Anal. Calcd. for $C_{24}H_{24}NO$: C, 84.17; H, 7.06. Found: C, 84.48; H, 6.88.

Duryl 2,3-Dimethoxyphenyl Ketimine.—*n*-Butyllithium was prepared from 19.5 g. (0.2 mole) of *n*-butyl chloride, 3 g. of lithium and 100 ml. of ether. After this solution had been heated under reflux for 2 hours, 20.7 g. (0.15 mole) of veratrole in 75 ml. of ether was added. The reaction mixture was heated under reflux for 24 hours. A solution of 15.9 g. (0.1 mole) of duronitrile in 100 ml. of ether was then added; the solution turned bright yellow and heating was continued overnight. The reaction mixture was decomposed in the usual manner and the imine hydrochloride was collected; m.p. 100–102°, yield 21 g. (62%). An additional 5 g. of the hydrochloride was isolated from the water solution; total yield 26 g. (77%).

The imine was obtained as a bright yellow oily solid by shaking the hydrochloride with sodium carbonate solution. Treatment with acetic anhydride converted it to the **acetyl derivative**, which was recrystallized from ethanol; m.p. 124–125°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.41; H, 7.41; N, 4.17.

Duryl Phenyl N-Methylketimine Methiodide.—A mixture of 5 g. of duryl phenyl ketimine, 20 ml. of 5% sodium carbonate solution and 10 g. of methyl iodide was heated under reflux for 2 hours and cooled. The yellow crystals which separated proved to be insoluble in water but very soluble in ethanol. Treatment of the alcohol solution with silver nitrate solution gave an immediate precipitate. The methiodide was recrystallized from a mixture of ethanol and ethyl acetate in a 1:3 ratio, m.p. 232–234° dec., yield 6.2 g. (80%).

Anal. Calcd. for $C_{19}H_{26}NI$: C, 58.03; H, 6.15. Found: C, 57.94; H, 6.42.

The infrared spectrum[13] has a band (1628 cm.$^{-1}$) corresponding to the imine group, and the N–H band is absent.

Duryl Phenyl N-Methylketimine.—A mixture of 1 g. of duryl phenyl ketimine and 1 g. of redistilled methyl sulfate was allowed to stand until it became homogeneous. The process was accompanied by the evolution of heat. A solution of 4 g. of sodium bicarbonate in 25 ml. of water was added and the mixture was heated on a steam-bath for 15 minutes, cooled and extracted with ether. The imine was recrystallized repeatedly from a methanol–water mixture; m.p. 100–101°, yield 0.6 g. (60%).

Anal. Calcd. for $C_{15}H_{21}N$: C, 86.01; H, 8.42. Found: C, 86.26; H, 8.49.

Infrared analysis showed that the bond attributed to the N–H group had disappeared.

When the methylimine was treated with methyl iodide it was converted into the same methiodide that was obtained from the unmethylated imine.

Duryl *o*-Methoxyphenyl N-Methylketimine Methiodide.—This salt was obtained in a 50% yield by a procedure similar to the foregoing; m.p. 228–232°, dec.

Anal. Calcd. for $C_{20}H_{26}INO$ C, 56.75; H, 6.19; N, 3.31. Found: C, 56.87; H, 6.44; N, 3.41.

Duryl *p*-Methoxyphenyl N-Methylketimine Methiodide.—The yield of this iodide was 40%, m.p. 231–233° dec.

Anal. Calcd. for $C_{20}H_{26}INO$: C, 56.75; H, 6.19; N, 3.31. Found: C, 56.49; H, 6.11; N, 3.56.

Duryl 2,3-Dimethoxyphenyl N-Methylketimine Methiodide.—This iodide was obtained in a yield of 78%, m.p. 122–124° dec.

Anal. Calcd. for $C_{21}H_{28}INO_2$: C, 55.63; H, 6.23; N, 3.09. Found: C, 55.49; H, 6.46; N, 2.75.

