The Synthesis of Some New Esters of *p*-Carboxybenzamidine*,†

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Because it had previously been shown that some of the simple *n*-alkyl-*p*-carboxybenzamidines possessed significant local anesthetic activity, several new esters were prepared in order to test their activities. Representative examples of halogenated alcohols, aromatic alcohols, and cyclohexanol were chosen for the alcohol portion of the molecule. Several of these new esters were more active than both cocaine when instilled in guinea-pig eyes and procaine when administered intracutaneously in guinea-pig skin. Toxicities were favorable; however, they produced an undesirable pruritis when injected in the forearm of man.

IN A PREVIOUS publication a number of *n*-alkyl esters of *p*-carboxybenzamidine were prepared (1) and a subsequent screening of their local anesthetic activities showed that the esters prepared from *n*-amyl and *n*-hexyl alcohol and *p*-carboxybenzamidine had definite anesthetic activity. As one phase of a continuation of this field of research, it was deemed advisable to prepare esters other than the *n*-alkyl series to test them for their possible anesthetic activity. A miscellaneous group of esters has been prepared and some of these compounds exhibited marked topical and infiltration anesthesia.

EXPERIMENTAL

The esters were prepared essentially by the procedure described by DiGangi and Gisvold with some modifications. *p*-Cyanobenzoic acid was prepared by the usual procedure (2) with some modifications that will be the subject of a future publication.

p-Cyanobenzoyl Chloride.—This intermediate was prepared as previously described (1) with the exception that the crude acid chloride was recrystallized from absolute ether.

p-Cyanobenzoic Acid Esters.—These esters were made by direct condensation of the acyl chloride and alcohol or by using pyridine as a catalyst. As an illustration of the former procedure, 16.5 Gm. (0.1 *M*) of *p*-cyanobenzoyl chloride and 14.4 Gm. (0.1 *M*) of 2,3-dichloropropanol were heated on a steam bath for three hours in a 500-cc. round-bottom flask carrying a condenser and a calcium chloride drying tube. After standing overnight at room temperature, the solid mass which had formed was crushed, digested with 5% sodium carbonate solution, filtered, and washed with water. The crude ester thus obtained was recrystallized from alcohol after decolorizing with charcoal.

As an illustration of the latter procedure, 8.5 Gm. (0.05 *M*) of *p*-cyanobenzoyl chloride was dissolved in 20 cc. of benzene to which 5 cc. of *p*-chlorophenol in 5 cc. of dry pyridine was added. The mixture was refluxed on a steam bath for one hour. Upon cooling, the solid mass which formed was filtered off, washed with 5% sodium carbonate solution, then with water, and finally dried. The crude product was recrystallized from benzene and finally from alcohol.

p-Carbethoxyimidobenzoic Acid Ester Hydrochlorides.—These were prepared by the method of Pinner (1, 3); however, in all but two cases dry dioxane gave much better results than dry ether. In those cases where the iminoether hydrochloride did not separate after two to seven days in the ice chest, light petroleum ether was subsequently added. This caused the separation of an oil which, when washed several times with light petroleum ether and finally with anhydrous ether, solidified in a few hours. The above variations can be illustrated by the following experiment: 16.8 Gm. (0.08 *M*) of β-chloroethyl *p*-cyanobenzoate was partially dissolved in 150 cc. of dioxane. Eight cubic centimeters of absolute ethyl alcohol was then added and the reaction mixture was saturated with dry hydrogen chloride gas at 0–5° over a period of an hour in an Erlenmeyer flask equipped with a calcium chloride tube and a gas inlet tube. During this period the cyanoester gradually passed into solution. The flask was stoppered and left in the ice chest for five days but no separation occurred. Light petroleum ether was added until the solution was turbid and the flask returned to the ice chest. In a few hours a white crystalline mass formed which was filtered, washed with anhydrous ether, and dried. A second crop was obtained by adding more light petroleum ether to the mother liquor.

p-Carboxybenzamidine Esters.—The iminoether hydrochlorides were converted to the corresponding amidine hydrochlorides either by warming the iminoether hydrochlorides with a slight excess of 28% ammonium hydroxide (1, 3) in 95% alcohol at 60–80° for two to three hours, or by warming the iminoether free base in 95% alcohol with the theoretical amount of ammonium chloride dissolved in a trace of water (1, 4, 5). Although the above procedures gave the desired *p*-carboxybenzamidine esters, success was not encountered in all cases. For example, even though diethylaminoethyl *p*-carbethoxyimidobenzoate could be prepared, con-

