purity are slightly low. The other calculation of purity is based on the tetrabromide number, in which the value of 102.9 for the tetrabromide number twelve-times recrystallized alpha-linoleic acid (see Matthews, Brode and Brown)[6] is taken as the standard for pure *cis,cis*-9-12-octadecadienoic acid. The values by this calculation are obviously lower than those by the iodine number. If the differences are small, we are very cautious in concluding the presence of isomeric acids, which do not yield insoluble tetrabromides. On the other hand, when the differences are large we believe they represent definite indications of the presence of octadecadienoic acids which do not yield these characteristic bromides (m. p. 114–115°). In view of the work of Kass and Burr[7] it is likely that the isomeric acid is either the *cis–trans* or the *trans–cis* modification, and that it is definitely not the *trans–trans* form.

The difficulties in applying the crystallization method to the isolation of linoleic acid from olive oil are due, no doubt, to the presence in this oil of isomeric linoleic acids, solubilities of which prevent clean-cut separations.

(7) Kass and Burr, THIS JOURNAL, **61**, 1062 (1939).

Summary

1. Linoleic acid has been prepared from sesame, cottonseed, grapeseed and poppyseed oils by low temperature crystallization.

2. The linoleic acid from these oils, isolated by crystallization, is essentially identical with corn oil linoleic acid prepared by this method and with recrystallized alpha-linoleic acid, prepared by reduction of tetrabromostearic acid.

3. The crystallization method was applied somewhat less successfully in the isolation of linoleic acid from olive oil.

4. Analytical data on a number of fractions from olive oil were interpreted as meaning that the linoleic acid of this oil is a mixture of octadecadienoic acids, of which linoleic is the principal component.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Antispasmodics. I. Basic Esters of Some Arylacetic Acids[1]

BY ROBERT R. BURTNER AND JOHN W. CUSIC

Antispasmodics may be divided into two classes, those which act to prevent or abolish the action of stimulation of autonomic nerves, and those which are not thus related to innervation. The latter class may be referred to as musculotropic and the former neurotropic. The neurotropic drugs may be still further divided into sympatholytic and parasympatholytic, depending upon whether the action is on the sympathetic or parasympathetic system. Of greatest practical importance are the drugs belonging to the parasympatholytic group (the prototype of which is atropine) and to the group "not related to innervation" (whose chief representatives are papaverine and the nitrites).

The drugs of both groups, however, have a number of disadvantages. Thus papaverine has little effect in abolishing spasms induced by neural excitation, while on the other hand atropine is almost ineffective against spasms of entirely muscular origin brought about by such substances as histamine. In addition, papaverine relaxes all the smooth muscles equally, thus when relaxation of the intestinal tract is required, there results also a prolonged and undesirable fall in arterial blood pressure. The nitrites are rarely used to combat intestinal spasms because of their transient action and undesired side-effects on the circulation. Furthermore, the parasympathetic inhibition of atropine occurs in all organs activated by nerves of the autonomic system, thus causing three undesired side-effects, namely, cyclopegia, dryness in the mouth, tachycardia and sometimes a rise in arterial pressure.

For these reasons attempts were made to synthesize substances which have both a neurotropic and musculotropic action in one molecule, and in which the neurotropic or atropine-like action is somewhat differently directed; in other words, compounds which have a selective atropine-like action on the smooth muscles of the hollow viscera, and no, or only slight, effect, on the pupils, salivary glands and circulation.

In the present work our efforts have been directed toward modifying the structure of atropine to attain this end. Consequently a series of esters were prepared from acids which might substitute for the acid fraction of atropine and various amino alcohols corresponding to the

(1) Presented before the Medicinal Section of the American Chemical Society at the Atlantic City meeting, September, 1941.