Reaction of Duryl Phenyl N-Methylketimine Methiodide with *t*-Butylmagnesium Chloride.—The powdered methiodide (13 g.) was added to a Grignard reagent prepared from 19 ml. of *t*-butyl chloride. The mixture, which had become deep red in color, was heated under reflux overnight and decomposed with ice and hydrochloric acid. The light yellow product which appeared at the ether–water interface was washed with water and ether, dried and recrystallized from an ethanol–ethyl acetate mixture, m.p. 255–260° dec., yield 9 g. (62%)

Anal. Calcd. for $C_{23}H_{32}IN$: C, 61.47; H, 7.18; N, 3.11. Found: C, 61.41; H, 7.34; N, 3.31.

The infrared spectrum of this compound shows the presence of bands atrributable to the *t*-butyl (1377, 1388 cm.$^{-1}$), imino (1637 cm.$^{-1}$) and para substituted phenyl (850 cm.$^{-1}$) groups.

The same product was obtained by the interaction of duryl *p*-methoxyphenyl N-methylketimine methiodide with the *t*-butyl reagent.

URBANA, ILLINOIS

(13) The infrared spectra were observed and interpreted by Miss Elizabeth Petersen and Miss Helen Miklas.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Acid-catalyzed Decarbobenzoxylation

BY NOEL F. ALBERTSON AND FRANK C. MCKAY

RECEIVED MAY 13, 1953

In agreement with the recent publication of Ben-Ishai and Berger decarbobenzoxylation by means of phosphonium iodide has been recognized to be an acid-catalyzed reaction and not a reduction as generally assumed. As a consequence, a very rapid and simplified method of decarbobenzoxylation (using preferably hydrogen bromide in nitromethane) has been developed. Applications to peptide chemistry are discussed and examples are presented. Explanations are advanced for certain cases of diketopiperazine formation in acid solution and for the decomposition of carbalkoxyamino acids on heating.

In a recent contribution to urethan chemistry Ben-Ishai and Berger[1] point out that the removal of a carbobenzoxy group from an amine by means of the "phosphonium reduction" method of Harington and Mead[2] is actually an acid-catalyzed reaction. We had independently reached the same conclusion on the basis of published experimental data.[3] However, our application of this knowledge to peptide chemistry differs from that of Ben-Ishai and Berger.

When hydrogen bromide was bubbled into a solution of carbobenzoxy-DL-phenylalanine in nitromethane, the hydrobromide of DL-phenylalanine precipitated in a few minutes. Treatment of the

(1) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(2) C. Harington and T. Mead, *Biochem. J.*, **29**, 1603 (1935).

(3) C. Stevens and R. Watanabe, THIS JOURNAL, **71**, 725 (1950). These authors found that whereas the carboallyloxy group behaved like the carbobenzoxy group in its cleavage by catalytic hydrogenation, sodium in liquid ammonia and phosphonium iodide, the carbopropyloxy group was cleaved only by phosphonium iodide. Incidentally, data in the original paper of Harington and Mead[2] indicate that the cleavage of a carbobenzoxy group by phosphonium iodide is not a reduction.

In an interesting paper published after the completion of our work, G. Anderson, J. Blodinger and A. Welcher, *ibid.*, **74**, 5309 (1952), report the removal of a carbobenzoxy group by hydrogen bromide in acetic acid. They state that their method was a development of the work of E. Waldschmidt-Leitz and K. Kuhn, *Ber.*, **84**, 381 (1951). The latter authors still referred to the phosphonium iodide method as a reduction.

TABLE I[a]

Peptide	Yield	M.p., °C.	Formula	Calcd. N(AP)	Calcd. N(K)	Found N(AP)	Found N(K)
Glycylglycine	81	>250	$C_4H_8N_2O_3$		21.20		21.16
DL-Valylglycine	69	247–248	$C_7H_{14}N_2O_3$	8.04		7.87	
DL-Alanylglycine	73	220–223[b]	$C_5H_{10}N_2O_3$	9.59	19.17	9.65[b]	19.00[b]
Glycyl-D-threonine	50	206–209	$C_6H_{12}N_2O_4$	7.95	15.90	7.63	15.70
Glycyl-DL-phenylalanine	80	272–273	$C_{11}H_{14}N_2O_3$	6.30		6.41	
β-Alanyl-DL-phenylalanine	56	253–256	$C_{12}H_{16}N_2O_3$	5.93		5.82	
S-Benzyl-DL-homocysteinylglycine	52	201–204[b]	$C_{13}H_{18}N_2O_3S$	4.95	9.92	4.72[b]	9.99[b]
DL-α-Aminopelargonylglycine	80	219–220[b]	$C_{11}H_{22}N_2O_3$	6.08	12.16	6.04[b]	11.96[b]

[a] N(AP) refers to nitrogen determined by titration in acetic acid with perchloric acid; N(K) refers to Kjeldahl nitrogen; and N(D) refers to Dumas nitrogen. [b] Value for crude reaction product.

hydrobromide in ethanol with pyridine afforded a good yield of DL-phenylalanine.

