Analogs of Tetrahydrofolic Acid XIV

Facile Synthetic Route to the 2-Amino-5-(3-anilinopropyl)-6-methyl-4-pyrimidinol Type of Folic Reductase and Thymidylate Synthetase Inhibitor

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A four-step synthesis of the title compound (X*b*) from *p*-tolylsulfonanilide has been described which proceeds in 35 per cent over-all yield *via* ethyl 2-acetyl-5-(*N*-tosylanilino)valerate (IV*b*) and the *N*-tosyl derivative of X*b* (VII*b*). That this synthetic route had considerable generality was shown with four other examples—namely, 2-amino-6-methyl-5-(*p*-nitroanilinopropyl)-4-pyrimidinol (X*c*), 2-amino-5-(*p*-carbethoxyanilinopropyl)-6-methyl-4-pyrimidinol (X*d*), 2-amino-5-(3-anilinopropyl)-6-benzyl-4-pyridiminol (XVII*b*), and 2-amino-5-(3-anilinopropyl)-6-phenyl-4-pyrimidinol (XVII*a*). XVII*a* and *b* were good inhibitors of rat liver folic reductase, being complexed five and two times better, respectively, than the substrate, folic acid. Since XVII*a* and *b* are 35 and 16 times better, respectively, than the 6-methylpyrimidine (X*b*), the phenyl ring at the 6-position is probably an additional point of binding to the enzyme.

INTRACELLULAR REDUCTION of folic acid by the enzyme, folic reductase, leads to the cofactor form, tetrahydrofolic acid. This cofactor form then participates in at least 14 known enzymatic reactions for acceptance and transfer of one-carbon fragments (1–4). The pyrimidyl analog (X*a*) was chosen as a likely candidate to be an inhibitor of enzymes utilizing tetrahydrofolic acid or its derivatives for reasons previously described (4). The original synthesis of X*a* was designed to have the largest possible scope for subsequent molecular manipulation so that the mode of binding of X*a* to a number of these 15 enzymes could be studied. The key step in this synthesis was the reductive condensation of the 5-pyrimidylpropionaldehyde (V) with substituted anilines (VIII), followed by base cleavage of the N^2-acetyl group of IX (5, 6).

That this synthesis was quite general was shown by synthesis of analogs of X where (*a*) the 4-hydroxyl group was replaced by 4-mercapto (7), which resulted in increased binding to folic reductase (7), 5,10-methylene-tetrahydrofolic dehydrogenase (7), and thymidylate synthetase (8); (*b*) replacement of the 6-methyl group with 6-phenyl (9), which also resulted in increased binding to the first two enzymes; (*c*) variation of the R group to determine the mode of binding of the carboxy-L-glutamate residue to folic reductase (10) and other enzymes; and (*d*) the variation of the 2-amino and 4-hydroxyl groups to assess their role in enzyme binding (8).

As a result of the study on the mode of binding of the carboxy-L-glutamate fragment to folic reductase, it was clear that its complete removal to give X*b* resulted in only a nominal decrease in binding to folic reductase (10) and thymidylate synthetase (8). Therefore, the authors considered it important to find a shorter synthesis of compounds of type X, even though it might not be so general in scope as the original synthesis (5, 6). This new synthesis of class X inhibitors and some aspects of its scope are the subjects of this paper.

DISCUSSION

The general approach undertaken was to combine a β-keto ester, a trimethylene fragment, and an aniline residue to give a key intermediate akin to VII. A number of variants of this approach were investigated, and the successful one will be described first.

Condensation of excess 1,3-dibromopropane (I) with *p*-toluenesulfonanilide (II*b*) in dimethylsulfoxide in the presence of potassium carbonate—a general method used for alkylation of other acidic NH compounds (11, 12)—gave pure *N*-bromopropyl-*p*-tolylsulfonanilide (III*b*), m.p. 64–65°, in 74% yield; the use of *N*,*N*-dimethylformamide as a solvent gave a 75% yield. The older alkylation method, using sodium ethoxide in ethanol, gave yields of 40–45% of intermediate purity product. The more recent sodium hydride-*N*,*N*-dimethylformamide method (13) afforded 60–65% of III*b*; its one advantage over the potassium carbonate method was that reaction was complete in 8 hours. However, the potassium carbonate method is considered the method of choice because of its simplicity.

Condensation of the *N*-bromopropyl-*p*-toluenesulfonanilide (III*b*) with sodio ethyl acetoacetate in absolute ethanol proceeded poorly; cleavage of keto ester (IV*b*) to VI (R=CH_3 or C_2H_5O) appeared to be a serious side reaction. The cleavage was avoided by using *tert*-butanol as the solvent for alkylation of sodio ethyl acetoacetate with III*b*; the keto ester (IV*b*) was obtained as an oil in quantitative yield

