The filtrate was adjusted to *p*H 10.5 using 90 cc. of 10 *N* sodium hydroxide. After stirring for thirty minutes to allow for hydrolysis of the ester groups, the mixture was again adjusted to *p*H 3.5. This solution then reacted in the usual manner[1] with 46.0 g. of 2,4,5-triamino-6-hydroxypyrimidine bisulfate and 43.0 g. of barium chloride dihydrate in 750 cc. of water, 39.0 g. of dibromopropional in 50 cc. of acetic acid and 9.0 g. of sodium dichromate in 75 cc. of water. The yield of crude product was 114.5 g.; chemical assay 19.7%.

This crude pteroyl derivative was purified by a previously described method[1] carrying the procedure through the second precipitation at *p*H 0.9. This yielded 5.9 g. of material, 69% pure by chemical assay.[10] This material seems to be soluble in wet acetone or wet alcohol; therefore, it was never washed with organic solvents. A portion of this (1.4 g.) was dissolved in 190 cc. of dilute sodium hydroxide at *p*H 11.0 and the resulting solution was acidified to *p*H 6.0. This was filtered through Celite; 4 g. of Celite was added to the filtrate and it was acidified to *p*H 2.1 at 50°. After cooling this was filtered and the solid dissolved in 130 cc. of a dilute sodium hydroxide solution. The material was then further purified by repeating the previously described[1] purification treatment. The resulting free acid was collected by centrifuging. It was washed twice with water, mixed with a little Norite and enough magnesium oxide to bring to *p*H 9.0 in 8 cc. of water. After heating to 80° it was filtered, cooled, and the magnesium salt of the pteroyl-α-glutamyl-γ-glutamylglutamic acid was thrown out by adding alcohol; yield 100 mg. The chemical assay was 83%. However, the ultraviolet absorption spectra were almost identical with those of pteroylglutamic acid and the other pteroylpolyglutamic acids except in regard to the extinction coefficient.

**Ultraviolet Absorption Spectra.**—The 5 isomeric pteroyltriglutamic acids had essentially the same ultraviolet absorption spectra which were very similar to pteroylglutamic acid. In 0.1 *N* sodium hydroxide the compounds had maxima of about equal magnitude at 257 and 286 mμ and another at 365 mμ. There were minima at 235, 265 and 334 mμ. In 0.1 *N* hydrochloric acid there was a plateau at 240 to 248 mμ, a maximum at 290 mμ, and a minimum at 262.5 mμ.

**Acknowledgment.**—The authors wish to acknowledge the assistance of Calco Chemical Division in the preparation of carbobenzoxyglutamic anhydride, Mr. Louis Brancone and associates for the microanalyses, Miss Eleanora Boggiano for the microbiological assays and Mrs. Anna deGrunigen for chemical analysis.

## Summary

The synthesis of tetraethyl *p*-nitrobenzoyl-α-glutamyl-α-glutamylglutamate, tetraethyl *p*-nitrobenzoyl - α - glutamyl - γ - glutamylglutamate, tetraethyl *p*-nitrobenzoyl-γ-glutamyl-α-glutamylglutamate and their corresponding *p*-amino derivatives have been described. The three corresponding isomeric pteroylglutamylglutamylglutamic acids have been prepared and purified, and have been shown to be different from the fermentation *L. casei* factor.

A comparison of the five isomers of pteroylglutamylglutamylglutamic acid (Table I) has shown conclusively that the fermentation *L. casei* factor is pteroyl-γ-glutamyl-γ-glutamylglutamic acid.

