[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY, INSTITUTE OF SCIENCE, BOMBAY]

Reactions of Nitrohydroxychalcones: Synthesis of Nitrohydroxyflavones

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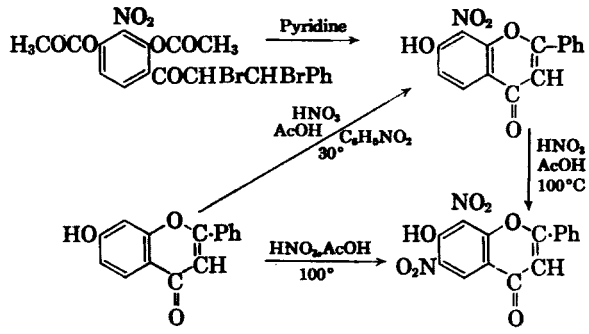
The conversion of 2′,4′-dihydroxy-3′-nitrochalcone derivatives to 7-hydroxy-8-nitroflavone derivatives is described. The formation of the 6- and 8-nitro-5-hydroxyflavone derivatives from 2′,6′-dihydroxy-3′-nitrochalcone derivatives by different routes is described and discussed. Modified procedures for the nitration of 5-hydroxyflavone and 7-hydroxyflavone are given.

In an earlier communication,[2] the preparation of several nitrohydroxychalcones and their isomerization to the flavanones was reported. The present paper deals with the conversion of the chalcones to flavones.

As already reported, the cyclization of the 2′,4′-dihydroxy-3′-nitrochalcones could not be generally effected in good yields and hence the only route to the synthesis of flavones in this case was the dehydrobromination of the corresponding chalcone dibromides. It was found desirable to protect the free hydroxyl groups by acetylation to prevent bromination of the benzene ring. The dibromides were obtained readily by the bromination of the diacetates in chloroform solution. The bromination of the chalcones with alkoxy substituents in the styryl part did not go to completion with molecular proportions of bromine. The dibromides were, however, obtained when more than molecular proportions of bromine were employed. The dehydrobromination of the dibromides was effected by boiling with pyridine, whereupon 7-hydroxy-8-nitroflavone derivatives were obtained. That both the acetyl groups are removed is shown by the positive ferric reaction as well as the instantaneous reaction with alkali. This easy deacetylation can be ascribed to the labile nature of the acetoxyl groups in a position ortho or para to a nitro group. The constitution of the flavone obtained from chalcone diacetate Ia, *viz.*, 7-hydroxy-8-nitroflavone, was confirmed by its identity with the mononitration product of 7-hydroxyflavone as well as by its nitration to the known 7-hydroxy-6,8-dinitroflavone.[3] The sequence of reactions is shown in Chart I.

In the case of 2′,6′-dihydroxy-3′-nitrochalcones, both routes for the synthesis of flavones, *i.e.*, dehydrobromination of the 3-bromoflavanones as well as of the chalcone dibromides, were investigated. The flavanones, on bromination, gave the corresponding 3-bromoflavanones. More than molecular proportions of bromine were required

Chart I



to brominate the flavanones with alkoxy substituents in the 2-phenyl nucleus. The yields of pure bromoflavanones, in such cases, were poor and in one case the pure bromoflavanone could not be isolated. The crude bromination product could, however, be directly dehydrobrominated by boiling pyridine when the flavones crystallized from the reaction mixture. The flavanones obtained by the cyclization of 2′,6′-dihydroxy-3′-nitrochalcones had earlier[2] been assigned the constitution of 5-hydroxy-6-nitro flavanones, on theoretical considerations. This has now been confirmed by the formation of 5-hydroxy-6-nitroflavone from the flavanone obtained by the cyclization of 2′,6′-dihydroxy-3′-nitrochalcone. This flavone was found to be identical with the 5-hydroxy-6-nitroflavone prepared by Kostanecki-Robinson benzoylation of 2,6-dihydroxy-3-nitroacetophenone.[4] It also resisted acetylation showing the hindered nature of the 5-hydroxyl group.

