was crystallized from a mixture of benzene and petroleum ether (b.p. 50–70°) to give colorless crystals of IIa, m.p. 144°; yield *ca.* 80%.

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.84; H, 4.59; N, 4.94; S, 11.30. Found: C, 67.61; H, 4.62; N, 4.91; S, 11.45.

IIa is insoluble in petroleum ether (b.p. 50–70°), but is soluble in hot benzene. It gives no color with concentrated sulfuric acid.

(b) *p-Thiocresol.* The reaction was carried out as mentioned above. The corresponding adduct IIb was obtained as colorless crystals from a mixture of benzene and petroleum ether (b.p. 50–70°), m.p. 135°; yield *ca.* 82%.

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.68; H, 5.05; N, 4.71; S, 10.77. Found: C, 68.81; H, 5.20; N, 4.81; S, 10.82.

IIb is insoluble in petroleum ether (b.p. 50–70°) but soluble in hot benzene. It gives no color with concentrated sulfuric acid.

Action of piperidine on Ia–e. *General procedure.* A mixture of 0.01 mole of each of Ia–e and 0.01 mole of piperidine in dry benzene (30 ml.) was allowed to stand at room temperature for a few minutes. The yellow color of the benzene solution soon disappeared and, on addition of petroleum ether (b.p. 50–70°), the colorless adducts (listed in TableI) separated. The product was filtered, washed with petroleum ether (b.p. 50–70°), and finally recrystallized from petroleum ether (b.p. 90–120°).

Thermal decomposition of IIIa. IIIa (0.3 g.) was heated in a dry test tube-shaped vessel, at 150° (bath temp.) for 1 hr. The yellow oily residue, left at the bottom of the vessel, solidified, and finally crystallized from petroleum ether (b.p. 50–70°) to give yellow crystals, m.p. 92°, identified as Ia, by melting point and mixed melting point determinations).

Friedel-Crafts reactions with N-arylmaleimides. General procedure. A solution of 0.01 mole of the *N*-arylmaleimide (Ia–b) and 0.015 mole of benzene, toluene, *m*-xylene and/or *m*-dimethoxybenzene in 20 ml. of dry carbon disulfide was stirred and warmed on a water bath, while 1.5 g. of finely powdered aluminum chloride were gradually added. Heating was continued for 6 hr. then the reaction mixture was poured into 40 ml. of dilute hydrochloric acid and heated to remove the carbon disulfide. It was then extracted with benzene, and the extract was dried (sodium sulfate) and evaporated. The oily residue left behind was washed with petroleum ether (b.p. 40–60°) and finally crystallized from the suitable solvent (*cf.* Table III).

The derivatives Va–h were colorless crystalline substances which melted without decomposition and gave no color with sulfuric acid.

Action of barium hydroxide on Va. A suspension of 0.4 g. of Va in 20 ml. of a saturated solution of barium hydroxide was refluxed for 4 hr. The resulting solution was cooled, acidified with ice-cold dilute hydrochloric acid and the precipitate formed was filtered off and crystallized from methyl alcohol, m.p. 169°, not depressed when admixed with an authentic specimen prepared after Hann and Lapworth.[11]

Action of acetyl chloride on phenylsuccinanilic acid. A solution of 0.5 g. of phenylsuccinanilic acid was heated in 5 ml. of acetyl chloride for 2 hr. The reaction mixture was cooled and decomposed with cold water. The precipitate formed was crystallized from methyl alcohol, m.p. 140° not depressed when admixed with Va.

GIZA, CAIRO, EGYPT
U. A. R.

(11) A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, **85**, 1365 (1904).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

The Swamping Catalyst Effect. III. The Halogenation of Pyridine and Picolines

D. E. PEARSON, W. W. HARGROVE, JUDITH K. T. CHOW, AND B. R. SUTHERS

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3-Chloropyridine and 3-chloro- and 3-bromo-4-picoline have been prepared in 30–40% yields by halogenation of the appropriate pyridine under swamping catalyst conditions. 3,5-Dichloro-4-picoline and 5-bromo-2-picoline have been prepared in lower yields. The above method is the best, if not the only, method of preparing these compounds in the laboratory. Further experiments showed that the maximum yield of halogenated pyridine, based on pyridine, is probably 50%.