PEARL RIVER, NEW YORK RECEIVED NOVEMBER 17, 1948

---

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY OF THE HEBREW UNIVERSITY AND THE DANIEL SIEFF RESEARCH INSTITUTE]

# β,β-Diarylacrylic Acids. III. Esters with Diethylaminoethanol as Anesthetics[1]

BY MOSHE WEIZMANN, SAUL PATAI, ELCHANAN DIMANT AND FELIX BERGMANN

The anesthetic activity of esters of benzoic acid is usually ascribed to the presence of the resonating aromatic system, because intercalation of a methylene group between the benzene ring and the carboxyl group destroys this effect.[2] On the other hand, an extension of the resonating system, as *e. g.*, in cinnamic acid should be expected to increase the pharmacological activity. In a few examples this seems to be the case—*e. g.* cinnamamide is a much stronger hypnotic than benzamide[3]—although in the majority of esters of cinnamic acid no improvement over the corresponding derivatives of benzoic acid is found.[4] However, the strong anesthetic activity of the diethylaminoethyl ester of β,β-diphenylacrylic acid (I) has been established,[5] and it seemed of interest to study the influence of substituents in the aromatic rings of (I), since a large number of substituted diarylacrylic acids has recently become available.[1]

It was especially attractive to study the *p*-amino derivatives of (I). A monoamino derivative could not be prepared so far, because *p*-nitrobenzophenone resisted both reaction with a Grignard reagent and Reformatsky condensation with ethyl halogenoacetates. The same inactivity was observed for *p,p'*-dinitrobenzophenone. However, direct nitration of (I) was found to introduce two nitro groups in the *p,p'*-positions (II, R = H), since oxidation of (II) with potassium permanganate yielded *p,p'*-dinitrobenzophenone.[6] Conditions of nitration were rather drastic and resulted in a partial decarboxylation of the acid, thus producing a considerable amount of tarry by-products. Nitration of the methyl ester of (I) was a more convenient procedure[7] and gave the crystalline ester (II, R = $CH_3$) in 52% yield.

(1) For Part I see F. Bergmann, *et al.*, THIS JOURNAL, **70**, 1612 (1948).

(2) Pyman, *J. Chem. Soc.*, **111**, 167 (1917).

(3) S. Fränkel, "Die Arzneimittel Synthese," Julius Springer, Berlin, 1927, p. 536.

(4) Pyman, *J. Chem. Soc.*, **111**, 1119 (1917).

(5) Burtner and Cusic, THIS JOURNAL, **65**, 262 (1943); Lehmann and Knoefel, *J. Pharm. Exp. Therap.*, **74**, 274 (1942).

(6) Actually isomeric dinitro derivatives may be present in the non-crystalline by-products, which were not investigated further.

(7) Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945).

TABLE I

DIETHYLAMINOETHYL ESTERS OF β,β-DIARYLACRYLIC ACIDS (III)

| $R_1$ = | $R_2$ = | M. p. of salt[a] | Solvent for crystallization | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | Concn., % (in 0.9% NaCl solution) | Duration of corneal anesthesia[b] min. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | ..... | ..... | ..... | .. | .. | .. | .. | ... | ... | 0.4 | 20–25 |
| F | H | Ci- 98–100° | Isopropyl alc. | $C_{27}H_{32}O_9NF$ | 60.8 | 6.0 | | 60.6 | 5.9 | | 1.0 | 15–20 |
| F | F | Ci- 104–105° | Isopropyl alc. | $C_{27}H_{31}O_9NF_2$ | 58.8 | 5.6 | | 58.8 | 5.9 | | 1.0 | 15–20 |
| Cl | Cl | Ci- 124–125° | Acetone | $C_{27}H_{31}O_9NCl_2$ | | | 2.4 | | | 2.6 | 0.2 | 20–25 |
| Br | Br | Ci- 138–139° | Ethanol–ether | $C_{27}H_{31}O_9NBr_2$ | | | 2.1 | | | 2.3 | 0.2 | 50–60 |
| $OCH_3$ | $OCH_3$[c] | Ox- 137° | Ethanol | $C_{25}H_{31}O_8N$ | | | 2.95 | | | 3.0 | 0.4 | 10–15 |
| $CH_3$ | $CH_3$[d] | Ci- 108–109° | Acetone–ether | $C_{29}H_{37}O_9N$ | | | 2.6 | | | 2.6 | 0.2 | Weak |
| | | | | | | | | | | | 0.4 | 50 |
| $NH_2$ | $NH_2$ | Dipi- 146° | Acetone–ether | $C_{41}H_{43}O_{12}N_{11}$ | 55.8 | 4.85 | | 55.4 | 4.6 | | 1.0 | Nil |