Since the method worked with an amino acid, it was tried with a peptide. Hydrogen bromide was bubbled through a solution of carbobenzoxyglycyl-DL-phenylalanine in nitromethane for three minutes. After 15 minutes the reaction mixture was diluted with methanol and the peptide precipitated in 76% yield with ammonium hydroxide. A second experiment gave an 83% yield.

This same method has been applied to the synthesis of peptides containing the following amino acids: glycine, alanine, β-alanine, 2-aminobutyric acid, valine, leucine, lysine, glutamic acid, threonine, phenylalanine, tyrosine, tryptophan, ε-aminocaproic acid, 2-amino-4-pentenoic acid and 2-amino-5-chloro-4-pentenoic acid. Some representative peptides are given in Table I.

In general, one would expect that hydrogen bromide would give essentially the same results as phosphonium iodide. Tryptophylglycine was obtained in poor yield. Acids in which the amino group was not alpha (namely, β-alanine and ε-aminocaproic acid) gave very variable yields—in some cases giving no peptide at all. This was undoubtedly due to the increased solubility of these peptides.

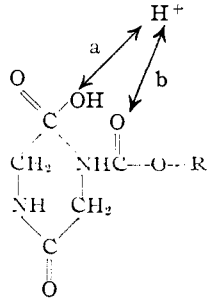
It was noted, for example, that although no peptide was isolated from carbobenzoxy-DL-alanyl-β-alanine, treatment of the solution with phenyl isocyanate gave the expected carbanilino-DL-alanyl-β-alanine. In another instance, isolation of a β-alanine peptide from its hydrobromide by the use of Amberlite resin more than doubled the yield over that obtained from a nitromethane–methanol solution. DL-α-Aminopelargonylglycine was obtained in the same yield (80%) by both hydrogenation and by HBr cleavage.

It is known that a benzylcarbonium ion will displace the methyl group of methionine.[4] Thus, it is not surprising that treatment of carbobenzoxy-DL-methionylglycine with hydrogen bromide in nitromethane gave S-benzyl-DL-homocysteinylglycine when the reaction mixture was worked up in five minutes. By using hydrogen chloride in acetic acid or in nitromethane at room temperature for about a week it was possible to obtain methionine from carbobenzoxymethionine although a small amount of S-benzylhomocysteine could have been present as a contaminant.

Hydrogen chloride catalyzed reactions were slow compared to those catalyzed by hydrogen bromide. Boron trifluoride caused a very rapid decarbobenzoxylation but the product was obtained as a boron trifluoride complex and the benzyl group was polymerized.

Nitromethane was a particularly effective solvent and the commercial product was dry enough to use as obtained. Even carbobenzoxyglycylglycine which is especially insoluble in nitromethane is readily decarbobenzoxylated in suspension. Commercial acetic acid contains sufficient water to hydrolyze completely the glycylglycine bond, but more hindered peptide bonds were quite stable in this solvent. Hydrogen bromide reacts with nitromethane to give ammonium bromide, but this side reaction has not interfered with peptide synthesis since it is slower than the decarbobenzoxylation reaction and since ammonium bromide is soluble in methanol.

In his early work on peptides, Fischer sought to use the carbethoxy group as a protecting group, but he was unable to remove it at the end of the synthesis.[5] The success of Stevens and Watanabe[3] in removing the carbopropyloxy protecting group from an amino acid with phosphonium iodide suggested that perhaps other carbalkoxy groups could be removed by acid-catalyzed cleavage. It was found, however, that treatment of carbisopropoxyglycyl-DL-phenylalanine with hydrogen bromide in nitromethane gave primarily the diketopiperazine *via* a relatively slow reaction. Examination of the structural formula of a typical peptide suggests a possible explanation.



