ment of III with potassium carbonate and the infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.51, 61.34; H, 10.00, 10.19; N, 17.62, 17.59.

Acknowledgment. The author expresses his appreciation to Mr. R. F. Cornuet for a very able technical assistance, to Drs. C. L. Parris and W.-H. Chang for stimulating discussions and suggestions, to Drs. H. L. Gerhart, S. W. Gloyer, and R. M. Christenson for continued interest and encouragement, and to Professor C. D. Hurd for reading the manuscript.

SPRINGDALE, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

The Synthesis of Some Derivatives of Methioprim and Related Pyrimidines[1,2]

J. GRAHAM NAIRN[3-5] AND HOWARD TIECKELMANN

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Methioprim (2-methylthio-4-amino-5-hydroxymethylpyrimidine) was used for the preparation of several 2-substituted 4-amino-5-hydroxymethylpyrimidines. The conversions were conveniently accomplished by oxidation of the acetate of methioprim to 2-methanesulfonyl-4-amino-5-acetoxymethylpyrimidine which was subsequently treated with ammonia or amines to give the 2-substituted pyrimidines. The preparation of several esters and amides of methioprim and several sulfones of related pyrimidines are also described.

Interest in 2-methyl-4-amino-5-hydroxymethylpyrimidine (toxopyrimidine), 5-hydroxymethylcytosine, and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I, methioprim)[2] has led to the synthesis of analogs of these substances in several laboratories. Emphasis has been centered on 2-substituted-4-amino-5-hydroxymethylpyrimidines, some of which have been used as intermediates in the synthesis of thiamin analogs. Usually these 5-hydroxymethylpyrimidines are prepared by reduction of the corresponding 5-carbethoxypyrimidines with lithium aluminum hydride[2,6] although other routes have been useful. For example, 5-hydroxymethyluracil and related compounds have been prepared by the addition of formaldehyde to the pyrimidones.[7]

The discovery by Guthrie[8] of the unusual antimetabolite activity of I has led to a search for related, more potent compounds for experimental cancer chemotherapy. 2-Trifluoromethyl-, 2-methylthio-4-arylamino-5-carbethoxy-, and 2-methylthio-4-arylamino-5-hydroxymethylpyrimidines have been prepared.[6c,9a,b,c]

The present report deals mainly with the synthesis of derivatives from I. The availability of this compound[10] has made it an attractive intermediate for the synthesis of other 2-substituted-4-amino-5-hydroxymethylpyrimidines. The presence of the 5-hydroxymethyl group in the starting material avoids its repeated formation. In addition, the presence of the 2-methylthio group suggested facile substitution at this position. Sprague and Johnson[11] have shown that the oxidation of 2-alkylthiopyrimidines to 2-alkanesulfonylpyrimidines followed by amination or hydrolysis is a convenient route to 2-aminopyrimidines, 2-alkoxypyrimidines, and 2-pyrimidones. Chlorine water was used as the oxidizing agent. This method is often effective in cases where direct substitution of amino for alkylthio is difficult. However, failures have been noted.[12]

We were unable to substitute amino- or alkylamino- for methylthio- in I. Furthermore, it was not possible to isolate 2-methanesulfonyl-4-amino-5-hydroxymethylpyrimidine (V) from a reaction mixture of I and chlorine water. When the hydroxyl group was protected by acetylation (II), the sulfone (III) could be prepared by oxidation with chlorine. This sulfone was readily converted to V, 2,4-

(1) Supported in part by a Grant, CY-2857, from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) For leading references see T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1958).

(3) In part from the dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Buffalo.

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(6) (a) A. Dornow and G. Petsch, *Ann.*, **588**, 45 (1954). C. S. Miller, *J. Am. Chem. Soc.*, **77**, 752 (1955). (b) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956). (c) J. A. Barone, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, **24**, 198 (1959).

