was immunologically distinct from other antigens present in castor beans was shown by the Schultz–Dale uterine strip method.

Positive passive transfer reactions were produced with 1×10^{-10} g. of CB-1A. Positive cutaneous tests, on castor bean hypersensitive subjects, were obtained with CB-1A diluted $1:10^6$.

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

Antispasmodics. V

BY F. F. BLICKE AND NATHANIEL GRIER[1,2]

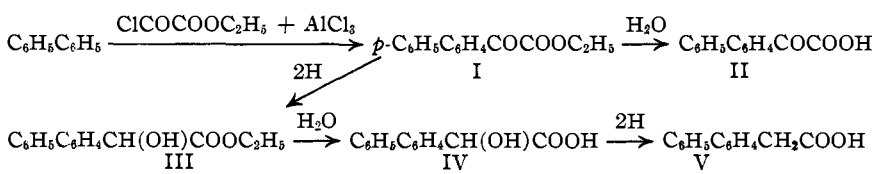
The two principal naturally-occurring antispasmodics are atropine and papaverine; the former is a basic ester, the latter a cyclic amine. In the search for synthetic antispasmodics the structures of these two compounds have served as patterns for the preparation of a wide variety of basic esters and amines.[3]

At the present time three antispasmodics of the ester type are on the market: Syntropan (the primary phosphate of β,β-dimethyl-γ-diethylaminopropyl tropate), Trasentin (the hydrochloride of β-diethylaminoethyl diphenylacetate)[4] and Demerol (Dolantin, the hydrochloride of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate).[5]

Since Trasentin is not only an effective antispasmodic but is relatively easy to synthesize, the preparation and pharmacological study of esters, similar in structure to this substance, offers an inviting field.

In this paper (Table III) are described hydrochlorides of basic-alkyl esters of the general type p-$C_6H_5C_6H_4CH(R)COOR'$: R = hydrogen, phenyl cyclohexyl, methyl, ethyl or propyl; R′ = β-diethylaminoethyl, β-piperidinoethyl, β-dibutylaminoethyl, γ-diethylaminopropyl or γ-piperidinopropyl.

p-Xenylacetic acid was obtained by the series of reactions outlined below



We were able to increase the reported yield of ethyl p-xenylglyoxylate (I) by a modification of Rousset's[6] procedure. Hydrolysis of the ester yielded p-xenylglyoxylic acid (II), while catalytic reduction converted it into ethyl p-xenylhydroxyacetate (III). The latter was hydrolyzed to p-xenylhydroxyacetic acid (IV), and this acid was reduced with red phosphorus and iodine to p-xenylacetic acid (V).

The substituted p-xenylacetic acids, $C_6H_5C_6H_4CH(R)COOH$, were obtained according to method A[7] or B.[8]

The esters were prepared by two procedures: (C) the required acid, dissolved in isopropyl alcohol, was heated with a molecular equivalent amount of the basic alkyl chloride[9]; (D) the necessary acid chloride was allowed to react with two molecular equivalents of the basic alcohol in benzene solution whereupon a part of the basic alcohol precipitated as the hydrochloride, and the desired ester base remained in solution.

Our products were examined pharmacologically by Dr. C. W. Geiter and Dr. A. N. Lands of Frederick Stearns and Company. A detailed ac-

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

(2) Frederick Stearns and Company Fellow.

(3) Cheney and Bywater (THIS JOURNAL, **64**, 970 (1942)) have described a number of morpholinoalkyl esters which were tested for antispasmodic activity by Rowe (*J. Am. Pharm. Assoc.*, **31**, 57 (1942)). A number of references to the literature of this subject are to be found in the article by Cheney and Bywater. Recently Burtner and Cusic (THIS JOURNAL, **65**, 262 (1943)) published the syntheses of a number of basic esters of arylacetic acids which have been examined pharmacologically by Lehmann and Knoefel (*J. Pharmacol.*, **74**, 217, 274 (1942)).

