TABLE II

Ester or acid	Yield, %	M.p., °C.	Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Z-Gly-Gly-OMe[a]	71	63–65	10.00	9.83				
Z-DL-Val-Gly-OMe	92	130–132	8.69	8.73	59.60	59.91	6.88	6.90
Z-DL-Ala-Gly-OMe	68	74–76	9.52	9.57				
Z-Gly-DL-Phe-OMe	81	83–84	7.56	7.56	64.85	64.96	5.99	5.98
Z-β-Ala-DL-Phe-OMe	90	96–99	7.28	7.15				
Z-DL-Met-Gly-OMe	78	79–81	7.91	7.83				
Z-DL-Val-Gly-OH[b]	91	160–162	9.09	9.04	58.41	58.59	6.54	6.87
R-Gly-DL-Phe-OMe[c]	95	116–119	8.69	8.72	59.61	59.43	6.88	7.10
R-Gly-DL-Phe-OH	81	107–110	[d]					

[a] Carbobenzoxyglycylglycine methyl ester. This is essentially the system of abbreviations devised by B. Erlanger and E. Brand, THIS JOURNAL, **73**, 3509 (1951). [b] Acids prepared by saponification of the ester. [c] R is carbisopropoxy. [d] Acid used without analysis after one recrystallization from isopropyl alcohol.

pendently by Boissonnas, Vaughan and Wieland and Bernhard.[13] The following minor modification was used.

To a solution of 0.1 mole of carbobenzoxy amino acid in reagent grade acetone containing 14 ml. of triethylamine cooled to −10° was added 14 ml. of isobutyl chlorocarbonate. The mixture was stirred at −10° for 20 minutes and 0.1 mole of amino acid ester hydrochloride in chloroform containing 14 ml. of triethylamine was added. The mixture was stirred four hours at room temperature, the solvents removed *in vacuo* and the residue taken up in ethyl acetate and water. The ethyl acetate layer was washed with dilute hydrochloric acid, salt water, sodium bicarbonate and salt water. After drying, filtering and concentrating to small volume the product could normally be obtained by addition of petroleum ether. Representative carbobenzoxy peptide esters are given in Table II.

Thermal Decomposition of Carbobenzoxy-DL-phenylalanine.—Fifteen grams of carbobenzoxy-DL-phenylalanine was heated to 160–170° for seven hours. Evolution of carbon dioxide began at the melting point. Toward the end of the heating period long needles separated from the reaction mixture, and gas evolution had almost ceased. The mixture was stirred with chloroform which left the crystals undissolved. These were insoluble in acid and base and most organic solvents. Recrystallization from acetic acid gave 3,6-dibenzyl-2,5-diketopiperazine melting at 295–297° uncor. Fischer[14] reports a melting point of 300° cor. A small amount (0.2 g.) of starting material was recovered, but the major portion of the reaction product was not obtained crystalline.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: N, 9.52. Found: N(K), 9.31.

Cleavage of Carbisopropoxyglycyl-DL-phenylalanine.—A solution of 5 g. of the acid in 25 ml. of nitromethane was saturated with hydrogen bromide and allowed to stand for four days at room temperature during which time an oil and a few crystals (plates) separated. The crystals were removed by filtration and the solvent by evaporation *in vacuo*. The residue was dissolved in methanol and made just basic with ammonium hydroxide. Cooling gave 0.7 g. (21%) of the diketopiperazine melting at 264–266° dec. (uncor.).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: N(AP), none N(K), 13.72. Found: N(AP) negligible; N(K), 13.55.

Acknowledgment.—The authors are indebted to Mrs. C. Diacetis and Miss Mary Podoba for technical assistance and to Mr. Morris E. Auerbach and Kenneth D. Fleischer and staff for analytical results. Our ideas about acid-catalyzed diketopiperazine formation have been considerably influenced by a stimulating discussion of this work with Dr. C. F. Koelsch.

(13) (a) R. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); (b) J. Vaughan, THIS JOURNAL, **73**, 3547 (1951); (c) T. Wieland and K. Bernhard, *Ann.*, **572**, 190 (1951).

