topography of the hypothetical antihistaminic receptor and/or drug-bound receptor is unknown, *A* and *B* should only be looked upon as highly schematized two-dimensional representations of a three-dimensional pattern for the bound receptor. In addition, the structures presented here are not necessarily uniformly representative of the conformations of the bound drug. There is no evidence to suggest that the conformationally mobile antihistamines are bound in their most stable conformations nor is there any evidence to suggest that I, II, and IV bind to the hypothetical receptor in the same way.

Finally, it is clear that Barlow's (1) rationalization leading to assignment of the (S)-configuration for the antihistaminically more active antipode of isothipendyl (I) is subject to the same objections already discussed. Accordingly, this assignment of configuration, if correct, is only fortuitously so. While the α-methyl may sterically inhibit the drug receptor binding as apparently suggested (1), it may instead contribute to and thus re-enforce the other drug–receptor interactions through hydrophobic and more highly distant specific van der Waals interactions with the receptor. The latter possibility would lead to selection of the (R)-configuration as the more active antipode. Neither observation is necessarily productive of sound configuration-activity relationships without data on the desmethyl analog as well.

The finding (6) that the absolute configuration of all the (+)-pheniramines is (S) and not (R) as proposed by Barlow (1) does not affect this critique, and we obviously defer assignment of configuration to the hypothetical antihistaminic receptor until more definitive experiments, now in progress, are completed.

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Received January 26, 1967.
Accepted for publication June 6, 1967.

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Tumor Localizing Agents III. Radioiodinated Quinoline Derivatives

Sir:

For several years we have been interested in developing an agent which would be useful for the diagnostic localization and treatment of melanotic tumors. Our approach to this problem has involved the synthesis of radiolabeled compounds which would selectively localize in these tumors much like radioiodine localizes in the thyroid. In order to achieve this tumor selectivity, the initial selection of compounds for radiolabeling has fallen into two categories, namely: (*a*) precursors of melanin and (*b*) compounds which are known to interact with melanin. Previous publications (1, 2) from this laboratory described the results with several radiolabeled melanin precursors.

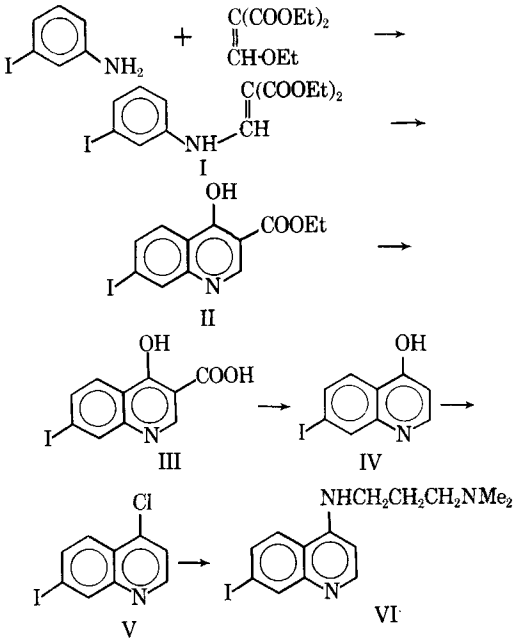
In recent years, several reports have appeared indicating that chloroquine has a marked affinity for melanin and is only slowly released from pigmented tissues (3–5). This information prompted us to synthesize a number of radioiodinated analogs of chloroquine and study their distribution in mice with transplanted melanomas. This report describes initial results with one of these radioiodinated analogs.

The general procedure of Price and Roberts (6) was employed to obtain the key intermediate 4-chloro-7-iodoquinoline (V). (Scheme I.)

Ethoxymethylenemalonic ester was condensed with 3-iodoaniline to give ethyl α-carbethoxy-β-(3-iodophenylamino)acrylate (I) in 77% yield, m.p. 88–89°.

Anal.—Calcd. for $C_{14}H_{16}INO_4$: C, 43.21; H, 4.14. Found: C, 43.34; H, 4.11.

