

chloro-5-phenylazopyridine⁵ was autoclaved with an alcoholic solution of dimethylamine.

Experimental

Mills Reaction with 2-Dimethylamino-5-aminopyridine.—2-Dimethylamino-5-nitropyridine⁶ was reduced in a Parr apparatus with 5% palladium on carbon in 95% ethanol. The diamine was unstable to air and on treatment with nitrosobenzene in acetic acid gave no isolable azo compound.

2-N,N-Dimethylamino-5-phenylazopyridine.—2-Chloro-5-phenylazopyridine, once recrystallized from ethanol, was prepared in 94% yield by the method of Mills.⁵ Six grams of this compound was treated with a solution of 10.2 g. of dimethylamine in 65 ml. of absolute ethanol in a sealed tube at 150° for 4 hr. The solvent and excess dimethylamine were removed *in vacuo* and the product was recrystallized twice from ethanol; m.p. 114.5–115.2°; the yield of yellow plates was 3.4 g. (54.5%).

Anal. Calcd. for C₁₃H₁₄N₄: C, 69.03; H, 6.20; N, 24.77. Found: C, 68.95; H, 6.32; N, 24.55.

Biological Testing and Results.—Young male rats of the Sprague-Dawley strain, approximately 8 weeks of age and weighing 150 to 200 g., were distributed as equally as possible by initial body weight into groups of 10 animals each. Each group was fed a diet, patterned after the "low protein, low riboflavine" diet of Miller, *et al.*,⁷ to which had been added one of the azo compounds at a level of 0.06%. The composition of the basal diet on a kilogram basis was as follows: crude casein, 120 g.; cerelese, 770 g.; Osborne and Mendel salt mixture, 40 g.; corn oil, 50 g.; Vitab (rice bran concentrate, obtained from Charles Bowman Co.), 20 g.; riboflavine, 0.5 mg.; vitamin A palmitate, 67,500 IU (we are grateful to Charles Pfizer and Co., Inc., for a generous supply). The control group received only the basal diet. All the rats were kept individually in screen-bottomed cages and were offered food and water *ad libitum*. Laparotomies were performed at the indicated times and microscopic examinations were made whenever an animal died or at the end of the experiment. Feeding 2-N,N-dimethylamino-5-phenylazopyridine at 0.06% level produced no tumors in 12 months. The data are indicated in Table I.

TABLE I
CARCINOGENICITIES OF THE AZO COMPOUNDS

Code	Incidence of liver tumors ^a —		
	4 months	7 months	12 months
Control (no dye)	0/10	0/10	0/10
N,N-Dimethyl- <i>p</i> -phenylazo-aniline ^b	7/10	9/10	10/10
N,N-Dimethyl- <i>p</i> -(3-pyridylazo)-aniline	1/8	7/8	8/8
5-Phenylazo-2-N,N-dimethylpyridine	0/10	0/10	0/10

^a Number of rats with tumors/number of rats in experiment. All azo compounds were fed at the 0.06 level. ^b Commonly called Butter yellow.

(7) J. A. Miller and E. C. Miller, *Advan. Cancer Res.*, **1**, 339 (1953).

Some 5-Fluoropyrimidines^{1a}

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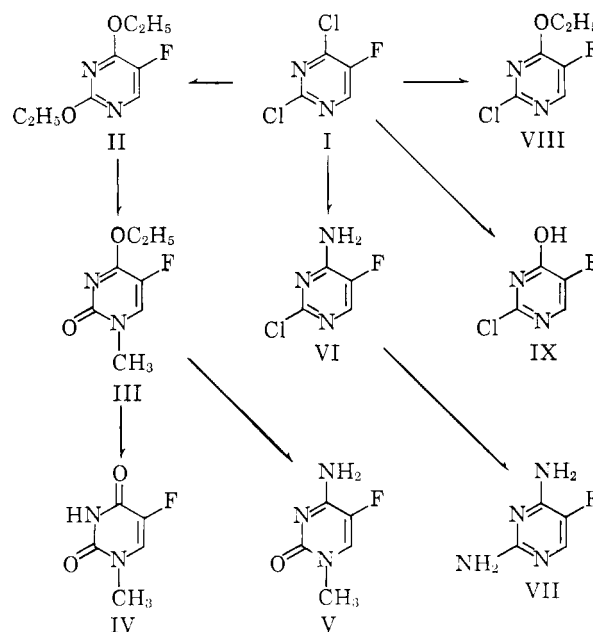
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Since the synthesis of 5-fluorouracil by Duschinsky, Plevin, and Heidelberger² this compound has attracted

