PHARMACOLOGICAL STUDIES WITH SOME NEWLY SYNTHESIZED PHENOTHIAZINES EXHIBITING LESSER EXTRAPYRAMIDAL REACTIONS

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The signs and symptoms due to extrapyramidal tract involvement are amongst the most common side effects in tranquillizer therapy, which is uniformly present in all the six group of drugs used in medicine (1). With many of these drugs, severe extrapyramidal symptoms are uncommon, but with those phenothiazines which contain a piperazine moiety in their side chain such untoward effects are the rule rather than exception; e.g. trifluoperazine, prochlorperazine and perphenazine. Since these are the valuable drugs in psychiatry, control of their extrapyramidal side effects offers an important challenge.

Several intriguing views, regarding the relationship of tranquillizing activity and extrapyramidal reactions are reported in literature. Freyhan (2), Brune *et al.* (3) and Haase (4) are of the opinion that the ability of a drug to induce parkinson like syndrome bears a positive correlation with its therapeutic efficacy, and that the fine motor extrapyramidal reactions are "conditio sine qua non" for the essential efficacy of neuroleptic drugs. Conversely, Cole and Clyde (5), Brooks (6) and Hollister (1), believe that the suppression of parkinsonism does not lead to the impairment of therapeutic efficacy of tranquillizers and that the clinical appearance of extrapyramidal syndrome in no way predicts the therapeutic response of a tranquillizer.

An endeavour to find out the inter-relationship of parkinsonism and antipsychotic activity of tranquillizers can profitably be made by taking the hypothesis of McGeer *et al.* (7) into consideration. According to these suggestions, there is an equilibrium within the brain between the two groups of biogenic amines: serotonin-catecholamine on one hand, while acetylcholine-histamine on the other. Parkinsonism is characterized by an imbalance between these two systems and can be corrected either by increasing the neurohumoral content of one system or by decreasing that of the other.

Since the therapeutic efficacy of phenothiazine group of tranquillizer bears a close correlation with their antiserotonin (8) and antiadrenergic (9) activity, the two possible ways to inhibit parkinsonism, without interfering with antipsychosis, could be to enhance their antihistaminic or antiacetylcholine action. But potent antihistaminics amongst phenothiazine series e.g. promethazine, or ethopropazine possess little tranquillizing activity, while perphenazine and trifluoperazine which are weak antihistaminics are on

the other hand potent tranquillizers. Therefore, the only way to reduce their parkinsonism liability is to increase their antiacetylcholine like action. Since oximes are well known as antidotes for organophosphorous poisoning (anti DFP), we speculated that anticholinergic quaternary oximes of phenothiazine drugs can provide a tranquillizer with lesser liability of extrapyramidal reaction and that the study with these compounds is likely to furnish certain clues for the inter-relationship of these two actions, one desirable and the other unwanted.

MATERIALS

Three well established phenothiazine tranquillizers, viz. chlorpromazine hydrochloride (CPZ), trifluoperazine dihydrochloride (TFP) and perphenazine dihydrochloride (PER) were selected for the present study. From the free bases of these drugs, phenocyloxime chlorpromazine bromide (I), diphenacyloxime trifluoperazine dibromide (II) and diphenacyloxime perphenazine dibromide (III) were synthesized by the procedure already reported (10). These compounds (I, II and III) were assessed for their parkinsonism liability and CNS depressant properties. The results were compared to their parent drugs viz. CPZ, TFP and PER respectively. The structural formulae of the compounds I, II and III are shown in Fig. 1.

FIG. 1. Structural formulae of the compounds I, II and III, under study.

METHODS

I. Solutions of the drugs

The weighed quantity of each drug (I, II and III) was dissolved in a minimal but a known amount of warm ethanol and the volume was made up with warm distilled

water so that the solution in no case contained more than 5% ethanol. It was then cooled to room temperature before use. Experiments were run simultaneously with solutions of the drugs as well as with the solvent alone (5% aq. ethanol v/v). Since the control animals which received the solvent did not exhibit any pharmacological actions, the activities of the drugs will only be described here. The solutions of CPZ, TFP, PER, pentobarbitone sodium and *d*-amphetamine sulphate were made in distilled water.

