[Contribution from the Department of Organic Chemistry, Radium Institute, University of Paris]

The Pfitzinger Reaction with Ketones Derived from *o*-Hydroxydiphenyl

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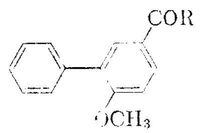
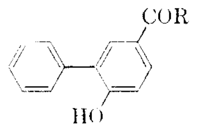
2-Methoxydiphenyl has been shown to undergo Friedel-Crafts acylations with aliphatic and aromatic acid chlorides in the position *para* to the methoxy group. 5-Acetyl-, 5-propionyl-, 5-butyryl-, and 5-phenacetyl-2-methoxydiphenyl were prepared and gave normal Pfitzinger reactions with isatin, whereas neither 5-valeryl-2-methoxydiphenyl nor any 5-acyl-2-hydroxydiphenyl investigated underwent the reaction within the standard time limit.

It has frequently been pointed out that the Pfitzinger reaction represents the most convenient route to 2- and 2,3-substituted quinolines, were it not for the limitations to its generality imposed by steric hindrance.[1] Another anomaly recently brought to light in this connection, is the fact that isatin reacts with *p*-hydroxyaryl ketones at a considerably slower rate than with the corresponding *p*-methoxy ketones.[2] The present work extends these observations to the Pfitzinger reaction with *p*-hydroxy and *p*-methoxy ketones derived from 2-hydroxydiphenyl.

The preparation of the intermediary ketones required the study of Friedel-Crafts acylations of 2-methoxydiphenyl, a question which hitherto had been investigated only slightly. Auwers and Fittig[3] briefly mentioned that the aluminum chloride-catalyzed reaction of acetyl chloride with *o*-methoxydiphenyl yielded 5-acetyl-2-methoxydiphenyl (I). A more detailed investigation of these Friedel-Crafts reactions with aliphatic and aromatic acid chlorides showed that the substitution occurs exclusively in the position *para* to the methoxy group, and 5-propionyl- (II), 5-butyryl- (III), 5-valeryl- (IV), 5-benzoyl- (V) and 5-phenacetyl-2-methoxydiphenyl (VI) were obtained in high yields. Thus, in the molecule of 2-methoxydiphenyl the directing influence of the methoxy group overrides that of the phenyl radical, in contrast with 4-methoxyphenyl,[4] which is acylated to mixtures of 2- and 4′-acyl-4-methoxydiphenyl, and with 2-methoxynaphthalene,[5] which undergoes substitution in position 6 with aliphatic acid chlorides and in position 1 with aromatic acid chlorides when nitrobenzene is the solvent.



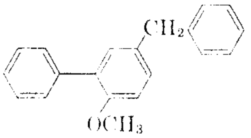
I R = CH_3
II R = C_2H_5
III R = $CH_2CH_2CH_3$
IV R = $(CH_2)_3CH_3$
V R = C_6H_5
VI R = $CH_2C_6H_5$



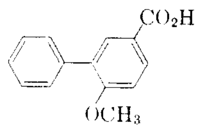
VII R = CH_3
VIII R = C_2H_5
IX R = $CH_2CH_2CH_3$
X R = $(CH_2)_3CH_3$
XI R = C_6H_5
XII R = $CH_2C_6H_5$

Treatment of the ketones I to VI with boiling pyridine hydrochloride afforded the corresponding hydroxy ketones VII to XII. This was a more satisfactory method for preparing ketones of this type than the Fries rearrangement of esters of 2-dihydroxyphenyl which gives mixtures of 3-acyl- and 5-acyl-2-hydroxydiphenyls.

Friedel-Crafts benzylation of 2-methoxydiphenyl likewise occurred in the position *para* to the methoxy group, the 5-benzyl-2-methoxydiphenyl (XIII) thus obtained being identical with the Kishner-Wolff reduction-product of ketone V. The constitution of the latter ketone was confirmed by its alternative preparation through a Friedel-Crafts reaction of the chloride of 4-methoxy-3-phenylbenzoic acid (XIV) with benzene; this acid was readily obtained by sodium hypobromite degradation of 5-acetyl-2-methoxydiphenyl.