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(9) (a) J. F. Holland, R. Guthrie, F. Sheehe, and H. Tieckelmann, *Cancer Research*, **18**, 776 (1958). (b) J. F. Holland, R. Guthrie, H. Tieckelmann, and R. Cuddihy, *Cancer Research Suppl.*, **18**, 335 (1958). (c) E. Peters, J. F. Holland, B. Bryant, H. J. Minnemeyer, C. Hohenstein, and H. Tieckelmann, *Cancer Research* **19**, 729 (1959).

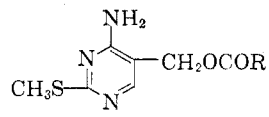
(10) We thank Dr. Stanton Harris, Merck, Sharp & Dohme, Inc. for a generous sample of methioprim.

(11) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 2252 (1935); **58**, 423 (1936) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

(12) K. J. M. Andrews, N. Anand, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 2490 (1949).

TABLE I

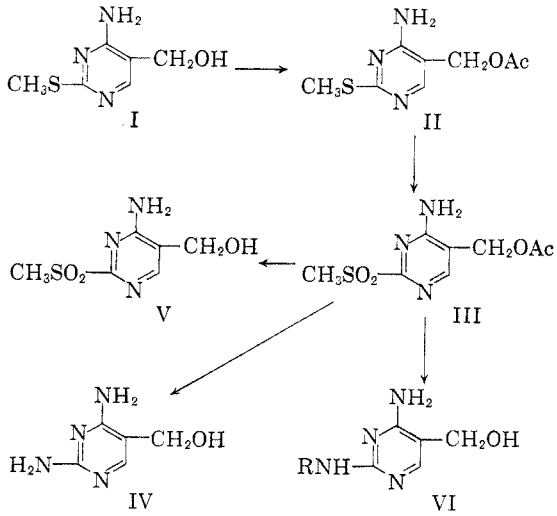
ESTERS OF METHIOPRIM



R	Yield, %	M.P.	Formula	Analyses	
				Calc., %	Found, %
CH_3 (II)[a]	94	137–138	$C_8H_{11}N_3O_2S$	C 45.0	44.8
				H 5.2	5.1
C_2H_5	64	159–161	$C_9H_{13}N_3O_2S$	C 47.6	48.1
				H 5.8	6.0
				S 14.1	13.7
$(CH_2)_2CH_3$	47	110–111	$C_{10}H_{15}N_3O_2S$	S 13.3	13.5
$(CH_2)_2COOH$[b]	47	184–187	$C_{10}H_{13}N_3O_4S$	C 44.3	44.2
				H 4.8	4.8
				S 11.8	11.3
C_6H_5[c]	84	186–187	$C_{13}H_{13}N_3O_2S$	N 15.3	15.0

[a] 50 ml. of ethyl acetate used, recrystallized from carbon tetrachloride. [b] 0.7 g. of succinic anhydride in 25 ml. ethyl acetate added to I in ethyl acetate, recrystallized once from dioxane and once from ethyl alcohol. [c] 13.5 g. of benzoic anhydride and 2 g. of methioprim in 100 ml. of ethyl acetate used. After evaporation of solvent the residue was extracted with 10% hydrochloric acid. The extract was treated with sodium hydroxide to precipitate product, which was recrystallized from methanol.

diamino-5-hydroxymethylpyrimidine (IV), and 2-substituted aminopyrimidines (VI).



The properties of IV were different from those previously reported. Huber[13] has recorded a melting point of 265° with decomposition and a picrate which decomposed at 244–246°. Our compound (IV) melted at 231–234° with decomposition and formed a picrate which decomposed at 243–244°. A discussion of the structure of these substances appears in the succeeding paper.[14]

Peters, *et al.*,[9c] have prepared some 2-methylthio-4-arylamino-5-carbethoxypyrimidines and have found that members of this series inhibit the growth of mouse tumors. The conversion of two of these pyrimidines to 2-methanesulfonyl- and 2-aminopyrimidines has been accomplished. In general, pyrimidines with electron-attracting groups on the 5- position were converted to sulfones in good yields.

