Experimental

(I) **1,2,3-Trihydroxy-5,8-dimethylnaphthalene.**—One mole of pyrogallol and one-half mole of diacetone were introduced into an Erlenmeyer flask and 70% sulfuric acid was added slowly until solution was complete. The flask with the reaction mixture was then placed in an ice-bath. In twenty-four hours the dark red liquid had solidified and was drained off on a porous tile. The crystals were then triturated with water to remove unchanged pyrogallol, dried and extracted with boiling chloroform. Upon cooling of the filtered chloroform extract the naphtho-pyrogallol crystallized out; m. p. 187° (uncor.).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.59; H, 5.90; mol. wt., 204. Found: C, 70.55, 70.62; H, 6.04, 6.05; mol. wt., 197.

(Ia) **Acetate.**—Ten grams of the above naphthopyrogallol (I) was refluxed for six hours with 50 cc. of acetic anhydride. The excess acetic anhydride was distilled off and hot alcohol was added to the residue. The resulting solution was filtered, and upon concentration the acetate crystallized out; m. p. 148–150° (uncor.).

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 65.40; H, 5.40; mol. wt., 330. Found: C, 64.00; H, 5.28; mol. wt., 324.

(Ib) **Phenylurethan.**—One gram of the naphthopyrogallol (I) was treated with one cc. of phenyl isocyanate in a sealed test-tube and warmed for three hours on a steam-bath. The resulting semi-solid material was transferred to a porous tile and allowed to dry. The urethan was recrystallized from boiling benzene; m. p. 198° (uncor.).

Anal. Calcd. for $C_{33}H_{27}N_3O_6$: N, 7.48. Found: N, 7.43.

(II) **1,4,5,8-Tetramethylanthraquinone.**—To a solution of one mole of hydroquinone and one-half of a mole of diacetone in glacial acetic acid, was added one mole equivalent of 70% aqueous sulfuric acid. After two days of standing the solidified mass was extracted exhaustively with water and crystallized from 95% boiling ethyl alcohol. The crystals, which are insoluble in alkali, were then recrystallized from diisobutylene; m. p. 235° (uncor.).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.20; H, 6.76. Found: C, 81.13; H, 6.78.

Summary

Further studies in the condensations of diketones with di- and trihydroxybenzenes showed that, aside from the previously reported indano-indanes ("dindanes"), known types of polycyclic compounds result. Thus diacetone with pyrogallol yielded an alkylated trihydroxynaphthalene while the same diketone with hydroquinone gave a tetraalkylated anthraquinone, thus adding a new method of synthesis for these types of compounds. A rather simple reaction mechanism was shown to be applicable to all these condensation reactions.

WASHINGTON SQUARE COLLEGE
NEW YORK, N. Y. RECEIVED SEPTEMBER 18, 1940

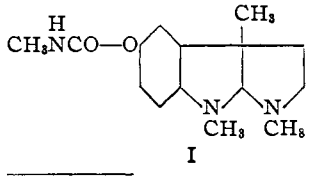
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Physostigmine Substitutes

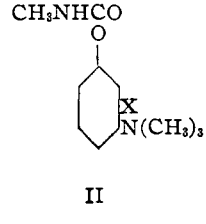
BY JOSEPH R. STEVENS AND RALPH H. BEUTEL

Stedman and co-workers have reported[1] that compounds of the types II and III showed marked physostigmine (I) activity whereas members of the corresponding ortho and para series were only slightly active.

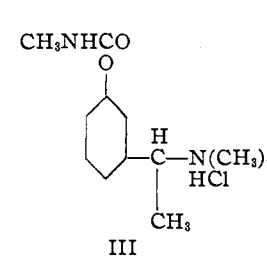
These results seem surprising in view of the *p*-aminophenol structure of physostigmine. It occurred to us that this anomaly may be the result of activation by the alkyl residue ortho to the amino group attached to the benzene ring in physostigmine. In order to test this assumption, compounds with the formula (IV) and (V) were syn-



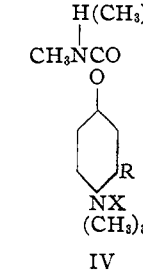
I



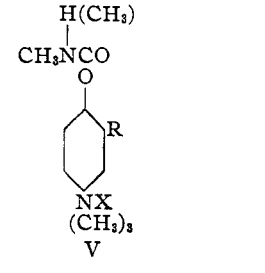
II



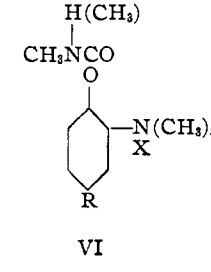
III



IV



V



VI

(1) E. Stedman, *Biochem. J.*, **20**, 719–734 (1926). E. Stedman, *ibid.*, **23**, 17–24 (1929). E. and E. Stedman, *J. Chem. Soc.*, 609–617 (1929).