The dehydrobromination of the 2′,6′-diacetoxy-3′-nitrochalcone dibromides was next investigated. 2′,6′-Dihydroxy-3′-nitro-2-methoxychalcone and 2′,6′dihydroxy -3′-nitro-3-methoxychalcone did not yield a pure acetate by any method. The other chalcone diacetates were obtained pure and were brominated in chloroform solution. The proportions of bromine required were the same as in the case of the corresponding 2′,4′-diacetoxy-3′-nitrochalcone derivatives. The dehydrobromination of the chalcone dibromides gave 5-hydroxy-8-nitroflavone derivatives. These could be acetylated to give the 5-acetoxy-8-nitroflavone derivatives, thus showing

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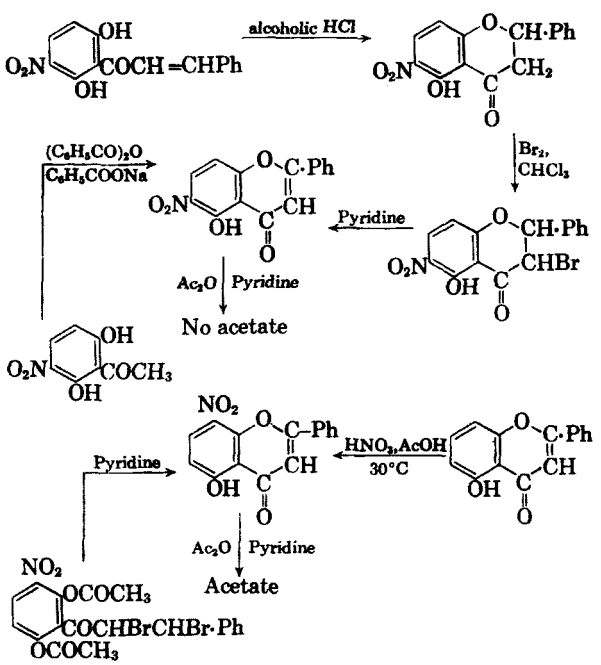
(2) S. Seshadri and P. L. Trivedi, *J. Org. Chem.*, 22, 1633 (1957).

(3) A. M. Mehta, G. V. Jadhav, and R. C. Shah, *Proc. Indian Acad. Sci.*, 29A, 314 (1949).

(4) R. M. Naik and V. M. Thakor, *Proc. Indian Acad. Sci.*, 37A, 774 (1953).

that the 5-hydroxyl group is not hindered. The formation of 5-hydroxy-8-nitroflavones shows that the acetoxy group ortho to both the nitro and the carbonyl groups suffers deacetylation first and cyclization occurs preferentially at that position. 5-Hydroxy-8-nitroflavone thus obtained was found to be identical with the mononitration product of 5-hydroxyflavone. The formation of 5-hydroxy-6-nitroflavone by one method and of 5-hydroxy-8-nitroflavone by the other method is indicated in Chart II.

Chart II



The characteristic sulfuric acid colorations of the flavones are set out in Table III and show the enhanced halochromism with *o-p* alkoxy substitution in the 2-phenyl nucleus.

EXPERIMENTAL

Acetylation of the chalcones. All the chalcones were acetylated by acetic anhydride–pyridine. Some of the chalcones were heated on a water bath and some reacted at room temperature (*ca.* 30°) as shown below. Chalcones Ia, If, IIa, IId, IIe were prepared by dissolving the corresponding hydroxy chalcones (500 mg.) in hot acetic anhydride (10 cc.) and pyridine (1 cc.) and leaving overnight at room temperature. The solid obtained on treating with cold water was crystallized from alcohol. The yield was 400 mg.

Chalcones Ib, Ic, Id, Ie were prepared by dissolving the hydroxy chalcone in acetic anhydride–pyridine as before, heating on a boiling water bath for 4 hr., and leaving overnight at room temperature. The solid obtained on working up as usual was triturated with a little alcohol and filtered. The residue was then crystallized twice from alcohol. Yields were 200 to 250 mg. All the chalcone acetates were colorless or very pale yellow crystalline substances giving no color with alcoholic ferric chloride. The melting points and analyses are set out in Table I.