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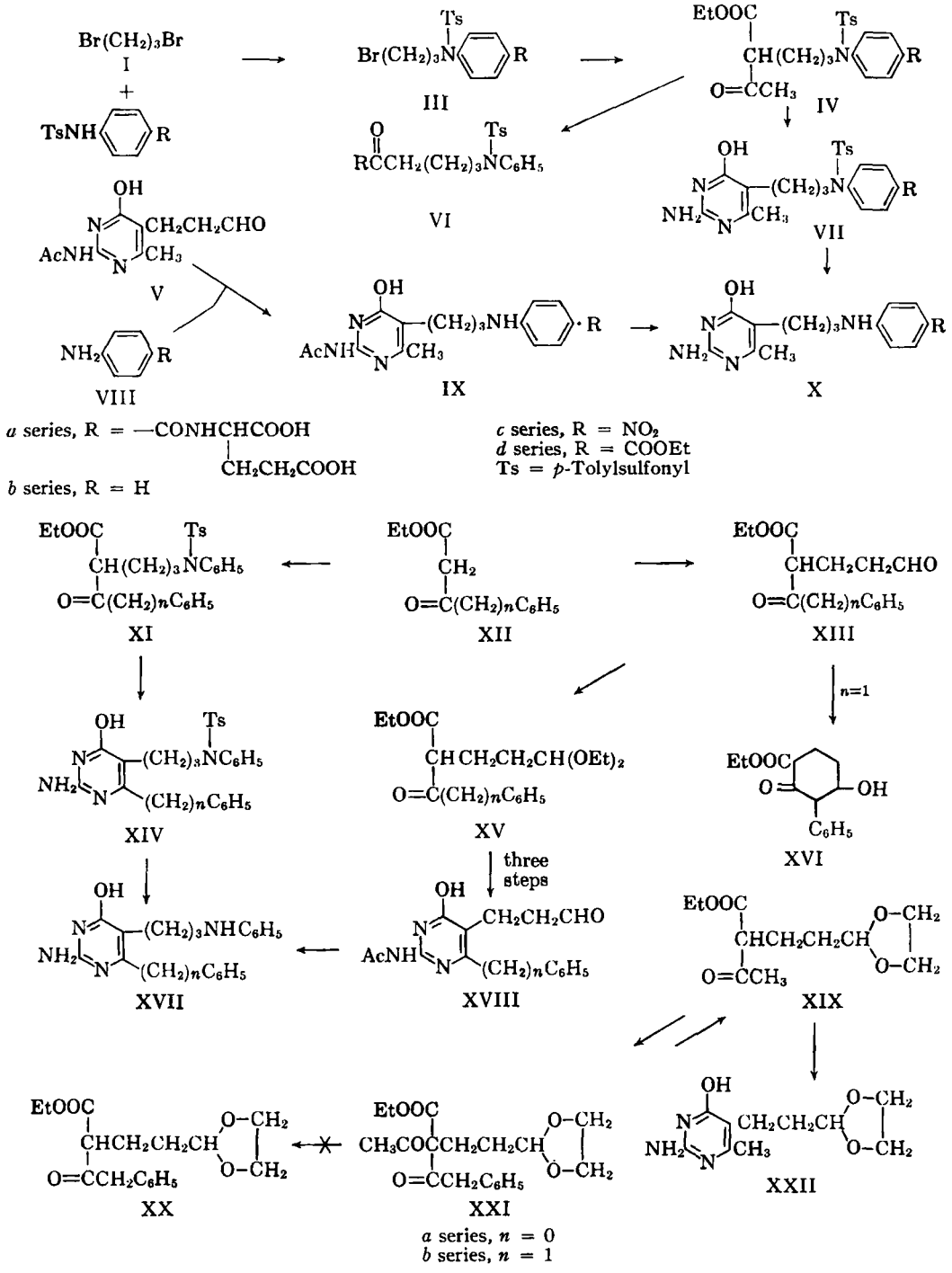
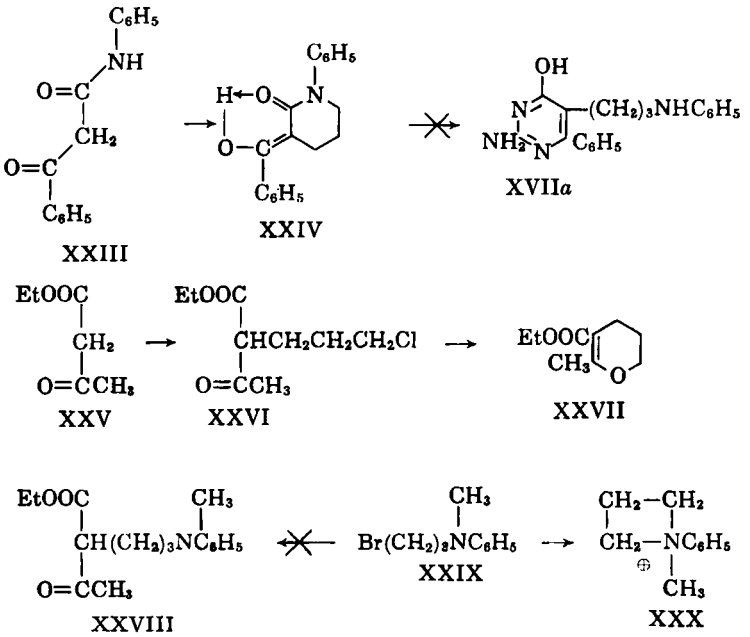


which was estimated to be 84% pure by ultraviolet analysis in 0.1 *N* methanolic sodium methoxide (see *Experimental*).

Since the keto ester (IV*b*) seemed to be labile to ethanol, containing a base, it was not surprising to find that condensation of IV*b* with guanidine carbonate proceeded poorly to the pyrimidine (VII*b*) in absolute ethanol. The product (VII*b*) could not be crystallized after processing the reaction mixture unless it was dissolved in hot 1 *N* sodium hydroxide, separated from insoluble material, then cooled, and the relatively insoluble sodium salt of VII*b* isolated; conversion of the sodium salt back to the free pyrimidine readily gave the crystalline pyrimidine (VII*b*) but in less than 50% yield, based on the quantity of pure keto ester (IV*b*) employed. To avoid alcoholysis, condensation of the keto ester (IV*b*) with guanidine carbonate was carried out in *tert*-butanol (9); the desired blocked pyrimidine (VII*b*) crystallized directly from the reaction solvent, and further



processing of the filtrate gave 80% yield of VII*b* based on the amount of pure keto ester (IV*b*) initially employed.

Attempts to remove the *N*-tosyl group from VII*b* by hydrolysis with 96% sulfuric acid at room temperature or with boiling concentrated hydrochloric acid (14) resulted in nearly quantitative recovery of starting material. However, reductive cleavage of the *N*-tosyl group with sodium and liquid ammonia (15) proceeded smoothly to give the pure, recrystallized anilinopropyl pyrimidine (X*b*) in 53% yield that was identical to the material prepared by the earlier synthetic route (10). The elegant *N*-tosyl cleavage method using hydrogen bromide in glacial acetic acid in the presence of phenol (16) gave a 71% conversion of VII*b* to recrystallized X*b*. The over-all yield of X*b* in this four-step sequence from *p*-toluenesulfonanilide was a satisfactory 35%, compared to 7% over-all yield in the earlier six-step sequence (6, 10).

The apparent generality of the method was then shown by synthesis of four more examples, two of which could not be synthesized by the earlier method (6, 9, 10). Two of the four examples were the synthesis of *p*-nitroanilinopropyl pyrimidine (X*c*) and the *p*-carbethoxyanilinopropyl pyrimidine (X*d*); the other two examples were variants in the 6-position of the pyrimidine ring (XVII*a* and XVII*b*).

Reaction of *p*-nitroaniline (VIII*c*) and ethyl *p*-aminobenzoate (VIII*d*) with a 10% excess of *p*-tolylsulfonyl chloride in pyridine at 90–100°, followed by direct crystallization by addition of 50% methanol, gave 95–97% yields of crystalline II*c* and II*d* suitable for further transformation. This hot pyridine method has been previously used for conversion of *p*-substituted anilines to sulfonanilides (14*a*) and gives higher yields of II*c* and II*d* than previously recorded in the literature. Alkylation of II*c* and II*d* with excess 1,3-dibromopropane (I) in dimethylsulfoxide was performed essentially as described for II*a*; the *p*-carbethoxy sulfonanilide (III*d*) required 2–3 days for completion, while III*c* required 5 days for completion, primarily because the more acidic NH group of II*c* rapidly formed an insoluble potassium salt with the potassium carbonate. After removal of the excess 1,3-dibromopropane, the remaining gummy *p*-carbethoxy sulfonanilide (III*d*) was analytically pure and was obtained in 84% yield; III*d* could be crystallized from petroleum ether, but such a step was considered unnecessary. The crystalline *p*-nitro sulfonanilide was obtained in 80% yield.

Conversion to the keto esters (IV*c* and IV*d*) proceeded in excellent yield in the same fashion as for IV*b*, except that the *p*-nitroanilino derivative (IV*c*) could be crystallized. Condensation of IV*c* with guanidine carbonate in *tert*-butanol gave the pyrimidine (VII*c*) which was best purified as its insoluble sodium salt; regeneration of the salt gave the crystalline pyrimidine (VII*c*) in 72% yield. The *p*-carbethoxyanilino pyrimidine (VII*d*) was obtained in quantitative crude yield but could not be purified through the sodium salt in 1 *N* sodium hydroxide due to concomitant saponification. Thin-layer chromatography of crude VII*d* showed several spots; but after the tosyl group was removed, the resultant X*d* could be purified.