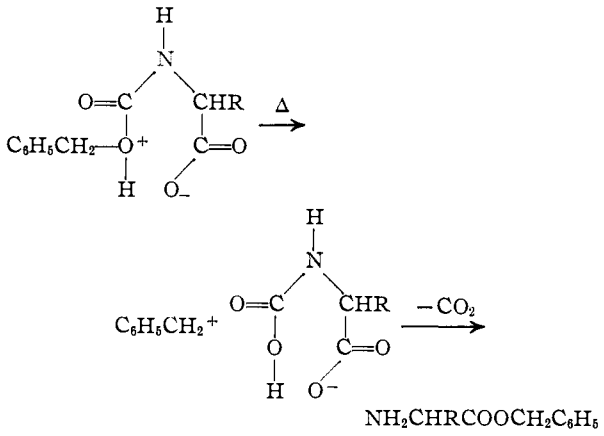
Of the various centers in the carbobenzoxy peptide which can attract a proton, attack at only two can lead to reaction under the experimental conditions used. An occasional attack of the type shown by "a" above will lead to bond formation as shown by the dotted line, with expulsion of CO_2 and R^+ to give a diketopiperazine. An attack *via* route "b" can lead to $R^+ + CO_2 +$ peptide.

(4) C. Dekker and J. Fruton, *J. Biol. Chem.*, **173**, 471 (1948).

(5) E. Fischer and E. Fourneau, *Ber.*, **34**, 2868 (1901).

If R is benzyl or allyl, a high percentage of the attacks *via* route "b" will be successful and the peptide will predominate over the diketopiperazine. If R is isopropyl reaction "a" becomes of more importance and diketopiperazine predominates. The same sort of reasoning may be used to explain the formation of diketopiperazine in the mild acid hydrolysis of acetyl-DL-phenylalanyl-L-glutamic acid.[6]

One consequence of the recognition of Harington's phosphonium iodide "reduction" as being an acid-catalyzed decomposition is the idea that carboalkyloxyamino acids or peptides should catalyze their own decompositions. The decomposition should be especially facile with α-amino acid derivatives, and one would expect an amino acid ester as the first product.



When carbobenzoxy amino acids were heated in test-tubes, copious evolution of carbon dioxide started at the melting point. A sample of carbobenzoxy-DL-phenylalanine, heated at 160–170° for seven hours, gave as the only crystalline product 3,6-dibenzyl-2,5-diketopiperazine. Carbon dioxide evolution started at the m.p. and water evolution was noted at an intermediate temperature. These facts support, but do not prove, the reaction course suggested above.

In their paper, Ben-Ishai and Berger point out that some unintentional and previously unexplained reactions of urethans are merely examples of acid-catalyzed cleavage. An additional example is furnished by the observation of Dyer and Ballard[7] that 15–20% of β-alanine hydrochloride is obtained as a by-product in the preparation of carbobenzoxy-β-alanyl chloride with thionyl chloride at 50°. Barkdoll and Ross[8] obtained tyrosyltyrosine ethyl ester hydrochloride from carbobenzoxytyrosyltyrosine and alcoholic hydrogen chloride in an attempt to prepare the carbobenzoxy peptide ester. Experience in this Laboratory suggests that acid-catalyzed decompositions in the presence of water or alcohols leads to rupture of the peptide bond at a rate dependent upon the steric hindrance around the peptide bond so that the Barkdoll–Ross procedure does not appear to be generally applicable. For example, with methanolic hydrogen chloride methyl carbobenzoxyglycylphenylalaninate gave a mixture of amino acid ester hydrochlorides.

Because of the speed and experimental simplicity of acid-catalyzed decarboxylations using anhydrous hydrogen bromide in nitromethane this method should be useful in many cases of peptide synthesis, particularly in the preparation of peptides or intermediates containing reducible groups. In many cases the peptides are analytically pure as obtained from the reaction mixture.

Other phases of urethan chemistry, including some extensions of acid-catalyzed cleavage, will be described at some future date.

