Synthesis of Amides of Diphenic Acid as Potential Antispasmodic Agents

By GLENN L. JENKINS, CHARLES S. DAVIS, ADELBERT M. KNEVEL, and DAVID S. YODER†

Twenty-six new amides of diphenic acid have been synthesized as potential antispasmodics. All of the described compounds were screened for pharmacological activity; none of the new structures demonstrated significant antispasmodic activity to warrant further investigation. Details of the pharmacological screening will be reported by G. K. W. Yim in another paper.

It is well documented that many compounds containing the ester group have demonstrated pharmacological activity as antispasmodics and local anesthetics. Since the amide group is quite similar to the ester both chemically and pharmacologically, it might be expected that the amides of diphenic acid would produce "active" compounds (1, 2). In some instances in which the ester group has been substituted by an amide group (as in the case of procainamide) the pharmacological action has been prolonged and the toxicity reduced. The prolonged activity has been attributed to the slow rate of hydrolysis of the amide as compared to the ester (3).

Diphenic acid as an inert nontoxic substance (4) has properties which may make it desirable as a carrier of pharmacologically active groups. Demers and Jenkins (5) prepared a number of derivatives of diphenic acid which were found to possess spasmolytic activity about equal to that of atropine (6).

EXPERIMENTAL

Diphenic acid was prepared by the method of Atkinson and Lawler (7) with the modification of Demers and Jenkins (5). Diphenic anhydride was prepared by the general procedure of Roberts and Johnson (8). Diphenic acid, diphenimide, and the monoethyl ester of diphenic acid were prepared by the methods of Underwood and Kochmann (9). Potassium diphenimide was prepared by reacting equimolar quantities of potassium ethoxide in anhydrous ethanol with diphenimide; ethyl diphenoyl chloride by the procedure described by Demers and Jenkins (5). The amines used for this investigation were supplied through the courtesy of Union Carbide and Carbon; β-diethylaminoethyl chloride HCl and β-dimethylaminoethyl chloride HCl were supplied through the generosity of the Michigan Chemical Corp. The dialkylaminoalkyl chlorides not commercially available were synthesized by the method of Mason and Block (10) and according to Adams and Whitmore (11). Liberation of the "free" chloro-base compounds from the hydrochloride salts was accomplished by the procedure of Burtner (12).

It is interesting to note that in the attempted preparations of diphenimide derivatives the imide ring opened to produce an ester and an amide. The product formed was identical to that prepared from the ester-acid chloride reaction.

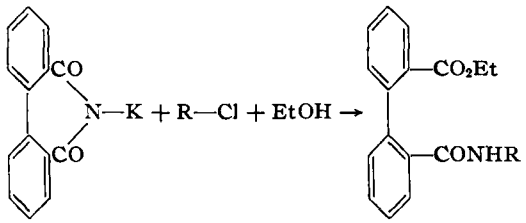

Table I lists the amide derivatives synthesized by one of the following procedures.

Procedure A

Ethyl N-(Dialkylaminoalkyl)-diphenamate.—To 100 ml. of anhydrous ethyl alcohol was added 43 m*M* of metallic potassium with cooling. A 43-m*M* quantity of diphenimide was added to the potassium ethoxide solution. After the diphenimide had dissolved, 43 m*M* of the appropriate dialkylaminoalkyl chloride was added and the mixture was refluxed for 12–14 hours. At the conclusion of the reflux period, a white precipitate formed which was removed by filtration. The filtrate was concentrated under vacuum and the residue taken up in anhydrous ether. Dry hydrogen chloride was passed into the etheral extract; a white precipitate formed, which crystallized upon standing. The crystals were collected, dried, and recrystallized.

Procedure B

Ethyl N-(Dialkylaminoalkyl)-diphenamate.—To 25 m*M* of ethyl diphenoyl chloride in 20 ml. of dry benzene was added slowly 25 m*M* of the appropriate dialkylaminoalkylamine in 10 ml. of dry benzene with stirring and cooling in an ice bath. After completion of the reaction, the mixture was cooled overnight in a refrigerator. If the product did not crystallize, the syrupy residue was treated with fresh portions of cold dry ether until a precipitate was formed. The crystals were collected, dried, and recrystallized.