When the *N*-tosyl-*p*-nitroanilino pyrimidine (VII*c*) was treated with sodium and ammonia, the characteristic blue which usually bleaches did not appear, but the solution immediately became dark brown and did not bleach. After 6 mole equivalents of sodium were added, the reaction mixture was processed to give a brown gummy product that was intractable; apparently the nitro group is not compatible with sodium-ammonia. Fortunately, the election-withdrawing *p*-nitro group activated the sulfonanilide linkage to cleavage by 96% sulfuric acid at room temperature (14); after 5 hours, the detosylated *p*-nitroanilino pyrimidine (X*c*) could be isolated in 77% yield as analytically pure yellow crystals.

The crude *N*-tosyl *p*-carbethoxyanilino pyrimidine (VII*d*) also appeared to react abnormally with sodium-ammonia leading to highly insoluble, intractable, amorphous powders. However, hydrolysis of

VII*d* with 96% sulfuric acid proceeded smoothly. After purification by solution in cold 3 *N* hydrochloric acid and neutralization with ammonium hydroxide, the desired detosylated *N*-carbethoxyanilino pyrimidine (X*d*) was isolated as an analytically pure, although amorphous, powder in 51% yield and was uniform on thin-layer chromatography. Saponification of X*d* gave the corresponding acid (X, R = COOH) in 77% yield, identical to that prepared by the earlier route (10).

The *N*-tosyl anilinopropylpyrimidine (VII*b*), which is obtained in 50% over-all yield for the three steps from *p*-toluenesulfonanilide, also proved to be a useful intermediate for further transformations on the pyrimidine ring where it was necessary to have the anilino function blocked—for example, synthesis of 2,4-diamino-5-(3-anilinopropyl)-6-methylpyrimidine (17). Since transformations on the 6-phenylpyrimidine moiety of XVII*a* also required blocking of the anilino group, the synthesis of the blocked 6-phenyl-5-(3-anilinopropyl) pyrimidine (XIV*a*) by the new route was investigated.

Alkylation of sodio ethyl benzoylacetate (XII*a*) in *tert*-butanol with *N*-(3-bromopropyl)-*p*-tolylsulfonanilide (III*b*) gave XI*a* as an oil. Condensation of the crude XI*a* with guanidine carbonate in boiling *tert*-butanol gave the crystalline blocked pyrimidine (XIV*a*) in 41% over-all yield for the two steps. Reductive cleavage of the *N*-tosyl group of XIV*a* with hydrogen bromide–acetic acid (16) afforded 90% yield of XVII*a*, identical to XVII*a* prepared *via* the 5-pyrimidylpropionaldehyde (XVIII*a*).

When the *N*-tosyl derivative (XIV*a*) was reduced with sodium in liquid ammonia, the *N*-tosyl group was removed. Surprisingly, the product appeared to be the 5,6-dihydro derivative of XVII*a*, since the product no longer contained the peak near 280 mμ characteristic of the 6-phenyl pyrimidine (XVII*a*) (18). Apparently the 6-phenyl group of XVII*a* activates the 5,6-double bond toward reduction; other marked differences between the chemistry of 5-alkyl-6-phenylpyrimidines and the corresponding 6-methyl derivatives have been noted in this laboratory. For example, a 5-alkyl-2-amino-4-chloro-6-methyl-pyrimidine failed to react with thiourea in boiling *tert*-butanol (7), whereas the 6-phenyl derivative readily formed the 4-mercapto derivative under these conditions (19). Furthermore, a 5-alkyl-2-amino-6-methyl-4-pyrimidinethiol was stable to hot hydrochloric acid, but the corresponding 6-phenyl derivative was rapidly hydrolyzed to the 4-pyrimidinol (19).

The 6-phenylpyrimidine (XVII*a*) was a good inhibitor[1] of rat liver folic reductase with $K_i = 1.8 \times 10^{-6}$, binding about five times better than the substrate, folate ($K_m = 10 \times 10^{-6}$), and 35 times better than the corresponding 6-methylpyrimidine (XI*b*) ($K_i = 63 \times 10^{-6}$) (10). Thus, the loss in inhibition when the carboxy-L-glutamate moiety is removed from X*a* ($K_i = 2.0 \times 10^{-6}$) (10) is compensated by increased binding of the 6-phenylpyrimidyl moiety of XVII*a*. The increased inhibition by XVII*a* compared to X*b* suggested that the 6-benzyl analog (XVII*b*) should be synthesized for evaluation as an inhibitor of folic reductase. The synthesis of XVII*b* by the new route *via* XI*b* was successful, whereas the synthesis of XVII*b* by the old route (9, 10) was not. XVII*b* had $K_i = 4 \times 10^{-6}$ with folic reductase,[1] which is 16 times better than the 6-methylpyrimidine (XI*b*).

One of the possible explanations (9) for the tighter binding of the 6-phenylpyrimidine (XVII*a*) and its *p*-carboxy-L-glutamate analog to folic reductase than to the corresponding 6-methylpyrimidines (*Xa* and *b*) was that the 6-phenyl group favorably influenced the possible tautomeric forms of the pyrimidyl moiety to increase binding. The binding of the 6-benzyl pyrimidine (XVII*b*) 16 times tighter than the 6-methylpyrimidine (XI*b*) to folic reductase is not tenable with a tautomeric shift increasing binding of the pyrimidyl moiety, since the phenyl group of XVII*b* is insulated from the pyrimidyl moiety by a methylene group. A more plausible explanation is that both the 6-phenyl and 6-benzyl groups also bind to some point on folic reductase to give a net tighter binding. Whether this binding is by charge-transfer complex (20), by hydrophobic binding (21), or by some other means (20, 22) is being investigated.

It is interesting that replacement of the 6-methyl group of X*a* by a 6-phenyl group (9) does not change the extent of binding to thymidylate synthetase, although this 6-phenyl derivative binds 20 times tighter than X*a* to folic reductase. Thus, this additional binding point, apparently present on folic reductase, is absent on thymidylate synthetase.

Condensation of ethyl γ-phenylacetoacetate (XII*b*) with acrolein under the base-catalyzed conditions previously used for XII*a* (9) did not give the expected adduct (XIII*b*). Apparently a further internal aldol condensation occurred to give XVI, as shown by the absence of aldehyde CH at about 2600 cm.$^{-1}$ in the infrared and the presence of hydroxyl at 3500 cm.$^{-1}$ in the infrared. When the acrolein condensation was performed under milder conditions, either starting material (XII*b*) was recovered, or mixtures of XIII*b* and XVI were obtained. Clearly, this route to XVII*b* *via* XIII*b*→XV*b*→XVIII*b* was unattractive, if not impossible.

A second route involved reaction of phenylacetyl chloride with the sodio derivative of the dioxolanyl-keto ester (XIX) (7), prepared with sodium hydride and XIX in benzene. The resultant product (XXI), on cleavage with methanolic sodium methoxide, did not give the expected XX by cleavage of the acetyl group (23), but mainly the phenylacetyl group was cleaved to regenerate XIX; the regenerated XIX was characterized by conversion to the previously synthesized (7) 6-methylpyrimidine (XXII).

