six hours. The solution was cooled and a white solid separated, m. p. 84–86°.[3] On recrystallization from acetone pure (X) was obtained, m. p. 81–82°. A mixed melting point determination with an authentic sample of (X) gave no depression of melting point.

Modified Raney Nickel Catalyst.[4]—The catalyst was prepared in the usual manner except that after the addition of the alloy the reaction mixture was allowed to stand at room temperature overnight.

Hydrogenolysis of (IV).—A mixture of 100 mg. of cholestanone-3 thioacetal in 15 cc. of dioxane and 1.5 g. of modified Raney nickel catalyst was heated on the steam-bath for seventeen hours. The cooled mixture was filtered through Celite and the recovered catalyst was washed with dioxane and ether. The filtrate on evaporation gave an oil which on working with methanol solidified. The solid cholestane was collected by filtration and washed with methanol, m. p. 73–74.5°, wt. 67 mg. An additional milligram of material was obtained from the mother liquor. All-told the yield of impure cholestane was 91%. On recrystallization from acetone–methanol pure cholestane was obtained, m. p. 78.5–79°. It gave a negative nitroprusside test for the presence of sulfur and a negative Liebermann test.

Hydrogenolysis of (V).—To a solution of 0.1 g. of 3-ketocholanic acid thioacetal in 15 cc. dioxane there was added 1.5 g. of modified Raney nickel catalyst, and the mixture was heated on the steam-bath for six hours. It was filtered through Celite and gave a water-white filtrate which on evaporation gave an extremely small amount of solid which was insoluble in cold alcohol.

The recovered catalyst was leached with 0.9 *N* sodium hydroxide which when acidified gave only a slight turbidity. The catalyst was treated with hydrochloric acid. The insoluble material was collected by filtration and was washed well with water. It was then washed successively with hot alcohol, chloroform and acetone. The organic washings were evaporated and this gave a slightly yellow oil which solidified on the addition of alcohol. Water was added and the solid was collected by filtration, wt. 50 mg., m. p. 115–129°. This material gave a negative nitroprusside test for sulfur, was soluble in chloroform and became electrified on rubbing similar to cholanic acid. After three recrystallizations from dilute alcohol low melting cholanic acid was obtained, m. p. 157–159°.

(3) See Barton and Jones, *J. Chem. Soc.*, 391 (1942), for the higher melting form of (X).

(4) See Bougault, Cattelain and Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938), and Mozingo, *et al.*, THIS JOURNAL, **65**, 1013 (1943), for the preparation of similar modified Raney nickel catalysts.

Hydrogenolysis of (VI).—A mixture of 0.61 g. of VI, 9 g. of modified Raney nickel catalyst and 40 cc. of dioxane was refluxed for eleven hours. It was filtered and the recovered catalyst was washed thoroughly with ether. The filtrate was evaporated *in vacuo* and gave a slightly yellow viscous oil which on working with methanol solidified. The solid was collected by filtration and was washed with cold methanol, m. p. 76–78°, wt. 0.245 g. From the mother liquor 77 mg. more of material was isolated, m. p. 71–75°. The yield of crude methyl cholanate was 0.322 g. (69.7%). The main fraction of crystals was recrystallized from acetone–methanol, m. p. 78.5–79.5°. Two more recrystallizations did not improve the melting point and the material analyzed as follows:

Anal. Calcd. for $C_{25}H_{42}O_2$: C, 80.2; H, 11.3. Found: C, 80.3; 80.2; H, 11.5, 11.4.

The melting point in the literature for methyl cholanate is 86–87°.[5] The material was therefore hydrolyzed in the usual manner and gave pure cholanic acid, m. p. 162–162.5°.

Acknowledgment.—The microanalyses were carried out by Dr. J. A. Kuck of the Stamford Laboratories of the American Cyanamid Co., and by Mr. Philip Weiss of this laboratory.

Summary

1. The diethyl thioacetals of cholestanone-3, 3-ketocholanic acid and methyl 3-ketocholanate have been prepared.

2. The enol ethyl thioether of Δ^4-cholestenone-3 has been prepared. Hydrolysis of this compound with alcoholic hydrochloric acid gave back Δ^4-cholestenone-3.