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TABLE I.—ESTERS OF *p*-CYANOBENZOIC ACID

No.	Ester Residue	Method	Yield, %	M. P., °C.	Analysis, Calcd.	% C and H Found
1	2-Chloroethyl	A[a]	65.8	87–90	C, ...	...
					H, ...	...
2	2-Bromoethyl	A	74.8	89–90	C, 47.26	C, 46.99
					H, 3.17	H, 3.47
3	2,3-Dichloropropyl	A	62.0	93–95	C, 51.19	C, 51.64
					H, 3.57	H, 3.63
4	2,3-Dibromopropyl	A	51.9	78–79	C, 38.07	C, 38.03
					H, 2.62	H, 2.80
5	2,2,2-Trichloroethyl	B	63.5	91–93	C, 43.12	C, 43.72
					H, 2.17	H, 2.37
6	Benzyl	A	85.9	56–57.5	C, 75.92	C, 76.14
					H, 4.68	H, 4.73
7	Cyclohexyl	A	71.3	62–63	C, 73.33	C, 73.14
					H, 6.59	H, 6.79
8	Dimethylaminoethyl	A	98.4	197–198	C, ...	...
					H, ...	...
9	Diethylaminoethyl	A	88.2	157.5–159.5	C, ...	...
					H, ...	...
10	*p*-Chlorophenyl	B[b]	45.0	142–142.5	C, 65.27	C, 65.11
					H, 3.13	H, 3.43
11	Furfuryl	B	91.9	72–73	C, 68.69	C, 68.45
					H, 3.99	H, 4.17
12	Tetrahydrofurfuryl	B	64.6	40–42	C, ...	...
					H, ...	...

[a] Method A: Direct interaction of acyl chloride and alcohol.
[b] Method B: Using pyridine as a catalyst.

TABLE II.—ESTERS OF *p*-CARBETHOXYIMIDOBENZOIC ACID HYDROCHLORIDE[a]

No.	Ester Residue	Anhydrous Solvent	Method	Yield, %	M. P., °C.	Analysis— Calcd.	Found
1	2-Chloroethyl	Dioxane	I[c]	68.7	163–164	...	...
2	2-Bromoethyl	Dioxane	I	86.3	169–170	...	...
3	2,3-Dichloropropyl	Dioxane	II[d]	91.1	119–120	...	...
4	2,3-Dibromopropyl	Dioxane	II	82.4	112–113	...	...
5	2,2,2-Trichloroethyl[b]	Dioxane	I	74.9	212–214	...	...
6	Benzyl	Ether	III[e]	87.7	114–115	...	...
7	Cyclohexyl	Ether	III	66.8	108–109	...	...
8	Dimethylaminoethyl	Dioxane nitrobenzene	I	77.0	97–101	...	...
9	Diethylaminoethyl	Dioxane	II	93.1	128–129	C, 52.62 H, 7.18	C, 52.35 H, 7.09

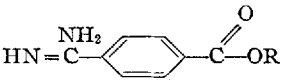
[a] Iminoether hydrochloride not obtained: furfuryl. Iminoether hydrochloride obtained in very low yields: tetrahydrofurfuryl and *p*-chlorophenyl.
[b] Using ether as a solvent, compounds 1–5 could not be obtained in good yield.
[c] Method I: Dry dioxane as solvent, product separated as a solid.
[d] Method II: Dry dioxane as solvent, product separated out as an oil.
[e] Method III: Anhydrous ether as solvent, product separated out as a solid.

