2,4-Diamino-5-methyl-6-benzylthieno[2,3-*d*]pyrimidine (2b).—Benzylacetone was brominated in cold $CHCl_3$ by the method of Janetzky and Verkade,[22] and vacuum distilled twice using a 20-cm vacuum-sealed Vigreux column. The fraction boiling at 88–92° (0.6–0.8 mm) was used for reaction with the pyrimidine. A mixture of 32.6 g (0.23 mole) of 2,4-diamino-6-mercaptopyrimidine, 12 g (0.23 mole) of NaOMe, and 300 ml of $(CH_2OH)_2$ was heated to 80° with stirring, at which point a clear solution was present. The above bromo ketone (52 g) was then added, and the mixture was heated at 110° for 30 min. A clear dark red solution formed. After cooling, this was poured into H_2O; the resultant pH was about 6. The solid which precipitated was collected and recrystallized directly from 95% EtOH; 39 g (63% calculated as **2b**). Further recrystallization from EtOH (*ca.* 75 ml/g) produced white needles: mp 231–232°; pmr spectrum (DMSO-d_6), δ 2.43 (CH_3), 4.04 (CH_2), 5.95 (NH_2), 6.42 (NH_2), 7.27 (C_6H_5); uv spectrum, see ref 13. *Anal.* ($C_{14}H_{14}N_4S$) C, H, N, S.

The bromination product of benzylacetone, 3-bromo-4-phenyl-2-butanone (**7**), was found to be quite unstable. In some preparations, the crude bromo ketone was used directly in the next reaction, but in all cases this led to mixtures. In many cases, the distilled fractions were found to consist of mixtures of two and three products, as determined by their pmr spectra and by tlc. In a typical case which showed two other components to be present to the extent of 25–30%, the bromo ketone was treated directly with the mercaptopyrimidine as above, calculated on the basis that the bromo ketone was pure. At the end of the reaction, after pouring the mixture into H_2O, the solution was quite alkaline, and the product separated as a gum. This was extracted (warm H_2O, Et_2O–EtOAc). A white solid resulted which had a pmr spectrum with two sharp benzene singlets at 7.27 and 7.30 ppm (δ) in a ratio of 7:1, which appeared to correspond to a 7:1 ratio of uncyclized to cyclized product. The uncyclized portion was evidenced by a sharp singlet at 5.75 ppm which integrated for one-fifth of the large benzene singlet (pyr 5-H), broad singlets at 6.08 and 6.01 (2 NH_2), a doublet and triplet at 3.97 and 3.35, respectively (J = 9 Hz) (–$CHCH_2$–), a broad singlet at 1.35 (CH_3), and broad singlets at 2.98, 2.78, and 1.57 ppm, each integrating for about one-half a proton, plus small additional absorption in the 2.5–4 region. The location of the methyl peak indicated that it was not next to a keto function; possibly the ketone was hydrated or partially converted to an acetal.

The uv spectra of this substance in neutral and alkaline solutions were quite different from that of the cyclized product, and the lack of isobestic points indicated that a mixture was present. When the solution was acidified, the spectrum immediately became the same as that of the cyclized product. A 0.5-g sample of the substance was slurried in 20 ml of 0.1 *N* HCl. Most of it dissolved, and then a heavy precipitate formed, which remained insoluble upon heating the mixture to the boiling point. The precipitate was isolated, treated with alkali to reconvert it to the free base, and recrystallized from ethanol. The properties were now identical with those of the first-described cyclized product (**2b**).

(22) E. F. J. Janetzky and P. E. Verkade, *Rec. Trav. Chim.*, **64**, 129 (1945).

Acknowledgment.—The author is greatly indebted to Dr. George H. Hitchings for his constant encouragement and advice throughout the course of this investigation. Discussions with Dr. Richard Baltzly and Professor J. F. Bunnett were very helpful. Mr. Robert Ferone carried out the isolated enzyme studies reported here, and Mr. George Tharrington performed the microbiological assays. Miss Renée Laube ably assisted in several of the preparations. Dr. S. W. Blackman and his staff performed the microanalyses.

Tumor Localizing Agents. VII.[1] Radioiodinated Quinoline Derivatives

R. E. COUNSELL, P. POCHA, V. V. RANADE, J. STERNGOLD, AND W. H. BEIERWALTES

Laboratory of Medicinal Chemistry, College of Pharmacy, and Department of Medicine (Nuclear Medicine), The University of Michigan, Ann Arbor, Michigan 48104

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Several radioiodinated analogs of chloroquine were synthesized in an effort to find an agent which would selectively localize in melanomas. One compound, 4-(3-dimethylaminopropylamino)-7-iodoquinoline-^{125}I was found to have a marked affinity for melanin-containing tissues and for melanotic tumors in animals.

