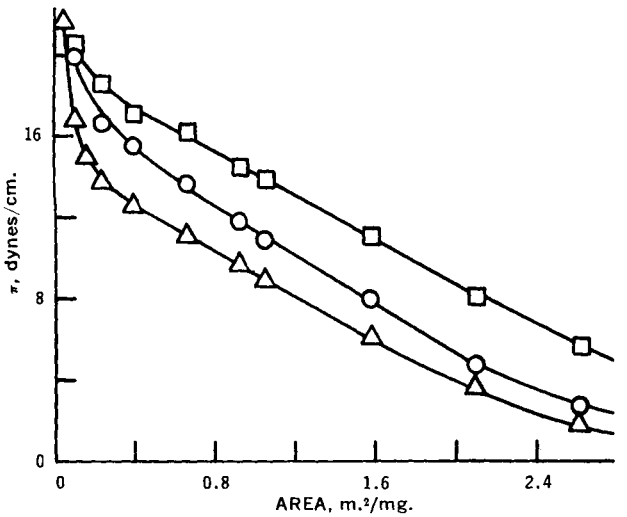

Figure 2—π–A *curves for Copolymer 735. Key:* △, *water subphase;* ○, *subphase containing* p-*hydroxybenzoic acid, 1 g./l.; and* □, *subphase containing benzoic acid, 0.5 g./l.*

of the area occupied by each polymer unit and resulted in a surface pressure above that exhibited by the monolayer containing polymer only.

Figure 1 shows that Copolymer 335 is penetrated by benzoic acid but that the effect of *p*-hydroxybenzoic acid is quite small. Copolymer 735 interacts with both substances (Fig. 2); once again, benzoic acid is more strongly adsorbed than is *p*-hydroxybenzoic acid. Although both of these substances are bound by polyvinylpyrrolidone in bulk solution, *p*-hydroxybenzoic acid is more strongly bound than benzoic acid (14, 15); the opposite is true in the monolayer experiments. It is possible that this difference is due to the more highly organized and spatially oriented structure which polymers assume at an interface (11). Benzoic acid, with a single hydrophobic group located at one end of the molecule, can assume an orientation in which the polar group is immersed in the subphase and the benzene ring extends above it in contact with nonpolar polymer groups. *p*-Hydroxybenzoic acid is not as easily accommodated at the interface, because this molecule has a polar group at each end.

Based on the results reported here, one may conclude that orientation in a polymer monolayer may be a determining factor in monolayer penetration by dissolved molecules. Furthermore, it is dangerous to extrapolate data obtained in bulk solution studies to conditions at interfaces or membranes.

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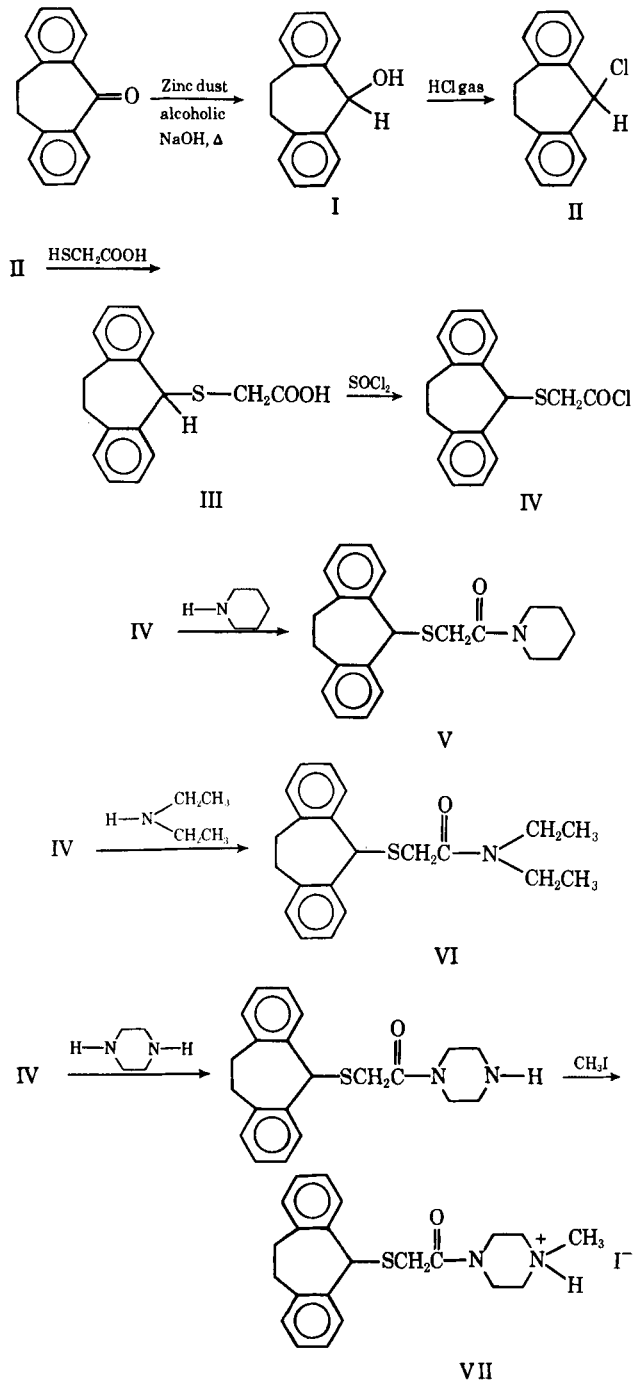
New Compounds: Amides Derived from [(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetic Acid

