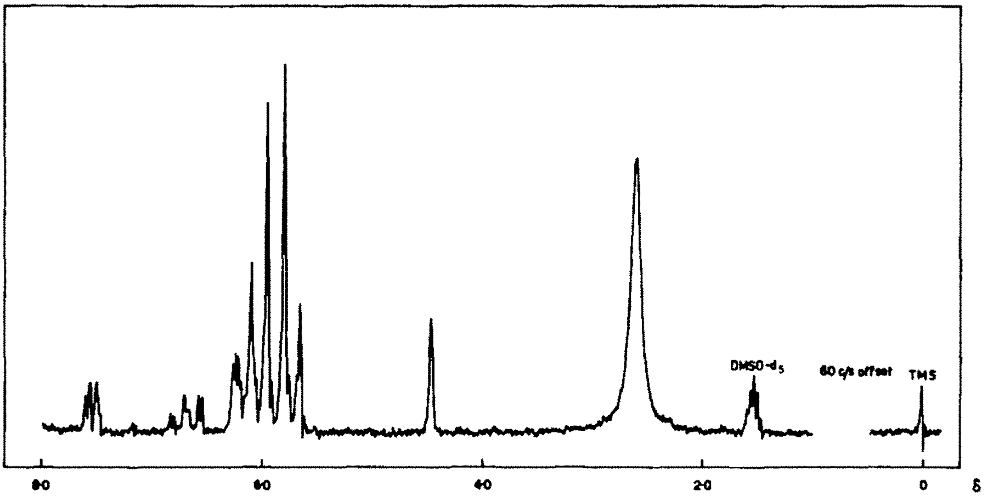


FIG. 1 PMR spectrum of 4,4'-dihydroxydiphenyl(2-pyridyl)methane (I).

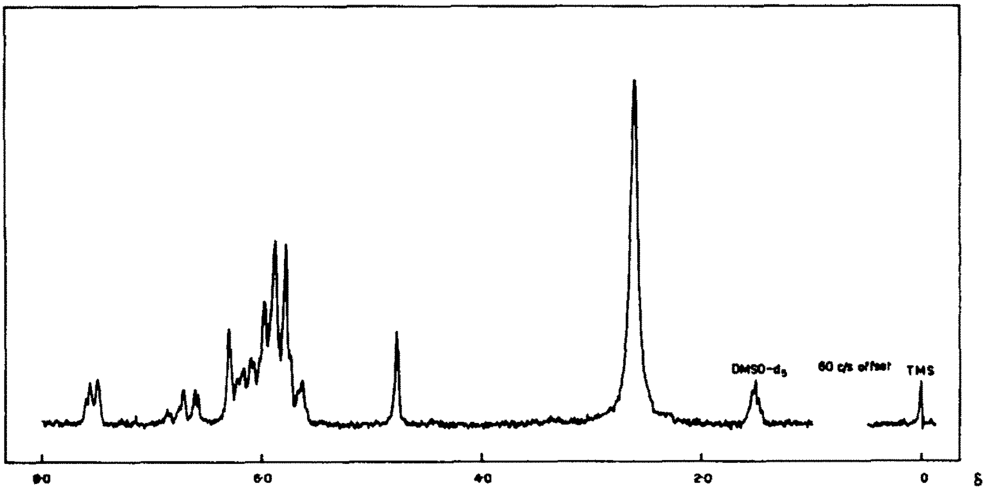
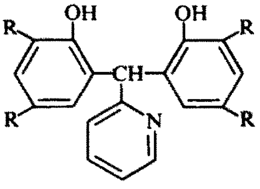


FIG. 2 PMR spectrum of 2,4'-dihydroxydiphenyl(2-pyridyl)methane (II).