While malignant melanoma is only one of the many varieties of malignant tumors, its appearance and manifest virulence has stimulated study over the ages. It comprises about 2% of all cancers and about 80–90% of them arise in the skin.[2] Although no age group is immune, the majority of melanomas arise in persons 31–60 years of age and there appears to be no sex predilection.[2] Despite its low incidence, Raven[3] has emphasized the urgent need for new agents which will assist the physician in diagnosing the metastic nature of the tumor. The early recognition of the tumor before dissemination occurs, as well as determining the spread of the tumor once metastases have appeared, is important for determining the course of treatment and survival of the patient.

As part of a broad program aimed at the development of an agent which would be useful for the diagnostic localization and treatment of melanotic tumors, studies in our laboratory have concentrated on finding radiolabeled compounds that would selectively concentrate in these tumors. Such compounds labeled with γ-emitting radionuclides could serve as diagnostic agents when used in conjunction with external scintillation scanners and cameras. Moreover, it is possible that the same compounds could be employed therapeutically when the radionuclide decays with emission of β rays.

In order to achieve the essential selective localization in melanomas, our studies have fallen into two categories, namely, (a) precursors of melanin[4] and (b) compounds which are known to interact with melanin.[5] Although our results to date with radiolabeled melanin precursors have been discouraging, preliminary studies

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(3) R. W. Raven, *Ann. N. Y. Acad. Sci.*, **100**, 142 (1963).

(4) R. E. Counsell, T. D. Smith, J. Doelle, D. Meier, and W. H. Beierwaltes, *J. Pharm. Sci.*, **56**, 1019 (1967).

(5) R. E. Counsell, P. Pocha, J. O. Morales, and W. H. Beierwaltes, *ibid.*, **56**, 1042 (1967).

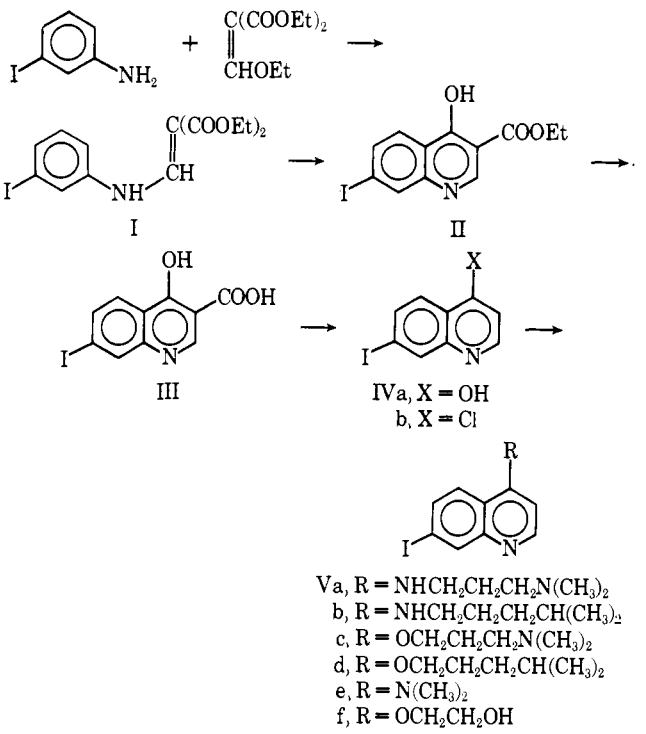
with radiolabeled melanin-seeking compounds have been most promising. This report is an extension of our studies with compounds which have an affinity for melanin.

Potts[6] was the first to recognize that several phenothiazine compounds localize in remarkably high concentration in the uveal tract of pigmented animals and that such localization is not observed in albino animals. On the basis of this information, he postulated that this localization phenomenon is related to a reaction between the compounds and the uveal melanin. Moreover, he suggested that this reaction might also explain the visual side effects associated with compounds in the phenothiazine and chloroquine series. In a subsequent study, Potts[7] evaluated over 40 compounds for their ability to interact with melanin in aqueous suspension. He found that a number of quinoline, acridine, phenothiazine, and other polycyclic drugs and dyes were rapidly adsorbed by melanin, whereas monocyclic compounds, such as pyridine and hydroquinone, as well as aliphatic compounds had no affinity for the biopolymer.

