ride. It showed a double melting point in an evacuated capillary, decomposing at about 106–107°, resolidifying and melting again at 183–177° dec.

8-[3-Bis(2-chloroethylamino)propionamido]-6-methoxylepidine. The chloropropionamide was prepared as in the above cases from 8-amino-6-methoxylepidine.[42] A solution of 15 g. of the chloropropionamide and 11.3 g. of redistilled diethanol amine in 225 ml. of absolute ethanol was refluxed for 40 hr. and concentrated to dryness. The residue was dissolved in chloroform and washed free of diethanolamine hydrochloride with water. After drying over anhydrous carbonate, the residue was crystallized from 150 ml. of absolute ethanol to give the diol as large prisms. The mustard was prepared in chloroform solution as described above. The dihydrochloride was recrystallized from methanol-ether with excess hydrogen chloride and showed a double melting point, decomposing at 178°, resolidifying as large plates, and melting again at 207–220° dec. in an evacuated capillary.

8-[3-Bis(2-chloroethylamino)propionamido]-2-methoxyquinoline (XXII) *and 8-[3-bis(2-chloroethylamino)propionamido]-1-methyl-2-quinolone* (XXIII). The chloropropionamide was prepared from 8-amino-2-methoxyquinoline as described above. The diol (XXI) was obtained as the monohydrochloride from methanol-ether with a slight excess of hydrogen chloride.

Direct treatment of the crude free base (XXI) with thionyl chloride gave no characterizable product. A solution of 2.0 g. of the monohydrochloride of XXI in water was made alkaline with sodium hydroxide and extracted with alcohol free chloroform. After drying the extract over anhydrous potassium carbonate, a solution of 10 ml. of redistilled thionyl chloride in 20 ml. of alcohol-free chloroform was gradually added. The mixture was protected by a calcium chloride tube. An oily precipitate that did not crystallize formed. Excess thionyl chloride was decomposed by addition of 10 ml. of methanol during which the oil solidified. It was too hygroscopic to collect on a filter satisfactorily. The tacky mass was dried in a desiccator to give a hard hygroscopic mass. Recrystallization from 2-propanol with excess alcoholic hydrogen chloride gave 112 mg. of material, m.p. 200–201.5° dec. The major portion of the product was recovered by concentrating the original chloroform-methanol filtrate and recrystallizing the residue from methanol-ether. This gave two slightly pink crops of 0.5 g. (46%) each. The first sintered from 180° and melted at 182–183° and the second melted at 163–164° dec. Recrystallization of the first fraction from methanol-ether gave material, m.p. 199.5–201.5° dec., which showed carbonyl absorption in the infrared at 1670 and 1705 cm.$^{-1}$ As no methoxyl was present on analysis, this is the *N*-methyl-2-quinolone (XXIII). Analytical data eliminate the carbostyril from consideration.

Anal. Calcd. for $C_{17}H_{21}Cl_2N_3O\cdot HCl$: C, 50.20; H, 5.45; N, 10.33; Cl, 26.15. Calcd. for $C_{16}H_{19}Cl_2N_3O_2\cdot HCl$: C, 48.93; H, 5.13; N, 10.70; Cl, 27.09. Found: C, 50.24; H, 4.99; N, 10.45; Cl, 25.95.

The second crop of crystalline material showed only a single carbonyl band in the infrared at 1680 cm.$^{-1}$ Recrystallization from methanol-ether left the melting point substantially unchanged. This was the monohydrochloride of the desired mustard (XXII).

When the hydrochloride of XXI was treated with thionyl chloride in chloroform as in the above examples, the hydrochloride of XXII was obtained in 54% yield with none of the quinolone being isolated.

ANN ARBOR, MICH.

(42) K. N. Campbell, *et al.*, *J. Am. Chem. Soc.*, 69, 1465 (1947).

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

Synthesis of Potential Anticancer Agents. IV. Synthesis of Certain Substituted Amino- and Aziridinopyrimidines[1,2]

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Received March 7, 1960

Candidate cytotoxic agents have been prepared by condensation of 2,4-dichloro-6-methyl-5-nitropyrimidine with various cyclic amines. The relative activating influence of a nitro, chloro, and bromo substituent in the 5-position of 2,4-dichloro-6-methylpyrimidine toward nucleophilic displacement of the chlorines has been studied.

Since 1946, when Gilman and Philips[4] reported the cytotoxic activity of bis-β,β'-dichloroethylmethylamine (nitrogen mustard), a number of cytotoxic substances containing the bis-β,β'-dichloroethylamine functions have been reported.[5] Most of these, except for some derivatives of amino acids[6–8] and sugars[9] are derivatives of parent compounds which are not of natural occurrence. Curiously, attention to the biologically important purines and pyrimidines has been largely directed to the preparation of analogs of them as possible antimetabolites and, until comparatively recently, few reports of incorporation of alkylating functions such as the bis-β,β'-dichloroethylamino or aziridino groups into these parent molecules have appeared. The rationale underlying the present work, a portion of which is presented,

(1) This investigation was supported by Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(2) For paper III in this series see *J. Org. Chem.*, 25, 1576 (1960).

(3) On leave of absence from the Chemistry Department, B. N. College, Patna University, India.

(4) A. Gilman and F. S. Philips, *Science*, 103, 409 (1946).

(5) See *Comparative Clinical and Biological Effects of Alkylating Agents*, Annals of the New York Academy of Sciences, Vol. 68, Art. 3 (April 24, 1958) for an exhaustive review.

(6) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

(7) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).

(8) W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955).

(9) L. Varga, O. Feher, and S. Lendvai, *Acta Chim. Acad. Sci. Hung.*, 19, 308 (1959) and earlier papers.

therefore, is based on the concept that incorporation of such functions into a pyrimidine or purine might provide cytotoxic agents capable of acting in a dual capacity—as antimetabolites and as alkylating agents. Prior to the present investigation cytotoxic activity had been reported for 6-methyl-5-bis(β,β'-dichloroethylamino)-uracil[10] and during the course of this work similar activity was reported for 5-bis(β,β'-dichloroethylamino)uracil.[11] Hendry and co-workers[12] report the synthesis and anti-tumor evaluation of a number of aziridino derivatives of pyrimidine and conclude that, in general, these substances show no selective cytotoxic activity with respect to tumor cells as compared to normal cells. There thus appears to be a division of opinion as far as selective cytotoxic activity of pyrimidines carrying an alkylating function is concerned. In view of the known usefulness of 2,4,6-triaziridinotriazine in the management of certain cases of lymphatic and chronic myologeneous leukemia, it appeared that preparation of further representative aziridinopyrimidines was indicated.

