[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

A Synthesis of Thyronamine and Its Lower Homolog

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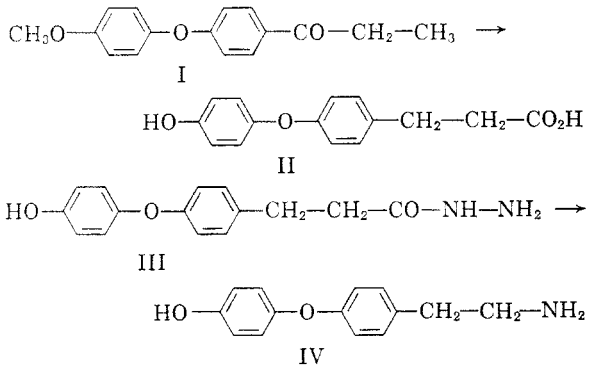
Received March 30, 1961

A four-step synthesis of thyronamine is reported, starting from 4'-methoxy-4-phenoxypropiophenone, and a similar preparation of its lower homolog, 4'-hydroxy-4-phenoxybenzylamine, starting from 4'-methoxy-4-phenoxyacetophenone, is described. In the course of this work, the Pfitzinger reaction of ketones of this type is investigated.

Thyronamine, or β-(4'-hydroxy-4-phenoxy)-phenylethylamine (IV), is the theoretical product of total reductive deiodination of thyroxamine, the biologically active decarboxylation-product of the thyroid gland hormone thyroxine.[1] As several β-phenylethylamines are known to display interesting pharmacological properties as sympathomimetic amines,[2] as inhibitors of monoamine oxidase,[3] or as appetite-depressing agents, it was deemed worthwhile to elaborate a convenient method for synthesizing thyronamine and similar compounds.

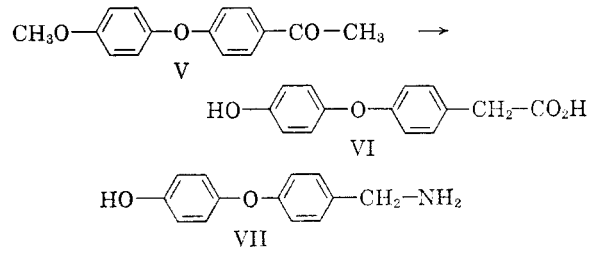
Our synthesis started with 4-phenoxyanisole, which underwent



Friedel-Crafts reaction with propionyl chloride to give 4'-methoxy-4-phenoxypropiophenone (I) in excellent yield. A Willgerodt reaction of this ketone with morpholine and sulfur[4] led to the thiomorpholide of β-(4'-methoxy-4-phenoxy)phenylpropionic acid, which was hydrolyzed by means of hydrobromic acid in acetic acid, an operation which also brought about demethylation, to give β-(4'-hydroxy-4-phenoxy)phenylpropionic acid (II). When, in the Willgerodt reaction, other secondary amines such as diethylamine or piperidine were used in place of morpholine, the results were far less satisfactory; lengthening of the side-chain also had an adverse effect, as could be expected,[5] since we were unable to prepare an acid from 4'-methoxy-4-phenoxybutyrophenone.

β-(4'-Hydroxy-4-phenoxy)phenylpropionic acid was converted *via* its ethyl ester into the corresponding hydrazide (III), which in turn underwent a Curtius degradation to give thyronamine. The preparation of thyronamine was briefly mentioned by Funke and Favre,[6] who chloromethylated 4-phenoxyanisole and condensed the resulting chloromethyl compound with potassium cyanide; the nitrile obtained was hydrogenated and the methoxyamine formed was demethylated. No experimental details however were given for any of these steps.