Other investigators have also noted the marked affinity of certain drugs such as chloroquine and chlorpromazine for pigmented tissues.[8-10] Several reports have noted that chloroquine is found in much larger concentrations in the iris and choroid of the eye in pigmented animals than in albino animals following repeated oral administration.[8,11] In addition, McChesney and coworkers[12] found that when the eye was excluded, the order of tissue concentration in rats was generally spleen > liver = lung > kidney > heart > muscle. Similar tissue distribution studies in melanotic mice were performed by Blois[13] with ^{35}S-labeled chlorpromazine. Analysis of the tissues 12 hr following intraperitoneal administration gave the following distribution of radioactivity: kidney > eye > liver > adrenal > tumor = spleen = gut > brain. If the animals were sacrificed 3 days following the last dose, the radioactivity was primarily in the tumor and eye.

Chloroquine was selected as the model compound for our distribution studies in normal and melanotic mice because ^{14}C-chloroquine is commercially available and the synthesis of a stable radioiodinated analog was considered more readily accomplished in this series than in the chlorpromazine series. For our studies 4-chloro-7-iodoquinoline (IVb) was required for the preparation of the desired iodo analogs for chloroquine. Although this compound had been prepared previously by Surrey and Hammer,[14] we selected the usually more satisfactory general procedure of Price and Roberts.[15] As shown in Scheme I this involved condensation of 3-iodoaniline with ethoxymethylenemalonic ester. The resulting acrylate (I) was converted to IVb by cyclization, saponification, decarboxylation, and subsequent treatment of the crude 4-hydroxy-7-iodoquinoline (IVa) with $POCl_3$. The spectral and physical properties of IVb agreed with those previously reported. The nmr spectrum displayed the typical AB pattern for the C-2 and C-3 protons at 8.71 and 7.43 ppm (J_{AB} = 5 cps), respectively.

SCHEME I



I II III IVa, X = OH b, X = Cl

With this key intermediate in hand, it was now possible to obtain a number of 4-substituted 7-iodoquinolines for radiolabeling experiments and subsequent tissue distribution studies. It was hoped that subtle molecular changes in this series would provide useful information with regard to structure and tissue distribution. Compounds Va–e were synthesized for this purpose by treatment of IVb with the appropriate amine or alcohol.

Introduction of radioiodine by isotope exchange with iodide-125 or -131 posed more of a problem in this series than in our previous studies.[16] The major problem was the relative instability of the compounds under the conditions required for exchange. In the past, ethylene glycol at temperatures above 170° has been an efficient exchange media. Aside from the 4-hydroxy compound (IVa), however, this method gave rise to by-products and required repeated recrystallizations of the final product to achieve the required chemical and radiochemical purity. In the case of the 4-dimethylamino compound (Ve), for example, heating with ethylene glycol at 185° for 16 hr afforded a good yield of the 4-hydroxyethoxy derivative (Vf). Pivalic acid was useful in one instance, *i.e.*, Vb, but gave rise to 4-hydroxy-7-indoquinoline (IVa) when used as the solvent for exchange of the oxygen isosteres Vc and Vd. In the lat-

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(7) A. M. Potts, *ibid.*, **3**, 399 (1964).
(8) H. Bernstein, N. Zvaifler, M. Rubin, and A. M. Mansour, *ibid.*, **2**, 384 (1963).
(9) W. M. Sams, Jr., and J. H. Epstein, *J. Invest. Dermatol.*, **45**, 482 (1965).
(10) F. M. Forrest, I. S. Forrest, and L. Roizin, *Rev. Agressol.*, **4**, 259 (1963).
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(14) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 113 (1946).
(15) C. C. Price and R. M. Roberts, *ibid.*, **68**, 1204 (1946).
(16) R. E. Counsell, R. E. Willette, and W. D'Guilio, *J. Med. Chem.*, **10**, 975 (1967).

TABLE I

DISTRIBUTION OF Va-^{125}I IN MICE WITH MELANOMAS[a]

No. of mice	Time, hr	Distribution, cpm/mg ± SE							
		Melanoma	Eye	Skin	Liver	Adrenal	Thyroid	Muscle	Blood
3	24	315 ± 21	490 ± 47	154 ± 6	133 ± 9	306 ± 19	1528 ± 629	27 ± 4	28 ± 3
3	72	187 ± 27	582 ± 99	197 ± 9	28 ± 8	192 ± 44	2296 ± 986	5 ± 1	5 ± 1
3	96	85 ± 24	545 ± 178	167 ± 56	10 ± 3	119 ± 29	2742 ± 1791	11 ± 7	2 ± 1

[a] Dose of 10 μCi/mouse administered intraperitoneally.