TABLE I

No.	Compound	Formula	Analyses Calcd.	Found	M. p., °C.	L. D. 50 in mice
		A. Dimethylurethan of				
	p-Dimethylamino-					
1	-phenol methiodide	$C_{12}H_{19}O_2N_2I$	N, 7.97	8.00	195.5–196	120
2	-*o*-cresol hydrochloride	$C_{12}H_{19}O_2N_2Cl$	Cl, 14.0	14.0	189	>400
3	-*o*-cresol methiodide	$C_{13}H_{21}O_2N_2I$	[a]H, 5.81	5.99	189–190	6.5
4	-*m*-cresol hydrochloride	$C_{12}H_{18}O_2N_2$	[b]H, 8.17	8.15		105
5	-*m*-cresol methiodide	$C_{13}H_{21}O_2N_2I$	N, 7.40	7.69	169	13.0
6	-*m*-ethylphenol hydrochloride	$C_{13}H_{21}O_2N_2Cl$	Cl, 13.0	12.8	144–144.5	45
7	-*m*-ethylphenol methiodide	$C_{14}H_{23}O_2N_2I$	I, 33.6	33.9	149.5	1.15
8	-*m*-isopropylphenol methiodide	$C_{15}H_{25}O_2N_2I$	N, 7.09	6.72	170	0.075
9	-thymol hydrochloride	$C_{15}H_{25}O_2N_2Cl$	N, 9.32	9.26	163–164	160
10	-thymol methiodide	$C_{16}H_{27}O_2N_2I$	N, 6.89	6.89	171.5	0.72
11	-carvacrol hydrochloride	$C_{15}H_{25}O_2N_2Cl$	N, 9.32	9.29	185.5	20
12	-carvacrol methiodide	$C_{16}H_{27}O_2N_2I$	N, 6.89	6.97	169.5	0.24
	o-Dimethylamino-					
13	-*p*-cresol hydrochloride	$C_{12}H_{19}O_2N_2Cl$	[c]H, 7.41	7.13	174.5	Approx. 200
14	-*p*-cresol methiodide	$C_{13}H_{21}O_2N_2I$	[d]H, 5.81	5.51	154–155	2.0
15	-*p*-ethylphenol hydrochloride	$C_{13}H_{21}O_2N_2Cl$	Cl, 13.0	13.1	144–145	27
16	-*p*-ethylphenol methiodide	$C_{14}H_{23}O_2N_2I$	I, 33.6	33.4	148–149	1.25
17	-*p*-isopropylphenol hydrochloride	$C_{14}H_{23}O_2N_2Cl$	Cl, 12.4	12.4	168.5	>400
18	-*p*-isopropylphenol methiodide	$C_{15}H_{25}O_2N_2I$	[e]H, 6.42	6.35	171	4.8
	o-Dimethylamino-					
19	-*p*-*t*-butylphenol hydrochloride	$C_{16}H_{25}O_2N_2Cl$	Cl, 11.8	11.8	186.5	>500
20	-*p*-*t*-butylphenol methiodide	$C_{16}H_{27}O_2N_2I$	I, 31.2	31.2	162	13.5
21	-*p*-*t*-amylphenol hydrochloride	$C_{16}H_{27}O_2N_2Cl$	Cl, 11.3	11.3	175.5–176.5	>500
22	-*p*-*t*-amylphenol methiodide	$C_{17}H_{29}O_2N_2I$	I, 30.2	30.1	146.3	12
23	Prostigmine				143	0.45
24	Prostigmine methiodide	$C_{12}H_{19}O_2N_2I$	N, 7.99	7.83	162–163	0.55
25	β-Hydroxypyridine hydrochloride	$C_8H_{11}O_2N_2Cl$	N, 13.8	13.7	89	120
		B. Monomethylurethan of				
	p-Dimethylamino-					
26	-thymol hydrochloride	$C_{14}H_{23}O_2N_2Cl$	N, 9.77	9.76	199	23
27	-thymol methiodide	$C_{15}H_{25}O_2N_2I$	N, 7.14	6.87	182	0.22
28	-carvacrol hydrochloride	$C_{14}H_{23}O_2N_2Cl$	N, 9.77	9.57	192	2.1
29	-carvacrol methiodide	$C_{15}H_{25}O_2N_2I$	N, 7.14	7.32	159	0.09
30	Physostigmine[3]					0.5
31	Physostigmine methiodide[3]				188	0.75–1.0