2,4-Bisaziridino-6-methyl-5-nitropyrimidine (I) was readily prepared in 70% yield by condensation of aziridine with 2,4-dichloro-6-methyl-5-nitropyrimidine (II) in the presence of an equivalent amount of triethylamine. I is very susceptible to decomposition during purification especially in the presence of moisture. I was also prepared in low yield by adding an aqueous solution of aziridine and potassium hydroxide to an aqueous suspension of II and by successive reaction of II with sodium hydride and aziridine in ether or tetrahydrofuran.

Treatment of I with dry hydrogen chloride in ether resulted in opening of the aziridine rings and formation of a hydrochloride (III) for which a number of structures are possible. Cyclization to a piperazinium salt (IIIA) in a manner analogous to that noted by Golumbic[13] and Huber[14] with other β-chloroethylamines is suggested by the high decomposition point and insolubility of the salt in water. Reclosure of the opened aziridine ring on one of the pyrimidine nitrogens to give an imidazopyrimidine derivative (IIIB) is possible on the basis of the observation of Schaefer[15] that 1-aziridino-*s*-triazines rearrange in the presence of acid catalysts to dihydroimidazo[1.2-*a*]-*s*-triazines. It is impossible to distinguish between III, IIIA, and IIIB on the basis of elementary analyses. However, titration of the substance with 0.01*N* sodium hydroxide solution showed that it was a monohydrochloride which eliminates structure IIIA. The product of the titration without neutralization can then be represented by IV, IVA, or IVB. It was also obtained by the action of sodium methoxide in benzene on III. A substance of structure IV would be expected to be soluble in ether and insoluble in water which was found to be so. This, as well as elementary analyses, in all probability rules out structures IVA and IVB leaving III as representing the initial product of the action of anhydrous hydrogen chloride on I and IV as representing the product resulting from the action of base on III. We assume that the presence of the nitro group in the 5-position weakens the basicity of the nitrogens in the 2- and 4-positions sufficiently to render salt formation difficult.

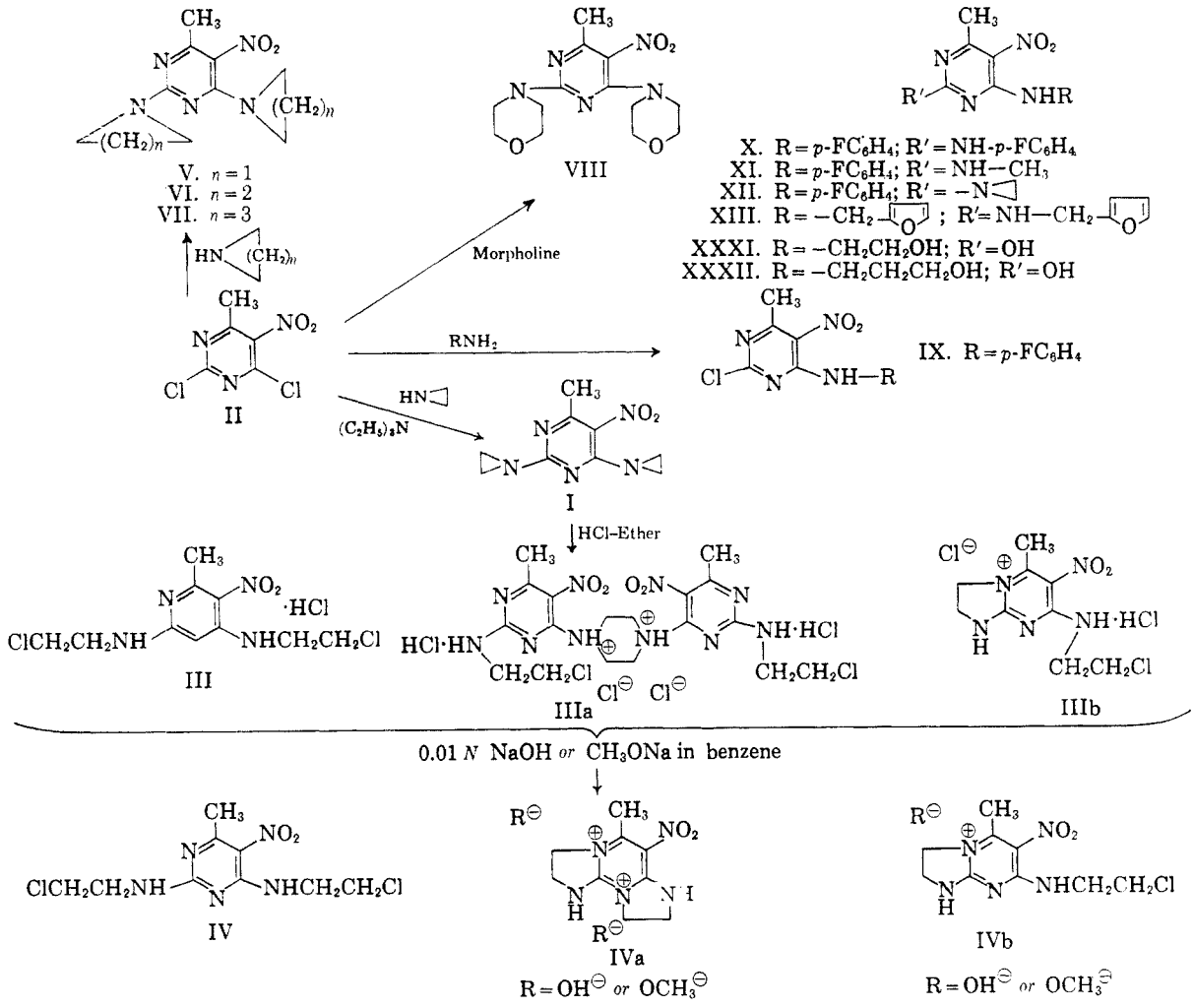
Preliminary data on the action of I on animal tumors[16] was exceedingly encouraging. Since it was not known whether I was functioning as an alkylating agent, as an antimetabolite or in a dual capacity, it appeared to be of advantage to substitute other amines for aziridine in the reaction with II. Therefore II was condensed with azetidine, pyrrolidine, piperidine, and morpholine to give V, VI, VII, and VIII respectively. As the saturated heterocyclic ring system was expanded the color of the compounds changed progressively from light lemon yellow in the case of I to a very dark yellow in the case of VIII. All of the substances showed similar insolubility in water and solubility in most organic solvents.