Bromination of the chalcone diacetates. Bromination of chalcones Ia, If, IIa. The chalcone diacetate (500 mg.) in chloroform (2 cc.) was treated with bromine in chloroform (2 cc.; 10%). The mixture was left at room temperature for 2 hr. Chloroform was removed by evaporation and petroleum ether (b.p. 40–60°) added to the residue. The solid obtained was crystallized from a mixture of benzene–petroleum ether. The yield was 400 mg. Bromination of the other chalcone diacetates was carried out similarly with the exception that 3.5 cc. of the bromine solution was employed and the yields were 200 to 250 mg. The bromides gave no color with alcoholic ferric chloride. The melting points and analyses are set out in Table I.

Bromination of the flavanones. Bromoflavanone IIA was obtained by reacting 5-hydroxy-6-nitroflavanone (500 mg.) in chloroform (2 cc.) with bromine in chloroform (2.5 cc.; 10%) at room temperature for 2 hr. Chloroform was evaporated and petroleum ether added to the residue. The solid obtained was recrystallized from a mixture of benzene–petroleum ether. The yield was 400 mg. The other bromoflavanones, IIB, IIC, IID, IIE were similarly obtained with the difference that 4 cc. of the bromine solution was employed. The pure bromoflavanones were obtained after repeated crystallizations. The yields were 80 to 100 mg. Bromoflavanone IIC could not be isolated in a pure condition and the crude reaction product was used as such for further reaction. The melting points of the bromoflavanones and their analyses are given in Table II.

Dehydrobromination of the chalcone dibromides and the bromoflavanones. The bromo derivatives (500 mg.) were refluxed in pyridine (5 cc.) for 10 min. In many cases the flavanone separated out quantitatively as a crystalline solid during the reaction or on cooling the reaction mixture. The solid was filtered and washed with alcohol and crystallized further from acetic acid (nitrobenzene was used for flavones 9 and 14). If no solid separated even on cooling, dilute hydrochloric acid was added and the solid obtained filtered and recrystallized from acetic acid. All the flavones were white or pale yellow in color and gave negative Beilstein test for halogen. The melting points and the characteristic sulfuric acid colorations are set out in Table III. The 7-hydroxy-8-nitroflavone derivatives gave pale brown color with alcoholic ferric chloride, while the 5-hydroxy flavone derivatives gave brownish red colors.

Nitration of 7-hydroxyflavone. The procedure for nitration of 7-hydroxyflavone as reported in the literature[3] was found unsuitable as it led to the formation of di- and tri-nitro derivatives. The following was the method employed; 7-hydroxyflavone (2 g.) was dissolved in acetic acid (100 cc.) and nitrobenzene (50 cc.) and treated with concd. nitric acid (d. 1.42, 5 cc.) in the cold. The mixture was left overnight at room temperature. Water was then added and the nitrobenzene layer extracted with dilute alkali solution (1%). The alkaline extract was washed with ether and acidified. The solid obtained was treated with dilute sodium bicarbonate solution (2%) in which part of it dissolved to give a yellow solution. The solution was filtered and acidified. The solid obtained was crystallized from acetic acid, melting range 185–215°, yield, 200 mg. It was purified by conversion to the acetate, m.p. 168–170° (after two crystallizations from alcohol).

Anal. Calcd. for $C_{17}H_{11}NO_6$: N, 4.31. Found: N, 4.35.

This product was hydrolyzed by dissolving in 80% sulfuric acid and keeping overnight at room temperature. The solid obtained on adding to ice was crystallized from acetic acid as fluffy white needles, m.p. 228°, mixed melting point with flavone (1) obtained through the chalcone dibromide (see Table III) was undepressed.

7-Hydroxy-6,8-dinitroflavone,[3] m.p. 289° was obtained by nitration of 7-hydroxyflavone in acetic acid at 100°. Flavone (1) on similar nitration gave the same compound, m.p. and mixed m.p. 289°.