XIII



XIV

The Pfitzinger condensation of isatin with the *methoxy* ketones I, II, III, and VI readily afforded 2-(2-methoxy-5-diphenylyl)- (XV), 2-(2-methoxy-5-diphenylyl)-3-methyl- (XVI), 2-(2-methoxy-5-diphenylyl)-3-ethyl- (XVII), and 2-(2-methoxy-5-diphenylyl)-3-phenylcinchoninic acid (XVIII), but ketone IV gave no sizable amount of a cinchoninic acid under the same experimental conditions. Again, as in the case of hydroxy ketones previously investigated,[2] ketones VII, VIII, IX, and XII failed to condense with isatin even when the standard time of heating was doubled. 2-(2-Hydroxy-5-diphenylyl)-(XIX), 2-(2-hydroxy-5-diphenylyl)-3-methyl- (XX), 2-(2-hydroxy-5-diphenylyl)-3-

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[1] Buu-Hoï and Cagniant, *Rec. trav. chim.*, **62**, 519, 713 (1943); **64**, 214 (1945); *Bull. soc. chim.*, **13**, 123, 134 (1946); Buu-Hoï, *J. Chem. Soc.*, 795 (1946); Buu-Hoï and Royer, *Bull. soc. chim.*, **13**, 374 (1946); **17**, 489 (1950); *J. Chem. Soc.*, 106 (1948); *Rec. trav. chim.*, **70**, 825 (1951); Buu-Hoï, Royer, Xuong, and Jacquignon, *J. Org. Chem.*, **18**, 1209 (1953).

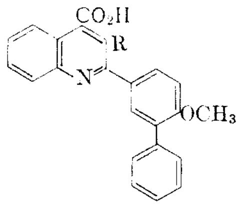
[2] Buu-Hoï and Miquel, *J. Chem. Soc.*, 3768 (1953).

[3] von Auwers and Fittig, *J. prakt. Chem.*, **108**, 106 (1925).

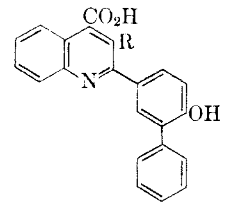
[4] Fieser and Bradsher, *J. Am. Chem. Soc.*, **58**, 1738, 2337 (1936).

[5] Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

ethyl- (XXI), and 2-(2-hydroxy-5-diphenyl)-3-phenyl-cinchoninic acid (XXII) however were readily prepared by demethylation of the corresponding methoxy acids by means of pyridine hydrochloride. In both series of cinchoninic acids, thermal decarboxylation yielded the corresponding quinolines.



XV R = H
XVI R = CH_3
XVII R = C_2H_5
XVIII R = C_6H_5



XIX R = H
XX R = CH_3
XXI R = C_2H_5
XXII R = C_6H_5

EXPERIMENTAL

5-Acetyl-2-methoxydiphenyl (I). To an ice-cooled solution of 28 g. of 2-methoxydiphenyl and 14 g. of acetyl chloride in 200 ml. of carbon disulfide, 24 g. of finely powdered aluminum chloride was added in small portions with stirring, and the mixture was kept for two hours at room temperature. After decomposition with ice-cooled dilute hydrochloric acid, the organic layer was washed with an aqueous solution of sodium carbonate, then with water, dried over sodium sulfate, and the solvent was removed. Vacuum-distillation of the residue gave a 93% yield (33 g.) of ketone I, which crystallized from ethanol in lustrous colorless needles, melting at 94°, and giving a *semicarbazone,* m.p. 211°; the literature[3] gave m.p. 91.5–92° for the ketone, and 209–210° for the semicarbazone. No sizable amount of an isomeric ketone was obtained in this reaction, nor when nitrobenzene was the solvent.

6-Hydroxy-3-acetyldiphenyl (VII). A mixture of one part of ketone I with four parts of redistilled pyridine hydrochloride was gently refluxed for one hour, and on cooling, the reaction mixture was treated with water. The solid precipitate (90% yield) crystallized from methanol in colorless needles, m.p. 173°; the literature [2,6] gave m.p. 173° for 5-acetyl-2-hydroxydiphenyl.

4-Methoxy-3-phenylbenzoic acid (XIV). The foregoing ketone (23 g.) was shaken at 40° with an excess of an aqueous solution of sodium hypobromite in the presence of a few ml. of dioxane until the solid had disappeared. After decomposition of the hypobromite in excess with hydrogen sodium sulfide, the ether-extraction of the bromoform, the aqueous layer was acidified with dilute hydrochloric acid. Yield: 82% of an *acid* which crystallized from aqueous ethanol in shiny colorless leaflets, m.p. 219°.

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.5; H, 5.3.

2-(2-Methoxy-5-diphenylyl)cinchoninic acid (XV). A solution of 23 g. of 5-acetyl-2-methoxydiphenyl, 15 g. of isatin, and 17 g. of potassium hydroxide in 110 ml. of ethanol and 10 ml. of water was refluxed for 72 hours. After evaporation of the ethanol, water was added, and the neutral impurities were removed by ether extraction. Acidification with acetic acid gave an 82% yield of *cinchoninic acid* XV, crystallizing from acetic acid in colorless needles, m.p. 248°.