A difference in reactivity of the chlorine atoms in II was noted and advantage was taken of this to introduce two different amine residues in the 2- and 4-positions. By analogy with the reaction of 2,4-dichloro-5-nitropyrimidine with ammonia under mild conditions to give 4-amino-2-chloro-5-nitropyrimidine[17] we assume that the 4-chlorine is most readily displaced in II. Thus when II was allowed to react with one equivalent of *p*-fluoroaniline at 0°, 2-chloro-4-(*p*-fluoroanilino)-6-methyl-5-nitropyrimidine (IX) was formed. When IX was treated with a second equivalent of an amine under more severe conditions 2,4-diaminopyrimidines (X, XI and XII) resulted.

On the other hand when II was allowed to react with excess representative amines, *p*-fluoroaniline and furfurylamine, in boiling ethanol both chlorines were replaced with the formation of diamino derivatives (X and XIII) respectively.

The reaction of II with 2-aminoethanol or 3-aminopropanol took a somewhat different course. On refluxing the reactants in ethanol the 4-chlorine of II readily underwent displacement by the amine, but the 2-chlorine was hydrolyzed, possibly

(10) L. F. Sarinov, *Brit. J. Cancer*, **10**, 26 (1956).
(11) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, **80**, 6359 (1958).
(12) J. A. Hendry, R. F. Homer, F. L. Rose, and A. L. Walpole, *Brit. J. Pharmacol.*, **6**, 357 (1951); U. S. Patent **2,675,386**, Apr. 13, 1954.
(13) C. Golumbic, J. S. Fruton, and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946).
(14) G. Huber, *Angew. Chem.*, **68**, 706 (1956).
(15) F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).
(16) Private communication from Dr. Ralph Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Fla.
(17) D. Isay, *Ber.*, **39**, 250 (1906).



by water present in the system, with the formation of 2-hydroxy-4-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidine and 2-hydroxy-4-(3-hydroxypropylamino)-6-methyl-5-nitropyrimidine respectively.

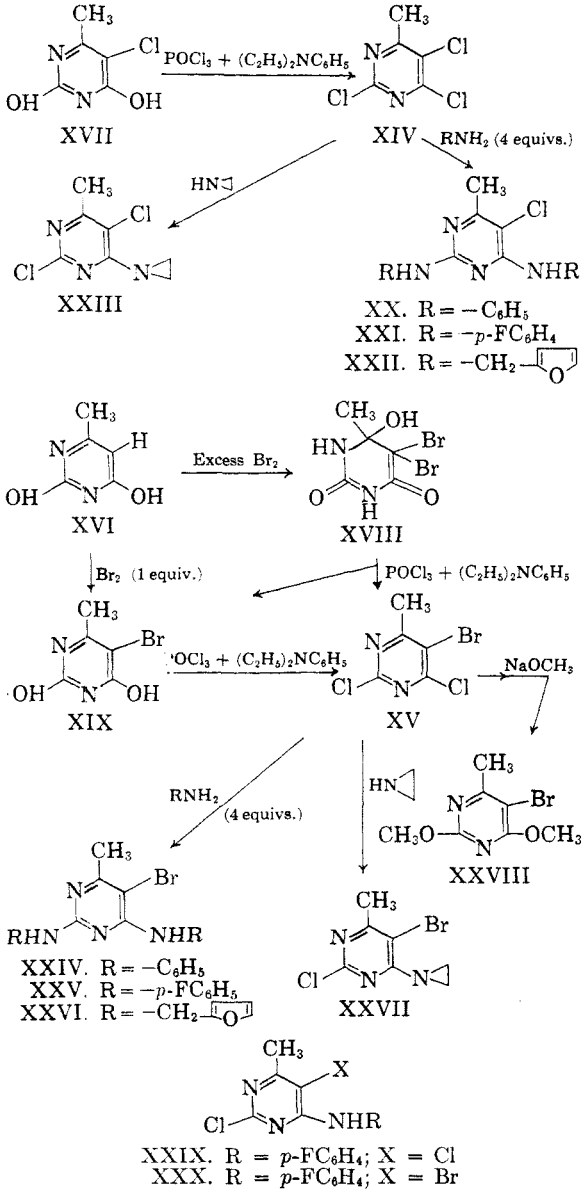
Finally, since the nitro group in II is obviously activating the chlorines in positions 2 and 4, it was of interest to study the effect of other substituents in the 5-position of the pyrimidine ring. For this purpose the 5-chloro- and 5-bromo- analogs (XIV and XV) of II were investigated. Behrend[18] prepared XIV by heating 6-methyluracil (XVI) with phosphorus pentachloride and phosphorus oxychloride in a sealed tube. We have obtained XIV in almost quantitative yield by heating 5-chloro-6-methyluracil (XVII)[19] with phosphorus oxychloride and diethylaniline. For the preparation of XV Behrend's method[20] was not followed. This was found to be lengthy and necessitates the initial formation of 5,5-dibromo-6-hydroxy-6-methyldihydropyrimidine-2,4-dione (XVIII) which has almost the same melting point as 5-bromo-6-methyluracil (XIX). Rather, essentially the procedure of Wang[21] for the bromination of uracil was applied to the bromination of XVI to give XIX which could be purified very easily from traces of XVIII by solution in a large volume of hot dilute potassium hydroxide solution and reprecipitation while still hot by acetic acid. Filtration of XIX from the acetic acid solution while still hot removed any unchanged 6-methyluracil (XVI) since the solubilities of XIX, XVIII, and XVI in the dilute acetic acid were roughly in the ratio 0.36:1.36:5.00. Actually treatment of XVIII with hot dilute potassium hydroxide probably results in extensive decomposition since no product could be isolated when XVIII alone was subjected to this procedure. XVIII with phosphorus oxychloride and dimethylaniline gave a poor yield of XV together with some XIX. The procedure of Overberger for the preparation of XV by treatment of XIX with phosphorous oxychloride alone[22] was improved by use of diethylaniline to provide an 85–95% yield of XV in less than three hours.

