[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

PYRIDINE ANALOGS OF 1,1,2-TRIPHENYLETHYLENE

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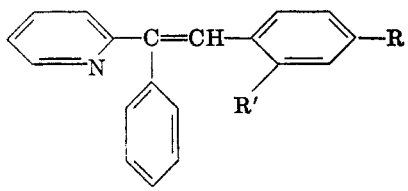
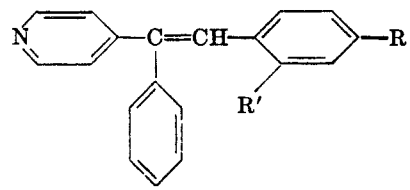
A large number of derivatives of 1,1,2-triphenylethylene are of biological interest because of their prolonged estrogenic activity (1), and some have found threapeutic use in cancer of the breast and prostate (2). Several analogs of 1,1,2-triphenylethylene bearing heterocyclic nuclei had already been investigated, especially those derived from thiophene (3), but the pyridine analogs had not yet been examined, although Bergmann and Pinchas (4) recently prepared 2,6-di-(4′-ethoxy-α-ethylstyryl)pyridine, a higher vinylog of stilbestrol diethyl ether, and found it to be slightly estrogenic. A number of analogs of 1,1,2-triphenylethylene bearing an α- or γ-pyridine nucleus have now been synthesized, and their estrogenic activity has been determined.

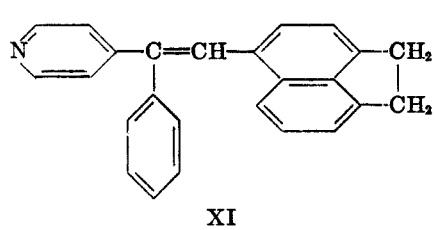


I R = R′ = H
II R = H, R′ = Cl
III R = Cl, R′ = H
IV R = OCH_3, R′ = H
V R = H, R′ = $OCOCH_3$

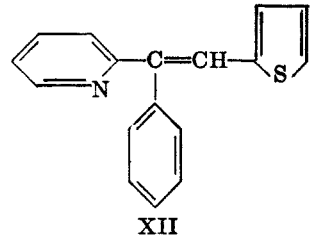


VI R = R′ = H
VII R = H, R′ = Cl
VIII R = Cl, R′ = H
IX R = OCH_3, R′ = H
X R = H, R′ = $OCOCH_3$

Koenigs, Köhler, and Blindow (5) prepared 1,2-diphenyl-1-(2-pyridyl)ethylene (I) and 1,2-diphenyl-1-(4-pyridyl)ethylene (VI) by condensing benzaldehyde with 2- and 4-benzylpyridine in the presence of dehydrating agents. This seemed to be the most direct method for preparing compounds of this type, and consequently it was adopted throughout the present work, α- and γ-benzylpyridine being readily accessible through the Tschitschibabin-von Braun reaction (6). The condensation technique of Koenigs, Köhler, and Blindow was modified by the use of acetic anhydride as solvent and dehydrating agent.



XI

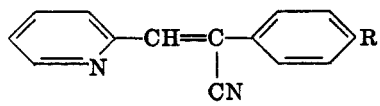


XII

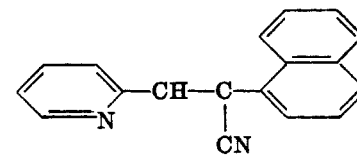
1,2-Diphenyl-1-(2-pyridyl)ethylene (I) was found inactive at a dosage of 20 mg. in the Allen-Doisy test in mice, but its isomer VI was estrogenic at 10 mg.

(1,1,2-triphenylethylene is estrogenic at 0.1 mg.). The biological activity is affected by the site and nature of nuclear substitution, as 1-phenyl-2-*o*-chlorophenyl-1-(2-pyridyl)ethylene (II) was estrogenic at 10 mg., whereas the isomeric compound III showed no activity at 20 mg. On the other hand, at the same dose level 1-phenyl-2-*p*-chlorophenyl-1-(4-pyridyl)ethylene (VIII) was inactive, while both 1-phenyl-2-*p*-methoxyphenyl-1-(4-pyridyl)ethylene (IX) and 1-phenyl-2-*o*-acetoxyphenyl-1-(4-pyridyl)ethylene (X) showed activity. The last compound was isolated in the condensation of *o*-acetoxybenzaldehyde with γ-benzylpyridine; unlike most phenol esters, it was stable in aqueous ammonia or hydrochloric acid. Compound V, prepared from α-benzylpyridine, behaved similarly.

Departure from structure VI resulted in loss of activity, as was the case with 1-phenyl-2-(5-acenaphthyl)-1-(4-pyridyl)ethylene (XI), and with 1-phenyl-1-(2-pyridyl)-2-(2-thienyl)ethylene (XII), prepared from 2-thenaldehyde and α-benzylpyridine. Similarly, compounds of the stilbazol type such as 1-phenyl-2-2-(2-pyridyl)ethylene were found inactive, as were 1-aryl-2-(2-pyridyl)acrylonitriles (XIII) to (XV), obtained by the alkali-catalyzed condensation of α-pyridinaldehyde with various arylacetonitriles. In view of the known activity of certain diarylacrylonitriles as mitotic poisons (7), these new acrylonitriles are being examined as tumor growth inhibitors.