(1) (a) Supported largely by a Michigan Cancer Foundation Grant. (b) Chemistry Department, Le Moyne College, Syracuse, N. Y. 13214.

a great deal of attention as an antimetabolite in the treatment of cancer.³ Thus, it was desirable to prepare several derivatives of 5-fluoropyrimidine.

In this project the key intermediate was 2,4-dichloro-5-fluoropyrimidine (I).⁴ The versatility of 2,4-dichloropyrimidines as intermediates in synthetic pyrimidine chemistry is well known⁵ and is due to the reactive halogen atoms attached to the electrophilic pyrimidine ring. The conversion of I to 2,4-diethoxy-5-fluoropyrimidine (II) was effected with sodium ethoxide and is reported elsewhere.⁶ Reaction of II with methyl iodide gave 4-ethoxy-5-fluoro-1-methyl-2(1H)-pyrimidone (III). The assignment of the methyl group to the N-1 position is based on the known reactions of 2,4-diethoxypyrimidines with alkyl halides and with O-acylglycosyl halides (Hilbert-Johnson synthesis of nucleosides) to yield N-1 alkyl derivatives and N-1 glycosyl nucleosides.⁷ Hydrolysis and aminolysis of III resulted in the formation of 5-fluoro-1-methyluracil (IV) and 5-fluoro-1-methylcytosine (V), respectively.



Reaction of I with alcoholic sodium ethoxide (1 mole) or sodium hydroxide resulted in the formation of 2-chloro-4-ethoxy-5-fluoropyrimidine (VIII) and 2-chloro-5-fluoro-4-hydroxypyrimidine (IX), respectively.⁸ Attempts to replace the chlorine atom of IX by amino or methoxy groups failed.

The partial structural relationship between the folic acid antagonist, aminopterin, and 2,4-diamino-5-

(2) R. Duschinsky, E. Plevin, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).

(3) J. A. Montgomery, *Cancer Res.*, **19**, 447 (1959).

(4) (a) R. Duschinsky, U. S. Patent 3,040,026 (1962); (b) M. G. Biresi, M. Carrissini, and F. Ravenna, *Gazz. chim. ital.*, **93**, 1268 (1963); (c) L. D. Protosenko and Yu. I. Bogodist, *Zh. Obshch. Khim.*, **33**, 537 (1963).

(5) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp. 183–208.

(6) G. J. Durr, *J. Med. Chem.*, **8**, 140 (1965).

(7) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001, 4489 (1930); J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 328 (1959).

(8) Compound IX was prepared independently by Dr. R. Duschinsky of Hofmann-La Roche, Inc., who has verified that substitution took place at the 4-position. Dr. Duschinsky has also prepared and identified 2-chloro-5-fluoro-4-methoxypyrimidine. Allocation of the ethoxy group to the 4-position of VIII is based on analogy to this work: private communication by Dr. R. Duschinsky.

TABLE I

Compd.	Dose, mg./kg.	Survivors	Animal wt. diff. $T - C^a$	Tumor wt., g. T/C^a	% T/C^a
P1798 Lymphosarcoma					
II	250	0/10			
	62	10/10	-1.1	1810/2863	63
	62	10/10	0.2	1310/966	135
	62	6/10	-2.4	1233/1516	
P1798 Lymphosarcoma					
III	250	0/10			
	50	10/10	-0.8	1410/2863	49
	50	10/10	-0.7	1337/1516	88
HS1 Human Sarcoma (Embryonated Egg)					
VIII	20	6/6	-0.4	97/742	13
	20	3/6	0.0	358/890	
	20	2/6	-0.3	420/1308	
	10	3/6	-0.1	1100/1554	
	5	2/6	0.1	465/1116	
	2.5	5/6	0.0	335/682	49
	2.5	3/6	-0.3	388/1443	
P1798 Lymphosarcoma					
IX	200	4/6	-4.5	122/1762	6
	200	2/6	-3.1	53/1706	
	200	0/6			
	100	1/6	-5.4	0/139	
	50	6/6	-5.1	105/1798	5
	50	6/6	-5.0	162/2170	7
	50	6/6	-3.6	182/1867	9
	50	5/6	-7.7	120/2293	5
Sarcoma 180					
IX	50	6/6	-5.6	318/1753	18
	50	5/6	-1.6	484/2541	19
Adenocarcinoma 755					
IX	50	10/10	-3.4	349/1480	23
	50	4/10	-7.5	180/1047	
	50	0/10			
	25	10/10	-4.1	392/1580	24