On the basis of the above results, structure II could be reasonably attributed to the secondary product which forms in condensing phenol with pyridine-2-aldehyde. Nevertheless, we wanted to unquestionably confirm this assignment by indirect route, synthesizing 2,2'-dihydroxydiphenyl(2-pyridyl)methane (III), the third isomer possible in this condensation. To obtain III, we utilized a procedure which would exclude *a priori* formation of other isomers and would be in itself demonstrative of this structure. That is, we reacted pyridine-2-aldehyde with a phenol 2,4-disubstituted with halogens, which could then be easily eliminated after condensation. Thus, 2,2'-dihydroxy-3,3',5,5'-tetrachlorodiphenyl(2-pyridyl)methane (IV) was obtained from 2,4-dichlorophenol and was, in turn, reductively dechlorinated by nickel–aluminium alloy in alkaline solution, to yield III. Yields were about 80% in both cases.

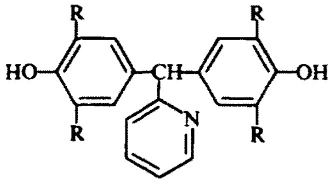


III: R = H
IV: R = Cl

Compound III has a m.p. and a thin layer $R_f$ value higher than those of its isomer II. As expected, the IR and PMR spectra are also radically different from those of II. Two strong absorption bands occur at 762 $cm^{-1}$ (pyridine hydrogens) and at 754 $cm^{-1}$ (hydrogens of the two *ortho* substituted benzenes). The methine proton is further deshielded to 6·13 $\delta$ by the two *ortho* OH groups. As observed for II, the hydrogens of the *ortho* substituted benzenes give rise to a complex absorption which has its maximum peak at 6·87 $\delta$.

Having thus finally ascertained the identity of II, we carried out a quantitative analysis of the crude products obtained from five condensations of pyridine-2-aldehyde with phenol, all performed according to the method described in the literature.[3a] The yields varied from 77 to 85% based on pyridine-2-aldehyde, with an average value of 81%. Integrating the chemically different methine proton signals of I and II revealed a content of II varying from 24 to 29%. Repeated crystallizations from 95% ethanol were required to obtain I free from the isomer, and these lowered the yield of I from 81% to about 25%. Consequently, this procedure also proved very inconvenient.

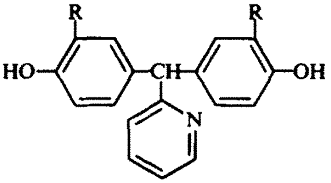
While seeking a method which would give a higher yield of I and would be inexpensive, and after having observed that pyridine-2-aldehyde not only condenses with the phenol *para* hydrogen atom but also, even though to a lesser extent, with those in the *ortho* position, we adopted a procedure similar to that used in preparing III. Pyridine-2-aldehyde was then reacted with phenols 2,6-disubstituted with halogens, to prevent formation of *ortho* condensation products. Thus, 4,4'-dihydroxy-3,3',5,5'-tetrachlorodiphenyl(2-pyridyl)methane (V) and 4,4'-dihydroxy-3,3',5,5'-tetrabromodiphenyl(2-pyridyl)methane (VI) were respectively obtained from



V: R = Cl
VI: R = Br

2,6-dichlorophenol and 2,6-dibromophenol, with about 87% yields in both cases. Reductive dehalogenation of both V and VI afforded I in 80–85% yield. Based on pyridine-2-aldehyde, the average yield of I was consequently about 72%, thus indicating an improvement on the previous method.

By reacting pyridine-2-aldehyde with phenols substituted with a halogen atom in only one of the two *ortho* positions, we were able to establish that this has a marked influence on the degree of *ortho* condensation, compared with phenol. 4,4′-Dihydroxy-3,3′-dichlorodiphenyl(2-pyridyl)methane (VII) and 4,4′-dihydroxy-3,3′-dibromodiphenyl(2-pyridyl)methane (VIII) were respectively obtained from 2-chlorophenol and



I: R = H
VII: R = Cl
VIII: R = Br

2-bromophenol, both showing an average content of 10% in relative isomers, i.e. 2,4′-dihydroxy-3,3′-dichlorodiphenyl(2-pyridyl)methane (IX) and 2,4′-dihydroxy-3,3′-dibromodiphenyl(2-pyridyl)methane (X). Consequently, it was sufficient to wash the crude products with boiling ethanol to obtain pure VII and VIII in 70% yield. Reductive dehalogenation of these compounds gave I with a yield which, based on pyridine-2-aldehyde, was about 65% in both cases. Therefore, there is also a marked improvement on the method in the literature,[3a] a 2-halophenol is used instead of phenol. According to their structures, both IX and X afforded II on reductive dehalogenation.