5-Hydroxy-6-nitroflavone was obtained by the reaction of 2,6-dihydroxy-3-nitroacetophenone with sodium benzoate and benzoic anhydride.[4] The melting point of the product crystallized from acetic acid was 209° (previous shrinking at 200°). This agrees with the reported melting point. The

TABLE I

CHALCONE DIACETATES AND THEIR DIBROMIDES

No.	Chalcone	M.P., °C.	Formula	Analysis, N % Calcd.	Found	Dibromide M.P., °C.	Formula	Analysis, Br % Calcd.	Found
Ia	2',4'-(OAc)$_2$-3'-NO$_2$	133–135	$C_{19}H_{15}NO_7$	3.79	3.75	181–183	$C_{19}H_{15}Br_2NO_7$	30.24	30.60
Ib	2',4'-(OAc)$_2$-3'-NO$_2$-2-OMe	103–105	$C_{20}H_{17}NO_8$	3.51	3.26	147–148	$C_{20}H_{17}Br_2NO_8$	28.62	28.76
Ic	2',4'-(OAc)$_2$-3'-NO$_2$-3-OMe	105–107	$C_{20}H_{17}NO_8$	3.51	3.50	118	$C_{20}H_{17}Br_2NO_8$	28.62	29.05
Id	2',4'-(OAc)$_2$-3'-NO$_2$-4-OMe	84–85	$C_{20}H_{17}NO_8$	3.51	3.28	141–142	$C_{20}H_{17}Br_2NO_8$	28.62	28.54
Ie	2',4'-(OAc)$_2$-3'-NO$_2$-3,4-O$_2$CH$_2$	124–125	$C_{20}H_{15}NO_9$	3.39	3.24	148–149	$C_{20}H_{15}Br_2NO_9$	27.90	28.30
If	2',4'-(OAc)$_2$-3'-NO$_2$-4-Me	137–139	$C_{20}H_{17}NO_7$	3.66	3.60	163–165	$C_{20}H_{17}Br_2NO_7$	29.47	28.98
IIa	2',6'-(OAc)$_2$-3'-NO$_2$	104–105	$C_{19}H_{15}NO_7$	3.79	3.89	163	$C_{19}H_{15}Br_2NO_7$	30.24	30.70
IId	2',6'-(OAc)$_2$-4-OMe-3'-NO$_2$	109–110	$C_{20}H_{17}NO_8$	3.51	3.59	146–148	$C_{20}H_{17}Br_2NO_8$	28.62	28.99
IIe	2',6'-(OAc)$_2$-3'-NO$_2$-3,4-O$_2$CH$_2$	141–142	$C_{20}H_{15}NO_9$	3.39	3.40	150–151	$C_{20}H_{15}Br_2NO_9$	27.90	28.17

TABLE II

No.	Flavanone	M.P., °C.	Formula	Analysis, Br % Calcd.	Found
IIA	5-OH-6-NO$_2$-3-Br	147	$C_{15}H_{10}BrNO_5$	22.60	22.39
IIB	5-OH-6-NO$_2$-2'-OCH$_3$-3-Br	181–182	$C_{16}H_{12}BrNO_5$	20.30	20.75
IIC	5-OH-6-NO$_2$-3'-OCH$_3$-3-Br	[a]			
IID	5-OH-6-NO$_2$-4'-OCH$_3$-3-Br	179–180	$C_{16}H_{12}BrNO_5$	20.30	20.13
IIE	5-OH-6-NO$_2$-3',4'-O$_2$CH$_2$-3-Br	270[b]	$C_{16}H_{10}BrNO_7$	19.60	19.65

[a] Could not be isolated. [b] Becomes brown at 205° and chars at 270°.