(14) E. Fischer, *Ber.*, **34**, 451 (1901).

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSTIY]

Heterocyclic Diphenylmethane Derivatives

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Several *gem*-diphenyl substituted heterocyclic derivatives have been prepared to test for possible analgetic activity. Synthetic methods are described for the preparation of 2,2-diphenyl-4-methyl-3-morpholone (I), 3,3-diphenyl-4-methyl-2-morpholone (II), methyl α-morpholino-α,α-diphenylacetate, 3-methyl-6,6-diphenyl-3,4,5,6-tetrahydro-1,3-oxazine (III) and 2,6,6-triphenyl-3-methyl-3,4,5,6-tetrahydro-1,3-oxazine (IIIa). Some of the physiological properties of these compounds are reported.

The repeated occurrence of a *gem*-diphenyl group in physiologically active compounds such as Methdone, Trasentin, Benadryl, Dilantin and Pavatrine, suggested an investigation of a series of heterocyclic compounds derived from diphenylacetic acid. Similar studies, published recently by Morrison and co-workers[4–6] and Geissman,[7] have prompted a report of our work at this time.

We were primarily interested in oxazine derivatives of types I, II and III.

(1) Taken in part from the Ph.D. Thesis of Milton B. Frankel, Stanford University, June, 1949.

(2) Parke, Davis and Co. Research Fellow, 1947–1949.

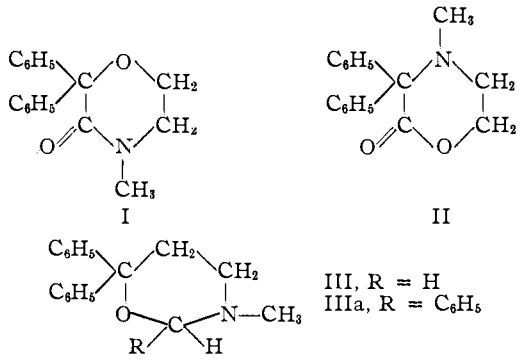
(3) Taken in part from the M.S. Thesis of Marilyn Gregory, Stanford University, June, 1951.

(4) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 1510 (1950).

(5) A. L. Morrison, M. Konigstein and A. Cohen, *ibid.*, 2887 (1950).

(6) A. L. Morrison, R. F. Long and M. Konigstein, *ibid.*, 952 (1951).

(7) T. A. Geissman, M. Bassin and E. J. Zeilberger, THIS JOURNAL, **73**, 5874 (1951).