The nuclear halogenation of aromatic aldehydes and ketones using large excesses of strong electrophilic reagents such as aluminum chloride has been reported recently.[1] The method has been termed the swamping catalyst effect and so defined as to include those reactions in which at least one equivalent of strong electrophilic reagent is used to complex the substrate material and a second equivalent is used to generate an active attacking species of reagent. The addition of the second equivalent of catalyst is sometimes simply a matter of convenience to accelerate the rate of reaction, but, as will be shown in this paper, it can be essential to the success of the completion of the reaction.

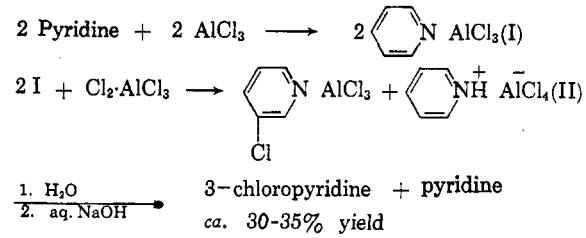
Pyridines are not easily halogenated. To summarize the review by Mosher,[2] substitution of pyridine by bromine or chlorine at 500°, tends to yield 2- or 4-substituted halopyridines- at 300° substitution by bromine yields 3-bromopyridine and some 3,5-dibromopyridine. Evidently the higher temperature favors a free radical rather than an ionic mechanism. The method of choice for synthesis of 3-bromo- or 3,5-dibromopyridine is the pyrolysis of pyridine perbromide hydrobromide at around 200°, the yield being 30–40%.[2] Interestingly enough, the preparation of 3-chloropyridine does not seem feasible by any direct chlo-

(1) D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).

(2) H. S. Mosher in R. C. Elderfield, *Heterocyclic Compounds*, Vol. I, p. 504, John Wiley and Sons, New York 1950.

rination method although the preparations of di- and perchloropyridines can be carried out.[3] But what is still more interesting is that the preparations of any halopicolines by substitution appear to be almost completely impractical. The evidence suggests that the halogen displaces the side-chain hydrogen in preference to nuclear hydrogen, and the resulting chloromethylpyridines polymerize.

We were thus attracted to filling in the gaps in these syntheses by using the swamping catalyst method for the chlorination of pyridine and for both the chlorination and bromination of picolines. The chlorination of pyridine was studied in most detail, and the results are shown in the following equations:



In words, half the pyridine was chlorinated to give 3-chloropyridine, and the other half was deactivated toward chlorination by protonation. We were able to show in separate experiments that the complex of pyridine hydrochloride and aluminum chloride (II) was completely inert to halogenation. Attempts to displace the hydrogen chloride from II by sweeping with nitrogen or by the addition of triethylamine failed. In only one experiment, the exhaustive chlorination of 4-picoline yielding 40% 3-chloro-4-picoline and 15% 3,5-dichloro-4-picoline, was there any indication that more than a 50% yield (based on picoline) could be obtained. The total yield was still so close to 50% that very little hydrogen chloride must have been displaced from II (or, alternately, II is chlorinated with great difficulty).

The bromination of 4-picoline gave 3-bromo-4-picoline, a new compound, in 32% yield. A gas chromatography study suggested that a 50% yield was possible, but the attrition accompanying isolation and purification limited runs to 30–40% yields. We were fortunate in all of the identification work to be able to distinguish between the 2-(or 4-)-halopyridines and the 3-halopyridines by differences in the activities of the halogens in the two positions. Aniline readily displaced halogen from the 2-(or 4-)-halopyridines under conditions where the 3-halopyridines showed no reaction at all. Simple kinetic studies indicated that all of the halopyridines obtained by the swamping catalyst method were 3-substituted.