R. V. SAENZ▲ and J. W. SOWELL*

Abstract □ Synthesis of sulfide amides from [(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetic acid is described. Preliminary pharmacological results are reported.

Keyphrases □ Amides—synthesized from [(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetic acid, pharmacological screening □ [(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetic acid—used as a starting material for synthesis of sulfide amides, products tested for pharmacological activity □ Antihistamines, potential—synthesis of sulfide amides, pharmacological screening

Many compounds of diversified chemical structure have been found to possess histamine-antagonizing activity (1–6). In addition to this activity, many possess other pharmacological activities including antispasmodic, sedative, local anesthetic, sympathomimetic, and antiacetylcholine actions (7). Studies have attempted to find a more selective antihistaminic activity, including analogs possessing the sulfide linkage (8).



Scheme I

Hence, it appeared that the preparation of appropriately substituted sulfide amides might possess some degree of histamine-antagonizing ability. Thus, three sulfide amides, [(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)thio]-*N*,*N*-diethylacetamide, 1-{[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)thio]acetyl}-piperidine, and 1-{[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene-5-yl)thio]acetyl}-4-methylpiperazine methiodide were prepared (Scheme I) and tested.

EXPERIMENTAL

5-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (II)—10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (I) (20.0 g., 0.096 mole) was dissolved in ethyl alcohol (200 ml., 95%). To this was added sodium hydroxide pellets (20 g.) and zinc dust (30 g.). The system was refluxed for 1.5 hr. 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene-5-ol was isolated by filtering off the solid, removing the ethanol by distillation, adding water, and allowing the solution to precipitate in the cold overnight. Recrystallization from ethyl ether–petroleum ether gave the desired product, m.p. 92–93°. The alcohol (16.5 g.) was then suspended in anhydrous toluene, and hydrogen chloride was bubbled through. After 30 min., the toluene was distilled under reduced pressure and hexane (100 ml.) was added to the residue. The desired chlorinated compound (11.0 g.), recrystallized from hexane, was obtained, m.p. 104–105° [lit. (9) m.p. 105°].

[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)thio]acetic Acid (III)—To Compound II (2.29 g., 0.01 mole) in anhydrous isopropyl ether was added mercaptoacetic acid (1.84 g., 0.02 mole), and the reaction mixture was allowed to react for 2 hr. The reaction mixture was then extracted with 10% sodium hydroxide (4 × 20-ml. portions) and the combined extracts were acidified. Recrystallization from alcohol–water of the precipitate thus formed yielded a product with a melting point of 154–154.5°.

Anal.—Calc. for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67. Found: C, 71.77; H, 5.63.

1-{[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)thio]acetyl}-piperidine (V)—To Compound III (8.5 g., 0.03 mole) in anhydrous ether was added thionyl chloride (3.6 g., 0.03 mole) in anhydrous ether (25 ml.), and the reaction mixture was allowed to reflux for 12 hr. At this time, piperidine (5.1 g., 0.06 mole) in anhydrous ether was added and allowed to stir for 6 hr. The ethereal solution was washed with distilled water (50 ml.), 10% hydrochloric acid (3 × 50-ml. portions), 10% sodium hydroxide (2 × 50-ml. portions), and a saturated solution of sodium chloride. It was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was chromatographed on alumina, using petroleum ether, isopropyl ether, and ethyl ether (10–25-ml. fractions each, 50/50 v/v mixtures) and characterized by IR spectra and analytical analysis.

Anal.—Calc. for $C_{22}H_{25}NOS$: C, 75.17; H, 7.17. Found: C, 74.95; H, 7.02.

