cooling, the precipitated sodium chloride was removed by filtration, and the residue was washed with absolute methanol. The filtrate was evaporated under reduced pressure in a rotary evaporator, then crystallized from dilute alcohol to give 21 Gm. of crude material, m.p. 130–145°. This was dissolved in the least amount of hot alcohol and allowed to crystallize. After cooling in an ice bath, 12 Gm. of crystals was collected, m.p. 205–210°. Water was added to the mother liquor until cloudy; after further cooling in an ice bath, a second crop of crystals of another compound was collected (6 Gm.), m.p. 143–147°. This latter material was recrystallized several times from dilute alcohol to give 3 Gm. (8.5%) of product, m.p. 151–152°.

The infrared absorption spectrum of this compound showed a weak absorption peak at 2565 cm.$^{-1}$, indicating the presence of a mercapto group, and a peak at 1635–1640 cm.$^{-1}$, indicating a secondary amide carbonyl group. The mercaptan content of this compound was determined by dissolving in alcohol, adding excess standard iodine solution, and titrating the excess with standard sodium thiosulfate. Three samples of the compound were found to consume 101.1, 100.3, and 101.4% of the amount of iodine theoretically required to oxidize the mercaptan to the corresponding disulfide.

Bis-(2-acetamido-1-phenyl-1-propyl) Disulfide.—The first fraction isolated in the above preparation, m.p. 205–210°, was recrystallized from dilute alcohol to give 8 Gm. (22%) of the disulfide, m.p. 215–216°. The analytical sample was recrystallized further from acetone with no change in melting point. The infrared spectrum showed no absorption in the region of 2550–2600 cm.$^{-1}$, an indication of the absence of a mercapto group. A strong absorption band for the secondary amide carbonyl group was observed at 1635–1640 cm.$^{-1}$.

Anal.—Calcd. for $C_{22}H_{28}N_2O_2S_2$: C, 63.44; H, 6.78; N, 6.73; O, 7.68; S, 15.37. Found: C, 63.01; H, 6.82; N, 6.75; O, 7.82; S, 15.67.

Bis-(2-amino-1-phenyl-1-propyl) Disulfide Dihydrobromide.—*Preparation A.*—A solution of 1 Gm. of bis-(2-acetamido-1-phenyl-1-propyl) disulfide in 30 ml. of ethanol and 20 ml. of concentrated hydrochloric acid was refluxed for 6 hr. The mixture was evaporated under reduced pressure in a rotary evaporator, and the residue was recrystallized from dilute alcohol to give 0.8 Gm. of starting material, m.p. 214–216°, with no depression of melting point upon admixture with the starting material.

Preparation B.—A mixture of 4.2 Gm. (0.01 mole) of bis-(2-acetamido-1-phenyl-1-propyl) disulfide and 25 ml. of concentrated hydrochloric acid was refluxed for 48 hr. After evaporation under reduced pressure in a rotary evaporator, the residue was recrystallized several times from isopropyl alcohol to give 1.5 Gm. (37%) of the hydrochloride salt, m.p. 242–243°. Because of difficulty with solvent of crystallization with this salt, it was converted to the free base, extracted into ether, treated with hydrobromic acid to convert it to the hydrobromide salt, evaporated to dryness, and recrystallized from isopropyl alcohol, m.p. 265–267°.

Anal.—Calcd. for $C_{18}H_{26}Br_2N_2S_2$: C, 43.73; H, 5.29; Br, 32.32; N, 5.67; S, 12.97. Found: C, 43.93; H, 5.25; Br, 32.46; N, 5.50; S, 12.70.

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Synthesis of Some Diamides of 2-Chlorobenzaldehyde, 2,4-Dichlorobenzaldehyde, and 3,4-Dichlorobenzaldehyde

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The synthesis of some *N,N'*-bis-(amido) chlorotoluenes is described. These compounds are prepared by the condensation of various amides with the appropriate chlorinated benzaldehyde.

THE IDEAL antiepileptic drug should be long acting, nonsedating, well tolerated, and effective against the various types of seizures, including mixed types, and devoid of unwanted side effects (1). None of the drugs available meet all the requirements of an ideal antiepileptic drug completely.

