zation from benzene yielded the pure 2-hydroxyphenyl sulfone, m. p. 190–191°. In a similar manner, 2-hydroxyphenyl sulfoxide was oxidized to the sulfone.

3,5,6-Trichloro-2-hydroxyphenyl Sulfide.—To a mixture of 70 g. of anhydrous aluminum chloride and 500 cc. of ethylene dichloride was added slowly, under stirring, a warm solution of 100 g. of 2,4,5-trichlorophenol in 100 g. of ethylene dichloride, whereby hydrogen chloride gas was evolved. A solution of 30 g. of sulfur dichloride in 50 g. of ethylene dichloride was dropped in during one hour. The mixture was then heated to 45° for another hour, allowed to stand overnight and quenched with ice. The solvent and unchanged trichlorophenol were removed by steam distillation. The solid residue was dissolved in hot 10% sodium hydroxide solution, the solution filtered and reprecipitated with hydrochloric acid. After filtering, washing and drying, 85 g. of a brownish powder was obtained. Crystallizations from acetic acid with the addition of a small amount of decolorizing carbon and from toluene yielded 35 g. of 3,5,6-trichloro-2-hydroxyphenyl sulfide in form of feathery needles, m. p. 156–157°.

Anal. Calcd. for $C_{12}H_4O_2SCl_5$: Cl, 50.1. Found: Cl, 49.8.

The diacetate formed colorless, thin needles, m. p. 174–175°.

Anal. Calcd. for $C_{16}H_8O_4SCl_5$: Cl, 41.8. Found: Cl, 41.6.

5-Bromo-2-hydroxyphenyl Sulfoxide (V).—Anhydrous aluminum chloride (100 g.) was added under stirring to 800 cc. of ethylene dichloride kept in an ice-bath. After that, 240 g. of 4-bromophenol was added in small portions, and then a solution of 120 g. of thionyl chloride in 100 cc. of ethylene dichloride dropped in during one hour. The ice-bath was removed and stirring continued for four hours. The mixture was allowed to stand overnight and was then quenched with ice. Steam distillation removed the ethylene dichloride and the unreacted 4-bromophenol. After cooling, the crystalline product obtained was filtered, washed with water and dried (75 g., m. p. 198–200°). Crystallization from alcohol yielded the pure 5-bromo-2-hydroxyphenyl sulfoxide in the form of colorless, thin platelets, m. p. 203–204°.

3,5-Tetrachloro-2-hydroxyphenyl Sulfoxide.—3,5-Tetrachloro-2-hydroxyphenyl sulfoxide was prepared in a similar manner from 2,4-dichlorophenol and thionyl chloride. Crystallizations of the crude product (m. p. 210–212°) from toluene containing 10% of alcohol and from alcohol alone yielded white, fine needles of 3,5-dichloro-2-hydroxyphenyl sulfoxide, m. p. 221–223°.

3,5,6-Trichloro-2-hydroxyphenyl Sulfoxide.—3,5,6-Trichloro-2-hydroxyphenyl sulfide (20 g.), glacial acetic acid (200 cc.) and 30% hydrogen peroxide (12 g.) were refluxed for one hour. After cooling, the formed crystals were filtered, washed with 50% acetic acid and water and dried (17 g.; m. p. 222–224°). Crystallization from toluene yielded the pure 3,5,6-trichloro-2-hydroxyphenyl sulfoxide (14 g., m. p. 224–225°).

5-Chloro-2-hydroxyphenyl Sulfone.—A mixture of 20 g. of 5-chloro-2-hydroxyphenyl sulfide,[8] 150 cc. of glacial acetic acid and 35 g. of 30% hydrogen peroxide was refluxed for two hours and water added until precipitate started to form and the mixture allowed to cool. The obtained crystals were filtered, washed with 50% acetic acid and water and dried (17 g.; m. p. 189–190°). Crystallization from 70% acetic acid yielded pure 5-chloro-2-hydroxyphenyl sulfone of the m. p. 190–191°. The other substituted sulfones were prepared in the same way from the corresponding sulfides or sulfoxides.

5-Methyl-2-hydroxyphenyl Sulfide

(a) **From *p*-Cresol and Sulfur Dichloride.**—*p*-Cresol (108 g.) was dissolved in 500 cc. of petroleum ether. A solution of 55 g. of sulfur dichloride in 60 cc. of petroleum ether was dropped in during one hour. The mixture was allowed to stand overnight. The petroleum ether layer was then poured off from the brown, semi-solid mass which was crystallized from 100 g. of toluene; 27 g. of a white, crystalline powder was obtained. Crystallizations from toluene (100 cc.) and glacial acetic acid (100 cc.) yielded colorless crystals of 5-methyl-2-hydroxyphenyl sulfide, melting at 114–115°.

