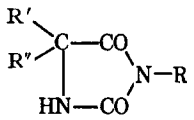
New Compounds: Derivatives of Some Imido Compounds Likely to Possess Therapeutic Activity

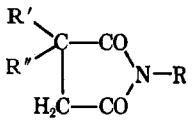
By S. EL-ZANFALLY, M. KHALIFA, and Y. M. ABOU-ZEID

The synthesis of certain *N*-alkylated derivatives of hydantoin, barbituric acid, succinimide, and glutarimide is described. The alkylation was achieved either by direct fusion of the imide with the halo compound in the presence of anhydrous potassium carbonate or by heating the sodio derivative of the imide with the halo compound in the presence of dimethylformamide as solvent. In the case of barbiturates, a dialkylated product was always obtained even when equimolecular amounts of reactants were used.

ALKYLATION of the imido nitrogen in hydantoins, barbiturates, succinimides, and glutarimide has recently become the subject of several patents. The vast majority of these *N*-substituted derivatives have been prepared as potent sedatives, analgesics, and hypnotics (1, 2). Motivated, in part, by the desire of producing other such new derivatives and in the light of what has been reported on the analgesic properties of *N*-substituted saccharin (3) and phthalimide (4), the authors decided to synthesize derivatives of hydantoins, barbiturates, succinimides, and glutarimide with the *N*-alkyl grouping containing the saccharino or phthalimido moieties.[1]



I

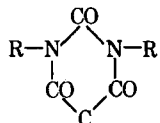


II

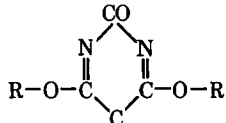
Derivatives having the above general formulas were synthesized by condensing the imido compound with β-substituted ethyl bromide. β-Saccharino ethyl bromide and ω-bromophenacetin were prepared according to reported procedures (5, 6). On the other hand β-phthalimido ethyl bromide was prepared from potassium phthalimide and ethylene bromide applying Gabriel's procedure after being modified by the use of dimethylformamide as solvent. As a result the dark colored reaction tars—frequently accompanying the Gabriel reaction—were completely excluded and a product of high purity was obtained. 5,5-Disubstituted hydantoins were synthesized from the appropriate ketones by decomposing the bisulfite addition products with potassium cyanide and heating the cyanohydrins, thus obtained, with ammonium carbonate (7). Glutarimide was obtained by fusing a mixture of glutaric anhydride and ammonium carbonate for 30 min. only instead of passing gaseous ammonia in the molten anhydride (8) or heating glutaric acid with concentrated ammonium hydroxide solution for 7 hr. (9). This modification, besides improving the yield, resulted in a considerable reduction in the reaction time.

Condensation of the imides with the halides was realized *via* two different procedures: (*a*) direct fusion of the starting materials in the presence of anhydrous potassium carbonate, and (*b*) heating the sodio derivative of the imide with the halo compound in the presence of dimethylformamide. Procedure *b*, which is essentially that described for the *N*-alkylation of saccharin, proved to be superior to *a* since through its application many of the compounds not obtainable by Procedure *a* were successfully prepared.

When sodium barbital was condensed with β-saccharino ethyl bromide according to Procedure *b*, two molecules of the latter condensed with one molecule of the former although equimolecular quantities of the reactants were used. For such a condensation product two structures, III*a* and III*b*,



III*a*



III*b*

are theoretically possible. A choice between the two structures was made possible by infrared analysis[2] because the observed frequencies of about 1776 and 1675 cm.$^{-1}$ may be ascribed to the 4- and 2-position carbonyls, respectively, of Structure III*a* (10, p. 221). On the other hand, the strong sharp band at 768 cm.$^{-1}$ may be assigned to the out-of-plane deformation vibration of the four adjacent ring hydrogen atoms (10, p. 77). Furthermore, the strong sharp bands at 1193 cm.$^{-1}$ and 1211 cm.$^{-1}$ may be attributed to the structure $Et_2C<$ by analogy with the structure $Me_2C<$ which absorbs at 1195 and 1210 cm.$^{-1}$, respectively (10, p. 26). Finally, it has been reported (11) that although the alkali salts of 5,5-dialkyl barbituric acids are known to exist in the enolic form, alkyl products prepared from them are known to occur only in the keto form; a fact which supports Structure III*a*.

