

Substituted Diphenyl-(2-pyridyl)-methanes

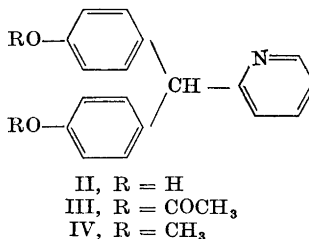
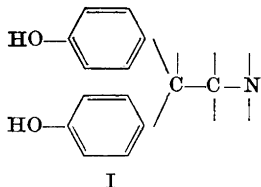
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In order to gain further insight into the relationship between chemical structure and laxative activity three substituted diphenyl-(2-pyridyl)-methanes were prepared by condensing *p*-methoxyphenyl-2-pyridyl carbinol with phenol, *m*-cresol and *m*-chlorophenol, respectively.

In another approach to the synthesis of diphenyl-(2-pyridyl)-methanes from *bis*-(*p*-methoxyphenyl)-2-pyridyl carbinol the reactions took an unexpected course with the production of a new red-brown compound, the structure of which is discussed.

In the course of investigations on the relationship between chemical structure and laxative activity, Schmidt and Seeger¹ found the grouping I to be of particular importance for the attainment of laxative effect (*cf.* Ref.²). Recently, the substituted diphenyl-(2-pyridyl)-methanes, II—IV, were synthesized³⁻⁶; pharmacological evaluation demonstrated II and III to be very potent laxatives^{1,2}. Again, laxative activity was reported for IV³, yet without presentation of pharmacological data.

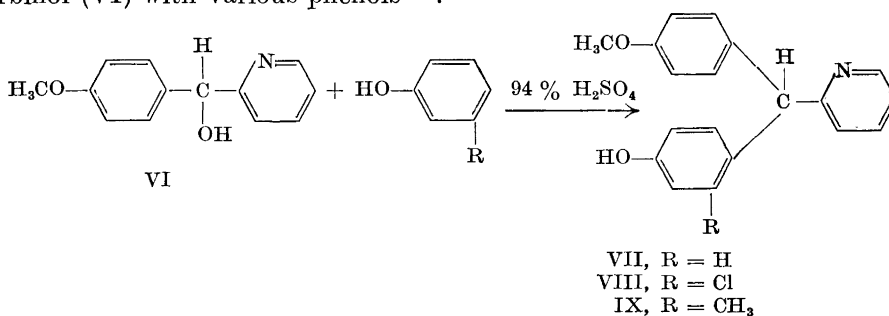


The dimethoxy compound IV has been reported as an oil^{3,6}. In our hands, however, a sample of IV crystallized after having been stored in a closed vessel for some time. After recrystallization from petroleum ether the pure substance melted at 62—63°. Pharmacological evaluation showed IV to possess a laxative effect comparable to that of III.

Schultz and Geller^{6,7} lately reported the surprising observation that IV on standing in an open flask at room temperature suffers hydrolytic cleavage to pyridine and *p,p'*-dimethoxybenzhydrol (V) (no m.p. or analytical data were presented), the latter claimed to possess high laxative activity. We have

not been able to detect any laxative activity of authentic V (m.p. 70—71°). The similarity in melting points of IV and V, however, leaves the identity of Schultz and Geller's active product open to discussion*.

In order to gain further insight into the relationship between chemical structure and laxative activity, a series of *p*-hydroxy-*p*'-methoxy-diphenyl-(2-pyridyl)-methanes were synthesized and pharmacologically evaluated. Previously reported methods for preparing substituted diphenyl-(2-pyridyl)-methanes³⁻⁶ are limited to yielding compounds with identical substituents in the benzene rings. The present paper, however, reports a synthetic route to diphenyl-(2-pyridyl)-methanes, VII—IX, dissimilarly substituted in the two aromatic rings, *viz.* the condensation of *p*-methoxyphenyl-2-pyridyl carbinol (VI) with various phenols**.



When R = H it was found, as expected, that condensation took place at the *p*-position to the aromatic hydroxy group. This course of reaction was proved by transforming VII into the known *bis*-(*p*-hydroxyphenyl)-(2-pyridyl)-methane (II), which was, in turn, acetylated to its known diacetyl derivative *bis*-(*p*-acetoxyphenyl)-(2-pyridyl)-methane (III). In those cases where R = Cl and R = CH₃ it is believed that condensation proceeds analogously at the position located *para* to the hydroxy grouping.

