NOVEL RING TRANSFORMATION REACTIONS AND THEIR APPLICATIONS TO THE SYNTHESES OF POTENTIAL ANTICANCER HETEROCYCLIC COMPOUNDS.[1]

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Abstract — Novel heterocyclic ring transformation reactions developed recently in our laboratory are described. They include pyrimidine to pyrimidine, pyrimidine to pyridine transformations. Also discussed are novel one-step procedures for conversion of 1,3-dimethyluracil derivatives into the pyrido[2,3-d]pyrimidine system. Some applications of these novel reactions to the syntheses of compounds of biological interest are also described.

In 1975[2] we synthesized the C-nucleoside, 5-(β-D-ribofuranosyl)isocytosine (ψ-isocytidine, Fig. 1), as an isostere of cytidine and 5-azacytidine. The latter, synthesized originally by Piskala and Sorm[3] in 1964, was later isolated from Streptomyces ladakamus as a nucleoside antibiotic.[4] 5-Azacytidine is known to be of value in the treatment of human acute myelogenous leukemia resistant to arabinosylcytosine (ara-C),[5] and has shown some activity in patients with breast cancer,[6,7] melanoma,[6] and colon cancer.[6] In almost all clinical cases, however, undesirable side effects of this antibiotic have been observed.[5-8] Moreover, 5-azacytidine is relatively unstable in aqueous media and is very susceptible to enzymatic hydrolysis forming, eventually, ribosyl derivatives of N-amidinourea or N-formylbiuret and biuret.[9] ψ-Isocytidine was therefore prepared as a stable analog of 5-azacytidine. This synthetic C-nucleoside exhibited excellent inhibitory activity against a number of mouse and human leukemic cell lines in culture.[10] ψ-Isocytidine was found to be more active than 5-azacytidine against ara-C resistant mouse leukemia P815 in vivo.[10] These preliminary biological results prompted us to prepare large amounts of this C-nucleoside for further biological studies and for the synthesis of ^{14}C-labeled ψ-isocytidine required for preclinical pharmacological investigations.

We modified[11] our original procedure and synthesized [2-^{14}C]-ψ-isocytidine (Fig. 2) by treatment of the crystalline 2-ribosyl-3-methoxyacrylate (4) with ^{14}C-guanidine.[12] Compound 4 and its acrylonitrile analog are versatile intermediates for the syntheses of various types of C-nucleosides.[13-15]

