

Iodoxuridine—A Preliminary Report

By LOUIS J. RAVIN, CHARLES A. SIMPSON, and ALFRED F. ZAPPALA

Data are presented to show that the principal decomposition products of idoxuridine ophthalmic solution in acidic media (pH 1.3 to 6.7) are 5-iodouracil and 2-deoxyribose. A trace of 2'-deoxyuridine was also detected. Uracil was not formed under the conditions of these experiments.

DURING THE development of a clinically acceptable idoxuridine ophthalmic solution it was necessary to determine the type of breakdown products formed during storage at temperatures ranging from 5 to 60°. This note presents some preliminary information concerning the nature of the decomposition products formed when idoxuridine ophthalmic solution is artificially decomposed in acidic media (pH 1.3 to 6.7).

A column partition chromatographic procedure was developed (1) and subsequently used to separate the decomposition products from the idoxuridine. The individual components were then assayed by spectrophotometric methods.

Iodoxuridine, some possible decomposition products, and an artificially decomposed solution of idoxuridine ophthalmic solution were chromatographed on paper using a *n*-butanol-3 *N* ammonia solvent system. A comparison of the approximate *R*_f values obtained are listed in Table I.

It can be seen from these data that the principal products formed when idoxuridine ophthalmic solution decomposes in acidic solution are 5-iodouracil, 2-deoxyribose, and 2'-deoxyuridine. Subsequent analysis of degraded samples by the partition column procedure substantiated that the breakdown products formed under these conditions

Received June 13, 1963, from the Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pa.

Accepted for publication October 14, 1963.

TABLE I.—COMPARISON OF APPROXIMATE *R*_f VALUES OBTAINED FOR IDOXURIDINE, SOME POSSIBLE DECOMPOSITION PRODUCTS, AND AN ARTIFICIALLY DECOMPOSED OPHTHALMIC SOLUTION

Material	Known Soln.	<i>R</i> _f Values	
		Artificially Decomposed Soln.	Artificially Decomposed Soln.
2'-Deoxyuridine	0.23	0.23 (Trace)	...
Uracil	0.28
Iodoxuridine	0.31	0.31 (Large)	...
2-Deoxyribose	0.37	0.39 (Significant)	...
5-Iodouracil	0.50	0.48 (Significant)	...

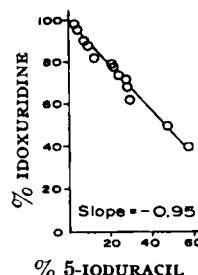


Fig. 1.—Plot showing decreasing idoxuridine and increasing 5-iodouracil concentrations for artificially decomposed idoxuridine ophthalmic solutions.

are 5-iodouracil, 2-deoxyribose, and a trace of 2'-deoxyuridine. Figure 1 shows a plot of per cent idoxuridine *versus* per cent 5-iodouracil. The linear relationship having a slope of 0.95 indicates that for every mole of idoxuridine that decomposes, approximately 1 mole of 5-iodouracil is formed, further indicating that 5-iodouracil and 2-deoxyribose are the principal breakdown products. Uracil was not detected in the decomposed samples under the conditions of this study.

REFERENCE

(1) Smith Kline and French Laboratories, to be published.

Thin-Layer Chromatography of Iodochlorhydroxyquin

By B. P. KORZUN, S. M. BRODY, and F. TISHLER

A thin-layer chromatographic method is described for the separation of iodochlorhydroxyquin and its intermediates. The method is applicable not only to the substance but also to its pharmaceutical formulations, in which the material is suspended in ointment or cream.

THE PRESENT analytical procedures (1-4) available for determining iodochlorhydroxyquin,¹ both as the substance and in formulations, do not distinguish between iodochlorhydroxyquin and its possible intermediates. The colorimetric procedure of Haskins and Luttermoser (2) and the paper chro-

matographic procedure of Castiglioni (3), although capable of separating 8-hydroxyquinoline from iodochlorhydroxyquin, do not separate iodochlorhydroxyquin from other halogenated hydroxyquinoline intermediates.

A semiquantitative thin-layer chromatographic procedure, using polyamide as the adsorbant, has been developed which separates iodochlorhydroxyquin from all probable intermediates, except 5,7-dichlorohydroxyquinoline. In combination with iodochlorhydroxyquin, the limit of detection is 0.25 mcg.

Received October 18, 1963, from the Research Department, Ciba Pharmaceutical Company, Division of Ciba Corporation, Summit, N. J.

Accepted for publication November 12, 1963.

