wise with stirring, whereupon a vigorous exothermic reaction set up. The red mixture was then refluxed for 1 hr. on a water bath; after cooling, the acrylonitrile in excess was distilled off in a vacuum, and the residue was recrystallized twice from acetone, giving a 75% yield of fine colorless needles, m.p. 163°. Like its sulfur analog, this nitrile was readily soluble in benzene and acetone, sparingly soluble in ethanol.

Anal. Calcd. for $C_{15}H_{12}N_2Se$: C, 60.2; H, 4.1; N, 9.4. Found: C, 60.2; H, 4.1; N, 9.4.

β-(2-Chloro-10-phenoselenazyl)propionitrile (VI). This nitrile was obtained in 75% yield from 15 g. of 2-chlorophenoselenazine and 19 ml. of acrylonitrile, as for the above. It crystallized from acetone in colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{15}H_{11}ClN_2Se$: Cl, 10.6; N, 8.4. Found: Cl, 10.8; N, 8.5.

β-(10-Phenoselenazyl)propionic acid (VII). A solution of 22 g. of β-(10-phenoselenazyl)propionitrile and 18.5 g. of sodium hydroxide in 350 ml. of ethanol was gently refluxed for 15 hr.; after cooling, 500 ml. of water was added, a small amount of solid was filtered off, and the filtrate was acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, giving 16.5 g. of lustrous colorless leaflets, m.p. 193°.

Anal. Calcd. for $C_{15}H_{13}NO_2Se$: C, 56.7; H, 4.1; N, 4.4. Found: C, 56.7; H, 4.3; N, 4.4.

β-(2-Chloro-10-phenoselenazyl)propionic acid (VIII). Similarly prepared by hydrolysis of nitrile VI, this acid crystallized from ethanol in shiny colorless needles, m.p. 188°, giving a cherry red coloration in sulfuric acid.

Anal. Calcd. for $C_{15}H_{12}ClNO_2Se$: C, 51.1; H, 3.4; N, 4.0. Found: C, 51.1; H, 3.5; N, 4.1.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (IX). To a solution of 5 g. of acid VII in 100 ml. of anhydrous benzene, 20 g. of phosphorus pentoxide was added and the mixture was refluxed for 1 hr. on a water bath. After cooling, the benzene was decanted from a dark solid mass, which was cautiously treated with ice, and the reaction product was taken up in benzene. The benzene solution was washed with aqueous sodium carbonate, then with water, dried over sodium sulfate, the solvent was distilled off, and the residue recrystallized several times from ethanol. Yield: 3 g. of shiny yellow needles, m.p. 115°, giving in sulfuric acid a blue halochromy rapidly turning pinkish orange.

Anal. Calcd. for $C_{15}H_{11}NOSe$: C, 60.1; H, 3.7; N, 4.7. Found: C, 60.0; H, 3.9; N, 4.6.

This ketone gave a *phenylhydrazone*, which crystallized from ethanol in shiny dark yellow leaflets, m.p. 180°.

10-Chloro-2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (X). This ketone, prepared in 70% yield by cyclization of acid VIII with phosphorus pentoxide, crystallized from ethanol in microscopic yellow needles, m.p. 146°, giving a brownish red halochromy in sulfuric acid. No isomeric ketone could be isolated, although in the preparation of the corresponding sulfur analog, Fujii[8] detected some of the isomer in the form of its oxime.

Anal. Calcd. for $C_{15}H_{10}ClNOSe$: C, 53.8; H, 3.0; N, 4.2 Found: C, 54.1; H, 3.2; N, 4.3.

Acknowledgment. Our thanks are due to Dr. Nathan L. Smith (University of Florida, Gainesville) for the gift of benzyltrimethylammonium methoxide used in this work. We are also indebted to Professors H. Maureu and P. Chovino and Dr. Lévy, of the Laboratoire Municipal (Paris), for several microanalyses.

PARIS V^e^, FRANCE

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Orientation in Friedel-Crafts Acylations of 3-Chloro-2-methoxybiphenyl

N. P. BUU-HOÏ AND LOUIS PETIT

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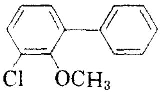
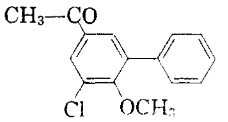
Friedel-Crafts acetylation of 3-chloro-2-methoxybiphenyl is shown to occur in position 5 when the catalyst is stannic chloride, and in both positions 5 and 4′ when aluminum chloride is used. In the course of this investigation, a number of new derivatives of 3-chloro-2-methoxybiphenyl have been prepared.

As a part of a general study of biphenyl derivatives,[1] both theoretical (orientation problems) and practical (search for potential pharmaceuticals and germicides), the reactivity of 3-chloro-2-methoxybiphenyl (I) has been investigated.