TABLE I

Ester hydrochlorides: Acid	Basic alcohol	Melting point, °C.	Method of preparation	Crystallization solvent	Chlorine analyses, % Calcd.	Obs.	Reciprocal spasmolytic activity: Acetylcholine	Histamine	L. D.[50] g./kg.
Tropic	β-Diethylaminoethanol	[a]	B				1	20	0.46
Tropic	β-Dimethyl-γ-diethylaminopropanol (phosphate)	[b]					15	30	
Tropic	Tropine (sulfate)	[c]					0.14	4	0.24
Atropic	β-Diethylaminoethanol	98–99	B	[d]	12.49	12.68	30	3	0.25
Atropic	1-Methyl-4-hydroxypiperidine	[e]	A	[f]	12.58	12.49	30	2	0.13
α-Phenyltropic	β-Diethylaminoethanol	143–144	B	EtAc	9.4	9.7	5	2	0.26
Diphenylacetic	β-Dimethylaminoethanol	164	B	*i*-PrOH	11.08	11.20	8	1.6	0.26
Diphenylacetic	β-Diethylaminoethanol	112	A or B	EtAc	[g]		6	1.5	0.24
Diphenylacetic	1-Methyl-4-hydroxypiperidine	[e]	A	EtAc	10.28	10.15	1.8	0.5	0.18
Diphenylacetic	1-*n*-Butyl-4-hydroxypiperidine	162	A	EtOH	9.13	9.30	10	1.5	0.15
Diphenylacetic	1-(β-Phenylethyl)-4-hydroxypiperidine	218–219	A	EtOH	8.13	8.19	>10	3.7	0.46
Diphenylacetic	1,2,6-Trimethyl-4-hydroxypiperidine	[e]	A	EtAc	9.50	9.41	4.6	2	0.3
Benzilic	β-Diethylaminoethanol	177–178	B	*i*-PrOH	[g]		0.7	0.7	0.08
β-Phenyl-β-hydroxypropionic	β-Diethylaminoethanol	141–142	B	Ether *i*-PrOH	(N) 3.70	(N) 3.87	6	5	0.14
Anisilic	β-Diethylaminoethanol	172	B	*i*-PrOH	8.36	8.50	10	6	0.14
α-Chlorodiphenylacetic	β-Diethylaminoethanol	149–151	A	[h]	18.60	18.25	0.7	0.7	0.08
β-Diphenylacrylic	β-Diethylaminoethanol	159–160	B	Acetone	9.85	10.3	6	1.7	0.14
γ-Diphenylcrotonic	β-Diethylaminoethanol	114–118[e]	A	[f]	(N) 3.75	(N) 3.87	>10	10	0.71
Diphenylmethylcarbamic	β-Diethylaminoethanol	184–185	[i]	EtOH	(N) 7.72	(N) 7.58	6.5	1.5	0.13
N-β-Diethylaminoethyl diphenylacetamide (hydrochloride)		145	A	EtOH	(N) 8.08	(N) 7.95	10	2.5	0.15
Fluorene-9-carboxylic	β-Diethylaminoethanol	143–144	B	EtAc–*i*-PrOH	10.25	10.29	1	1	0.32
Fluorene-9-carboxylic	γ-Diethylaminopropanol	220	B	Acetone	(N) 3.85	(N) 3.69	4	5	0.22
Fluorene-9-carboxylic	β-Diethylaminopropanol	177	B	Acetone	9.85	10.04	>10	4.5	0.32
Fluorene-9-carboxylic	β-Di-*n*-butylaminoethanol	165	B	EtAc	(N) 3.79	(N) 3.92	>12	9	0.40
Fluorene-9-carboxylic	β-Monoisobutylaminoethanol	160	A	Acetone	(N) 4.06	(N) 4.16	5	2.5	0.20
Fluorene-9-carboxylic	1-Methyl-4-hydroxypiperidine	218	A	EtOH	10.31	10.35	1	0.6	0.15
Fluorene-9-carboxylic	1-(β-Phenylethyl)-4-hydroxypiperidine	157–158	A	EtOH	(N) 3.23	(N) 3.23	6	3.5	0.28
Fluorene-9-carboxylic	1,2,6-Trimethyl-4-hydroxypiperidine	217–218	A	Acetone	9.53	9.80	2.8	1	0.23
N-β-Diethylaminoethyl fluorene-9-carboxylic acid amide (hydrochloride)		[j]	A				12	5	0.07
2-Aminofluorene-9-carboxylic	β-Diethylaminoethanol	92–94	[i]	*i*-PrOH	(N) 7.79	(N) 7.62	20	9	0.13
9-Hydroxyfluorene-9-carboxylic	β-Diethylaminoethanol	204	B	*i*-PrOH	9.79 [k]	9.95	1.2	2	0.13
Fluorene-9-acetic	β-Diethylaminoethanol	130–132	B	Et-Ac	9.90	9.96	11	1	0.26
γ-Diphenylenecrotonic	β-Diethylaminoethanol	205	A	EtOH	9.55	9.25	>10	>10	0.48
Di-1-naphthylacetic	β-Diethylaminoethanol	211	B	*i*-PrOH	7.93	7.62	>50	20	0.35
Di-2-naphthylacetic	β Diethylaminoethanol	151	B	EtAc–*i*-PrOH	7.93	7.99	200	40	0.63
1-Naphthilic	β-Diethylaminoethanol	143–144,	B	EtOH	(N) 3.02	(N) 3.2	50	4	0.44
2-Naphthilic	β-Diethylaminoethanol	195	B	EtOH	(N) 3.02	(N) 3.18	>100	5	0.15
α-Phenyl-β-(2-furyl)-acrylic	β-Diethylaminoethanol	157	B	Acetone	(N) 4.00	(N) 4.19	20	4	0.15
Anthracene-9-carboxylic	β-Diethylaminoethanol	162	B	Acetone	(N) 3.91	(N) 4.02	10	3	0.28
Hydrindene-2-carboxylic	β-Diethylaminoethanol	132–133	B	*i*-PrOH	(N) 4.70	(N) 5.0	100	5	0.13
d,l-Camphoric	(bis)-β-Diethylaminoethanol	[e]	A	Acetone	15.06	15.29	100	100	0.25