In addition to the acetate, other esters of I have been prepared. A rapid disappearance of I in serum and a poor recovery in urine has been noted.[15] Experiments with rat liver homogenates showed that, in this system, I is oxidized to the corresponding 5-formylpyrimidine and 5-pyrimidinecarboxylic acid.[16] These observations and the inactivity of I in clinical trials[15] has suggested that esters, which are less susceptible to oxidation, might be better candidates. The hydrochloride of II was prepared from I and acetyl chloride using the method of Bretschneider.[17] The amides of esters of I were relatively difficult to prepare requiring an excess of the anhydride and long reflux.

EXPERIMENTAL[18,19]

Esters of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I). Three ml. of the anhydride was added to a solution of 1.0 g. of I in 100 ml. of ethyl acetate. After refluxing for 2 hr., the solvent was removed under reduced pressure. The esters were recrystallized from toluene after decolorizing with Norit. Yields given in Table I are for recrystallized materials.

2-Methylthio-4-amino-5-acetoxymethylpyrimidine hydrochloride. This compound was prepared from I by the method developed for esters of aminoalcohols by Bretschneider[17] in 69% yield. It was recrystallized from methanol–ethyl acetate, m.p. 155–159°.

(13) W. Huber, *J. Am. Chem. Soc.*, **65**, 2222 (1943).

(14) H. Tieckelmann, R. Guthrie, and J. G. Nairn, *J. Org. Chem.* **25**, 1257 (1960).

(15) J. F. Holland and R. Guthrie. Unpublished results.

(16) I. J. Slotnick, A. W. Spears, and H. Tieckelmann, *Proc. Soc. Exptl. Biol. Med.* **102**, 239 (1959).

(17) H. Bretschneider, *Monatsh.*, **76**, 368 (1947); H. Bretschneider, K. Biemann, W. Koller, and W. Sachsenmaier, *Monatsh.*, **81**, 31 (1950).

(18) Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected.

(19) Analyses by Geller Microanalytical Laboratories, Bardonia, N. Y.

Anal. Calcd. for $C_8H_{12}N_3O_2SCl$: C, 38.5; H, 4.8; S, 12.8. Found: C, 38.1; H, 5.0; S, 13.0.

When dissolved in water and treated with 10% ammonium hydroxide the free amino ester was formed, m.p. 134–137°. A mixed melting point with 2-methylthio-4-amino-5-acetoxymethylpyrimidine (II) prepared from I and acetic anhydride gave no depression.

2-Methylthio-4-acetamido-5-acetoxymethylpyrimidine. Acetic anhydride (150 ml.) was added to 5.0 g. of I dissolved in 500 ml. of ethyl acetate. After reflux for 15 hr. the solvent was removed under reduced pressure. The dry solid was recrystallized from carbon tetrachloride to give 4.3 g. (58%), m.p. 135–138°. The analytical sample, m.p. 141–142°, was obtained by crystallizing from carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{13}N_3SO_3$: C, 47.0; H, 5.1; S, 12.6. Found: C, 47.4; H, 5.0; S, 12.3.

2-Methylthio-4-propionamido-5-propionoxymethylpyrimidine. Eight ml. of propionic anhydride was added to a solution of 1.7 g. of I dissolved in 50 ml. of ethyl acetate. After reflux for 15 hr. the solvent was removed under reduced pressure. The residue was mixed with methanol and after removal of the methanol, the residue was crystallized from ethyl alcohol and water to give 1.85 g. (65%). The analytical sample, m.p. 93–94°, was recrystallized again from alcohol-water.

Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: N, 14.8. Found: N, 14.9.

2-Methylthio-4-n-butyramido-5-n-butyroxymethylpyrimidine. Butyric anhydride (20 ml.) was refluxed with 1.7 g. of I and 40 ml. of ethyl acetate for 22 hr. The solvent and some excess anhydride were removed under reduced pressure. Alcohol was added to the oil and removed under reduced pressure. This procedure was repeated twice with benzene. On standing, the oil solidified. After washing thoroughly with 3% hydrochloric acid, the residue was crystallized from ethyl alcohol–water to give 0.95 g. (30%) of a white solid, m.p. 76–86°. The analytical sample, m.p. 88–89°, was recrystallized from ligroin-ether.