EXPERIMENTAL

***N*-(β-Bromoethyl) Phthalimide**—This compound

Received January 30, 1968, from the Faculty of Pharmacy, Cario University, Cario, U.A.R.

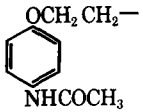
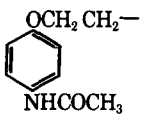
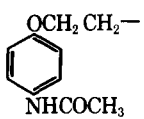
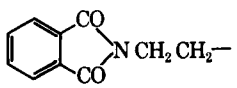
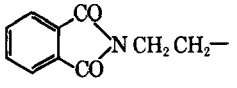
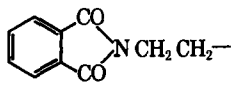
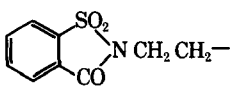
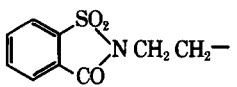
Accepted for publication May 2, 1968.

The authors express their appreciation to J. R. Geigy, S.A., Basle, Switzerland, and to Bayer, Leverkusen, Germany, for a donation of 1 kg. of dimethylformamide from each.

[1] The products at present are under preliminary screening for possible sedative and hypnotic action or any other possible pharmacological activity.

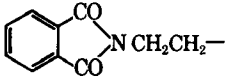
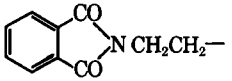
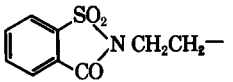
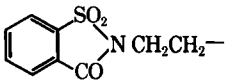
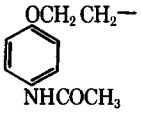
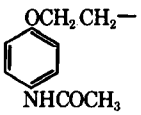
[2] The infrared spectra were determined on a 300-mg. KBr disk containing 1 mg. of sample. The spectra were run on a Perkin-Elmer model 21.

TABLE I—METHODS OF PREPARATION, SOLVENTS OF CRYSTALLIZATION, YIELDS, MELTING POINTS, AND ANALYSES FOR SOME *N*-SUBSTITUTED IMIDO COMPOUNDS

Chemical Name	R	R′	R″	Method of Preparation	Yield, %	Solvent of Crystallization[a]	M.p., °C.[b]	Formula	Anal.,[c] % Calcd.	Found
				***N*-Substituted Hydantoins (I)**						
3-[β-(*p*-Acetamidophenoxy) ethyl]-5,5-dimethyl-hydantoin		CH_3	CH_3	*b*	66	B	189–191	$C_{15}H_{19}N_3O_4$	N 13.77	N 13.27
3-[β-(*p*-Acetamidophenoxy) ethyl]-5,5-diphenyl-hydantoin		C_6H_5	C_6H_5	*b*	95	A	208–210	$C_{25}H_{23}N_3O_4$	C 69.92 H 5.36 N 9.49	C 70.49 H 5.71 N 9.50
3-[β-(*p*-Acetamidophenoxy) ethyl]-5-ethyl-5-methyl-hydantoin		C_2H_5	CH_3	*a*	70	C	174–175	$C_{16}H_{21}N_3O_4$	C 60.18 H 6.58 N 13.16	C 59.82 H 6.75 N 13.19
3-(β-Phthalimidoethyl)-5,5-dimethylhydantoin		CH_3	CH_3	*a*	42	D	189–190	$C_{15}H_{15}N_3O_4$	C 59.80 H 4.98 N 13.95	C 59.71 H 4.92 N 13.72
3-(β-Phthalimidoethyl)-5,5-diphenylhydantoin		C_6H_5	C_6H_5	*b*	70	A	236–237	$C_{25}H_{19}N_3O_4$	N 9.88	N 9.78
3-(β-Phthalimidoethyl)-5-ethyl-5-methylhydantoin		C_2H_5	CH_3	*a*	42	B	163–165	$C_{16}H_{17}N_3O_4$	C 60.95 H 5.39 N 13.33	C 60.63 H 5.94 N 13.27
3-(β-Saccharinoethyl)-5,5-dimethylhydantoin		CH_3	CH_3	*b*	43	A	200–201	$C_{14}H_{16}N_3O_5S$	C 49.85 H 4.45 N 12.46	C 49.89 H 5.00 N 12.15
3-(β-Saccharinoethyl)-5,5-diphenylhydantoin		C_6H_5	C_6H_5	*b*	90	A	238–240	$C_{24}H_{19}N_3O_5S$	N 9.11	N 8.82