The new route for synthesis of X *via* III*b* was successful when applied to the synthesis of XVII*b*, an indication that this new route probably has more diversity than the older route (6, 7, 9, 10). Condensation of sodio ethyl γ-phenylacetoacetate (XII*b*) with *N*-(3-bromopropyl)-*p*-tolylsulfonanilide (III*b*) in *tert*-butanol gave crude XI*b*, which was condensed with guanidine carbonate in *tert*-butanol, to give after purification a 46% over-all yield of analytically pure XIV*b*, which was converted to XVII*b*.

Four alternate routes for insertion of a 1,3-dihalopropane between a keto ester and an aniline residue were investigated before the fifth alternative *via* III→IV→VII→X*b* was established.

The dianion of benzoylacetanilide (XXIII) (24),

[1] The authors thank Dr. W. C. Werkheiser, Roswell Park Memorial Institute, for the assays on folic reductase from rat liver.

prepared from XXIII with sodium hydride in *N,N*-dimethylformamide, reacted with 1,3-dibromopropane to give the crystalline benzoyl piperidone (XXIV) in 25% yield. This benzoyl piperidone was fully enolic in neutral solution and apparently existed as the stable chelate, XXIV. That the piperidone was apparently fully enolized was shown by the broad acidic OH group at 3300–2000 cm.$^{-1}$, a bonded piperidone carbonyl at 1610 cm.$^{-1}$, the enolic peak at 345 mμ of nearly the same molecular extinction in neutral as basic solution, and the disappearance of this peak at pH 1, and finally a chelated hydrogen at δ 13.70 in the NMR in deuterochloroform that integrated for a full single proton (100% enolization).

Although the strong enolic chelate properties of XXIV were interesting, these properties stymied attempts to convert the highly stable chelate XXIV to a pyrimidine (XVII*a*). Reaction of XXIV with guanidine carbonate in ethanol, *tert*-butanol, or dimethylsulfoxide (9) was sluggish, and XXIV could be recovered unchanged. When conditions were forced, apparently C-benzoyl cleavage (9) of the molecule took place. With guanidine hydrochloride in polyphosphoric acid, decomposition occurred. Attempts to form an enol ether with boiling ethyl orthoformate or ethyl orthoacetate (25) with (9) or without acid catalysis gave complete recovery of unchanged XXIV. Attempts to form an enamine with ammonium formate (26) in *tert*-butanol or with piperidine in refluxing benzene (27) under a constant water separator were fruitless. An attempt to convert XXIV to an enol *O*-mesylate with methanesulfonyl chloride in pyridine also failed. Although it may have been possible to convert XXIV to an enol ether with diazomethane (28), thence to XVII*a*, this possibility was not investigated since the alternate route *via* XIV*a* was an obviously better preparative value than a route which would need large-scale use of the treacherous diazomethane.

Alkylation of ethyl acetoacetate with 1-bromo-3-chloropropane in ethanolic sodium methoxide has been reported to give a low yield of the chloropropyl keto ester (XXVI); the main by-product was the dihydropyran (XXVII), formed by cyclization of XXVI (29). If the chloropropyl ester (XXVI) could be obtained in better yield, if the chloropropyl ester could then be converted with guanidine to 2-amino-5-(3-chloropropyl)-6-methyl-4-pyrimidinol, and if the latter could be converted to the anilino derivative (X*b*) with aniline, this could be an attractive route to X*b*. Study of the effect of solvent on the initial alkylation reaction to form XXVI showed that yields were on the order of 5–10%, obviously unfeasible for a preparative route to X*b*.

Two alternate routes related to the sequence II→III→IV were investigated earlier. The anion of acetanilide, prepared with sodium hydride in dry *N,N*-dimethylformamide (13), rapidly reacted with 1,3-dibromopropane. However, the reaction was not clean-cut, and considerable acetanilide was regenerated, from which it was difficult to separate the desired *N*-(3-bromopropyl) acetanilide by simple means of preparative value.

Reaction of *N*-methylaniline with excess 1,3-dibromopropane gave XXIX, which was a distillable but unstable oil. On standing the distilled product soon deposited crystals that were presumably XXX bromide, and redistillation at 0.2 mm. always led to large losses, probably due to cyclization to XXX. Furthermore, attempted condensation of excess XXIX with ethyl sodioacetoacetate led to rapid formation of sodium bromide, but the solution remained strongly basic, and no XXVIII was formed. These results would be compatible with rapid cyclization to XXX as its methoxide salt. The four alternate routes to 5-(3-anilinopropyl) pyrimidines were not investigated further when the route *via* IV*a* was so successful.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Mel-Temp block, and those below 230° are corrected. Infrared spectra were determined in KBr disk (unless otherwise indicated) with a Perkin-Elmer model 137B spectrophotometer; ultraviolet spectra were determined with a Perkin-Elmer model 202 spectrophotometer and NMR spectra with a Varian A 60 spectrophotometer. Thin-layer chromatograms (TLC) were run on silica gel G (Brinkmann) in the solvent systems specified, and spots were detected by iodine vapor.

N-(p-Nitrophenyl)-p-tolylsufonamide (IIc).—The tosylation procedure for 4-amino-4′-nitrodiphenylsulfide (14*a*) was readily adaptable to large-scale preparation of II*c*. To a stirred solution of 13.8 Gm. (0.1 mole) of *p*-nitroaniline in 50 ml. of reagent pyridine was added 21.0 Gm. (0.11 mole) of *p*-tolylsulfonyl chloride. The mixture was heated on a steam-bath for 30 minutes protected from moisture. Dilution of the hot reaction mixture with 150 ml. of 50% ethanol and chilling gave 27.7 Gm. (95%) of product, m.p. 186–187°, that was suitable for the next step [lit. m.p. 193° (30)]. Recrystallization of a sample from ethanol gave light yellow crystals, m.p. 193°.

N-(p-Carbethoxyphenyl)-p-tolylsulfonamide (IId).—Similarly, ethyl *p*-aminobenzoate gave this compound in 95% yield, m.p. 205–208°, that was suitable for further transformations. Recrystallization of a sample from ethanol gave white crystals, m.p. 206–207°; $\nu_{max.}$ 3200 (NH); 1675 (ester C=O); 1600 (C=C); 1325, 1150 (−SO_2N−); 807, 765, 695 cm.$^{-1}$ (phenyl CH). Although this compound is used several times in the literature, no physical constants for it could be found.

Anal.—Calcd. for $C_{16}H_{17}NO_4S$: C, 60.2; H, 5.37; N, 4.38. Found: C, 60.2; H, 5.19; N, 4.16.