In contrast to the isolation of a single brominated product from 4-picoline, the bromination of 2-picoline yielded a mixture of 5-bromo- and 3-bromo-2-picoline from which the crystalline 5-bromo-2-picoline could be isolated in about 8% yield. This behavior seems to be general for the swamping catalyst effect in halogenation, namely that *meta*- and *ortho*-substituted compounds tend to yield mixtures of halogenated products.[4]

It is our opinion that the above study has opened up a new and better means of obtaining 3-chloropyridine, 3-halo-4-picolines, 3,5-dihalo-4-picolines, and mixtures of halo-2 (or perhaps 3)-picolines even though the yields are less than 50% based on the pyridine or picoline used. The question may be asked why does the swamping catalyst work in this reaction. We believe that the complex between pyridine and aluminum chloride (I) is a Lewis salt type. In this covalent form of the complex, the electrons on the nitrogen are not as immobilized as they are in pyridine hydrochloride. Therefore, the ring is not as deactivated towards electrophilic reagents. Furthermore, the excess aluminum chloride increases the activity of the attacking agent. Indeed, the most active, electrophilic species of bromine is probably found in this medium where bromine is added to excess aluminum chloride. The aluminum chloride not only tends to remove one of the bromine atoms from its shared electrons, $Br_2 + AlCl_3 \rightarrow Br^+ + AlCl_3Br^-$, but serves also as a medium of high dielectric constant. This activation was made particularly clear in the study of the bromination of 4-picoline. If only enough aluminum chloride were used to complex 4-picoline and not the bromine, no brominated product was obtained at all.

Boron trifluoride was found to be inactive as a swamping catalyst in bromination of 4-picoline. Difficulty was encountered in keeping excess boron trifluoride present in the reaction flask, but all our experiences indicated that the reagent is much less reactive in complexing than aluminum chloride or ferric chloride.[5,6] Ferric chloride, either alone or mixed with aluminum chloride, was also ineffective as a catalyst under the conditions of our experiments.

EXPERIMENTAL[7]

3-Chloropyridine. Dry pyridine (26.6 g., 0.33 mole) was added dropwise to stirred, anhydrous aluminum chloride

(3) Chlorination of isonicotinic acid with thionyl chloride has also been carried out: H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **23**, 64 (1958).

(4) Ref. 1 for bromination of *m*-methylacetophenone. Unpublished work for bromination of methyl *o*- and *m*-toluate.

(5) When anhydrous ferric chloride was added to the complex of 4-picoline-boron trifluoride, heat was evolved with apparent displacement of boron trifluoride.

(6) For heats of complexing of boron halides and pyridine, see W. Gerrard and M. F. Lappert, *Chem. Revs.*, **58**, 1102 (1958) and H. C. Brown and R. R. Holmes, *J. Am. Chem. Soc.*, **78**, 2176 (1956).

(7) Analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points are corrected, and boiling points are uncorrected.

(113 g., 0.84 mole, Baker and Adamson, resublimed) in the apparatus previously described.[1] Considerable heat was evolved and the mixture passed through a pasty transition phase, needing manual stirring, before the complex was formed completely. The temperature was maintained at approximately 80°. Chlorine (16 ml., measured in a trap at Dry Ice temperature) was passed slowly (13 hr.) underneath the surface of the complex. Another cold trap was placed in the exhaust line to reclaim unchanged chlorine. The unchanged chlorine (about half the original volume) was recycled through the mixture now raised to a temperature of 115°. The black, surprisingly fluid mixture was allowed to cool to room temperature and poured cautiously onto vigorously hand-stirred cracked ice. The aqueous solution was then made extremely basic by adding a saturated aqueous solution of sodium hydroxide to neutralize all the acid and to dissolve aluminum hydroxide. The addition was done rather rapidly as aged precipitates of aluminum hydroxide did not dissolve completely in alkali. The base solution was extracted continuously with ether in order to recover the pyridine as well as the 3-chloropyridine. If the 3-chloropyridine alone is desired, simple ether extraction in a separatory funnel would probably suffice. The ether extract was dried with solid potassium hydroxide. On removal of the ether, a small amount of benzene was added to aid in the removal of water by azeotropic distillation. The residue was separated by fractionation in an 18-in. spinning band column at atmospheric pressure. Pyridine (10 g., 37%, n_D^{25} 1.5061) and 3-chloropyridine (12.6 g., 33%, b.p. 148°, n_D^{25} 1.5309), was obtained. The melting point of the picrate (146–147°) of 3-chloropyridine corresponded to that reported,[8] and the infrared spectrum was identical to an authentic sample (Aldrich Chemical Co., Milwaukee, Wis.).[9]

Variations in the chlorination procedure. Exhaustive chlorination at 130° for 5 hr. gave a 35% yield of 3-chloropyridine with no indication of dichlorinated pyridines.