(4) Trasentin-H is the hydrochloride of β-diethylaminoethyl cyclohexylphenylacetate.

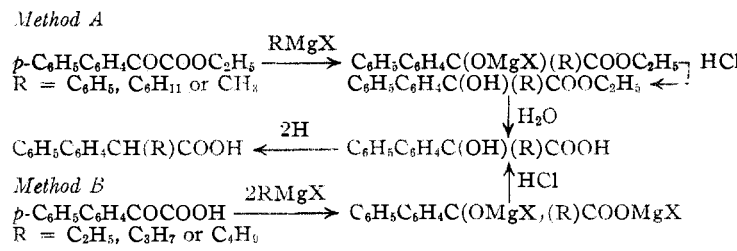
(5) Syntropan and Trasentin, like atropine, are esters in which the basic nitrogen is in the alcoholic radical of the ester; in Demerol, however, the basic nitrogen is found in the acyl group.

(6) Rousset, *Bull. soc. chim.*, [3] **17**, 809 (1897).

(7) Grignard (*Ann. chim. phys.*, [7] **27**, 548 (1902)) was the first to study the action of aliphatic Grignard reagents on ethyl phenylglyoxylate.

(8) McKenzie and Ritchie (*Ber.*, **70**, 33 (1937)) showed that ethylphenylhydroxyacetic acid can be obtained in good yield from ethylmagnesium bromide and phenylglyoxylic acid.

(9) General method of Horenstein and Pählicke, *ibid.*, **71**, 1654 (1938).



count will be published soon by them in another journal. However, it may be stated here that all of our esters[10] produced relaxation of the untreated, isolated intestine. In general, esters of alkyl-*p*-xenylacetic acid are more active than corresponding esters of *p*-xenylacetic acid; the most active esters are those of methyl-*p*-xenylacetic acid.

Experimental Part

Ethyl *p*-Xenylglyoxylate (I).—One hundred and eighty-two grams (1.18 moles) of biphenyl and 175 g. of ethyl oxalyl chloride[11] (1.28 moles) were dissolved in 750 cc. of dry carbon disulfide and the solution poured into a 3-liter, 3-necked, round-bottomed flask equipped with a mercury-sealed stirrer and a reflux condenser; a long calcium chloride tube was attached to the latter. One neck of the flask was connected with a 500-cc. Erlenmeyer flask by means of a piece of wide rubber tubing about 8 inches long. The Erlenmeyer flask was supported by a ring stand, neck down, and 173 g. (1.30 moles) of aluminum chloride, which had been placed in the flask, was added to the reaction mixture in portions. This was effected with the aid of two pinch clamps which had been attached to the rubber tubing a few centimeters apart. The mixture was heated until it began to boil, and the aluminum chloride was added at such a rate that the mixture continued to reflux without the aid of external heat. During this operation the mixture was stirred vigorously. A red complex precipitated[12] and continued to increase in amount until the end of the reaction. After complete addition of the aluminum chloride, the mixture was stirred for ten hours. The carbon disulfide solution and the precipitate were treated separately with ice and then combined. The greenish-yellow carbon disulfide layer was separated, washed thoroughly with water, dried and the solvent removed on a steam-bath. When the residue was distilled under reduced pressure there was obtained 15.5 g. of biphenyl and 188.0 g. (70%) of ethyl *p*-xenylglyoxylate which boiled at 205° (5 mm.).[13] The ester was recrystallized from a mixture of ether and petroleum ether (30–60°); m. p. 38–39°.[14]

***p*-Xenylglyoxylic Acid (II).**—Thirty-nine grams of ethyl *p*-xenylglyoxylate, 500 cc. of a 10% sodium carbonate solution and 100 cc. of alcohol were refluxed for three hours. The sodium *p*-xenylglyoxylate, which separated when the solution was cooled, was filtered and dissolved in 2 liters of hot water. The mixture was cooled, acidified with dilute hydrochloric acid and the xenylglyoxylic acid extracted with ether. The extract was shaken with water, the ether layer separated, the solvent removed and the oily residue dried thoroughly at 100° under reduced pressure. The product solidified when cooled, and was recrystallized from carbon disulfide; yield 29 g. (84%); m. p. 105–107°.[15] When moistened with concd. sulfuric acid, the material turned deep red.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42. Found: C, 74.19; H, 4.56.

