the adsorbed material eluted with dilute aqueous sodium hydroxide. The alkaline solution was filtered from the aluminum oxide and upon acidification with hydrochloric acid a light brown crystalline precipitate was obtained. After recrystallization from dilute ethanol, the substance was obtained in slightly colored crystals, m. p. 136°, which tend to decompose on exposure to air.

Anal. The substance contained no methoxyl. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 79.8, 79.5; H, 6.5, 6.5.

After saponification of the di-propionic ester described below, the di-hydroxy derivative was again obtained as the same unstable and slightly colored, though crystalline, product, m. p. 136°, giving the same analysis low in carbon.

2-(*p*-Acetoxyphenyl)-3-ethyl-6-acetoxy-indene (VII).—200 mg. of 2-(*p*-hydroxy-phenyl)-3-ethyl-6-hydroxy-indene (V) was refluxed for three hours with 15 cc. of acetic anhydride and 1 g. of anhydrous sodium acetate. After cooling, the reaction mixture was diluted with water and an oil separated which soon crystallized. After recrystallization once from dilute ethanol and twice from ligroin (b. p. 70–90°), the substance was obtained in almost colorless crystals, m. p. 118–120°. Contrary to the free hydroxyl compound, the acetylated derivative is perfectly stable.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.3; H, 6.3.

2-(*p*-Propoxyphenyl)-3-ethyl-6-propoxy-indene (VIII).—650 mg. of 2-(*p*-hydroxy-phenyl)-3-ethyl-6-hydroxy-indene (V) was dissolved in 5 cc. of dried pyridine, 3 g. of propionic anhydride (redist.) was added, and the mixture refluxed under nitrogen for ninety minutes at 105° bath temperature. After cooling and diluting with water, an oil separated which crystallized slowly on standing in the cold. After repeated recrystallization from methanol, the dipropionic ester crystallized in colorless leaflets, m. p. 88–89°.

Anal. Calcd. for $C_{23}H_{24}O_4$: C, 75.8; H, 6.6. Found: C, 75.8; H, 6.8.

2-(*p*-Hydroxyphenyl)-3-ethyl-6-hydroxy-indane (X).—Two grams of 2-(*p*-methoxy-phenyl)-3-ethyl-6-methoxy-indene (VI), m. p. 87–88°, was dissolved in 30 cc. of hot absolute methanol and hydrogenated in the presence of palladium. One mole of hydrogen was taken up within two and one-half hours, the catalyst was filtered off, the filtrate evaporated *in vacuo* and the remaining oil dissolved in 25 cc. of glacial acetic acid and 6 cc. of hydrobromic acid (48%). After refluxing under nitrogen for two hours, the reaction mixture was diluted with water and made strongly alkaline with sodium hydroxide. Some tarry material separated but went almost completely into solution when warming the mixture on the steam-bath. The alkaline solution was shaken three times with ether, the extract being discarded. The aqueous layer was filtered, acidified with hydrochloric acid, extracted three times with ether, and the combined ether extracts washed repeatedly with water until the washings were no longer acid to congo. The ether solution was dried over sodium sulfate, evaporated *in vacuo* and the residue recrystallized first from benzene, then repeatedly from ethanol; yield 1.25 g., m. p. 162–163°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.2; H, 7.2. Found: C, 80.3; H, 7.0.

Summary

1. 2-(*p*-Hydroxy-phenyl)-3-ethyl-6-hydroxy-indene and some of its derivatives have been synthesized and were found to possess considerable estrogenic activity. The subcutaneous activity of the most active indene derivative is one-twelfth of that of stilbestrol, though the ratio of oral to subcutaneous activity is less favorable than for stilbestrol.

2. The absorption spectra of phenyl-indene derivatives and of *cis*- and *trans*-stilbene have been compared with those of stilbestrol and its diacetate. Contrary to expectation the latter were found not to correspond to those of 2-phenyl-indene derivatives and *trans*-stilbene.

NUTLEY, NEW JERSEY RECEIVED JULY 19, 1943

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Unsymmetrical Diacyl Derivatives of 4,4'-Diaminodiphenyl Sulfone

BY H. A. SHONLE AND A. M. VANARENDONK

In the search for new chemotherapeutic agents, it was early observed that 4,4'-diaminodiphenyl sulfone was more effective, on a weight basis, than sulfanilamide in combatting streptococcic and certain other infections in white mice. Bauer and Rosenthal[1] reported a therapeutic index of 6 for 4,4'-diaminodiphenylsulfone and a therapeutic index of 3.3 for sulfanilamide in white mice infected with hemolytic streptococcus. Because of the relatively high toxicity of 4,4'-diaminodiphenyl sulfone, many derivatives have been prepared and tested in the hope that in some of these a more favorable therapeutic index might be found.