II. Their CNS depressant property was studied by employing the following battery of tests*

1) Qualitative assessment of spontaneous motor activity (SMA) ptosis and influence of tactile and auditory stimuli on the mobility of mice by a double blind observational method (11)

These observations were made, upto 6 hours at hourly interval, after the intraperitoneal administration of different doses of drugs to a group of eight mice in each. The effects were rated and compared to the group of ten control animals which received the solvent alone. The doses employed and the observations are recorded in Table 1.

TABLE 1. Effects of the phenothiazines on spontaneous motor activity of the albino mice.

Drug	Dose mg/kg	No. of animals	Spontaneous motor activity	Response to the auditory and tactile stimuli	Ptosis
CPZ	3	8	###	###	###
I	3	8	+	+	+
I	10	8	##	+	++
TFP	3	8	###	###	###
TFP	1	8	##	++	##
II	3	8	##	##	++
II	1	8	+	+	+
PER	3	8	###	###	###
PER	1	8	###	##	##
III	3	8	##	++	##
III	1	8	++	++	++
Control	--	10	+	+	+

+ Normal ; ++ insignificant ; ## significant ; ### marked effects

2) Potentiating effect of pentobarbitone sodium induced hypnosis

The procedure followed was that as described by Dandiya and Cullumbine (12). The experiments were conducted at room temperature ($25 \pm 1^\circ\text{C}$). Control animals received the solvent and pentobarbitone (40 mg/kg) only. The test animals were pre-treated with different doses of phenothiazine derivatives before administering pentobarbitone sodium (40 mg/kg). The duration of sleep was calculated from the time taken by mouse when it had fallen asleep and when it regained the righting reflex. The doses of drugs, number of animals used and the results are enlisted in Table 2.

* The attitude that quaternary compounds do not cross blood brain barrier, was largely based on the lack of evidence to the contrary. During the past decade, reports have been made with increasing frequency and persistence that quaternaries do reach CNS to a sufficient degree to induce responses. Some quaternary phenothiazines have been reported to possess antitremorine activity which tempt to suspect the validity of the rule that quaternaries are devoid of direct CNS action because of their inability to pass blood brain barrier. Our findings also, seem to invalidate this widely accepted rule. For details in this regard refer Sharma *et al.* (10).

TABLE 2. Effects of the phenothiazine drugs on pentobarbitone induced hypnosis.

Compound	No. of animals	Dose mg/kg	Average sleeping time in min $\pm$ S.E.	P value	Percentage change in sleeping time
Control	24	—	74.20 $\pm$ 8.76	—	—
CPZ	10	5	162.90 $\pm$ 6.85	<0.001	+119.54
I	10	5	100.10 $\pm$ 20.90	—	+ 34.95
TFP	16	3	121.60 $\pm$ 14.50	<0.02	+ 63.88
II	16	3	120.77 $\pm$ 10.94	<0.01	+ 62.76
PER	10	1	91.70 $\pm$ 8.35	—	+ 23.58
III	10	1	86.80 $\pm$ 13.90	—	+ 16.98
PER	10	3	126.20 $\pm$ 11.85	<0.01	+ 70.08
III	10	3	117.00 $\pm$ 10.11	<0.02 but >0.01	+ 57.68

TABLE 3. Effect of phenothiazine drugs on fighting behaviour of paired mice.