Fig. 1

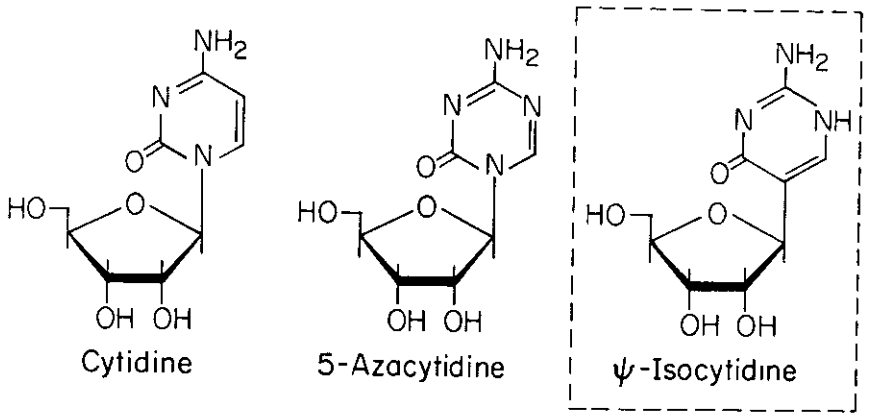
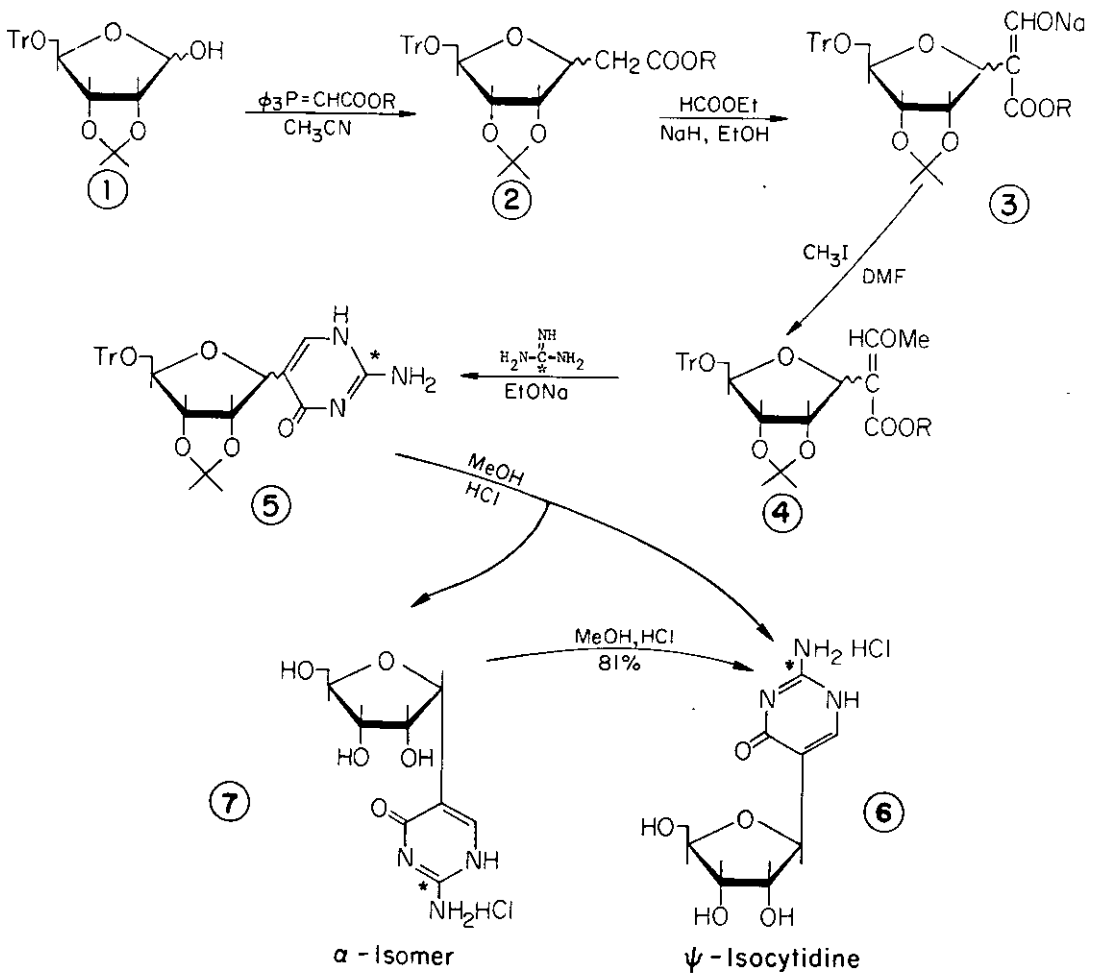

Cytidine
5-Azacytidine
ψ-Isocytidine

Fig. 2


TrO
OH
CH2 COOR
CHONa
COOR
HCOMe
NH2
NH2 HCl
NH
HO
OH
Φ3P=CHCOOR
CH3CN
HCOOEt
NaH, EtOH
CH3I
DMF
EtONa
MeOH
HCl
MeOH,HCl
81%
α - Isomer
ψ - Isocytidine

Heterocyclic compounds are prepared mainly by two routes: (a) by total synthesis by cyclization of acyclic compounds, and (b) by introduction or modification of functional groups on a preformed heterocyclic ring. The procedure shown in Fig. 2 for the synthesis of ψ-isocytidine (6) belongs to the total synthesis category (route a). This method, however, was rather unsatisfactory for large scale preparation of 6 required for clinical trials. Modification of the 2-carbonyl group of ψ-uridine by route (b) into an amino function, although achieved later by Wise et al.[16], was also not amenable to large scale preparations. Thus, introduction of a novel synthetic approach for a facile preparation of ψ-isocytidine was urgently needed. This problem was solved by exploitation of pyrimidine-to-pyrimidine transformation reaction developed in our laboratory.

Pyrimidine to pyrimidine ring transformation by replacement of one ring nitrogen with another nitrogen atom has long been known [viz., the Dimroth rearrangement and its related reactions[17]]. Replacement of a pyrimidine ring carbon by an exocyclic carbon atom by the Dimroth type mechanism has also been reported.[18] Moreover, displacement of the urea fragment of the pyrimidine skeleton by another fragment has been known, e.g., conversion of uracil derivatives into a pyrazolone or isoxazolone by treatment with hydrazine or hydroxylamine[19] (Fig. 3). These reactions have been little explored for their synthetic utility but were used later for other purposes, such as the preparation of apyrimidinic acids from nucleic acids.[20]