4'-Methoxy-4-phenoxyacetophenone (V) underwent the Willgerodt reaction more easily than its higher homolog (I), and the thiomorpholide of 4'-



methoxy-4-phenoxyphenylacetic acid was readily hydrolyzed with aqueous sulfuric acid to the corresponding acid; this in turn was demethylated to 4'-hydroxy-4-phenoxyphenylacetic acid (VI), whose hydrazide underwent a Curtius degradation to afford 4'-hydroxy-4-phenoxybenzylamine (VII).

In the course of this work, we investigated the behavior of 4'-methoxy-4-phenoxyacetophenone and several of its higher homologs in the Pfitzinger reaction. These ketones were prepared in good yields by Friedel-Crafts reaction of 4-phenoxyanisole with the corresponding acid chloride. As could be expected from earlier investigations,[7] ketones V, I, and 4'-methoxy-4-phenoxybutyrophenone gave good yields of the corresponding 2-(4'-methoxy-4-phenoxyphenyl)cinchoninic acids (VIII), (IX), and (X), whereas in the same experi-

(1) See O. Thibault and A. Lachaze, *Compt. rend.*, 232, 1318 (1951); *Compt. rend. Soc. Biol.*, 145, 797 (1951); 146, 50 (1952).

(2) See A. Burger, *Medicinal Chemistry*, 1st. Ed., Vol. I, Interscience Publishers, Inc., New York, 1951, p. 294.

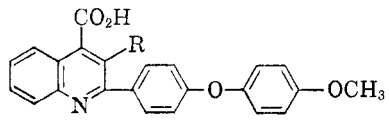
(3) M. Ozaki, H. Weissbach, A. Ozaki, B. Witkop, and S. Udenfriend, *J. Med. Pharm. Chem.*, 2, 591 (1960).

(4) *Cf.* K. Kindler and T. P. Li, *Ber.*, 74, 321 (1941).

(5) This effect is not without analogy with what is observed in Pfitzinger reactions.

(6) A. Funke and C. Favre, *Bull. soc. chim. France*, 832 (1951).

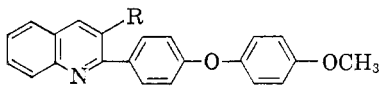
(7) N. P. Buu-Hoï and P. Cagniant, *Bull. soc. chim. France*, 13, 123 (1946); N. P. Buu-Hoï, R. Royer, N. D. Xuong, and P. Jacquignon, *J. Org. Chem.*, 18, 1209 (1953).



VIII. R = H
IX. R = CH_3
X. R = C_2H_5

mental conditions, 4′-methoxy-4-phenoxyisovalerophenone gave no cinchoninic acid. Thermal decarboxylation of the cinchoninic acids obtained readily gave the corresponding 2-(4′-methoxy-4-phenoxyphenyl)quinolines (XI), (XII), and (XIII).

Preliminary biological tests indicate that thyronamine does not possess the prominent sympathomimetic properties of tyramine.



XI. R = H
XII. R = CH_3
XIII. R = C_2H_5

EXPERIMENTAL

Preparation of intermediates. 4-Phenoxyanisole, b.p. 168–170°/15 mm., was prepared in 70% yield by heating at 150–170° for 1 hr. an equimolar mixture of 4-bromoanisole and the potassio derivative of phenol in the presence of copper powder.

4′-Methoxy-4-phenoxypropiophenone (I), b.p. 239–241°/15 mm., was obtained in 90% yield by adding dropwise propionyl chloride (0.1 mole) to an ice-cooled solution of 4-phenoxyanisole (0.1 mole) and finely-powdered aluminum chloride (0.15 mole) in 250 ml. of anhydrous carbon disulfide; the mixture was left at room temperature for 12 hr., with frequent shaking, and the reaction terminated by a brief heating on the water bath, then worked up in the usual way. After recrystallization from ethanol, the ketone melted at 66° (lit.,[8] m.p. 64°).