Drug	Dose mg/kg	No. of pairs tried	No. of pairs which did not fight	% pair of mice in which response was blocked
Control	—	12	—	—
CPZ	3	12	3	25
CPZ	5	12	7	58.33
CPZ	10	12	12	100
I	5	12	1	8.33
I	10	12	5	41.66
TFP	3	12	—	—
TFP	5	12	7	58.33
TFP	10	12	12	100
II	5	12	5	41.66
II	10	12	11	91.66
PER	1	12	—	—
PER	5	12	10	83.33
PER	10	12	12	100
III	5	12	7	58.33
III	10	12	12	100

3) Influence on the fighting behaviour in paired mice

The technique was similar to that of Tedeschi *et al.* (13) as modified by Dandiya and Menon (14) in all essential details. Pairs of mice were placed on the apparatus and were covered with a bell jar. These were then subjected to a mild intermittent electric shocks. When tested in this way, at least 60% of the randomly selected pairs of mice exhibited two to three fights in one minute. These pairs were then kept in individual cages and were re-examined after one hour of the drug treatment, for the assessment of fighting response. The pairs of mice not fighting even once in one minute were taken as showing no response. All details regarding the drug, doses, and number of pairs tried are mentioned in Table 3.

4) Influence on conditioned avoidance behaviour of trained rats

The apparatus used and the procedure followed was the same as described by Cook

and Weidley (15). The unconditioned stimulus consisted of an electric shock of 40 volts through a copper grid floor. Rats were then conditioned so that at the sound of an electric bell, they climb over the ladder kept in a slanting position at the centre of the grid floor of the chamber. During training if the animal failed to respond the sound of the electric bell within 10 seconds, shock was given and the escape response (ER) terminated the shock. Over 90% of rats learned the required response (CAR) after 4 trials daily for five consecutive days and were judged to be fully conditioned. Intraperitoneally administered doses of the test drugs were given to a group of such trained rats. At hourly intervals, for 3 hours after the drug treatment, these responses (ER or CAR) of each animal were tested. One group of rats receiving only the solvent served as a control. The details are recorded in Table 4.

TABLE 4. Effects of phenothiazine drugs on conditioned avoidance response (CAR) and escape response (ER) of trained rats.

Drug	Dose mg/kg	No. of animals	1 hr			2 hr			3 hr		
			Loss CAR	Loss ER	% loss CAR	Loss CAR	Loss ER	% loss CAR	Loss CAR	Loss ER	% loss CAR
Control	—	12	—	—	—	—	—	—	—	—	—
CPZ	7	12	10	6	83.33	11	6	91.66	11	6	91.66
CPZ	3	12	6	—	50	6	—	50	6	—	50
I	10	12	5	—	41.66	7	—	58.33	6	—	50
I	7	12	2	—	16.66	3	—	25	3	—	25
I	3	12	0	—	—	—	—	—	—	—	—
TFP	3	10	8	6	80	10	8	100	10	8	100
TFP	1	10	4	1	40	8	2	80	9	—	90
II	3	12	6	—	50	8	—	66.6	10	2	83.3
II	1	8	1	—	12.5	2	—	25	2	—	25
PER	3	10	10	10	100	10	10	100	10	10	100
PER	1	10	4	—	40	8	2	80	8	3	80
III	3	12	4	—	33.3	11	4	91.66	11	4	91.66
III	1	12	—	—	—	5	—	41.66	5	—	41.66

TABLE 5. Effects of phenothiazines on the amphetamine toxicity in aggregated mice.

Drug	Dose mg/kg	No. of animals	No. of the animals died after						% death after 18 hr
			1 hr	2 hr	3 hr	4 hr	6 hr	18 hr	
CPZ	3	10	—	1	—	—	—	1	20
I	10	10	2	—	—	—	—	1	30
I	3	10	4	1	1	—	2	—	80
TFP	3	10	—	—	—	—	—	—	0
TFP	1	10	—	1	1	—	—	—	20
II	3	10	2	—	—	—	—	—	20
II	1	10	2	2	1	—	2	—	70
PER	3	10	—	—	—	—	—	—	0
PER	1	10	—	1	1	1	—	—	30
III	3	10	—	—	—	—	—	—	0
III	1	10	—	1	1	—	1	—	30