[a] C, calcd., 42.8; found, 43.0. [b] C, calcd., 64.8; found, 65.3. [c] C, calcd., 55.7; found, 55.4. [d] C, calcd., 42.8; found 43.2. [e] C, calcd., 45.9; found 46.3.

thesized. Positive results were obtained, and the investigation was extended to include nuclear alkyl derivatives in the *o*-aminophenol series (VI). The dimethyl as well as the monomethyl urethans were made. The former are much more stable but somewhat less active than the latter.[2]

The substances were tested pharmacologically by Dr. Klaus Unna, of the Merck Institute for Therapeutic Research, who will report his findings in detail elsewhere. The activity of these compounds has been determined by toxicity tests on mice. The toxicity is expressed by the L. D. 50 (the amount of substance in mg. per kg. body weight necessary to kill 50% of the mice by subcutaneous injection). The results are summarized in Table I.

The alkyl groups have a marked effect on the activity of these compounds. This is well illustrated by a comparison of the isopropyl derivative in the *p*-aminophenol series (8) with the parent substance (1). The former is 1600 times as active as the latter. The activity of the *p*-cresol derivative (*o*-aminophenol) was surprising. It was the most active of the cresol group. However, the corresponding isopropyl homolog was disappointingly low in activity. Considering their convenience of preparation, the carvacrol

(2) J. Aeschlimann, U. S. Patent 1,905,990, Disubstituted Carbamic Acid Esters of Phenols Containing a Basic Constituent.

(3) J. Aeschlimann and M. Reinart, *J. Pharmacol.*, **43**, 413–444 (1931).

and thymol derivatives appear to be the best of the substances investigated for future therapeutic trials.

Experimental Part

General Procedure.—With the exception of thymol and carvacrol, the alkyl phenol was coupled with diazotized aniline. The diazo compound was reduced catalytically to the aminophenol, which was methylated to form the quaternary methiodide and distilled to give the alkyl dimethyl aminophenol.

The dimethyl urethan was prepared by treating the phenol thus obtained with dimethylcarbamyl chloride in dry pyridine. The urethan base was dissolved in ether and saturated with hydrogen chloride gas to form the hydrochloride. The methiodide was prepared by converting the pure hydrochloride back to the base and treating with methyl iodide.

The monomethyl urethan was prepared from the phenol and methyl isocyanate. Due to the instability of the monomethyl urethans in alkaline solution, the methiodide was prepared directly from the base.

Aminothymol and carvacrol were prepared by reduction of the nitroso compounds.[4]

The procedure is given in detail for the preparation of *m*-ethyl-*p*-dimethylaminophenol dimethyl urethan methiodide and *p*-dimethylaminocarvacrol monomethyl urethan methiodide. The other methiodides were made similarly, the yields being approximately the same.

***m*-Ethyl-*p*-aminophenol.**—Forty grams of aniline was dissolved in a mixture of 104 g. of concentrated hydrochloric acid and 250 ml. of water and diazotized with 30 g. of sodium nitrite in 150 ml. of water. The diazotized aniline was added to 53.7 g. of *m*-ethylphenol in 1000 ml. of 6% sodium hydroxide at 0–5° with vigorous stirring and the mixture was allowed to stand one-half hour. After filtering off the insoluble material, the filtrate was acidified with sulfuric acid and extracted with ether. The extract was dried over sodium sulfate and the ether was distilled off. The oily residue was taken up in methanol and reduced catalytically in the presence of palladium oxide. After filtering, the methanol was distilled off until crystallization began to take place. The concentrate was cooled in ice, filtered and washed with ether; yield, 44.5 g., 74%; recrystallized from ethanol, m. p. 169.5°.