XIII R = Cl
XIV R = Br



XV

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EXPERIMENTAL

Preparation of α- and γ-benzylpyridine. The condensation of benzyl chloride with pyridine in the presence of copper powder was performed according to Crook and McElvain (8). From 300 g. of benzyl chloride, 200 g. of pyridine, and 3 g. of copper powder, there was obtained 175 g. of a crude mixture of benzylpyridines, b.p. 260–310°. Fractionation with a Vigreux column afforded 100 g. of a portion boiling at 279–288°, 35 g. of a portion boiling at 282–288°, and 14 g. of a portion boiling at 288–300°. Repeated vacuum-fractionation of the two last portions yielded 28 g. of γ-benzylpyridine, b.p. 149–150°/17 mm.; α-benzylpyridine (83 g., b.p. 142°/15 mm.) was prepared from the first portion according to Müller and Krauss (9), by fractional crystallization of the picrate mixture in acetone.

1-Phenyl-2-o-chlorophenyl-1-(2-pyridyl)ethylene (II). A mixture of 5 g. (0.03 mole) of α-benzylpyridine, 4.6 g. (0.033 mole) of *o*-chlorobenzaldehyde, and 5 g. (0.05 mole) of acetic anhydride was refluxed for 15 hours, the reaction mixture was treated with 30 ml. of 50% hydrochloric acid, and the aldehyde in excess was removed by steam-distillation. After basification with sodium hydroxide, steam-distillation was resumed to remove unreacted α-benzylpyridine, and the ethylene was taken up in ether and recrystallized from aqueous

methanol. Yield, 6.6 g. (75%) of colorless needles, m.p. 83°. A similar technique was used for the two following ethylenes.

Anal. Calc'd for $C_{19}H_{14}ClN$: C, 78.1; H, 4.8; N, 4.8.
Found: C, 77.8; H, 4.6; N, 4.5.

Picrate: yellow prisms (from methanol), m.p. 175°.

Anal. Calc'd for $C_{25}H_{17}ClN_4O_7$: N, 10.8. Found: N, 10.3.

1-Phenyl-2-p-chlorophenyl-1-(2-pyridyl)ethylene (III) was obtained in 72% yield (6.3 g.) from *p*-chlorobenzaldehyde. This ethylene crystallized from aqueous methanol in shiny colorless prisms, m.p. 92°.

Anal. Calc'd for $C_{19}H_{14}ClN$: N, 4.8. Found: N, 4.5.

Picrate: shiny yellow prisms (from ethanol), m.p. 177°.

Anal. Calc'd for $C_{25}H_{17}ClN_4O_7$: C, 57.6; H, 3.3; N, 10.8.
Found: C, 57.6; H, 3.5; N, 10.6.

1-Phenyl-2-p-methoxyphenyl-1-(2-pyridyl)ethylene (IV). This compound, obtained from anisaldehyde in only 20% yield, crystallized from methanol in silky colorless needles, m.p. 115°.

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.6; H, 6.0; N, 4.9.
Found: C, 84.0; H, 6.1; N, 4.6.

Picrate: deep yellow needles (from ethanol), m.p. 169°.

Anal. Calc'd for $C_{26}H_{20}N_4O_8$: C, 60.4; H, 3.9; N, 10.9.
Found: C, 60.8; H, 3.7; N, 10.8.

1-Phenyl-2-o-acetoxyphenyl-1-(2-pyridyl)ethylene (V). In the preparation of this compound from salicylaldehyde, basification was effected with aqueous ammonia in place of sodium hydroxide. Yield, 4.5 g. (56%) of a compound which crystallized from methanol in colorless prisms, m.p. 135°.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4; N, 4.4.
Found: C, 80.2; H, 5.6; N, 4.6.

Picrate: bright yellow prisms (from ethanol), m.p. 179°.

Anal. Calc'd for $C_{27}H_{20}N_4O_9$: C, 59.5; H, 3.7; N, 10.4.
Found: C, 59.2; H, 3.6; N, 10.1.

1-Phenyl-2-o-chlorophenyl-1-1-(4-pyridyl)ethylene (VII). The technique adopted for the condensation of aldehydes with γ-benzylpyridine was the same as for the α-isomer. Compound VII thus was obtained in 72% yield from *o*-chlorobenzaldehyde, as a pale yellow oil, b.p. 210–212°/3 mm.

Anal. Calc'd for $C_{19}H_{14}ClN$: N, 4.8. Found: N, 5.0.

Picrate: shiny yellow prisms (from ethanol), m.p. 147°.

Anal. Calc'd for $C_{25}H_{17}ClN_4O_7$: C, 57.6; H, 3.3; N, 10.8.
Found: C, 57.2; H, 3.1; N, 10.5.

1-Phenyl-2-p-chlorophenyl-1-(4-pyridyl)ethylene (VIII). This compound, obtained in 75% yield from *p*-chlorobenzaldehyde, boiled at 203–204°/0.5 mm., and crystallized from methanol in shiny colorless needles, m.p. 89°.