^a T = test, C = control.

fluoropyrimidine (VII)⁹ made the synthesis of VII particularly attractive. Attempts to prepare VII directly from I failed. Brown prepared 2,4-diaminopyrimidine by the reaction of 2,4-dichloropyrimidine with ammonia in phenol at 190°.¹⁰ In order to avoid the use of boiling phenol, 2,4-diamino-5-fluoropyrimidine (VII) was finally prepared by reaction of 4-amino-2-chloro-5-fluoropyrimidine (VI) with alcoholic ammonia at 140° in a Parr bomb, the reaction being acid catalyzed by ammonium chloride. The 4-amino-2-chloro-5-fluoropyrimidine (VI) was prepared by a modification of the method described by Duschinsky.^{4a}

Table I gives the screening test reports for these compounds. The testing was done under the auspices of the Cancer Chemotherapy National Service Center, and the testing procedures have been described previously.¹¹

Compounds II-IV and VII-IX were without significant effect on L1210 lymphoid leukemia. The results of preliminary screening against P1798 lymphosarcoma were as follows: compounds V, VII, and VIII

were nontoxic inactive; II and III passed stage 1 of sequential screen; IX passed second confirmation test of screen. Two compounds were screened against HS1 human sarcoma, II being nontoxic and inactive and VIII passing stage 2 of the screening. Of the three compounds tested against Sarcoma 180, IV and VI were without significant effect, and IX has passed stage 2 of the screening sequence. In testing against Adenocarcinoma 755, IV was without significant effect, IX passed stage 2 of the screening, and the other compounds have not been tested. The three compounds (VII-IX) tested against Dunning leukemia (ascites) were nontoxic and inactive. The parent compound, 5-fluorouracil (5FU),² showed significant inhibition against Sarcoma 180, L1210 leukemia, P1798 lymphosarcoma, and HS1 human sarcoma.¹² Insufficient data were obtained in testing 5FU against Adenocarcinoma 755.¹³

Experimental¹⁴

4-Ethoxy-5-fluoro-1-methyl-2(1H)-pyrimidone (III).—A solution of 700 mg. (3.7 mmoles) of II in 7 ml. of methyl iodide was allowed to stand for 2 days. The methyl iodide was removed *in vacuo*, and the residue was triturated with anhydrous ether and filtered, yielding 200 mg. of product, m.p. 129-133°. The ethereal filtrate was evaporated to an oil, and the above procedure was repeated twice (the methyl iodide solution now being refluxed) to yield an additional 300 mg. (m.p. 125-131°), giving a total yield of 77%. Recrystallization from 2-propanol-ether raised the m.p. to 135-136°; $\lambda_{\text{max}}^{\text{water}}$ 282 m μ (log ϵ 3.90); $\lambda_{\text{max}}^{\text{NaOH}}$ 6.01, 6.14, 6.55, 6.73, 7.48, 8.05, 8.59, 8.74, 9.09, 9.45, 9.80, 10.40, 10.71, 11.11, 12.98, 13.67, 14.54 μ .

Anal. Calcd. for $C_7H_9FN_2O_2$: C, 48.84; H, 5.27; F, 11.04. Found: C, 48.71; H, 5.25; F, 11.25.