Ethyl *p*-Xenylhydroxyacetate (III) and *p*-Xenylhydroxyacetic Acid (IV).—A mixture of 25.4 g. of ethyl *p*-xenylglyoxylate, dissolved in 175 cc. of absolute alcohol, 0.85 g. of platinized charcoal (Norite) and 6 cc. of water, which contained 0.35 g. of palladium chloride,[16] was shaken for eight hours in the presence of hydrogen under an initial pressure of 3 atmospheres. Slightly more than the calculated amount of hydrogen was absorbed. Since some of the ethyl *p*-xenylhydroxyacetate precipitated, the mixture was filtered and the precipitate extracted with ethyl acetate. The extract was added to the alcoholic filtrate, the solvents removed under diminished pressure and the residue, ethyl *p*-xenylhydroxyacetate, refluxed for two hours with 235 cc. of 10% alcoholic potassium hydroxide. The mixture was poured into an equal volume of water, treated with Norite and filtered. Upon acidification of the filtrate with dilute hydrochloric acid, 22.0 g. (97%) of colorless *p*-xenylhydroxyacetic acid was obtained; m. p. 201–203°[17] after recrystallization from acetic acid. When moistened with concd. sulfuric acid, the acid became pale yellow-green in color.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.70; H, 5.26. Found: C, 73.65; H, 5.30.

***p*-Xenylacetic Acid** (V).—A mixture of 15.5 g. of *p*-xenylhydroxyacetic acid, 1.4 g. of iodine, 3.2 g. of red phosphorus and 135 cc. of acetic acid was refluxed for twelve hours, filtered and the *p*-xenylacetic acid precipitated by the addition of a small amount of water to the filtrate. After recrystallization from acetic acid, 10.1 g. (70%) of product was obtained; m. p. 161–162°.[18] The

(10) The hydrochloride of β-piperidinoethyl and of γ-piperidinopropyl phenyl-*p*-xenylacetate were not tested.

(11) Adickes, Brunnert and Lücker, *J. prakt. Chem.*, **130**, 168 (1931). We found that the use of stirring and a solvent were unnecessary, and that five times the quantity of acid chloride mentioned by Adickes and co-workers could be prepared at one time with no diminution in yield.

(12) A general discussion relative to the preparation of pure arylglyoxylic acids has been published by Bouveault (*Bull. soc. chim.*, [3] **17**, 363 (1897)). It might be advantageous to use a mixture of carbon disulfide and nitrobenzene, as he suggested, and thus prevent the precipitation of the complex

(13) Rousset (ref. 6) reported 232° (9 mm.).

(14) Rousset (ref. 6) found 39°.

(15) It was stated by Rousset (ref. 6) that *p*-xenylglyoxylic acid, which he obtained by hydrolysis of the ethyl ester, decomposed at 170° after recrystallizing from benzene. Since he must have obtained the acid, we believe that the melting point was reported incorrectly.

(16) The catalyst was prepared according to the directions of Zelinsky and Turowa-Pollak, *Ber.*, **68**, 1295 (1929).

(17) Riebsomer, Stauffer, Glick and Lambert (THIS JOURNAL, **64**, 2081 (1942)) found 192°.

(18) Lesser (German Patent 658,114; *Chem. Zentr.*, **109**, I, 4385 (1938)) reported the same melting point.