I II

III, R = H
IIIa, R = C_6H_5

These compounds were prepared as outlined in the equations

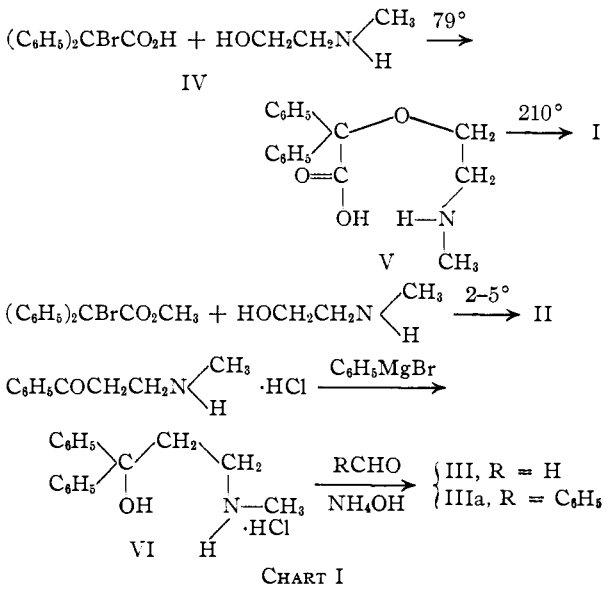


CHART I

When α-bromo-α,α-diphenylacetic acid (IV) was refluxed in benzene solution with β-methylaminoethanol, α-(β-methylaminoethoxy)-α,α-diphenylacetic acid hydrobromide was obtained in a yield of 73.5%. The hydrobromide was converted to the free base V by the use of silver oxide. Attempts to cyclize V using sulfuric acid, glacial acetic acid, phosphorus pentoxide, phosphorus oxychloride, thionyl chloride, anhydrous sodium sulfate and zinc chloride were unsuccessful. However, it was found that by heating V just above its melting point for 10 minutes, water was split out and I was formed in 91.5% yield. The cyclized compound was neutral, failing to form a hydrochloride or picrate derivative, a property which was to be expected from an amide type of linkage. Recently this compound has been prepared independently[5] by an alternate route and a product obtained with the same melting point. There was no indication that any of the isomeric compound II was formed in this series of reactions.

The basic oxazine II was prepared in 46.1% yield by the action of β-methylaminoethanol on methyl α-bromo-α,α-diphenylacetate in the absence of a solvent. Decomposition resulted if these reactants were warmed together above 60°, but the cyclized product was obtained when solution was brought about at 40° and the mixture allowed to stand at 2–5° for about three days. It is very interesting that the intermediate methyl α-(β-hydroxyethylmethylamino)-α,α-diphenylacetate was never isolated but spontaneously cyclized under these reaction conditions. The product readily formed a picrate derivative, as would be expected for the cyclic amine II. Attempts to prepare compound II from α-chloro-α,α-diphenylacetyl[8] chloride and β-methylaminoethanol were unsuccessful. Methyl α-morpholino-α,α-diphenylacetate was prepared in 77.8% yield by treating methyl α-bromo-α,α-diphenylacetate with morpholine.

Compound III, R = H, was prepared in 67% yield by the action of formaldehyde upon 1,1-diphenyl-3-methylamino-1-propanol hydrochloride (VI). We obtained this intermediate in 56% yield by treating β-methylaminopropiophenone hydrochloride with phenylmagnesium bromide while Morrison and Rinderknecht[4] used the corresponding benzylamine derivative and removed the benzyl group by hydrogenolysis. Our experiments as well as those of Morrison and Rinderknecht indicated that the Grignard reaction on the free base of such amino ketones was unsatisfactory but was successful with the hydrochloride derivative.[9] This compound III was prepared independently under different conditions by Morrison and Rinderknecht[4] and the reported properties agree. In addition, we prepared the phenyl derivative, IIIa (R = C_6H_5), by the use of benzaldehyde.

Pharmacological Results[10]

α-(β-Methylaminoethoxy)-α,α-diphenylacetic acid hydrobromide (V·HBr) was not amebicidal at 1:500 dilution *in vitro*, and showed only a slight activity as an analgetic. 2,2-Diphenyl-4-methyl-3-morpholone (I) was inactive as an antihistamine agent, was not amebicidal at 1:500 dilution *in vitro*, showed no appreciable analgetic activity below toxic levels, exhibited a mouse toxicity of LD_{50} 100 mg./kg. body weight, and was 80% as active as papaverine as an antispasmodic on guinea pig muscle. 3,3-Diphenyl-4-methyl-2-morpholone (II) showed no appreciable analgetic activity below toxic doses (200 mg./kg.), and was inactive as an antihistamine agent, sympatholytic and anticonvulsant. 3-Methyl-6,6-diphenyl-3,4,5,6-tetrahydro-1,3-oxazine (III) was amebicidal at 1:7,500 dilution *in vitro*, showed some possible analgetic activity, was inactive as an antihistamine agent, and on guinea pig muscle was 100% as active as papaverine as an antispasmodic but was toxic (LD_{50}, mice intraperitoneal, 200 mg./kg. body weight). III failed to show promising results at dose levels of 100 mg./kg. daily, administered intraperitoneally, against schistosomiasis in mice. 2,6,6-Triphenyl-3-methyl-3,4,5,6-tetrahydro-1,3-oxazine (IIIa) was inactive as an antihistamine agent, and 30% as active as papaverine on guinea pig muscle as an antispasmodic. It had an LD_{50} in mice (i.p.) of 180 mg./kg. body weight and was not substantially effective as an analgetic.