(b) **By Reduction of 5-Methyl-2-hydroxyphenyl Sulfoxide.**—5-Methyl-2-hydroxyphenyl sulfide was obtained by reduction of the sulfoxide by means of zinc dust in acetic acid solution (Gazdar and Smiles[2]) and melted at 114–115°; mixed with sulfide prepared by method a, m. p. 114–115°.

Anal. Calcd. for $C_{14}H_{14}O_2S$: S, 13.0. Found: S, 12.8.

5-Methyl-5-acetoxyphenyl sulfide, prepared in the usual manner and crystallized from alcohol, formed thin, large platelets of the m. p. 125–126°.

Anal. Calcd. for $C_{16}H_{18}O_4S$: S, 9.7. Found: S, 9.5.

Summary

1. 2-Hydroxyphenyl sulfoxide has been synthesized.

2. A series of halogenated 2-hydroxyphenyl sulfoxides and sulfones has been prepared.

DELAWANNA, NEW JERSEY RECEIVED JULY 17, 1944

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Ethyl- and Propylamines which Contain the 2-(1,5-Diphenyl)-pyrryl or the 2-(1-Methyl-5-phenyl)-pyrryl Nucleus[1]

BY F. F. BLICKE, J. E. GEARIEN, R. J. WARZYNSKI AND J. A. FAUST

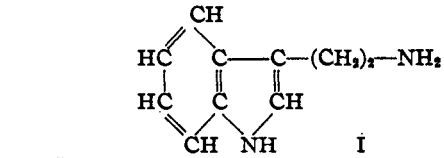
Our interest in amines which contain phenylpyrryl nuclei was aroused by the fact that tryptamine (I, β-(3-indolyl)-ethylamine) exhibits oxytocic activity to some degree,[2] an effect which was demonstrated by Chen and Chen[3] on the isolated guinea pig uterus.

Since it is of general interest to know the extent to which a phenylpyrryl radical might replace an indolyl group in a pharmacologically-active product, we decided to prepare amines such as those represented by general formula II. In these compounds the basic-alkyl side chain is attached to a 2 carbon atom of the pyrrole ring instead of a 3 carbon atom as in the case of tryptamine.

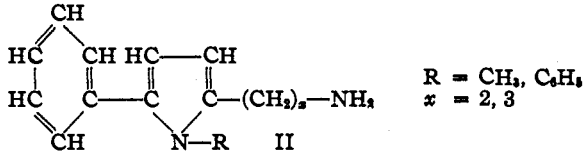
(1) We wish to express our indebtedness to Eli Lilly and Company, the Board of Governors of the Horace H. Rackham School of Graduate Studies, and Park, Davis and Company for their joint support of this project.

(2) Barger ("Some Applications of Organic Chemistry to Biology and Medicine," page 99 (1930)) stated that tyramine has been manufactured in Japan for medicinal use. See also Guggenheim, "Die biogenen Amine," page 541 (1940).

(3) Chen and Chen, *J. Am. Pharm. Assoc.*, **22**, 813 (1933).



I



II

One substance of this type, namely, β-[2-(5-phenyl)-pyrryl]-ethylamine,[4,5] already has been prepared by Robinson and Todd with the aid of the Curtius degradation. All of the steps in this process took place satisfactorily except the one in which the hydrazide was converted into the azide by nitrous acid. In this step the reaction product consisted almost entirely of a black tar, and the azide, and consequently the amine itself, were obtained in very poor yield. We found that the tar formation could be prevented entirely by replacement of the 1-hydrogen atom of the pyrrole nucleus by a methyl or phenyl group.

The required hydrazides for the Curtius process were prepared from esters of β-[2-(1,5-diphenyl)-pyrryl][6]- and β-[2-(1-methyl-5-phenyl)-pyrryl]-propionic acid.[6] Since the two propionic acids were available,[6] it seemed desirable to determine whether or not propylamines in this series could be obtained by the series of conversions: acid → acid chloride → nitrile → amine. It was found that the amines could be prepared satisfactorily by this procedure.

The two ethyl amines were found to be devoid of oxytocic activity. The propyl amines, as would be expected, proved to be of little or no pharmacological interest.

Experimental Part

β-[2-(1,5-Diphenyl)-pyrryl]-ethylamine Acetate.—A mixture of 14.8 g. of β-[2-(1,5-diphenyl)-pyrryl]-propionazide[7] and 250 cc. of absolute methyl alcohol was refluxed, with exclusion of moisture, for five hours. After removal of the alcohol on a steam-bath under reduced pressure, the methyl β-[2-(1,5-diphenyl)-pyrryl]-ethylcarbamate was obtained as a viscous red oil. The latter was refluxed with 37 g. of potassium hydroxide, dissolved in 250 cc. of 95% alcohol, for forty hours. The precipitated potassium carbonate was removed by filtration, the filtrate concentrated to a volume of about 75 cc., diluted with 200 cc. of water, and the mixture extracted with ether. The ether extract was shaken with water, dried with magnesium sulfate, and then acetic acid was added, dropwise, until further addition produced no turbidity. The precipitated amine acetate weighed 9 g. (59%). After two recrystallizations from toluene the product melted at 137–139°. The acetate is very soluble in water.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.30; H, 6.92; N, 8.60.