N-(3-Bromopropyl)-p-tolylsulfonanilide (IIIb).—To a solution of 2.47 Gm. (0.01 mole) of *p*-tolylsulfonanilide in 10 ml. of practical dimethylsulfoxide was added 1.38 Gm. (0.01 mole) of anhydrous potassium carbonate and 8.07 Gm. (0.04 mole) of 1,3-dibromopropane. The mixture was magnetically stirred for 3 days at room temperature, then poured into 75 ml. of water. The mixture was extracted with 75 ml. of benzene. The benzene solution was washed with several portions of 1 *N* sodium hydroxide until acidification of the washing was clear. The extract was further washed with water (2 × 75 ml.), dried with magnesium sulfate, then spin-evaporated *in vacuo;* the last of the dimethylsulfoxide and 1,3-dibromopropane were removed at 1 mm. The residue was crystallized from 5 ml. of hot methanol by allowing the solution to cool to room

temperature undisturbed. (Fast cooling or mixing leads to a voluminous precipitate which is difficult to filter and is solvated.) The product was collected on a filter and washed with a small amount of ice-cold methanol; yield, 2.72 Gm. (74%), m.p. 64–65°; $\nu_{max.}$ 1580 (C=C); 1340, 1160 (−SO_2N−); 812 (*p*-C_6H_4−); 710, 700 (C_6H_5−); and no NH near 3400 cm.$^{-1}$.

Anal.—Calcd. for $C_{16}H_{18}BrNO_2S$: C, 52.2; H, 4.93; Br, 21.7. Found: C, 52.2; H, 4.94; Br, 21.9.

N - (3 - Bromopropyl) - N - (p - nitrophenyl) - p-tolylsulfonamide (IIIc).—This was prepared from 2.92 Gm. (0.01 mole) of II*c* as described for *IIIb*, except the reaction time was 5 days. Recrystallization by solution in the minimum amount of hot ethyl acetate (about 5 ml.), then addition of 25 ml. of ethanol and chilling gave 3.29 Gm. (80%) of product, m.p. 111–113°, that was suitable for further transformation. Recrystallization from methanol gave yellow crystals, m.p. 119–120°; $\nu_{max.}$ 1590 (C=C); 1510 (NO_2); 1334 (broad, −SO_2N−, NO_2); 1160 (−SO_2N−); 727, 695 (*p*-C_6H_4); no NH near 3400 cm.$^{-1}$.

Anal.—Calcd. for $C_{16}H_{17}BrN_2O_4S$: C, 46.6; H, 4.32; Br, 19.5. Found: C, 46.5; H, 4.15; Br, 19.3.

N - (3 - Bromopropyl) - N - (p - carbethoxyphenyl)-p-tolylsulfonamide (IIId).—This was prepared from 3.19 Gm. (0.01 mole) of II*d* as described for *IIIb*. After removal of the excess 1,3-dibromopropane *in vacuo*, a nearly white thick oil remained that was analytically pure and could be used for further transformations. This material could be crystallized from petroleum ether (b.p. 60–110°) with considerable loss: white crystals, m.p. 77–79°; $\nu_{max.}$ 1710 (C=O); 1600 (C=C); 1340, 1160 (−SO_2N−); 770, 812 (*p*-C_6H_4−), and no NH near 3200 cm.$^{-1}$.

Anal.—Calcd. for $C_{19}H_{22}BrNO_4S$: C, 51.8; H, 5.04; Br, 18.2. Found (oil): C, 52.0; H, 5.11; Br, 18.4. Found (crystals): C, 52.0; H, 5.15; Br, 18.2.

Ethyl 2-Acetyl-5-anilino-N-(p-tolylsulfonyl)valerate (IVb).—A mixture of 73 ml. of *tert*-butyl alcohol, 3.90 Gm. (0.03 mole) of ethyl acetoacetate, and 1.43 Gm. of sodium hydride (0.03 mole) (as a 53.5% suspension in mineral oil) was warmed with stirring and protection from moisture until the sodium hydride dissolved, and hydrogen evolution was complete. After the addition of 7.37 Gm. (0.02 mole) of III*b*, the mixture was refluxed for 20 hours with stirring, then spin-evaporated *in vacuo*. The residue was partitioned between water and chloroform. The chloroform layer was dried with magnesium sulfate, then spin-evaporated *in vacuo*. The residual ethyl acetoacetate was removed at 1 mm. (bath 80–100°); yield, 8.32 Gm. (100%) of a glass that had a maximum purity of 84% based on ultraviolet analysis. The glass had $\nu_{max.}^{film}$ 1725 (ester C=O); 1700 (ketone C=O); 1580 (C=C); 1340, 1160 (−SO_2N−); 815 (*p*-C_6H_4−); 710, 695 cm.$^{-1}$.

The ultraviolet analysis was based on (*a*) $\lambda_{max.}$ 284 (ε 12,000) in 0.1 *N* methanolic sodium methoxide for simple ethyl α-alkylacetoacetates, such as the α-allyl derivative; (*b*) the *N*-alkyl-*p*-toluenesulfonanilide moiety, such as III*b*, has $\lambda_{max.}$ 240 mμ (ε 10,900) in neutral or basic solution; and (*c*) the only impurities will be derived from II*b*. Thus, pure IV*b* should have an absorbance ratio of 1.09 for 284/240 mμ. Without weighing a sample, the per cent purity of IV*b* could be estimated as:

$$\% \text{ purity} = \frac{\text{observed O.D. ratio } 284/240}{1.09}$$

The preparation described above had an absorbance ratio (284/240) of 0.92 or a maximum purity of 84%. When the alkylation reaction was run in absolute ethanol, the purity was only 50%, indicating extensive ethanolysis of the β-keto ester to VI.

Ethyl 2-Acetyl-5-(p-nitroanilino)-N-(p-tolylsulfonyl)valerate (IVc).—This was prepared as described for *VIb*. Although the crude glassy product was best used for further transformations, this material could be obtained with some loss as nearly white crystals from petroleum ether (b.p. 60–110°), m.p. 107–108°; $\nu_{max.}$ 1730 (ester C=O); 1700 (ketone C=O); 1580 (C=C); 1500 (NO_2); 1340 (NO_2, −SO_2N−); 1150 (−SO_2N−); 810, 750, 720, 690 cm.$^{-1}$ (phenyl H).

Anal.—Calcd. for $C_{22}H_{26}O_7S$: C, 57.1; H, 5.63; N, 6.06. Found: C, 57.2; H, 5.80; N, 6.00.

2 - Amino - 6 - methyl - 5 - [N - (p - tolylsulfonyl anilino)propyl]-4-pyrimidinol (VIIb).—A mixture of 8.32 Gm. of crude IV*b* (0.017 mole, 84% pure), 2.0 Gm. of guanidine carbonate, and 50 ml. of *tert*-butyl alcohol was refluxed with stirring for 48 hours. The cooled mixture was filtered and the precipitate washed with *tert*-butyl alcohol. The solids were suspended in 50 ml. of water with stirring and the pH brought down to neutrality with dilute acetic acid. The solid was collected on a filter and dried; yield, 5.80 Gm., m.p. 220–224°. Recrystallization from hot 2-methoxyethanol by addition of water gave about 5.54 Gm. (66% based on III*b* or 80% based on crude IV*b*) of white crystals, m.p. 226–228°; $\nu_{max.}$ 3500, 3100; 2900, 2700 (broad NH, OH); 1650, 1600 (broad NH, pyrimidine, C=C); 1340, 1180 (SO_2); 805 (*p*-C_6H_4−); 710, 690 cm.$^{-1}$ (C_6H_5−).