[a] Could not be isolated in crystalline state; see Von Braun, *Ber.*, **55**, 1666 (1922). [b] Fromherz, *Arch. f. exper. Path. u. Pharmakol.*, **173**, 86 (1933). [c] Atropine. [d] Could not be recrystallized from a variety of solvents. [e] Too hygroscopic to permit satisfactory m. p. [f] Could not be recrystallized; washed with acetone after pptn. [g] Halpern, *Arch. int. de Pharmacodynam. et de Therap.*, **59**, 149 (1938). [h] Could not be recrystallized; washed with ether after pptn. [i] See text for method of preparation. [j] Could not be isolated in crystalline state. [k] German Patent 657,526.

alcoholic portion of that molecule. Previous investigators have shown that certain basic esters of phenylalkyl- and diphenylacetic acids exhibit varying degrees of antispasmodic activity. We elected to study diphenylacetic acid and related types and have employed basic alcohols varying in structure from those resembling tropine to the relatively simple dialkylaminoalkanols. Since in previous studies on local anesthetics it was observed that cyclization of certain polynuclear carboxylic acid derivatives occasionally led to enhanced activity,[2] the cyclized or bridged forms of the diarylacetic acids were also stud-

(2) Burtner and Lehmann, THIS JOURNAL, **62**, 527 (1940).

ied in order to examine this phenomenon more critically.

Pharmacological Part

The pharmocological studies were carried out by Dr. Gerhard Lehmann of the Department of Physiology and Pharmacology, University of Louisville.[3] Spasmolytic activity was determined on the isolated rabbit intestinal muscle by measuring the relaxation produced by the drug in question against spasm induced by 10^{-6} acetylcholine bromide and spasm caused by 2×10^{-4} histamine acid phosphate. The activities are expressed as reciprocal functions and are referred to β-diethylaminoethyl fluorene-9-carboxylate which has the most favorable therapeutic coefficient of the entire series and whose activity is arbitrarily designated as unity. Thus the smaller the number a given compound shows under the heading Reciprocal Spasmolytic Activity, the greater is its activity. Toxicities were determined by intraperitoneal injection in mice and are expressed as the L. D.[50]

Experimental Part

Preparation of the Acids

Fluorene-9-carboxylic Acid.—This acid may be prepared by the interaction of benzilic acid and aluminum chloride or by metalation of fluorene with an organoalkali compound followed by carbonation. In our work we have found the latter method more convenient as illustrated by the following examples

(a) **From *n*-Butyllithium.**—A solution of *n*-butyllithium prepared in the customary manner from 92.5 g. (1.0 mole) of *n*-butyl chloride and 15.2 g. (2.2 atoms) of lithium in 600 cc. of ether was diluted with 400 cc. of ether and treated portionwise with stirring with 124.5 g. (0.75 mole) of fluorene.[4] The solution immediately assumed an orange-red color accompanied by vigorous evolution of butane. The mixture was refluxed with stirring for one hour and then poured jet-wise onto crushed dry-ice. As soon as the mixture warmed up to laboratory temperature, the unreacted lithium was skimmed off and two liters of water were added cautiously. The insoluble residue was filtered out and extracted thrice with 300-cc. portions of lukewarm 2% sodium hydroxide. Acidification of the combined aqueous solutions precipitated the desired acid. The yield of practically colorless product melting at 228–230° was 118 g. or 75% of the theoretical based upon fluorene.