Procedure C

Ethyl N-Alkyldiphenamate.—A 25-m*M* quantity of ethyl diphenoyl chloride was added with stirring and cooling to 50 m*M* of alkylamine in 10 ml. of dry benzene or chloroform. After the mixture was allowed to stand overnight in a refrigerator, the

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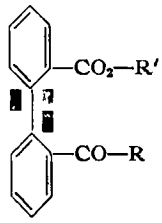
† Present address: Mead-Johnson and Co., Evansville, Ind.

TABLE I.—AMIDES OF DIPHENIC ACID



R	R′	Yield, %	M.p., °C.[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Method of Synthesis
Diethylaminoethylamino . HCl	Ethyl	60	161–162	6.91	6.96	A
Dimethylaminoethylamino . HCl	Ethyl	74	159–160	7.45	7.33	A
Pyrrolidinoethylamino . HCl	Ethyl	43	120–121	6.95	6.97	A
Piperidinoethylamino . HCl	Ethyl	46	156–157	6.73	7.02	A
Morpholinoethylamino . HCl	Ethyl	40	147–149	6.70	6.95	A
Diethylaminopropylamino . HCl	Ethyl	51	140–141	6.70	6.85	A and B
Piperidinopropylamino . HCl	Ethyl	47	131–132	6.50	6.39	A
Dimethylaminopropylamino . HCl	Ethyl	60	124–126	7.17	7.42	B
Di-*n*-butylamino	Ethyl	70	51–52	3.67	3.60	C
Di-*n*-butylamino	H	57	140–142	3.79	3.59	E
2-Hydroxyethylamino	Ethyl	67	88–89	4.47	4.30	C
N,N-di-(2-hydroxyethyl)amino	Ethyl	54	84–85	3.92	3.93	C
2-Hydroxypropylamino	Ethyl	80	93–95	4.28	4.30	C
N,N-(Di-isobutyl)amino	H	38	206–208	3.79	3.59	E
N,N-(Di-isopropyl)amino	H	21	185–186	4.10	3.95	E
N,N-Diphenylamino	Ethyl	55	136–137	3.32	3.40	D
Morpholino	H	81	250–251	4.50	4.37	E
Piperidino	H	75	157–159	4.52	4.40	E
2-Methylpiperidino	H	68	161–162	4.32	4.43	E
N′-Methylpiperazino	H	65	254–256	8.63	8.51	E
Pyrrolidino	H	81	206–208	4.74	4.62	E
Pyrrolino	H	72	188–189	4.77	4.63	E
N,N-Diallylamino	H	80	124–126	4.36	4.30	E
2,6-Dimethylmorpholino	H	62	201–205	4.13	4.00	E
N,N-Dimethylamino	H	61	160–163	5.20	5.39	E
N,N-Diethylamino	H	70	179–181	4.71	4.53	E

[a] All melting points are corrected.

precipitate of alkylamine hydrochloride was filtered. The filtrate was partially evaporated and the amide was induced to crystallize by the addition of petroleum ether. The crystals were collected, dried, and recrystallized.

Procedure D

Ethyl N,N-Diphenyldiphenamate.—To a solution of 22 m*M* of ethyl diphenoyl chloride in 25 ml. of dry benzene was added 80 m*M* of dipnenylamine dissolved in 25 ml. of dry benzene. The mixture was refluxed for 10 hours; then the benzene solvent was removed under vacuum. The resulting residue was cooled overnight and then washed with cold methyl alcohol. The gummy solid was recrystallized from an aqueous methanol mixture to produce white crystals.

Procedure E

N,N-Dialkyldiphenamic Acid.—One-hundred millimoles of N,N-dialkylamine was added slowly with rapid stirring to 22 m*M* of diphenic anhydride. Heat was evolved and the mixture turned a brown color. Upon cooling, the reaction mixture was washed with ether to remove the excess amine. The residue was then dissolved in water and filtered. The filtrate was diluted with 150 ml. of water and then acidified with 10% hydrochloric acid. Upon standing, a precipitate was formed which could be further purified by recrystallizing from ethyl alcohol and water.

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