(18) R. Behrend, *Ann.*, **229**, 25 (1885).
(19) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1623 (1938).
(20) R. Behrend, *Ann.*, **236**, 57 (1886).
(21) S. Y. Wang, *J. Org. Chem.*, **24**, 11 (1959).
(22) C. G. Overberger, I. C. Kogen, and W. J. Einstman, *J. Am. Chem. Soc.*, **76**, 1953 (1954).

Nucleophilic displacement of the chlorines in positions 2 and 4 of XIV by aniline, *p*-fluoroaniline, and furfurylamine was easily accomplished to give XX, XXI, and XXII respectively. In general two equivalents of amine per atom of chlorine to be replaced were required. Thus, when only two equivalents of *p*-fluoroaniline per equivalent of trichloropyrimidine (XIV) were used only one chlorine was replaced with the formation of 2,5-dichloro-6-methyl-4-(*p*-fluoroanilino)pyrimidine. On the other hand reaction of XIV with two equivalents of aziridine in the presence of triethylamine in boiling ether resulted only in the displacement of the 4-chlorine and the formation of XXIII. When the reaction was carried out in boiling benzene there appeared to be some decomposition of the XXIII formed. From the amount of triethylamine hydrochloride recovered from the reaction mixture it appeared that only a trace of disubstitution product was formed.

The reactions of XV paralleled those of XIV. Displacement of both chlorines by aniline, *p*-fluoroaniline, and furfurylamine gave XXIV, XXV, and XXVI respectively. With aziridine only one chlorine was displaced to give XXVII. In contrast, sodium methoxide very readily gave 5-bromo-2,4-dimethoxy-6-methylpyrimidine (XXVIII).

We therefore conclude that a nitro group in the 5-position exerts a strong activating influence on chlorine atoms in the 2- and 4-positions, particularly on the 4-chlorine atom. Chlorine and bromine in the 5-position exert a much weaker activating influence as would be expected. However, the ease of displacement of the 2-chlorine seems to be dependent also on the nucleophilicity of the attacking reagent.



EXPERIMENTAL[23,24]

2,4-Bisaziridino-6-methyl-5-nitropyrimidine (I). *Procedure A.* Through a mixture of 2.4 g. of sodium hydride dispersion (courtesy of Metal Hydrides, Inc., Beverly, Mass.) in 20 ml. of freshly dried and distilled tetrahydrofuran and 2.15 g. of aziridine, dry nitrogen was passed for a few minutes. A solution of 5.2 g. of II in 50 ml. of tetrahydrofuran was slowly added and the gas which was immediately evolved was collected over water. Substantially the theoretical amount of hydrogen was liberated and the reaction mixture turned deep brown. After 1 hr. the mixture was hydrolyzed with water and extracted with four 50-ml. portions of ether. After drying the combined extracts over anhydrous magnesium sulfate, removal of the solvent left a yellow residue which, on recrystallization from petroleum ether (b.p. 90–100°) with Norit, gave 0.9 g. of light lemon-yellow needles, m.p. 120–122° dec. When anhydrous ether was substituted for tetrahydrofuran the yield was raised to 1.2 g.

Procedure B. An ice cold mixture of a solution of 3.0 g. of potassium hydroxide in 100 ml. of water and a solution of 2.15 g. of aziridine in 50 ml. of water was added to a well stirred ice cold suspension of II prepared by adding a solution of 5.2 g. of II in 50 ml. of acetone to 200 ml. of water. When the addition was complete (30 min.) the ice bath was removed and stirring was continued for 16 hr. during which a voluminous precipitate separated. The solid was filtered, washed with water, and dried. The yield was 1.3 g.

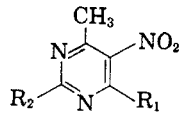
Procedure C. To a well stirred and chilled solution of 10.4 g. of II in 200 ml. of anhydrous ether was added dropwise a solution of 4.4 g. of aziridine and 10.2 g. of triethylamine in 200 ml. of dry benzene at a rate such that the temperature of the mixture did not exceed 10°. When the addition was complete (30–45 min.) 200 ml. of dry benzene was added to dilute the thick paste which formed. After stirring for an additional 30 min. below 10°, the ice bath was removed and the mixture was stirred for 12–15 hr. at room temperature. The mixture was filtered and the filtrate was evaporated to dryness below 40° under reduced pressure. The residue was crystallized from petroleum ether (b.p. 90–100°) to give 7.7 g. of lemon yellow needles, m.p. 122–123°. Concentration of the mother liquor gave additional material and raised the total yield to 8.2 g. Analyses for this and other pyrimidines prepared from II are given in Table I. Compound I is quite susceptible to light and slowly

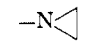
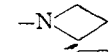
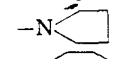
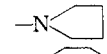
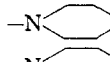
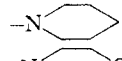
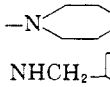
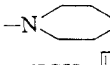
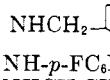
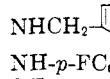
(23) All melting points are uncorrected for stem exposure.

