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## Effects of the Halogenation of Oxyquinoline on Biological Activity.*

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(Introduced by C. D. Leake.)

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Chiniofon, N. N. R., introduced commercially as "yatren", and first tried clinically in amebiasis by Mühlens and Menk[1] in 1921, has had some popularity as an amebicidal agent. Chemically chiniofon is sodium-iodoxy-quinoline-sulphonate, and is related to chinosol N. N. R. (oxyquinoline sulphate) and vioform N. N. R. (iodochloroxyquinoline). Since chiniofon has been claimed to have amebicidal activity, we thought it might be of interest to study it from this standpoint in comparison with as many related compounds as we could secure. Such an effort we thought might yield significant information regarding the relation of chemical constitution to

TABLE I.
*Summary of some Data Relating to Toxicity, Balantidicidal Action, and Amebicidal Concentration of Certain Halogenated Oxyquinoline Derivatives.*

| Drug. | Proportion of Deaths and Oral Lethal Dose in Guinea Pigs | Oral Balantidicidal Dose in Guinea Pigs | Amebicidal Concentration *in vitro* 24 hours |
|---|---|---|---|
| Oxyquinoline | 2/10 at 1200 mgm./Kg. | 20% cured at 1250 mgm./Kg. | Not tested, insoluble in water |
| Oxyquinoline sulphate | 1/10 at 1200 " " | No cures at 1250 mgm./Kg. | 1:10,000 |
| Chloroxyquinoline | 5/15 at 1200 " " | Not tested | 1:10,000† |
| Na-Iodoxyquinoline sulphonate | 7/15 at 900 " " | 60% cured at* 600 mgm./Kg. | 1:500 |
| Iodochloroxyquinoline | 7/10 at 200 " " | 80% cured at* 150 mgm./Kg. | Not tested, insoluble |
| Diethyl-amino-dimethylene-hydroxy-iodochlorquinoline HCl | 5/10 at 250 " " | Not tested | 1:50,000 |

* 20% mortality at this dose.
† In 25% buffered ethylene glycol, which has no amebicidal action in itself.

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[1] Mühlens, P., and Menk, W., *Munch. Med. Wochnschr.*, 1921, **68**, 802.

pharmacological action in this series of oxyquinoline derivatives, particularly with reference to the effects on biological activity of introducing various halogens into the oxyquinoline molecule.

We secured the following compounds for this investigation: 1. Oxyquinoline, from Dr. J. V. Barrow. 2. Oxyquinoline sulphate (Chinosol, N. N. R.). 3. Chloroxyquinoline, from the Ciba Co., Inc. 4. Sodium-iodoxyquinoline sulphonate (Chiniofon, N. N. R.). 5. Iodochloroxyquinoline (Vioform—Ciba, N. N. R.). 6. Diethylamino-dimethylene-hydroxy-iodochlorquinoline HCl, from the Ciba Co., Inc.

In this series, compounds 3 and 4 are monohalogenated derivatives of oxyquinoline, while in compounds 5 and 6, two different halogen atoms have been placed in the oxyquinoline molecules.

These substances have been studied with respect to toxicity on oral administration to guinea-pigs, rabbits, and cats; balanticidal action in naturally infested guinea pigs; amebicidal action *in vitro,* and therapeutic effect in monkeys naturally infested with intestinal parasites. The techniques followed have been previously described.[2] A general summary of part of this study appears in Table I.

It may be noted that toxicity increases with halogenation of oxyquinoline, and in proportion to the atomic weight of the halogen. Thus chloroxyquinoline is slightly more toxic than oxyquinoline, and the iodoxyquinoline compound is slightly more toxic than the one containing chlorine. The addition of both iodine and chlorine to oxyquinoline results in a considerable increase in toxicity, but the further addition of a solubilizing group reduces the toxicity somewhat. Similarly balanticidal action in naturally infested guinea pigs seems to increase with increasing halogenation of oxyquinoline. But amebicidal action *in vitro* does not seem to be related in this same way to the chemical constitution of this series of drugs.

In monkeys naturally infested with *Endameba histolytica,* 900 mgm./Kg. of iodochloroxyquinoline was tolerated in divided doses over a 6 weeks period with eradication of amebae during the time of observation. Further studies are indicated in order to evaluate the usefulness of these compounds in treating protozoan infestation in mammals.

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[2] Anderson, H. H., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 267; Leake, C. D., Koch, D. A., and Anderson, H. H., *Ibid.,* 1930, **27**, 717; *Am. J. Trop. Med.,* 1930, **10**, 249; David, N. A., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1930, **28**, 196.