2-Aminobenzenethiol Derivatives as Potential Psychotherapeutic Agents II

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A similarity between reserpine and the phenothiazine type psychotherapeutic agents is described and illustrated with Stuart-Briegleb molecular models. In an attempt to validate this similarity a series of 2-aminobenzenethiol derivatives was synthesized and screened, resulting in unusual pharmacological properties.

IN A PREVIOUS report (1), a similarity between reserpine and the phenothiazine-type psychotherapeutic agents was described. This relationship involves a five-point correlation which was illustrated by two-dimensional figures and will be further demonstrated here with Stuart-Briegleb molecular models. The correlation is shown by a template (Fig. 1) which is constructed using reserpine as a model. Reserpine was used since it is a relatively rigid structure of known configuration and facilitates the location of the various groups (2). The circles represent the location of the oxgyen on carbon number 11, the aromatic nitrogen, the aliphatic nitrogen, and the carbonyl group attached to position 16. The hash marks show an area of aromaticity. Figure 2 illustrates how reserpine appears when viewed under the template outlining the five areas of interest.

Chlorpromazine has the structural features characteristic of the more active phenothiazine tranquilizers, and when examined under the reserpine template, demonstrates the similarity mentioned before. Figure 3 shows that the sulfur is in the same area as the methoxy of reserpine; the aromatic nitrogen of chlorpromazine occupies the same area as the aromatic nitrogen of reserpine; the aliphatic nitrogens of both compounds are in the same area; the chlorine atom is in the same area as the carbonyl group of reserpine; and there is an area of aromaticity under the hash marks in both compounds. Several types of substituents are found in position two of marketed compounds, such as chloro (chlorpromazine), trifluoromethyl (trifluprom azine), methylmercapto (thioridazine), acetyl (acepromazine), and many others. Due to the possibility of free rotation around the single bonds of the alkyl chain, chlorpromazine could be placed under the template with all of the groups in position, except the chlorine atom, which could be attached to the benzene ring under the hash marks, presenting a situation similar to that existing with the unsubstituted phenothiazines.

The positioning of *trans*-chlorprothixine under the template is illustrated in Fig. 4. The presence of the double bond limits the amount of rotation in this compound, and if three of the groups are in position, the final groups must be in the correct area. This increased rigidity may be responsible for the fact that in some pharmacological tests, such as motor activity reduction upon intraperitoneal injection, *trans*-chlorprothixene is six times as active as chlorpromazine (3).

The *cis* isomer of chlorprothixene is only one-tenth as active as the *trans* isomer or on the order of activity of phenothiazine derivatives without

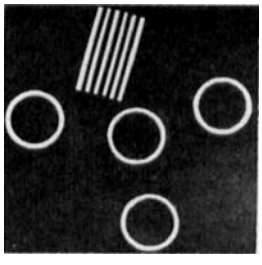

Fig. 1.—Template used to show relationship between reserpine, chlorpromazine, and chlorprothixene.

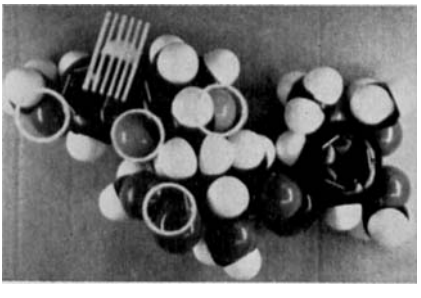

Fig. 2.—Reserpine viewed under the template.

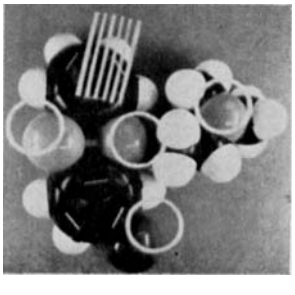

Fig. 3.—Chlorpromazine.

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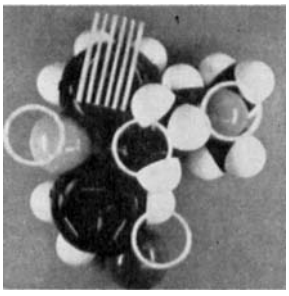


Fig. 4.—*trans*-Chlorprothixene.