The addition of I to refluxing diphenylether afforded 3-carbethoxy-4-hydroxy-7-iodoquinoline (II) in 94% yield. Recrystallization from pyridine gave an analytical sample which starts to sublime at 255°.



Scheme I

Anal.—Calcd. for $C_{12}H_{10}INO_3$: C, 42.02; H, 2.94. Found: C, 42.11; H, 2.83.

Saponification in aqueous ethanol followed by acidification furnished the carboxylic acid (III) in 98% yield, melting with decarboxylation at 278°.

Anal.—Calcd. for $C_{10}H_6INO_3$: C, 38.13; H, 1.92. Found: C, 38.18; H, 1.88.

When III was recrystallized from dimethysulfoxide a crystalline solvate was obtained which sublimed at 280–290°, γ_{max}. 1720 (C=O) and 1030–1010 cm.$^{-1}$ (S=O).

Anal.—Calcd. for $C_{10}H_6INO_3 \cdot C_2H_6SO$: C, 36.66; H, 3.08. Found: C, 36.58; H, 2.96.

Decarboxylation of III in refluxing diphenylether afforded crude 4-hydroxy-7-iodoquinoline (IV) which, without further purification, was treated with phosphorous oxychloride. Recrystallization of the resulting product from chloroform furnished 4-chloro-7-iodoquinoline (V) in 70% yield, m.p. 97–98°. [Reported m.p. 95.5–97° (7).] Treatment of V with refluxing 3-dimethylaminopropylamine gave the desired chloroquine analog, 4-(3-dimethylaminopropylamino)-7-iodoquinoline (VI) in 65% yield, m.p. 101–103°. The NMR spectrum ($CDCl_3$) showed a singlet at 7.64 δ (NCH_3), a triplet at 7.43 δ ($-CH_2N$) (J = 6.0 c.p.s.), and a multiplet centered at 6.67 δ (CH_2NH—) which became a triplet upon deuteration (J = 6.0 c.p.s.).

Anal.—Calcd. for $C_{14}H_{18}IN_3$: C, 47.35; H, 5.11. Found: C, 47.36; H, 5.17.

Iodine-125 or ^{131}I was introduced into VI by isotope exchange with radioactive sodium iodide in ethylene glycol at 170–175°. By this procedure the ^{125}I and ^{131}I-labeled compounds were obtained with specific activities of 2.03 and 1.42 mc./mmoles, respectively. The radiolabeled compounds were purified by recrystallization and analyzed by thin-layer chromatography (TLC). In both cases, a radiochromatogram scan showed a single radioactive area coincident with the single TLC spot seen under ultraviolet light.

Four to five-week-old male, black mice of the BL6J strain were injected intraperitoneally with 10 μc. of 4-(3-dimethylaminopropylamino)-7-iodoquinoline-^{125}I and sacrificed at 12, 24, and 48 hr. Control mice were injected *via* the same route with 10 μc. of sodium iodide-^{125}I and sacrificed at the same time intervals. Counting was done in a commercial well counter. Table I shows the concentrations in six tissues, two of

TABLE I—TISSUE DISTRIBUTION OF SODIUM IODIDE-^{125}I AND 4-(3-DIMETHYLAMINOPROPYLAMINO)-7-IODOQUINOLINE-^{125}I IN c.p.m./mg. ± S.E. AFTER INTRAPERITONEAL INJECTION IN MICE