Anal.—Calcd. for $C_{21}H_{24}N_4O_3S$: C, 61.1; H, 5.78; N, 13.3. Found: C, 61.1; H, 5.86; N, 13.6.

When ethanol was used as a solvent, the yield was about 30%. The product could not be directly crystallized; it was purified by solution in hot 1 *N* sodium hydroxide, decantation, then chilling to give the insoluble sodium salt of VII*b*. The sodium salt was dissolved in hot water, then acidified with acetic acid to give the crystalline product.

2 - Amino - 6 - methyl - 5 - [N - (p - tolylsulfonyl-p-nitroanilino)propyl]-4-pyrimidinol (VIIc).—A mixture of 1.156 Gm. (2.5 mmoles) of IV*c* and 0.255 Gm. (1.25 mmoles) of guanidine carbonate in 5 ml. of *tert*-butanol was refluxed for 48 hours. Since the product did not separate from the reaction mixture, the latter was neutralized with acetic acid, then spin-evaporated *in vacuo*. The residue was partitioned between chloroform and water. The separated chloroform layer, dried with magnesium sulfate, was spin-evaporated *in vacuo*. The residual glass was dissolved in 25 ml. of hot 1 *N* sodium hydroxide, the solution was decanted from a little insoluble gum, then cooled. The yellow sodium salt was collected on a filter and washed with a little 1 *N* sodium hydroxide. The sodium salt was dissolved in about 10 ml. of hot 50% aqueous ethanol, then added to about 50 ml. of 15% aqueous acetic acid with stirring. Recrystallization from absolute ethanol gave

0.825 Gm. (72% based on crude IV*c*, 69% for two steps based on III*c*) of buff-colored amorphous powder, m.p. 125–155° dec.; $\nu_{max.}$ 3600–3100 (broad NH, OH); 1650–1590 (broad NH, C=C, C=N); 1500 (NO_2); 1340 (NO_2, $-SO_2N-$); 1150 ($-SO_2-N-$); 810, 725, 695 cm.$^{-1}$ (phenyl H).

Anal.—Calcd. for $C_{21}H_{23}N_5O_5S$: C, 55.1; H, 5.09; N, 15.3. Found: C, 54.9; H, 5.29; N, 15.2.

2-Amino-6-methyl-5-[N-(p-tolylsulfonyl-p-carbethoxy anilino)propyl]-4-pyrimidinol (VIId).—This was prepared as described for *VIIc*. Evaporation of the chloroform solution *in vacuo* finally in high vacuum gave a buff-colored glass in 98% yield (97% yield based on III*d*) that could not be purified further; the sodium salt purification obviously could not be used because of concomitant saponification of the carbethoxy group. TLC in 3:1 benzene–methanol showed several spots.

2-Amino-6-methyl-5-(anilino propyl)-4-pyrimidinol (Xb).—*Preparation A.*—To a stirred solution of 1.03 Gm. (2.5 mmoles) of VII*b* in about 50 ml. of liquid ammonia was added small pieces (about 50 mg. each) of sodium. The blue color was allowed to bleach before the next piece was added. When the blue failed to fade in 15 minutes, a total of 340 mg. of sodium had been used. The mixture was acidified with 1 Gm. of ammonium chloride, then allowed to evaporate; the final traces of ammonia were removed *in vacuo*. The residue was suspended in 25 ml. of water, and the pH was adjusted to 1 with hydrochloric acid. The solution was filtered, then neutralized to pH 8 with sodium hydroxide. The product was collected on a filter and recrystallized from alcohol–water; yield, 0.34 Gm. (53%), m.p. 219°. This material was identical to X*b* prepared *via* V (10). No attempt was made to process the mother liquors for additional material.

Preparation B.—A mixture of 2.19 Gm. (5.3 mmoles) of VII*b*, 1.0 Gm. of phenol, and 11.5 Gm. of 30% hydrogen bromide in acetic acid (16) was magnetically stirred for 16 hours protected from moisture, then diluted with ether. The hydrobromide salt was collected on a filter, washed with ether, then dissolved in 20 ml. of 3 *N* hydrochloric acid. The acid solution was made slightly basic with ammonia water. The product was collected on a filter and recrystallized from aqueous ethanol; yield, 0.965 Gm. (71%), m.p. 219–220°, that was identical to *Preparation A*.

2-Amino-6-methyl-5-(p-nitroanilinopropyl)-4-pyrimidinol (Xc).—A solution of 1.00 Gm. of VII*c* in 2 ml. of 96% sulfuric acid was allowed to stand at room temperature for 5 hours, then poured into about 10 Gm. of ice. The resultant solution was poured in 25 ml. of a 1:1 mixture of concentrated ammonia-water and ice. The product was collected on a filter and washed with water. The solid was dissolved in warm 3 *N* hydrochloric acid, and the solution was poured into excess ice and ammonia-water. Recrystallization of the product from ethanol-water gave 0.513 Gm. (78%) of yellow crystals, m.p. 260–261°; $\lambda_{max.}^{EtOH}$ 230 (ε 17,300), 294 mμ (ε 10,600); $\lambda_{max.}^{pH\ 1}$ 230 (ε 17,300), 265 mμ (inflection, ε 11,400); $\lambda_{max.}^{pH\ 13}$ 280 mμ (ε 10,000).

Anal.—Calcd. for $C_{14}H_{17}N_5O_3$: C, 55.4; H, 5.65; N, 23.1. Found: C, 55.2; H, 5.76; N, 22.9.

If the acid solution of X*c* is gradually neutralized by the addition of base, the product is a mixture of the base and a base-salt.

2-Amino-6-methyl-5-(p-carbethoxyanilinopropyl)-4-pyrimidinol (Xd).—This was prepared as described for *Xc*, except that purification was effected by use of ice-cold 3 *N* hydrochloric acid. Final reprecipitation from ethanol by addition of water gave 0.84 Gm. (51%) of pure X*d* as a buff-colored powder, m.p. 194–196°; $\lambda_{max.}^{EtOH}$ 228 (ε 14,700), 308 mμ (ε 32,500); $\lambda_{max.}^{pH\ 1}$ 228 (ε 17,500), 271 mμ (ε 10,600); $\lambda_{max.}^{pH\ 13}$ 290–315 (broad, ε 7,950).

Anal.—Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.8; H, 6.71; N, 17.0. Found: C, 61.7; H, 6.91; N, 16.6.

A solution of 150 mg. of X*d* in 2 ml. of 5% sodium hydroxide was heated on a steam-bath for 30 minutes. The hot solution was filtered, then adjusted to pH 4.5 with 3 *N* hydrochloric acid. The solid was collected by centrifugation and washed with water. A solution of the solid in 3 *N* ammonium hydroxide was filtered from a trace of insolubles, then the filtrate was adjusted to pH 4.5 with 3 *N* hydrochloric acid. The product was collected by centrifugation, then washed with hot water (2 × 2 ml.) and hot ethanol (2 × 2 ml.); yield, 105 mg. (77%) of the acid (X, R = COOH) that was identical to the sample previously prepared *via* V (10). Both samples showed an identical single spot on Whatman No. 1 paper with the upper phase of 4:1:5 *n*-butanol/acetic acid/water. The spot was detected under ultraviolet light and had an R_f value of 0.72. The same solvent system with silica gel G gave an R_f value of less than 0.1.