TABLE II

DISTRIBUTION OF RADIOIODINATED QUINOLINES IN MELANOTIC MICE AT 24 HR

Compd	Tissue:blood ratios (cpm/mg)				
	Eye	Melanoma	Liver	Kidney	Muscle
Va	17.7	11.3	4.8	2.9	1.0
Vb	10.4	2.1	1.1	0.6	0.2
Vc	182.0	8.8	1.0	6.5	1.0
IVa	1.2	2.3	12.8	2.4	2.0

ter instance, isotope exchange without decomposition was only effected when the precursor alcohols, 3-dimethylamino-1-propanol and 4-methyl-1-pentanol, were employed as the exchange media.

The affinity of the substituted quinolines with synthetic melanin in 0.067 *M* phosphate buffer at pH 5.9 was investigated. The experiments were conducted in a manner similar to that reported by Cohen and Yielding[17] for affinity studies with DNA. Unfortunately, the lack of solubility of the quinolines in the buffer media limited the study to compounds Va, Vc, and Ve. Since 5,6-dihydroxyindole is the proposed precursor of melanin,[18] the synthetic melanin used in these studies was prepared by saponification of 5,6-diacetoxyindole previously prepared in our laboratory.[4] In the presence of air, the 5,6-dihydroxyindole rapidly polymerized and the black, melanin-like precipitate was readily collected by filtration. The uv absorption of the quinoline-containing solutions remaining after interaction with varying amounts of melanin was examined. Under these conditions, all three quinolines displayed similar affinity for the synthetic melanin. This suggests that the nature of the side chain has little effect on the ability of these agents to bind strongly to melanin.

Tissue Distribution Studies.—A preliminary communication from this laboratory demonstrated the marked affinity of 4-(3-dimethylaminopropylamino)-7-iodoquinoline-^{125}I (Va-^{125}I) for melanin-containing tissues.[5] Further studies with this compound have now shown its ability to concentrate in malignant melanomas of tumored mice, Syrian hamsters,[19] dogs,[20] and man.[21] Table I shows the concentration of radioactivity in several tissues of melanotic mice following administration of 10 μCi of Va-^{125}I. While at 1 day a number of tissues showed considerable radioactivity, only tumor, eye, skin, adrenal, and thyroid contained appreciable radioactivity after 4 days. It is not certain at this stage whether the high radioactivity in the thyroid represents deiodination of the parent compound followed by uptake of iodide or uptake of Va-^{125}I itself. This concentration in the thyroid, however, represented only $^1/_{500}$ the radioactivity found in control animals given the same dose of Na^{125}I.

A similar distribution of radioactivity was observed in Syrian hamsters with melanomas. Moreover, the malignant melanoma tissues were sharply visualized as a positive image by scintillation scanning as seen in Figure 1. The location and size of this tumor was in good agreement with the photoscan.

Table II compares the tissue distribution of Va-^{125}I with the other radiolabeled quinolines. The values were obtained after 24 hr in melanotic mice and are expressed as a ratio of counts per minute per milligram in the particular tissue to that for blood. While it is impossible to draw any conclusions from these preliminary findings, certain trends appear to be emerging. For example, both quinolines with a basic side chain (Va and Vc) showed the greatest predilection for the tumor and melanin-containing tissues. Moreover, replacement of the side chain with groups that can be readily conjugated by the liver (*i.e.*, IVa) destroys the tumor specificity and most of the radioactivity concentrates in the liver. To date, Va-^{125}I has shown the best ability to seek out and localize in melanotic tumor.[22]

Experimental Section[24]

Ethyl α-Carbethoxy-β-(3-iodophenylamino)acrylate (I).—A mixture of 3-iodoaniline (25 g) and diethyl ethoxymethylenemalonate (30 g) was heated on a steam bath and the EtOH which formed was continuously removed under reduced pressure. When the theoretical volume of EtOH had been collected (6.6 ml, 1 hr), the reaction mixture was allowed to cool. The solid (56 g) was collected and recrystallized twice (Me$_2$CO–H$_2$O) to give pure I (34 g, 77%) as white needles, mp 88–89°. The ir and nmr spectra were as expected. *Anal.* ($C_{14}H_{16}INO_4$) C, H.

3-Carbethoxy-4-hydroxy-7-iodoquinoline (II).—I (4 g) was added in portions to refluxing diphenyl ether (100 ml) and the

(17) S. N. Cohen and K. L. Yielding, *J. Biol. Chem.*, **240**, 3723 (1965).

