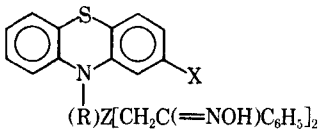
Phenothiazines as Anticholinergics

V. N. SHARMA, N. S. PANCHOLI, H. L. SHARMA, R. L. MITAL*, and DHARMA CHANDRA*

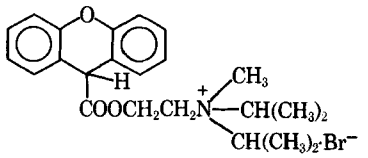
Abstract □ The synthesis and anticholinergic activity of a new series of quaternary oximes of some 10-*N*-substituted phenothiazines are reported.

Keyphrases □ Phenothiazine oximes—synthesis, pharmacological screening as possible anticholinergic agents □ Anticholinergics, potential—synthesis, pharmacological evaluation of quaternary oximes of 10-*N*-substituted phenothiazines □ Quaternary phenothiazine oximes—anticholinergic activity

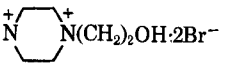
Earlier attempts (1, 2) showed that one way to reduce the Parkinsonism liability of phenothiazine drugs, with little loss of tranquilizing efficacy, is to increase the anti-acetylcholinelike activity. Since chemically related quaternary salts such as banthine and probanthine are well-known anticholinergic drugs, the authors speculated that quaternary oximes of phenothiazines might also exhibit enhanced anticholinergic activity. The CNS effects of a few phenothiazine oximes were already reported (1, 2). Some other quaternary oximes of various 10-*N*-substituted phenothiazines (I–IX) synthesized in the authors' laboratory recently were, however, found to be devoid of any significant CNS-depressant activity (3). When assayed for their activity as acetylcholine inhibitors on frog rectus abdominis muscle preparation (4), they exhibited pronounced anticholinergic activity as

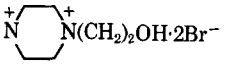


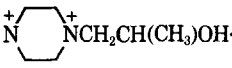
I–IX

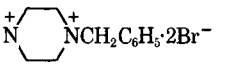


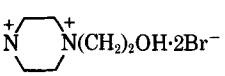
X: Probanthine

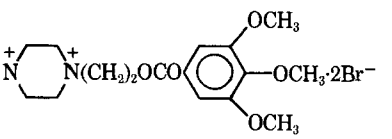
I: X = H, R = $COCH_2$, Z =  $N(CH_2)_2OH \cdot 2Br^-$

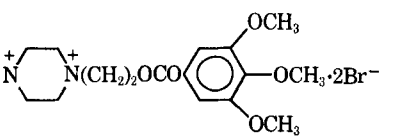
II: X = Cl, R = $COCH_2$, Z =  $N(CH_2)_2OH \cdot 2Br^-$

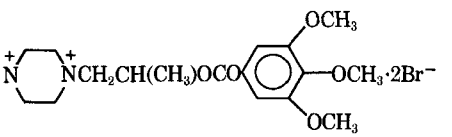
III: X = Cl, R = $COCH_2$, Z =  $NCH_2CH(CH_3)OH \cdot 2Br^-$

IV: X = Cl, R = $(CH_2)_3$, Z =  $NCH_2C_6H_5 \cdot 2Br^-$

V: X = Cl, R = $CH_2CH(CH_3)CH_2$, Z =  $N(CH_2)_2OH \cdot 2Br^-$

VI: X = Cl, R = $CH_2CH(CH_3)$, Z =  $OCH_3 \cdot 2Br^-$

VII: X = OCH_3, R = $CH_2CH(CH_3)$, Z =  $OCH_3 \cdot 2Br^-$

VIII: X = Cl, R = $(CH_2)_3$, Z =  $OCH_3 \cdot 2Br^-$

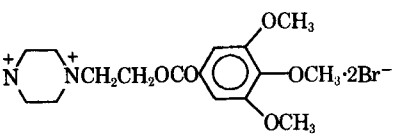
IX: X = Cl, R = $(CH_2)_4$, Z =  $OCH_3 \cdot 2Br^-$

Table I—Phenacyloxime (Phenothiazine) Dibromides and Their Pharmacological Test Data