TABLE I

SUBSTITUTED *p*-XENYLHYDROXYACETIC ACIDS, *p*-$C_6H_5C_6H_4RC(OH)COOH$

All of the acids were recrystallized from dilute acetic acid except compound 2; in this instance glacial acetic acid was used.

	R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Neut. equiv. Calcd.	Neut. equiv. Found	Color with concd. H_2SO_4
1	C_6H_5	168–170	$C_{20}H_{16}O_3$	78.94	5.26	79.12	5.41	304	303	Purple
2	C_6H_{11}[b]	202–203	$C_{20}H_{22}O_3$	77.41	7.10	77.51	7.22	310	306	Pink
3	CH_3	168–169	$C_{16}H_{14}O_3$	74.39	5.79	74.58	5.96	242	241	Red
4	C_2H_5	175–177	$C_{16}H_{16}O_3$	75.00	6.25	74.91	6.29	256	254	Purple
5	C_3H_7	142–143	$C_{17}H_{18}O_3$	75.56	6.67	75.69	6.75	270	268	Purple
6	C_4H_9	178–179	$C_{18}H_{20}O_3$	76.07	7.04	76.18	7.09	284	282	Reddish-purple

[a] Method of preparation. [b] C_6H_{11} = cyclohexyl.

TABLE II

SUBSTITUTED *p*-XENYLACETIC ACIDS, *p*-$C_6H_5C_6H_4RCHCOOH$

The acetic acids remained colorless when moistened with concd. sulfuric acid. All acids were recrystallized from acetic acid except compound 1; the latter was recrystallized from dilute alcohol.

	R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Neut. equiv. Calcd.	Neut. equiv. Found
1	C_6H_5	141–142	$C_{20}H_{16}O_2$	83.34	5.56	83.18	5.75	288	286
2	C_6H_{11}[a]	204–205	$C_{20}H_{22}O_2$	81.63	7.48	81.77	7.58	294	291
3	CH_3	145–147	$C_{16}H_{14}O_2$	79.66	6.19	79.75	6.27	226	225
4	C_2H_5	123–125	$C_{16}H_{16}O_2$	80.00	6.67	79.86	6.80	240	242
5	C_3H_7	116–117	$C_{17}H_{18}O_2$	80.33	7.09	80.33	7.21	254	252
6	C_4H_9	99–101	$C_{18}H_{20}O_2$	80.62	7.46	80.73	7.64	268	265

[a] C_6H_{11} = cyclohexyl.

acid remained colorless when moistened with concd. sulfuric acid.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.26; H, 5.66. Found: C, 79.30; H, 5.84.

Phenyl-*p*-xenylhydroxyacetic Acid (Method A).—Phenylmagnesium bromide was prepared from 21.7 g. of bromobenzene, 3.6 g. of magnesium and 65 cc. of ether. A solution of 25.4 g. of ethyl *p*-xenylglyoxylate in 150 cc. of ether was cooled with an ice–salt mixture and stirred while the solution of the Grignard reagent was added to it dropwise. A yellow complex precipitated immediately. After all of the ester had been added, the mixture was kept cold for one hour and then refluxed for three hours. The material was poured into dilute sulfuric acid, the ether layer separated and washed with water. The solvent was removed and the residue, ethyl phenyl-*p*-xenylhydroxyacetate, was refluxed for one hour with 250 cc. of 10% alcoholic potassium hydroxide. The mixture was poured into 500 cc. of water, stirred, treated with Norite and filtered. The light yellow filtrate was cooled, stirred and acidified. The precipitate, which weighed 27.6 g. (91%), was recrystallized from dilute acetic acid.[19]

Phenyl-*p*-xenylacetic Acid.—A mixture of 27.5 g. of phenyl-*p*-xenylhydroxyacetic acid, 1.9 g. of iodine, 4.6 g. of red phosphorus and 120 cc. of acetic acid was boiled for four hours. The hot solution was filtered and poured into an equal volume of water. The pink precipitate was dissolved in acetic acid and precipitated with water. The product was washed with 25% acetic acid and then with water; yield 23.8 g. (91%). After the material had been dissolved in dilute alcohol and the solution treated with Norite, it was obtained in the form of colorless needles.[19]