(18) A. Meister, "Biochemistry of the Amino Acids," Vol. II, 2nd ed, Academic Press Inc., New York, N. Y., 1965, p 919.

(19) W. H. Beierwaltes, V. M. Varma, R. E. Counsell, and L. M. Lieberman, *J. Nucl. Med.*, **9**, 489 (1968).

(20) W. H. Beierwaltes, V. M. Varma, L. M. Lieberman, R. E. Counsell, and J. O. Morales, *J. Lab. Clin. Med.*, **72**, 485 (1968).

(21) W. H. Beierwaltes, L. M. Lieberman, V. M. Varma, and R. E. Counsell, *J. Am. Med. Assoc.*, **206**, 97 (1968).

(22) Since completion of these studies, Blois[23] has reported on the melanin-binding properties of radioiodinated 4-(4-diethylamino-1-methylbutylamino)-7-iodoquinoline. Its properties appear to be similar to those reported here and previously[5] for Va-^{125}I.

(23) M. S. Blois, *J. Invest. Dermatol.*, **50**, 250 (1968).

(24) Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were taken on a Perkin-Elmer 337 spectrophotometer. The nmr spectra were obtained with a Varian A-60 spectrometer in CDCl$_3$ at a concentration of 10%, with TMS as internal reference. Uv spectra were recorded on a Beckman DK2A spectrophotometer in 0.067 *M* phosphate buffer at pH 5.9 or EtOH. Tlc were run with 1-in. wide Eastman chromagrams, Type K301R, with fluorescence indicator and spots detected with uv light. Chromatograms of radioiodinated compounds were scanned with an Atomic Associates RCS-363 radiochromatogram scanner. The specific activities were determined with a Beckman scintillation spectrometer Model 530.