4′-Methoxy-4-phenoxyacetophenone (V), b.p. 234–236°/16 mm., was obtained in the same way, from acetyl chloride, in 90% yield; the ketone crystallized from ethanol in shiny leaflets, m.p. 61°, giving a *2,4-dinitrophenylhydrazone*, crystallizing from acetic acid in crimson needles, m.p. 171° (lit.,[9] m.p. 61° for the ketone).

Willgerodt reaction of I. A mixture of 51.2 g. of 4′-methoxy-4-phenoxypropiophenone, 9.6 g. of sulfur, and 26.1 g. of morpholine was heated, cautiously to start with because of a lively evolution of hydrogen sulfide, then more vigorously for 10 to 15 hr.; the product was then stirred into 150 ml. of hot ethanol, and after cooling, the solid was filtered and recrystallized twice from ethanol. Yield: 26 g. (70%) of β-(4′-methoxy-4-phenoxy)phenylpropionic acid thiomorpholide, yellowish needles, m.p. 98°.

Anal. Calcd. for $C_{20}H_{23}NO_3S$: C, 67.2; H, 6.5; N, 3.9. Found: C, 67.0; H, 6.4; N, 3.9.

β-(4′-Hydroxy-4-phenoxy)phenylpropionic acid (II). A suspension of 20 g. of the foregoing thiomorpholide in a mixture of 100 ml. of acetic acid and 100 ml. of 40% hydrobromic acid was refluxed for 5 hr. After cooling, 300 ml. of water was added and the solid precipitate which formed was collected, washed with water, and purified by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid. It recrystallized from benzene to give 11.3 g. of colorless prisms, m.p. 162°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.7; H, 5.5.

The *ethyl ester* was prepared by dissolving 25.8 g. of the foregoing acid in 1000 ml. of absolute ethanol saturated with hydrogen chloride, the solution being kept at room temperature for 18 hr., then refluxed for 3 hr. After vacuum-distillation of almost all the ethanol, the residue was taken up in ether, the ethereal solution was washed with aqueous sodium carbonate then with water, and dried over sodium sulfate. The residue from evaporation of the solvent was recrystallized from aqueous ethanol to give 24.3 g. of colorless prisms, m.p. 78°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3. Found: C, 71.4; H, 6.2.

β-(4′-Hydroxy-4-phenoxy)phenylpropionic acid hydrazide (III). A solution of 56 g. of the above ethyl ester and 13 ml. of 85% hydrazine hydrate in 50 ml. of absolute ethanol was refluxed for 6 hr. The solid obtained on cooling was collected and recrystallized from aqueous ethanol, giving 41.7 g. of the *hydrazide*, fine colorless prisms, m.p. 195–196°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.2; H, 5.8; N, 10.3.

β-(4′-Hydroxy-4-phenoxy)phenylethylamine (IV). A suspension of 27.2 g. of the foregoing hydrazide in 100 ml. of ether was diazotized with 7.5 g. of sodium nitrite in the presence of 17 ml. of 6*N* hydrochloric acid (in 150 ml. of water), the temperature being maintained at −4°. A yellow coloration occurred, and after completion of the reaction the orange-red organic phase was decanted, the water phase extracted several times with cold ether, and the ethereal solution was washed with cold aqueous hydrogen sodium carbonate and dried rapidly over calcium chloride. After addition of 40 ml. of ethanol, the solvent and the ethanol in excess were distilled, and the brownish-red cake of the urethane thus obtained was treated with 20 ml. of hydrochloric acid and 10 ml. of acetic acid. The mixture was refluxed for 12 hr., when a homogenous solution was obtained. The acids were distilled *in vacuo*, and the residue of thyronamine hydrochloride was purified by recrystallization from ethanol, and converted by means of ammonia into *thyronamine*, which crystallized from ether in colorless prisms (9.5 g.), m.p. 136°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6. Found: C, 73.3; H, 6.6.