5) *Protective effects to the amphetamine toxicity in aggregated mice*

Albino mice of either sex were divided into twelve groups of 10 animals each, distributing males and females equally in each group. These were kept aggregated in metallic cages (25 cm × 13 cm × 12 cm) having wire meshed walls. In one group of mice, solvent was administered and followed one hour later by *d*-amphetamine sulphate in a dose of 70 mg/kg given intraperitoneally as suggested by Morpurgo (16). The other groups were pretreated with subcutaneous injections of different doses of test compounds and received the same dose (70 mg/kg) of *d*-amphetamine (i. p.) after one hour. These groups were then observed at hourly intervals till first four hours, then at 6th and lastly at 18th hour. The dead animals were removed at the time of each observation. At the end of the experiment, the number of the surviving animals in each group were noted. The results are shown in Table 5.

TABLE 6. Solubilities at pH 7.4 of the phenothiazine derivatives under study.

S. No.	Drug	λ Max $m\mu$	Solubility in parts/million	Calculated relative solubility at pH 7.4
1.	CPZ	255	100	1
2.	TFP	258	40	0.4*
3.	PER	255	38	0.38*
4.	I	255	458	4.58
5.	II	258	83	0.83
6.	III	255	60	0.60

*lit¹⁸ reports. 0.3 and 0.35 for TFP and PER respectively.

6) **Relative solubilities at pH 7.4*

The method followed was the same as described earlier by Sharma *et al.* (17). The solubilities of the drugs expressed in parts per million are listed in the third column of the Table 6 while the calculated solubility of each drug at pH 7.4, relative to that of CPZ are given in the final column of the same Table. Since the optical densities of the saturated solutions of each compound, at the wave length of the maximum absorption, were generally not within the scale of the spectrophotometer, these were diluted as follows :

Compound	Dilution	Solution used
CPZ	100	Saturated/100
TFP	50	Saturated/50
PER	25	Saturated/25
I	100	Saturated/100
II	50	Saturated/50
III	25	Saturated/25

The optical density thus obtained for each solution of unknown concentration was then converted into the concentration of the dissolved compound, using a calibration graph obtained by plotting optical densities against the known concentrations of the compound

* Such a study was undertaken because Green (18) has recently shown that the potent tranquillizing drugs of phenothiazine series, all have relative solubilities of one or less, with CPZ as standard. These findings are, therefore, expected to support the pharmacological data qualitatively, if not quantitatively.

FIG. 2. A comparative intensity of the cataleptic response (%) at 4th hour.

in phosphate buffer (pH 7.4). The value of the concentration thus obtained (ppm) was multiplied by the required dilution factor to get the solubilities in parts per million (ppm). Typical plots are shown in Fig. 2.

III. Scoring of the intensity of the cataleptic reaction in rats*

The study of drug induced catalepsy on white albino rats of average weight of 200–250 g was made, by evaluating their failure to correct the imposed postures of the body. The intensity of the response was scored for each animal according to the stages III and IV as described by Wirth *et al.* (19) and Morpurgo (16). In stage III the rats were

* Though it is difficult to produce parkinsonism in laboratory animals, few means are, however, available to produce symptoms similar to those of parkinsonism (20). A characteristic property of a neuroleptic drug is the ability to induce catatonic like state in experimental animals, which may be regarded as the counterpart of extrapyramidal reaction in human beings (16). Therefore, some workers have used a method of "drug induced catalepsy on rats" for an assessment of parkinsonism liability of a drug. In the present study, this method was, however, followed because of the following reason.