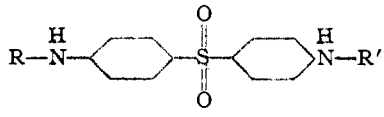
Nitti, Bovet and Hamon[2] investigated some of the lower aliphatic diacyl derivatives of 4,4'-diaminodiphenyl sulfone and determined the amount of free 4,4'-diaminodiphenyl sulfone in the blood after oral administration. They found that the blood concentration of the free amino compound varied inversely with the length of the carbon chain with the exception of the diacetyl derivative which produced a low concentration of the amino compound in the blood stream. They believed that these varying concentrations represented the relative rates of hydrolysis. In the work here reported, we have prepared and tested a series of unsymmetrical 4,4'-diacylaminodiphenyl sulfones in order to ascertain whether any of these new derivatives would be sufficiently effective to possess clinical usefulness.

Pharmacological Part.—These unsymmetrical 4,4'-diacylaminodiphenyl sulfones were used in the treatment of mice infected with hemolytic streptococcus (C 203) and pneumococcus Type I (from Park; original Neufeld I). The experi-

(1) H. Bauer and S. M. Rosenthal, *U. S. Pub. Health Rep.*, **53**, 40 (1938).

(2) F. Nitti, D. Bovet and V. Hamon, *Compt. rend. soc. biol.*, **128**, 26 (1938).

TABLE I



R	R'	M. p., °C. (uncor.)	N analyses, % Calcd.	Found	Relative activity Streptococcus	Pneumococcus	Toxicity, mg. per 20 g. mouse
CH_3CO-	CH_3CH_2CO-[a]	227–228	8.09	8.27	+++	++	40/20
CH_3CO-	$CH_3(CH_2)_2CO$-[a]	223.4	7.77	7.80	+++	+	20/10
CH_3CO-	$CH_3(CH_2)_4CO$-	197–198	7.22	7.12	+	+	?/80
CH_3CO-	$CH_3(CH_2)_8CO$-	176–178	6.30	6.15		+	?/80
CH_3CO-	$CH_3(CH_2)_{10}CO$-	168–170	5.93	6.10		+	?/80
CH_3CO-	$CH_3(CH_2)_{12}CO$-	164–165	5.60	5.48		+	?/80
CH_3CO-	$CH_3(CH_2)_{14}CO$-	158–160	5.31	5.20		+	?/80
CH_3CO-	$CH_3(CH_2)_{16}CO$-	157–162	5.04	4.99	+	+	?/80
CH_3CO-	$CH_3CH{=}CHCO$-	231–232	7.82	7.78	+++		?/80
CH_3CO-	$HOOCCH{=}CHCO$-	230–231	7.21	7.06	++	+	40/20
CH_3CO-	$(C_6H_5)CH{=}CHCO$-	180–181	6.67	6.52	++	0	?/80
CH_3CO-	$ClCH_2CO$-	214–215	7.65	8.69	+++	+	10/5
CH_3CO-	Cl_2CCO-	268–270	6.43	6.45	+++	+	?/80
CH_3CO-	β-$(C_5H_4N)CO$-	282–283	10.61	10.63		+	?/80
CH_3CO-	C_6H_5CO-[b]	212–213	7.11	7.14		±	?/80
CH_3CO-	p-$(NO_2)C_6H_5CO$-	239–240	9.57	9.50	+	0	?/80
CH_3CO-	α-$(C_4H_3O)CO$-	240–241	7.27	7.35		±	?/80
CH_3CH_2CO-	$CH_3(CH_2)_2CO$-[a]	201–202	7.51	7.63	+++	+++	80/40
CH_3CH_2CO-	$HOOCCH{=}CHCO$-	223–224	6.97	7.09	+++	+	40/20
CH_3CH_2CO-	$ClCH_2CO$-	201–202	7.37	7.52	+++	+	40/20
$CH_3(CH_2)_2CO$-	$ClCH_2CO$-	178–179	7.11	7.10	+++	+	80/40
H	H	...	...	...	+++	+++	5/2
Sulfanilamide (control)		...	...	...	++		80/40
Sulfapyridine (control)		...	...	...		++	?/80

[a] British Patent 517,421, June 20, 1940. [b] British Patent 533,565, Feb. 17, 1941.