2-Amino-4-hydroxy-6-phenyl-5-pyrimidylpropanol.—To a magnetically stirred solution of 0.50 Gm. (1.7 mmoles) of XVIII*a* (9) in 10 ml. of *N,N*-dimethylformamide and 50 ml. of reagent methanol was added portionwise 1.0 Gm. of sodium borohydride. After being stirred for about 18 hours, the mixture was diluted with 25 ml. of 0.1 *N* sodium hydroxide, then spin-evaporated *in vacuo*. The residue was dissolved in 25 ml. of water, then acidified to pH 8–9 with 3 *N* hydrochloric acid. The product was collected on a filter, washed with water, and recrystallized from ethanol; yield, 0.349 Gm. (84%) of white crystals, m.p. 265–268°; $\nu_{max.}$ 3450, 3100 (NH, OH); 1670, 1640, 1610, 1570 (NH, pyrimidine, C=C); 765, 740, 695 cm.$^{-1}$ (phenyl CH).

Anal.—Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.8; H, 6.22; N, 17.1; O, 13.1. Found: C, 63.7; H, 6.21; N, 17.4; O, 13.2.

The compound moved as a single spot TLC in 3:1 benzene–methanol or in methanol with a mobility slightly less than XVII*a*.

2-Amino-6-phenyl-[N-(p-tolylsulfonyl)-anilinopropyl]-4-pyrimidinol (XIVa).—To a solution of 0.294 Gm. of a 55.6% sodium hydride dispersion in mineral oil and 1.94 Gm. (10 mmoles) of ethyl benzoylacetate in 25 ml. of *tert*-butanol was added 2.50 Gm. (6.79 mmoles) of III*b*. After being refluxed with magnetic stirring for 20 hours protected from moisture, the solution had dropped to pH 9 when tested on moist pH paper. The mixture was spin-evaporated *in vacuo*. The residue was partitioned between 20 ml. of benzene and 10 ml. of water. The separated benzene layer was washed with ice-cold 3% sodium hydroxide (2 × 10 ml.) to remove unchanged ethyl benzoylacetate. After being washed further with water (2 × 10 ml.), the benzene solution was dried with magnesium sulfate, then spin-evaporated *in vacuo;* yield, 3.27 Gm. of

crude XI*a* as an oil; $\nu_{max.}^{film}$ 1620 (ester C=O); 1670 (ketone C=O); 1590 (C=C); 1340, 1150 (−SO_2-N−); 1040 (broad ester C—O—C); 813, 690 cm.$^{-1}$ (phenyl CH).

To 3.26 Gm. of the crude XI*a* was added 15 ml. of *tert*-butyl alcohol and 0.61 Gm. (3.39 mmoles) of guanidine carbonate. After being refluxed with magnetic stirring for 51 hours, the mixture was spin-evaporated *in vacuo*. The residue was triturated with hot ethyl acetate. The insoluble material was recrystallized twice from ethanol to give 0.327 Gm. of white crystals, m.p. 222–224°; $\nu_{max.}$ 3400, 3100–3030 (broad NH, OH); 1650 (broad NH, C=C, C=N); 1330, 1150 (−SO_2NH−); 815, 770, 695 cm.$^{-1}$ (phenyl CH); $\lambda_{max.}^{pH\ 1}$ 235 (ε 24,300), 275 mμ (ε 10,500); $\lambda_{max.}^{pH\ 7}$ 235 (ε 23,900), 297 mμ (ε 6530); $\lambda_{max.}^{pH\ 13}$ 288 mμ (ε 6300).

Anal.—Calcd. for $C_{26}H_{26}N_4O_3S \cdot {}^1/_2H_2O$: C, 64.8; H, 5.60; N, 11.6; O, 11.6. Found: C, 65.1; H, 6.13; N, 11.4; O, 11.2.

The ethyl acetate filtrate was spin-evaporated *in vacuo*, and the residue was crystallized from ethanol; yield, 0.804 Gm. (total 41% for two steps based on III*b*), m.p. 221–224°.

2-Amino-5-(3-anilinopropyl)-6-phenyl-4-pyrimidinol (XVIIa).—*Preparation A.*—A solution of 2.0 Gm. (7 mmoles) of XVIII*a* (9) and 6.5 Gm. of aniline (70 mmoles) in 40 ml. of *N,N*-dimethylformamide was magnetically stirred for 30 minutes. After addition of 300 ml. of reagent methanol, the solution was treated portionwise with 4.0 Gm. of sodium borohydride. After being stirred for about 18 hours, the mixture was diluted with 100 ml. of 0.1 *N* aqueous sodium hydroxide, then spin-evaporated *in vacuo* to near dryness. The residue was dissolved in 200 ml. of water and the solution acidified to about pH 8. The crude product was collected on a filter and washed with water. Two recrystallizations from 50% aqueous ethanol gave 1.52 Gm. (68%) of pure product as white crystals, m.p. 235–241° dec.; $\lambda_{max.}^{pH\ 1}$ 230 (ε 14,400), 276 mμ (ε 9200); $\lambda_{max.}^{pH\ 7}$ 236 (ε 22,600), 292 mμ (ε 8000); $\lambda_{max.}^{pH\ 13}$ 288 mμ (ε 8000); $\nu_{max.}$ 3500 (NH, OH); 1640, 1600, 1550, 1490 (NH, pyrimidine, C=C); 770, 745, 705, 696 cm.$^{-1}$ (phenyl CH).

Anal.—Calcd. for $C_{19}H_{20}N_4O$: C, 71.5; H, 6.27; N, 17.6. Found: C, 71.7; H, 6.36; N, 17.4.

Preparation B.—A solution of 500 mg. (1.06 mmoles) of XIV*a* and 200 mg. (2.12 mmoles) of phenol in 2.3 Gm. of 30% hydrogen bromide in acetic acid (16) was allowed to stand for 30 hours, then diluted with 20 ml. of ether. The hydrobromide salt was collected on a filter, dissolved in warm 70% ethanol, then neutralized to about pH 6 with 10% sodium hydroxide. After being chilled in an ice-bath, the product was collected on a filter and washed with water; yield, 300 mg. (89%) of white crystals that were identical to *Preparation A*, as shown by its ultraviolet and infrared spectra and by mixed melting point.

Ethyl γ-Phenylacetoacetate (XIIb).—Reaction of phenylacetyl chloride with ethyl ethoxymagnesiomalonate, as described by Ames and Davey (31), gave ethyl phenylacetylmalonate. After removal of unchanged ethyl malonate in high vacuum, the crude oil (74.3 Gm.) was refluxed with 400 ml. of water with stirring for 3 hours. This treatment removed one carbethoxy group (32). Distillation gave 15.7 Gm. (43% based on phenylacetyl chloride) of product, b.p. 80–107° (0.05 mm.), n_D^{22} 1.054–1.059.