***m*-Ethyl *p*-Dimethylaminophenol.**—Eighteen grams of *m*-ethyl-*p*-aminophenol was dissolved in 500 ml. of ethanol, and 20 g. of anhydrous sodium carbonate and 80 g. of methyl iodide were added. The mixture was refluxed overnight. The hot solution was filtered free from excess sodium carbonate and concentrated until crystallization commenced. The concentrate was cooled in ice, filtered, washed with a mixture of equal parts of ether and alcohol, and finally with ether. The quaternary salt thus obtained was destructively distilled under a pressure of 10–20 mm. in an oil-bath at 220–250°. The distillate was taken up in 10% sodium hydroxide, extracted with ether to get rid of alkali-insoluble products, acidified with sulfuric acid and neutralized with sodium bicarbonate. The product was extracted with ether, and the extract was dried over sodium sulfate and concentrated; yield 6.5 g., 30%.

(4) Klages, *Ber.*, **32**, 1518 (1899).

The yield could be increased considerably at this point by refluxing the alkali-insoluble material with 57% hydriodic acid for several hours and working up as usual. In some cases, as much as 50% of the yield is in the form of the methoxy compound.

***m*-Ethyl *p*-Dimethylaminophenol Dimethyl Urethan Hydrochloride.**—Six and one-half g. of *m*-ethyl-*p*-dimethylaminophenol was dissolved in 15 ml. of dry pyridine and 5 g. of dimethylcarbamyl chloride was added. The mixture was heated overnight on the steam-bath, cooled and taken up in ether and water. Sodium hydroxide was added until the water layer was neutral and a further 100 ml. of 2% sodium hydroxide solution was added. The mixture was separated and the ether extract was washed several times with water. The extract was dried and distilled at 14 mm. to remove most of the pyridine. The oily residue was transferred to a Washburn molecular still and distilled in the vacuum of a mercury vapor pump at 110°; yield, 7.5 g., 81%.

The thick pale yellow oil was dissolved in anhydrous ether and saturated with dry hydrogen chloride. The resulting crystals were filtered off and washed with ether. They were recrystallized from a minimum amount of absolute alcohol by the slow addition of anhydrous ether. The crystals were washed with ether and dried *in vacuo* at 76°; yield, 7.8 g., m. p. 141–143°. Recrystallization gave 7 g., m. p. 144.0–144.5°.

***m*-Ethyl-*p*-dimethylaminophenol Dimethyl Urethan Methiodide.**—Five grams of *m*-ethyl-*p*-dimethylaminophenol dimethyl urethan hydrochloride was dissolved in water, made alkaline with ammonia and extracted with ether. The extract was dried and concentrated and the residue was taken up in a small amount of acetone. An excess of methyl iodide was added and, after three days, several volumes of ether. The mixture was filtered and washed with ether, yielding 3.6 g. of the methiodide, m. p. 148–149°. On evaporating down the mother liquors, taking the residue up in methyl iodide and standing for ten days, a further 2.8 g. was obtained; yield, 6.4 g., 97%. Recrystallization from alcohol and ether gave 6.2 g., m. p. 148.5–149.5°.

***p*-Dimethylaminocarvacrol Monomethyl Urethan Methiodide.**—*p*-Dimethylaminocarvacrol was dissolved in an excess of freshly prepared methyl isocyanate.[5] After two days the excess methyl isocyanate was evaporated off under vacuum at room temperature. The hydrochloride was prepared by dissolving the oil in ether and passing in dry hydrogen chloride. The salt was filtered off and washed with ether. It was recrystallized by dissolving it in cold alcohol, precipitating with ether and drying *in vacuo* at 76°; m. p. 192°.

The methiodide was prepared by dissolving the urethan in a little acetone, adding an excess of methyl iodide, letting stand for two to three days, and adding several volumes of ether. The crystalline product was filtered off and recrystallized from alcohol and ether; m. p. 159°. Yields were almost the theoretical.

***p*-Isopropylnitrobenzene.**—The preparation of *p*-isopropylphenol by the methods reported[6] was unsatisfactory.

(5) Slotta and Lorenz, *ibid.*, **58**, 1322 (1925).

(6) Béhal and Tiffeneau, *Bull. soc. chim.*, [4] **3**, 318 (1908); Constam and Goldschmidt, *Ber.*, **21**, 1157 (1888).