The synthesis of VI from anisaldehyde and 2-bromopyridine by the Grignard reaction has been previously described⁸. It was found advantageous, however, to employ 2-pyridinealdehyde and *p*-bromoanisole as reactants in the Grignard synthesis, which under these conditions proceeded to give VI in a yield of 82 %.

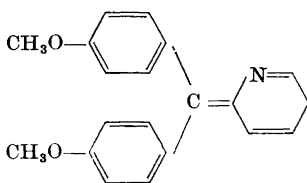
In another approach to the synthesis of diphenyl-(2-pyridyl)-methanes *bis*-(*p*-methoxyphenyl)-2-pyridyl carbinol (X), formerly synthesized from 2-pyridyl lithium and *p,p*'-dimethoxybenzophenone⁹, was prepared from ethyl picolinate and *p*-bromoanisole by Grignard reaction. Attempted reduction of X with formic acid to give IV (*cf.* the synthesis of triphenyl methane by formic acid reduction of triphenyl carbinol¹⁰) resulted in the production of a red-brown compound (XI), m.p. 146°. Similarly, XI was obtained on attempted dealkylation of X with anhydrous aluminium chloride in carbon disulphide.

* Note added in proof: Schultz, O. E. and Schnekenburger, J. (*Arch. Pharm.* **291/63** (1958) 356) now report that the cleavage of IV to pyridine and V could not be reproduced. The product obtained was crystalline IV (m.p. 63—63.5°).

** Patent pending.

The observed diamagnetic properties of XI excluded its free radical character.

The alternative possibility of XI representing the 'double' molecule, 1,1,2,2-tetrakis-(*p*-methoxyphenyl)-1,2-bis-(2-pyridyl)-ethane, is ruled out by its colour as well as by a comparison of its infrared spectrum with that of IV. The absorption patterns indicate that the methoxysubstituted aromatic rings are retained in the coloured product whereas the pyridine moiety seems to be involved in the formation of a quinoid system. On basis of the available evidence a structure such as XII appears to be a likely proposal, compatible also with the cryscopically determined molecular weight. No further attempts have been made to substantiate the structure XII.



XII

EXPERIMENTAL *

bis-(*p*-Methoxyphenyl)-(2-pyridyl)-methane (IV). IV was prepared according to Schultz and Geller⁶. After having been stored in a closed vessel for some time, IV crystallized. After recrystallization from petroleum ether the m. p. of IV was 62–63°. (Found: C 78.8; H 6.2; N 4.7. Calc. for C₂₀H₁₉NO₂ (305.4): C 78.7; H 6.3; N 4.6.)

p,p'-Dimethoxybenzhydrol (V). V was prepared according to Bergmann and Hervey¹¹. The m. p. of V was 70–71° (previously reported¹¹ 70–72°). (Found: C 74.0; H 6.6; OCH₃ 25.4. Calc. for C₁₅H₁₆O₃ (244.3): C 73.8; H 6.6; OCH₃ 24.9.)

p-Methoxyphenyl-2-pyridyl carbinol (VI). Magnesium turnings (97.2 g, 4.0 moles) were placed in a 10 l three-necked flask fitted with a stirrer, dropping funnel and a reflux condenser protected by a calcium chloride tube. *p*-Bromoanisole (936 g, 5.0 moles), dissolved in anhydrous ether (2.4 l), was added in small portions until the reaction started and then, at such a rate (1.5 h) that gentle reflux was maintained. The reaction mixture was further heated under reflux for 2 h and cooled in an ice-salt mixture whereupon 2-pyridinealdehyde (214 g, 2.0 moles), dissolved in anhydrous ether (400 ml), was gradually added in the course of 1 h. Stirring was continued for another hour at room temperature. 4 N Hydrochloric acid (2.4 l), followed by conc. hydrochloric acid (800 ml), were added during 1 h to the cooled solution. The reaction mixture was left standing overnight, and the ether layer removed. The aqueous layer was further extracted with ether (2 × 800 ml) and then made alkaline by adding 15 % aqueous ammonia under cooling. The precipitate formed was removed by filtration and dried. The yield was 401 g (93 %) of crude VI, m. p. 128–131°. Crystallization from ethanol (3 l) gave 353 g (82 %) of VI as colourless crystals, m. p. 132–134° (previously reported⁸ 133–134°).