mental details of this investigation were those which have been described by H. M. Powell and associates.[3] The table summarizes the results obtained. In reporting the relative activity, we have followed the system used by Northey[4] wherein +++ indicates greater activity than the drug used for comparison; ++, a comparable activity to the control drug; +, a moderate amount of action; ±, a slight or uncertain action; 0, no activity, and −, toxicity (treated animals dead before controls). In this work, the drug used as a control in streptococcus infections is sulfanilamide and in pneumococcus infections, sulfapyridine. The toxicity data reported are only approximate. The numerator represents a dose which is fatal and the denominator a dose on which the animals survived when mice were given a series of doses, each dose being twice the preceding dose. In the case of streptococcic infections, therapy comprised two doses given orally on the first day of infection. Pneumococcic infection therapy comprised a total of five oral doses given on three successive days. The surviving mice were observed for fourteen days.

(3) H. M. Powell and K. K. Chen, *J. Pharmacol.*, **67**, 79 (1939); E. H. Stuart, H. M. Powell, C. L. Rose and F. E. Bibbins, *J. Am. Pharm. Assoc.*, **28**, 90 (1939); H. M. Powell and K. K. Chen, *J. Ind. State Med. Assn.*, **33**, 503 (1940); H. M. Powell and K. K. Chen, *ibid.*, **34**, 602 (1941).

(4) E. H. Northey *Chem. Rev.*, **27**, 85 (1940).

Acknowledgment.—We wish to express our appreciation to Dr. H. M. Powell and Misses Marjorie Fogas and Lorraine Meyers of our Laboratories for the physiological testing of these compounds, and to Mr. J. T. Bryant for the microanalyses.

Experimental Part

4,4′-Diaminodiphenyl sulfone was prepared by oxidation of technical thioaniline according to previously published directions.[5]

Preparation of 4-Acetylamino-4′-aminodiphenyl Sulfone.[6]—To a boiling solution of 24.8 g. (0.1 mole) of 4,4′-diaminodiphenyl sulfone in 200 cc. of dioxane was added 10.2 g. (0.1 mole) of acetic anhydride. The boiling was continued for a few minutes after the addition, and after cooling to room temperature, was poured into 1.5 liters of water containing about 150 cc. of hydrochloric acid (sp. gr. 1.2). The resulting suspension was allowed to stand for several hours until the 4,4′-diacetylaminodiphenyl sulfone precipitated. The precipitate was filtered off, the filtrate partially neutralized with ammonium hydroxide until a cloudiness appeared and cooled overnight in the refrigerator. The precipitate of 4-acetylamino-4′-aminodiphenyl sulfone was filtered off and recrystallized several times from methyl alcohol. The pure 4-acetylamino-4′-aminodiphenyl sulfone melted at 232–233° (uncor.). Further neutralization of the filtrate with ammonium hydroxide yielded a precipitate from which a small amount of 4-acetylamino-4′-aminodiphenyl sulfone was obtained. The

(5) A. M. VanArendonk and E. C. Kleiderer, THIS JOURNAL, **62**, 3521 (1940).

(6) H. A. Shonle and A. M. VanArendonk, U. S. Patent 2,325,344, July 27, 1943.

total yield amounted to about 40–50%. The monopropionyl and mono-butyryl derivatives were prepared in a similar manner. The greater solubility of these derivatives in most organic solvents made them more difficult to purify. 4-Propionylamino-4'-aminodiphenyl sulfone melted at 201–202° (uncor.) and 4-butyrylamino-4'-aminodiphenyl sulfone melted at 192–193° (uncor.).

Preparation of 4-Acetylamino-4'-propionylaminodiphenyl Sulfone.—To 2.9 g. (0.01 mole) of 4-acetylaminodiphenyl sulfone dissolved in 15 cc. of pyridine was added slowly and with stirring 1 g. (0.01 mole) of propionyl chloride. The solution after standing for fifteen minutes was warmed to 80° on the water-bath for a few moments, then poured into 200 cc. of water containing 30 cc. of hydrochloric acid (sp. gr. 1.2), stirred well to induce crystallization and cooled for several hours in the refrigerator. The 4-acetylamino-4'-propionylaminodiphenyl sulfone after recrystallization from alcohol melted at 227–228° (uncor.). The yield of pure material was 90–95%. The other diacyl derivatives were prepared in the same manner. The melting points and analytical data are given in the table.

Summary

A series of twenty-one unsymmetrical diacyl derivatives of diaminodiphenyl sulfone has been prepared, and their effectiveness in streptococcus and pneumococcus infections in white mice has been compared to sulfanilamide and sulfapyridine.