¹ Marketed as Vioform by Ciba Pharmaceutical Co., Summit, N. J.

for 8-hydroxyquinoline and 5-chloro-8-hydroxyquinoline, and it is 2 mcg. for 5-iodo and 5,7-diodo 8-hydroxyquinoline.

EXPERIMENTAL

Preparation of Plates. The plates (20 × 20 cm.) are prepared by mixing 5 Gm. of Woelm's polyamide powder¹ and 3.5 Gm. calcium sulfate with 10 ml. distilled water. The mixture is poured into the Desaga² applicator and spread on five plates.³ The approximate thickness of the coat is 250 μ . The coated plates are air-dried for 16 hours at room temperature. Prior to use, the plates are heated at 80° for 10 minutes and allowed to cool.

Preparation of Samples.—Weigh an amount of the formulation equivalent to 100 mg. of iodochlorhydroxyquin into a 250-ml. conical flask. Add about 100 ml. of acetone and heat on a steam bath for about 15 minutes, shaking frequently. Cool to room temperature, and filter into a suitable round-bottom flask. Wash the conical flask with several 5-ml. portions of acetone and filter, combining all extracts. Evaporate the acetone, and dissolve the residue in 10 ml. of dimethylformamide-methanol (1:2) with the aid of a little heat.⁴ Centrifuge, if necessary, and use the clear solution for sampling (1% solution). Reference standard solutions of iodochlorhydroxyquin (1%), 5-chloro-8-hydroxyquinoline (0.025%), 8-hydroxyquinoline (0.025%), 5,7-diodo-8-hydroxyquinoline (0.05%), and 5-iodo-8-hydroxyquinoline (0.05%) in dimethylformamide-methanol (1:2) are prepared.

Application and Development of Plates.—Five microliters of each solution, except 8-hydroxyquinoline (2 μ l.) and 5-chloro-8-hydroxyquinoline (2 μ l.), are applied to the plate at a point 2 cm. from the lower edge of the plate and 2 cm. apart. The plates are placed into a chamber (22.5 × 10 × 26 cm.), the bottom of which is covered with 100 ml. of methanol. The chamber is covered, and the solvent is allowed to ascend to a line drawn 15 cm. from the point of application. The time of development is approximately 1 hour. The plates are removed, air-dried, and the compounds detected by viewing either under an ultraviolet light (2660 Å) or after spraying with Pauly reagent (5).

RESULTS AND DISCUSSION

Figure 1 shows a typical separation of the individual compounds and also a separation of a mix-

¹ Available from Aluparm Chemicals, New Orleans, La.

² Available from Brinkmann Instruments, Long Island, N. Y.

³ In many cases not all of the residue will dissolve due to the insolubility of many ointments in the solvent.

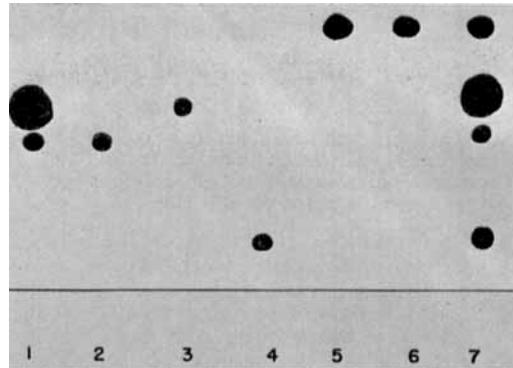
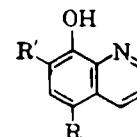


Fig. 1.—Portion of thin-layer chromatogram of (1) iodochlorhydroxyquin, (2) 5-chloro-8-hydroxyquinoline, (3) 5,7-dichloro-8-hydroxyquinoline, (4) 8-hydroxyquinoline, (5) 5-iodo-8-hydroxyquinoline, (6) 5,7-diodo-8-hydroxyquinoline, and (7) mixture of all compounds, illustrating relative sizes of the spots. Line shows finish of solvent front.

TABLE I.— R_f VALUES FOR IODOCHLORHYDROXYQUIN AND INTERMEDIATES



R	R'		R_f
H	H	8-Hydroxyquinoline	0.90
Cl	H	5-Chloro-8-hydroxyquinoline	0.83
Cl	Cl	5,7-Dichloro-8-hydroxyquinoline	0.63
Cl	I	Iodochlorhydroxyquin	0.63
I	H	5-Iodo-8-hydroxyquinoline	0.50
I	I	5,7-Diodo-8-hydroxyquinoline	0.50

ture. Table I lists the R_f values for the compounds. Once the contaminant is identified, a graded series of known concentrations could be run, and an approximation of the amount present can be made by comparing spot size and intensity.

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