2-Amino-6-benzyl-4-pyrimidinol.—A mixture of 4.0 Gm. of (XII*b*), 1.75 Gm. of guanidine carbonate, and 40 ml. of absolute ethanol was refluxed with stirring for 17 hours, during which time the product precipitated. After being kept at 3–5° (17 hours) overnight, the product was collected on a filter and washed with ethanol; yield, 1.72 Gm. (56%), m.p. 260–271°. The combined mother liquors and washings were evaporated *in vacuo* and gave 2.2 Gm. of a hard orange-red gum which was dissolved in hot 65% aqueous ethanol and neutralized to pH 7 with 3 *N* HCl and cooled at 3–5° to give an additional 0.34 Gm. (total 72%) of product, m.p. 275°. Recrystallization of the combined products from 2-methoxyethanol gave 1.64 Gm. (53%) of pure material, m.p. 278–280°; $\nu_{max.}$ 3400 (NH, OH); 1670, 1640 (NH, pyrimidine); 705 cm.$^{-1}$ (C_6H_5−).

Anal.—Calcd. for $C_{11}H_{11}N_3O$: C, 65.8; H, 5.48; N, 20.9. Found: C, 65.5; H, 5.60; N, 20.7.

2-Amino-6-benzyl-5-(N-tosylanilinopropyl)-4-pyrimidinol (XIVb).—This was prepared by alkylation of 20.3 Gm. (50 mmoles) of XII*b* with 12.5 Gm. (34 mmoles) of III*b*, followed by condensation with guanidine for 67 hours, as described for the preparation of XIV*a* from III*b*. Evaporation of the *tert*-butanol solution *in vacuo* gave a red-brown gum, which was purified by several recrystallizations from ethanol-water; yield, 7.4 Gm. (46%) of white crystals, m.p. 133–135°; $\lambda_{max.}^{pH\ 13}$ 235 (inflection, ε 23,500), 280 mμ (ε 7,800); $\nu_{max.}$ 3500 (NH, OH); 1660, 1630, 1600, 1490 (NH, pyrimidine, C=C); 1340, 1160 (−SO_2N−); 815, 770, 695 cm.$^{-1}$ (phenyl CH).

Anal.—Calcd. for $C_{27}H_{28}N_4O_3S$: C, 66.5; H, 5.75; N, 11.5; O, 9.85. Found: C, 66.6; H, 5.65; N, 11.3; O, 9.86.

2-Amino-5-(anilinopropyl)-6-benzyl-4-pyrimidinol (XVIIb).—Reduction of 450 mg. (0.92 mmole) of XIV*b*, as described for X*b*, gave 378 mg. of crude product on neutralization of the hydrochloric acid solution. Solution of the product in 10% sodium hydroxide, acidification of the solution to about pH 8 with hydrochloric acid, then two recrystallizations from ethanol-water gave an analytical sample that appeared amorphous. After being dried in high vacuum over P_2O_5 at room temperature, then at 80°, the sample weighed 133 mg. (44%), m.p. 181°, with sintering at 89°; $\nu_{max.}$ 3450, 3330, 3080 (NH, OH); 1650, 1640, 1600, 1490 (NH, pyrimidine, C=C); 745, 690 cm.$^{-1}$ (phenyl CH); $\lambda_{max.}^{pH\ 1}$ 233 (ε 14,500), 265 mμ (ε 10,200); $\lambda_{max.}^{pH\ 7}$ 237 (ε, 20,700), 295 mμ (ε 11,600); $\lambda_{max.}^{pH\ 13}$ 237 (ε 20,300), 283 mμ (ε 9,900).

Anal.—Calcd. for $C_{20}H_{22}N_4O$: C, 72.0; H, 6.61; N, 16.8. Found: C, 71.9; H, 6.48; N, 17.1.

No attempt was made to isolate additional material from the mother liquors.

3-Benzoyl-1-phenyl-2-piperidone (XXIV).—To a magnetically stirred suspension of 0.728 Gm. of 55% sodium hydride (16.7 mmoles) dispersed in mineral oil and 20 ml. of anhydrous *N,N*-dimethylformamide protected from moisture was added 2 Gm. of α-benzoylacetanilide (8.35 mmoles) (XXIII) (24). When evolution of hydrogen had ceased, the turbid yellow solution was treated with a solution of 1.69 Gm. (8.35 mmoles) of 1,3-dibromopropane in 15 ml. of *N,N*-dimethylformamide. After being stirred for 48 hours, the mixture was neutralized with

glacial acetic acid, then spin-evaporated *in vacuo* on a hot water bath. The syrupy residue was partitioned between 25 ml. each of chloroform and water. The separated aqueous phase was extracted with an additional 25 ml. of chloroform. The combined organic extracts, dried with magnesium sulfate, were spin-evaporated *in vacuo*. Crystallization from ethyl acetate gave 0.586 Gm. (25%) of product, m.p. 158–161°. Recrystallization gave white crystals, m.p. 160–162°; $\nu_{max.}$ 2800–1700 (broad acidic OH); 1620 (C=O); 1590, 1530, 1500, 1490 (C=C); 760, 725, 695, 690 cm.$^{-1}$ (phenyl CH); $\lambda_{max.}^{pH\ 1}$ 252 mμ (ε 12,800); $\lambda_{max.}^{pH\ 7}$ 235 (ε 10,100), 345 mμ (ε 17,100); $\lambda_{max.}^{pH\ 13}$ 240 (inflection), 345 mμ (ε 19,500); δ 13.70, one chelated hydrogen.

Anal.—Calcd. for $C_{18}H_{17}NO_2$: C, 77.5; H, 6.10; N, 5.01. Found: C, 77.2; H, 5.95; N, 4.90.

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Phase Solubility Technique in Studying the Formation of Complex Salts of Triamterene

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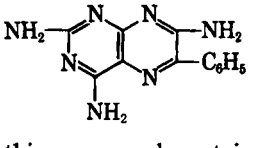
Profiles of the apparent solubility (37°) of triamterene (2,4,7-triamino-6-phenylpteridine) as a function of pH were obtained in the presence of hydrochloric, nitric, sulfuric, phosphoric, and acetic acids. These diagrams permitted detection of complex salt species containing both protonated and unprotonated triamterene. The stoichiometries of the complexes were determined from the slopes of log ($S - S_o$) *versus* pH plots and were confirmed by elemental analysis of the solid phases. Equilibria which explain the pH-solubility profiles of the various acids are proposed. The utility of the phase solubility technique in detecting and studying complex salts is discussed.

SALT SPECIES, other than simple salts, are normally discovered accidentally or incidentally in other studies. Since these complex salts often have solubilities considerably different from normal salts, they may be important pharmaceutically from standpoints such as better *in vivo* availability, greater stability, ease of formulation, etc. In the present study, the phase solubility technique was used to detect complex salt species of triamterene in the presence of various acids. Although this study is limited to triamterene, it is apparent that the procedure is applicable to other systems.

Triamterene (2,4,7-triamino-6-phenylpteridine) is a pteridine diuretic with the structure



Although this compound contains three primary amine groups, it is only weakly monobasic, *e.g.*, toward perchloric acid in glacial acetic acid. Probably because of this weak basicity, most attempts to form classical salts have failed.

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