(24) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

TABLE I

DERIVATIVES OF 6-METHYL-5-NITROPYRIMIDINE



R_1	R_2	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
		$C_9H_{11}N_5O_2$	48.86	4.97	31.67	48.78	4.97	31.86
		$C_{11}H_{15}N_5O_2$	53.00	6.07	28.10	52.97	6.04	28.21
		$C_{13}H_{19}N_5O_2$	56.31	6.86	25.27	56.52	6.82	25.14
		$C_{15}H_{23}N_5O_2$	59.01	7.54	22.95	58.93	7.57	22.91
		$C_{13}H_{19}N_5O_4$	50.48	6.14	22.62	50.70	5.84	22.67
		$C_{15}H_{15}N_5O_4$	54.71	4.55	21.27	54.32	4.46	21.18
NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}F_2N_5O_2$	57.14	3.64		57.28	3.73	
$NHCH_2CH_2OH$	OH	$C_7H_{10}N_4O_4 \cdot 0.5H_2O$	37.66	4.93	25.11	37.67	5.03	24.72
$NH(CH_2)_3OH$	OH	$C_8H_{12}N_4O_4$	42.10	5.26	24.56	42.35	5.20	24.39
NH-*p*-FC_6H_4	Cl	$C_{11}H_8ClFN_4O_2$	46.72	2.83		46.78	2.98	
NH-*p*-FC_6H_4	$NHCH_3$	$C_{12}H_{12}FN_5O_2$	51.98	4.33	25.27	52.23	4.52	25.11
NH-*p*-FC_6H_4		$C_{13}H_{12}FN_5O_2$	53.97	4.15	24.22	54.32	4.36	23.89
$NHCH_2CH_2Cl$	$NHCH_2CH_2Cl$	$C_9H_{13}Cl_2N_5O_2 \cdot HCl$	32.67	4.23	21.18	32.38	4.05	21.26

turns brown with some decomposition. It can be stored indefinitely in a brown or green bottle even in full sunlight.

2,4-Bisazetidino-6-methyl-5-nitropyrimidine (V).[25] From a solution of 11.1 g. of moist azetidine[26] dried over potassium hydroxide according to Marckwald[27] and 11.1 g. of triethylamine in 50 ml. of dry ether and a solution of 10.4 g. of II in 700 ml. of dry ether, 7.83 g. of V was obtained by Procedure C above. The substance was recrystallized first from benzene–petroleum ether and finally from petroleum ether (b.p. 60–80°). It formed long bright yellow needles, m.p. 135°. One more recrystallization raised the melting point to 141–142°.

2,4-Bis-1'-pyrrolidino-6-methyl-5-nitopyrimidine (VI). A solution of 7.1 g. of pyrrolidine in 50 ml. of absolute ethanol was added with stirring during 45–60 min. to an ice cold solution of 8.32 g. of II in 100 ml. of absolute ethanol. When the addition was complete the mixture was heated gently on the steam bath for 24 hr. during which a light brown pasty mass was formed. The magma was triturated with acetone and filtered from 1.5 g. of high melting (256–258°) material which was not investigated further. The filtrate was concentrated to about 20 ml. and poured with stirring into 300 ml. of ice water. The pasty mass which separated solidified after standing at room temperature for 48 hr. yielding 5.5 g. (50%) of brownish yellow material, m.p. 146–148°. After two recrystallizations from aqueous acetone bright yellow granular crystals, m.p. 149–150°, were obtained. The same substance was obtained in 61% yield by Method C described above for the preparation of I.

2,4-Bis-1'-piperidino-6-methyl-5-nitropyrimidine (VII). Separate solutions of 5.2 g. of II in 60 ml. of benzene and 5.1 g. of triethylamine in 20 ml. of benzene were mixed. To the cold and well stirred mixture was added a solution of 4.25 g. of piperidine in 40 ml. of benzene over 15 min. After stirring for 16 hr. at room temperature the mixture was refluxed for 4 hr., filtered while still hot, and concentrated. The residual pasty mass was taken up in 100 ml. of hot ethanol and the solution was diluted with 200 ml. of water. On slow evaporation 4.8 g. (63%) of yellow crystals were obtained. After two recrystallizations from aqueous acetone bright yellow micro needles, m.p. 99–100°, resulted.

2,4-Bis-4-morpholino-6-methyl-5-nitropyrimidine (VIII). This was prepared by the method used for VII. The yield of material, m.p. 162–163°, after recrystallization from aqueous acetone was 64%.

2,4-Bisfurfurylamino-6-methyl-5-nitropyrimidine (XIII). To a cold solution of 7.8 g. of II in 100 ml. of absolute methanol 14.6 g. of freshly distilled furfurylamine (courtesy of the Quaker Oats Co.) was added dropwise over 15–20 min. during which solid material separated. The mixture was then refluxed gently on the steam bath during which the solids dissolved. After addition of 150 ml. of benzene the solution was boiled down to about half its volume and filtered while still hot. On cooling, the filtrate deposited 6.5 g. (52%) of light yellow solids. Recrystallization from ethyl acetate–petroleum ether (b.p. 90–100°) gave crystalline material, m.p. 115–116°.

2,4-Bis(β-chloroethylamino)-6-methyl-5-nitropyrimidine hydrochloride (III). Dry hydrogen chloride was passed slowly through a solution of 1.1 g. of I in 200 ml. of anhydrous ether chilled in an ice-salt bath for 30 min. The temperature of the solution was held below 10°. A voluminous white precipitate separated and further absorption of hydrogen chloride ceased. The solids were collected and washed thoroughly with cold anhydrous ether to give 1.63 g. (98%) of cream colored material which decomposed slowly above 200°. Two recrystallizations from anhydrous acetone–petroleum ether (b.p. 40–60°) gave an analytically pure sample although the melting point was still indefinite. III, however, was found to melt with decomposition at 175–177°, when put in a bath previously heated to 175°. If

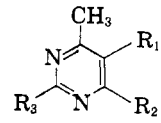
(25) This preparation was carried out by Dr. R. S. McElhinney of these laboratories.

(26) The azetidine was prepared in these laboratories by an improved procedure devised by Dr. W. R. Vaughan of these laboratories which will be described elsewhere.

(27) W. Marckwald and A. B. v. Droeste-Huelshoff, *Ber.*, **31**, 3264 (1898); C. C. Howard and W. Marckwald, *Ber.*, **32**, 2032 (1899).