## EXPERIMENTAL

M.ps were taken on a Büchi capillary m.p. apparatus and are corrected. The $R_f$ values were determined on glass chromatostrips coated with silica gel G Merck; the TLC was performed with cyclohexane-ethyl acetate-methanol (7:3:2) in the case of I, II and III, and with cyclohexane-ethyl acetate-methanol-water (10:10:6:1) in the case of VII, VIII, IX and X. The spots were detected with a 1:1 mixture of conc $H_2SO_4$ and 3% potassium dichromate aq. IR spectra were recorded as nujol mulls using a Perkin–Elmer 337 grating spectrometer. PMR spectra were run in a 2·5:1 mixture of DMSO-$d_6$ and $CDCl_3$ on a Varian A-60 A spectrometer, operating at 60·00 Mc/s in a radio-frequency range of 0·04–0·06 milligauss; the reference zero was internal TMS and the chemical shifts were expressed in ppm down-field from this point (δ-scale). Microanalyses were carried out by Dr. R. Perego.

*Reaction of phenol with pyridine-2-aldehyde*

Phenol (69 g, 0·734 mole) was condensed with pyridine-2-aldehyde (24·2 g, 0·226 mole) in the presence of $H_2SO_4$, according to the method in the literature,[3a] giving 50 g (81%) of a mixture of *4,4'-dihydroxydiphenyl(2-pyridyl)methane* (I) and *2,4'-dihydroxydiphenyl(2-pyridyl)methane* (II). Analysis by PMR showed that II was present to the extent of 25%. Recrystallization from 95% EtOH (500 ml) gave a product containing about 4% of II. Further crystallization from the same solvent (300 ml) furnished 15·5 g (25%) of pure I as colourless crystals m.p. 248–250·5° (lit.[3a] 254°), TLC $R_f$ 0·36 (violet). (Found: C, 77·72; H, 5·44; N, 4·98. $C_{18}H_{15}NO_2$ requires: C, 77·96; H, 5·45; N, 5·05%.)

The combined mother liquors of the above crystallizations gave, when concentrated, a mixture enriched in II. This was repeatedly crystallized from 95% EtOH to give 3 g (4·8%) of pure II as colourless crystals m.p. 204·5–206°, TLC $R_f$ 0·44 (nut-brown). (Found: C, 77·99; H, 5·47; N, 4·96. $C_{18}H_{15}NO_2$ requires: C, 77·96; H, 5·45; N, 5·05%.)

On repeating this reaction 4 times, the yields of the crude mixture were 85, 79· 82 and 77%, with a content in II of 24, 25, 24 and 29%, respectively. The final yields of pure I varied from 22 to 28%.

*2,2'-Dihydroxydiphenyl(2-pyridyl)methane* (III)

5 g (0·046 mole) of pyridine-2-aldehyde was added during 1 hr to a thoroughly homogeneous mixture of 2,4-dichlorophenol (19·04 g, 0·116 mole) and conc $H_2SO_4$ (12·5 ml), stirring vigorously and keeping the temp from 0 to 5°. After the addition, stirring was continued for 30 min, and then the temp was allowed to rise spontaneously for 2 hr, taking care that it did not exceed internal 30°. Finally, the reaction mixture was warmed at 50° for 2 hr, allowed to stand overnight at room temp, and then dissolved with external cooling in 5% $Na_2CO_3$aq. The soln was filtered with charcoal and the pH adjusted to with 5% AcOH. The ppt which formed was filtered off, washed with water, dried, and taken up with ether to remove the unreacted 2,4-dichlorophenol, to give 14·7 g (77%) of *2,2'-dihydroxy-3,3',5,5'-tetrachlorodiphenyl(2-pyridyl)methane* (IV). Recrystallization from 95% EtOH gave a pure sample as colourless crystals m.p. 228·5–229·5°. (Found: C, 51·83; H, 2·72; Cl, 33·81; N, 3·30. $C_{18}H_{11}Cl_4NO_2$ requires: C, 52·08; H, 2·67; Cl, 34·17; N, 3·38%.) The PMR spectrum showed the methine proton signal at 6·18 $\delta$. The crude product was used for further work.