(*Continued on next page.*)

TABLE I (*Continued.*)

Chemical Name	R	R′	R″	Method of Preparation	Yield, %	Solvent of Crystallization[a]	M.p., °C.[b]	Formula	Anal.,[c] % Calcd.	Found
				***N*-Substituted Succinimides (II)**						
N-(β-Phthalimidoethyl)-α-phenylsuccinimide		C_6H_5	H	*b*	38	D	143–145	$C_{20}H_{16}N_2O_4$	C 68.96 H 4.60 N 8.04	C 69.25 H 4.54 N 7.86
N-(β-Phthalimidoethyl)-succinimide		H	H	*a*	50	D	162–163	$C_{14}H_{12}N_2O_4$	C H N 10.29	C H N 10.14
N-(β-Saccharinoethyl)-α-phenylsuccinimide		C_6H_5	H	*b*	33	A	173–174	$C_{19}H_{16}N_2O_5S$	C 59.37 H 4.17 N 7.29	C 59.62 H 4.86 N 7.11
N-(β-Saccharinoethyl)-succinimide		H	H	*b* & *a*	40 60	D	219–220	$C_{13}H_{12}N_2O_5S$	C 50.65 H 3.89 N 9.09	C 50.76 H 3.95 N 9.43
N-(β-Saccharinoethyl)glutarimide				*a*	25	A	200–201	$C_{14}H_{14}N_2O_5S$	C H N 8.69 S 9.94	C H N 9.23 S 9.58
α-(*p*-Acetamidophenoxy)-β-saccharinoethane				*b*	43	A	163–164	$C_{17}H_{16}N_2O_5$	C 56.66 H 4.44 N 7.77	C 56.62 H 5.23 N 7.22
ω-Phthalimidoethyl salicylate				*b*	81	A	139–141	$C_{17}H_{13}NO_5$	C 65.59 H 4.18 N 4.50	C 65.34 H 4.84 N 4.58
ω-Saccharinoethyl salicylate				*b*	82	A	138–140	$C_{16}H_{13}NO_6S$	C 55.33 H 3.74 N 4.03	C 54.93 H 4.15 N 4.04
				***N*-Substituted Barbiturates (IIIa)**						
1,3-Bis[β-(*p*-Acetamidophenoxy)ethyl]-5,5-diethylbarbituric acid		C_2H_5	C_2H_5	*b*	50	B	165–167	$C_{28}H_{34}N_4O_7$	C 62.45 H 6.32 N 10.41	C 62.79 H 6.93 N 10.48
1,3-Bis[β-(*p*-Acetamidophenoxy)ethyl]-5-ethyl-5-phenylbarbituric acid		C_2H_5	C_6H_5	*b*	55	A	219–220	$C_{32}H_{34}N_4O_7$	C 65.53 H 5.79 N 9.56	C 65.02 H 6.17 N 9.56

(*Continued on next page.*)

TABLE I (*Continued.*)