Barbeau (21) has proposed the following modification to McGeer's hypotheses: (i) an imbalance in a system linking dopamine-acetylcholine, would result in symptoms like rigidity and akinesia (ii) a disequilibrium between serotonin-histamine system would produce tremors and akathisia. Since our aim was to correct the extrapyramidal dysfunction by decreasing the neurohumoral content of acetylcholine (of dopamine-acetylcholine system), the method of choice to assess and compare the parkinsonism liability should have been to study the drug induced catatonia in rats. It is pertinent here to mention that the percent incidence and frequency of tremors and akathisia caused by phenothiazines has been reported (22) to be less as compared to akinesia and rigidity. This further strengthened our view to increase the antiacetylcholine like activity of phenothiazine tranquilizers.

placed with one of the front paws set on a cork of 3 cm height, while the other paw remained on the table. In stage IV, one of the front paws was set on a cork of 9 cm height, the other hanging free. The failure to correct the imposed posture within 10 seconds was considered as the positive catatonic reaction. Both the stages (III and IV) were tested on the right and the left sides. Half ($\frac{1}{2}$) point for each side of stage III, and one (1) point for each side of stage IV were arbitrarily assigned for each positive response. The catatonic reactions were evaluated at hourly intervals, after the administration of phenothiazine derivatives, till the fourth hour. The percent catatonic response was employed as a criterion to assess parkinsonism liability of the phenothiazine derivatives under study. The results are listed in Table 7. A graphic representation of the comparative intensity of the cataleptic response at 4th hour, induced by three test compounds (I, II III and their parent drugs (CPZ, TFP and PER) are shown in Fig. 3.

TABLE 7. Effects of phenothiazine drugs on the cataleptic reaction in rats.
Max. points : 24

Drug	Dose mg/kg	No. of animals	Score of catatonic response							
			1 hr		2 hr		3 hr		4 hr	
			Points	%	Points	%	Points	%	Points	%
CPZ	10	8	12	50	14	58.3	15	62.5	14	58.3
CPZ	15	8	13	54.2	15	62.5	15	62.5	14	58.3
CPZ	20	8	14	58.3	15	62.5	14	58.3	15	62.5
CPZ	30	8	16	66.6	20	83.3	20	83.3	19	79.1
I	10	8	0	0	0	0	0	0	0	0
I	15	8	1	4.1	2	8.3	2	8.3	2	8.3
I	20	8	4	16.6	4	16.6	5	20.8	5	20.8
I	30	8	6	25	6	25	5	20.8	6	25
TFP	1	8	1	4.16	9	37.50	11	45.83	12	50
TFP	3	8	13	54.16	21	87.50	24	100	24	100
TFP	10	8	12	50	22	91.66	24	100	24	100
TFP	15	8	12	50	24	100	24	100	24	100
II	1	8	0	0	0	0	0	0	0	0
II	3	8	0	0	1 $\frac{1}{2}$	6.25	5	20.83	4	16.66
II	10	8	2 $\frac{1}{2}$	10.41	12 $\frac{1}{2}$	52.08	11	45.83	11 $\frac{1}{2}$	47.91
II	13	8	3	12.50	11 $\frac{1}{2}$	47.91	15	62.50	15 $\frac{1}{2}$	64.58
PER	1	8	17	70.83	15	62.50	20	83.33	20	83.33
PER	3	8	20	83.33	24	100	24	100	24	100
PER	10	8	24	100	24	100	24	100	24	100
PER	15	8	24	100	24	100	24	100	24	100
III	1	8	$\frac{1}{2}$	2.08	3 $\frac{1}{2}$	12.81	5	20.83	5	20.83
III	3	8	6 $\frac{1}{2}$	27.08	6	25	8	33.33	8	33.33
III	10	8	11	45.83	17	70.83	21	87.50	21	87.50
III	15	8	14	58.33	23	95.83	24	100	24	100

FIG. 3. Plot of optical densities against the concentration of phenothiazines (CPZ, TFP, PER, I, II and III), showing their relative solubilities at pH 7.4.