[a] Ci = Citrate; Ox = oxalate; Dipi = dipicrolonate. [b] Standard: novocaine hydrochloride, 2% solution, duration of anesthesia fifteen to twenty minutes. [c] Picrate (from ethanol) m. p. 143°. *Anal.* Calcd. for $C_{29}H_{32}O_{11}N_4$: N, 9.15. Found: N, 8.9. [d] Oxalate (from ethanol) m. p. 158–160°. *Anal.* Calcd. for $C_{25}H_{31}O_6N$: N, 3.2. Found: N, 3.3.

TABLE II

DIETHYLAMINOETHYL ESTERS OF β,β-DIARYLPROPIONATES (IV)

| $R_1$ = | $R_2$ = | M. p. of salt | Solvent for crystallization | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | Concn., % (in 0.9% NaCl solution) | Duration of corneal anesthesia, min. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F | H | Ci- 108–109° | Isopropyl alc. | $C_{27}H_{34}O_9NF$ | 60.6 | 6.35 | 2.6 | 60.5 | 6.2 | 2.8 | 1.0 | Nil |
| F | F | Ci- 116–117° | Isopropyl alc. | $C_{27}H_{33}O_9NF_2$[a] | 58.6 | 6.0 | 2.5 | 58.4 | 6.2 | 3.0 | 1.0 | 5–10 |
| Br | Br | Ci- 110–112° | Ethanol–ether | $C_{27}H_{33}O_9NBr_2$[b] | | | 2.1 | | | 2.0 | 0.2 | 10–15 |
| $CH_3$ | $CH_3$[c] | Ci- 115–116° | Ethanol–ether | $C_{29}H_{39}O_9N$ | | | 2.5 | | | 2.6 | 0.4 | 20–25 |
| $NH_2$ | $NH_2$ | Dipi- 135° | Acetone–ether | $C_{41}H_{45}O_{12}N_{11}$ | 55.7 | 5.1 | 17.4 | 55.9 | 5.1 | 17.2 | 1.0 | Nil |

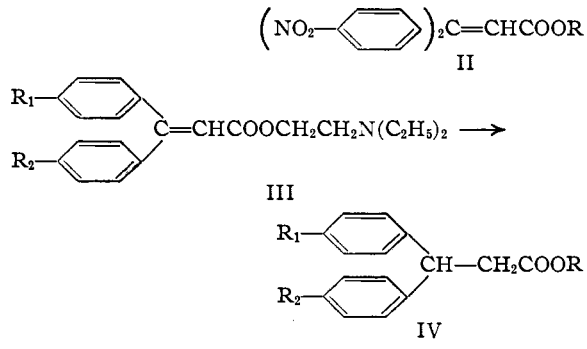
[a] The free ester boils at 173° (0.1 mm.). *Anal.* Calcd. for $C_{21}H_{25}O_2NF_2$: C, 69.8; H, 6.9; N, 3.85. Found: C, 69.7; H, 7.0; N, 3.5. [b] Analysis for bromine: Calcd. Br, 23.7. Found: Br, 23.6. [c] Oxalate (from ethanol) m. p. 116–118°. *Anal.* Calcd. for $C_{25}H_{33}O_6N$: N, 3.2. Found: N, 3.5.

The diethylaminoethyl esters (III) were prepared by conventional methods and were reduced catalytically to the diarylpropionates (IV). It is noteworthy that in contrast to the free acids or their methyl esters, the chloro- and bromo-derivatives of (III) did not lose halogen during hydrogenation, presumably because of the presence of a strong basic group in the molecule.