Ethyl-*p*-xenylhydroxyacetic Acid (Method B).—The solution of the Grignard reagent, obtained from 37.0 g. (0.3 mole) of ethyl bromide, 7.3 g. of magnesium, a crystal of iodine and 125 cc. of ether, was added slowly, in a stream of nitrogen, to a well-stirred solution of 25.0 g. (0.1 mole) of *p* xenylglyoxylic acid in 350 cc. of ether which was cooled with ice and salt. A lemon-yellow precipitate formed at once. After addition of the Grignard reagent, the mixture was kept cold for one hour and then refluxed for three hours. At this stage the precipitate was colorless. The mixture was poured into cold, dilute sulfuric acid, the ether layer separated, washed with water and the solvent removed. The residue was recrystallized from dilute acetic acid; yield 20.2 g. (71%) of colorless needles.[19]

Ethyl-*p*-xenylacetic Acid.—A mixture of 18.0 g. of the hydroxy acid, 1.8 g. of iodine, 4.4 g. of red phosphorus and 200 cc. of acetic acid was refluxed for fourteen hours. The cold solution was filtered and the filtrate dropped slowly into 400 cc. of water while the latter was stirred. The precipitate was washed with dilute acetic acid and recrystallized from glacial acetic acid; yield 13.6 g. (81%).

β-Diethylaminoethyl *p*-Xenylacetate Hydrochloride (Method C).—A mixture of 3.18 g. (0.0150 mole) of *p*-xenylacetic acid, 2.05 g. (0.0151 mole) of β-diethylamino ethyl chloride and 75 cc. of dry isopropyl alcohol[20] was refluxed for twelve hours, the solvent removed under reduced pressure, the residue washed with dry ether and recrystallized from a mixture of dry ether and absolute alcohol; yield 2.58 g. (49.5%).[21]

β-Diethylaminoethyl Phenyl-*p*-xenylacetate Hydrochloride (Method D).—Six grams of phenyl-*p*-xenylacetic acid and 8 cc. of thionyl chloride were refluxed for one

(19) The melting points and analytical data for the substituted xenylhydroxyacetic and xenylacetic acids are reported in Tables I and II.

(20) Twenty grams of calcium oxide and 80 g. of isopropyl alcohol (91% grade) were refluxed for eight hours; the alcohol was then distilled directly from the mixture.

(21) See Table III for melting points and analyses.

TABLE III

ESTER HYDROCHLORIDES, p-$C_6H_5C_6H_4RCHCOOR'\cdot HCl$

All of the ester salts were recrystallized from a mixture of absolute alcohol and absolute ether.

