TABLE I—PHYSICAL AND CHEMICAL CHARACTERISTICS OF SIX PROTEIN FRACTIONS

Fraction	Mobilities, cm.²/sec. v.	Sugars	U.V. Abs. Maxima mμ	Nitrogen, %	Ash Content, %
a	1.07×10^{-6}	Mannose, fructose	204, 208	12.8	1.5
b	6.4×10^{-7}	Mannose, rhamnose	204, 265	11.6	1.5
c	2.2×10^{-6}	Mannose, glucosamine	204, 280	5.7	3.9
d	1.2×10^{-6}	Mannose, glucosamine	204, 280	6.2	0
e	1.2×10^{-6}	Mannose, glucosamine	204, 265	13.6	6.0
f	1.6×10^{-6}	Mannose, glucosamine rhamnose	204, 240, 280	14.08	6.0

TABLE II—PRELIMINARY AMINO ACID ANALYSIS OF *Caesalpinia* PROTEINS

Amino Acids	% μm. of Amino Acids I	II	III	IV
Aspartic acid	10.5	6.01	10.7	10.5
Threonine	6.04	7.66	5.81	5.08
Serine	6.66	13.00	5.88	6.01
Glutamic acid	16.20	7.18	13.60	15.80
Proline	5.02	3.32	4.90	4.95
Glycine	11.30	7.62	10.1	9.73
Alanine	8.89	13.3	10.9	8.90
Cystine	2.82	0.522	0.783	1.02
Valine	5.07	3.72	6.57	6.05
Methionine	1.04	0.522	1.52	1.27
Isoleucine	3.22	1.62	4.28	4.23
Leucine	6.02	3.53	7.75	7.87
Tyrosine	2.23	0.731	2.01	2.25
Phenylalanine	3.19	1.25	3.75	3.64
Lysine	3.99	2.41	3.21	3.57
Histidine	1.51	0.731	1.59	1.78
Arginine	6.24	1.51	5.95	6.73
Glucosamine	...	1.50[a]	0.644	0.454
Hydroxyproline	...	23.8[a]	...	...

[a] Estimated values.

1540 cm.$^{-1}$. Table II represents the results of an amino acid analysis using a Beckman analyzer model 120B.

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Synthesis of Some Substituted Amides of Terephthalic and Isophthalic Acids

By JOSEPH P. LAROCCA* and MOHAMED A. Y. SHARKAWI†

The syntheses of 14 diamide derivatives of terephthalic acid and six diamide derivatives of isophthalic acid are described. Evaluation of reaction conditions and solvent systems led to the use of anhydrous ether at 0° as the preferred method of preparing these amides from the corresponding acid chloride and amine. Preliminary pharmacological screening is reported.

A LARGE NUMBER of drugs are available which depress the central nervous system. These drugs elicit sedative, hypnotic, anticonvulsant, and psychotherapeutic effects. Many of these drugs contain a carbonyl-nitrogen-carbonyl group-

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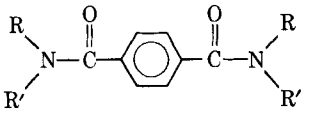
TABLE I—SELECTION OF SOLVENT FOR DIAMIDE SYNTHESIS: AMINE WITH TEREPHTHALOYL CHLORIDE

Method	Solvent	Amine	% Yield[a]	Reaction Temp.
A	Aq. NaOH	Propyl	52.4	...
B	CCl_4	Propyl	58.4	24°
C	Diethyl ether	Propyl	76.6	20°
	Diethyl ether	Di-*n*-butyl	74.7	20°
D	No solvent	Di-*n*-butyl	82.4	[b]

[a] Based on crude yield. [b] Vigorous exothermic reaction with discoloration. Difficulties in purification made this procedure less desirable.

ing; however, similar effects have been noted in other compounds such as simple amides, *N*-substituted amides, dehydes, alalcohols, and glycols. The anticonvulsant *N*-benzyl-2-chloropropionamide is an example of such a compound (1). Numerous *N*-substituted amides have been synthesized in this laboratory and reported in the literature (2–6). Since these compounds have shown various degrees

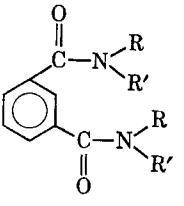
TABLE II—AMIDES OF TEREPHTHALIC ACID



No.	R	R′	% Yield	M.p., °C.[a]	%N Calcd.	%N Found
1	Hydrogen	*n*-Propyl	75.7	243–244	11.29	10.85 11.12
2	Hydrogen	*i*-Propyl	65.3	285–286	11.29	11.18 11.25
3	*n*-Propyl	*n*-Propyl	74.1	103.5–104	8.43	8.31 8.33
4	*i*-Propyl	*i*-Propyl	73.4	274–275	8.43	8.46 8.46
5	Hydrogen	*n*-Butyl	68.1	225–226	10.14	10.03 10.07
6	*n*-Butyl	*n*-Butyl	74.7	81.5–82.5	7.21	8.14 7.20
7	*i*-Butyl	*i*-Butyl	83.2	133–134	7.21	7.25 7.28
8	Hydrogen	Allyl	57.2	208–210	11.47	11.63 11.39
9	Hydrogen	Phenyl	94.3	340–345	8.86	8.69 8.54
10	Hydrogen	α-Methylbenzyl	65.3	275–278	7.53	7.66 7.36
11	Phenyl	Phenyl	99.1	340–341	5.98	6.29 6.34
12	Hydrogen	Cyclohexyl	34.7	273–275	8.54	8.40 8.34
13	Piperidino[b]		38.3	208–209	9.33	9.05 9.16
14	Morpholino[b]		7.89	212–215	9.21	9.85

[a] All melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. [b] For compounds *13* and *14*, R and R′ together represent piperidine and morpholine, respectively.