Anal. Calc'd for $C_{23}H_{17}NO_3$: C, 77.7; H, 4.8. Found: C, 77.8; H, 5.0.

This acid was heated above its melting point, and the residue was vacuum-distilled; crystallization from cyclohexane gave *2-(2-methoxy-5-diphenylyl)quinoline,* fine colorless prisms, m.p. 100°. This base gave a *picrate,* shiny yellow prisms, m.p. 190°.

Anal. Calc'd for $C_{22}H_{17}NO$: C, 84.9; H, 5.5. Found: C, 84.6; H, 5.4.

2-(2-Hydroxy-5-diphenylyl)cinchoninic acid (XIX). A mixture of one part of acid XV and four parts of pyridine hydrochloride was gently refluxed for one hour; after cooling, water was added, and the precipitate was collected and redissolved in an aqueous solution of sodium hydroxide. Acidification with acetic acid afforded, in 72% yield, a product which crystallized from ethanol in yellowish needles, m.p. 296–297°. This compound could not be obtained by a Pfitzinger reaction, even after six days' heating.

Anal. Calc'd for $C_{22}H_{15}NO_3$: C, 77.4; H, 4.4. Found: C, 77.5; H, 4.5.

This acid was heated at about 300° until carbon dioxide ceased to evolve, and the residue was crystallized from ethanol, giving *2-(2-hydroxy-5-diphenylyl)quinoline,* pale yellow prisms, m.p. 205°.

Anal. Calc'd for $C_{21}H_{15}NO$: C, 84.8; H, 5.1. Found: C, 84.5; H, 5.3.

5-Propionyl-2-methoxydiphenyl (II). Prepared in 86% yield from 18 g. of 2-methoxydiphenyl, 11 g. of propionyl chloride, and 16 g. of aluminum chloride in 200 ml. of carbon disulfide (4 hours at room temperature), this *ketone* crystallized from ethanol in shiny colorless leaflets, m.p. 92°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.8; H, 6.7.

The corresponding *semicarbazone* crystallized from ethanol in shiny colorless needles, m.p. 191°.

Anal. Calc'd for $C_{17}H_{19}N_3O_2$: N, 14.1. Found: N, 14.0.

Treatment of ketone II with pyridine hydrochloride as for the lower homolog, gave *5-propionyl-2-hydroxydiphenyl,* m.p. 148–149°, in accordance with the literature.[2,6]

2-(2-Methoxy-5-diphenylyl)-3-methylcinchoninic acid (XVI). Obtained in 68% yield after four days' heating, this *acid* crystallized from acetic acid in colorless needles, m.p. 292–293°.

Anal. Calc'd for $C_{24}H_{19}NO_3$: C, 78.0; H, 5.1. Found: C, 77.8; H, 5.0.

2-(2-Methoxy-5-diphenylyl)-3-methylquinoline crystallized from cyclohexane in colorless needles, m.p. 100°; the corresponding *picrate* melted at 179°.

Anal. Calc'd for $C_{23}H_{19}NO_3$: C, 84.9; H, 5.8. Found: C, 85.1; H, 6.0.

2-(2-Hydroxy-5-diphenylyl)-3-methylcinchoninic acid (XX). This substance could not be obtained by a Pfitzinger reaction, even after eight days' heating. It was prepared by the demethylation method, and it crystallized from acetic acid in colorless needles, m.p. 312°.

Anal. Calc'd for $C_{23}H_{17}NO_3$: C, 77.7; H, 4.8. Found: C, 77.6; H, 4.9.

2-(2-Hydroxy-5-diphenylyl)-3-methylquinoline crystallized from aqueous ethanol in yellowish needles, m.p. 196°.

Anal. Calc'd for $C_{22}H_{17}NO$: C, 84.9; H, 5.5. Found: C, 84.6; H, 5.7.

5-Butyryl-2-methoxydiphenyl (III). Prepared in 90% yield as for the lower homolog, this *ketone* boiled at 243–245°/18 mm., and crystallized from light petroleum in colorless leaflets, m.p. 64°. No isomeric ketone was formed.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.5; H, 7.1.

Its *semicarbazone* crystallized from ethanol in silky colorless needles, m.p. 186°.

Anal. Calc'd for $C_{18}H_{21}N_3O_2$: N, 13.5. Found: N, 13.3.

5-Butyryl-2-hydroxydiphenyl (IX). This *ketone* crystallized from aqueous ethanol in shiny colorless leaflets, m.p. 123°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.1; H, 7.0.

2-(2-Methoxy-5-diphenylyl)-3-ethylcinchoninic acid (XVII). Obtained in 66% yield after five days' heating, this *acid* crystallized from acetic acid in colorless needles, m.p. 274–285°.