γ-[2-(1,5-Diphenyl)-pyrryl]-propylamine Acetate.—Five and eight-tenths grams of the propionamide,[7] 4 g. of filter-cel[8] and 170 cc. of dry xylene were placed in a 3-necked flask fitted with a stirrer and condenser; the latter was closed with a calcium chloride tube. The mixture was stirred, heated to the boiling point, and 10 g. of phosphorus pentoxide added. After it had been stirred and refluxed for two hours it was cooled, filtered and the filter-cel and pentoxide washed with hot xylene. The latter was removed on a steam-bath under reduced pressure. The yellow, oily residue crystallized when cooled; yield 3.5 g. (63%); m. p. 113–115°. After three recrystallizations from isopropyl alcohol the propionitrile melted at 115–116°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.28. Found: C, 83.72; H, 5.79; N, 10.39.

To a boiling solution, obtained from 16.4 g. of the nitrile and 350 cc. of absolute alcohol, 27.6 g. of sodium was added during the course of one hour. After the sodium had disappeared, 150 cc. of water was added, and then about 230 cc. of liquid removed on a steam-bath under reduced pressure. The oily residue solidified when cooled. It was extracted with 150 cc. of ether, the extract shaken with water, and dried with magnesium sulfate. Acetic acid (about 2 cc.) was dropped into the ether solution until no more precipitate formed. The latter, the amine acetate, weighed 11.5 g. (57%); m. p. 140–141° after recrystallization from ethyl acetate. The amine acetate is soluble in cold water.

Anal. Calcd. for $C_{21}H_{24}O_2N_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.97; H, 7.22; N, 8.14.

γ-[2-(1-Methyl-5-phenyl)-pyrryl]-ethylamine Acetate.—A solution prepared from 17.8 g. of β-[2-(1-methyl-5-phenyl)-pyrryl]-propionhydrazide[7] and 300 cc. of absolute alcohol was refluxed for ten hours. As soon as the solution became warm, nitrogen was evolved. After the removal of 180 cc. of alcohol, 90 cc. of water and 40 g. of sodium hydroxide were added, and the material was heated for forty-eight hours on a steam-bath. The mixture was cooled and 400 cc. of water added whereupon an oil precipitated. The latter was extracted with three 100-cc. portions of ether, and the extract dried with solid sodium hydroxide. After filtration, enough acetic acid was added to precipitate the amine acetate. The latter was filtered and washed with 100 cc. of ether. The lemon-yellow, crystalline acetate weighed 10.3 g. (57%). After two recrystallizations from 100 cc. of toluene the colorless product melted at 139–141°.

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10 76. Found: C, 69.26; H, 7.77; N, 10.81.

γ-[2-(1-Methyl-5-phenyl)-pyrryl]-propylamine Acetate.—The propionitrile was prepared in the same manner as the 1-phenyl analog from 9.5 g. of the propionamide,[7] 16.0 g. of phosphorus pentoxide, 6 g. of filter-cel and 190 cc. of xylene; yield 4.2 g. (48%) after recrystallization from isopropyl alcohol; m. p. 115–116°.

Anal. Calcd. for $C_{14}H_{14}N_2$: N, 13.32. Found: N, 13.24.

When 10.5 g. of the nitrile was treated with 18.4 g. of sodium and 300 cc. of absolute alcohol, and the amine precipitated with acetic acid, there was obtained 5.0 g. (39%) of the amine acetate; m. p. 162–163° after recrystallization from ethyl acetate. The amine acetate is soluble in cold water.

Anal. Calcd. for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.15; H, 8.13; N, 10.08.

Summary

The preparation of γ-[2-(1,5-diphenyl)-pyrryl]-ethylamine, γ-[2-(1-methyl-5-phenyl)-pyrryl]-ethylamine and the two corresponding γ-substituted propylamines has been described.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 28, 1944

(4) Robinson and Todd, *J. Chem. Soc.*, 1743 (1939).

(5) Its action on the uterine musculature was studied by Graham (*Quart J. Pharm. Pharmacol.*, **13**, 305 (1940)).

(6) Blicke, Warzynski, Faust and Gearien, THIS JOURNAL, **66**, 1675 (1944).

(7) Blicke, Faust, Warzynski and Gearien, *ibid.*, **67**, 205 (1945).

(8) This substance was employed because we had been informed of its successful use by Dr. G. M. Kosolapoff in a different field.