(b) **From Phenylsodium.**—A mixture of 11.5 (0.5 atom) of powdered sodium, 22.5 g. (0.2 mole) of chlorobenzene and 200 cc. of thiophene-free benzene was heated with stirring under an atmosphere of nitrogen at 60–65° until the reaction started. The reaction is only mildly exothermic and is usually evidenced by a slight rise in temperature or in some cases failure of the temperature to fall after removal of the heating bath. This induction period generally requires thirty to fifty minutes. The stirred mixture was then held at 50–55° for two hours. Twenty-eight and nine-tenths grams (0.174 mole) of fluorene was then added all at one time (no visible exothermic effect) and the solution refluxed with stirring for two hours. The reaction mixture was cooled to laboratory temperature, diluted with 200 cc. of absolute ether and carbonated as above. The unreacted sodium was destroyed by cautious addition of 100 cc. of 50% alcohol. Three hundred cubic centimeters of water was then added, any insoluble material filtered out and extracted with dilute alkali as described above and the aqueous alkaline solution acidified to give 21.5 g. of the desired acid melting at 227°.

β-Diethylaminoethyl Diphenylmethylcarbamate.—Diphenylacetic acid hydrazide hydrochloride, m. p. 298°, was obtained in the conventional manner from diphenylacetyl chloride and hydrazine hydrate.

Anal. Calcd. for $C_{14}H_{15}ON_2Cl$: N, 10.65. Found: N, 10.50.

Thirteen grams (0.05 mole) of the hydrazide hydrochloride was dissolved in 175 cc. of water, covered with 100 cc. of toluene and a solution of 3.5 g. (0.05 mole) of sodium nitrite in 50 cc. of water added to the stirred mixture at 5°. After filtration the toluene solution of the azide was dried over sodium sulfate, 11.7 g. (0.1 mole) of β-diethylaminoethanol added and the mixture warmed on a water-bath until evolution of nitrogen ceased (about one hour). A small amount of insoluble material was filtered out and the solvent and excess amino alcohol removed under reduced pressure. The oily residue was taken up in 50 cc. of ethanol, filtered, treated with one equivalent of absolute alcoholic hydrogen chloride and diluted with several volumes of ether to precipitate 10 g. of crude product. Crystallization from absolute ethanol gave 7 g. of the desired ester hydrochloride melting at 184–185°.[5]

Anal. Calcd. for $C_{20}H_{27}O_2N_2Cl$: N, 7.75. Found: N, 7.69.

1-Naphthilic Acid.—A solution of 2.3 g. (0.058 atom) of potassium in 30 cc. of absolute ethanol was added to a suspension of 17 g. (0.054 mole) of 1-naphthil in 1500 cc. of absolute ether contained in a two-liter round-bottom flask. The flask was then filled to the neck with ether, tightly stoppered and let stand with occasional shaking for fifteen hours. Extraction with water followed by acidification of the aqueous layer and crystallization of the crude product from 200 cc. of benzene gave 11 g. of acid, m. p. 133–134° (dec.).[6]

2-Naphthilic Acid.—A solution of 11.5 g. (0.037 mole) of 2-naphthil in 1500 cc. of absolute ether was treated with a solution of 2.2 g. of potassium in 25 cc. of absolute ethanol as described above. After standing overnight, the mixture was extracted twice with 200-cc. portions of water and the aqueous solution acidified to precipitate a tacky solid which became granular after a short time. The crude

(3) See Lehmann and Knoefel, *J. Pharmacol.*, **74**, 217, 274 (1942), for detailed report of the pharmacological studies.

(4) The fluorene used in this study was 90% pure, m. p. 112–114°, obtained from Reilly Tar and Chemical Corp.

(5) This compound has since been described by Donleavy and English, THIS JOURNAL, **62**, 218 (1940), who report a melting point of 179°.

(6) Gomberg and Van Atta, *ibid.*, **51**, 2243 (1929), employed potassium hydroxide instead of potassium and reported a m. p. of 137°.

product was dried and crystallized from toluene to give 8 g. of the acid melting at 175° (dec.). Unlike the 1-isomer in cold concentrated sulfuric acid 2-naphthilic acid imparts a brilliant scarlet color to the solution.

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.49; H, 4.87. Found: C, 80.65; H, 4.74.