It is known that Friedel-Crafts acylation of 2-methoxybiphenyl with acetyl chloride in the presence of aluminum chloride[2] occurs at position 5, and that other acid chlorides behave in the same way.[3] Hence it was of interest to investigate the orientation in similar reactions with 3-chloro-2-methoxybiphenyl. In this molecule, the presence of a chlorine atom in position 3 suggests that it would have a deactivating influence on position 5, the prospective site of substitution, and, this being the case, then heteronuclear substitution, *e.g.* at position 4′, should also



(I)



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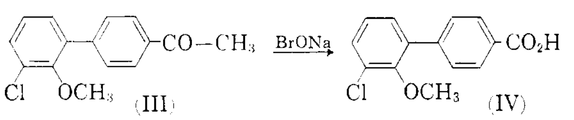
(1) *Cf.* N. P. Buu-Hoï and R. Royer, *Bull. soc. chim. France*, **17**, 489 (1950); *Rec. trav. chim.*, **70**, 825 (1951); N. P. Buu-Hoï, M. Sy, and J. Riché, *J. Org. Chem.*, **22**, 668 (1957); G. Viel, M. Sy, and N. P. Buu-Hoï, *Bull. soc. chim. biol.*, in press.

(2) K. von Auwers and G. Wittig, *J. prakt. Chem.*, **108**, 106 (1925).

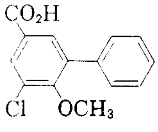
(3) *Cf.* N. P. Buu-Hoï and M. Sy, *J. Org. Chem.*, **21**, 136 (1956).

be expected to occur concurrently with the normal 5-substitution.

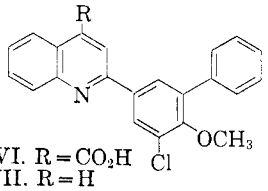
It is now found that the reaction between 3-chloro-2-methoxybiphenyl and acetyl chloride in the presence of aluminum chloride does in fact yield a mixture of two products, one a solid, m.p. 75°, the other an isomeric ketone which was liquid. The solid ketone proved to be 5-acetyl-3-chloro-2-methoxybiphenyl (II), as it was obtained in good yield and as sole product when, in place of aluminum chloride, stannic chloride was used; the latter is known to be a satisfactory catalyst for the acylation of phenol ethers but not for that of non-condensed aromatic hydrocarbons. The homogeneity of the liquid ketone to which the structure of 4′-acetyl-3-chloro-2-methoxybiphenyl (III) could thus be assigned,



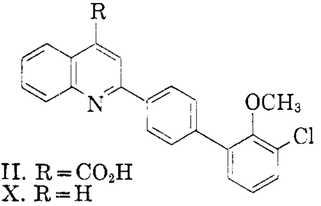
was proven by its oxidation with sodium hypobromite to give only one acid, which was therefore 3-chloro-2-methoxybiphenyl-4′-carboxylic acid (IV). Oxidation of the solid ketone II under similar conditions afforded 3-chloro-2-methoxybiphenyl-5-carboxylic acid (V), whose high melting point (257°) is consistent with that of the corresponding nonchlorinated acid (m.p. 219°) previously reported.[3] Both ketones II and III readily underwent Pfitzinger reaction with isatin in the presence of potassium hydroxide to give 2-(3-chloro-2-methoxy-5-biphenylyl)- (VI) and 2-(3-chloro-2-methoxy-4′-biphenylyl)-cinchoninic acid (VIII), which underwent thermal decomposition to the corresponding quinolines VII and IX.



(V)



VI. R = CO_2H
VII. R = H



VIII. R = CO_2H
IX. R = H

At variance with acetylation, in which the two isomeric ketones could be separated, aluminum chloride-catalyzed acylations with higher acid chlorides such as propionyl and butyryl chloride furnished liquid products, which were probably mixtures of ketones, but which could not be resolved. The same observation was made with benzoyl and phenacetyl chloride.

EXPERIMENTAL

Aluminum chloride–catalyzed acetylation of 3-chloro-2-methoxybiphenyl. To a water-cooled mixture of 22 g. of 3-chloro-2-methoxybiphenyl (prepared from the corresponding phenol by methylation with dimethyl sulfate and sodium hydroxide in aqueous methanol) and 14 g. of finely powdered aluminum chloride in 150 ml. of anhydrous carbon disulfide, 8.3 g. of acetyl chloride was added in small portions. After 12 hr. standing at room temperature, the mixture was heated on a warm water bath, and on cooling, decomposed with dilute hydrochloric acid. The reaction product was taken up in chloroform, washed with 10% aqueous sodium hydroxide, then with water, dried over calcium chloride, the solvents distilled off, and the residue vacuum-fractionated. Yield: 23 g. (88%) of a portion, b.p. 200–237°/20 mm., consisting of a ketonic mixture which crystallized partly after 45 days in the refrigerator.