(8) Cilag, Swiss Patent 240,070, Nov. 30 (1945).

(9) Compare J. J. Denton, *et al.*, THIS JOURNAL, **71**, 2048, 2050, 2053 (1949); **72**, 3792, 3795 (1950).

(10) These pharmacological data were determined in the laboratories of Parke, Davis and Co.

Acknowledgment.—We wish to thank Parke, Davis and Company for the fellowship grant which made this investigation possible, and also for the pharmacological results reported in this paper.

Experimental[11,12]

α-(β-Methylaminoethoxy)-α,α-diphenylacetic Acid (V).—To a solution of 331 g. (1.14 moles) of α-bromo-α,α-diphenylacetic acid[13] in 1 l. of benzene was added over a one-hour period a solution of 85.3 g. (1.14 moles) of β-methylaminoethanol[14] in 200 ml. of benzene. The mixture was refluxed for eight hours, cooled, and the hydrobromide of the product which had separated was filtered, 306.4 g. (73.5%), m.p. 182–193° dec. A sample was crystallized from isopropyl alcohol three times, m.p. 196–197° dec.

Anal. Calcd. for $C_{17}H_{20}O_3NBr$: C, 55.44; H, 5.43; Br, 21.82. Found: C, 56.04, 55.95; H, 5.64, 5.69; Br, 21.73, 21.75.

The hydrobromide salt was dissolved in a 50% water–ethanol solution and converted to the free base by shaking with silver oxide. The base was recrystallized from ethanol, m.p. 209–210° dec.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 71.72; H, 6.79.

2,2-Diphenyl-4-methyl-3-morpholone (I).—α-(β-Methylaminoethoxy)-α,α-diphenylacetic acid (V), 24.5 g., was heated in a distilling flask at 210° for ten minutes. The water was removed under vacuum and the remaining light yellow liquid distilled, b.p. 171–174° (0.2 mm.), 21.0 g. (91.7%). The product solidified to white crystals, which on crystallization from petroleum ether melted at 96–97°. The product was neutral and failed to form a hydrochloride or picrate.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41. Found: C, 76.11; H, 6.34.

Morrison, Konigsten and Cohen[5] reported a melting point of 97–98° for this compound prepared by an alternate method.

Methyl α-Bromo-α,α-diphenylacetate.—Methyl benzilate (131 g.) was treated with phosphorus tribromide (300 g.) in refluxing benzene for eight hours in a manner similar to that reported by Carothers[15] where phosphorus pentabromide was employed. The crude ester was purified by pouring onto excess ice, and washing the benzene layer with water, sodium bicarbonate and finally with water until neutral. The benzene layer was dried over magnesium sulfate and the ester distilled under vacuum, 242 g. (76%), b.p. 125° (0.05 mm.). This crystallized on standing and could be recrystallized from an acetone–water mixture, m.p. 38° if the mixture was not heated above 40°. This substance caused a severe allergic skin reaction in two of the four persons who worked with it.

3,3-Diphenyl-4-methyl-2-morpholone (II).—A mixture of 15 g. (0.05 mole) of methyl α-bromo-α,α-diphenylacetate and 15 g. (0.20 mole) of β-methylaminoethanol was very cautiously warmed (not above 40°) until solution was complete and then kept at 2–5° for three days. The white crystals which slowly formed were removed by filtration in a Skau tube, washed with a little cold methanol, and recrystallized from methanol; 7.4 g. (46.1%), m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.19; N, 5.12.

This material readily formed a picrate from alcoholic solution, m.p. 174–175°.