TABLE II

DERIVATIVES OF 6-METHYL-5-BROMO- OR 5-CHLOROPYRIMIDINE



				Analyses, %					
				Calcd.			Found		
R_1	R_2	R_3	Formula	C	H	N	C	H	N
Cl	Cl	Cl	$C_5H_3Cl_3N_2$	30.37	1.51	14.17	30.46	1.53	14.19
Br	Cl	Cl	$C_5H_3BrCl_2N_2$	24.79	1.23		24.80	1.17	
Br		Cl	$C_7H_7BrClN_3$	33.80	2.81	16.90	33.84	2.65	16.88
Br	NHC_6H_5	NHC_6H_5	$C_{17}H_{16}BrN_4$	57.41	4.32	15.89	57.46	4.22	15.77[a]
Br	NH-*p*-FC_6H_4	Cl	$C_{11}H_8BrClFN_3$	41.70	2.52	13.27	41.82	2.68	13.10
Br	NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}BrF_2N_4 \cdot HCl$	47.71	3.27	13.07	47.24	3.33	12.94
Br	$NHCH_2$- 	$NHCH_2$- 	$C_{15}H_{15}BrN_4O_2$	49.58	4.13		49.17	4.20	
Br	OCH_3	OCH_3	$C_7H_9BrN_2O_2$	36.05	3.86	12.01	36.09	4.04	12.01
Br	OH	OH	$C_5H_5BrN_2O_2$	29.12	2.42		29.18	2.44	[b]
Cl		Cl	$C_7H_7Cl_2N_3$	41.17	3.43	20.58	41.20	3.47	20.62
Cl	NHC_6H_5	NHC_6H_5	$C_{17}H_{15}ClN_4 \cdot HCl$	58.76	4.61	16.13	58.95	4.68	15.72
Cl	NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}ClF_2N_6 \cdot HCl$	53.26	3.65	14.62	52.99	3.78	14.57
Cl	NH-*p*-FC_6H_4	Cl	$C_{11}H_8Cl_2FN_3$	48.52	2.94	15.44	48.72	3.09	15.41
Cl	$NHCH_2$- 	$NHCH_2$- 	$C_{15}H_{15}ClN_4O_2$	56.51	4.70	17.58	56.43	4.75	17.64

[a] Br: calcd. 22.52, found 22.53. [b] Br: calcd. 38.83, found 39.07.

the bath temperature was lower than 175°, the substance did not melt sharply but slowly decomposed up to 200°.

2,4-Bis(β-chloroethylamino)-6-methyl-5-nitropyrimidine (IV). *A. By the action of sodium hydroxide.* A suspension of 0.661 g. of III in 50 ml. of ice water was titrated with 0.01*N* sodium hydroxide solution to phenolphthalein end point. Calculated for one equivalent of sodium hydroxide: 200 ml. Found: 203 ml. The suspended yellowish solids were collected, washed thoroughly with water, and dried. The yield was 0.58 g. (98.6%). Recrystallization from ether–petroleum ether (40–60°) gave lemon needles, m.p. 145–146° dec. in a bath preheated to 145°. If the bath temperature was lower than 145°, the substance did not melt sharply but slowly decomposed up to 200°. The infrared spectrum was quite different from that of III.

Anal. Calcd. for $C_9H_{13}N_5O_2Cl_2$: C, 36.74; H, 4.40; N, 23.80; Cl, 24.16. Found: C, 36.76; H, 4.45; N, 23.92; Cl, 23.97.

B. By the action of sodium methoxide. To a suspension of 0.888 g. of III in 80 ml. of dry benzene was added dropwise with vigorous stirring a solution of 0.069 g. of sodium in 30 ml. of absolute methanol. The suspended solid went into solution and sodium chloride separated. After stirring for 2 hr. at room temperature, about 50 ml. of solvent was distilled off in the course of an hour. The mixture was then taken to dryness under reduced pressure and the residue was extracted with 300 ml. of ether in a Soxhlet extractor for 12 hr. The ether extract was boiled with carbon, filtered and, while still hot, was slowly added to 150 ml. of boiling petroleum ether (b.p. 40–60°). On cooling fine yellow needles separated. This substance was identical with that obtained by Procedure *A* as judged by melting point behavior and identical infrared spectra.

Anal. Found: C, 36.98; H, 4.53; N, 23.86; Cl, 24.24.

2,4-Bis(p-fluoroanilino)-6-methyl-5-nitropyrimidine (X). To a solution of 5.2 g. of II in 200 ml. of absolute ethanol was added 6.1 g. of *p*-fluoroaniline. There was an immediate separation of yellow solid. The mixture was heated on the steam bath on which the solid material went into solution but within 5 min. a precipitate reappeared. The mixture was refluxed for 1 hr. and allowed to stand overnight at room temperature. The solid material, 8.5 g., m.p. 215–220 dec., was collected and recrystallized from cyclohexane-benzene to narrow the melting point to 218–220° dec. On slow heating the substance melted at 185–187° dec.

2-Chloro-4-(p-fluoroanilino)-6-methyl-5-nitropyrimidine (IX). To a stirred solution of 5.2 g. of II chilled in an ice-salt bath was added dropwise a solution of 2.8 g. of *p*-fluoroaniline in 20 ml. of absolute ethanol. After stirring for 30 min. in the freezing bath, the mixture was stirred for an additional 30 min. at room temperature, cooled, and filtered to give 2.5 g. of dark yellow crystalline material. The filtrate on concentration gave an additional 3.0 g. of the same substance. (Total yield, 77%.) On recrystallization from methylcyclohexane, 4.2 g. of yellow woolly crystals, m.p. 152–154°, resulted.

4-(p-Fluoroanilino)-6-methyl-2-methylamino-5-nitropyrimidine (XI). A mixture of 2.8 g. of IX, 20 ml. of 40% aqueous methylamine, and 100 ml. of absolute ethanol was heated gently on the steam bath for 48 hr., without reflux. Substantially dry light yellow crystalline material, m.p. 165–175°, remained. This was triturated with dilute sodium hydroxide solution, collected, and washed thoroughly with water. After recrystallization from aqueous methanol and two recrystallizations from petroleum ether (b.p. 90–100°) fine yellow micro-crystals, m.p. 172–173°, were obtained.

4-(p-Fluoroanilino)-2-aziridino-6-methyl-5-nitropyrimidine (XII). To a well stirred solution of 2.82 g. of IX in 400 ml. of absolute ether was added gradually a solution of 0.53 g. of aziridine and 1.1 g. of triethylamine in 100 ml. of absolute ether, the temperature being maintained at 15–20°. After the addition was complete the mixture was stirred at room temperature for 18 hr. and the separated solid material was filtered. The filtrate was concentrated to about 50 ml. and added to a solution of 0.23 g. of aziridine and 0.5 g. of triethylamine in 100 ml. of benzene. The mixture was heated

at 60–70° for 3 hr., filtered through Norit and the filtrate was taken to dryness at a temperature below 35°. The oily residue was triturated with 60 ml. of anhydrous ether and the solution taken to dryness to give 2.0 g. (69%) of yellow crystalline material, m.p. 116–119° dec. Four recrystallizations from petroleum ether (b.p. 40–60°) gave an analytical sample, m.p. 135–137° dec. The substance gave a negative test for chlorine.