Direct displacement of the urea portion of the uracil aglycon in ψ-uridine (Fig. 3) with guanidine should offer a simple preparation of ψ-isocytidine and, indeed, this conversion will be discussed later. Pyrimidine to pyrimidine transformation by replacement of the N_1-C_2-N_3 portion of the pyrimidine with 1,3-ambident nucleophiles, however, has not been known until very recently.[21] Transformation of uracil (or mono-N-alkylated uracil) (Fig. 4) into isocytosine by treatment with guanidine did not occur due, obviously, to the generation of a uracil anion by the base guanidine which electrostatically hindered the approach of a nucleophile to the negatively charged uracil. Consequently, we treated 1,3-dimethyluracil (8a) (which does not contain dissociable proton) with guanidine and, indeed, demonstrated the smooth conversion to isocytosine (9a).[22] Several isocytosine derivatives were also prepared by treatment of substituted 1,3-dimethyluracils (8b-e) with guanidine (Fig. 4). The reaction is highly dependent on the electronic nature of the substituent at C5. Thus, while 5-fluoro-1,3-dimethyluracil (8d) was converted into 5-fluoroisocytosine (9d) in a few hours in refluxing ethanol, transformation of 1,3-dimethylthymine (8b) required more stringent conditions, such as fusion with guanidine at 80-90°. Methyl substitution at C6 of 8 also retarded the reaction. 1,3,6-Trimethyluracil (8c) did not undergo conversion to 6-methylisocytosine (9c) in refluxing ethanol and, again, fusion conditions were required to effect this

Fig. 3

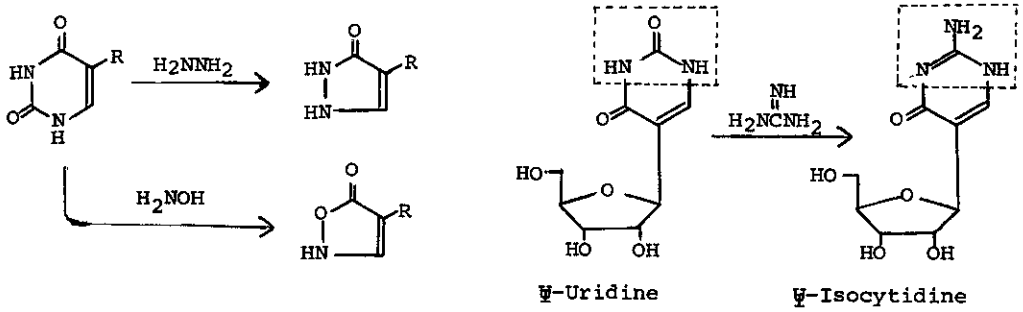
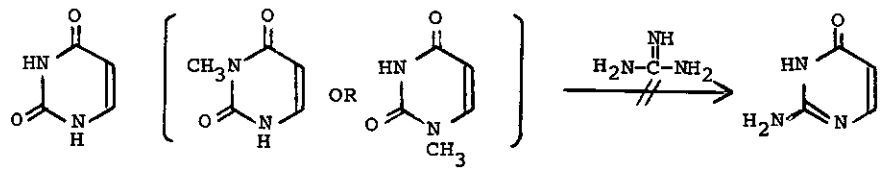
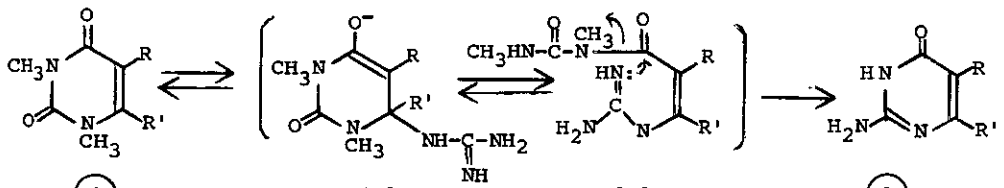


Fig. 4





8

8a	R = R' = H
8b	R = CH_3, R' = H
8c	R = H, R' = CH_3
8d	R = F, R' = H
8e	R = Br, R' = H
8f	R = NO_2, R' = H

9

	mp(°C)	Yield(%)
9a	245-247	66
9b	281-283	91
9c	290-292	49
9d	274-276	18
9e	250	22

aci-nitronium salt

reaction. On the other hand 5-bromo-1,3,6-trimethyluracil (8e) was readily converted into 5-bromo-6-methylisocytosine (9e) by treatment with guanidine in refluxing ethanol.[22,23] 5-Nitro-1,3-dimethyluracil (8f) formed a stable adduct with guanidine, but further transformation did not occur[23] apparently due to an aci-nitronate salt formation.