5-Fluoro-1-methyluracil (IV).—A solution of 282 mg. (1.64 mmoles) of III and 10 ml. of 30% methanolic HCl was allowed to stand at room temperature for 3 days. During this time 170 mg. of product (m.p. 261-263°) crystallized and was removed by filtration. An additional 46 mg. (m.p. 257-259°) was obtained from the mother liquors increasing the yield to 92%. Recrystallization from 80% ethanol raised the m.p. to 264-265° when placed on the hot stage at 260°; $\lambda_{\text{max}}^{\text{water}}$ pH 7: 274 m μ (log ϵ 3.84), pH 1.4: 273.5 m μ (log ϵ 3.84), pH 12.1: 271.5 m μ (log ϵ 3.70); $\lambda_{\text{max}}^{\text{NaOH}}$ 5.95, 6.08, 7.59, 8.10, 8.31, 8.70, 9.32, 10.71, 11.10, 11.55, 12.80, 13.38, 14.31, 15.90 μ .

Anal. Calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; F, 13.19. Found: C, 41.95; H, 3.42; F, 13.48.

5-Fluoro-1-methylcytosine (V).—A solution of 142 mg. (0.83 mmole) of III and 10 ml. of 5% ethanolic ammonia was heated in a Parr bomb at 110° for 21 hr., the alcohol then being removed *in vacuo*. Addition of 1 ml. of water to the residue and filtration gave 45 mg. of product, m.p. 295-299°. An additional 38 mg. of product (m.p. 285-290°) was obtained from the filtrate raising the yield to 70%. Recrystallization was effected from 30% ethanol giving pure V: m.p. 297-299°; $\lambda_{\text{max}}^{\text{water}}$ pH 7: 282 m μ (log ϵ 3.84), pH 1.3: 293.5 m μ (log ϵ 3.99), pH 12.2: 282 m μ (log ϵ 3.84); $\lambda_{\text{max}}^{\text{NaOH}}$ 3.00, 3.18, 5.99, 6.20, 6.62, 7.00, 8.23, 8.78, 9.18, 9.48, 10.15, 12.85, 14.35 μ .

Anal. Calcd. for $C_5H_6FN_3O$: C, 41.97; H, 4.23; N, 29.37. Found: C, 42.10; H, 4.00; N, 29.31.

4-Amino-2-chloro-5-fluoropyrimidine (VI).—2,4-Dichloro-5-fluoropyrimidine (I, 200 mg., 1.2 mmoles) was added to 5 ml. of liquid ammonia in a pressure flask and allowed to warm to room temperature. The ammonia was then allowed to escape. On the

(12) Erich Hirschberg, *ibid.*, **23**, 606 (1963).

(13) D. P. Griswold, W. R. Lacter, Jr., M. Y. Snow, F. M. Schabel, Jr., and H. E. Shipper, *ibid.*, **23**, 343, 351 (1963).

(14) Melting points were determined using a Kofler hot stage. Paper chromatograms were carried out on Whatman No. 1 paper and the chromatograms were developed by a descending technique in the solvent systems (A) saturated aqueous ammonium sulfate-2-propanol-water (2:28:70) and (B) 2-propanol-water-concentrated HCl (6.5:77:16.5). After developing, the paper was dried and the spots were located by visual examination under ultraviolet light. Ultraviolet absorption spectra were determined on a Beckman DU spectrophotometer.

(9) The product VII was also prepared independently by Dr. R. Duschinsky.

(10) D. J. Brown, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **69**, 353 (1950).

(11) J. Leiter, A. R. Bourke, S. A. Schepartz, and I. Wodinsky, *Cancer Res.*, **20**, 734 (1960); J. Leiter, A. R. Bourke, D. B. Fitzgerald, S. A. Schepartz, and I. Wodinsky, *ibid.*, **22**, 221 (1962).

addition of water, 170 mg. (97%) of crude product, m.p. 192–194°, was obtained. Recrystallization from water gave needles, m.p. 194–195°. The pyrimidine VI traveled as a single spot on paper, R_f 0.67, solvent system A. Paper chromatography of the mother liquors showed the same spot only, thus indicating that the isomeric 2-amino-4-chloro-5-fluoropyrimidine was not formed in the reaction. The ultraviolet and infrared spectra were similar to those found by Duschinsky.^{4a}

Anal. Calcd. for $C_4H_5ClFN_3$: C, 32.52; H, 2.05; Cl, 24.04; N, 28.49. Found: C, 32.46; H, 1.98; Cl, 24.28; N, 28.38.

