TABLE I.—MORPHINE CONTENT IN OPIUM SAMPLE

Opium Sample	Morphine Content, %—G.L.C. Method[a]—Value Determined	Calcd. to Anhydr. Basis	Other Methods
U.S.P.	11.4	...	10.5[b]
UN2A	14.0	14.9	13.5[c]
UN15	16.5	17.5	16.1[d]
UN38G	18.5	19.7	17.0,[c] 20.3[d]
UN137A	15.1	16.1	13.8[c]
UN25A	18.3	19.5	18.1,[c] 19.07[d]
UNE529	13.8	14.6	13.8[c]
UNE531	11.0	11.7	12.0[c]
UN265	12.8	13.6	13.1[c]
UNE612	15.5	16.3	15.5[c]
UNE627	12.4	13.1	11.0[c]
UNE631	12.2	13.2	12.0[c]

[a] Average values based on two or more determinations. [b] Opium assay U.S.P. XVI (13). [c] Modified Mannich method (14); sample analyzed without drying. [d] United Nations' Secretariat (15); calculated to anhydrous basis.

TABLE II.—GAS CHROMATOGRAPHIC DETERMINATION OF MORPHINE IN OPIUM BEFORE AND AFTER PURIFICATION *via* DICHLOROACETIC ACID

Opium Sample	Morphine, %—No Special Treatment	Purification *via* $CHCl_2COOH$
UN38G	18.6	18.6
	18.4	18.4
UNE265	12.8	12.6
UNE612	15.4	15.4
	15.6	15.5

in many of its reactions and extractions. They are present in amounts up to 1.5% and may lead to high results if the analytical procedure is not sufficiently specific. It is possible to remove them by extracting the acidified morphine fraction with chloroform in the presence of dichloroacetic acid (15). These alkaloids do not interfere in the gas chromatographic determination of morphine. Table II shows that inclusion of an extra purification step *via* dichloroacetic acid does not change the results.

The generally higher results obtained by the gas chromatographic method than by the other procedures referred to in Table I are probably due to a more complete extraction of opium by the ion-exchange resin and a more quantitative recovery during the purification steps.

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2-Aminobenzenethiol Derivatives as Potential Psychotherapeutic Agents

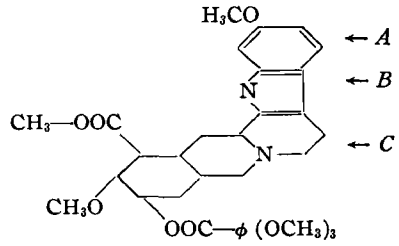
By KARL A. NIEFORTH

A structural similarity between reserpine and chlorpromazine is described and a series of derivatives of 2-aminobenzenethiol designed to match the similarity is synthesized and tested for pharmacologic activity.

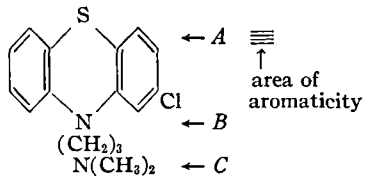
THE APPARENT tranquilizing activity of reserpine and chlorpromazine is qualitatively the same, although the two compounds are quite different structurally. It is postulated that the two compounds act by two pharmacologically distinct mechanisms—reserpine by trophotropic stimulation and chlorpromazine by ergotropic inhibition according to the terminology of Hess (1).

With the use of molecular models, a structural similarity may be seen between the two compounds (see Fig. 1). The diagram represents the positional relationships of three atoms in the two compounds and shows the location of an aromatic structure. Position *A* represents the phenolic oxygen of reserpine or the sulfur of chlorpromazine; position *B*, the aromatic nitrogen of each compound; and position *C*, the aliphatic nitrogen of each compound. It must be kept in mind that the positions also could represent any bioisosteric modification. A similarity of

Received February 28, 1963, from the Medicinal Chemistry Research Laboratories, Pharmacy Research Institute, University of Connecticut, Storrs.
Accepted for publication April 9, 1963.
This study was supported by Grant MY-6063 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.
The author expresses his appreciation to the Michigan Chemical Corporation, St. Louis, Mich., for their generous supply of dialkylaminoalkylchloride hydrochlorides, and to the American Cyanamid Co., New York, N. Y., for supplying a part of the 2-aminobenzenethiol used in this project.
The technical assistance of Mr. John Rosazza is gratefully acknowledged.



Reserpine



Chlorpromazine

Fig. 1.—Structural similarity of reserpine and chlorpromazine as obtained with Stuart-Briegleb molecular models.

the compounds which is difficult to express by a diagram but readily visible by the use of molecular models is the proximity in space occupied by substituents on position 2 of promazine and position 16 of reserpine. This may explain why substituents on position 2 of promazine have a greater effect on activity than do similar substituents on other positions of the phenothiazine structure.

