using one counter on each side of the head, can be accomplished. With this method, localization of an area of radioactivity can be more sharply defined. To date, difficulty has been encountered in finding effective tracers to carry the positron-emitting isotopes:

Brief mention of the parallel development of instrumentation for isotope encephalometry should be made. When the original G-M counters were employed, large doses of the radioactive dye had to be given to ensure adequate counting rates. Later, more efficient tubes such as the bismuth-cathode tube became available and the dosage could be reduced. The development of stable scintillation counters has further reduced the amount of radioactivity necessary.

At this clinic an instrument which fits over the head and contains eighteen counter units has been tested. However, until certain mathematical calculations can be solved, it offers little advantage over the use of a single scintillation counter (Fig. 1).

SUMMARY

The advent of isotope encephalometry has given neurosurgeons an additional adjunctive diagnostic method for the localization of the brain tumors. It is innocuous and can be carried out without the use of an operative procedure. The accuracy of localization obtained with this method approaches that of the other diagnostic techniques and, when interpreted with the neurological findings of the patient, results in a diagnostic accuracy of approximately 90 per cent.

It would seem that, in the future, tracer diagnostic agents with lesser biological limitations will be found for the localization of tumors not only in the brain but also in other parts of the body.

REFERENCES

(1) Moore, G. E., *Science*, **106**, 139(1947).
(2) Moore, G. E., *ibid.*, **107**, 569(1948).
(3) Moore, G. E., Caudill, C. M., Marvin, J. F., Aust, J. B., Chou, S. N., and Smith, G. A., *Am. J. Roentgenol. Radium Therapy*, **66**, 1(1951).
(4) Wrenn, F. R., Good, M. L., and Handler, P., *Science*, **113**, 525(1951).

The Synthesis of Azo Compounds for Urogenital Analgesia*

By ELIOT STEINBERG, GUY M. MATTSON, and GEORGE E. PHILLIPS†

Eight azo-type dyes and their hydrochlorides have been synthesized. These compounds have potential therapeutic use for analgesia of the genitourinary tract. The physical and chemical properties of these compounds are reported.

CERTAIN azo compounds have found clinical acceptance for the treatment of genitourinary infections. Two examples are 3-phenylazo-2,6-diaminopyridine monohydrochloride,[1] I (1) and *p*-ethoxyphenylazo-2′4′-diaminobenzene monohydrochloride,[2] II (2). The usefulness of these drugs is apparently due primarily to their analgesic action rather than to their relatively slight antiseptic potency (3).

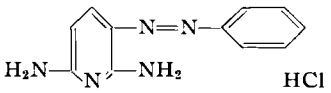
Esters of *p*-aminobenzoic acid have been widely accepted for therapeutic use as analgesics and local anesthetics (4). Ethyl *p*-aminobenzoate, in particular, is satisfactory as a local anesthetic because of its low toxicity. It is also reported to be active as a bladder analgesic (5).

In an attempt to enhance the analgesic properties of compounds of the above type for bladder analgesia, azo dyes of types III and IV were prepared from alkyl esters and from dialkylaminoalkyl esters of *p*-aminobenzoic acid.

The alkyl esters of *p*-aminobenzoic acid, where not commercially available, were prepared by esterification of the acid with the appropriate alcohol saturated with dry hydrogen chloride gas (6). *n*-Propyl *p*-aminobenzoate and isopropyl *p*-aminobenzoate were prepared in this manner. Adams, *et al.* (7), prepared these esters by the reaction of *p*-nitrobenzoyl chloride with

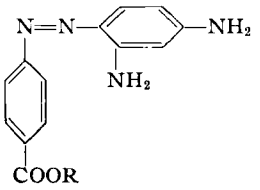
* Received January 25, 1952, from the Warner-Chilcott Research Laboratories, Division of the Maltine Co., Morris Plains, N. J.
† The authors wish to thank G. Feri and J. Ernst for the analytical and solubility data.
[1] Trademark name: "Pyridium" and "Mallophene."
[2] Trademark name: "Serenium."

the appropriate alcohol and the subsequent reduction of the nitro ester with iron and hydrochloric acid. The butyl *p*-aminobenzoate and N,N-dibutylaminopropyl *p*-aminobenzoate were supplied through the courtesy of the Special Chemicals Division of the Abbott Laboratories. The