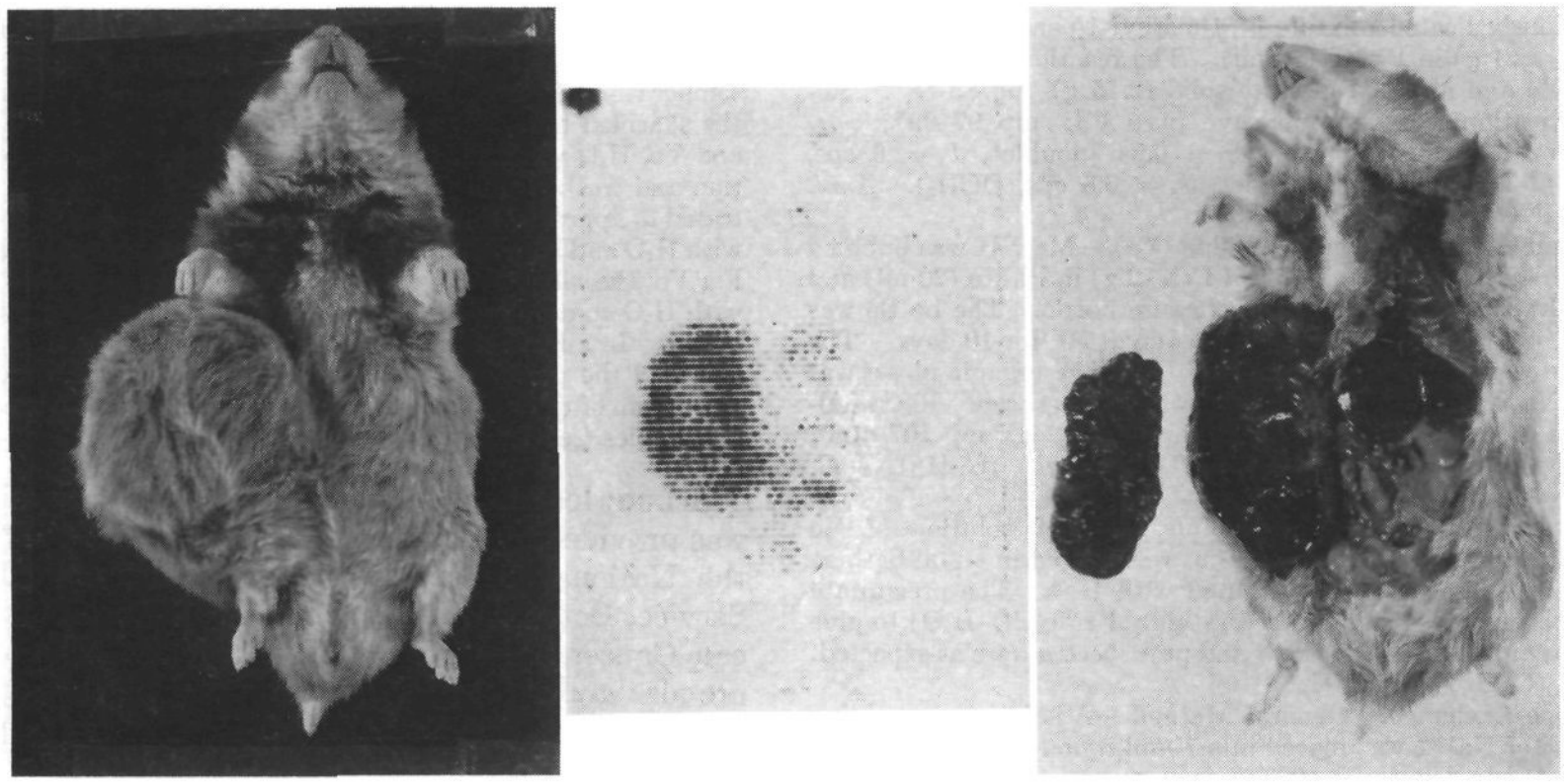

Figure 1: Syrian hamster with melanoma. The photoscan following administration of Va-^{125}I (100 μCi) is in agreement with the size and location of tumor observed at autopsy.

TABLE III

RADIOIODINATED QUINOLINE DERIVATIVES

Compd	Solvent[a]	Bath temp, °C	Reaction time, hr	Recrystn solvent	% recovery	% exchange	Sp act., μCi/mg
IVa	A	205–210	24	Me_2CO–H_2O	82	34.1	6.83
Va	A	170–175	16	Me_2CO–H_2O	53	56.6	5.66
Vb	B	190–195	48	EtOH–H_2O	15	49	14.5
Vc	C	205–210	24	Me_2CO–H_2O	55	2.5	0.51
Vd	D	175–180	48	EtOH–H_2O	7	4.8	1.44

[a] A = ethylene glycol, B = pivalic acid, C = 3-dimethylamino-1-propanol, D = 4-methyl-1-pentanol.

EtOH was allowed to escape through a short air condenser. After addition was complete (about 15 min), the resulting pale yellow solution was cooled to 50°. The white solid that formed was collected by filtration and washed several times with hot hexane to give II as a white solid (3.3 g, 94%). Recrystallization from pyridine gave an analytical sample which started to sublime at 255°. The ir spectrum was as expected. *Anal.* ($C_{12}H_{10}INO_3$) C, H.

3-Carboxy-4-hydroxy-7-iodoquinoline (III).—II (3 g) was added to a solution of NaOH (3 g) in H_2O (20 ml) and EtOH (10 ml) and the mixture was heated under reflux until the solid dissolved. The solution was cooled and acidified with 10% HCl to precipitate the acid III (2.7 g, 98%) as a fine white powder, mp 278° with evolution of CO_2. The ir spectrum was as expected. *Anal.* ($C_{10}H_6INO_3$) C, H. Recrystallization of a sample from DMSO afforded a crystalline DMSO adduct, subliming at 280–290°. The ir spectrum was as expected. *Anal.* ($C_{10}H_6INO_3 \cdot C_2H_6SO$) C, H.

4-Chloro-7-iodoquinoline (IVb).—Decarboxylation of III (8 g) was effected by adding portions to refluxing diphenyl ether (200 ml) over a period of 30 min. After the evolution of CO_2 had ceased, the solution was cooled to 50° and the precipitate was collected. The product was washed with hot hexane, dried, and added to $POCl_3$ (45 ml). The mixture was refluxed for 2 hr, the excess reagent was removed under reduced pressure, and the residual oil was poured into NH_4OH-containing crushed ice. The pale gray precipitate was collected, dried, and recrystallized from $CHCl_3$ to give IVb (5 g), mp 97–98° (lit.[14] 95.5–97°). The ir and nmr spectra were as expected.

4-(3-Dimethylaminopropylamino)-7-iodoquinoline (Va).—A solution of IVb (2.5 g) in 3-dimethylaminopropylamine (10 ml) was heated at the reflux temperature for 23 hr. The excess amine was removed by distillation under reduced pressure and the residual oil dissolved in a minimum of acetone. NH_4OH was added and the resulting yellow precipitate was collected by filtration and washed with H_2O. Several recrystallizations (Me_2CO) afforded pale yellow needles (2 g, 65%) of Va: mp 101–102°; nmr peaks at 7.64 (NCH_3), 7.43 (CH_2N, triplet, J = 6 cps), and 6.67 ppm (CH_2NH, multiplet). The latter became a triplet upon deuteration (J = 6 cps). The ir spectrum was as expected. *Anal.* ($C_{14}H_{18}IN_3$) C, H.