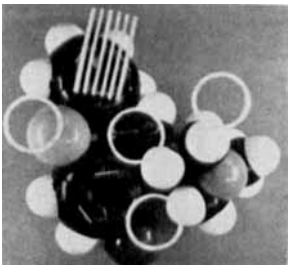


Fig. 5.—*cis*-Chlorprothixene.

substituents on the two position. The sulfur, ethylenic group, and the aliphatic nitrogen could be placed in position, but then the chlorine atom would be attached to the benzene ring under the hash marks. This is similar to the mentioned alternate arrangement of chlorpromazine. Also, as illustrated in Fig. 5, the sulfur, ethylenic group, and the chlorine could be in position and the aliphatic nitrogen would be out of its correct area.

This arrangement is not meant to be an absolute prerequisite for psychotherapeutic activity for compounds which do not have all of the features known to have activity. One such compound is tetrabenazine. Although most of the compounds with these features are tranquilizers, a few (such as imipramine) are stimulants.

A series of derivatives of 2-aminobenzenethiol was synthesized and screened in an attempt to determine the necessity of both aromatic rings of the phenothiazine nucleus. Due to the small number of compounds synthesized and the limited number of animals used in the screening, the interpretations of the pharmacological results must be very general.

EXPERIMENTAL

The synthetic procedures for all of these compounds are thoroughly described in a previous report (1). Nine additional compounds have been synthesized (Table I); the pharmacology of all 17 compounds will be discussed.

The following compounds were reported in the first paper of this series: KN15, methyl *N*-(*N'*-dimethylaminopropyl)-*N*-methylaminophenyl sulfide; KN16, ethyl *N*-(*N'*-dimethylaminopropyl)-*N*-methylaminophenyl sulfide; KN17, isopropyl *N*-(*N'*-dimethylaminopropyl)-*N*-methylaminophenyl sulfide; KN18, methyl *N*-(*N'*-diethylaminopropyl)-*N*-methylaminophenyl sulfide; KN19, ethyl *N*-(*N'*-diethylaminopropyl)-*N*-methylaminophenyl sulfide; KN20, isopropyl *N*-(*N'*-diethylaminopropyl)-*N*-methylaminophenyl sulfide; KN32, ethyl *N*-(*N'*-diethylaminoethyl)-*N*-methylaminophenyl sulfide; and KN33 isopropyl *N*-(*N'*-diethylaminopropyl)-aminophenyl sulfide.

The screening technique used was that of Malone and Robichaud (4), in which the compounds were injected intraperitoneally over a wide range of logarithmically spaced dosages into intact unanesthetized albino rats and the qualitative and semiquantitative symptomology carefully observed using a standardized work sheet.

RESULTS AND DISCUSSION

The dose–time-response profiles of compounds KN15, KN16, KN17, KN18, KN19, KN20, KN29, KN30, KN31, and KN32, although exhibiting slight quantitative differences, are qualitatively identical. Compound KN15 will be described to represent this group.

At 10 mg./Kg., there was a transient increase in motor activity accompanied by a pronounced exophthalmus, mydriasis, and a mild but persistent pilomotor erection. No mitigation of an aggressive personality or drop in body temperature was noticed at this dose.

At 32 mg./Kg., the animal exhibited a pronounced hyperemia of ears and feet, an increase in motor activity, body tremors, exophthalmus, mydriasis, a short burst of clonic convulsions with recovery, pilomotor erection, stereotypy consisting of head shaking, chewing motions, prancing of forelegs, and evidence of disorientation. The peak of stimulation was at approximately 15 minutes after injection. Biphasic activity is evidenced at 1 hour after injection by ataxia and a decrease in motor activity. During this period of decreased motor activity, some of the compounds other than KN15 brought about a perceptible drop in body temperature. Four hours after injection, the animal had returned to an essentially normal state.

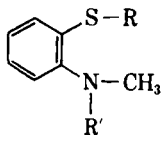
At 100 mg./Kg., an increase in motor activity, hyperemia, tremors, exophthalmus, Straub tail erection, mydriasis, clonic convulsions, apparent salivation, positive Robichaud test, loss of grip strength, and loss of righting reflex were noticed. The animal died of respiratory arrest 10 minutes after injection.