(*a*) The crystalline portion (16 g.) was recrystallized several times from benzene plus petroleum ether, to give *5-acetyl-3-chloro-2-methoxybiphenyl* (II), shiny colorless prisms, m.p. 75°, giving a red halochromism with sulfuric acid.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 69.2; H, 5.1.

(*b*) The liquid fraction was redistilled *in vacuo*, to give 6 g. of *4′-acetyl-3-chloro-2-methoxybiphenyl* (III), a pale yellow viscous oil, b.p. 231–235°/25 mm., n_D^{25} 1.6256, also giving a red halochromism with sulfuric acid.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 68.9; H, 5.0.

Stannic chloride–catalyzed acetylation of 3-chloro-2-methoxybiphenyl. This reaction, performed as above with 26.5 g. of stannic chloride in place of aluminum chloride, afforded a 77% yield of a product which solidified completely, and gave on recrystallization from ethanol, ketone II, m.p. and mixed m.p. 75°.

3-Chloro-2-methoxybiphenyl-4′-carboxylic acid (IV). A solution of 2.6 g. of the liquid ketone (III) in dioxane was shaken with aqueous sodium hypobromite in excess, first at room temperature, then at 45–50°; the aqueous layer was extracted with chloroform and the excess of the oxidant was destroyed by addition of aqueous sodium hydrogen sulfite. The precipitate formed on acidification with hydrochloric acid was recrystallized from acetic acid, to give shiny colorless prisms, m.p. 172°; yield: 80%.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.0; H, 4.2. Found: C, 64.0; H, 4.3.

3-Chloro-2-methoxybiphenyl-5-carboxylic acid (V). Similar oxidation of the solid ketone (II) afforded an 80% yield of an acid, crystallizing from acetic acid in colorless, sublimable needles, m.p. 250°.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.0; H, 4.2. Found: C, 63.8; H, 4.3.

Pfitzinger reaction of ketone II. A solution of 2.6 g. of the ketone, 1.5 g. of isatin, and 1.5 g. of potassium hydroxide in 12 ml. of ethanol was refluxed for 78 hr.; after cooling, water was added and the neutral impurities extracted with ether. Acidification of the aqueous layer with acetic acid gave a precipitate of *2-(3-chloro-2-methoxy-5-biphenylyl)-cinchoninic acid* (VI), crystallizing from acetic acid in shiny yellowish prisms, m.p. 232°. Yield: 65%.

Anal. Calcd. for $C_{23}H_{16}ClNO_3$: C, 70.9; H, 4.2; N, 3.6. Found: C, 70.9; H, 4.2; N, 3.6.

Decarboxylation of this acid was effected by heating above its melting point, followed by vacuum-distillation of the reaction product; *2-(3-chloro-2-methoxy-5-biphenylyl)-quinoline* (VII) crystallized from ethanol in shiny colorless prisms, m.p. 201°. Yield: 80%.

Anal. Calcd. for $C_{22}H_{16}ClNO$: N, 4.1. Found: N, 4.1.

The corresponding *picrate* crystallized from ethanol in shiny yellow needles, m.p. 192°.

Anal. Calcd. for $C_{28}H_{19}ClN_4O_8$: C, 58.5; H, 3.3. Found: C, 58.4; H, 3.3.

Pfitzinger reaction of ketone III. The reaction with the liquid ketone (III) was performed in a similar manner, giving a 65% yield of *2-(3-chloro-2-methoxy-4'-biphenylyl)-cinchoninic acid* (VIII), crystallizing from acetic acid in yellowish prisms, m.p. 209°.

Anal. Calcd. for $C_{23}H_{16}ClNO_3$: Cl, 9.1. Found: Cl, 9.0.

2-(3-Chloro-2-methoxy-4'-biphenylyl)quinoline (IX), obtained on thermal decarboxylation of the above acid, crystallized from ethanol in shiny colorless prisms, m.p. 199°.

Anal. Calcd. for $C_{22}H_{16}ClNO$: N, 4.1. Found: N, 4.1.

The corresponding *picrate* crystallized from ethanol in bright yellow needles, m.p. 188°.

Anal. Calcd. for $C_{28}H_{19}ClN_4O_8$: N, 9.7. Found: N, 9.8.

Other acylations of 3-chloro-2-methoxybiphenyl. (*a*) Reaction of 22 g. of I with 9.8 g. of propionyl chloride in the presence of 14 g. of aluminum chloride furnished a 73% yield of *propionyl-3-chloro-2-methoxybiphenyl*, viscous, pale yellow oil, b.p. 230–235°/20 mm., which failed to solidify even partly, on standing in the refrigerator. Red halochromism forms with sulfuric acid.

Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 70.2; H, 5.5. Found: C, 69.8; H, 5.5.

(*b*) Similar reaction with 11.2 g. of butyryl chloride afforded a 69% yield of an oily *butyryl-3-chloro-2-methoxybiphenyl*, b.p. 230°/15 mm.

Anal. Calcd. for $C_{17}H_{17}ClO_2$: C, 70.7; H, 5.9. Found: C, 70.8; H, 5.8.

(*c*) With 14.7 g. of benzoyl chloride, the reaction gave a 77% yield of a viscous, oily ketone, b.p. 265–270°/16 mm.

Anal. Calcd. for $C_{20}H_{15}ClO_2$: C, 74.4; H, 4.7. Found: C, 74.6; H, 4.6.

(*d*) With 16.3 g. of phenacetyl chloride, the reaction gave a 68% yield of an oil, b.p. 270–280°/16 mm.

Anal. Calcd. for $C_{21}H_{17}ClO_2$: C, 74.9; H, 5.1. Found: C, 74.9; H, 5.0.

This last ketone mixture underwent a positive Pfitzinger reaction with isatin, to give in 68% yield and after 5 days' refluxing, a *cinchoninic acid*, crystallizing from acetic acid in yellowish prisms, m.p. 295°.

Anal. Calcd. for $C_{29}H_{20}ClNO_3$: C, 74.8; H, 4.3. Found: C, 74.5; H, 4.3.

The corresponding *quinoline* crystallized from ethanol in colorless needles, m.p. 164°.

Anal. Calcd. for $C_{28}H_{20}ClNO$: C, 79.7; H, 4.8. Found: C, 79.7; H, 4.8.

PARIS V^e, FRANCE

[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Rearrangement of Methyl 3-Azabenzocycloheptene-4,7-dione-6-carboxylate to 2,4-Dihydroxyquinoline-3-acetic Acid in Acid and Base

T. A. GEISSMAN AND A. K. CHO

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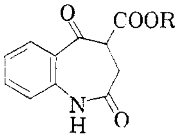
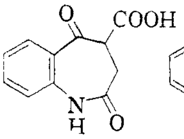
The preparation of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate (I) and its rearrangement in aqueous acid and base to 2,4-dihydroxyquinoline-3-acetic acid (III) are described. The quinoline structure of the rearrangement product is shown by its ultraviolet spectrum and by its conversion to dihydrodictamnine (VI). The ring closure of 2,4-dihydroxy-3-(2'-hydroxyethyl)quinoline to dihydrodictamnine was achieved in this work with sodium hydride and *p*-toluenesulfonyl chloride.

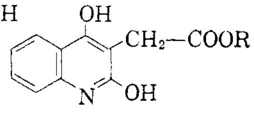
The azabenzocycloheptenedione (I) was prepared by carrying out a Dieckmann cyclization of methyl *N*- β-carbomethoxypropionylanthranilate with sodium in boiling toluene. The corresponding ethyl ester has been prepared recently by MacPhillamy *et al.*[1] who described the resistance to decarboxylation of the acid obtained by hydrolysis of Ia. A similar observation was made in the course of this work and an explanation for the stability of the product, assumed to be the β-ketoacid (II), was provided by investigation of the acid obtained by the basic and acid hydrolysis of the azabenzocycloheptenedione (I). The ultraviolet spectrum and subsequent reactions of the hydrolysis product showed it to be 2,4-dihydroxyquinoline-3-acetic acid (III). The ultraviolet spectrum of the hydrolysis product had double maxima in the 270 mμ and 300–340 mμ range, characteristic of 2,4-dihydroxyquinolines.[2]



I. R = CH_3
Ia. R = C_2H_5



II



III. R = H
IIIa. R = CH_3

Further evidence for the quinoline nature of the hydrolysis product was provided by its conversion to dihydrodictamnine (VI). This was accomplished by treating III with excess ethereal diazomethane to give 4-methoxy-2-hydroxyquinoline-3-acetic acid methyl ester (IV), which was reduced to 4-methoxy-2-hydroxy-3-(2'-hydroxyethyl)quinoline (V). Cooke[3] has prepared dictamnine using this approach but was able to obtain the quinoline acetic acid ester (IIIa) directly. Treatment of V with sodium hydride in tetrahydrofuran followed by *p*-toluenesulfonyl chloride[4] gave dihydrodictamnine.

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[1] H. B. MacPhillamy, R. L. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Am. Chem. Soc.*, **80**, 2172 (1958).

[2] R. F. C. Brown, J. J. Hobbs, G. K. Hughes, and E. Ritchie, *Australian J. Chem.*, **7**, 348 (1954).

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[4] J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, Jr., *J. Am. Chem. Soc.*, **74**, 4283 (1952).