[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

A New Series of Anticonvulsant Drugs: Branched-Chain α-Aminoacetamides

SIDNEY D. UPHAM[1] AND OTIS C. DERMER

Received January 2, 1957

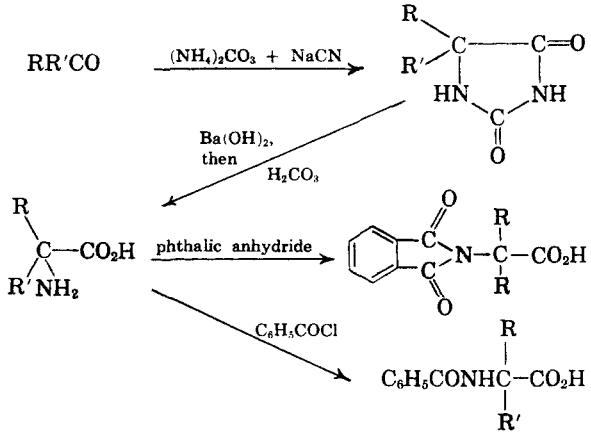
A number of α,α-dialkyl-α-phthalimidoacetamides and α,α-dialkyl-α-benzamidoacetamides have been synthesized from ketones by way successively of the hydantoins, aminoacetic acids, acylaminoacetic acids, and acylaminoacetyl chlorides. The most serious difficulties in this scheme were the resistance of some hydantoins to hydrolysis and of some aminoacetic acids to phthaloylation. Both types of acetamides proved to be highly active anticonvulsants.

The search for new hypnotics, sedatives, and anticonvulsants has led to the production of a number of acid amides and ureides now in medical use. The di- and trisubstituted acetamides and acetylureas in particular have been shown to have value as therapeutic agents. A literature search in this field revealed that while halogen, alkyl, and aryl groups had been used as α-substituents, very little was known about the effect of an amino group in this position. Billman and Hidy[2] postulated that α,α-diphenyl-α-aminoacetamide is a product in the hydrolysis of 5,5-diphenylhydantoin. They accordingly prepared this amide and a number of derivatives and found that some of these compounds possess anticonvulsant and antispasmodic activity. This work was substantiated and extended by R. Duschinsky.[3]

Since the trisubstituted acetamides, as a group, are low in activity when compared to the barbiturates, it was deemed advisable to synthesize a series of α,α-disubstituted-α-aminocetamides in which the amino group is acylated. It was hoped that in such compounds, which contain two or more amide groups, the pharmacological activity would be enhanced. Benzoyl chloride and phthalic anhydride were chosen as acylating agents with the thought that the acyl groups might confer more resistance to elimination by the body and thus produce a longer-acting drug.

The scheme of synthesis used is outlined in Chart I. It was chosen because of the ready availability of the ketones required, as well as the excellence of yields of amino acids. While phthaloylation of natural amino acids by fusion with phthalic anhydride[4] proceeds smoothly and in high yields, such is not the case with the α,α-disubstituted amino acids. Unexpected resistance to reaction and susceptibility to side reaction contributed to the low yields; moreover, much difficulty was met in crystallizing the phthaloylated acids and amides. The considerable effect of the α-benzamido and α-phthalimido groups on the reactivity of the acids and their derivatives was evident when attempts were made to synthesize the ureides. Methods which were successful with α,α-dialkylacetic acids[5] failed to give any ureides when the acylamino acid chlorides were used.

Both the α-benzamido- and α-phthalimidoacetamides proved to be highly active as anticonvulsants when tested by the supramaximal electrocorneal shock test described by Swinyard.[6] Members of the α-phthalimido series were the more active. For 94 rats, the ED_{50} (effective oral dose[6]) for α,α-diethyl-α-phthalimidoacetamide was 13.2 (95% confidence interval estimate, 10.3–16.9) mg./kg., whereas Dilantin showed ED_{50} of 26.5 (16.6–42.3) mg./kg. Tables 3 and 5 show the relative activities of the amides prepared when tested by the above method.



EXPERIMENTAL

Preparation of hydantoins and amino acids. The hydantoins were prepared by the method of Henze and Holder[7] (Table I). Hydrolysis of the hydantoins was carried out in a manner like that of Nadeau and Gaudry.[8] Barium hydroxide (1.5 moles) was dissolved in 1200 ml. of hot water and the hydantoin (0.5 mole) was added and dissolved by stirring. The solution was autoclaved in steam at 50 to 60 lbs/sq.