5·9 g of Ni–Al alloy was added during 4 hr, with vigorous stirring and at room temp, to a soln of IV (6 g, 0·0144 mole) in 5% NaOH aq (80 ml). The mixture was then stirred overnight at room temp, filtered, and the soln acidified to pH 5 with 10% AcOH. The ppt was filtered off, washed with water, dried, and then taken up with boiling 95% EtOH (200 ml) to remove the salts. Evaporation of the alcohol gave 3·24 g (81%) of crude III. Recrystallization from 95% EtOH afforded an analytical sample as colourless crystals m.p. 244·5–245·5°, TLC $R_f$ 0·47 (brown). (Found: C, 77·48; H, 5·61; N, 5·02. $C_{18}H_{15}NO_2$ requires: C, 77·96; H, 5·45; N, 5·05%.)

*4,4'-Dihydroxydiphenyl(2-pyridyl)methane* (I)

(a) *By reductive dehalogenation of both 4,4'-dihydroxy-3,3',5,5'-tetrachlorodiphenyl(2-pyridyl)methane* (V) and *4,4'-dihydroxy-3,3',5,5'-tetrabromodiphenyl(2-pyridyl)methane* (VI). V was prepared essentially as was IV. 16·5 g (86%) of crude V was obtained from 19·04 g (0·116 mole) of 2,6-dichlorophenol and 5 g (0·046 mole) of pyridine-2-aldehyde. Recrystallization from 95% EtOH afforded a pure sample as colourless crystals m.p. 231–232°. (Found: C, 51·58; H, 2·72; Cl, 33·99; N, 3·31. $C_{18}H_{11}Cl_4NO_2$ requires: C, 52·08; H, 2·67; Cl, 34·17; N, 3·38%.) The PMR spectrum showed the methine proton signal at 5·57 $\delta$. VI was prepared similarly from 54 g (0·214 mole) of 2,6-dibromophenol and 9·2 g (0·086 mole) of pyridine-2-aldehyde, obtaining 44·8 g (88%) of crude VI. Recrystallization from 95% EtOH gave a pure sample as colourless crystals m.p. 223·5–225°. (Found: C, 36·57; H, 1·91; Br, 53·51; N, 2·30. $C_{18}H_{11}Br_4NO_2$ requires: C, 36·46; H, 1·87; Br, 53·91; N, 2·36%.) The PMR spectrum showed the methine proton signal at 5·60 $\delta$. The crude products were used for further work.

Reductive dehalogenation of both V and VI was accomplished as was described for IV. Dechlorination of 50 g (0·120 mole) of V with 49 g of Ni–Al alloy gave 26·7 g (80%) of I, m.p. and m.m.p. 248–250°. The yield was 69%, based on pyridine-2-aldehyde. Debromination of 20 g (0·034 mole) of VI with 18 g of Ni–Al alloy gave 7·9 g (85%) of I, m.p. and m.m.p. 249–250·5°. The yield was 75%, based on pyridine-2-aldehyde.