4-(4-Methylpentylamino)-7-iodoquinoline (Vb).—A solution of IVb (2 g) in 4-methylpentylamine[25] (4 ml) was heated under reflux for 23 hr and the excess solvent evaporated under reduced pressure. Addition of acetone to the residue gave a solid hydrochloride (1.75 g), mp 168–173°, ν_{max} 2700 cm^{-1} (N^+H). Recrystallization from EtOH–Me_2CO gave an analytical sample, mp 183–184°. *Anal.* ($C_{15}H_{20}ClN_2I$) C, H. The mother liquors afforded a second fraction (0.35 g), mp 130–135°, which upon recrystallization from EtOH–H_2O gave pure Vb, mp 144–145°. Treatment of an EtOH solution of the HCl salt gave the same free base. *Anal.* ($C_{15}H_{19}IN_2$) C, H. The ir and nmr spectra were as expected.

4-(3-Dimethylaminopropoxy)-7-iodoquinoline (Vc).—A mixture of 3-dimethylamino-1-propanol (1.42 g, 0.014 M) and $NaNH_2$ (0.67 g, 0.017 M) in dry PhMe (15 ml) was heated under reflux until the evolution of NH_3 ceased (about 3 hr). The gray suspension was cooled and a solution of IVb (1 g, 0.0034 M) in PhMe (5 ml) was added dropwise with stirring. The reaction mixture was heated under reflux for 18 hr. On cooling, H_2O was added to dissolve the solid material, and the PhMe phase was separated, dried (Na_2SO_4), and evaporated to leave a pale brown oil which solidified upon addition of petroleum ether (bp 30–40°). The white solid (0.7 g, 57%), mp 85–90°, was recrystallized (Me_2CO) to give an analytical sample of Vc: mp 93–94°; ν_{max} 1180 cm^{-1} (COC); nmr peaks at 2.29 (NMe_2), 2.50 (triplet, J = 6 cps, NCH_2), and 4.23 ppm (triplet, J = 6 cps, OCH_2). *Anal.* ($C_{14}H_{17}IN_2O$) C, H.

4-(4-Methylpentyloxy)-7-iodoquinoline (Vd).—A solution of IVb (3.1 g) in PhMe (5 ml) was added dropwise with stirring to

(25) Prepared by reduction of 4-methylvaleronitrile with $LiAlH_4$–Et_2O; bp 118–121° (lit.[26] bp 122–123°).

(26) T. Curtius, W. Sieber, F. Nadenheim, D. Hambsch, and W. Ritter *J. Prakt. Chem.*, **125**, 152 (1930); *Chem. Abstr.*, **24**, 3217 (1930).

a previously heated mixture of 4-methyl-1-pentanol (4.4 g) and $NaNH_2$ (2.1 g) in PhMe (10 ml). The reaction was carried out as for Vc and afforded a white solid (2.45 g), mp 85–88°. Recrystallization from hexane gave pure Vd: mp 97–99°; ν_{max} 1115 cm^{-1} (COC); nmr peaks at 0.94 [doublet, J = 6 cps, $C(CH_3)_2$] and 4.15 ppm (triplet, J = 6.5 cps, OCH_2). *Anal.* ($C_{15}H_{18}INO$) C, H.

4-Dimethylamino-7-iodoquinoline (Ve).—Me_2NH was bubbled through an ice-cooled solution of IVb (2 g) in PhMe (20 ml) and MeCOEt (10 ml) for 3 hr in a pressure bottle. The bottle was tightly stoppered and placed in an oven at 50° for 10 days. The mixture was cooled and washed (H_2O). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Recrystallization of the solid residue gave pure Ve (1.1 g), mp 107–108°, and an nmr peak at 2.99 ppm (NCH_3). *Anal.* ($C_{11}H_{11}IN_2$) C, H.

4-Hydroxyethyoxy-7-iodoquinoline (Vf).—A solution of Ve (100 mg) in ethylene glycol (1.5 ml) was heated in an oil bath at 185° for 16 hr, cooled, and diluted with H_2O. The precipitate (70 mg), mp 153–155°, was recrystallized (Me_2CO–H_2O) to give pure Vf, mp 154–155°. The ir and nmr spectra were as expected. *Anal.* ($C_{11}H_{10}INO_2$) C, H.