(1) American Cyanamid Co., Fine Chemicals Division, Princeton, N. J.

(2) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943).

(3) R. Duschinsky, U. S. Patent 2,642,433 (June 16, 1953).

(4) J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.*, **71**, 1856 (1949).

(5) R. W. Stoughton, H. L. Dickison, and O. G. Fitzhugh, *J. Am. Chem. Soc.* **61**, 408 (1939).

(6) E. A. Swinyard, *J. Am. Pharm. Assoc.*, **38**, 201 (1949)

(7) H. R. Henze and C. B. Holder, *J. Am. Chem. Soc.*, **63**, 1943 (1941).

(8) G. Nadeau and R. Gaudry, *Can. J. Research*, **27B**, 421 (1949).

TABLE I

PREPARATION OF 5,5-DISUBSTITUTED HYDANTOINS

Substituents	Me, Et	Et, Et	Me, *iso*-Bu	Me, n-C_5H_{11}	Et, Bu	Me, Ph	Et, Ph	Pentamethylene	*iso*-Pr, *iso*-Pr	*iso*-Bu, *iso*-Bu
Yield, %	55	64	64	54	60	52	38	90	20	12
M.p., °C.	144–5	163	145	101	122–3	194–5	198	215	205	147–8
Lit. m.p., °C.	145–6[a]	165[b]	148[c]	102[c]	[d]	197[e]	199[f]	215[g]	207[c]	[h]

[a] H. T. Bucherer and W. Steiner, ref. 10. [b] G. Errera, *Gazz. chim. ital.*, **26**, I, 197 (1896). [c] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942). [d] H. R. Henze, Document No. 1603, American Documentation Institute, Washington, D. C. [e] K. Abe, *Science Repts. Tokyo Bunrika Daigaku*, Sec A, **2**, 1 (1934). [f] W. T. Read, *J. Am. Chem. Soc.*, **44**, 1746 (1922). [g] H. T. Bucherer and V. A. Libe, *J. prakt. Chem.*, **141**, 5 (1934). [h] A. Lumiére and F. Perrin, *Bull. soc. chim. France*, **35**, 1022 (1924).

in. for 1 to 2 hr. or at 15 to 20 lbs/sq. in. for 15 hr. The mixture was then filtered hot to remove the precipitated barium carbonate and treated with carbon dioxide until a pH of about 7 was reached. The additional barium carbonate thus formed was removed by filtration and the amino acid isolated by vacuum evaporation of the clear filtrate. The amino acids thus obtained were crystalline compounds which were characterized as the phthalimido or benzamido derivatives. Table II lists the amino acids prepared.

TABLE II

PREPARATION OF SUBSTITUTED AMINOACETIC ACIDS

Substituents in Alpha Position	Pressure to Hydrolyze Hydantoin, Lb./Sq. In.	Time, Hr.	Yield, %
Dimethyl[a]	50–60	1	80
Methyl ethyl[a]	50–60	1	70
Diethyl[b]	15	10	67
Methyl isobutyl[c]	15	15	93
Methyl n-pentyl[d]	50–60	1	51
Methyl phenyl[a]	50–60	1	74
Ethyl phenyl[a]	50–60	1	50
Pentamethylene[a,e]	50–60	2	55
Diisopropyl	50–60	1	0
Diisobutyl[b]	50–60	1	11

[a] H. T. Bucherer and W. Steiner, ref. 10. [b] H. Felkin, *Compt. rend.*, **227**, 510 (1948). [c] H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 3121 (1948). [d] New compound, but used as intermediate without analysis. [e] From cyclohexanone; better named 1,3-diazaspiro[4.5]decane-2,4-dione.

5,5-Diphenylhydantoin could not readily be prepared from benzophenone and was obtained by the method of Sikdar and Ghosh.[9] This hydantoin could not be hydrolyzed by the above method but was finally hydrolyzed with 60% sulfuric acid according to the method of Bucherer and Steiner.[10]

Because of difficulty in effecting hydrolysis of 5,5-diisopropyl- and 5,5-diisobutylhydantoin, no further work was done on these compounds.