No. of Mice	Av. Wt. of Group, Gm.	Dose, μc.	Time of Sacrifice After Injection, hr.	Tissues					
				Eyes	Skin[b]	Liver	Adrenal	Kidney	Thyroid
Sodium Iodide-^{125}I									
4	23.4	10	12	14.6 ± 2.1	30.9 ± 4.5	26.5 ± 2.9	32.6 ± 7.7	43.9 ± 7.4	3.18×10^5 ± 1.78×10^{5a}
3	20.6	10	24	11.0 ± 1.1	23.1 ± 1.2	36.3 ± 3.6	26.7 ± 15.2	79.6 ± 8.5	8×10^5 ± 3.17×10^{5a}
	21.2	10	48	13.2 ± 2.5	21.8 ± 5.0	70.7 ± 20.4	28.3 ± 7.7	249.6 ± 58.8	5.4×10^5 ± 1.24×10^{5a}
4-(3-Dimethylaminopropylamino)-7-iodoquinoline-^{125}I									
4	22.6	10	12	259.1 ± 14.7[a]	90.5 ± 3.1[a]	170.0 ± 11.0[a]	415.6 ± 32.4[a]	133.4 ± 8.6[a]	1120.5 ± 385.1
4	21.8	10	24	338.9 ± 26.3[a]	97.8 ± 13.6[a]	224.9 ± 85.4	460.6 ± 108.2[a]	234.4 ± 133.0	2047.6 ± 1247.3
3	22.8	10	48	461.0 ± 69.4[a]	88.5 ± 5.6[a]	83.7 ± 12.4	221.3 ± 13.3[a]	81.0 ± 20.0	1645.6 ± 795.4

[a] $p < 0.05$. [b] Skin radioactivity was obtained by counting the ear lobe. Therefore, the concentration in skin *per se* is probably at least twice that shown.

which are known to contain large amounts of melanin (eye, skin). The distribution of activity of the radioiodinated analog of chloroquine was similar to that seen with chloroquine in rats (8) and chloroquine-^{14}C in mice (9). Moreover, the low thyroid activity observed for the animals receiving the radioiodinated compound *versus* those given radioiodide, indicates that significant deiodination did not occur. Studies using mice with transplanted melanomas are now in progress.

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Received April 21, 1967.
Accepted for publication June 6, 1967.

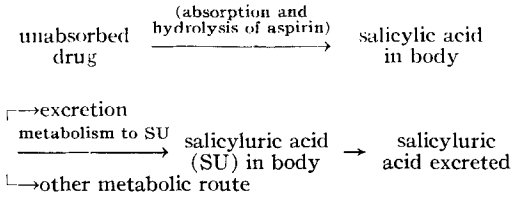
This work was supported by research grants CA-08349-02 and CA-08429-02 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and PRA-18 from the American Cancer Society, New York, N. Y.

Evidence for Nonfirst-Order Kinetics of Salicylate Elimination—A Rebuttal

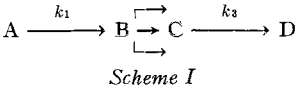
Sir:

Wagner's recent article (1) relating to the pharmacokinetics of salicylate elimination contains unwarranted conclusions and therefore requires an early rebuttal.

He claims that our pharmacokinetic model for salicylate elimination in man, which assumes capacity-limited formation of salicyluric acid at doses of 1 Gm. aspirin and above (2), is unjustified, and that all processes are likely to be apparent first-order. He bases his reasoning on a model involving a catenary chain of the type shown in Scheme I.

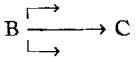


i.e.,



Scheme I

where all processes are first-order and the over-all rate constant for decline of B is defined as k. A direct and unambiguous test of this model is available by using experimental conditions which reduce the model to that shown in Scheme II.



Scheme II

This is accomplished by injecting B intravenously and following its concentration in the plasma as a function of time.[1]

Wagner's model requires that the half-life for the decline of salicylate concentrations in the plasma after intravenous injection of sodium salicylate be independent of dose. In fact, the average half-life [or the apparent half-life, since we do not consider the kinetics at higher doses to be first-order (2)] is 2.4 hr. with 0.25-Gm. doses (4), 6.1 hr. with 1.3-Gm. doses (5), and 19 hr. with 10–20-Gm. doses (6). In all instances, the drug was injected intravenously as salicylate.[2] These data, which were cited in our original paper, provide direct evidence that Wagner's contention is incorrect.

Wagner's pharmacokinetic model consists entirely of first-order rate processes. As a consequence (and in addition to the requirement stated in the preceding paragraph), the time course of urinary excretion of drug in all forms,

[1] Salicylate distribution is so rapid relative to elimination (3) that blood level data are not distorted by the distributive process beyond a very short time following intravenous injection.

[2] Only with the lowest dose was the half-life determined from urinary excretion data (which is acceptable in the context of the present discussion since it yielded the shortest half-life).