Results of pharmacological testing[8] are reported in Tables I and II. It is of interest that the diamino derivatives have no anesthetic action on the rabbit's cornea. The influence of fluorine in benzoic esters was studied by Fosdick[9] who observed that esters of *p*-fluorobenzoic acid possessed lower toxicity than the *p*-amino derivatives, but equal or higher activity. The mono- and difluoro esters (III) were less active than the unsubstituted compound and definitely inferior to the chloro- and bromo- derivatives. The ester of β,β-di-(*p*-bromophenyl)-acrylic acid was the most active compound of the series.

In accordance with the introductory assertion, saturation of the double bond in (III) reduced the pharmacological activity appreciably.

$$\underset{\text{I}}{(C_6H_5)_2C{=}CHCOOR} \xrightarrow{HNO_3}$$




## Experimental

All melting points uncorrected.

(1) **Nitration of β,β-Diphenylacrylic Acid.**—Nitric acid (d. 1.48, 70 cc.) was cooled to 0° and β,β-diphenylacrylic acid (16 g.) was added in small portions over a period of thirty minutes. Stirring was continued for fifteen minutes. The resulting brown mixture was poured into ice-water (250 cc.), the yellow, semi-solid precipitate was filtered off and redissolved in 10% sodium hydroxide solution by gentle heating. The sodium salt of β,β-di-(*p*-nitrophenyl)-acrylic acid (II) crystallized overnight; yield, 4 g., 17%. The free acid (II) was recrystallized from dilute acetic acid, faint yellow needles, m. p. 230°.

*Anal.* Calcd. for $C_{15}H_{10}O_6N_2$: C, 57.3; H, 3.2. Found: C, 57.2; H, 3.2.

The constitution of acid (II) was proved by oxidation with potassium permanganate in alkaline solution. In view of the fact that the isomeric dinitrobenzophenones have almost the same melting point (4,4'-dinitro deriva-

(8) Leser, *J. Pharm. Exp. Therap.*, **68**, 389 (1940).

(9) Fosdick and Campaigne, THIS JOURNAL, **63**, 974 (1941).

tive: m. p. 189°; 2,2'- 188–189°; 2,4'- 196°), the oxidation product was reduced by stannous chloride in hydrochloric acid to 4,4'-diaminobenzophenone, m. p. 239–240°.

(2) **Nitration of Methyl β,β-Diphenylacrylate.**—Nitration was carried out as above, at 10°, and the reaction mixture poured into ice-water. The yellow precipitate was recrystallized from methanol, yellow rods, m. p. 157°; yield, 52%.

*Anal.* Calcd. for $C_{16}H_{12}O_6N_2$: C, 58.5; H, 3.7. Found: C, 58.5; H, 3.8.

Hydrolysis of the methyl ester gave acid (II) of m. p. 230°.

(3) **Reduction of Methyl β,β-Di-(p-nitrophenyl)-acrylate.**—In view of the extreme hygroscopicity of the diamino acid or its methyl ester, the following reduction method was applied: the dinitro ester was reduced by the stannous chloride–hydrochloric acid–acetic acid method and the diamine precipitated by an ice-cold solution of sodium hydroxide. Ether was added to extract the diamino ester from the aqueous phase, the ether solution dried over potassium carbonate and mixed with excess ethereal solution of oxalic acid. The precipitate was dissolved in methanol and reprecipitated by ether. The melting point of the dioxalate dihydrate of methyl β,β-di-(p-aminophenyl)-acrylate was not sharp, 130–135°; yield, 60%.

*Anal.* Calcd. for $C_{20}H_{20}O_{10}N_2 \cdot 2H_2O$: C, 49.6; H, 5.0; N, 5.7. Found: C, 49.5; H, 5.3; N, 6.0.

Upon drying at 100° the substance lost its water of crystallization and melted at 125–127°.

*Anal.* Calcd. for $C_{20}H_{20}O_{10}N_2$: C, 53.5; H, 4.5. Found: C, 53.4; H, 4.8.