Phthaloylation of amino acids. This reaction was tried by various methods, including that of Kidd and King.[11] These authors used pyridine as a solvent in which to convert the amino acid and phthalic anhydride to the phthalamic acid, which in turn was cyclized to the phthalimido acid with acetic anhydride. This method gave poor results with the α,α-dialkylated amino acids. Likewise glacial acetic acid as a solvent and Carbitol and toluene as a suspending agent proved useless. The process used finally was that described by Sheehan,[4] who fused phthalic anhydride and natural amino acids together at 175–180° for 15 min. The nature of the alkyl groups on the amino acid affected the ease of phthaloylation greatly, the yields varying between 0 and 70%. Unlike the phthaloylated natural amino acids, the substituted acids gave great difficulty in crystallization, showing a strong tendency to oil out of solution and remain as oils or gums.

The general procedure is given in the following description of the preparation of α,α-diethyl-α-phthalimidoacetic acid. α,α-Diethyl-α-aminoacetic acid (13.3 g., 0.1 mole) was thoroughly stirred into 14.8 g. (0.1 mole) of molten phthalic anhydride. The temperature was then quickly raised to 180° and kept there for 20 min., during which time frothing occurred and water was given off. Clear melts were not obtained although the reaction mixture became fluid. The mixture was then cooled to 100° and treated with 500 ml. of water. The oily suspension was stirred and boiled for 5 min. During this time or on cooling the oil usually set to a solid which was removed by filtration. The solid was then recrystallized from 50% aqueous methanol. Results of various preparations are given in Table III.

TABLE III

PREPARATION AND PROPERTIES OF PHTHALIMIDOACETIC ACIDS

α,α-Dialkyl-α-Aminoacetic Acid, Phthaloylated	Yield, %	Neut. Equiv. Calcd.	Neut. Equiv. Found	M.P., °C.
Dimethyl	76	233	230	152–153[a]
Methyl ethyl	54	247	253	137–138[b]
Diethyl	57	261	258	163–164[c]
Methyl isobutyl	70	275	278	133–135
Methyl phenyl	47	299	304	186–187

[a] S. Gabriel, *Ber.*, **44**, 57 (1911) obtained the value 153–154°, and J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948) gave 152–153°. [b] P. Freytag, *Ber.*, **48**, 648 (1915) found 141.5–143°, and Billman and Harting 139–140°. [c] Freytag found 161–162°.

No phthaloylated acid was formed from α-ethyl-α-phenyl-α-aminoacetic acid but an almost quantitative yield of the diketopiperazine was obtained instead. This result was duplicated repeatedly. The 3,6-diphenyl-3,6-diethyl-2,5-piperazinedione was recrystallized from glacial acetic acid.

(9) J. Sikdar and T. N. Ghosh, *J. Indian Chem. Soc.*, **25**, 109 (1948).

(10) H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, **141**, 5 (1934).

(11) D. A. A. Kidd and F. E. King, *Nature*, **162**, 776 (1948); F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).

TABLE IV

PROPERTIES OF α,α-DIALKYL-α-PHTHALIMIDOACETAMIDES

Alkyl Groups Present	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	M.P., °C.	Oral Dose, Mg./Kg.	Protection Against Maximal Electroshock Seizure[a]
Dimethyl	62.06	62.43	5.17	5.28	12.07	11.91	258–260	50	3+
Methyl ethyl	63.41	63.27	5.69	5.76	11.30	11.35	208	40	4+
Diethyl	64.61	64.63	6.15	6.26	10.76	10.88	190–191	30	4+
Methyl isobutyl	65.69	65.64	6.57	6.98	10.21	10.59	170	200	2+

[a] E. A. Swinyard, ref. 6.

TABLE V

PREPARATION AND PROPERTIES OF BENZAMIDOACETIC ACIDS

α,α-Dialkyl-α-aminoacetic Acid Benzoylated	Yield, %	Neut. Equiv. Calcd.	Neut. Equiv. Found	M.P., °C
Dimethyl	72	207	203	196[a]
Methyl ethyl	54	221	227	204–205[b]
Diethyl	72	235	232	211[c]
Methyl isobutyl	53	249	246	179–180
Methyl *n*-pentyl	57	264	261	131
Methyl phenyl	44	269	263	145–146[d]
Ethyl phenyl	85	283	280	180–181
Pentamethylene	13.5	247	244	190–191[e]