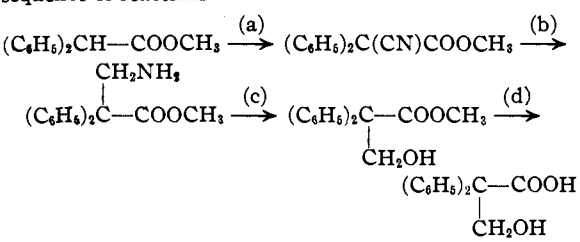
Di-1-naphthylacetic Acid.—Ninety grams of constant boiling hydriodic acid was added to a hot solution of 10 g. of 1-naphthilic acid in 180 cc. of acetic acid and the resulting solution refluxed for three hours. The mixture was allowed to stand at laboratory temperature overnight and then chilled and scratched with a glass rod to give 6.7 g. of crystalline product. Purification was effected by heating to boiling in 25 cc. of carbon tetrachloride, chilling and washing the crystals with 10 cc. of cold carbon tetrachloride. The yield of acid melting at 224° was 6.5 g.[7]

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.62; H, 5.24. Found: C, 84.85; H, 5.11.

Di-2-naphthylacetic Acid.—Eight and three-tenths grams of 2-naphthilic acid was treated with 70 g. of hydriodic acid as described above. After washing with carbon tetrachloride and crystallization from benzene the yield of acid melting at 190° was 4 g.

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.62; H, 5.24. Found: C, 84.72; H, 5.30.

α-Phenyltropic Acid.—This acid was synthesized by a sequence of reactions



(a) Methyl α-cyanodiphenylacetate was prepared according to Bickel.[8]

(b) A solution of 20 g. of methyl α-cyanodiphenylacetate in 100 cc. of absolute ethanol was reduced in the presence of Raney nickel at laboratory temperature under a pressure of approximately forty-five pounds of hydrogen over a period of twenty-seven hours. After removal of the catalyst and concentration of the filtrate to a volume of 100 cc. the amine hydrochloride was precipitated by neutralization with alcoholic hydrogen chloride and dilution with several volumes of ether. The yield of methyl α-diphenyl-β-aminopropionate hydrochloride melting at 202° (dec.) was 11 g.

Anal. Calcd. for $C_{16}H_{18}O_2NCl$: N, 4.8. Found: N, 4.72.

Heating a sample of the ester on a steam-bath in 5% potassium hydroxide solution for three hours gave the corresponding acid, m. p. 360°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.80. Found: N, 5.75.

(c) A solution of 2.6 g. (0.038 mole) of sodium nitrite in 15 cc. of water was added dropwise with stirring at 0° to a solution of 11 g. (0.038 mole) of methyl α-diphenyl-β-aminopropionate hydrochloride in 50 cc. of water containing three drops of 10% hydrochloric acid. After fifteen minutes the white precipitate was filtered out, washed with water and dried to give 8 g. of crude melting at 92–93° (dec.). A sample upon crystallization from benzene melted at 103°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.25. Found: C, 75.12; H, 6.07.

(d) Ten grams of the crude ester obtained above was hydrolyzed by refluxing in a solution of 2.2 g. of potassium hydroxide in 50 cc. of ethanol for three hours. Dilution and acidification gave 2 g. of the desired acid melting at 167–168° after crystallization from benzene and petroleum ether.

Neut. equiv. Calcd. for $C_{15}H_{14}O_3$: 243. Found: 247. *Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.5; H, 5.78. Found: C, 74.1; H, 5.96.

β-Diethylaminoethyl-2-aminofluorene-9-carboxylate.—2-Nitrofluorene-9-carboxylic acid was prepared by the method of Rose.[9] An intimate mixture of 12.5 g. (0.05 mole) of the nitro acid and 10.4 g. (0.05 mole) of phosphorus pentachloride was heated on a water-bath for forty-five minutes. After removal of the phosphorus oxychloride under reduced pressure the crude acid chloride was dissolved in 100 cc. of benzene, decolorized with charcoal and treated with 5.8 g. (0.05 mole) of β-diethylaminoethanol. Upon standing for two days at laboratory temperature the mixture had set to a crystalline slush. The supernatant benzene was decanted, the crude nitro ester hydrochloride dissolved in absolute ethanol and reduced in a low pressure reduction apparatus over a period of two hours in the presence of Raney nickel. The resulting solution was evaporated to dryness in a vacuum desiccator to yield an oil which soon solidified. Crystallization from isopropanol gave 4 g. of the desired ester hydrochloride, m. p. 92–94° (dec.).