Anal. Calcd. for $C_{14}H_{21}N_3O_3S$: N, 13.5. Found: N, 13.3.

2-Methanesulfonyl-4-amino-5-acetoxymethylpyrimidine. (III). Five g. of II was dissolved in 300 ml. of 1% hydrochloric acid. The solution was cooled to 1–2° and chlorine passed in rapidly for 10 min. Seven g. of sodium bisulfite was added with stirring and the temperature maintained below 5°. After stirring for an additional 5 min. the white precipitate was filtered, washed thoroughly with ice cold water, and immediately dried at room temperature under vacuum. The dried solid was recrystallized from dry isopropyl alcohol to give 3.1 g. (53%) of III, m.p. 153–154°. The analytical sample, m.p. 154–155°, was recrystallized from dry isopropyl alcohol.

Anal. Calcd. for $C_8H_{11}N_3O_4S$: C, 39.2; H, 4.9; S, 13.1. Found: C, 39.4; H, 5.1; S, 12.6.

Chlorination of 5.0 g. of II in 300 ml. of 5% hydrochloric acid for 17 min. at 3° gave a yellow precipitate, which was washed with water and a little 10% sodium bisulfite solution. The precipitate changed to a gum which crystallized on standing in water. It was crystallized from water and gave a compound which melted at 217–220° in 15% yield. The analysis corresponded to 4-amino-5-acetoxymethyl-5-chloro-5,6-dihydro-6-hydroxypyrimidine-2(1H)-one.

Anal. Calcd. for $C_7H_{10}N_3O_4Cl$: C, 35.7; H, 4.3; Cl, 15.1. Found: C, 35.6; H, 3.8; Cl, 14.7.

Chlorination of 1 g. of II in 60 ml. of 5% hydrochloric acid cooled to below 5° for 75 min. 0.95 g. of a compound, m.p. 191–192°, crystallized from water, which corresponded to a 4-amino-2,5-dichloro-5,6-dihydro-6-hydroxy-5-hydroxymethylpyrimidine.

Anal. Calcd. for $C_5H_7N_3O_2Cl_2$: C, 28.3; H, 3.3; Cl, 33.5. Found: C, 28.3; H, 2.8; Cl, 33.9.

2-Methanesulfonyl-4-amino-5-hydroxymethylpyrimidine (V). Nine-tenths g. of III was dissolved in 18 ml. of warm methanol. After the addition of 9 ml. of concd. ammonium hydroxide, the solution was allowed to stand at room temperature for 2 hr. and then cooled overnight at 0–5°. The solvent was removed at reduced pressure and the residue recrystallized from isopropyl alcohol and methanol to give 0.48 g., m.p. 157–159° (64%) of V. The analytical sample from isopropyl alcohol and methanol melted at 172–173°.

Anal. Calcd. for $C_6H_9N_3O_3S$: C, 35.5; H, 4.5. Found: C, 35.9; H, 4.5.

2,4-Diamino-5-hydroxymethylpyrimidine (IV). Five g. of III was dissolved in 75 ml. of methanol and saturated with ammonia at 0° in a Carius tube. After heating to 110–115° for 9 hr. the mixture was cooled to 0° and filtered to give 1.5 g. (53%), m.p. 218–223° of VI. The analytical sample, m.p. 231–234°, was recrystallized from methanol.

Anal. Calcd. for $C_5H_8N_4O$: C, 42.9; H, 5.8; N, 40.0. Found: C, 43.1; H, 5.9; N, 39.8.