[a] The literature values vary: 198°, E. Mohr and T. Geis, *Ber.*, **41**, 798 (1908) and *J. prakt. Chem.*, (2) **81**, 56 (1910); 199°, G. Heller and H. Lauth, *Ber.*, **52**, 2302 (1919); 193–198°, J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, **66**, 538 (1944); 202°, R. E. Steiger, ref. 13; 196–197°, E. Shaw and J. McDowell, *J. Am. Chem. Soc.*, **71**, 1691 (1949). [b] M. D. Slimmer, *Ber.*, **35**, 400 (1902) gave the value 198–199° and A. Kjaer, *Acta Chem. Scand.*, **7**, 889 (1953), 196°. [c] Kjaer found 210°. [d] Kjaer found 146–147°. [e] H. T. Bucherer and W. Steiner, ref. 10, found 190°.

tallized from 1-butanol and then aqueous methanol, m.p. 220° (lit.,[12] 225°).

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.51; H, 4.49; N, 4.86. Found: C, 79.85; H, 5.07; N, 4.69.

Although phthaloylation of α-methyl-α-*n*-pentyl-α-aminoacetic acid seemed to take place, the product could not be crystallized. Attempts were made to form the amide from the oil.

α,α-Dialkylated-α-phthalimidoacetamides. The acid chlorides of the substituted acetic acids were prepared by suspending the acids in benzene with an equivalent weight of PCl_5 and refluxing for 0.5 hr. The benzene was removed by vacuum distillation and enough dry dioxane added to the residue to dissolve the acid chloride. This solution was then dipped into concentrated aqueous ammonia at 0° with stirring to form the amide. The oily α-methyl-α-*n*-pentyl-α-phthalimidoacetic acid treated by the standard procedure gave a gummy reaction mixture which could not be crystallized. Yields varied considerably and difficulty was again encountered in crystallization. Amides formed are listed in Table IV.

α,α-Dialkyl-α-benzamidoacetic acids and their amides. These acids were prepared by the excellent method of Steiger.[13] No difficulty nor abnormality was encountered except with α,α-diphenyl-α-aminoacetic acid, the sodium salt of which was so insoluble that reaction with benzoyl chloride would not take place. Acids prepared are listed in Table V.

TABLE VI

PROPERTIES OF α,α-DIALKYL-α-BENZAMIDOACETAMIDES

Alkyl Groups Present	N, % Calcd.	N, % Found	M.P., °C	Oral Dose, Mg./Kg.	Protection Against Maximal Electroshock Seizure[a]
Dimethyl	13.60	13.58	199[b]	50	3+
Methyl ethyl	12.72	12.44	158[c]	44	1+
Diethyl	11.96	12.21	211–212[d]	500	3+
Methyl isobutyl	11.28	11.03	145–148	44	1+
Methyl *n*-pentyl	10.68	10.35	125	500	4+
Methyl phenyl	10.44	9.90	127[e]		
Ethyl phenyl	9.92	9.54	99	250	2+
Pentamethylene	11.38	11.12	187	200	4+

[a] E. A. Swinyard, ref. 6. [b] E. Mohr and T. Geis, *Ber.*, **41**, 798 (1908) gave 201°. [c] Kjaer, *Acta Chem. Scand.*, **7**, 889 (1953) gave 161–162°. [d] Kjaer gave 198–200°. [e] Kjaer gave 129–130°.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.84; N, 8.70. Found: C, 74.13; H, 7.05; N, 8.54.

α,α-Pentamethylene-α-aminoacetic acid was recovered unchanged from the phthaloylation mixture. α,α-Diphenyl-α-aminoacetic acid underwent decarboxylation as well as phthaloylation, giving *N*-benzohydrylphthalimide, recrys-

The acid chlorides and amides of the benzamido compounds were prepared in the manner described for the

(12) G. Vanags, *Acta Univ. Latviensis Kim. Fakultat.*, Ser. 4, No. 8, 405 (1939); *Chem. Abstr.*, **34**, 1982 (1940).

(13) R. E. Steiger, *J. Org. Chem.*, **9**, 396 (1944).

phthalimido amides. Crystalline amides prepared are listed in Table VI.

Acknowledgment. The authors gratefully acknowledge the kind assistance of Dr. Raymond Cunningham, Mr. Frank Smith, and Mr. Charles Rauh of the Pharmacology Department of Lederle Laboratories Division of American Cyanamid Company, who performed the pharmacological tests. The authors are also indebted to Mr. Louis Branconne who performed the analysis. Finally they wish to thank the Lederle Laboratories Division of American Cyanamid Company for financial support of the work in the form of a research fellowship.