Anthracene-9-carboxylic Acid.—Although this acid has been prepared by Liebermann and Zsuffa,[10] who obtained it by the interaction of anthracene and oxalyl chloride in sealed tubes, in our hands this method was so tedious and the yields so low as to warrant the search for a more satisfactory synthesis. Consequently, attempts were made to oxidize 9-acetylanthracene by means of sodium hypochlorite and chromic acid. Neither method was successful, since the first was without effect whereas the latter yielded only anthraquinone.

However, 9-anthraldehyde, which is readily available,[11] may be oxidized easily to the desired acid in the following manner: 10.3 g. (0.05 mole) of 9-anthraldehyde was refluxed and stirred with silver oxide (from 18 g. of silver nitrate) in 300 cc. of 50% ethanol containing 8 g. of sodium hydroxide for four hours. After dilution with two volumes of hot water and filtration the hot filtrate was acidified to yield 8 g. of acid, m. p. 204–206°, which was sufficiently pure for our purpose. (The pure acid melts at 216°.)

γ-Diphenylenecrotonic Acid.—A mixture of 29 g. (0.15 mole) of 9-formylfluorene,[12] 16 g. (0.15 mole) of malonic

(7) Schmidlin and Massini, *Ber.*, **42**, 2381 (1909), who prepared this acid through the Grignard reagent reported a m. p. of 223°.

(8) Bickel, *ibid.*, **22**, 1537 (1889).

(9) Rose, *J. Chem. Soc.*, 2360 (1932).

(10) Liebermann and Zsuffa, *Ber.*, **44**, 204 (1911).

(11) Fieser, *Org. Syn.*, **20**, 11 (1940).

(12) Wislicenus, *Ber.*, **42**, 786 (1909).

acid and 12.7 g. (0.15 mole) of piperidine was heated on a water-bath at 85° for five hours and then allowed to stand overnight. After acidification with dilute hydrochloric acid and extraction with ether the ethereal extract was washed with dilute sodium carbonate solution. Acidification of the resulting aqueous alkaline solution gave the desired acid, which after crystallization from acetic acid weighed 14 g. and melted at 202–203°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.3; H, 5.11. Found: C, 81.0; H, 5.2.

γ-Diphenylcrotonic Acid.—The reported reduction of benzoin[13] to dihydrobenzoin by means of stannous chloride in alcoholic solution was unsuccessful in our hands. However, the reduction is readily effected by hydrogenation in dioxane solution at low pressure in the presence of Raney nickel. Filtration and dilution of the filtrate with water gave practically a quantitative yield of pure dihydrobenzoin.

Diphenylacetaldehyde was prepared in approximately 50% yield by the interaction of dihydrobenzoin and oxalic acid according to Danilov.[14]

Equimolar proportions of diphenylacetaldehyde, malonic acid and piperidine were heated for three hours at 85°. The reaction mixture was then cooled, acidified, extracted with ether, the ethereal extract washed well with sodium carbonate solution and the resulting aqueous alkaline solution acidified to precipitate the crude product. Crystallization from dilute acetic acid gave a 73% yield of γ-diphenylcrotonic acid melting at 115–116°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.93. Found: C, 81.0; H, 5.95.

Tropic Acid.—The following method constitutes a novel and more direct synthesis of tropic acid. Forty-four grams of ethyl formylphenylacetate[15] was reduced at low pressure in alcohol solution using Raney nickel as the catalyst over a period of twenty-seven hours to give 44 g. of crude ethyl tropate, b. p. 125–150° (6 mm.). Hydrolysis according to Willstätter[16] yielded 12 g. of tropic acid, m. p. 114°, whose identity was confirmed by a mixed melting point with an authentic sample.

Atropic acid,[17] α-phenyl-β-(2-furyl)acrylic acid,[18] hydrindene-2-carboxylic acid,[19] anisilic acid,[20] β-hydroxy-β-diphenylpropionic acid,[21] fluorene-9-acetic acid[22] and β-diphenylacrylic acid[21] were prepared by known methods.