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

Basic-alkyl Esters of p-(Aminoalkyl)-benzoic Acids. II

BY F. F. BLICKE AND W. M. LILIENFELD[1,2]

The syntheses of p-(aminomethyl)-, p-(β-aminoethyl)- and p-(γ-aminopropyl)-benzoic acid, as well as of basic-alkyl esters of these acids, have been described in an earlier publication.[3] Subsequently we discovered another preparative procedure for p-(aminoalkyl)-benzoic acids, one which would seem to be applicable for the synthesis of any acid of this type. By means of this procedure we have prepared p-(β-aminoethyl)- and p-(β-aminopropyl)-benzoic acid.

β-Phenylethyl bromide (I) was transformed into the corresponding amine (II) with the aid of the Gabriel synthesis. The amine was acetylated, and the acetyl derivative (III) reacted with acetyl bromide and aluminum chloride to produce p-(β-acetylaminoethyl)-acetophenone (IV).[4] The latter was oxidized with hypobromite to p-(β-acetylaminoethyl)-benzoic acid (V)[5] which, upon hydrolysis, yielded p-(β-aminoethyl)-benzoic acid (VI).

I $BrCH_2CH_2—C_6H_5$
II $NH_2CH_2CH_2—C_6H_5$
III $CH_3CONHCH_2CH_2—C_6H_5$
IV $CH_3CONHCH_2CH_2—C_6H_4—COCH_3$
V $CH_3CONHCH_2CH_2—C_6H_4—COOH$
VI $NH_2CH_2CH_2—C_6H_4—COOH$

The procedure for p-(β-aminopropyl)-benzoic acid (XI) is entirely analogous to the one described above; in this instance it was possible to begin the synthesis with the use of benzedrine (VII).

VII $NH_2CH(CH_3)CH_2—C_6H_5$
VIII $CH_3CONHCH(CH_3)CH_2—C_6H_5$
IX $CH_3CONHCH(CH_3)CH_2—C_6H_4—COCH_3$
X $CH_3CONHCH(CH_3)CH_2—C_6H_4—COOH$
XI $NH_2CH(CH_3)CH_2—C_6H_4—COOH$

The hydrochlorides of the ethyl ester and of the four basic-alkyl esters of p-(β-aminopropyl)-benzoic acid—the β-piperidinoethyl, γ-piperidinopropyl, γ-morpholinopropyl and the β,β-dimethyl-γ-piperidinopropyl—were prepared by interaction of the aminoalkylbenzoyl chloride hydrochloride with the required basic alcohol hydrochloride in the same manner described previously.[3]

The esters were examined for local anesthetic and pressor activity by L. W. Rowe in the Parke, Davis and Company laboratories. In 2% solution none of the esters produced anesthesia when applied to the rabbit's cornea; only slight anesthesia was obtained by injection. Ethyl p-(β-aminopropyl)-benzoate dihydrochloride brought about only a very moderate rise in blood pressure, while the effect of the other esters was negligible.[6]

Experimental Part

β-Phenylethyl bromide[7] (I), β-phenylethylamine[8] (II) and its acetyl derivative (III)[9] (b. p. 160–162° (3 mm.)) were prepared according to published methods.

p-(β-Acetylaminoethyl)-acetophenone (IV).—To 41 g. of the acetylated amine, dissolved in 100 cc. of dry tetrachloroethane, there was added 48 cc. of acetyl bromide. The solution was cooled to 0° and maintained at that temperature while it was stirred, and 110 g. of aluminum chloride added in small portions. After complete addition, the material was heated on a steam-bath for one-half hour,

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by W. M. Lilienfeld in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis and Company Fellow.

(3) Blicke and Lilienfeld, THIS JOURNAL, **65**, 2281 (1943).

(4) Kunckell (*Ber.*, **33**, 2641 (1900)) showed that acetanilide, acetyl bromide and aluminum chloride react to form p-acetylaminoacetophenone.

(5) The fact that this substance was a *para* substituted compound was proven by oxidation of compound V to terephthalic acid, and identification of the latter through its dimethyl ester (see Norris, "Experimental Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., first edition, 1915, p. 168).

(6) In this connection, it is interesting to note that Allewelt and Day (*J. Org. Chem.*, **6**, 384 (1941)) stated that certain basic alcohols which they prepared exhibit both local anesthetic and pressor activity.

(7) Norris, Watt and Thomas, THIS JOURNAL, **38**, 1078 (1916).

(8) Ing and Manske, *J. Chem. Soc.*, 2350 (1926).

(9) Bischler and Napieralski, *Ber.*, **26**, 1905 (1893).