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(6) Buu-Hoï and Séailles, Jr., *J. Org. Chem.,* **20,** 606 (1955).

Anal. Calc'd for $C_{25}H_{21}NO_3$: C, 78.3; H, 5.5. Found: C, 78.0; H, 5.6.

2-(2-Hydroxy-5-diphenylyl)-3-ethylcinchoninic acid (XXI) crystallized from ethanol in gray-tinged needles, m.p. 328°. No trace of this acid was obtained after ten days' refluxing of an ethanol solution of ketone IX, isatin, and potassium hydroxide.

Anal. Calc'd for $C_{24}H_{19}NO_3$: C, 78.0; H, 5.1. Found: C, 78.1; H, 5.2.

2-(2-Hydroxy-5-diphenylyl)-3-ethylquinoline crystallized from ethanol in yellowish needles, m.p. 184°.

Anal. Calc'd for $C_{23}H_{19}NO$: C, 84.9; H, 5.8. Found: C, 85.1; H, 6.0.

5-Valeryl-2-methoxydiphenyl (IV). Prepared in 85% yield, this *ketone* was a pale yellow oil, b.p. 275–280°/27 mm., n_D^{27} 1.5857.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.5; H, 7.5.

Its *semicarbazone* crystallized from ethanol in colorless prisms, m.p. 141°.

Anal. Calc'd for $C_{19}H_{23}N_3O_2$: N, 12.9. Found: N, 13.1.

5-Valeryl-2-hydroxydiphenyl (X) crystallized from methanol in fine colorless needles, m.p. 75°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.5; H, 7.1.

5-Phenacetyl-2-methoxydiphenyl (VI). Prepared in 90% yield, this *ketone* crystallized from ligroin in silky colorless needles, m.p. 124°.

Anal. Calc'd for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.3; H, 6.2.

5-Phenacetyl-2-hydroxydiphenyl (XII) crystallized from methanol in fine colorless prisms, m.p. 145°.

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.5; H, 5.6.

2-(2-Methoxy-5-diphenylyl)-3-phenylcinchoninic acid (XVIII). This *acid*, obtained in 60% yield after five days' heating, crystallized from acetic acid in yellowish needles, m.p. 275°.

Anal. Calc'd for $C_{29}H_{21}NO_3$: C, 80.7; H, 4.9. Found: C, 80.5; H, 5.0.

2-(2-Hydroxy-5-diphenylyl)-3-phenylquinoline crystallized from methanol in colorless prisms, m.p. 118°.

Anal. Calc'd for $C_{28}H_{21}NO$: C, 86.8; H, 5.4. Found: C, 87.0; H, 5.5.

2-(2-Hydroxy-5-diphenylyl)-3-phenylcinchoninic acid (XXII) crystallized from ethanol in yellowish leaflets, m.p. 295°.

Anal. Calc'd for $C_{28}H_{19}NO_3$: C, 80.6; H, 4.6. Found: C, 80.3; H, 4.7.

2-(2-Hydroxy-5-diphenylyl)-3-phenylquinoline crystallized from ethanol in fine colorless prisms, m.p. 204°.

Anal. Calc'd for $C_{27}H_{19}NO$: C, 86.9; H, 5.1. Found: C, 87.1; H, 5.3.

5-Benzoyl-2-methoxydiphenyl (V). Prepared in 85% yield, this *ketone* crystallized from ligroin in shiny colorless prisms, m.p. 70–71°.

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.2; H, 5.6.

The same substance was obtained in lower yield from 4-methoxy-3-phenylbenzoyl chloride, benzene, and aluminum chloride.

5-Benzoyl-2-hydroxydiphenyl (XI) crystallized from methanol in lustrous colorless leaflets, m.p. 196°.

Anal. Calc'd for $C_{19}H_{14}O_2$: C, 83.2; H, 5.1. Found: C, 83.5; H, 5.0.

5-Benzyl-2-methoxydiphenyl (XIII). Prepared either from ketone V, hydrazine hydrate, and potassium hydroxide in diethylene glycol following the usual procedure,[7] or from 2-methoxydiphenyl, benzyl chloride and fused zinc chloride,[8] this *substance* was a pale yellow viscous oil, b.p. 268–270°/28 mm., n_D^{25} 1.6298.

Anal. Calc'd for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.5; H, 6.6.

Its demethylation with pyridine hydrochloride (one hour's refluxing) yielded *5-benzyl-2-hydroxydiphenyl*, crystallizing from light petroleum in colorless prisms, m.p. 51°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2. Found: C, 87.5; H, 6.5.

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[7] Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

[8] Buu-Hoï and Demerseman, *J. Org. Chem.*, **20**, 1129 (1955).