3. Hydrogenolysis of cholestanone-3 thioacetal with a modified Raney nickel catalyst in dioxane gave cholestane.

4. Hydrogenolysis of methyl 3-ketocholanate thioacetal with a modified Raney nickel catalyst in dioxane gave a low-melting methyl cholanate from which on hydrolysis pure cholanic acid was obtained.

(5) Reichstein and Alther, *Helv. Chim. Acta*, **25**, 805 (1942).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of Arylpropylamines. III. From Nuclear Nitration[1]

BY T. M. PATRICK, JR.,[2] E. T. MCBEE AND H. B. HASS

Many of the more important arylpropylamines which have shown sympathomimetic activity are distinguished by hydroxy, methoxy, or methylenedioxy substituents in nuclear positions. On the other hand, little has been published concerning the synthesis or physiological activity of the corresponding nitro and amino derivatives.

In addition to their potential use as pharmaceuticals *per se*, the nitrated phenylpropylamines can serve as intermediates for synthesis of other derivatives not readily prepared by other methods. Thus, Hoover[3] reported that 1-(*p*-aminophenyl)-2-propylamine can be selectively diazotized and hydrolyzed to 1-(*p*-hydroxyphenyl)-2-propylamine (known commercially as Paredrine). Other nuclear amino derivatives should likewise undergo selective diazotization and accordingly several different substituents could conceivably replace the amino group by known methods.

1-Nitro-3-phenylpropane, 2-chloro-1-(*p*-chloro-

(1) Based upon a thesis submitted by T. M. Patrick, Jr., to the Faculty of Purdue University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, April, 1943.

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(3) Hoover, Ph.D. Thesis, Purdue University, 1941.

TABLE I

NITRATED AMINES

Compound, propylamine	Crude yield, %	B. p., °C.	mm.	M. p. of hydrochloride, °C.	d^{20}_{20}	$n^{20}D$	Analyses,[a] %	Calcd.	Found
1-(*p*-Nitrophenyl)-2-	82.5	115–116	1	202	1.1342	1.5570	C	49.9	49.9
							H	6.1	6.0
2-(*p*-Nitrophenyl)-1-	94	128–129	2	198	1.1483	1.5618	Cl	16.4	16.6
1-(4-Chloro-3-nitrophenyl)-2-	*ca.* 85[b]			196			C	43.1	43.4
							H	4.9	5.0
3-(4-Chloro-3-nitrophenyl)-1-	*ca.* 85[b]			212.5			C	43.1	43.2
							H	4.9	5.1
N-Methyl-1-(*p*-nitrophenyl)-2-	*ca.* 90	117–118	1.5	186–187	1.1036	1.5462	Cl	15.4	15.4
N-Methyl-2-(*p*-nitrophenyl)-1-	89	130–131	2	183	1.1050	1.5462	Cl	15.4	14.4

[a] Analyses were of the pure amine hydrochlorides. [b] Mixed isomers.

phenyl)-propane, and six arylpropylamines were treated with fuming nitric acid or a sulfuric acid–nitric acid mixture to give 80–94% yields of nitrated derivatives. 1-Nitro-3-(*p*-nitrophenyl)-propane was reduced with iron to a 43% yield of the diamine. 1-(*p*-Nitrophenyl)-2-propylamine was reduced to the corresponding diamine in 70% yield with Raney nickel and hydrogen. The latter method had the advantage of much simpler recovery of the product from the reaction mixture.

Ingold, who investigated the nitration of phenylalkylamines, reported that *para* derivatives predominated, *ortho* derivatives were next in proportion, and that the *meta* substituted product decreased with the number of carbon atoms between the amino and phenyl groups.[4] We have found that unsubstituted phenylpropyl amines gave predominantly *para* derivatives on nitration, which were readily separated from the other isomers by several crystallizations of the hydrochlorides. No attempt was made to ascertain the amount of other isomers formed nor to isolate them. When the *para* position was occupied by a chlorine atom, the nitro group became attached in the 2 and 3 positions in roughly equal amounts, so that separation was considerably more difficult, and losses by fractional crystallization were high.

Physiological Properties

The pharmacological testing of the new compounds described in this series of papers was carried out at Abbott Laboratories. Data are reproduced by permission. Tests were made only for toxicity in rats and mice, and for pressor effect on anesthetized dogs. Benzedrine was used as a reference material. The following general conclusions were reached:

1. All of the arylpropylamines showed some pressor activity, and, although some of the compounds were approximately as effective as benzedrine, probably none was more effective.

