It is washed on the filter with 300 cc. of a 2:1 mixture of petroleum ether and ether, and finally three times with ether. The washed product is dried in a vacuum desiccator over potassium hydroxide and the ether is removed by repeated evacuation. The yield from 450 g. of frozen glands is about 6 g.

A summary of the yields obtained from approximately 20 kg. of frozen posterior lobes by the method described is given in Table II. Each of the "lots" listed in the table represents a combination of the ether precipitate obtained from several 450 g. batches of posterior lobes. From the averages it can be seen that 1 kg. of frozen glands yields approximately 13 g. of a product which possesses a pressor and oxytocic potency of 9 to 10 units per mg. Approximately 120,000 units of each activity can therefore be obtained from one kg. of posterior lobes.

TABLE II

YIELDS OF ETHER PRECIPITATE AND PRESSOR AND OXYTOCIC ACTIVITY FROM FROZEN POSTERIOR LOBES

Lot	Frozen glands used, kg.	Ether ppt. per kg. of glands, g.	Activity per kg. of frozen glands: Pressor units	Oxytocic units
B	1.8	11.9	119,000	119,000
C	4.1	11.4	114,000	91,200
D	2.4	11.3	89,000	90,400
E	3.0	12.4	111,600	136,400
F[a]	5.9	13.2	118,800	145,200
G[b]	2.7	18.2	163,800	163,800
Averages		13.1	119,400	124,300

[a] Hog glands. All others are from beef. [b] The ether-precipitates included in Lot G were obtained from glands extracted by the use of the improved juice extractor.[6] All others were extracted using the 2¼-inch (5.8-cm.) test cylinder of the Carver press equipment.

The authors wish to express their appreciation to Mr. T. W. Loring for his assistance in this work.

Summary

A convenient laboratory method has been developed by which 80 to 90% of the pressor and oxytocic activities contained in frozen posterior lobes can be rapidly obtained in the form of a white, water-soluble, non-hygroscopic, stable powder possessing a pressor and oxytocic potency of 9 to 10 units per mg. In comparison with previous methods, desiccation of the glands with acetone and extraction of the residue are avoided; the volumes of solutions to be handled are small; and the expenditure of time, labor and solvents is less. The process can be used with equal efficiency to separate the active material from a few posterior lobes or from several kg. of glands.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

Some Schiff Bases with *p*-Aminothymol[1]

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Introduction

The toxicity of acetanilide is attributed to its hydrolytic product, aniline, while the febrifuge and analgesic properties of acetanilide depend upon its conversion in the body to *p*-aminophenol.[5] The most useful substitutes for acetanilide have been the acyl derivatives of *p*-ethoxyaniline (*e. g.*, acetylphenetidin) which presumably act more safely by being slowly converted to *p*-aminophenol.

Since cresols are more active and less toxic than the corresponding phenols and the toluidines[6] are less toxic than aniline, it was thought that a compound hydrolyzable in the body directly to a mono- or a di-alkyl substituted *p*-aminophenol would be an antipyretic and analgesic lacking in toxicity.

The RN=CR linkage of a Schiff base[7] formed by the elimination of water from a primary amine and an aldehyde or ketone is subject to hydrolysis in an acid medium.

Salicylaldehyde, piperonal, and vanillin, as well as other carbonyl compounds, are known to have pharmacological properties in common with, and hence possibly augmentative to, those of *p*-aminophenol. Jacquet[8] has found that Schiff bases prepared by condensing physiologically active amines and aldehydes possess, at least in part, the pharmacological action of their components.

(1) Presented before the Medicinal Section of the American Chemical Society at the Cincinnati Meeting, April, 1940.

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(5) Barrowcliff and Carr, "Organic Medicinal Chemicals," Bailliere, Tindall and Cox, London, 1921, pp. 113–114.

(6) Bogert and Connitt, THIS JOURNAL, **51**, 900 (1929).

(7) Sidgwick, "Organic Chemistry of Nitrogen," revised by Taylor and Baker, Clarendon Press, Oxford, 1937, p. 65.

(8) Jacquet, *Pharm. Ztg.*, 613 (1893).

The Schiff bases listed in Table I were prepared by condensing *p*-aminothymol (2-isopropyl-4-amino-5-methylphenol) and certain aromatic aldehydes with a view toward producing safer antipyretic and analgesic compounds. The *p*-aminothymol used in the synthesis of these compounds was obtained from thymol through *p*-nitrosothymol. *p*-Nitrosothymol may be reduced to the corresponding aminothymol by means of hydrogen sulfide, as described by Liebermann and Ilinski,[9] or it may be reduced quantitatively by catalytic methods.