Preparation of the Amino Alcohols and Dialkylaminoalkyl Chlorides.—The dialkylaminoalkyl chlorides were prepared in excellent yields, generally in the range of 90%, according to the method of Slotta and Behnisch.[23] The 1-alkyl-4-hydroxypiperidines were obtained by treating γ-pyrone-2,6-dicarboxylic acid with the appropriate primary amine, decarboxylating the resulting 1-alkylpyridone dicarboxylic acid and reducing the pyridone with sodium in ethanol according to known methods.[24] 1,2,6-Trimethyl-4-hydroxypiperidine was prepared in a similar manner by the method of Conrad and Guthzeit.[25] The 1,2,6-trimethyl-4-hydroxypiperidine obtained by Mannich[26] from the interaction of the mono ethyl ester of acetonedicarboxylic acid with acetaldehyde and methylamine followed by reduction of the resulting piperidone is apparently not identical with that described above as evidenced by discrepancies in the melting points of the respective picrates and *p*-nitrobenzoates.

Synthesis of the Esters.—In each instance the ester was prepared from the acid chloride[27] and the desired alcohol in the customary manner (method A) or by the interaction of the acid and the corresponding dialkylaminoalkyl chloride[28] (method B). The latter method has proved exceedingly useful, particularly in cases where the acid chlorides are unstable or could not be prepared because of the presence of reactive functional groups, as found in benzilic or tropic acids. This method appears to be quite generally applicable[29]; the yields are high and the products satisfactorily pure. The following synthesis presents a typical example.

Eight and four-tenths grams (0.062 mole) of β-diethylaminoethyl chloride was added to a hot solution of 16 g. (0.062 mole) of anisilic acid in 60 cc. of isopropanol and the solution refluxed for two and one-half hours. Upon cooling, a white crystalline precipitate formed which was filtered out and washed by suspension in ether to yield 21.5 g. of β-diethylaminoethyl anisilate hydrochloride melting at 172°. Recrystallization from isopropanol did not alter the melting point.

Isopropanol appears to be the most satisfactory solvent for this method of synthesis. In a number of instances the ester hydrochlorides were too soluble to permit direct crystallization, in which case the solvent was removed under reduced pressure and the solid residue crystallized from the appropriate solvent. Frequently the crude hydrochlorides obtained by either method of synthesis were viscous oils or glasses which could not be satisfactorily crystallized in such condition. In this event the hydrochloride was converted to the base by means of aqueous alkali, extracted with ether, the ethereal extract dried and the solvent removed (last traces under reduced pressure on a steam-bath to remove volatile impurities). The base was then weighed, dissolved in ether (10 cc. per g. of base), filtered if necessary and treated with one equivalent of absolute hydrogen chloride. The hydrochlorides usually precipitate as viscous oils which may crystallize within a few minutes or may require a day's storage in the refrigerator with occasional "scratching" to effect crystallization.

(13) Apitzsch and Metzger, *Ber.*, **37**, 1677 (1904).
(14) Danilov, *ibid.*, **59**, 1032 (1926).
(15) Wislicenus, *Ann.*, **291**, 164 (1896).
(16) Willstätter, *Ber.*, **51**, 1238 (1918).
(17) Hesse, *J. prakt. Chem.*, [2] **64**, 287 (1901).
(18) Maxim and Stanconi, *Bull. soc. chim.*, [5] **3**, 600 (1935).
(19) Perkin and Revay, *J. Chem. Soc.*, **65**, 232 (1894).
(20) Bachmann, THIS JOURNAL, **56**, 170 (1934).
(21) Natelson and Gottfried, *ibid.*, **61**, 970 (1939); Rupe and Busolt, *Ber.*, **40**, 4536 (1907).
(22) Wislicenus and Elbe, *Ber.*, **50**, 261 (1917).
(23) Slotta and Behnisch, *ibid.*, **68**, 754 (1935).
(24) Willstätter and Pummerer, *ibid.*, **37**, 3734 (1904).
(25) Conrad and Guthzeit, *ibid.*, **19**, 22 (1886).
(26) Mannich, *Arch. Pharm.*, **272**, 337 (1932).
(27) In most cases the acid chlorides used in this study could not be distilled without excessive or complete decomposition. Consequently they were employed in crude form directly upon removal of solvent and unreacted thionyl chloride.
(28) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).
(29) 1-Methyl-4-chloropiperidine, which is obtained in excellent yield from the corresponding piperidinol and thionyl chloride, will not react with diphenylacetic acid or other acids studied. There also is evidence that certain nitro carboxylic acids react with diethylaminoethyl chloride in an abnormal manner.

Summary

A series of thirty-nine basic esters of a variety of arylacetic acids were prepared and studied *in vitro* for spasmolytic action. Changes in structure, particularly in the acid portion of the molecule, gave a wider variation in the neurotropic potency than in musculotropic potency. The introduction of a carbon–carbon linkage or bridge between the two benzene nuclei in certain esters of diphenylacetic acid, thus forming derivatives of fluorene-9-carboxylic acid, results in an increase in spasmolytic activity with little or no increase in toxicity.