Hydrolysis was effected by 10% ethanolic potassium hydroxide; the crude product, after acidification, was dissolved in ether and the dioxalate of the acid precipitated by an ethereal solution of oxalic acid; m. p. 146–150°, after drying at 100°.

*Anal.* Calcd. for $C_{19}H_{18}O_{10}N_2$: N, 6.4. Found: N, 6.3.

(4) **Preparation of Diethylaminoethyl β,β-Di-(p-nitrophenyl)-acrylate.**—The chloride of acid (II) was prepared by means of thionyl chloride and heated with one mole of diethylaminoethanol in benzene solution. The crude ester, obtained after addition of aqueous ammonia, was dissolved in ether, and excess ethereal solution of citric acid was added. The citrate was recrystallized from absolute ethanol, white plates, m. p. 150°.

*Anal.* Calcd. for $C_{27}H_{31}O_{13}N_3$: C, 53.5; H, 5.15; N, 6.95. Found: C, 53.2; H, 5.4; N, 7.2.

The picrate was obtained in the same manner and recrystallized from butyl acetate as yellow needles, m. p. 155°.

*Anal.* Calcd. for $C_{27}H_{26}O_{13}N_6$: C, 50.5; H, 4.1. Found: C, 50.3; H, 4.2.

Reduction of the citrate was achieved by means of stannous chloride in hydrochloric–acetic acid. The crude product was again dissolved in ether, from which the dipicrolonate of diethylaminoethyl β,β-di-(p-aminophenyl)-acrylate was precipitated; m. p. 137–146°; yield, 45%.

Catalytic reduction of the citrate of the dinitro ester in acetic acid over Adams catalyst proceeded at room temperature and atmospheric pressure during four hours. The product was again isolated as the dipicrolonate. The dipicrolonate of diethylaminoethyl β,β-di-(p-aminophenyl)-propionate melted at 130–135°.

(5) **Preparation of Diethylaminoethyl Esters (III) (see Table I).**—The required acid chlorides were prepared from the corresponding diarylethylenes and oxalyl chloride and were used without further purification. Condensation with diethylaminoethanol was carried out in benzene solution, the hydrochloride of the ester formed was extracted with water, excess ammonia added and the free ester taken up with ether. From the ethereal solution the salt most suitable for characterization was precipitated.

The saturated esters (IV) (see Table II) were prepared either by catalytic reduction of the acrylates (III) in acetic acid over Adams catalyst or from the chlorides of the saturated acids and diethylaminoethanol. For the chloro- and bromo- derivatives only the first method is suitable, because it did not remove halogen from the aromatic rings. Reduction of the dibromo ester enabled us also to prepare for the first time β,β-di-(p-bromophenyl)-propionic acid by hydrolysis of its diethylaminoethyl ester with alcoholic potassium hydroxide. The crude acid was recrystallized from dilute ethanol, prisms of m. p. 184–185°; mixed m. p. with β,β-di-(p-bromophenyl)-acrylic acid (m. p. 191°), 160–165°.

*Anal.* Calcd. for $C_{15}H_{12}O_2Br_2$: C, 46.9; H, 3.2. Found: C, 47.1; H, 3.3.

(6) **Pharmacological Tests.**—All esters were applied as citrates in 0.9% NaCl solution. Wherever other salts only could be isolated in crystalline form, these salts were converted into the free esters. The latter were dissolved in ether, a slight excess of citric acid was added, the precipitate was washed with ether three times by decantation, the residue dried and dissolved in a given volume of saline to make up the required solution.

## Summary

The anesthetic activity of the diethylaminoethyl esters of β,β-diarylacrylic and β,β-diarylpropionic acids has been studied.

Nitration of β,β-diphenylacrylic acid yields the p,p'-dinitro derivative which has been reduced to the diamino compound.

JERUSALEM AHD RECHOVOT, ISRAEL

RECEIVED FEBRUARY 7, 1949