(b) *By reductive dehalogenation of both 4,4'-dihydroxy-3,3'-dichlorodiphenyl(2-pyridyl)methane* (VII) and *4,4'-dihydroxy-3,3'-dibromodiphenyl(2-pyridyl)methane* (VIII). VII was prepared by the method used for IV. 211 g (87%) of VII containing 11% of *2,4'-dihydroxy-3,3'-dichlorodiphenyl(2-pyridyl)methane* (IX) was obtained from 292·9 g (2·27 mole) of 2-chlorophenol and 75 g (0·7 mole) of pyridine-2-aldehyde. One washing with boiling 95% EtOH (430 ml) afforded 167 g (69%) of crude VII free from IX. Recrystallization from 95% EtOH gave a pure sample as colourless crystals m.p. 212–215·5°, TLC $R_f$ 0·68 (dark brown). (Found: C, 62·01; H, 3·80; Cl, 20·27; N, 3·98. $C_{18}H_{13}Cl_2NO_2$ requires: C, 62·44; H, 3·78; Cl, 20·48; N, 4·05%.) The PMR spectrum showed the methine proton signal at 5·48 δ. The mother liquor of the above washing was evaporated, the oily residue taken up with ether, the ethereal solution filtered and evaporated to dryness, and the new residue repeatedly triturated with pet. ether. The solid product was dissolved in 10% NaOH aq. and the soln filtered with charcoal and adjusted to pH 5 with 10% AcOH. The ppt which formed was filtered off, washed with water, and dried, to give 9·2 g (3·8%) of crude IX free from VII. Recrystallization from cyclohexane afforded a pure sample as colourless crystals m.p. 123·125°, TLC $R_f$ 0·73 (yellow). (Found: C, 62·08; H, 3·80; Cl, 20·13; N, 4·01. $C_{18}H_{13}Cl_2NO_2$ requires: C, 62·44; H, 3·78; Cl, 20·48; N, 4·05%.) The PMR spectrum showed the methine proton signal at 5·77 δ. VIII was prepared similarly to VII from 256 g (1·48 mole) of 2-bromophenol and 47·5 g (0·44 mole) of pyridine-2-aldehyde, obtaining 171 g (89%) of VIII containing 10% of *2,4'-dihydroxy-3,3'-dibromodiphenyl(2-pyridyl)methane* (X). One washing with boiling 95% EtOH (350 ml) furnished 135 g (70%) of crude VIII free from X. Recrystallization from 95% EtOH gave a pure sample as colourless crystals m.p. 173–175°, TLC $R_f$ 0·70 (brown). (Found: C, 49·88; H, 3·11; Br, 35·60; N, 3·09. $C_{18}H_{13}Br_2NO_2$ requires: C, 49·68; H, 3·01; Br, 36·73; N, 3·22%.) The PMR spectrum showed the methine proton signal at 5·52 δ. Isolation of X from the mother liquor of the above washing, accomplished as was described for IX, finally afforded a pure sample of X (6·1 g, 3·1%) as colourless crystals m.p. 95–96°, TLC $R_f$ 0·78 (yellowish). (Found: C, 49·55; H, 3·08; Br, 35·94; N, 3·12. $C_{18}H_{13}Br_2NO_2$ requires: C, 49·68; H, 3·01; Br, 36·73; N, 3·22%.) The PMR spectrum showed the methine proton signal at 5·79 δ. The crude products were used for further work.

Reductive dehalogenation of VII, VIII, IX and X was performed as described for IV. Dechlorination of 100 g (0·29 mole) of VII with 49 g of Ni–Al alloy gave 74 g (92%) of I, m.p. and m.m.p. 248–250°. The yield was 63·5%, based on pyridine-2-aldehyde. Debromination of 100 g (0·23 mole) of VIII with 49 g of Ni–Al alloy gave 60 g (94%) of I, m.p. and m.m.p. 247–249°. The yield was 66%, based on pyridine-2-aldehyde. Dechlorination of 5 g (0·014 mole) of IX with 2·5 g of Ni–Al alloy gave 3·4 g (88%) of II, m.p. and m.m.p. 204–206°. Debromination of 5 g (0·011 mole) of X with 2·5 g of Ni–Al alloy gave 2·8 g (90%) of II, m.p. and m.m.p. 203–205°.

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