RESULTS AND DISCUSSION

A contemplation of Fig. 3 and of the results cited in Table 7 would indicate that the catatonic liability of the compounds I, II and III is considerably less as compared to their parent drugs viz. CPZ, TFP and PER. The compound I exhibited only insignificant catatonia (24%) till 30 mg/kg dose while CPZ even at a dose level of 10 mg/kg produced 57.3% catatonic reaction. The compound II produced only about 65% catatonia at a dose level as high as 15 mg/kg which compared well with only 1 mg/kg dose of the parent drug TFP. upto 3 mg/kg, II practically did not produce any significant imbalance of posture (20% catatonia) while TFP, on the other hand, exhibited 100% catatonia at the same dose level. Similarly, compound III induced only 87% catatonia in rats at a dose as high as 10 mg/kg but PER itself produced equivalent catatonic reaction at a little over 1 mg/kg dose level.

Since these derivatives (I, II and III) offered a marked reduction in the liability of parkinsonism over their parent drugs (CPZ, TFP and PER) it is of interest to draw a conclusion as to what extent do these derivatives are devoid of tranquillizing activity.

In general these derivatives affected SMA to a lesser extent as compared to their parent drugs (cf. Table I). The compound I did not affect SMA, ptosis as well as the response of tactile and auditory stimuli at 3 mg/kg dose level. Ptosis and significant loss

of SMA could only be observed at a dose of 10 mg/kg while response to tactile stimuli was still normal. With compound II, though SMA was lowered at a little higher doses (e.g. 3 mg/kg of II compared well with 1 mg/kg dose of TFP), the response to tactile stimuli was still not lost. Similar was the case with compound III and PER.

A comparison of the potencies of all the six phenothiazines to potentiate pentobarbitone sodium induced hypnosis, indicated that it was not much altered in case of II and TFP or III and PER, but I has a markedly decreased ability to induce sleep as compared to its parent drug CPZ (cf. Table 2).

According to Tedeschi *et al.* (13) "the fighting behaviour in paired mice" is a useful test for the evaluation of centrally acting muscle relaxants like meprobamate. Turner (23) has however, suggested that this test is a more sensitive index for evaluation of the tranquillizing property. These views drew our interest in this technique. It was found that at a dose as low as 1 mg/kg of TFP which could significantly block CAR in rats failed to abolish fighting behaviour in paired mice till 5 mg/kg dose was employed (58.3% block). CPZ was found to be more effective than TFP in blocking the fighting response, because 3 mg/kg dose of CPZ could block 25% fighting response which was blocked by the equivalent dose of TFP at all. As CPZ is a weaker tranquillizer and a stronger sedative than TFP (24), it provides an additional evidence that this method is not an appropriate method for evaluating tranquillizers of phenothiazine series at least. Our findings are consistent with Tedeschi *et al.* (13) and thus the tranquillizers like phenothiazines can abolish this response only in doses which cause motor incapacitation and as such this technique is unsuitable for testing tranquillizing property.

As is evident from Table 4 a delayed onset of activity was observed with I, II and III as compared to their parent drugs viz. CPZ, TFP and PER. The compound I at a dose level of 10 mg/kg (50% block of CAR) compared well with 3 mg/kg dose of CPZ (50% block of CAR); thus indicating that it was about three times less potent than CPZ. Trifluoperazine (TFP) at 1 mg/kg dose exhibited 90% block of CAR while 83.3% block of CAR was obtained at a dose of 3 mg/kg of compound II; showing that the latter was approximately one third as potent as TFP. Both compounds III and PER at 3 mg/kg dose did not exhibit any marked difference in the activity, though the former was definitely less potent than the latter. Interestingly, all the three derivatives (I, II and III) blocked the escape response (ER) to a considerably lesser extent as compared to their parent drugs (CPZ, TFP and PER). Though less potent than their parent drugs, these compounds can prove to be better drugs owing to their negligible incapacitation of motor function.

The effects of these six phenothiazine derivatives were studied on amphetamine toxicity in aggregated mice (cf. Table 5). It was observed that PER and III were equipotent in providing protection to the toxicity. II at a dose of 3 mg/kg offered 20% protection which could be obtained by giving 1 mg/kg dose of TFP; showing thereby that it was one third as potent as TFP. The compound III was found to be roughly about 3 times less potent than CPZ as its 10 mg/kg dose offered 30% protection which

was obtained by 3 mg/kg dose of CPZ.