Product[a]	Melting Point	Yield, %	Formula	Analysis, % Calc.	Analysis, % Found	Dose, mcg./ml.	Reduction[b], %	Recovery, min.
I	163–165°	70	$C_{36}H_{39}Br_2N_5O_4S$	C, 54.20 H, 4.89 N, 8.78	C, 53.80 H, 4.72 N, 8.70	1 2	68.8 82.7	25 25
II	163–165°	80	$C_{36}H_{38}Br_2ClN_5O_4S$	C, 51.71 H, 4.57 N, 8.50	C, 51.52 H, 4.52 N, 8.40	1 2	50.6 56.4	15 40
III	163–165°	72	$C_{37}H_{40}Br_2ClN_5O_4S$	C, 52.51 H, 4.73 N, 8.23	C, 52.41 H, 4.28 N, 8.13	1 2	42.9 71.8	40 40
IV	143–144°	70	$C_{42}H_{44}Br_2ClN_5O_2S$	C, 57.43 H, 5.01 N, 7.97	C, 56.92 H, 4.82 N, 7.78	1 2	5.06 5.90	Immediate Immediate
V	143–145°	72	$C_{38}H_{44}Br_2ClN_5O_3S$	C, 56.05 H, 5.40 N, 8.60	C, 55.74 H, 5.00 N, 8.52	1 2	24.3 68.3	35 No recovery[c]
VI	150–153°	70	$C_{47}H_{52}Br_2ClN_5O_7S$	C, 54.98 H, 5.07 N, 6.82	C, 55.12 H, 4.85 N, 6.71	1 2	13.30 13.04	15 20
VII	148–153°	80	$C_{48}H_{55}Br_2N_5O_8S$	C, 56.41 H, 5.40 N, 6.85	C, 56.25 H, 5.12 N, 6.52	1 2	40.2 59.0	55 55
VIII	128–133°	75	$C_{48}H_{54}Br_2ClN_5O_7S$	C, 55.41 H, 5.10 N, 6.73	C, 55.31 H, 5.00 N, 6.51	1 2	32.1 49.4	35 35
IX	138–140°	80	$C_{48}H_{54}Br_2ClN_5O_7S$	C, 55.41 H, 5.10 N, 6.73	C, 55.22 H, 4.92 N, 6.67	1 2	31.3 40.3	40 40
X: Probanthine	—	—	—	—	—	1 2	57.0 59.0	Immediate 7

[a] The compounds were dissolved in ethanol, treated with carbon, and diluted with large volume of ether. The crystallized products were isolated by filtration and dried, and furnished satisfactory elemental analysis. [b] The height of contraction (millimeters) due to acetylcholine (0.1 mcg./ml.) was measured before and after each addition of different doses of compounds. The percent reduction in contraction produced by each dose of individual drug was thus determined. [c] Up to 1 hr.

expected. The results were compared with probanthine (X). The chemical and pharmacological test data of these compounds appear in Table I. Their structural formulas are shown (I–X).

It seems difficult to correlate the chemical structures of these compounds with their actual potencies from the results recorded in Table I. However, all these compounds were longer acting than the standard drug, in this case probanthine. The 10-*N*-acylaminophenothiazines (I–III) were more potent than the 10-*N*-alkylaminophenothiazines (IV–IX). Compound I was exceptionally more potent, while II and III were almost equipotent to probanthine. Since some reported acylaminophenothiazines were found to exhibit a spasmolytic effect (5), their enhanced activity might be attributed to an additive effect, exerted by the —CO— group in the presence of the oxime moiety.

EXPERIMENTAL

Melting points are uncorrected and were taken in open capillary tubes. IR and UV absorption spectra were measured on a Perkin-Elmer model 137 and Beckman quartz spectrophotometer model DU, respectively. Corex cells (1 cm.) were used to run UV spectra in ethanol, while IR spectra were run in KBr disks. These spectra were run in conjunction with melting points to ascertain the structures of the compounds. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. For pharmacological studies, the compounds were dissolved in a minimal amount of warm ethanol and then the required dilution was made with distilled water. Studies were always conducted with freshly prepared solutions of each drug. Since the control studies with solvent alone did not exhibit any antiacetylcholine activity, the activities of the compounds are reported here. Reaction to acetylcholine by the muscle was determined; then the test drug was allowed to act on the muscle preparation for 2 min., and acetylcholine (0.1 mcg./ml.) was added.

10-*N*-Acyl- or Alkylaminophenothiazines—10-[4′-(β′-Hydroxyethyl)piperazinyl-1′]acetylphenothiazine (Compound A), 2-chloro-10-(β′-hydroxyethyl)piperazinyl-1′]acetylphenothiazine (Compound B), 2-chloro-10-[4′-(β′-hydroxypropyl)piperazinyl-1′]acetylphenothiazine (Compound C) (6), 2-chloro-10-γ-[4′-(benzyl)piperazinyl-1′]propylphenothiazine difumarate (Compound D)[1], 2-chloro-10-β-methyl-[4′-(β′-hydroxyethyl)piperazinyl-1′]propylphenothiazine difumarate (Compound E)[1], 2-chloro-10-β-[4′-(β′-hydroxyethyl)-piperazinyl-1′]propylphenothiazine 3′,4′,5′-trimethoxybenzoic ester difumarate (Compound F), 2-methoxy-10-β-[4′-(β′-hydroxyethyl)piperazinyl-1′]propylphenothiazine 3′,4′,5′-trimethoxybenzoic ester difumarate (Compound G) (6), 2-chloro-10-γ-[4′-(β′-hydroxypropyl)piperazinyl-1′]propylphenothiazine 3′,4′,5′-trimethoxybenzoic acid ester dimaleate (Compound H) (6), and 2-chloro-10-δ-[4′-(β′-hydroxyethyl)piperazinyl-1′]butylphenothiazine 3′,4′,5′-trimethoxybenzoic ester (Compound J) (7) were prepared by adopting the procedures reported earlier.