2. 1-(*o*-Bromophenyl)-2-propylamine and 1-(*p*-bromophenyl)-2-propylamine were comparable in activity to benzedrine. 2-Phenyl-1-propylamine and 1-(*o*-chlorophenyl)-2-propylamine (previously reported compounds) were also placed in this category.

3. N-Methyl-1-(*p*-chlorophenyl)-2-propylamine, N-methyl-1-(*o*-chlorophenyl)-2-propylamine and 2-(*p*-chlorophenyl)-1-propylamine were nearly as effective as benzedrine.

4. 1-(4-Chloro-3-nitrophenyl)-2-propylamine was perhaps the weakest of the drugs tested. Other compounds containing a nuclear nitro group were not particularly effective; hence, it is probable that the nitro group is an undesirable substituent in this type of compound.

5. Most of the drugs exhibited tachyphylaxis. This effect appeared more rapidly than it did with ephedrine. Atropine when used in conjunction with the drugs retarded tachyphylaxis somewhat.

6. The toxicities of the compounds tested were of the same order of magnitude as that of benzedrine (L.D. by intravenous injection *ca.* 60 mg. per kg.). The compounds are more toxic than ephedrine (110 mg. per kg. i. v. in mice).

7. Most of the drugs seemed to possess central stimulating action, and convulsions occurred in the toxicity experiments.

Experimental

Nuclear Nitration of Phenylpropylamines.—The syntheses of the nitrated amines appearing in Table I were very similar as regards the final nitration step. The synthesis of 1-(*p*-nitrophenyl)-2-propylamine is typical. Ten grams of benzedrine was added through a capillary tube to 50 ml. of agitated C. P. fuming nitric acid (density 1.49–1.50) at −20 to −15°. The addition of the amine was complete in one hour, but stirring was continued for two hours longer. The mixture was then shaken with about four times its volume of crushed ice.

The acid solution was extracted with benzene to remove any non-basic organic material. The residue was then made strongly basic with excess 6 *M* sodium hydroxide. The liberated amine was separated and the aqueous layer was extracted several times with 20-ml. portions of benzene. These extractions were combined with the amine and the whole was dried over anhydrous potassium carbonate. The benzene was evaporated at atmospheric pressure, and the amine was distilled from a Claisen flask. There was obtained 11.0 g. of an amber liquid boiling at 114–115° at 1.5 mm. No unreacted benzedrine was present. The yield was 82.5%.

Undoubtedly some 1-(*o*-nitrophenyl)-2-propylamine, as well as the *para* isomer, was formed, but no attempt was made to separate these by distillation. The hydrochloride was readily prepared and was recrystallized without diffi-

(4) Ingold, *et al.*, *J. Chem. Soc.*, 250, 810 (1927).

culty. After three recrystallizations from absolute alcohol–ether, a constant-melting salt (115–116°) was obtained which was shown to be the *para* derivative by permanganate oxidation.

1-Nitro-3-(*p*-nitrophenyl)-propane.—A sample of 1-nitro-3-phenylpropane was re-rectified preparatory to nitration. The nearly colorless fraction distilling at 117° at 5 mm. was collected.

Twenty-five grams of the 1-nitro-3-phenylpropane was added dropwise over a one-hour period during stirring to 125 ml. of fuming nitric acid (density 1.49–1.50) at −15 to −20°. Stirring was continued for one-half hour longer. The nitration mixture was shaken with twice its volume of crushed ice. The non-aqueous layer was drawn off, and the residue was extracted once with a 20-ml. portion of benzene. The latter was added to the nitration product.

The benzene solution of nitration mixture was washed three times with dilute sodium bicarbonate solution and twice with water. The benzene was evaporated, and the residue was distilled at 0.2 mm. pressure. The boiling range of the amber liquid was 157–179° (oil-bath at 190–200°). The boiling range is probably influenced by superheating. The yield of crude product was 80%. Permanganate oxidation of the nitrated product gave a good yield of *p*-nitrobenzoic acid. Evidently the product was principally 1-nitro-3-(*p*-nitrophenyl)-propane; $n^{20}D$ 1.5564; sp. gr. 1.29.

Anal. Calcd. for $C_9H_{10}O_4N_2$: C, 51.4; H, 4.80. Found: C, 52.5; H, 4.83.