A perusal of Table 6 would indicate that there is no significant difference between the values of solubilities, of TFP and PER relative to that of CPZ as standard, obtained by our method (17) and those quoted by Green (18). According to Green the values of relative solubilities are 1.0 ; 0.30 ; and 0.35 for CPZ, TFP and PER while, our values are 1.00, 0.40 and 0.38 respectively. This minor difference between the values might have been due to several reasons e.g. Green (18) has determined the solubilities at temperature ($24\pm1^{\circ}\text{C}$) using the buffer (pH 7.4) as suggested by Gomori (25) ; while in the present study the solubilities were determined at ($31\pm1^{\circ}\text{C}$) using the phosphate buffer (pH 7.4) (26). Moreover some workers have reported that the aminoalkylphenothiazines have a high surface activity and a tendency to form miscelles (27, 28). Thus some supersaturation might have occurred during the precipitation of the free base from the solution during the preparation of the saturated solution of the drug in the buffer. As a consequence, the values of true solubilities would apparently be lower than those obtained by our procedure. The values of relative solubilities of all the test compounds are given in the final column of Table 6. It is evident that III have the relative solubilities of 0.83 and 0.60 respectively i.e. they fall in a group of potent tranquillizers while I with a relative solubility of 4.58 appears to be a weak tranquillizer. These findings are consistent with Green's (18) observations and support the pharmacological data at least qualitatively.

From the results discussed above it is apparent that the tranquillizing property of II is one third to that of TFP but 3 mg/kg dose of the former (II) produced 20% catatonia, while only 1 mg/kg dose of the latter (TFP) exhibited 65% catatonia ; equivalent dose (3 mg/kg of TFP exhibited 100% catatonia. Similarly, although, lesser potency was exhibited by III than PER, the latter even at a dose of 1 mg/kg induced catatonic reaction equivalent to 10 mg/kg dose of the former (PER). In case of I, though the catalepsy liability was almost negligible, it also lost the tranquillizing ability to a greater extent compared to CPZ. It could bring about tranquillization only when a dose of as 10 mg/kg was employed.

Therefore it could be speculated that the tranquillization potency it also decreased along with the decrease of parkinsonism liability. But this decrease is not proportional because, both II and III although exhibited little decrease in tranquillizing activity, there was a marked reduction in the catatonic liability as compared to TFP and PER respectively. Thus it seems that it is possible to decrease parkinsonism liability greatly, with a little loss of tranquillizing activity and probably a positive correlation between the extrapyramidal reactions and the antipsychotic activity does not exist. Perhaps, minor disturbance of the extrapyramidal tract are, however, always associated with tranquillization. Finally these studies indicate that diphenacyloxime trifluoperazine dibromide (II) and diphenacyloxime perphenazine dibromide (III) may prove to be promising therapeutic agents.

SUMMARY

Since phenothiazines are the valuable drugs in psychiatry, control of their extrapyramidal side effects offers an important challenge. A review of literature, regarding the biochemical alterations produced by drug induced parkinsonism, clearly indicates that the only way to reduce parkinsonism liability of these drugs is to increase their anticholinergic like activity. Since oximes are generally used as antidotes in case of organophosphorous poisoning, one can speculate that anticholinergic compounds of these kinds can provide a tranquillizer with lesser liability for Parkinson disease. Thus some quaternary oximes of phenothiazine drugs were synthesized. These compound were assessed for their parkinsonism liability. Their CNS depressant properties were also studied and compared with their parent drugs. From these studies, it appeared that it is possible to decrease the parkinsonism liability to a greater extent, with only a little loss of antipsychotic activity and probably a positive correlation between these two biological actions, one desirable and the other unwanted, does not exist.

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