Experimental

Glycylglycine.—Into a suspension of 18 g. of carbobenzoxyglycylglycine in 75 ml. of warm nitromethane was bubbled a stream of hydrogen bromide for five minutes. The reaction mixture was allowed to stand for three hours, filtered and washed with ether to give 15.6 g. of solid melting at 145–166°. This solid was dissolved in 150 ml. of methanol and 5 ml. of ammonium hydroxide added to precipitate the peptide. The yield was 8.0 g. (90%) free of halide. Recrystallization from aqueous methanol gave 7.2 g. (81%) melting above 250° (see Table I). This general procedure is satisfactory for the preparation of other peptides, although the method of isolation may have to be modified for some peptides which are somewhat soluble in methanol.

S-Benzylhomocysteinylglycine.—Hydrogen bromide was bubbled into a suspension of 6.8 g. of carbobenzoxy-DL-methionylglycine in 45 ml. of nitromethane. A clear solution resulted in two minutes and then the product precipitated rapidly. After a total reaction time of five minutes the solvent was decanted and the peptide precipitated from methanol with ammonium hydroxide (see Table I). The presence of the benzene ring was confirmed by an ultraviolet absorption curve. A recrystallized sample melted at 214–216° dec. (uncor.).

DL-Methionine.—Six grams of carbobenzoxy-DL-methionine[4] in 50 ml. of acetic acid was saturated with hydrogen chloride and allowed to stand five days. The solution was concentated *in vacuo*, the residue dissolved in ethanol and pyridine added to precipitate 3.0 g. of amino acid. This was recrystallized from water–ethanol, m.p. 251–252°. The product may have been contaminated with S-benzylhomocysteine.[4]

Anal. Calcd. for $C_5H_{11}NO_2S$: N, 9.39. Found: N(AP), 9.19.

D-Methionine.—This experiment was the same as for the DL except that 25 ml. of nitromethane was used in place of 50 ml. of acetic acid. The starting carbobenzoxy-D-methionine[4] had $[\alpha]^{25}D$ +18.2° (2% in ethanol). The product had $[\alpha]^{25}D$ −22.8° (5% in 3 *N* HCl). Duschinsky and Jeannerat report +23.4° for the L-isomer.[9]

DL-2-Aminobutyric Acid.—A solution of 4.3 g. of carbobenzoxy-DL-2-aminobutyric acid in 15 ml. of nitromethane gave 3.7 g. (theory for monohydrobromide, 3.3 g.)[10] of crystals after treating for three minutes with hydrogen bromide, filtering and washing with ether. These crystals gave 1.52 g. (81%) of unrecrystallized amino acid melting at 287–288° cor.

Anal. Calcd. for $C_4H_9NO_2$: N(AP), 13.59. Found: N(AP), 13.20.

D-2-Aminobutyric Acid.—Treatment of carbobenzoxy-D-2-aminobutyric acid[11] ($[\alpha]^{25}D$ +12.4° (1% in EtOH)) in the same manner as the DL compound gave D-2-aminobutyric acid, m.p. 288–290° dec., cor.; $[\alpha]^{26}D$ −20.9° (4% in 6 *N* HCl).[12]

Carbobenzoxy Peptide Esters.—These were most conveniently prepared by the elegant method developed inde-

(6) M. Bergmann, F. Stern and C. Witte, *Ann.*, **449**, 277 (1926).
(7) E. Dyer and E. Ballard, THIS JOURNAL, **59**, 1697 (1937).
(8) A. Barkdoll and W. Ross, *ibid.*, **66**, 951 (1944).
(9) R. Duschinsky and J. Jeannerat, *Comp. rend.*, **208**, 1359 (1939).
(10) The yields of hydrobromides frequently exceed the theoretical calculated for the monohydrobromide because of ammonium bromide formation.
(11) N. F. Albertson, THIS JOURNAL, **73**, 452 (1951).
(12) J. Greenstein, J. Gilbert and P. Fodor, *J. Biol. Chem.*, **182**, 451 (1950), report a value of −20.7° for the specific rotation at 23°.

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

BY HARRY S. MOSHER, MILTON B. FRANKEL[1,2] AND MARILYN GREGORY[3]

RECEIVED MAY 23, 1953

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).