Experimental

***p*-Aminothymol.**—*p*-Nitrosothymol (18 g., 0.1 mole), dissolved in 300 ml. of anhydrous ethanol, was shaken with palladiumized charcoal in an atmosphere of hydrogen until the calculated quantity (0.2 mole) of hydrogen was absorbed. The reaction mixture was immediately treated with sufficient alcoholic hydrogen chloride to convert the unstable *p*-aminothymol to its hydrochloride. The catalyst was filtered off, the alcohol evaporated and the compound washed with small portions of ethyl acetate. The yield was quantitative.

Schiff Bases of *p*-Aminothymol.—The following procedure for the preparation of 3,4-methyleneoxybenzylidene-4-aminothymol is substantially that used for preparing all the derivatives listed in Table I. Three grams (0.02 mole) of piperonal was dissolved in 12 ml. of anhydrous ethanol. To this was added 2.77 g. (0.02 mole) of powdered sodium acetate. The mixture was mechanically stirred and to it was slowly added a solution of 4 g. (0.02 mole) of *p*-aminothymol hydrochloride dissolved in 22 ml. of anhydrous ethanol. The crude Schiff base separated as a cream-colored solid which was collected, washed well with water and then dried. Recrystallization from 60% ethanol yielded 2.2 g. (75%) of iridescent scales; m. p. 161–162° (cor.).

Catalytic Reduction of 2-Hydroxybenzylidene-4-aminothymol.—In an attempt to reduce this compound (with hydrogen and a platinum catalyst) to the corresponding secondary amine it was found that cleavage occurred at the N=C linkage with the production of *p*-aminothymol and *o*-cresol. Better than 70% of the theoretical amount of *p*-aminothymol could be isolated as the hydrochloride.

Pharmacological.—In a preliminary study, it was determined that *p*-aminothymol hydrochloride reduced the body temperature of malaria-infected canary birds. The oral administration of 0.25 g. per kg. of 4-methoxybenzylidene-4-aminothymol and 2-hydroxybenzylidene-4-aminothymol to cats caused a reduction in temperature of these animals from 101 to 99° F. as determined by a rectal thermometer. A dose of 2-hydroxybenzylidene-4-aminothymol of 1 g. per kg. in cats showed no dangerous symptoms. The average lethal dose of acetanilide for cats is 0.25 g. per kg.

(9) Liebermann and Ilinski, *Ber.*, **18**, 3194 (1885).

TABLE I

Schiff bases of *p*-aminothymol	Formula	Yield, %	M. p., °C. (cor.)	Nitrogen, % Calcd.	Found
Benzylidene - 4 - aminothymol	$C_{17}H_{19}ON$[a,h]	95	149	5.53	5.48
2-Hydroxybenzylidene—	$C_{17}H_{19}O_2N$[b]	95	170	5.20	5.21
2 - Hydroxy - 4 - methylbenzylidene—	$C_{18}H_{21}O_2N$[c]	85	155	4.90	4.88
4-Methoxybenzylidene—	$C_{18}H_{21}O_2N$[d]	95	160	4.90	4.70
3 - Methoxy - 4 - hydroxybenzylidene—	$C_{18}H_{21}O_2N$[e]	83	194	4.90	4.80
3,4 - Methylene - oxybenzylidene—	$C_{18}H_{19}O_3N$[f]	75	161–62	4.71	4.56
Cinnamylidene—	$C_{19}H_{21}ON$[g]	70	154	5.01	4.88

[a] From benzene. [b] From 60% ethanol. [c] From 40% ethanol. [d] From carbon tetrachloride. [e] From chloroform. [f] From 60% ethanol. [g] From ethylene dichloride. [h] Previously prepared by Plancher, *Gazz. chim. ital.*, **25**, 390 (1895).

Summary

A method is described whereby *p*-aminothymol may be obtained in quantitative yields by the catalytic reduction of *p*-nitrosothymol.

Six new Schiff bases have been prepared and described.

An observation has been made that the N=C linkage of a Schiff base undergoes scission on catalytic reduction.

p-Aminothymol, and two Schiff bases thereof, have been shown to possess antipyretic properties and one Schiff base, 2-hydroxybenzylidene-4-aminothymol, was found to be relatively non-toxic.

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