TABLE III—AMIDES OF ISOPHTHALIC ACID



No.	R	R′	% Yield	M.p., °C.[a]	% N Calcd.	% N Found
1	Hydrogen	*n*-Propyl	58.4	131–132	11.29	11.33 11.46
2	Hydrogen	*i*-Propyl	56.4	210–211	11.29	11.27 11.32
3	*i*-Propyl	*i*-Propyl	43.9	132–133	8.43	8.37 8.39
4	Hydrogen	*n*-Butyl	71.3	131–132.5	10.14	10.19 10.12
5	*i*-Butyl	*i*-Butyl	88.6	104–105	7.21	7.20 7.19
6	Hydrogen	Allyl	20.5	119–120	11.47	11.30 11.35

[a] Footnote same as Table I.

of activity on the central nervous system, the synthesis of the diamides of terephthalic and isophthalic acids was undertaken.

EXPERIMENTAL

Methods—The best and most general reaction for the preparation of amides has been reported to be the acylation of amines by acyl halides (7). A study of the reaction medium best suited for the synthesis of the desired compounds was undertaken. For this purpose the reaction of terephthaloyl chloride with alkyl amines (propylamine and *N*-di-*n*-butyl amine) was selected for detailed investigation. The results are summarized in Table I.

As a result of these studies anhydrous ether was chosen as the reaction medium. The following procedure was employed for the synthesis of the compounds reported.

A fourfold excess of the amine was dissolved in 100 ml. of anhydrous ether and cooled to 4°. A solution of the chloride (0.05 mole in 150 ml. anhydrous ether) was added slowly with vigorous stirring. The reaction temperature was not allowed to exceed 20° during the addition process. After the addition was complete, the stirring was continued for 15 min. The reaction mixture was stored overnight at 4° during which time the desired product crystallized (if the product failed to crystallize, the ether was removed by evaporation). The crystals or residue obtained were washed with distilled water to remove the amine hydrochloride and recrystallized from 50% ethanol. The melting points, yields, and analytical data for the amides of terephthalic acid are given in Table II, and for the amides of isophthalic acid in Table III.

Pharmacological Survey[1]—The preliminary mouse toxicity study showed that, in general, these compounds are nontoxic and free of any major CNS activity. The *N,N'*-di-*n*-butylterephthalamide and the *N,N,N',N'*-tetra-isopropylisophthalamide were also screened as antidepressants. Although both showed some activity, the activity was not sufficient to warrant further study.

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[1] The authors are indebted to Dr. Warren J. Close, Abbott Laboratories, North Chicago, Ill., for the pharmacological screening.

Multi-Chamber System for Toxicity Studies in Mice at Simulated High Altitude

By I. P. BAUMEL, S. M. ROBINSON, and W. F. BLATT

Plastic desiccators have been adapted to serve as chambers in a simulated high altitude system. The multi-chambered system is convenient for observations of grouped mice or other small animals subjected to decompression. Toxicity data are given for representative drugs at sea level and a simulated altitude of 19,000 ft.

In examining the effects of simulated high altitude on drug toxicity in mice, it was necessary to utilize chambers which could accommodate a group of animals and permit a clear, unobstructed view of them. Accordingly, the authors devised a system incorporating relatively inexpensive plastic desiccators designed for routine laboratory use. The simulated altitude afforded by this system was used to evaluate the lethality to mice of agents representative of various drug classes.

EXPERIMENTAL

Apparatus—The modified spherical desiccators[1] shown in the lower portion of Fig. 1 can be evacuated to below 0.01 μ, a value considerably below that normally required for altitude studies. In single chamber operation, the air valve at the top portion of the chamber was attached directly to a vacuum pump. For air entry, a hole was drilled 2 in. above the level of the porcelain platform in the lower portion of the desiccator, and a suitable tubing adapter was inserted. If desired, additional openings can be made to accommodate separate manometers and/or monitoring equipment.

The operation of several chambers through a multi-port manifold requires the exact duplication of size and length for the air evacuation and entry lines. The $^3/_4$-in. tubing assembly, shown in the top portion of Fig. 1, was devised to serve four chambers. The upper manifold was attached to the pump; the lower section provided for the constant fresh air intake regulated by the control valve. Uniform pieces of thick-walled rubber tubing ($^1/_2$ in.) were used to attach the chambers to the manifold. A $^1/_{12}$-h.p. pump[2] was adequate for establishing a simulated altitude of 19,000 ft. at an air flow of 2.5 L./min. The barometric pressure within the system was monitored by a mercury manometer attached to the end chamber. The unit, during normal operation, is shown in the lower portion of Fig. 1. The speed of ascent was controlled by the air intake valve—more than adequate air flow was maintained at the 1,000

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[1] The Ace Glass Co., Vineland, N.J.

[2] Gelman Co., Ann Arbor, Mich.