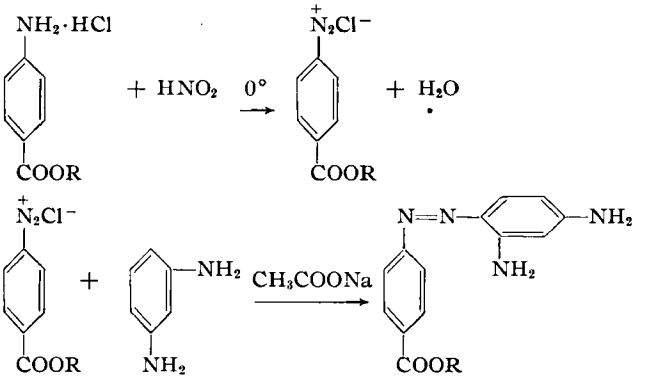
(I)

other *p*-aminobenzoates were obtained from the Matheson Co. and were used without further purification. The *m*-phenylenediamine, available in a technical grade, was recrystallized from benzene before using.



(III)

The diazotization and couplings were performed in the usual manner by diazotizing the local anesthetic and coupling it with *m*-phenylenediamine:

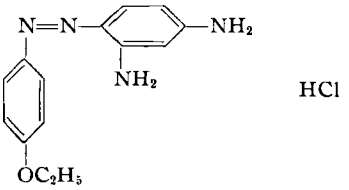


2-Diethylaminoethyl *p*-(2′,4′-diaminophenylazo)-benzoate and propyl *p*-(2′,4′-diaminophenylazo)-benzoate have previously been prepared for their histological staining properties (8). However, no experimental details, analytical data, or physical constants were reported.

Pharmacological studies of these compounds are in progress.

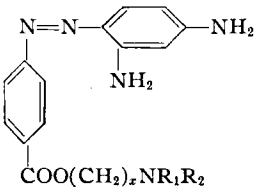
EXPERIMENTAL

***n*-Propyl *p*-Aminobenzoate.**—Sixty-nine grams (0.5 mole) of *p*-aminobenzoic acid was refluxed for forty-eight hours with 1 L. of *n*-propyl alcohol which had been saturated with dry hydrogen chloride gas. The resulting solution was diluted with an equal



(II)

volume of water and made basic with 20% sodium carbonate solution. An oil layer separated and slowly crystallized. The crystals, which were removed by filtration and recrystallized from hexyl ether, had a melting point of 73–76°; reported (7) 73–74°. A yield of 84.4 Gm. (93%) was obtained.



(IV)

Isopropyl *p*-aminobenzoate, prepared by the same procedure, had a melting point of 85–87°; reported (7), 85–86°.

Ethyl *p*-(2′,4′-Diaminophenylazo)-benzoate.—A quantity of 16.5 Gm. (0.1 mole) of ethyl *p*-amino-benzoate was dissolved in a solution of 200 cc. of water and 20 cc. of hydrochloric acid (sp. gr. 1.19). This solution was placed in an ice bath and diazotized with 1 *M* sodium nitrite solution. The solution of the diazonium salt was coupled with a solution of 10.8 Gm. (0.1 mole) of *m*-phenylene diamine and 42 Gm. (0.1 mole) of sodium acetate in 400 cc. of water. The resulting dark red solution was stirred for thirty minutes and then adjusted to a *p*H of 9 with ammonium hydroxide. The deep scarlet