The yield was dependent upon the excess β-methylaminoethanol employed. With equimolar amounts the yield was only 9%; the other products in this reaction were not identified. When methanol was used as a solvent, the major product was identified as methyl α-methoxy-α,α-diphenylacetate.[15]

Methyl α-Morpholino-α,α-diphenylacetate.—A mixture of 10.5 g. (0.034 mole) of methyl α-bromo-α,α-diphenylacetate and 18.0 g. (0.21 mole) of morpholine was gently heated on the steam-bath until homogeneous and then kept at 2–5° for 24 hours. The reaction mixture was stirred with 20 ml. of methanol and filtered. The crystals, which proved to be the free base, and not the hydrobromide, were washed with water and recrystallized from methanol; 8.2 g. (77.8%) m.p. 137–138°.

Anal. Calcd. for $C_{19}H_{21}NO_3$: N, 4.49. Found: N, 4.54.

1,1-Diphenyl-3-methylamino-1-propanol Hydrochloride (VI).—To the phenylmagnesium bromide reagent, prepared from 314 g. (2.0 moles) of bromobenzene and 48 g. of magnesium in 1.5 l. of absolute ether, was added over a one-hour period a total of 100 g. (0.50 mole) of β-methylaminopropiophenone hydrochloride[16–18] which had been finely powdered and dried over phosphorus pentoxide in a vacuum desiccator. As the solid came in contact with the Grignard solution there was an immediate precipitate but this rapidly redissolved. The reaction mixture separated into two layers soon after the addition was complete; it was stirred at room temperature for eight hours and refluxed for an additional hour. By pouring the reaction mixture onto a mixture of 1 kg. of crushed ice and 200 ml. of concentrated hydrochloric acid, a light yellow solid was precipitated which after washing with cold water and air drying weighed 143 g. This product contained solvent of crystallization. It was crystallized after treatment with Norit from 800 ml. of ethyl acetate to give 86.0 g. which melted at 70–73°. Drying under 2 mm. vacuum at 60° reduced the weight to 77 g. and raised the melting point to 155–160°. Concentration of the filtrate gave another 10 g.; total yield 87 g., 62%. Recrystallization from ethyl acetate raised the melting point to 164–165°.

Anal. Calcd. for $C_{16}H_{20}NOCl$: C, 69.18; H, 7.29. Found: C, 68.66; H, 7.27.

2,6,6-Triphenyl-3-methyl-3,4,5,6-tetrahydro-1,3-oxazine (IIIa).—A mixture of 24.6 g. (0.09 mole) of 1,1-diphenyl-3-methylamino-1-propanol hydrochloride, 9.4 g. (0.09 mole) of benzaldehyde and 200 ml. of dry toluene was refluxed under a water separator for three hours until 1.45 ml. of water was collected. The reaction mixture was shaken with concd. ammonium hydroxide, washed with water, and the toluene removed under vacuum. The resulting sirup was crystallized from ethanol, 17.0 g. (57.4%), m.p. 143–147°. Further crystallization gave a melting point of 146–147°.

Anal. Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.27; H, 6.92; N, 4.26.

A hydrochloride recrystallized from isopropyl alcohol melted at 194–195°.

The reaction with paraformaldehyde was conducted in the same manner using benzene instead of toluene to give a 67% yield of 3-methyl-6,6-diphenyl-3,4,5,6-tetrahydro-1,3-oxazine (III). This was recrystallized from methanol–water, m.p. 82–83°.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.55; H, 7.34; N, 5.20.

Morrison and Rinderknecht,[4] who carried out the same reaction using formalin and an alcoholic potassium carbonate solution, reported a melting point of 83–85°. A hydrochloride recrystallized from isopropyl alcohol melted at 189.0–189.5°.

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(11) All melting points are uncorrected.

(12) Microanalyses by Charles W. Koch, Microchemical Specialties Co., Berkeley, Calif.

(13) Prepared by the method of H. Meerwein and F. Kremers, *Ann.*, **396**, 261 (1913), in 73.8% yield.

(14) L. Knorr and H. Matthes, *Ber.*, **31**, 1069 (1898).

(15) W. H. Carothers, THIS JOURNAL, **48**, 3195 (1926).

(16) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

(17) F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 451 (1942).

(18) D. W. Adamson, *J. Chem. Soc.*, S144 (1949).