The most promising spasmolytic of the series is β-diethylaminoethyl fluorene-9-carboxylate.

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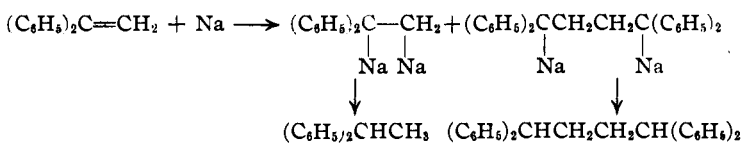
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Addition of Metals to Some Phenylated Olefins in Liquid Ammonia Solution[1]

BY HENRY GILMAN AND J. CLYDE BAILIE

It has been shown by Ziegler and co-workers[2] that when a solution of 1,1-diphenylethylene in ether was added to a solution of excess sodium in liquid ammonia the sole product of hydrolysis was 1,1-diphenylethane. Subsequently, Wooster and Ryan[3] also isolated a lesser quantity of 1,1,4,4-tetraphenylbutane.



Related reactions, as now reported, take place with lithium, calcium, strontium and barium. On the basis of some formulations on the relative reactivities of organometallic compounds, the following hypothesis was proposed: "In general, it may be stated that where there is a 1,4-addition or a dimerizing addition of a metal to 1,1-diphenylethylene to give 1,1,4,4-tetraphenylbutane an RM compound of this metal will add to an olefinic linkage."[4] This generalization now finds adequate support, inasmuch as the RM compounds of each of the five metals mentioned above add to an olefinic linkage. The addition of the newly prepared diethylstrontium to 1,1-diphenylethylene is described in the accompanying paper.[5]

Magnesium, manganese and aluminum, which form RM types of lesser activity, that are known not to add to any measurable extent to the olefinic linkage, showed no evidence of solution in liquid ammonia and were without action on 1,1-diphenylethylene in that solvent.

Liquid ammonia solutions of calcium, strontium, and barium, respectively, reduce 1,1,2-triphenylethylene to 1,1,2-triphenylethane.

An organobarium compound is also formed in liquid ammonia by interaction of triphenylmethane with barium, as shown by carbonation which yielded some triphenylacetic acid.

Experimental

Reactions with 1,1-Diphenylethylene.—To 200 cc. of liquid ammonia in a Dewar flask was added 10 g. (0.44 g. atom) of sodium metal in small portions. Then to the deep blue solution was added 10 g. (0.056 mole) of diphenylethylene in 10 cc. of ether. The solution became red (formation of organoalkali compound), and the color persisted for two hours and until the mixture was ammonolyzed with ammonium chloride. After the ammonia had evaporated, the residue was shaken with water and extracted with ether. The ether was distilled, and the remaining oil distilled under reduced pressure. The products isolated were 6.7 g. (67%) of 1,1-diphenylethane and 1.7 g. (17%) of 1,1,4,4-tetraphenylbutane. These results check essentially those of Wooster and Ryan.[3]

Under corresponding conditions, a reaction between 6 g. of calcium chips and 10 g. of diphenylethylene gave a red organocalcium solution in liquid ammonia. Subsequent to ammonolysis by ammonium chloride there was obtained a 45% yield of 1,1-diphenylethane. From a second experiment in which 8 g. of calcium was used, there was obtained (after hydrolysis of the residue by 10% hydrochloric acid) 7 g. (70%) of 1,1-diphenylethane and 1.4 g. (14%) of 1,1,4-4-tetraphenylbutane.

(1) Paper XLVI in the series: "Relative Reactivities of Organometallic Compounds." The preceding paper is THIS JOURNAL, **65**, 33 (1943).

(2) Ziegler, Colonius and Schäfer, *Ann.*, **54**, 473 (1929). See, also, Schlenk and Bergmann, *Ann.*, **479**, 78 (1930), for the addition of Li to 1,1-diphenyl-2-benzylethylene in ether.

(3) Wooster and Ryan, THIS JOURNAL, **56**, 1133 (1934). See, particularly, Wooster, *Chem. Rev.*, **11**, 48–52 (1932), for a full discussion of mechanisms proposed for these reactions.

(4) Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, p. 459.

(5) Gilman, Meals, O'Donnell and Woods, THIS JOURNAL, **65**, 268 (1943).