4′-Methoxy-4-phenoxyphenylacetic acid. A mixture of 53.4 g. of 4′-methoxy-4-phenoxyacetophenone, 10.5 g. of sulfur and 28 g. of morpholine was treated as for the higher homolog, giving 52.8 g. (70%) of a *thiomorpholide*, crystallizing from ethanol in yellowish needles, m.p. 107°.

Anal. Calcd. for $C_{19}H_{21}NO_3S$: C, 66.4; H, 6.1; N, 4.1. Found: C, 66.3; H, 6.2; N, 4.1.

Hydrolysis of 49 g. of this thiomorpholide with a mixture of 80 ml. of acetic acid, 18 ml. of water, and 12 ml. of sulfuric acid afforded 31 g. of the *acid*, which crystallized from aqueous ethanol in colorless leaflets, m.p. 92°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.7; H, 5.3.

A Willgerodt reaction similarly performed with 5.3 g. of the ketone, 1 g. of sulfur, and 2.8 g. of piperidine gave only a 45% yield of the corresponding *thiopiperidide*, crystallizing from ethanol in yellowish needles, m.p. 95°.

Anal. Calcd. for $C_{20}H_{23}NO_2S$: C, 70.3; H, 7.8; N, 4.1. Found: C, 70.3; H, 7.6; N, 4.1.

Similar experiments using cyclohexylamine and diethylamine gave no corresponding thioamide.

4′-Hydroxy-4-phenoxyphenylacetic acid (VI). Hydrolysis of the foregoing thiomorpholide (20 g.) with 40% hydrobromic acid (100 g.) in acetic acid (100 g.) afforded an 88% yield of the *hydroxy acid* (12.5 g.), crystallizing from aqueous ethanol in colorless leaflets, m.p. 185°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.9; H, 5.0. Found: C, 68.7; H, 5.0.

The corresponding *ethyl ester*, prepared as for the lower homolog, crystallized from ethanol in colorless prisms, m.p. 92°, b.p. 267–269°/23 mm.

(8) J. Walker, *J. Chem. Soc.*, 347 (1942).

(9) N. R. Campbell and F. W. Chattaway, *Proc. Roy. Soc.*, [B] 130, 435 (1942).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.6. Found: C, 70.5; H, 5.3.

The *hydrazide* crystallized from ethanol in colorless needles, m.p. 187–188°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.5; N, 10.9. Found: C, 65.0; H, 5.4; N, 10.8.

4'-Hydroxy-4-phenoxybenzylamine (VII). Curtius degradation of 25.8 g. of the foregoing hydrazide, effected as for the higher homolog, yielded 10 g. of the hydrochloride of VII; the free *base* obtained on alkalinization with aqueous ammonia crystallized from ethanol–petroleum ether (b.p. 35–40°) in colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.6; H, 6.0; N, 6.4.

2-(4'-Methoxy-4-phenoxyphenyl)cinchoninic acid (VIII). A solution of 24 g. of 4'-methoxy-4-phenoxyacetophenone, 14.7 g. of isatin, and 16.8 g. of potassium hydroxide (dissolved in a few milliliters of water) in 85 ml. of ethanol was refluxed on the water bath for 24 hr. After addition of water, the neutral impurities were extracted in ether and the aqueous layer was acidified with acetic acid. The solid precipitate was collected and recrystallized from acetic acid, to yield 26 g. of fine yellowish prisms, m.p. 223°.

Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.4; H, 4.6; N, 3.8. Found: C, 74.3; H, 4.8; N, 3.6.

Thermal decomposition of this acid gave a residue which was purified by vacuum distillation, furnishing after recrystallization from ethanol *2-(4'-methoxy-4-phenoxyphenyl)-quinoline* (XI), as colorless needles, m.p. 165°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.7; H, 5.2; N, 4.3. Found: C, 80.7; H, 5.2; N, 4.3.

This quinoline gave a *picrate*, crystallizing from benzene in shiny yellow prisms, m.p. 190°.