2-Chloro-1-(4-chloro-3-nitrophenyl)-propane.—A 58.7-g. portion of 2-chloro-1-(*p*-chlorophenyl)-propane was added with stirring to 72 g. of concentrated sulfuric acid. The mixture was cooled by an ice-bath and 44 g. of 80% nitric acid was added dropwise with vigorous stirring. When the acid was completely added, the flask was warmed by a water-bath to 50–60° for one and one-half hours. The reaction mixture was cooled, and shaken with crushed ice. The organic layer separated, and was completely removed by extracting with a small amount of benzene. The benzene solution was washed three times with dilute sodium hydroxide solution, and finally with water. The liquid was dried over anhydrous calcium chloride.

The benzene was evaporated and the residue was distilled from a Claisen flask. A light-yellow distillate of 64.0 g., boiling at 127–140° at 2 mm., was obtained. About 2 g. of residue remained from the distillation. No unreacted dichloro compound was recovered. The overall conversion to the mixed isomers was 88%.

The distilled liquid solidified on intense cooling with Dry Ice. A small portion of this solid was recrystallized five or six times from alcohol and water to give well-defined crystals melting at 43°. Permanganate oxidation of the product furnished 4-chloro-3-nitrobenzoic acid, establishing the position of the nitro group. The crystals were evidently 2-chloro-1-(4-chloro-3-nitrophenyl)-propane. The other isomer, having the nitro group in the 2-position, was undoubtedly formed, but was not isolated.

3-(*p*-Aminophenyl)-1-propylamine.—Twenty-one grams of 1-nitro-3-(*p*-nitrophenyl)-propane, 85 ml. of water, 40 g. of iron filings, 1 g. of ferric chloride and 12 ml. of concentrated hydrochloric acid were heated with vigorous stirring at 105–110° for twenty-five hours under reflux.

The cooled reaction mixture was made distinctly acid with hydrochloric acid and filtered. The clear brown filtrate was made basic by portion-wise addition of sodium hydroxide. In this way iron hydroxides were precipitated gradually, facilitating filtration which was performed after each addition of base. Finally no more hydroxides were precipitated, and the diamine was liberated. It was extracted with chloroform. The chloroform solution was dried over anhydrous potassium carbonate and distilled. A 43% yield (6.5 g.) of the diamine was obtained. The distillate was combined with the diamine from another run, and rectified at 1 mm. pressure. The temperature was constant at 106°, indicating that the 3-(*p*-aminophenyl)-1-propylamine obtained was probably not contaminated with any of the *ortho* isomer; $n^{20}D$ 1.5780; d^{20}_{20} 1.0344.

The dihydrochloride was made by adding an excess of dilute hydrochloric acid to the diamine, and evaporating nearly to dryness. Addition of alcohol caused the salt to precipitate in heavy white flocks. It was recrystallized from water and alcohol; hydrochloride m. p. 310–315°.

Anal. Calcd. for $C_9H_{10}N_2 \cdot 2HCl$: Cl, 32.1. Found: Cl, 31.1.

1-(*p*-Aminophenyl)-2-propylamine.—Five grams of 1-(*p*-nitrophenyl)-2-propylamine was dissolved in 30 ml. of dioxane and placed in a pressure bottle with 1 g. of Raney nickel. The air was evacuated from the bottle and a pressure of 60 lb. per sq. in. of hydrogen was admitted. The apparatus was mechanically shaken for forty-five minutes at room temperature. The pressure dropped steadily for the first thirty minutes to a minimum of 53.8 lb. as reduction proceeded.

The reaction mixture was filtered. The filtrate was distilled giving 2.9 g. of a viscous light-yellow oil boiling at 112–114° at 2 mm. The yield of 1-(*p*-aminophenyl)-2-propylamine was 70%. The dihydrochloride was precipitated by adding alcohol to a partially evaporated hydrochloric acid solution of the diamine.

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Summary

Six of the pharmacologically important phenylpropylamines have been nitrated in 82 to 94% yields. An arylnitropropane and an arylchloropropane were nitrated in 80 and 88% yields to precursors of sympathomimetic amines.

The nitro derivatives were reduced catalytically or with iron to the corresponding diamines.

The results of preliminary pharmacological tests on the arylpropylamines are given. Tests were made for toxicity and pressor activity.

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