TABLE II

No.	Compound	M. p., °C.	Formula	Analyses, % Calcd.	Found
1	*p*-Ethyl-*o*-aminophenol	139.5	$C_8H_{11}ON$	N, 10.2	9.87
2	*p*-Ethyl-*o*-dimethylaminophenol·HCl	157	$C_{10}H_{16}ONCl$	Cl, 17.6	17.6
3	*p*-Isopropyl-*o*-aminophenol	136	$C_9H_{13}ON$	N, 9.27	9.10
4	*p*-Isopropyl-*o*-dimethylaminophenol·HCl	172	$C_{11}H_{18}ONCl$	Cl, 16.4	16.7
5	*p*-*t*-Butyl-*o*-aminophenol	161.5	$C_{10}H_{15}ON$	N, 8.48	8.32
6	*p*-*t*-Butyl-*o*-dimethylaminophenol·HCl	217–218	$C_{12}H_{20}ONCl$	N, 6.23	5.99
7	*p*-*t*-Amyl-*o*-aminophenol	120	$C_{11}H_{17}ON$	N, 7.82	7.67
8	*p*-*t*-Amyl-*o*-dimethylaminophenol	44–45	$C_{13}H_{21}ON$	N, 6.76	6.71
9	*m*-Ethyl-*p*-aminophenol	169.5	$C_8H_{11}ON$	N, 10.2	10.4
10	*m*-Ethyl-*p*-dimethylaminophenol·HCl	179–180	$C_{10}H_{16}ONCl$	Cl, 17.6	17.6
11	*m*-Isopropyl-*p*-aminophenol	175.5	$C_9H_{13}ON$	N, 9.27	9.56
12	*m*-Isopropyl-*p*-dimethylaminophenol·HCl	218–219	$C_{11}H_{18}ONCl$	Cl, 16.4	16.8
13	*p*-Dimethylaminothymol·HCl	203–204	$C_{12}H_{20}ONCl$	N, 6.10	6.21
14	*p*-Dimethylaminocarvacrol·HCl	216–216.5	$C_{12}H_{20}ONCl$	N, 6.10	6.22

The substance was finally prepared through nitrocumene as follows. A mixture of 100 g. nitric acid (d. 1.44) and 150 g. of concentrated sulfuric acid was added slowly to 100 g. of cumene with vigorous stirring and cooling to 20–30°. When all of the acid had been added, the temperature was allowed to rise to 40° and the reaction mixture was allowed to stand until there was no further temperature rise with the cooling-bath removed. The mixture was poured onto ice, diluted with a large volume of water and extracted with ether. The dried extract was evaporated down, yielding crude, oily isopropyl nitrobenzenes.

***p*-Isopropylaniline.**—The oil was taken up in methanol and reduced catalytically. After filtering off the catalyst and distilling off the alcohol *in vacuo*, the residue was taken up in 2.5 *N* hydrochloric acid and extracted free from acid insoluble material with ether. The extracted product was made alkaline with sodium hydroxide and extracted with ether. The extract was dried and evaporated down, yielding a mixture of ortho and para isopropylaniline which was separated through the oxalate according to the method of Constam and Goldschmidt; yield, 56 g., 40%.

***p*-Isopropylphenol.**—Thirty-four grams of *p*-isopropylaniline in 500 cc. of water containing 62.5 g. of concentrated sulfuric acid was diazotized with 17.3 g. of sodium nitrite in 175 ml. of water. Some urea was added and the solution allowed to come to room temperature. The mixture was heated on the steam-bath at 50–60° for several hours, cooled, and extracted with benzene. The benzene solution was extracted with 10% sodium hydroxide. The alkaline extract was acidified and again extracted with benzene. The dried extract was evaporated and the residue crystallized out on cooling; yield, 25 g., 73.5%; m. p. 60°.

New intermediates prepared during the course of the investigation are summarized in Table II.

Acknowledgments.—The authors are grateful for the interest taken by Dr. Randolph T. Major in this investigation and for his helpful suggestions. The microanalyses were made by Messrs. Douglass Hayman, Wilhelm Reiss and Howard Clark.

Summary

A series of nuclear alkyl ortho and para aminophenol derivatives has been made which show marked physostigmine-like activity in contrast to the inactivity of the unalkylated parent substances.

RAHWAY, N. J. RECEIVED JULY 30, 1940