p-Hydroxy-*p'*-methoxy-diphenyl-(2-pyridyl)-methane (VII). VI (300 g, 1.4 moles) and phenol (329 g, 3.5 moles) were placed in a three-necked flask provided with stirrer and reflux condenser protected by a calcium chloride tube. Under cooling in an ice bath, 94 % sulphuric acid (210 g) was added with stirring. The reaction mixture was kept in

* All melting points are uncorrected. Microanalyses have been performed by Mr. P. Hansen, The Chemical Laboratory of the University of Copenhagen, and by Mr. W. H. Kirsten, University of Uppsala, Sweden.

the ice bath for 30 min, then at room temperature for 1.5 h and finally at 100° for 30 min. After cooling, 30 % sodium hydroxide (1.5 l) was added followed by water to a total volume of 8 l, whereby a clear solution was obtained. After extraction with ether (3 × 700 ml), the aqueous layer was neutralized with 50 % acetic acid. The precipitate formed was removed by filtration, washed with water, dried, and crystallized first from isopropyl alcohol (1 750 ml) and then from ethyl acetate (1 500 ml). The yield was 217 g (64 %) of VII (colourless crystals, m. p. 149–150°). (Found: C 78.2; H 5.8; N 4.8. Calc. for C₁₉H₁₇NO₂ (291.3): C 78.3; H 5.9; N 4.8.)

bis-(p-Acetoxyphenyl)-(2-pyridyl)-methane (III). VII (1.94 g) was dissolved in a 35 % solution (15 ml) of hydrogen bromide in 90 % acetic acid and the reaction mixture heated under reflux for 3 h. After cooling, water was added and the reaction mixture neutralized under cooling with 2 N sodium hydroxide. An oil was formed, which soon crystallized. Filtration, washing and drying gave 1.82 g (98 %) of crude *bis-(p-hydroxyphenyl)-(2-pyridyl)-methane (II)* which, without further purification, was dissolved in a mixture of acetic anhydride (9.1 ml) and pyridine (3.6 ml). The reaction mixture was heated under reflux for 15 min, cooled and poured into water (90 ml). An oil was formed which soon crystallized. After filtration, the product was stirred with ice-cold 3 % sodium hydroxide, removed by filtration, washed with water and dried. The yield was 2.22 g (94 %) of crude III (m. p. 132–133°). Crystallization from ethanol (10 ml) gave 2.00 g (84 %) of III (almost colourless crystals, m. p. 133–134°, previously reported⁶ 135–136°). The mixed m. p. of III and a specimen of *bis-(p-acetoxyphenyl)-(2-pyridyl)-methane*, prepared according to Schultz and Geller⁶ (m. p. 131–132°), was 131–133°.

p-Hydroxy-o-chloro-p'-methoxy-diphenyl-(2-pyridyl)-methane (VIII). VI (5.0) and *m*-chlorophenol (7.5 g) were condensed in 94 % sulphuric acid (3.5 g) for 2 h as described above for the preparation of VII. The crude product was crystallized twice from aqueous dimethyl formamide. The yield was 4.8 g (38 %) of VIII (colourless crystals, m. p. 220–222°). (Found: C 70.0; H 5.1; N 4.5; Cl 10.8. Calc. for C₁₉H₁₆ClNO₂ (325.8): C 70.1; H 4.9; N 4.3; Cl 10.8.)

p-Hydroxy-o-methyl-p'-methoxy-diphenyl-(2-pyridyl)-methane (IX). VI (5.0 g) and *m*-cresol (6.3 g) were condensed in 94 % sulphuric acid (3.5 g) for 30 min as described above for the preparation of VII. The crude reaction product was boiled with ethanol (200 ml). After filtration, the filtrate was evaporated and the residue recrystallized from aqueous dimethyl formamide. Another crystallization from methanol gave 2.5 g (35 %) of IX as colourless crystals with m. p. 205–207°. (Found: C 78.0; H 6.5; N 4.5. Calc. for C₂₀N₁₉NO₂ (305.4): C 78.7; H 6.3; N 4.6.)