2-Hydroxy-4-(2'-hydroxyethylamino)-6-methyl-5-nitropyrimidine (XXXI). To a solution of 8.6 g. of II in 125 ml. of warm ethanol was added 6.1 g. of 2-aminoethanol. An immediate reaction occurred and the mixture turned yellow with evolution of heat. The mixture was heated gently on the steam bath without reflux for 48 hr. leaving a viscous residue. Trituration of the residue with dry acetone gave 11.5 g. of light brown material, m.p. 126–130°. Two recrystallizations from acetone and a little benzene gave 3.0 g. of shining orange needles, m.p. 147.5–148.5°.

2-Hydroxy-4-(3'-hydroxypropylamino)-6-methyl-5-nitropyrimidine (XXXII). The procedure was the same as the preceding one using 8.62 g. of II and 7.51 g. of 3-aminopropanol in 150 ml. of absolute ethanol. The crude product was triturated with methanol and an analytical sample was prepared by solution of the crude material in hot dilute hydrochloric acid, filtration and neutralization to about *p*H 8 with ammonium hydroxide. On cooling 1.0 g. of granular crystals, m.p. 244.5–245.5° dec. separated.

6-Methyl-2,4,5-trichloropyrimidine (XIV). A mixture of 1.2 g. of XVII,[19] 10 ml. of phosphorus oxychloride, and 2 ml. of diethylaniline was heated under reflux with stirring for 3 hr. After standing at room temperature for 24 hr., the light brown solution was poured cautiously onto chopped ice. (In larger scale runs the excess phosphorus oxychloride was distilled from the mixture under reduced pressure.) The mixture, from which solid separated, was extracted with five 60-ml. portions of ether and the combined extracts were washed with four 50-ml. portions of ice water. After drying over anhydrous magnesium sulfate, removal of the solvent left a colorless oil (1.5 g.), b.p. 55–56° (0.2 mm.); reported[18] b.p. 245–247°. Analytical data for XIV, XV, and substances prepared from them are given in Table II.

5-Bromo-6-methyluracil (XIX). To a stirred suspension of 3.15 g. of XVI in 100 ml. of water was added dropwise 4.0 g. of bromine over 15 min. After addition of 150 ml. of water the mixture was refluxed for 25 min. and cooled to 50–60°. Solid potassium hydroxide was added until a clear solution was obtained. The solution was boiled with carbon, filtered, and, while still hot, was acidified with acetic acid. The white crystalline precipitate was collected, triturated with 200 ml. of hot water, and collected. The cake was washed successively with hot water, alcohol, and ether to give 4.4 g. (86%) of material, m.p. 240–242° dec.; reported[20] m.p. 230° dec. In a 1 mole run the yield was 94%. The substance gave a negative test for halogen when boiled with nitric acid and silver nitrate for 1 min. In contrast 5,5-dibromo-6-hydroxy-6-methyldihydrouracil (XVIII), m.p. 234–235° dec. after crystallization from water, prepared by bromination of XVI with excess bromine in water, gave an immediate precipitate with silver nitrate in boiling nitric acid.

5-Bromo-2,4-dichloro-6-methylpyrimidine (XV). A mixture of 41.2 g. of XIX, 300 ml. of phosphorus oxychloride, and 80 ml. of diethylaniline was stirred and slowly heated for 30 min. and then refluxed for 90 min. The excess oxychloride was distilled from the brown mixture at reduced pressure and the residue was poured onto cracked ice with vigorous stirring. The pinkish-white solid was collected, washed thoroughly with water, and sucked as dry as possible. The moist filter cake was dried in a vacuum desiccator over phosphorus pentoxide and sublimed at 40–50° (0.2 mm.) during 20 hr. to give 44 g. (88%) of analytically pure material, m.p. 42°, b.p. 114° (0.3 mm.).

4-Aziridino-2,4-dichloro-6-methylpyrimidine (XXIII). The procedure was the same as Procedure *C* for the preparation of I. The product (78% yield) was recrystallized first from dilute methanol and finally from aqueous acetone. It melted at 115–116°.

5-Chloro-2,4-dianilino-6-methylpyrimidine (XX). A solution of 4.6 g. of aniline in 50 ml. of dry ether was added to a solution of 1.5 g. of XIV in 50 ml. of dry ether. On warming for 15 min. the mixture solidified. The solid was collected and triturated with 10 ml. of benzene to give 1.6 g. of the hydrochloride of XX. After recrystallization first from dilute methanol and then from methanol-benzene, analytically pure material, m.p. 284–285° dec. was obtained.

2,5-Dichloro-4-(p-fluoroanilino)-6-methyl-pyrimidine (XXIX). The procedure was substantially the same as that for the preparation of XX except that the reaction mixture was allowed to stand for 48 hr. at room temperature for completion. The yield of cream colored needles of the hydrochloride, m.p. 124–125° after recrystallization from ether–petroleum ether (b.p. 40–60°), was 50%.

2,4-Bis(p-fluoroanilino)-5-chloro-6-methylpyrimidine (XXI). To a solution of 1.97 g. of XIV in 20 ml. of ether was added a solution of 4.4 g. of *p*-fluoroaniline in 20 ml. of ether. After evaporation of the ether on the steam bath the residual pasty mass was mixed with 30 ml. of water and heated on the steam bath for 72 hr. The brown residual solid was triturated with ether and collected. The material was taken up in hot ethanol, benzene was added, and the solution was evaporated to incipient crystallization to give 2.6 g. (66%) of slate colored crystals, m.p. 275–280° dec. Further recrystallization from aqueous ethanol and from benzene–petroleum ether (b.p. 40–60°) after solution with the aid of a little methanol raised the melting point to 282–287° dec. This is the hydrochloride of XXI.