STILLWATER, OKLA.

[CONTRIBUTION FROM THE "LABORATORIO DE QUÍMICA BIOLÓGICA," FACULTAD DE CIENCIAS MÉDICAS AND THE "LABORATORIO DE QUÍMICA ORGÁNICA," FACULTAD DE CIENCIAS EXACTAS Y NATURALES]

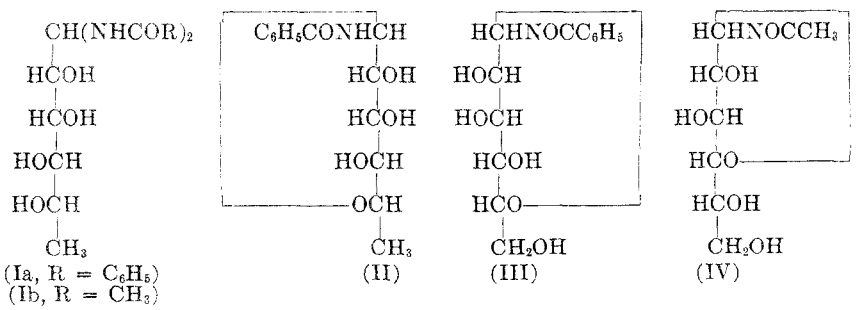
Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. IV. Derivatives of L-Rhamnose

JORGE O. DEFERRARI AND VENANCIO DEULOFEU

Received January 14, 1957

Tetrabenzoyl-L-rhamnose, on treatment with ammonia in methanol gave two products, *N,N'*-dibenzoyl-L-rhamnosylidenediamine and *N*-benzoyl-L-rhamnopyranosylamine. The products are analogous to those obtained previously from pentabenzoyl-D-mannose. Both tetraacetyl-L-rhamnose and pentaacetyl-7-desoxy-1-*glycero*-L-*gala*-heptononitrile, on treatment with ammonia in methanol, gave *N,N'*-diacetyl-L-rhamnosylidenediamine.

The formation of *N,N'*-diacetyl- and *N,N'*-dibenzoylhexosylidenediamines as the principal products, by the action of alcoholic ammonia on pentaacetyl- and pentabenzoylhexoses, is a general reaction which has been applied with success to derivatives of D-glucose,[1] D-mannose,[2] and D-galactose.[3] It has now been applied to tetraacetyl- and tetrabenzoyl-L-rhamnose, which is interesting for various reasons. In L-rhamnose, according to the mechanism of this reaction[4] only three acyl groups can participate in the intramolecular displacement and supply the elements for the formation of the amide molecules. Furthermore, benzoyl derivatives of this hexose, pentabenzoyl-D-mannose and hexabenzoyl-D-*glycero*-D-*gala*-heptononitrile, have a particular place in this reaction because they produce, at variance with the other hexoses, not only *N,N'*-dibenzoyl-D-mannosylidenediamine but also a cyclic monobenzamide compound, *N*-benzoyl-D-mannopyranosylamine.[2,5] Similar products were obtained when tetrabenzoyl-L-rhamnose was submitted to the ammonolysis. The principal one was *N,N'*-dibenzoyl-L-rhamnosylidenediamine (Ia) accompanied by *N*-benzoyl-L-rhamnopyranosylamine (II) in smaller amounts. L-Rhamnose was also present.



L-rhamnose has the same steric relationship in the asymmetric carbon atoms as D-mannose. The

That the *N*-benzoyl-L-rhamnosylamine and the *N*-benzoyl-D-mannosylamine (III) have a pyranose structure was determined by periodate oxidation. Each consumed two moles of periodate with production of one mole of formic acid; no formaldehyde was detected. For comparison purposes we studied the oxidation of *N*-acetyl-D-glucoforanosylamine (IV), to which a furanose structure was

(1) V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1093 (1952).

(3) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1097 (1952).

(4) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, **71**, 1579 (1949); V. Deulofeu and J. O. Deferrari, *Anales. Asoc. Quím. Argentina*, **38**, 241 (1950); R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Am. Chem. Soc.*, **82**, 1840 (1950).

(5) P. Brigl, H. Mühlschlegel, and R. Schinle, *Ber.*, **64**, 2921 (1931).