2-(4'-Methoxy-4-phenoxyphenyl)-3-methylcinchoninic acid (IX). Similarly prepared from 25.7 g. of ketone I, this *cinchoninic acid* (26.2 g.) crystallized from acetic acid in pale yellow needles, m.p. 276°.

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.8; H, 5.0; N, 3.6. Found: C, 74.6; H, 5.0; N, 3.5.

2-(4'-Methoxy-4-phenoxyphenyl)-3-methylquinoline (XII) crystallized from ethanol in colorless needles, m.p. 118°.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; N, 4.1. Found: C, 80.9; H, 5.5; N, 4.0.

The *picrate* crystallized from benzene in yellow prisms, m.p. 198°.

4'-Methoxy-4-phenoxybutyrophenone. Prepared as for the lower homolog, by Friedel-Crafts reaction with 20 g. of 4-phenoxyanisole and 10.7 g. of butyryl chloride, this *ketone* (21.6 g.), b.p. 230–232°/14 mm., crystallized from ethanol in shiny colorless leaflets, m.p. 77°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.5; H, 6.8.

A Pfitzinger reaction with 27 g. of this ketone yielded 25.9 g. of *2-(4'-methoxy-4-phenoxyphenyl)-3-ethylcinchoninic acid* (X), crystallizing from acetic acid in yellowish prisms, m.p. 295°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.2; H, 5.3; N, 3.5. Found: C, 75.2; H, 5.3; N, 3.5.

2-(4'-Methoxy-4-phenoxyphenyl)-3-ethylquinoline (XIII) crystallized from ethanol in shiny colorless prisms, m.p. 107°.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 6.0; N, 3.9. Found: C, 81.2; H, 5.9; N, 4.0.

The corresponding *picrate* crystallized from benzene in yellow needles, m.p. 189°.

4'-Methoxy-4-phenoxyisovalerophenone. This *ketone* (20 g.), b.p. 265–270°/36 mm., was prepared by a Friedel-Crafts reaction with 20 g. of 4-phenoxyanisole and 12 g. of isovaleryl chloride; it crystallized from methanol as lustrous colorless leaflets, m.p. 62°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1. Found: C, 76.1; H, 7.1.

This substance gave no cinchoninic acid under the usual conditions of the Pfitzinger reaction.

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[COMMUNICATION NO. 2144 FROM THE KODAK RESEARCH LABORATORIES]

The Structure of Certain Polyazaindenes. IX. Sensitivity of the Ultraviolet Absorption Spectra to *p*H Variation, and Amine Salts of Tetrazaindenes

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Received February 10, 1961

Ultraviolet absorbance data showing sensitivity to *p*H are reported for several polyazaindenes. The compound previously regarded as *N,N'*-bis(1,2,4-triazol-3-yl)-3-iminobutyramide is shown to be the salt of 3-amino-1,2,4-triazole and 6-methyl-4-oxo-1,3,3a,7-tetrazaindene. Other amine salts of tetrazaindenes are described.

Ultraviolet absorbance spectra recorded for aqueous solutions at acid and alkaline *p*H's demonstrate the existence of two possible structures for various tetra- and pentazaindenes and triazoles. Their extinction maxima are listed in Table I. Systematic variations in the spectra of three tetrazaindenes (I, VI, VII) observed over a range of *p*H's between 6 and 8 can be explained as representing intermediate mixtures of the neutral molecule and the anion produced by its dissociation at elevated *p*H's. Among the compounds studied, ionization appears to be negligible at *p*H 1 but complete at *p*H 10.

The present findings do not show the existence of a third, cationic structure in water, although it has been noted that 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I) can be titrated with perchloric acid in glacial acetic acid.[1] The quaternization of these compounds with methyl *p*-toluenesulfonate is, of course, a consequence of the ionic character. Existence of an anionic structure is in agreement with previous observations that I shows one acidic hydrogen in nonaqueous (dimethylformamide)

(1) D. D. Fix, these Laboratories, private communication.