2,4-Diamino-5-fluoropyrimidine (VII).—A mixture of 80 mg. (0.54 mmole) of VI, 5 ml. 5% ethanolic ammonia, and 200 mg. of ammonium chloride was heated at 140° for 19 hr. in a Parr bomb. The mixture was filtered, evaporated to dryness *in vacuo*, dissolved in 2 ml. of water, and brought to pH 12 with 0.2 ml. of 10% NaOH. This solution was evaporated to dryness *in vacuo*, and the desired product was separated by sublimation at 20 mm. and 140°, yielding 25 mg. (36%) of VII (m.p. 156–157° with partial recrystallization, remelting at 161–161.5°). Resublimation raised the m.p. to 164–165° with partial recrystallization, remelting at 166.5–167°; $\lambda_{\text{max}}^{\text{pH 7 buffer}}$ 289 m μ ($\log \epsilon$ 3.77); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.98, 3.15, 6.00, 6.23, 6.59, 6.71, 6.95, 8.25, 10.13, 10.65, 10.73, 12.90 μ .

Anal. Calcd. for $C_4H_5FN_4$: C, 37.51; H, 3.93; F, 14.83. Found: C, 37.65; H, 4.01; F, 15.11.

2-Chloro-4-ethoxy-5-fluoropyrimidine (VIII).—To a solution of 775 mg. (4.64 mmoles) of 2,4-dichloro-5-fluoropyrimidine (I) in absolute ethanol was added 2.9 ml. of 1.6 N ethanolic sodium ethoxide. The mixture was evaporated to 3 ml. and 7 ml. of water was added. An oil formed which solidified on cooling; this solid was removed by filtration, giving 800 mg. (96%) of product, m.p. 31–32°; purification by sublimation raised this to m.p. 35–36°; $\lambda_{\text{max}}^{\text{water}}$ 261.5 m μ ($\log \epsilon$ 3.72); $\lambda_{\text{max}}^{\text{film}}$ 3.40, 6.35, 6.78, 6.90, 7.14, 7.45, 8.05, 8.21, 8.68, 9.80, 10.32, 10.50, 11.45, 12.45, 13.05 μ .

Anal. Calcd. for $C_8H_8ClFN_2O$: C, 40.80; H, 3.43; Cl, 20.05; F, 10.76. Found: C, 40.76; H, 3.40; Cl, 19.98; F, 10.52.

2-Chloro-5-fluoro-4-hydroxypyrimidine (IX).—A mixture of 1.96 g. (11.7 mmoles) of I and 6.2 ml. (11.8 mmoles) of 1.9 N NaOH was warmed to 45° and stirred for 45 min. at the end of which time the mixture was neutral. An additional 6.2 ml. of 1.9 N NaOH was added, and the mixture was stirred until the oil dissolved, requiring 15 min. After cooling, 1 ml. of concentrated HCl was added, causing the immediate precipitation of 1.38 g. of product, m.p. 170–171°. An additional 0.1 g. (same as above by infrared spectrum) was recovered from the filtrate giving a total yield of 85%. Evaporation of the mother liquors *in vacuo* gave a solid material whose infrared spectrum was similar to the pure product. Paper chromatography gave single identical spots for the pure compound and the residue in the mother liquor; solvent system A, R_f 0.76, for pure compound and residue; solvent system B, R_f 0.93, for pure compound and residue. Recrystallization from absolute ethanol, prolonged heating being avoided, raised the melting point to 176–177° with partial recrystallization and remelting at 228–243°; $\lambda_{\text{max}}^{0.1 N CHCl_3}$ 229 m μ ($\log \epsilon$ 3.72), 258–259 m μ ($\log \epsilon$ 3.70); $\lambda_{\text{max}}^{\text{Nujol}}$ 6.09, 6.28, 6.48, 6.65, 7.75, 8.00, 8.60, 10.39, 10.90, 12.78, 14.55 μ . The material is the same as that prepared and characterized by Duschinsky.⁸

Anal. Calcd. for $C_4H_2ClFN_2O$: C, 32.34; H, 1.36; F, 12.80. Found: C, 32.35; H, 1.42; F, 14.64.