bis-(p-Methoxyphenyl)-2-pyridyl carbinol (X). Magnesium turnings (19.3 g, 0.80 moles) were placed in a three-necked flask fitted with a stirrer, a dropping funnel and a reflux condenser with a calcium chloride tube, and a stream of dry, oxygen-free nitrogen was passed through the apparatus. *p*-Bromoanisole (148 g, 0.80 moles), dissolved in anhydrous ether (310 ml), was added during 1 h and the reaction mixture was then heated under reflux for 1 h. After cooling in an ice bath, ethyl picolinate (20.0 g, 0.13 moles) dissolved in anhydrous ether (60 ml) was added during 1.25 h, and the reaction mixture was allowed to stand at room temperature for 1 h. After cooling in an ice bath, 4 N hydrochloric acid (650 ml) was slowly added, the mixture was filtered, and the aqueous layer separated, washed with ether (2 × 100 ml) and made alkaline by adding 10 % aqueous ammonia. An oil separated which was extracted with a chloroform-ether mixture, the extract was dried with magnesium sulphate and evaporated in a vacuum. The oily residue (41.6 g) was dissolved in hot methanol (50 ml). Cooling and addition of a little water gave 27.7 g of crude X. After crystallization from methanol (50 ml) the yield was 20.9 g (49 %) of colourless crystals with m. p. 90–92° (previously reported⁹ 90–91°).

XI. A mixture of X (1.00 g) and 99 % formic acid (15 g) was heated under reflux for 3 h. After cooling, water (15 ml) was added and the reaction mixture made alkaline by 2 N sodium hydroxide. A black oil formed which was extracted with benzene. After washing with water and drying with magnesium sulphate the benzene was distilled off in a vacuum and the residue (0.93 g) recrystallized from aqueous isopropyl alcohol. The yield was 0.75 g (79 %) of XI (red-brown crystals, m. p. 145–147°). Two further crystallizations from aqueous isopropyl alcohol furnished red-brown crystals, m. p. 146–147°. (Found: C 78.7; H 5.7; N 4.5; OCH₃ 19.8. Calc. for C₂₀H₁₉NO₂ (305.4): C 78.7; H 6.3; N 4.6; OCH₃ 20.4.)

XI was also obtained in the following experiment. A mixture of X (0.70 g), anhydrous carbon disulphide (20 ml) and anhydrous aluminium chloride (0.61 g) was heated under reflux for 7 h. After cooling, the reaction mixture was shaken with water and the organic layer dried with magnesium sulphate and evaporated in a vacuum. The residue (0.48 g) was recrystallized from aqueous isopropyl alcohol to yield 0.26 g (39 %) of XI as red-brown crystals, m. p. 145–147°. Two further crystallizations from the same solvent gave red-brown crystals, m. p. 146–148°. (Found: C 79.0; H 5.8; N 4.6; OCH₃ 20.1.)

Magnetic measurements. On basis of determination of the magnetic susceptibility of XI at four different field intensities it was concluded that the compound was diamagnetic, a result excluding its character as a free radical.

Infrared spectra. The infrared spectra of XI and IV were determined in the solid state (KBr pellets) on a Perkin-Elmer double-beam spectrophotometer (Model 21 B).

The C–H stretching modes of the aromatic rings (3 040 cm⁻¹) and the CH₃O-groupings (2 840 and 2 950 cm⁻¹) were detectable in both compounds. Again, bands attributable to the aromatic ether C–O vibration (1 250 cm⁻¹) and the corresponding aliphatic stretching mode (1 025 cm⁻¹) were conspicuously present in XI and IV, yet possibly masked by pyridine bands in the latter compound. A strong C=C absorption band in IV at 1 608 cm⁻¹ was substituted with a band at 1 620 cm⁻¹ in XI, possibly assignable to a C=N stretching vibration such as would be expected from the structure XII. In the C–H-deformation vibration region the band complex at 750 cm⁻¹, expected from a 2-substituted pyridine moiety, was present in IV but lacking in XI. Both compounds displayed strong absorption around 800 cm⁻¹ attributable to *para*-substituted aromatic rings.

Molecular weight determination. The molecular weight of XI was determined in camphor by the usual Rast method. (Found: 228. Calc.: 305.4.)

*Pharmacology.** III, IV, V, VII, VIII, IX and XI were evaluated orally in rats for laxative activity following a technique similar to that used by Schmidt². In doses of 11 mg/kg/day, III, IV and VII displayed strong laxative effect. IX was less active, and even in doses of 76 mg/kg/day the effect was not maximal. VIII was without appreciable effect in doses of 76 mg/kg/day. V was found devoid of laxative activity in a dose of 126 mg/kg/day. XI was found without laxative effect in a dose of 45 mg/kg/day. On a dose of approximately 70 mg/kg/day the rats fed with XI died in 4–5 days.

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