TABLE III

LIST OF FLAVONES PREPARED

No.	Flavone	M.P., °C.	H_2SO_4 Color	Formula	Analysis, N % Calcd.	Found
1	7-OH-8-NO$_2$	228	Yellow	$C_{15}H_9NO_5$	4.95	4.80
2	7-OH-8-NO$_2$-2'-OCH$_3$	258–260[a]	Orange	$C_{16}H_{11}NO_6$	4.47	4.26
3	7-OH-8-NO$_2$-3'-OCH$_3$	242–243	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	3.34
4	7-OH-8-NO$_2$-4'-OCH$_3$	260[a]	Orange	$C_{16}H_{11}NO_6$	4.47	4.23
5	7-OH-8-NO$_2$-3',4'-O$_2$CH$_2$	270[a] (dec.)	Orange-red	$C_{16}H_9NO_7$	4.28	4.12
6	7-OH-8-NO$_2$-4'-CH$_3$	250	Yellow	$C_{16}H_{11}NO_5$	4.71	4.88
7	5-OH-8-NO$_2$	215[c] (190)	Yellow	$C_{15}H_9NO_5$	4.95	5.19
8	5-OH-8-NO$_2$-4'-OCH$_3$	218[c] (200)	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.30
9	5-OH-8-NO$_2$-3',4'-O$_2$CH$_2$	300[b]	Orange-red	$C_{16}H_9NO_7$	4.28	4.50
10	5-OH-6-NO$_2$	232	Yellow	$C_{15}H_9NO_5$	4.95	4.74
11	5-OH-6-NO$_2$-2'-OCH$_3$	208–210	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.27
12	5-OH-6-NO$_2$-3'-OCH$_3$	216–217	Deep yellow	$C_{16}H_{11}NO_6$	4.47	4.46
13	5-OH-6-NO$_2$-4'-OCH$_3$	234–236	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.66
14	5-OH-6-NO$_2$-3',4'-O$_2$CH$_2$	290[b]	Orange-red	$C_{16}H_9NO_7$	4.28	4.54

[a] Melts with charring. [b] Chars but does not melt. [c] Softening occurs at the temperature indicated in brackets.

product was, however, found to be contaminated with 5-hydroxy-6-nitro-3-benzoylflavone. This impurity was removed by crystallization from chloroform, whereupon the melting point rose to 230–232°. Mixed melting point with flavone (10) was not depressed. It was recovered unreacted after boiling with acetic anhydride–pyridine.

Nitration of 5-hydroxyflavone. The nitration of 5-hydroxyflavone in sulfuric acid solution as reported in the literature[5] was found unsatisfactory. The following procedure was adopted: 5-hydroxyflavone (0.5 g.) in acetic acid (5 cc.) was treated with concd. nitric acid (5 cc.) in acetic acid (5 cc.) with cooling in running tap water. The flavone dissolved slowly and the nitroflavone started separating. After 15 min., the product was filtered, washed and crystallized from acetic acid, m.p. 215° (shrinking at 100°). Mixed melting point with flavone (7) was not depressed.

Anal. Calcd. for $C_{15}H_9NO_5$: N, 4.95. Found: N, 5.25.

Acetylation of flavones (7), (8), and (9). The flavones (200 mg.) were refluxed with acetic anhydride (5 cc.) and pyridine

(5) R. M. Naik, A. M. Mehta, G. V. Jadhav, V. M. Thakor, and R. C. Shah, *Proc. Indian Acad. Sci.*, **38A**, 31 (1953).

(0.5 cc.) for 4 hr. The solid obtained on working up as usual was ground with alcohol (10 cc.) and filtered. The residue was crystallized from a mixture of alcohol and acetic acid. They gave negative ferric reaction.

The following acetoxyflavones were thus obtained: 5-acetoxy-8-nitroflavone, m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{11}NO_6$: N, 4.3. Found: N, 4.2.

5-Acetoxy-8-nitro-4′-methoxyflavone m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{13}NO_7$: N, 3.94. Found: N, 4.00.

5-Acetoxy-8-nitro-3′-4′-methylenedioxyflavone, m.p. 215–217°.

Anal. Calcd. for $C_{18}H_{11}NO_8$: N, 3.79. Found: N, 3.80.

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BOMBAY, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Some Analogs of Toxopyrimidine and Methioprim[1]

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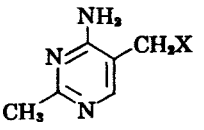
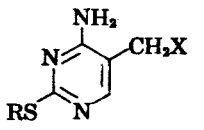
A number of new pyrimidines, related to 2-methyl-4-amino-5-hydroxymethylpyrimidine (I, toxopyrimidine) and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (VIII, methioprim) have been prepared and characterized.