R′	M[a]	M. p., °C.	Formula	Chlorine, % Calcd.	Found
Esters of p-Xenylacetic Acid (R = H)					
β-Diethylaminoethyl	C	158–159	$C_{20}H_{26}O_2NCl$	10.22	10.42
β-Piperidinoethyl	C	163–164	$C_{21}H_{26}O_2NCl$	9.87	9.66
γ-Diethylaminopropyl	C	113–115	$C_{21}H_{28}O_2NCl$	9.81	9.82
Esters of Phenyl-p-xenylacetic Acid (R = C_6H_5)					
β-Diethylaminoethyl	D	139–141	$C_{26}H_{30}O_2NCl$	8.38	8.29
β-Dibutylaminoethyl	C	128–130	$C_{30}H_{38}O_2NCl$	7.41	7.48
β-Piperidinoethyl	C	147–149	$C_{27}H_{30}O_2NCl$	8.15	8.19
γ-Diethylaminopropyl	C	117–119	$C_{27}H_{32}O_2NCl$	8.12	8.13
γ-Piperidinopropyl	C	103–105	$C_{28}H_{32}O_2NCl$	7.89	7.71
Esters of Cyclohexyl-p-xenylacetic Acid (R = C_6H_{11})					
β-Diethylaminoethyl	D	170–172	$C_{26}H_{36}O_2NCl$	8.27	8.38
β-Piperidinoethyl	C	179–181	$C_{27}H_{36}O_2NCl$	8.04	8.23
γ-Diethylaminopropyl	C	149–151	$C_{27}H_{38}O_2NCl$	7.99	8.07
Esters of Methyl-p-xenylacetic Acid (R = CH_3)					
β-Diethylaminoethyl	D	141–143	$C_{21}H_{28}O_2NCl$	9.82	9.68
β-Piperidinoethyl	C	162–164	$C_{22}H_{28}O_2NCl$	9.50	9.47
γ-Diethylaminopropyl	C	112–114	$C_{22}H_{30}O_2NCl$	9.46	9.49
γ-Piperidinopropyl	C	142–144	$C_{23}H_{30}O_2NCl$	9.16	9.37
Esters of Ethyl-p-xenylacetic Acid (R = C_2H_5)					
β-Diethylaminoethyl	D	154–156	$C_{22}H_{30}O_2NCl$	9.46	9.43
β-Piperidinoethyl	C	146–148	$C_{23}H_{30}O_2NCl$	9.16	9.31
γ-Diethylaminopropyl	C	97–99	$C_{23}H_{32}O_2NCl$	9.12	9.31
Esters of Propyl-p-xenylacetic Acid (R = C_3H_7)					
β-Diethylaminoethyl	D	122–124	$C_{23}H_{32}O_2NCl$	9.12	9.14
β-Piperidinoethyl	C	127–129	$C_{24}H_{32}O_2NCl$	8.85	9.08
γ-Diethylaminopropyl	C	100–102	$C_{24}H_{34}O_2NCl$	8.79	8.90

[a] Method of preparation.

hour and the excess thionyl chloride removed under reduced pressure; 40 cc. of dry benzene was added, the benzene distilled and the process repeated several times in order to remove all traces of thionyl chloride. The acid chloride crystallized when cooled and melted at 99–101° after recrystallization from petroleum ether (90–100°).

A solution, prepared from 2.6 g. (0.0085 mole) of phenyl-p-xenylacetyl chloride and 30 cc. of dry benzene, was added slowly, with agitation, to a solution of 6.0 g. (0.0510 mole) of β-diethylaminoethyl alcohol in 10 cc. of benzene. The mixture was refluxed for one-half hour on a steam-bath, cooled and the precipitated β-diethylaminoethyl alcohol hydrochloride removed by filtration; after it had been washed with benzene and ether it weighed 1.3 g. and melted at 133–135°.[22] The filtrate was shaken thoroughly with water, the benzene layer separated, dried with magnesium sulfate and then mixed with twice its volume of dry ether. Hydrogen chloride was passed into the solution whereupon a gummy precipitate separated; the latter turned into a colorless powder when rubbed. After recrystallization from a mixture of alcohol and ether there was obtained 2.3 g. (64%) of colorless needles.[21]

(22) Blicke and Maxwell, THIS JOURNAL, 64, 429 (1942).

Summary

Six substituted p-xenylhydroxyacetic acids, $C_6H_5C_6H_4C(OH)RCOOH$, and six substituted p-xenylacetic acids, $C_6H_5C_6H_4C(H)RCOOH$, have been described in which R = C_6H_5, C_6H_{11}, CH_3, C_2H_5, C_3H_7 or C_4H_9.

Twenty-one basic-alkyl esters of the xenylacetic acids have been synthesized and tested for antispasmodic activity on the untreated, isolated intestinal strip. The most active products were found to be the basic-alkyl esters of methyl-p-xenylacetic acid.

ANN ARBOR, MICHIGAN RECEIVED MARCH 8, 1943