2-Methylamino-4-amino-5-hydroxymethylpyrimidine. Methylamine was absorbed in 30 ml. of absolute methanol containing 2 g. of III in a Carius tube until the total volume was 50 ml. After heating for 12 hr. at 110–115°, the solvent was removed thoroughly under reduced pressure. Acetone was added to the resulting oil and the mixture cooled to 0–5°. A solid formed which was dissolved in 4 ml. of 5% sodium hydroxide and extracted four times with 10-ml. portions of acetone. The product, after removal of the acetone, weighed 0.89 g. (71%), m.p. 135–137°. The analytical sample was recrystallized from isopropyl alcohol and melted at 142–144°.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.7; H, 6.5; N, 36.3. Found: C, 47.0; H, 6.5; N, 36.1.

2-Ethylamino-4-amino-5-hydroxymethylpyrimidine. This compound was prepared by the same method used for the methyl homolog. Acetone treatment was omitted. Ether was used as the extraction solvent. The crude product, after removal of the ether, and after crystallization took place, was washed with ethyl acetate and recrystallized from chloroform. One g. of III gave 0.22 g. (32%) of 4-amino-2-ethylamino-5-hydroxymethylpyrimidine, m.p. 133–136°.

Anal. Calcd. for $C_7H_{12}N_4O$: N, 33.3. Found: N, 33.2.

2-n-Propylamino-4-amino-5-hydroxymethylpyrimidine. One g. of III in 13 ml. of methanol and 13 ml. of *n*-propylamine was heated at 115–120° for 19 hr. After removing the solvent under reduced pressure the oil was dissolved in 4 ml. of 5% sodium hydroxide. Ether was used as the extraction solvent. After dissolving in ethyl acetate the pyrimidine was precipitated with ligroin, 0.4 g. (54%). The analytical sample, m.p. 114–117°, was crystallized from benzene.

Anal. Calcd. for $C_8H_{14}N_4O$: N, 30.8. Found: N, 30.6.

2-Methylthio-4-amino-5-carboxamidopyrimidine. Ten g. of 4-amino-2-methylthio-5-cyanopyrimidine[20] was added to a boiling solution of 1 l. of 0.1*N* sodium hydroxide. After refluxing 15 min., the mixture was cooled rapidly and cooled overnight in the refrigerator. The amide was filtered and washed with cold water to give 8.9 g. (80%), m.p. 280–281°. Recrystallized from methanol, the analytical sample melted at 280–281°.

Anal. Calcd. for $C_6H_8N_4OS$: C, 39.1; H, 4.4; S, 17.4. Found: C, 39.4; H, 4.3; S, 17.1.

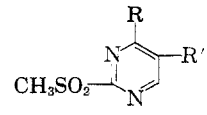
2-Methanesulfonylpyrimidines. 2-Methylthio-4-amino-5-cyanopyrimidine,[20] 2-methylthio-4-amino-5-pyrimidinecarboxamide, 2-methylthio-4-*o*-chloranilino-5-carbethoxypyrimidine,[9c] 2-methylthio-4-*o*-bromoanilino-5-carbethoxypyrimidine,[9c] and 2-methylthio-4-chloro-5-carbethoxypyrimidine[9c] were converted to the corresponding 2-methanesulfonylpyrimidines (Table II). The 2-methylthiopyrimidine (0.5 g.) was dissolved or suspended in 60 ml. of 1% hydrochloric acid and cooled to 0–5°. Chlorine was passed in rapidly for 5–10 min. After treatment with sodium bisulfite the precipitated sulfone was filtered while cold, washed with cold water, and dried thoroughly under vacuum. The sulfone was crystallized from isopropyl alcohol.

2-Amino-4-o-chloroanilino-5-carbethoxypyrimidine. 2-Meth-

(20) Steve G. Cottis, M. A. thesis, University of Buffalo, 1959.