Compound KN33 follows a different dose–time-response pattern. At 32 mg./Kg., there was a general quieting of the animal with enophthalmus, decrease of motor activity, positive Robichaud test, personality change to passivity and a drop of 3.5° in body temperature 1 hour after dosage. The animal was grossly normal 4 hours after the injection.

At 100 mg./Kg., there was a profound blanching of the skin, analgesia, mydriasis, enophthalmus, anoxia-induced clonic convulsions, and death by respiratory arrest 7 minutes after injection.

The piperidine and piperazine compounds KN34 through KN39 were probably the most interesting. KN34 will be described as typical of this group, although slight qualitative and quantitative differences occurred.

TABLE I.—ALKYL 2-DIALKYLAMINOALKYLPHENYL SULFIDES



KN	R	R′	B.p./Pressure	Yield, %	Nitrogen, %—Calcd.	Nitrogen, %—Found
29	CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	144/2.3	56	11.09	10.51
36	CH_3	$CH_2CH_2CH_2$—N⟨ ⟩	174/1.0	68	10.06	10.23
38	CH_3	$CH_2CH_2CH_2$—N⟨ ⟩N—CH_3	156/0.2	44	14.28	14.41
30	C_2H_5	$CH_2CH(CH_3)CH_2N(CH_3)_2$	142/2.3	53	10.51	10.35
37	C_2H_5	$CH_2CH_2CH_2$—N⟨ ⟩	181/0.75	68	9.58	9.94
34	C_2H_5	$CH_2CH_2CH_2$—N⟨ ⟩N—CH_3	144/0.05	47	13.67	13.99
31	$CH(CH_3)_2$	$CH_2CH(CH_3)CH_2N(CH_3)_2$	154/4.0	70	9.91	9.58
35	$CH(CH_3)_2$	$CH_2CH_2CH_2$—N⟨ ⟩	151/0.25	70	9.14	9.47
39	$CH(CH_3)_2$	$CH_2CH_2CH_2$—N⟨ ⟩N—CH_3	156/0.05	70	13.07	13.21

Ten minutes after injection of 10 mg./Kg., there was a transient decrease in motor activity and a general change of attitude from a more or less passive state to a rather fearful one. Thirty minutes after injection, the rat had apparently recovered and was grossly normal. The next day, in addition to a slightly decreased motor activity, the animal displayed a loss of grip strength and pilomotor erection. During the following days, the animal became progressively more excitable and slightly hyperemic. At 7 days after injection the rat seemed unable to remain quiet, continually pranced about, washed itself, etc.

At 32 mg./Kg., there was an immediate decrease in motor activity followed by progressive motor activity depression which reached a peak 30 minutes after injection. At this time the animal lost its grip strength, had mydriasis, pseudoblepharoptosis, blanching, salivation, pilomotor erection, and a loss of body temperature of 4°. During this time the animal would alternate between brief periods of motor activity stimulation and motor activity depression. The following day, the animal had a strange behavioral profile in that it seemed impervious to the investigator's actions. The animal would walk around, bump into objects, fall off bench tops, then remain perfectly still for a short time and then repeat the entire performance. It was felt that this was strongly suggestive of hallucinations. The animal had either the inability or lack of desire to cling to an inverted metal screen.

KN35 had much the same profile as KN34, except the motor activity change was not so pronounced. KN36 was similar to KN34 with perhaps even more "hallucinogenic" activity and less of the hypothermia. KN37 had no "hallucinogenic" activity at 32 mg./Kg., but one animal that survived the 100 mg./Kg. dose was similarly disorientated. KN39 was slightly different from the other compounds in that the lethal dose was 316 mg./Kg., rather than 100 mg./Kg., and that death took place 1 hour after injection, instead of the usual 10 minutes. The animals at the nonlethal doses were very disorientated, had a strongly positive Robichaud test, and a generally emaciated appearance. All animals were sacrificed at the end of 7 days and showed signs of possible hepatotoxicity.

A different animal was used for each dose level. In equivocal cases a second animal was injected. Thus, three rats were used in KN15, three rats were also used in KN37.

While the small number of animals used should not lead one to believe that "statistically" significant results were obtained, it is sufficient, we feel, to point out definite trends of behavior.

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