These ring transformation reactions most probably proceed by the S_N(ANRORC) mechanism[24] (*Addition of the Nucleophile, Ring Opening, and Ring Closure*). *Thus, the first step would be* attack of the nucleophile (such as guanidine) at C6 of 8 (Fig. 4) to form a Michael adduct [A] followed by scission of the N1-C6 bond to the ring opening intermediate [B]. Subsequent ring closure by attack of the terminal guanidine nitrogen of [B] with concommitant cleavage of C4-N3 linkage would produce isocytosine and 1,3-dimethylurea.

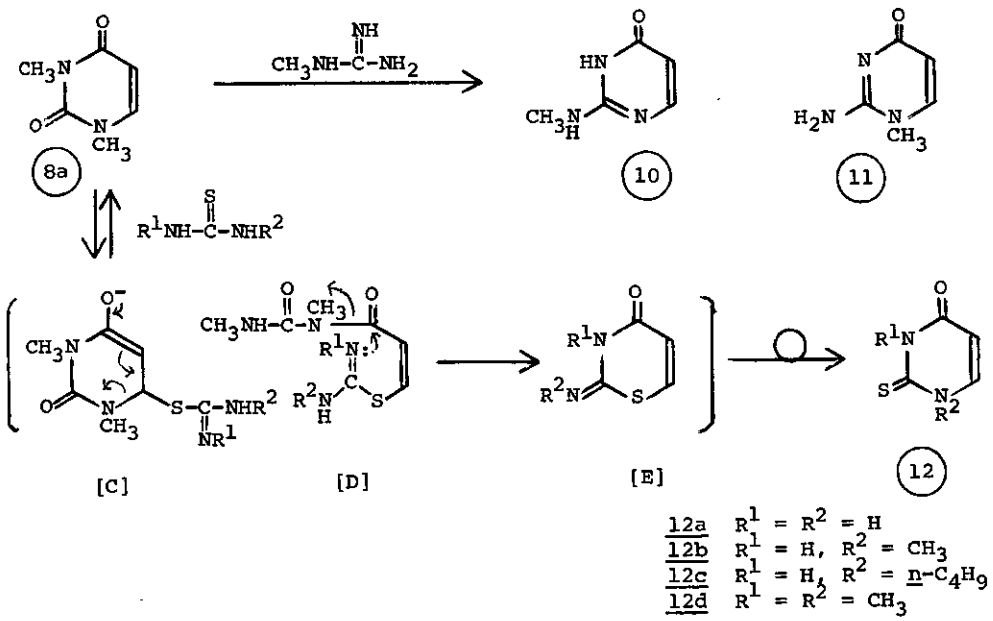
Treatment of 8a with methylguanidine afforded two products, N2-methyl- and N1-methylisocytosine (10 and 11, Fig. 7), in a 3:1 ratio. The formation of two isomers in this reaction is probably due to competition for attack on C6 of 8a between the stronger nucleophile (CH_3NH) and sterically less hindered nucleophile (NH_2 group) of the reagent.

Urea and thiourea, which are weaker bases than guanidine, did not react with 8a in ethanol. In the presence of sodium ethoxide, however, the reaction proceeded very smoothly and uracil and thiouracil (12a, Fig. 5) were obtained in good yields. Reaction of 8a with N-methylthiourea gave N1-methyl-2-thiouracil (12b)as the major product. Treatment of 8a with n-butylthiourea afforded only the N1-alkylated thiouracil (12c) and no isomer was detected in the reaction mixture. 1,3-dimethyl-2-thiouracil (12d) was obtained by treatment of 8a with N,N'-dimethylthiourea. For the synthesis of 1-akylated 2-thiouracils, this ring transformation is much simpler than the known multistep procedures.[25]

The reaction of 8 with thioureas most probably proceeds via initial attack on C6 of 8 by the sulfur nucleophile to give [C] (Fig. 5) followed by ring opening to [D]. Subsequent attack by the sterically less hindered nitrogen nucleophile in [D] on C4 with liberation of 1,3-dimethylurea would result in the formation of the 1,3-thiazine intermediate [E] which, then, would rearrange to 2-thiouracils (12) in the presence of excess alkali.[23] Alkali-catalyzed rearrangement of a 1,3-thiazine to a pyrimidine is known.[26]