It has been proposed that the sites involved in the activity of reserpine and chlorpromazine are specific for the corresponding drugs because of the apparent dissimilarity of structures. On the basis of the similarity shown in Fig. 1, it seems that the two sites involved in CNS activity may be closely related in physical characteristics or that only one site may be involved, the latter being more probable. This particular arrangement of atoms does not necessarily result in reserpine-chlorpromazine type CNS depression as illustrated by the stimulant imipramine (2). In some instances, activity may be found in compounds possessing only a part of the total arrangement such as the depressant tetrabenazine (3).

The compounds in this series (Table II) were designed to have a hybrid reserpine-chlorpromazine activity. Activity of this type would suggest the existence of a single site with differences which are observed in the pharmacodynamic actions accounted for by secondary effects of the drugs. Figure 2 shows the reaction scheme which was suitable for the synthesis of the test compounds.

The circuitous route to compound VII from compound II was necessitated by the difficulty encountered in separating the products of methylation of compound II. Methyl 2-acetamidophenyl sulfide and its N-methyl analog decomposed upon distillation and could not be used to form methyl 2-methylaminophenyl sulfide without tedious recrystallizations. For this reason, methyl 2-benzenesulfonamidophenyl sulfide and its N-methyl derivative were used as intermediates. These two compounds could be separated and purified easily by their solubilities in alkaline solution and were prepared in good yields. The sulfonamide procedure could have been used for the preparation of all of the alkyl 2-methylaminophenyl sulfides (Table I), but purification of the acetyl derivatives was more rapid than was recrystallization of the sulfonamide derivatives.

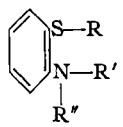
EXPERIMENTAL

Alkyl 2-Aminophenyl Sulfides (II).—These compounds were synthesized by well documented procedures in good yields. Running the reaction under nitrogen improved its appearance but had little effect on the yields.

Alkyl 2-Acetamidophenyl Sulfides (III).—One mole of alkyl 2-aminophenyl sulfide and 1 mole of pyridine were dissolved in 500 ml. of ether and 1 mole of acetyl chloride added over the period of 1 hour. The mixture was stirred for 1 hour, poured into diluted hydrochloric acid, extracted with ether, and distilled at reduced pressure.

Alkyl 2-(N-methyl)-acetamidophenyl Sulfides (IV).—Alkyl 2-acetamidophenyl sulfide (0.8 mole) was added to a sodium dispersion (1.0 mole in 300

TABLE I.—SUBSTITUTED 2-AMINOBENZENETHIOLS



R	R'	R''	Yield	B.p./Pressure M.p., °C.[a]	Formula	Nitrogen, %[d] Calcd.	Found
CH_3	H	H	94	112/6.5 mm.	C_7H_9NS		[b]
CH_3	CO—CH_3[c]	H	92	96–97	$C_9H_{10}NOS$	7.72	7.50
CH_3	SO_2—C_6H_6[c]	H	95	80–82	$C_{13}H_{14}NO_2S_2$	5.01	4.67
CH_3	SO_2—C_6H_6[c]	CH_3	92	115–116	$C_{14}H_{16}NO_2S_2$	4.79	4.58
CH_3	H	CH_3	57	98/4.7 mm.	$C_8H_{11}NS$	9.14	9.12
C_2H_5	H	H	93	84/1.3 mm.	$C_8H_{11}NS$		[b]
C_2H_5	CO—CH_3	H	77	164/6 mm.	$C_{10}H_{13}NOS$	7.17	7.01
C_2H_5	CO—CH_3	CH_3	98	121/0.42 mm.	$C_{11}H_{15}NOS$	6.75	6.62
C_2H_5	H	CH_3	64	121/7.5 mm.	$C_9H_{13}NS$	8.42	8.44
$CH(CH_3)_2$	H	H	89	87/1.0 mm.	$C_9H_{13}NS$		[b]
$CH(CH_3)_2$	CO—CH_3	H	85	161/6.5 mm.	$C_{11}H_{15}NOS$	6.75	6.82
$CH(CH_3)_2$	CO—CH_3	CH_3	77	171/6.5 mm.	$C_{12}H_{17}NOS$	6.32	6.30
$CH(CH_3)_2$	H	CH_3	73	126/8.0 mm.	$C_{10}H_{15}NS$	7.81	7.78

[a] Melting points were taken on a Thomas melting point apparatus and are uncorrected. [b] Prepared by Foster, D., and Reid, E., *J. Am. Chem. Soc.*, **46**, 1941(1924). [c] Recrystallized from 95% ethanol. [d] Microanalyses were carried out by Alfred Bernhardt, Mikroanalytisches Laboratorium, Max-Planck-Institut, Mulheim (Ruhr), Germany.