Phenacyl Bromide Oxime—This was synthesized by the method of Sharma *et al.* (1).

Phenacyloxime (Phenothiazine) Dibromides—The procedure employed was essentially the same as reported earlier (1). The free base was first libera ed from its respective salt by 20% aqueous NaOH, taken up by $CHCl_3$, and worked up as usual. The solution of the free base (0.005 mole) in anhydrous ether, when treated with phenacyl bromide oxime (0.0115 mole), resulted in an immediate precipitation of quaternary oxime (I–IX) from the respective compound (A–J).

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[1] These compounds were supplied by Dr. Toldy of the Institut für Arzneimittelforschung, Budapest, Hungary.

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Detection of CL-912, a 1,3-Dioxalane, in Collapsible Tube Liner by Attenuated Total Reflection Spectroscopy

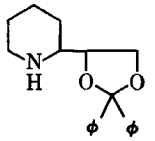
S. C. MUTHA

Abstract □ An attenuated total internal reflection technique was used to demonstrate the migration of the free base of CL-912C from a urological jelly to the lining of collapsible tubes during the sterilization cycle. This observation was substantiated by examination of isooctane extract of the sample liner by TLC and attenuated total internal reflection.

Keyphrases □ CL-912, a 1,3-dioxalane, in urological jelly—migration to collapsible tube liner, attenuated total internal reflection □ Attenuated total internal reflection—migration of CL-912 from urological jelly to collapsible tube lining □ Sterilization—migration of a 1,3-dioxalane from urological jelly to tube lining

Attenuated total internal reflection (ATR) has been established as a useful analytical tool. Briefly, the principles of ATR are as follows. When a beam of radiation enters a prism, it is reflected internally if the angle of incidence at the interface between the sample and prism is greater than the critical angle (Fig. 1). The internally reflected beam appears to penetrate slightly beyond the reflecting surface. If a sample that absorbs IR radiation is placed against the reflecting surface, the beam loses energy at those wavelengths where the sample absorbs.

A plot of intensity of reflected radiation as a function of wavelength resembles the absorption spectrum obtained by the transmission method. The apparent depth to which the radiation penetrates the sample is limited to a few microns and is dependent on the ratio of refractive indexes and the angle of incidence. Consequently, this technique has made possible the applications of IR spectroscopy in areas where it was not previously possible, such as with polymers, resins, leather, rubber, thin coatings, condensed GC fractions, fibers, and fabrics (1–3). Authentication of delicate objects like postage stamps have been carried out using ATR (4, 5); induced changes in biological tissues can also be detected (6). In this study, its usefulness in demonstrating the migration of (−)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxalane (CL-912) from a jelly to the lining of collapsible tubes is discussed.



CL-912

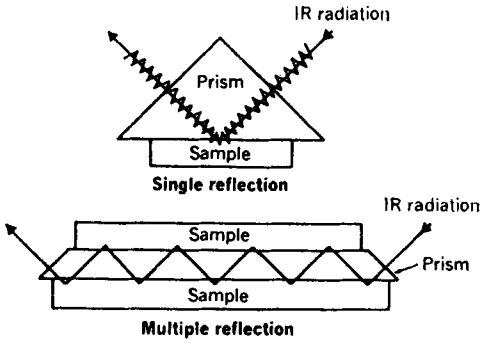


Figure 1—*Schematic diagram of single and multiple reflections.*

A prior-to-fill assay on urological jelly containing (−)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride (CL-912C)[1] indicated that the calculated amount of CL-912C was present in the formulation, but the assay immediately after sterilization of samples showed an 8–10% loss of the drug (7). Either the drug was degraded during the sterilization cycle or was bound to the liner. Hydrolysis of CL-912 gives benzophenone and 2-piperidyl-1,2-ethanediol, but no appreciable quantities of these were found in the jelly (7). The present studies were undertaken to determine if intact CL-912C, its free base (CL-912), or the degradation products are adsorbed on the linear surface.

EXPERIMENTAL

Materials—In all experiments, CL-912C[2] was used. The free base (CL-912) was prepared by dissolving the hydrochloride in a quantity of distilled water, liberating it by addition of 5 *N* sodium hydroxide, and extracting with isooctane. The solvent was removed under reduced pressure.

[1] Levoxadrol hydrochloride, Cutter Laboratories, Berkeley, CA 94710
[2] Cutter Laboratories, Batch BL-16.