Isotope Exchange. General Method.—A solution containing 1–3 mCi of $Na^{125}I$ was placed in a 10-ml round-bottom flask and evaporated to dryness at 100° under a gentle stream of N_2. The substituted 7-iodoquinoline (100 mg) dissolved in the appropriate solvent (2 ml) was added, a condenser was attached, and the bath temperature was raised. The mixture was stirred under N_2 for the specified time and allowed to cool. In the case of IVa, Va, and Vc, H_2O was added and the product was collected by filtration and washed well (H_2O). For Vb, the solution was concentrated to approximately 0.5 ml under reduced pressure and treated with H_2O and NH_4OH, and the precipitate was collected as above. For Vd, the solvent was removed *in vacuo*, the residue was treated with H_2O containing a little Me_2CO, and the precipitate was collected. In all cases, the products were purified by recrystallization and the purity was established by (a) tlc and a radiochromatogram of the strip and (b) mixture melting point with authentic samples (see Table III).

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S-2-(ω-Aminoalkylamino)ethyl Dihydrogen Phosphorothioates and Related Compounds as Potential Antiradiation Agents[1]

JAMES R. PIPER, CARL R. STRINGFELLOW, JR., ROBERT D. ELLIOTT, AND THOMAS P. JOHNSTON

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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A number of S-2-(ω-aminoalkylamino)ethyl and S-3-(ω-aminoalkylamino)propyl dihydrogen phosphorothioates (**3a–e**, **18a–c**) and some related compounds including the S-2-(ω-aminoalkylamino)ethyl hydrogen thiosulfates **10a–c** have been prepared and evaluated for radioprotective activity in mice. Intermediate N-(2-bromoethyl)-α,ω-alkanediamine dihydrobromides (**2a–e**) were prepared by the Cortese treatment of the 2-(ω-aminoalkylamino)ethanols **1a–e**; the potential of a Gabriel synthesis from the 3-(ω-phthalimidoalkyl)-2-oxazolidinones **7a–c** was demonstrated by the conversion of N-[3-(2-bromoethylamino)propyl]phthalimide hydrobromide (**8b**) into **2b**. The requisite N-(3-bromopropyl)-α,ω-alkanediamine dihydrobromides **17a–c** were prepared from the 3-(ω-aminoalkylamino)-1-propanols **16a** and **16b** and from the 3-(ω-phthalimidoalkyl)tetrahydro-1,3-oxazin-2-ones **14a** and **14b** in two steps involving selective cleavage of the tetrahydrooxazinone ring. Intermediates obtained by the addition of 2-methyl- and 2,2-dimethylaziridine to acrylonitrile led to several branched-chain analogs (**21a–d**, **23a**, and **23b**). Aziridine-ring opening by ammonium thiosulfate was employed in the preparation of the inner Bunte salts **10a**, **10b**, **21b**, and **21d** monohydrochlorides. The phosphorothioates, as a series of a novel type, exhibited an exceptionally high level of radioprotective activity, whereas the thiosulfates were essentially nonprotective.

Current interest in the radioprotective properties of N-substituted derivatives of 2-aminoethanethiol (with and without latentiating S-substitution) in which the N-substituent is a terminally and functionally substituted alkyl group is attested by a growing number of reported syntheses in this area.[2] This report concerns the synthesis and evaluation of N-(ω-aminoalkyl)-substituted derivatives (chiefly N and S disubstituted), a type that structurally resembles several recently described and more complex spermine and spermidine derivatives[3] and N,N′-polymethylene-bridged derivatives[4] in which some antiradiation activity has been observed.

Various modifications of 2-aminoethanethiol have been achieved by the use of α-amino acids as starting materials,[5] but the general reaction sequence was not successfully applied to L-lysine or its ethyl ester because of difficulties encountered in their reduction to the apparently as yet unknown L-lysinol [$H_2N(CH_2)_4CH(NH_2)CH_2OH$]. As a model for the planned conversion of L-lysinol the following sequence (eq 1)

$$\underset{\textbf{1a}}{H_2NCH_2CH_2NHCH_2CH_2OH} \xrightarrow{HBr} \underset{\textbf{2a}}{H_2NCH_2CH_2NHCH_2CH_2Br\cdot HBr} \xrightarrow{Na_2SPO_3} \underset{\textbf{3a}}{H_2NCH_2CH_2NHCH_2CH_2SPO_3H_2} \quad (1)$$

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