Chemical Name	R	R′	R″	Method of Preparation	Yield, %	Solvent of Crystallization[b]	M.p., °C.[b]	Formula	Anal.,[c] % Calcd.	Found
1,3-Bis(β-Phthalimidoethyl)-5,5-diethylbarbituric acid		C_2H_5	C_2H_5	*b*	41	A	184–185	$C_{28}H_{28}N_4O_7$	C 63.39 H 4.90 N 10.56	C 62.89 H 4.99 N 10.54
1,3-Bis(β-Saccharinoethyl)-5,5-diethylbarbituric acid		C_2H_5	C_2H_5	*b*	65	B	187–188	$C_{28}H_{28}N_4O_8S_2$	C 51.82 H 4.32 N 9.30 S 10.60	C 51.89 H 4.39 N 9.72 S 9.61
1,3-Bis(β-Saccharinoethyl)-5-ethyl-5-phenylbarbituric acid		C_2H_5	C_6H_5	*b*	47	A	199	$C_{30}H_{28}N_4O_8S_2$	C 55.38 H 4.00 N 8.61 S 9.84	C 55.67 H 4.16 N 9.80 S 9.70

[a] A, ethyl alcohol; B, aqueous ethyl alcohol; C, water; D, dilute acetic acid. [b] All melting points are uncorrected. [c] The microanalyses were performed by Dr. C. Janssen, Beerse, Belgium, and by El-Nasr Company, U.A.R.

was prepared in 70% yield from potassium phthalimide and ethylene bromide applying Gabriel's procedure with the modification of using dimethylformamide as solvent. The heating and occasional shaking was continued for 2 hr. at 130°. The product crystallized from aqueous ethanol melted at 80–81° as reported (12).

Glutarimide—This compound was obtained in 75% yield by fusing glutaric anhydride with ammonium carbonate for 0.5 hr. Crystallization from acetone yielded a product melting at 150–151°. Reported yield and melting point are 63% and 145–146°, respectively (9).

Procedures for Final Compounds—The final compounds were obtained *via* two different procedures according to the following general directions.

Direct Fusion Method—The imide (1 mole), the halo compound (1 mole), and anhydrous potassium carbonate (0.5 mole) were mixed and heated gently to a state of quiet fusion in a small flask fitted with an air condenser. The heating and occasional shaking were continued for 2 hr. After being cooled, the hard brown glossy mass was dissolved in boiling diluted acetic acid and the product which separated on cooling was filtered and crystallized from the appropriate solvent (see Table I).

Dimethylformamide Method—A mixture of equimolecular amounts of the sodio derivative of the imide and the halo compound was suspended in dimethylformamide (about 5 ml. solvent per 1 g. of mixture) and heated under reflux at 120–130° for 2 hr. with occasional shaking. The product which separated on pouring the cold reaction mixture onto crushed ice was filtered, dried, and crystallized from the appropriate solvent (see Table I).

REFERENCES

(1) Rowe, E. J., and Weinswig, M. H., *J. Pharm. Sci.*, **53**, 226(1964).

(2) Granger, R., and Giroux, J., French pat. 1,273,867 (1962).

(3) Grogan, C. H., and Rice, L. M., U. S. pat. 2,751,392 (1956).

(4) Kirchner, F. K., and Cavallito, C. J., U. S. pat 2,498,497 (1950).

(5) Rice, H. L., and Petit, G. R., *J. Am. Chem. Soc.*, **76**, 302(1954).

(6) Hinsberg, O., *Ann.*, **305**, 283 (1899).

(7) Bucherer, H. T., and Steiner, W., *J. Prakt. Chem.*, **140**, 291(1934).

(8) Crouch, W. W., and Lockte, H. L., *J. Am. Chem. Soc.*, **65**, 271(1943).

(9) Buckles, R. E., and Probst, W., *J. Org. Chem.*, **22**, 1728(1957).

(10) Bellamy, L. J., "The Infrared Spectra of Complex Molcules," Wiley, New York, N. Y., 1958, pp. 221, 77, and 26.

(11) Dox, A. W., and Jones, E. G., *J. Am. Chem. Soc.*, **51**, 316(1959).

(12) "Organic Synthesis," 2nd ed., Coll. vol. I, Wiley, New York, N. Y., 1941, p. 120.

Keyphrases

Alkylated imido derivatives—synthesis
Condensation reaction alkylation, imido derivatives
IR spectrophotometry—structure