Although most antiepileptic drugs currently in use contain a carbonyl-nitrogen-carbonyl grouping, anticonvulsant activity also is found in other compounds, such as simple amides, *N*-substituted amides, aldehydes, and alcohols. *N*-Benzyl-β-chloropropionamide has anticonvulsant activity and is an example of a compound which has a methylene-nitrogen-carbonyl grouping instead of the typical carbonyl-nitrogen-carbonyl group (2). Numerous *N*-substituted amides have been reported in the literature (3, 4). LaRocca and his associates have prepared some chloral and 2,2,3-trichlorobutyraldehyde amides, and LaRocca and Byrum reported the potentiality of the compounds as sedative-hypnotics and anticonvulsants (3, 4). LaRocca reported the synthesis and pharmacological activity of some *N*-(2,2,3-trichloro-1-hydroxypropyl)-amides, of which the acetamide derivative has shown a high degree of anticonvulsant activity (5). These compounds have a hydroxyl-nitrogen-carbonyl instead of the carbonyl-nitrogen-carbonyl group usually found in

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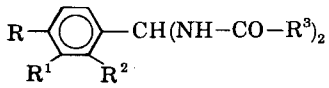
TABLE I.—*N,N'*-BIS-(AMIDO) CHLOROTOLUENES



Compd.	R	R^1	R^2	R^3	M.p.,[a] °C.	Yield, %	N, %[b] Calcd.	N, %[b] Found
1	Cl	H	Cl	Methyl	257	50	10.18	10.03 10.07
2	Cl	H	Cl	Ethyl	230–233	24	9.23	9.23 9.12
3	Cl	H	Cl	Propyl	203–204	20	8.45	8.45 8.48
4	Cl	H	Cl	*i*-Propyl	245–247	23	8.45	8.35 8.34
5	Cl	H	Cl	Butyl	187–189	20	7.79	8.02 8.04
6	Cl	H	Cl	*i*-Butyl	214–216	22	7.79	7.63 8.05
7	Cl	H	Cl	Phenyl	243–245	21	7.01	7.07 7.10
8	H	H	Cl	*i*-Propyl	234–236	15	9.43	9.33 9.10
9	H	H	Cl	Butyl	159–161	31	8.62	8.78 8.49
10	H	H	Cl	*i*-Butyl	227–229	10	8.62	8.90 8.88
11	Cl	Cl	H	Methyl	227–274	36	10.18	10.28 10.28
12	Cl	Cl	H	Ethyl	240–242	30	9.23	9.28 9.08
13	Cl	Cl	H	*i*-Propyl	226–228	10	8.45	8.81 8.12
14	Cl	Cl	H	Butyl	194–196	27	7.79	7.96 7.48
15	Cl	Cl	H	*i*-Butyl	242–245	32	7.79	7.52 8.10
16	Cl	Cl	H	Benzyl	233–235	5	6.55	6.19 6.82

[a] All melting points are uncorrected and were determined by use of a Thomas-Hoover capillary melting point apparatus.
[b] The nitrogen assays were determined with a Hengar-Kjeldahl apparatus using 20–30-mg. samples.

anticonvulsant drugs. As a result of these studies, the synthesis of diamides of various halogenated benzaldehydes was undertaken.

EXPERIMENTAL

Methods.—The condensation of amides with aldehydes has been reported by Bhatnagar and Pandya (6), Pulvermacher (7), Noyes and Forman (8), and LaRocca *et al.* (3).

Condensation of Halogenated Benzaldehydes with Various Amides.—The procedure described for the synthesis of chloral amides (3) was utilized for the preparation of these compounds. A mixture of the halogenated benzaldehyde (0.028 mole) and the appropriate amide (0.056 mole) was heated on a water bath at approximately 100°. Upon heating, the reaction mixture liquified or became moist, then resolidified with further heating for a period of from 1 to 8 hr. Several of the reaction mixtures developed a slight yellow color, which darkened upon continued heating. The solidified mass was pulverized and thoroughly washed with water to remove any unreacted amide. The solid then was recrystallized from dilute alcohol until a constant melting point was obtained. The same procedure was used for all the compounds prepared. The melting points, yields, and analytical data are summarized in Table I.

An extensive pharmacological survey[1] failed to uncover any significant activity. Actions for which the compounds were tested included anticonvulsant, systemic antibacterial, antifungal, antiparasitic, and psychotropic.

SUMMARY

Three new compounds of the type *N,N'*-bis-(amido)-2-chlorotoluene, seven new compounds of the type *N,N'*-bis-(amido)-2,4-dichlorotoluene, and two new *N,N'*-bis-(amido)-3,4-dichlorotoluene derivatives have been reported. These compounds have been screened for pharmacological action.

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