Anhydrous pyridine hydrochloride was made by passing hydrogen chloride into an ether solution of pyridine (13.3 g.) and by evaporating the ether and drying under reduced pressure. Aluminum chloride (56 g.) was added to the salt in the usual reaction vessel. Considerable heat was evolved and the reaction mixture liquified immediately. An oil bath was used to maintain the temperature at 80° while chlorine was added to the reaction mixture over a period of 14 hr. Only pyridine (b.p. 114°, 36 g., 63%) was recovered after the usual work-up.

To supplement the above experiment indicating the inactivity of pyridine hydrochloride complex to chlorination, dry hydrogen chloride was added to the previously formed complex of pyridine and aluminum chloride before the addition of chlorine. Again no 3-chloropyridine was formed. In an effort to sweep out the hydrogen chloride, a run was made in which dry nitrogen was passed through the pyridine–aluminum chloride complex alternately with the chlorine gas. The yield of 3-chloropyridine was unchanged (b.p. 147–148°, 12.8 g., 33%).

In another experiment, triethylamine (0.3 mole) was added half-way through the addition of chlorine (after purging the excess chlorine gas from the vessel with nitrogen) in an attempt to displace the hydrogen chloride from the pyridine hydrochloride–aluminum chloride complex (0.3 mole plus 0.24 mole excess aluminum chloride). The yield of the 3-chloropyridine was the same (32%) suggesting that the triethylamine does not displace the hydrogen chloride.

3-Chloro-4-picoline and 3,5-dichloro-4-picoline. Chlorine was passed slowly through a mixture of 4-picoline (31.2 g., 0.33 mole, b.p. 143°, n_D^{25} 1.5030, hygroscopic) and aluminum chloride (113 g., 0.84 mole) maintained at 92° for 5 hr. White vapors of picoline hydrochloride were observed to pass through the Dry Ice exhaust trap. About 50 ml. of chlorine collected in the exhaust trap during this addition. The excess chlorine was recycled during a second 5-hr. period. The mixture was cooled and decomposed cautiously in the usual manner, and the hydrolysate made strongly basic. The dark oil was extracted with ether and dried by evaporation and by azeotropic distillation with benzene. The residue was separated by fractionation with a spinning band column. Besides 4-picoline, there was obtained 3-chloro-4-picoline (b.p. 101° at 74 mm., n_D^{25} 1.5279, 14.6 g., 40%) and 3,5-dichloro-4-picoline (b.p. 125–127° at 74 mm., m.p. 48–49°, 7.9 g., 15%).

Anal. Calcd. for C_6H_6NCl: Cl, 27.78. Found: Cl, 28.01. Calcd. for $C_6H_5NCl_2$: Cl, 43.77. Found: Cl, 43.63.

The physical properties of the compounds corresponded with those of the literature,[10] but the authors gave no derivatives nor characterization. Our attempts to oxidize both compounds to their respective acids with aqueous potassium permanganate failed. We therefore turned to a study of the activities of the halogens in the 4-picoline of the two different positions available for attachment; the *alpha*-positioned halogen should be active toward nucleophilic reagents and the *beta*-positioned halogen unreactive. Weighed amounts (1 g.) of 2-chloropyridine, 4,7-dichloroquinoline, and both of the chlorinated picolines were dissolved each in 20 ml. of aniline containing about 1 g. of aniline hydrochloride (the salt catalyzes the reaction[11]). Each mixture was immersed in an oil bath maintained at 120°. Two-milliliter aliquots were removed at regular intervals, diluted with a mixture of 30 ml. of alcohol and water, and the liberated hydrochloric acid titrated with standard base. Half-life of 2-chloropyridine in the pseudo first order reaction was 3 hr. at 120°, that of 4,7-dichloroquinoline was less than 1 min. Considerable darkening had occurred by the end of the reactions. Neither of the chloropicolines showed any displacement of chloride ion as detected by titration over a period of 30 hr. at 120°. Therefore, *alpha*-substituted chlorine was not present in the picolines, and the products must be respectively 3-chloro-4-picoline and 3,5-dichloro-4-picoline.