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New 1-Aminomethylbenzocyclobutenes

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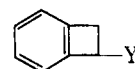
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In view of the chemical uniqueness of a four-membered ring fused to an aromatic nucleus and the simi-

larity of this system to the phenethyl chain, several amines containing the 1-benzocyclobutenyl group were synthesized for pharmacological evaluation. Until recently,¹ only two such compounds, 1-aminobenzocyclobutene² and N,N-dimethyl-1-aminomethyl-2-phenylbenzocyclobutene,³ were known. In addition to the first amine, we have prepared four new 1-aminomethylbenzocyclobutenes and a related morpholine derivative.

1-Cyanobenzocyclobutene⁴ (Ia), obtained by the benzyne-mediated cyclization of *o*-chlorohydrocinamonitrile,⁵ was hydrolyzed to benzocyclobutene-1-carboxylic acid (Ib). Treatment of the corresponding acid chloride Ic with sodium azide in toluene provided 1-aminobenzocyclobutene (Table I, III) in 40% yield. The direct conversion of the acid Ib to the amine III with hydrazoic acid² proceeded in somewhat higher yield.



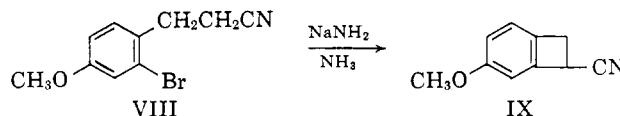
Ia, Y = CN
b, Y = CO₂H
c, Y = COCl

IIa, Y = CH₂NHCOCH₃
b, Y = CH₂OTs

1-Aminomethylbenzocyclobutene (IV) was prepared both by hydrolysis of the amide IIa from reductive acylation of 1-cyanobenzocyclobutene (Ia) and by lithium aluminum hydride reduction of the nitrile Ia.

The tosylate IIb of 1-hydroxymethylbenzocyclobutene was obtained with some modifications by the method of Cava and Mitchell⁶; aminolysis of this material with methylamine, dimethylamine, and morpholine provided compounds V, VI, and VII, respectively. As reported for the reaction of 1-hydroxymethyl-2-phenylbenzocyclobutene tosylate with dimethylamine,³ the tosyl group of IIb is displaced without any apparent ring enlargement.⁷ In order to substantiate the assigned structures, N,N-dimethyl-1-aminomethylbenzocyclobutene maleate (VI) was synthesized independently by reductive alkylation of 1-aminomethylbenzocyclobutene (IV) and was found to be identical by melting point and spectral comparison with the product obtained from the tosylate IIb.

Alkylation of ethyl cyanoacetate with 2-bromo-4-methoxybenzyl chloride, followed by hydrolysis of the resulting cyano ester and decarboxylation of the intermediate cyano acid, provided 2-bromo-4-methoxyhydrocinnamonitrile (VIII). Treatment of VIII with



sodamide in liquid ammonia afforded 1-cyano-5-methoxybenzocyclobutene (IX) in a 55% yield.

(1) After completion of this work, reports of amino- and aminoalkyl-substituted benzocyclobutenes appeared in the patent literature: (a) K. Ley, H. Walz, and W. Redetzky, Belgian Patent 630,171 (1963); (b) C. Kaiser and C. L. Zirkle, U. S. Patent 3,149,159 (1964); (c) Ciba S. A., French Patent 1,369,046 (1964).

(2) L. Horner, W. Kirmse, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(3) A. T. Blomquist and C. G. Bottomley, *Ann.*, **653**, 67 (1962).

(4) M. P. Cava, R. L. Little, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2257 (1958).

(5) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

(6) M. P. Cava and M. J. Mitchell, *ibid.*, **27**, 631 (1962).

(7) The quantitative conversion of 1-hydroxymethylindane tosylate to a 2-hydroxytetralin ester during formolysis has been noted by R. Huisgen G. Seidl, and I. Wimmer, *Tetrahedron*, **20**, 623 (1964).