Anal. Calc'd for $C_{19}H_{14}ClN$: C, 78.2; H, 4.8; N, 4.8.
Found: C, 78.2; H, 4.7; N, 4.6.

Picrate: shiny, bright yellow prisms (from ethanol), m.p. 170°.

Anal. Calc'd for $C_{25}H_{17}ClN_4O_7$: C, 57.6; H, 3.3.
Found: C, 57.9; H, 3.0.

1-Phenyl-2-p-methoxyphenyl-1-(4-pyridyl)ethylene (IX) was prepared from anisaldehyde; this compound crystallized from aqueous methanol in silky colorless needles, m.p. 113°; yield, 15%.

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.6; H, 6.0.
Found: C, 83.9; H, 6.0.

Picrate: shiny, deep yellow prisms (from ethanol), m.p. 198°.

Anal. Calc'd for $C_{26}H_{20}N_4O_8$: N, 10.9. Found: N, 11.1.

1-Phenyl-2-o-acetoxyphenyl-1-(4-pyridyl)ethylene (X). This compound, obtained in 50%

yield from salicylaldehyde, was as stable in hot aqueous ammonia as the isomer V. It crystallized from methanol in fine colorless needles, m.p. 153°.

Anal. Calc'd for $C_{21}H_{17}NO_2$: N, 4.4. Found: N, 4.5.

1-Phenyl-2-(5-acenaphthyl)-1-(4-pyridyl)ethylene (XI) was prepared from 5-formylacenaphthene [synthesized from acenaphthene by formylation with N-methylformanilide in the presence of phosphorus oxychloride (10)]. This compound crystallized from ethanol in shiny yellow leaflets, m.p. 140°, b.p. 322°/45 mm.

Anal. Calc'd for $C_{25}H_{19}N$: C, 90.0; H, 5.7.
Found: C, 89.8; H, 5.7.

Picrate: shiny yellow (from toluene), m.p. 236°.

1-Phenyl-1-(2-pyridyl)-2-(2-thienyl)ethylene (XII). This compound, prepared in 70% yield from 2-thenaldehyde (obtained by formylation of thiophene with dimethylformamide and phosphorus oxychloride), boiled at 290–292°/50 mm., and crystallized from methanol in shiny colorless prisms, m.p. 77°.

Anal. Calc'd for $C_{17}H_{13}NS$: C, 77.5; H, 4.9.
Found: C, 77.6; H, 5.2.

Picrate: shiny yellow leaflets (from toluene), m.p. 183°.

Anal. Calc'd for $C_{23}H_{16}N_4O_7S$: N, 11.4. Found: N, 11.6.

1-p-Chlorophenyl-2-(2-pyridyl)acrylonitrile (XIII). For the preparation of this nitrile and the following ones, a method similar to Walther's procedure for the synthesis of 1,2-diphenylacrylonitrile (11) was adopted. To a warm saturated solution of 2 g. of freshly distilled pyridine-2-aldehyde (12) and 3 g. of *p*-chlorobenzyl cyanide in ethanol, 3 drops of a 20% aqueous solution of sodium hydroxide was added with stirring; and the mixture was left to stand for one hour at room temperature. The solid precipitate which formed was collected and recrystallized twice from ethanol, giving 2 g. of shiny colorless prisms, m.p. 122°.

Anal. Calc'd for $C_{14}H_9ClN_2$: C, 69.9; H, 3.7.
Found: C, 70.2; H, 3.8.

1-p-Bromophenyl-2-(2-pyridyl)acrylonitrile (XIV) similarly was prepared from 1 g. of pyridine-2-aldehyde and 2 g. of *p*-bromobenzyl cyanide. This nitrile crystallized from ethanol in shiny colorless prisms, m.p. 128°.

Anal. Calc'd for $C_{14}H_9BrN_2$: C, 58.9; H, 3.1.
Found: C, 59.1; H, 3.2.

1-(1-Naphthyl)-2-(2-pyridyl)acrylonitrile (XV) was prepared from 2 g. of pyridine-2-aldehyde and 3.3 g. of 1-naphthylacetonitrile. This nitrile crystallized from ethanol in colorless needles, m.p. 127°.

Anal. Calc'd for $C_{18}H_{12}N_2$: C, 84.4; H, 4.7.
Found: C, 84.1; H, 4.9.

SUMMARY

1. The preparation of a number of 1,1-diaryl-2-pyridylethylenes from α- and γ-benzylpyridine, and of one thiophene analog from α-thenaldehyde and α-benzylpyridine is described.

2. Several of these compounds showed estrogenic activity, although to a far lesser degree than did 1,1,2-triphenylethylene. No activity was found in several derivatives of the stilbazole type.

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Added in page proof, Sept. 30, 1955—Since this work was sent to press, a paper by Castle and Seese has appeared [*J. Org. Chem.*, **20**, 987 (1955)], in which similar condensations of pyridine aldehydes with arylacetonitriles are described —Ng. Ph. Buu-Hoi.