3-Bromo-4-picoline. To the stirred complex of 4-picoline and aluminum chloride, prepared as for 3-chloropyridine, bromine (31 g., 0.2 mole[12]) was added dropwise over a period of 4 hr. at 95°. After the usual decomposition and work-up of the complex,[13] the residue was separated by fractionation in a 10 in. Helipak-filled column at reduced pressure. After the separation of 4-picoline with some bromopicoline, 3-bromo-4-picoline was obtained: b.p. 47–48° at 0.6 mm., n_D^{25} 1.5613; 19 g., 32%.

Anal. Calcd. for C_6H_6BrN: Br, 46.20. Found: Br, 46.24.

Again, it was necessary to demonstrate the inertness of the halogen atom in order to be certain of its position. Under conditions (in aniline at 121°) where 2-bromopyridine (Distillation Products, Inc.) had a half-life of 2 hr., 3-bromo-4-picoline, as well as known 3,5-dibromopyridine. (Distillation Products, Inc.), showed no bromine displacement over a period of 26 hr.

Variations in the bromination procedure of 4-picoline. The bromination could be and occasionally was carried out in a closed system. A slight pressure developed as the drops of bromine were introduced into the vessel, but, as the bromine reacted, the pressure returned to normal.

(8) E. R. Alexander, A. B. Herrick, and T. M. Roder, *J. Am. Chem. Soc.*, **72**, 2760 (1950).

(9) For reported spectrum: A. R. Katritzky, A. R. Hands, and R. A. Jones, *J. Chem. Soc.*, 3165 (1958).

(10) W. Reppe, H. Pasedach, and M. Seefelder, British Patent **726,378**; *Chem. Abstr.*, **50**, 4237 (1956). U. S. Patent **2,719,159**; *Chem. Abstr.*, **50**, 8744 (1956).

(11) N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1190 (1954).

(12) Although 0.3 mole of 4-picoline (a greater amount than 0.2 mole of bromine) was used to make the complex, it was nevertheless selected as the limiting reagent in the calculation of yield.

(13) Excess bromine was destroyed by portionwise addition of aqueous sodium bisulfite until no further color change took place.

The amount of 4-picoline (0.7 mole) was increased relative to the amount of aluminum chloride (0.84 mole) and bromine (0.35 mole). No brominated product at all was obtained.

Ferric chloride (0.42 mole) together with aluminum chloride (0.42 mole) was used as a catalyst in place of aluminum chloride alone. No brominated product at all could be found.

A small scale run similar to the best preparation of 3-bromo-4-picoline was made. The crude product was worked up carefully to avoid losses and was analyzed by gas chromatography (75 ml./min., furnace temperature 114°, Gowmac temperature 179°, 2 ft. of 4.5 mm. copper tubing packed with Columnpak impregnated with 20% Dow Corning High Vacuum Silicon Grease). Retention volume for 4-picoline was 195 ml., and for 3-bromo-4-picoline was 765 ml. The per cent of each was obtained by measuring the respective areas with a planimeter. The area ratio, obtained from a calibration curve, was related fortuitously to the per cent 3-bromo-4-picoline in 4-picoline within the 30–70% range by the equation; area ratio = 0.0975 per cent 3-bromo-4-picoline. The yield of 3-bromo-4-picoline was estimated to be 50%. The estimate is highly dependent on complete recovery of both starting material and product and is most likely to be a maximum yield.

Attempts to run bromination at 140° yielded considerable resinous material and no brominated picoline.

5-Bromo-2-picoline. 2-Picoline (b.p. 143°, n_D^{25} 1.5030, hygroscopic, 0.7 mole) and aluminum chloride (1.7 mole) were mixed in the usual manner, and bromine (0.7 mole) added to the mixture at 100° over a period of 5 hr. After the usual work-up, the crude product (48 g., 40% based on a monobromopicoline) was separated by slow fractionation in a Helipak-filled column at water-aspirator pressure. An impure liquid fraction was obtained (b.p. 79–83°, 20 g., n_D^{25} 1.5493–1.5561).