TABLE III.—ESTERS OF *p*-CARBOXYBENZAMIDINE HYDROCHLORIDE[a]

No.	Ester Residue	Method	Yield, %	M. P., °C.	Analysis, Calcd.	C and H Found
1	2-Chloroethyl[a]	1[d]	64.0	199–201	C, 45.62	C, 45.33
					H, 4.60	H, 4.63
2	2-Bromoethyl[b]	1	43.8	200–201[f]	C, 39.04	C, 39.65
					H, 3.93	H, 4.23
3	2,3-Dichloropropyl	1	79.1	168–169	C, 42.79	C, 42.39
					H, 4.25	H, 4.35
4	2,3-Dibromopropyl	1	75.4	159–160	C, 32.97	C, 33.16
					H, 3.25	H, 3.15
5	Benzyl[c]	1	88.0	181–182	C, 70.19	C, 70.17
					H, 5.14	H, 5.35
6	Cyclohexyl	1	90.0	202–203	C, 59.48	C, 58.95
					H, 6.79	H, 6.73
7	2,2,2-Trichloroethyl	2[e]	65.3	204–206	C, 36.07	C, 36.42
					H, 3.33	H, 3.34

[a] Compounds not obtained: dimethylaminoethyl, diethylaminoethyl.
[b] The identity of this compound is questionable.
[c] Analyzed as the ester benzoate.
[d] Method 1: Using 28% ammonium hydroxide.
[e] Method 2: Using ammonium chloride.
[f] The melting point of this compound was not sharp.

TABLE IV.—ANESTHETIC ACTIVITY OF SOME ESTERS OF *p*-CARBOXYBENZAMIDINE



Compound R=	Concn. of Solution, %	Duration of Anesthesia, Guinea Pigs—Eyes, Min.	Duration of Anesthesia, Guinea Pigs—Skin, Min.	Irritation, Rabbit Skin	LD_{50}, Mg./Kg., Mice—Intravenous	LD_{50}, Mg./Kg., Mice—Subcutaneous
n-Propyl	1	0	10	Severe	65	550
n-Butyl	1	0	45	Severe	70	350
	0.1		28	Moderate	...	...
n-Amyl	1	26	28	Severe	105	450
n-Hexyl	1	0	145	Severe	150	550
	0.1		20	Moderate	...	...
2-Chloroethyl[a]	1	0	155	Negligible	84.8	...
	0.5		90	Negligible	...	...
	0.25		0	...	...	...
2,2,2-Trichloroethyl	1	0	0	...	...	...
2,3-Dichloropropyl	1	0	25	...	...	...
2,3-Dibromopropyl	1	0	0	...	...	...
Cyclohexyl	1	130	360	Moderate to severe	112	...
	0.25	11	120	...	...	...
	0.1		20	Negligible		
Benzyl[b]	1	108	180	Moderate	58.7	...
	0.5	59				
	0.25	17	126	...	...	...
	0.1		85	...	...	...
	0.05		0	...	...	...

[a] Incomplete anesthesia, intradermally in man, plus initial stinging and widespread erythema for one and one-half hours.
[b] Man, intradermal injection of 0.1-cc. doses of a 0.25% solution gave a slight stinging on injection followed by intense pruritis over entire volar surface of forearm. Complete anesthesia was produced for one and one-third hours in one of two subjects.

version to the corresponding amidine by the above methods was unsuccessful. Ethyl *p*-amidinobenzoate was the only product that could be obtained and it was assumed that ester interchange had taken place along with the conversion of the iminoether group to the amidine group.

Several attempts to prepare the amidines directly from the corresponding *p*-cyanobenzoates by fusion with ammonium thiocyanate were unsuccessful (6). *p*-Carbamidobenzamidine was the only product that was identified as a result of the above reaction and it was assumed that ammonolysis occurred together with conversion of the cyano group to the amidine.

Tables I–III summarize the results obtained in the synthesis of the intermediates and final products, i.e., the esters of *p*-carboxybenzamidine.

Anesthetic Activity.—Through the courtesy of K. K. Chen of Eli Lilly and Company, the esters prepared and reported in this paper, together with those previously reported (1), were tested for their anesthetic activity by C. L. Rose. The results of these tests are tabulated as shown in Table IV.

SUMMARY

A practical procedure for the preparation of *p*-cyanobenzoic acid in 50 to 60 per cent yield has been described.

Ten new esters of *p*-cyanobenzoic acid were prepared from *p*-cyanobenzoyl chloride and the appropriate alcohols.

Nine new esters of *p*-carbethoxyimidobenzoate hydrochloride were prepared by Pinner's method.

Six new amidines (*p*-amidinobenzoates) were prepared by Pinner's method and modifications thereof.

The preparation of *p*-(dialkylaminoalkylcarboxy) benzamidines was not successful.

The anesthetic activity of the *p*-carboxybenzamidine esters has been reported, together with several others that had been previously prepared.

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