TABLE II

2-METHANESULFONYLPYRIMIDINE



R	R′	Yield, %	M.P.	Molecular Formula	Analyses Calcd.	Found
NH_2	CN	67[a]	211–214	$C_6H_6N_4O_2S$	N 28.3	28.6
NH_2	$CONH_2$	29[b,c]	216–218	$C_6H_8N_4O_3S$	N 25.9	25.4
o-NHC_6H_4Cl	—CO_2Et	87	180–181	$C_{14}H_{14}N_3O_4SCl$	N 11.8	11.6
o-NHC_6H_4Br	—CO_2Et	92	172–174	$C_{14}H_{14}N_3O_4SBr$	N 10.5	11.0
Cl	—CO_2Et	94[b]	129–130	$C_8H_9N_2O_4SCl$	N 10.6	10.1

[a] Oxidation solvent was 60 ml. of 5% hydrochloric acid for 0.5 g. of the pyrimidine. Recrystallization solvent was ethyl acetate. [b] Oxidation solvent was 30 ml. of 1% hydrochloric acid. [c] Recrystallization solvent was 95% ethyl alcohol.

ylsulfonyl-4-*o*-chloroanilino-5-carbethoxypyrimidine (0.5 g.) was heated in 15 ml. of absolute methanol. Ammonia was passed in for 10 min. while the mixture was still warm. After standing at room temperature for 12 hr. the mixture was allowed to cool to 0–5° for 12 hr. and filtered to give 0.3 g. (73%), m.p. 209–213°. The analytical sample, m.p. 215–216°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Cl$: C, 53.3; H, 4.5; N, 19.1. Found: C, 53.5; H, 4.6; N, 19.1.

2-Amino-4-o-bromoanilino-5-carbethoxypyrimidine. This compound was prepared by the method used for the 4-*o*-chloroanilino- analog. The yield was 0.3 g. (71%), m.p. 204–211° of 2-amino-4-*o*-bromoanilino-5-carbethoxypyrimidine from 0.5 g. of sulfone. The analytical sample, m.p. 213–214°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Br$: N, 16.6. Found: N, 16.8.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM HOFFMANN-LA ROCHE, INC.]

Pyridindene Derivatives. IV. Alkylated Pyridindenes

JOHN T. PLATI AND WILHELM WENNER

Received December 14, 1959

The reaction of crotonophenone and methylamine yielded a condensation product which on treatment with alkali gave 1,2,6-trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III). Dehydration followed by partial reduction gave 1,2,3-trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI). The reaction of methylmagnesium iodide with 1-methyl-3-benzoyl-4-phenyl-4-hydroxypiperidine (VIII) yielded a diol (IX) which on dehydration gave 2,9-dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XI).

This paper deals with an extension of our earlier work on pyridindene derivatives. Our first concern was the introduction of alkyl groups into the hetero ring in order to ascertain the antihistamine properties of the resulting compound. A type of Mannich reaction between acetophenone, methylamine, and acetaldehyde was briefly considered for the preparation of the starting material, but this scheme was discarded in favor of the reaction between crotonophenone and methylamine.

When the reaction was allowed to proceed for a relatively short period of time, it was possible to isolate the product (I) formed by the addition of one mole of methylamine to one mole of crotonophenone. The bis product (II) may also have been formed, but efforts at isolation were not pursued vigorously, since our primary concern was to obtain the piperidine derivative (III). It was reasoned after our earlier work[1] that this compound could be obtained not only by ring closure of the bis product (II) but also by disproportionation of the mono-addition product (I). The mother liquor from (I) should contain both products, with the bis product predominating after a prolonged reaction time. Accordingly, treatment with alkali should yield the piperidine (III), and actually this expectation was realized. By refluxing with hydrobromic acid, the piperidine (III) underwent dehydration and ring closure to give the pyridindene (IV). On hydrogenation, a mixture of (V) and (VI) was apparently obtained. The (VI) base was obtained by purification through the thiocyanate salt, followed by prolonged treatment with alkali. It is noteworthy that the ultraviolet spectrum (Curve 1) of the VI base is almost identical with that of VII.[2] The treatment with alkali was

(1) J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).

(2) J. T. Plati and W. Wenner, *J. Org. Chem.*, **20**, 1413 (1955).