The antimetabolite properties of toxopyrimidine[2] (I) stimulated our earlier work leading to the discovery of interesting antimetabolite and antitumor activity in "methioprim" (VIII).[3–6] We now wish to report the syntheses and characterization of a number of additional compounds related to these substances.

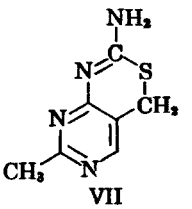
The analogs of toxopyrimidine were made by appropriate substitution reactions with the bromomethyl compound (X).[7] Reaction of X with thiourea, followed by neutralization of the crude isothiuronium salt, produced not only the disulfide III (presumably through the mercaptan) but led also to the isolation of the thiazinopyrimidine (VII), shown to be different from the isomeric thiocyanate (VI). XII, however, reacted normally with thiourea to produce the isothiuronium salt, XVII, which



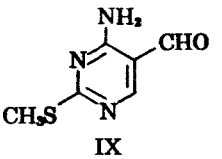
I, X = OH
II, X = SH
III, X =)$_2$S$_2$
IV, X =)$_2$S
V, X = SCH_3
VI, X = SCN
X, X = Br



VIII, R = CH_3, X = OH
XI, R = H, X = OH
XII, R = CH_3, X = Br
XIII, R = CH_3, X = OCH_3
XIV, R = CH_3, X = SCH_3
XV, R = CH_3, X = $SCOCH_3$
XVI, R = CH_3, X = SH
XVII, R = CH_3, X = $SC(NH_2)_2^+Br^-$
XVIII, R = CH_3, X =)$_2$S$_2$
XIX, R = C_2H_5, X = OH



VII

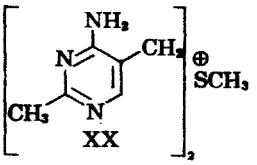


IX

was converted to disulfide, but did not give the analogous thiazinopyrimidine.

Oxidation of VIII by dichromate proceeded surprisingly smoothly to the aldehyde IX, which was also readily converted to the oxime.

When X was heated with sodium methyl mercaptide in ether, and then in dioxane, the sulfide IV instead of V was formed. This reaction may have proceeded through formation of a sulfonium salt (XX) as an intermediate.



XX

The replacement of the bromine atom of XII by methoxyl proceeded readily by solvolysis.

The reduction of 2-mercapto-4-amino-5-carbeth-

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(1) Supported in part by the U. S. Public Health Service Grant CY-2714.

(2) K. Makino, T. Kinoshita, T. Sasaki, and T. Shiei, *Nature*, 173, 34 (1954); K. Makino, T. Kinoshita, Y. Aramaki, and S. Shintani, *Nature*, 174, 275 (1954); K. Makino and M. Koike, *Nature*, 174, 1056 (1954); K. Makino and T. Kinoshita, *J. Vitaminol.*, 1, 14 (1955); S. Shintani, *J. Vitaminol.*, 8, 185 (1956).

(3) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, 21, 567 (1956); *Chem. & Ind. (London)*, 1221 (1955).

(4) T. L. V. Ulbricht and J. S. Gots, *Nature*, 178, 913 (1956); D. B. McNair-Scott, T. L. V. Ulbricht, M. L. Rogers, E. Chu and C. Rose, *Cancer Research*, in press; D. F. Dunning, T. L. V. Ulbricht, C. C. Price, and R. Jones, Jr., unpublished results; R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exptl. Biol. Med.*, 94, 792 (1957); R. Guthrie, J. F. Holland, E. A. Hyatt, M. Hillman, and D. T. Mount, *Proc. Am. Assoc. Cancer Research*, 2, 113 (1956); I. J. Slotnick, R. Guthrie, J. F. Holland, and M. J. Hillman, *Proc. Am. Assoc. Cancer Research*, 3, 251 (1957).

(5) F. Rosen, J. F. Holland, and C. A. Nichol, *Proc. Am. Assoc. Cancer Research*, 3, 243 (1957).

(6) This name has been suggested to us by Dr. Joseph S. Gots, Univ. of Pa., and Dr. Robert Guthrie, Roswell Park Memorial Institute.

(7) Kindly supplied by Dr. Max Tishler, Merck & Co., Rahway, N. J.