[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)thio]-*N*,*N*-diethylacetamide (VI)—This compound was prepared and characterized analogously to the piperidine analog.

Anal.—Calc. for $C_{21}H_{25}NOS$: C, 74.29; H, 7.42. Found: C, 74.38; H, 7.41.

Table I—Survival Ratios of Guinea Pigs after 30 min. Unprotected and Protected with Test Compounds when Exposed to Histamine Diphosphate Aerosol (12)

Compound	Dose	Number Died/Number Tested
Propylene glycol	1 ml./kg.	3/4
Compound VI	100 mg./kg.	1/2
Compound VI	200 mg./kg.	1/2
Compound VI	300 mg./kg.	0/2
Diphenhydramine hydrochloride	20 mg./kg.	0/4
Compound V	100 mg./kg.	1/1
Compound V	200 mg./kg.	1/1
Compound V	300 mg./kg.	1/1
Diphenhydramine hydrochloride	20 mg./kg.	0/3

Table II—Comparison of the Spasmolytic Activities of Diphenhydramine Hydrochloride and Compound VII against Histamine-Induced Spasm in the Isolated Guinea Pig Ileum

Compound	Milligram[a]	Millimole[a]
Diphenhydramine hydrochloride	0.01	3.43×10^{-5}
VII	0.18	34.8×10^{-5}

[a] Required to block, to the same extent, the spasm caused by 0.045 mg. of histamine diphosphate.

1-{[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetyl}-4-methylpiperazine Methiodide (VII)—The acyl halide was prepared as previously described. To this was added 1-methylpiperazine (6.0 g., 0.06 mole) dissolved in anhydrous ether, and the mixture was allowed to react for 8 hr. Extraction of the ethereal solution with 10% sodium hydroxide (4 × 50-ml. portions) followed by 10% hydrochloric acid resulted in a gummy precipitate in the aqueous layer. The aqueous layer was made alkaline and extracted with ether; the ether was washed with distilled water (6 × 50-ml. portions) and filtered and dried over anhydrous sodium sulfate. The desired sulfide was characterized as the methiodide salt prepared by conventional methods (10), IR spectra, and analytical data.

Anal.—Calc. for $C_{23}H_{29}IN_2OS \cdot {}^1/_2H_2O$: C, 53.37; H, 5.84. Found: C, 53.75; H, 6.40.

PHARMACOLOGICAL METHODS

Compounds V and VI were administered intraperitoneally to guinea pigs 20 min. before subjecting them to atomized histamine under conditions previously described (11). Because of the low solubility of the test compounds in propylene glycol, 0.05 ml. of polysorbate 20[1] was added to each milliliter of propylene glycol. Diphenhydramine hydrochloride[2] was used as the standard.

Compound VII as the methiodide salt was tested for its spasmolytic effects on spasms induced by histamine diphosphate on isolated guinea pig ileum.

Tables I and II give the results from the preliminary pharmacological testing.

[1] Tween 20, Atlas Chemical Co., Wilmington, Del.
[2] Benadryl, Parke-Davis and Co., Detroit, Mich.

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*Present address: University of Georgia, School of Pharmacy, Athens, GA 30310

▲ To whom inquiries should be directed.

COMMUNICATIONS

Multiple-Dose Kinetics of Pharmacological Effects of Indirect Anticoagulants

Keyphrases □ Anticoagulants (warfarin and dicumarol)—mathematical derivation of multiple-dose kinetic equations, pharmacological effects □ Pharmacokinetics, multiple-dose and pharmacological effects—calculations regarding behavior and optimal regimen for indirect anticoagulants □ Multiple-dose kinetics—pharmacological effects, indirect anticoagulants

Sir:

The pharmacological effects of hypoprothrombinemic anticoagulant drugs vary widely between individuals and preclude a predictable response to a fixed dose of these agents. A given dosage schedule may be totally inadequate to prevent thrombosis in one individual but may cause hemorrhage in another (1). In addition, the effects of the drugs can be appreciably influenced within individuals through interactions with other concurrently administered drugs (2–5). These facts, as well as a need to readjust therapeutic levels of activity during the course of therapy (1), obviously necessitate patient individualization of dosing regimens for these drugs and clearly emphasize the need for predictive interrelationships between dosage regimens and the magnitudes of their drug response. The purpose of the present communication is to describe the derivation of theoretical relationships which, provided adequate data in the form of blood coagulability and plasma drug levels are collected, could be useful for the characterization of multiple-dosing pharmacokinetic be-