The ether from trituration of the crude material was boiled with carbon, filtered, and added to hot petroleum ether (b.p. 40–60°) to give 0.7 g. of crystalline material, m.p. 121–123°. Further recrystallization from the same solvent gave cream-colored needles of 2,5-dichloro-4-(*p*-fluoroanilino)-6-methylpyrimidine (XXIX), m.p. 124–125°.

4-Aziridino-5-bromo-2-chloro-6-methylpyrimidine (XXVII). To a stirred solution of 2.41 g. of XV in 100 ml. of anhydrous ether chilled in an ice bath was added a solution of 0.9 g. of aziridine and 2.1 g. of triethylamine in 50 ml. of anhydrous ether over 15 min. A further 50 ml. of anhydrous ether was added and the mixture was stirred at room temperature for 15 hr. The precipitated triethylamine hydrochloride was filtered and the filtrate was evaporated to dryness under reduced pressure. Two recrystallizations of the residue from aqueous methanol gave white needles, m.p. 127–128° dec.

2,4-Bisfurfurylamino-5-chloro-6-methylpyrimidine (XXII). To an ethereal solution of 3.95 g. of XIV was added a solution of 7.8 g. of furfurylamine in 30 ml. of dry ether. The reaction was vigorous and the ether boiled off quickly with the temperature rising to 60°. The clear residue was heated on the steam bath for an hour and left at room temperature for 24 hr. After trituration with dry ether and then with water, the residue was crystallized from aqueous methanol to give white flakes, m.p. 127–128°. Additional material was obtained from the mother liquor bringing the total yield to 4.6 g. (71%).

2,4-Bisfurfurylamino-5-bromo-6-methylpyrimidine (XXVI). To a stirred solution of 2.42 g. of XV in 50 ml. of dry ether was added a solution of 1.94 g. of furfurylamine and 2.02 g. of triethylamine in 100 ml. of dry ether. The mixture was stirred for 4 hr. and then slowly evaporated. The pasty residue was left at room temperature for 5 days during which it solidified. After trituration with water, recrystallization from ether–petroleum ether (b.p. 40–60°) gave the pure substance, m.p. 119–120°.

2,4-Bis(p-fluoroanilino)-5-bromo-6-methylpyrimidine (XXV). The procedure was the same as that for XXVI. The crude product was triturated with dry ether to give a slate-colored residue (57%) and a brown ether solution. Crystallization of the residue from aqueous methanol and

then from methanol-benzene gave the hydrochloride of XXV, m.p. 243–244° dec.

The brown ether solution was evaporated to dryness and the residue was recrystallized from benzene–petroleum ether and then from ether–petroleum ether (b.p. 40–60°) to give 25% of 5-bromo-2-chloro-4-(*p*-fluoroanilino)-6-methylpyrimidine as white needles (XXX), m.p. 143°.

5-Bromo-2,4-dianilino-6-methylpyrimidine (XXIV). The procedure was substantially the same as that for XXVI except that the reaction mixture was warmed in benzene for 24 hr. at 40–60°. The insoluble product was washed with ether, taken up in methanol, and precipitated by addition of benzene to give crystalline material, m.p. 247–249° dec. This was probably the hydrochloride of XXIV. The free base (50% yield) was obtained by recrystallization of the salt from dilute acetic acid. Further recrystallization from ether–petroleum ether (b.p. 40–60°) gave micro-needles, m.p. 111–112°.

5-Bromo-2,4-dimethoxy-6-methylpyrimidine (XXVIII). To a solution of 5.06 g. of sodium in 200 ml. of absolute methanol at 10–15° was added with stirring a solution of 13.3 g. of XV in 100 ml. of absolute methanol over 25 min. The mixture was refluxed for an hour and stirred at room temperature for 15 hr. The solid was filtered and washed with methanol. Carbon dioxide was passed into the filtrate until the *p*H was about 8. The separated solids (5.2 g.) were collected and the filtrate was taken to dryness. The residue was triturated with water leaving 10.0 g. (78%) of white insoluble material. Distillation gave 7.2 g. of material, b.p. 96–99° (0.5 mm.), m.p. 76–77°.

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[CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Preparation and Infrared Absorption Spectra of Some Phenyl Ethers[1]

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The preparation and infrared absorption spectra of a number of aryl and alkyl–aryl ethers are recorded. In general, the assignments in the infrared regions of the spectra agree with those reported in the literature for benzene derivatives and aryl ethers. The *m*-disubstituted materials have their benzene-oxygen stretch band at a lower frequency than those previously reported.

A number of phenyl and alkyl-phenyl ethers were recently prepared for evaluation as radiation-resistant, high temperature lubricants.[2] Many of the products have not previously been reported. At the same time the infrared absorption spectra of both known and new compounds were recorded and the results compared with those of previous workers.[3–10]

Phenyl ethers and certain of their derivatives were prepared because, unlike alkyl ethers, they are very resistant to oxidation. Their thermal decomposition temperatures far exceed those of present synthetic lubricants and their resistance to radiolysis is excellent.

The high melting points of many of the products exclude them from consideration as lubricants for ordinary applications.[2] The literature shows that the better known *para*-linked polyphenyl ethers show a rise in melting point with increasing chain length. In the *meta*-linked series the melting point of certain compounds is surprisingly low. Thus, while *m*-diphenoxybenzene melts at 47° or 60° depending on crystal form, bis(*m*-phenoxyphenyl) ether (III) melts at 41°. The *meta*-linked ethers have a strong tendency to supercool; so far the higher members of the series (XI and XII) have not been obtained in crystalline form.

Most of the ethers were prepared by the Ullmann[11] ether synthesis. The exceptions (XXIX and XXX) were prepared from bis(chloromethyl)-durene and potassium *o*- or *p-tert*-butylphenate under milder conditions.

Synthetic problems arose only in the preparation of the *meta*-linked ethers. *m*-Dibromobenzene was prepared from *m*-bromoaniline *via* the Sandmeyer reaction. *m*-Bromophenyl phenyl ether was prepared either from *m*-phenoxyaniline by the same reaction or from phenol and *m*-dibromobenzene by the Ullmann procedure. *m*-Phenoxyphenol[12,13] was prepared by three different routes (Fig. 1), as stability problems connected with certain starting materials required clarification.

The most obvious method (A. R = H), reaction

(1) The greater part of this work was sponsored by Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

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