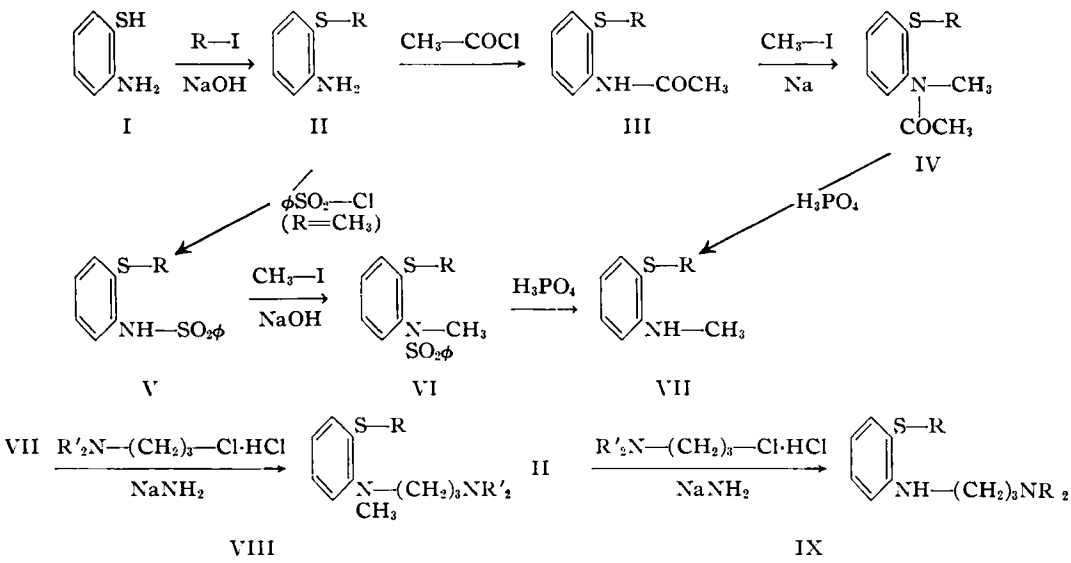


Fig. 2.—Synthetic procedure.

ml. of toluene) and stirred on a steam bath for 10 hours. After cooling to room temperature, methyl iodide (1.0 mole) was added with stirring over a period of 2 hours. The reaction was stirred for an additional hour without heating. The solvent was removed and 20 ml. of ethanol added to destroy excess sodium. An aqueous suspension of the residue was extracted with ether and the ethereal solution distilled at reduced pressure.

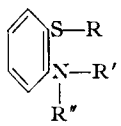
Methyl 2-Benzenesulfonamidophenyl Sulfide (V).—A mixture of methyl 2-aminophenyl sulfide (1.0 mole) and pyridine (1.0 mole) was dissolved in 500 ml. of ether. Benzenesulfonyl chloride (1.0 mole) was added with stirring over a period of 30 minutes. The reaction was heated on a steam bath for 30 minutes, after which it was extracted with dilute hydrochloric acid. The ether was evaporated and the residue solidified by cooling.

Methyl 2-(N-methyl)-benzenesulfonamidophenyl Sulfide (VI).—A solution of methyl 2-benzenesulfonamidophenyl sulfide (0.2 mole) was prepared by dissolving it in 275 ml. of 5% sodium hydroxide. Methyl iodide (0.24 mole) was added during 30 minutes with stirring. The reaction was then refluxed for 1 hour, cooled to room temperature, and filtered. The solid product was treated with 20% sodium hydroxide to remove any starting material and then recrystallized from 95% ethanol.

Alkyl 2-Methylaminophenyl Sulfides (VII).—These compounds could be prepared from either methyl 2-(N-methyl)-benzenesulfonamidophenyl sulfide (VI) or alkyl 2-(N-methyl)-acetamidophenyl sulfides (IV) in the same manner. The reactant was heated at 150° for 18 hours with an excess of orthophosphoric acid. The reaction was cooled and carefully neutralized with dilute sodium hydroxide solution. The mixture was extracted with toluene or benzene while still warm before the precipitation of sodium phosphate. The solvent was removed and the residue distilled at reduced pressure.