TABLE I

Compd. No.	Compound Diazotized	R	Formula	M. P., °C.[a]	Color	Analysis, % N Calcd.	N Found	Cl Calcd.	Cl Found	Solubility, Gm./100 Cc. C_2H_5OH	Solubility, Gm./100 Cc. H_2O
1	Methyl *p*-aminobenzoate	CH_3	$C_{14}H_{14}N_4O_2$	201–203	Red	20.7	20.0	...	...	0.310	0.017
			$C_{14}H_{14}N_4O_2 \cdot HCl$	247–248	Red	18.5	18.3	11.6	11.5	0.188	0.038
2	Ethyl *p*-aminobenzoate (Benzocaine)	C_2H_5	$C_{15}H_{16}N_4O_2$	160–163	Scarlet	19.7	19.7	...	...	1.93	0.012
			$C_{15}H_{16}N_4O_2 \cdot HCl$	264–265	Maroon	17.5	16.8	11.1	10.9	0.100	0.044
3	Propyl *p*-aminobenzoate (Propaesin)	C_3H_7	$C_{16}H_{18}N_4O_2$	153–155	Scarlet	18.7	18.3	...	...	0.958	0.017
			$C_{16}H_{18}N_4O_2 \cdot HCl$	256–257	Red	16.7	16.2	10.8	10.2	0.744	0.017
4	Isopropyl *p*-aminobenzoate	*i*-C_3H_7	$C_{16}H_{18}N_4O_2$	138–140	Scarlet	18.7	18.7	...	...	2.98	0.010
			$C_{16}H_{18}N_4O_2 \cdot HCl$	245.5	Red	16.7	16.4	10.8	11.4	0.580	0.304
5	Butyl *p*-aminobenzoate (Butesin)[b]	C_4H_9	$C_{17}H_{20}N_4O_2$	106–110	Brown	17.9	17.2	..	...	6.98	0.016
			$C_{17}H_{20}N_4O_2 \cdot HCl$	248–249	Brown	16.1	15.2	10.2	9.7	0.790	0.050
6	Isobutyl *p*-aminobenzoate (Cycloform[c])	*i*-C_4H_9	$C_{17}H_{20}N_4O_2$	114–119	Maroon	17.9	17.3	...	...	6.39	0.009
			$C_{17}H_{20}N_4O_2 \cdot HCl$	228–229	Red	16.1	15.5	10.2	10.7	0.806	0.046
7	N,N-Diethylaminoethyl *p*-aminobenzoate (Procaine)	$(C_2H_5)_2NCH_2CH_2$	$C_{19}H_{25}N_5O_2$	107–109	Scarlet	19.7	19.3	...	...	18.12	0.078
			$C_{19}H_{25}N_5O_2 \cdot 2HCl$	236–237	Red	16.4	15.8	16.4	16.3	0.570	27.79
8	N,N-Dibutylaminoethyl *p*-aminobenzoate (Butacaine[b])	$(C_4H_9)_2NCH_2CH_2$	$C_{24}H_{35}N_5O_2$	101–104	Scarlet	16.5	16.4	...	...	5.34	00.38
			$C_{24}H_{35}N_5O_2 \cdot HCl$	246–248	Red	14.1	13.5	14.1	14.0	0.664	08.50

[a] Uncorrected.
[b] Trade mark: Abbott Laboratories.
[c] Trade mark: Winthrop-Stearns, Inc.

colored crystals were removed by filtration, washed with dilute ammonium hydroxide and water, and dried in a desiccator. The yield was almost quantitative. When recrystallized from absolute methanol, the base melted at 160–163°.

Anal.—Calcd. for $C_{15}H_{16}N_4O_2$: N, 19.7. Found: N, 19.7.

The hydrochloride was formed by dissolving the free base in ether and passing dry hydrogen chloride gas through the solution. The precipitated hydrochloride was filtered by suction and washed with absolute ethanol and ether. Dark red crystals which melted at 264–265° were obtained.

Anal.—Calcd. for $C_{15}H_{16}N_4O_2 \cdot HCl$: N, 17.5; Cl, 11.1. Found: N, 16.8; Cl, 10.9.

Compounds 1, 3, 4, 5, 6, 7, and 8 and their hydrochlorides were prepared in a similar manner and are described in Table I. It has also been found possible to isolate the hydrochloride directly by salting it out of the coupling solution before neutralization.

REFERENCES

(1) Ostromislensky, I., U. S. pat. 1,680,109 (1929); through *Chem. Abstr.*, **22**, 3736 (1929); Chichibabin, A. E., and Zeide, E. C., *J. Russ. Phys.-Chem. Soc.*, **46**, 1276(1914); Chichibabin, A. E., and Ossetowa, E. D., *J. Am. Chem. Soc.*, **56**, 1711(1934); Ostromislensky, I., *ibid.*, **56**, 1713(1934).

(2) Ostromislensky, I., U. S. pat. 1,785,327 (1931); through *Chem. Abstr.*, **35**, 1036(1931).

(3) Krop, S., *Anesthesia & Analgesia*, **25**, 110(1946); Morrissey, J. H., and Spinelli, A. N., *J. Urol.*, **44**, 381(1940).

(4) Goodman, L., and Gilman, A., "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, 1941, pp. 286–316.

(5) Humphreys, G. A., *J. Urol.*, **37**, 715-(1937).

(6) "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, 1943, p. 300.

(7) Adams, R., *et al.*, *J. Am. Chem. Soc.*, **48**, 1758(1926).

(8) Fulton, J. F., *Am. J. Physiol.*, **57**, 153(1921).