with CD_3COOD[6] in ordinary or deuterated ethanol, it was found that introduction of three deuteriums in the α-position does not alter the reactivity of acetic acid much beyond the experimental error.

In most cases the reactions were slower, but even the largest effect was under 10%. These results confirm the expectation that there should be no very significant difference in electrical or other effects between CH_3– and CD_3– groups on the carboxyl hydrogen.

[6] We are indebted to Dr. Donald J. Cram for the preparation of this material by the procedure of C. L. Wilson, *J. Chem. Soc.*, 492 (1935).

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Urea Derivatives Related to Procaine

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Numerous substituted ureas have been prepared and found to possess physiological properties; however, very few of these are of the diaryl type.

In connection with an investigation[2] of the effect of change in structure of the 4-amino group in procaine on its pharmacological activity, we prepared 4,4′-di-(β-diethylaminocarboethoxy)-carbanilide[3] and tests[4] indicated that it is relatively active as a local anesthetic.

Accordingly, we have undertaken the syntheses of a number of diarylureas related to procaine by the reaction of the latter with various aryl isocyanates. The melting points, percentage yields, and analytical data for these compounds are recorded in Table I. As yet, they have not been tested for possible physiological properties.

Experimental[5]

Materials.—The aryl isocyanates were purchased from the Eastman Kodak Co. and were purified by distillation or crystallization immediately prior to use. The procaine base was prepared by treating the hydrochloride (Merck and Co., Inc.) with alkali, dissolving the resulting dihydrate in benzene and distilling the solution to a low volume. Upon cooling the residue, the desired base was obtained in almost quantitative yield; m.p. 58–59°.

Preparation of 4-(β-Diethylaminocarboethoxy)-carbanilide and its Hydrochloride.—This procedure is representative of the methods employed for the preparation of the compounds listed in Table I. To 11.8 g. (0.05 mole) of procaine base, dissolved in a mixture of 50 ml. of anhydrous benzene and 25 ml. of anhydrous toluene, was added 5.95 g. (0.05 mole) of phenyl isocyanate. The reaction mixture warmed spontaneously and was refluxed then for about 30 minutes. It was allowed to cool, and placed in a refrigerator until crystallization was completed. The white crystals were removed by filtration, washed with anhydrous benzene and dried to give 16.2 g. (91%) of a product which melted at 90–94°. Four recrystallizations from a mixture of ethyl acetate and petroleum ether (60–70°) raised the melting point to 94–96°.

TABLE I

UREA DERIVATIVES OF PROCAINE, $XC_6H_4NHCONHC_6H_4CO_2C_2H_4N(C_2H_5)_2$

X	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Bases				
H[a]	94–96	91	$C_{20}H_{25}O_3N_3$	67.58	67.67	7.09	7.14
2-CH_3[a]	87–89	96	$C_{21}H_{27}O_3N_3$	68.26	67.86	7.37	7.44
2-Cl[a]	86–88	87	$C_{20}H_{24}O_3N_3Cl$	61.61	61.68	6.20	6.44
3-Cl[a]	88–90	88	$C_{20}H_{24}O_3N_3Cl$	61.61	61.51	6.20	6.49
2,5-Cl[b]	155–156	89	$C_{20}H_{23}O_3N_3Cl_2$	56.61	56.39	5.46	5.53
4-Br[c]	174–176	87	$C_{20}H_{24}O_3N_3Br$	55.31	55.63	5.57	5.48
2-NO_2[c]	101–102	91	$C_{20}H_{24}O_5N_4$	59.99	60.30	6.04	6.26
4-NO_2[c]	156–158	84	$C_{20}H_{24}O_5N_4$	59.99	59.71	6.04	6.21
			Hydrochlorides				
H	202–204	97	$C_{20}H_{26}O_3N_3Cl$	61.29	61.26	6.68	6.88
2-CH_3[c]	174–175 (picrate)	92	$C_{27}H_{30}O_{10}N_6$	54.17	54.29	5.05	5.13
2-Cl	195–197	91	$C_{20}H_{25}O_3N_3Cl_2$	56.34	56.66	5.91	6.09
3-Cl	193–195	92	$C_{20}H_{25}O_3N_3Cl_2$	56.34	56.31	5.91	5.91
2,5-Cl	221–223	91	$C_{20}H_{24}O_3N_3Cl_3$	52.13	52.36	5.25	5.13
4-Br	215–217	86	$C_{20}H_{25}O_3N_3ClBr$	51.02	51.36	5.35	5.12
2-NO_2	202–203	97	$C_{20}H_{25}O_5N_4Cl$	54.98	55.11	5.77	6.09
4-NO_2	221–223	87	$C_{20}H_{25}O_5N_4Cl$	54.98	54.96	5.77	5.97

Crystallization solvents: [a] Ethyl acetate-petroleum ether (60–70°). [b] Ethyl acetate. [c] Absolute alcohol.

A sample (1.78 g.) of the purified substituted carbanilide was dissolved in 10 ml. of anhydrous ether and dry hydrogen chloride was passed through the solution. The precipitated hydrochloride was removed on a buchner funnel and dried over solid potassium hydroxide; wt. 1.94 g. (97%); m.p. 202–204°.

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[2] N. Rabjohn, T. R. Hopkins and R. C. Nagler, THIS JOURNAL, **74**, 3215 (1952).

[3] U. N. Narayana Rao, B. H. Iyer and P. C. Guha, *Current Sci.* (*India*), **19**, 180 (1950); *C. A.*, **44**, 11025 (1950).

[4] The authors are indebted to the McNeil Laboratories for screening this compound.

[5] All melting points are uncorrected. The semimicro analyses were performed by Mr. P. D. Strickler.