Anal. Calcd. for C_6H_6BrN: Br, 46.20. Found: Br, 46.25.

The next fraction solidified (8 g., 6.5%) which on recrystallization from hexane gave 5 g. of colorless crystals, m.p. 36.5–37°, reported[14] m.p. for 5-bromo-2-picoline 32°. The compound was oxidized to 5-bromo-2-picolinic acid, m.p. 176.5–178.5° after recrystallization from water, reported[14] m.p. 175°. Attempts to oxidize the impure liquid fraction gave only small amounts of the same acid. However, seeding the liquid bromopicoline with 5-bromo-2-picoline did not induce crystallization. The liquid fraction undoubtedly was a mixture of 5-bromo- and 3-bromo-2-picoline, as the other isomers were shown to be absent by the aniline test. The liquid fraction showed no displacement of bromine with aniline under conditions where 2-bromopyridine reacted rapidly.

Attempted bromination of 4-picoline using boron trifluoride as a catalyst. Boron trifluoride was passed through 4-picoline (33 g., 0.4 mole) for 1 hr. Considerable heat was evolved and a solid separated which melted approximately at 80–85°. Bromine (64 g., 0.4 mole) was added dropwise to the molten complex while a slow stream of boron trifluoride was passed over the surface. No reaction was evident at the end of 32 hr., but all the bromine had been swept out by the boron trifluoride. After the usual decomposition and work-up, 4-picoline (29 g., 88%, n_D^{25} 1.5026) was recovered with no indication of an accompanying brominated product.

Acknowledgment. The authors are indebted to the National Science Foundation for a grant in support of this work.

NASHVILLE 5, TENN.

(14) R. Graf, *J. prakt. Chem.*, **133**, 19 (1932).

[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. I. Synthesis of Pyrimidinethiols[1,2]

HENRY C. KOPPEL, ROBERT HENRE SPRINGER, ROLAND K. ROBINS, AND C. C. CHENG

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With the publication of this work all twenty-two possible isomers of pyrimidinethiols, aminopyrimidinethiols, and hydroxypyrimidinethiols substituted at positions 2, 4, and 6 of the pyrimidine ring have now been reported. Methods of synthesis for all the new compounds as well as improved methods for the preparation of some previously reported compounds in this series have been recorded.

Derivatives of pyrimidinethiols have also been prepared for preliminary screening as possible antitumor agents.

The inhibition of various animal tumors by certain pyrimidine derivatives[3] has focused attention on this group of compounds. It therefore seemed worth while to begin a systematic study of certain simple pyrimidines in order to gain additional information regarding the type of pyrimidine structure necessary for antitumor activity.

Purines and pyrimidines appear to be of similar importance in the formation of nucleic acids, and

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Presented in part before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

(3) See, for example: (a) L. F. Larionov, *Brit. J. Cancer*, 10, 26 (1956); (b) D. M. Shapiro and R. A. Fugman, *J. Nat. Cancer Inst.*, 18, 201 (1957); (c) C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duchinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, 179, 663 (1957); (d) A. R. Curreri, F. J. Ansfield, F. A. McIver, H. A. Waisman, and C. Heidelberger, *Cancer Research*, 18, 478 (1958); (e) W. H. Prusoff, *Cancer Research*, 18, 603 (1958); (f) M. A. Rich, J. L. Bolaffi, J. E. Knoll, L. Cheong, and M. L. Eidinoff, *Cancer Research*, 18, 730 (1958); (g) J. F. Holland, R. Guthrie, P. Sheehe, and H. Tickelmann, *Cancer Research*, 18, 776 (1958); (h) G. B. Elion, S. Bieker, H. Nathan, and G. H. Hitchings, *Cancer Research*, 18, 802 (1958); (i) J. J. Jaffe and J. R. Cooper, *Cancer Research*, 18, 1089 (1958); (j) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, 80, 6459 (1958); (k) D. A. Lyttle and H. G. Petering, *J. Nat. Cancer Inst.*, 23, 153 (1959).