Alkyl N-(N'-dialkylaminoalkyl)-N-methylaminophenyl Sulfides (IX).—Alkyl 2-methylaminophenyl sulfide (0.09 mole) was heated in 200 ml. of toluene with sodium amide (0.2 mole) for 24 hours. Dialkylaminoalkylchloride hydrochloride (0.08 mole) was added in one addition; the reaction was heated and stirred for an additional 24 hours. The toluene was

Table II.—Alkyl 2-Dialkylaminoalkylaminophenyl Sulfides



R	R'	R"	B.P./Pressure	Yield	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	$CH_2—CH_2—CH_2—N(CH_3)_2$	144/1.7 mm.	70	11.75	11.53
CH_3	CH_3	$CH_2—CH_2—CH_2—N(C_2H_5)_2$	156/2.2 mm.	89	10.51	10.55
C_2H_5	CH_3	$CH_2—CH_2—N(CH_3)_2$	135/1.75 mm.	39	11.75	11.47
C_2H_5	CH_3	$CH_2—CH_2—CH_2—N(CH_3)_2$	140/2.0 mm.	92	11.09	10.93
C_2H_5	CH_3	$CH_2—CH_2—CH_2—N(C_2H_5)_2$	154/2.0 mm.	92	9.91	10.06
$CH(CH_3)_2$	CH_3	$CH_2—CH_2—CH_2—N(CH_3)_2$	142/2.0 mm.	68	10.51	10.31
$CH(CH_3)_2$	CH_3	$CH_2—CH_2—CH_2—N(C_2H_5)_2$	155/1.5 mm.	77	9.44	9.43
$CH(CH_3)_2$	H	$CH_2—CH_2—CH_2—N(C_2H_5)_2$	135/1.75 mm.	82	9.91	9.78

removed, and a small amount of ethanol was added to destroy residual sodium amide. The ethanol was removed, the residue was suspended in a saturated solution of potassium carbonate, and extracted with ether. The ether was removed and the residue distilled at reduced pressure. This is a modification of a procedure reported by Huttrer (4).

Isopropyl N-(N'-Diethylaminopropyl)-aminophenyl Sulfide (VIII).—This compound was prepared in the same manner as compound IX. Isopropyl 2-methylaminophenyl sulfide (0.13 mole) was reacted with sodium amide (0.25 mole) in 200 ml. of toluene. After heating the mixture for 24 hours, 3-diethylaminopropylchloride hydrochloride was added and heated for 24 hours. The product was isolated in the manner described above in a yield of 82%. Compounds of this type have been previously reported (5).

These compounds were screened for gross pharmacologic activity using the Hippocratic screen method (6). Biphasic activity was exhibited by an initial increase in motor activity accompanied by evidence of disorientation and stereotypy in the form of head shaking, chewing motions, and prancing of the forelimbs. This was followed by ataxia and decreased motor activity 1 hour after intraperitoneal injection. One compound, isopropyl N-(N'-diethylaminopropyl)-aminophenyl sulfide exhibited only motor activity depression without an initial increase.[1]

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[1] Preliminary pharmacological data were provided by Dr. Marvin M. Malone and Mr. Roger C. Robichaud, Division of Pharmacology, Pharmacy Research Institute, University of Connecticut, Storrs.

Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient III

Tablet Lubricants

By GERHARD LEVY and ROBERT H. GUMTOW

A hydrophobic tablet lubricant (magnesium stearate) has been found to retard the dissolution of salicylic acid from model compressed tablets, while a water-soluble, surface-active lubricant (sodium lauryl sulfate) enhanced markedly the dissolution rate. Experiments with nondisintegrating disks indicate that the more commonly used hydrophobic lubricants (magnesium stearate, aluminum stearate, stearic acid, talc) decrease the effective drug-solvent interfacial area and thereby decrease the rate of dissolution of the drug, while water-soluble lubricants (sodium oleate, sodium lauryl sulfate) do not have this effect. The dissolution rate enhancing effect of sodium lauryl sulfate (in the case of conventional tablets) is not due to any modification of microenvironmental pH or solubilization by micelles, but rather to the better penetration of solvent into tablets and their component granules and the resulting greater availability of drug surface.

THE EFFECT of formulation and processing factors on the dissolution rate of active ingredients of compressed tablets has been the subject of extended investigation in this laboratory (1, 2). The present report deals with the effects of tablet lubricants and the mechanisms by which they may modify the dissolution rate of pharmaceuticals contained in tablets.

The more commonly used tablet lubricants are hydrophobic substances. Their water-repellent effect is evidenced by their tendency to increase markedly the disintegration time of tablets (3–5). When lubricants are added to a tablet granulation, they form a coat around individual granules which remains more or less intact during the process of tablet compression (3). Interference by these agents with the dissolution of drugs in aqueous media is therefore a likely possibility.

An extensive study of currently used and potentially useful tablet lubricants by Strickland, *et al.* (6), revealed that a few water-soluble substances are effective lubricants. Presumably, these substances, unlike hydrophobic lubricants, will not interfere with the dissolution of tablet ingredients. For this reason, both hydrophobic lubricants as well as certain water-soluble lu-

Received February 27, 1963, from the Biopharmaceutics Laboratory, School of Pharmacy, State University of New York at Buffalo, Buffalo.
Accepted for publication March 26, 1963.