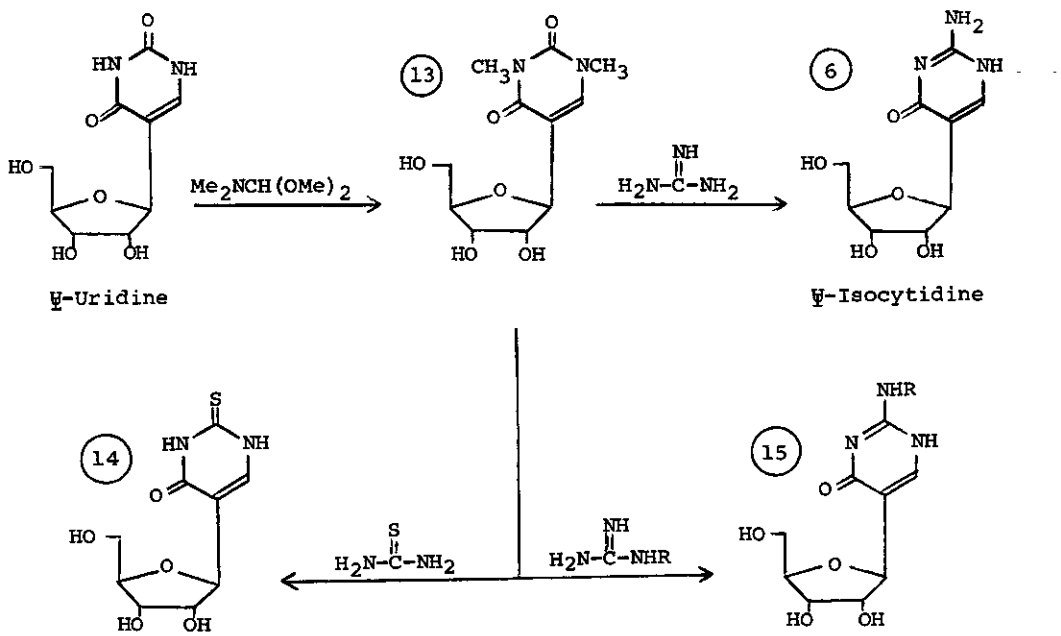
The novel pyrimidine to pyrimidine ring transformation by displacement of the N_1-C_2-N_3 fragment *by the N-C-N fragment of 1,3-ambident nucleophiles* (intermolecular transfragment reaction[27]) with simple pyrimidines (such as 8) has thus been developed as described above.[22,23] Application of this pyrimidine to pyrimidine ring transformation reaction to 1,3-dimethyl-ψ-uridine (13, Fig. 6) (which was obtained in good yield by treatment of ψ-uridine with DMF-dimethylacetal) afforded ψ-isocytidine (6) in excellent yield.[22,23] (Methylation of ψ-uridine with conventional alkylating agents gave a mixture of several products[28]). Large amounts of ψ-isocytidine prepared by this

Fig. 5



12a $R^1 = R^2 = H$
12b $R^1 = H$, $R^2 = CH_3$
12c $R^1 = H$, $R^2 = n\text{-}C_4H_9$
12d $R^1 = R^2 = CH_3$

Fig. 6



ring transformation procedure were used in Phase I clinical trials. Unfortunately, this C-nucleoside was found to cause severe hepatotoxicity to patients.[29] 2-Thio-ψ-uridine (14) and N2-methyl-ψ-isocytidine (15) were also prepared (Fig. 6) by this approach.[23] It was interesting to note that in the preparation of the latter, no isomeric N1-methylated product was found in the reaction although 8a gave a mixture of N2-methylated and N1-methylated products (Fig. 5).

In the above reactions, the urea portion of the 1,3-dimethyluracil ring (8, Fig. 7) is displaced by a 1,3-ambident reagent A-B-C which contains two nitrogen nucleophilic centers (A = C = nitrogen) in the molecule, and the product [F] is a pyrimidine. The ease with which the pyrimidine to pyrimidine transformation occurred prompted us to investigate the application of this trans-fragment reaction to the preparation of ring systems other than pyrimidine in the following order (Fig. 7).

1. To explore transformation of the pyrimidine (8) into the pyridine system [H] using 1,3-ambident nucleophiles containing a C-C-N fragment.
2. To synthesize a bicyclic system [G] using cyclic ambident nucleophiles.
3. To convert the pyrimidine ring [8] into the benzene system [I] using 1,3-ambident reagents bearing two carbon nucleophilic centers in each molecule.
4. To apply this transformation reaction to s-triazine to s-triazine (16 to [J]) transformation.
5. To prepare pyrimidines [F] from s-triazines (16).

For the pyrimidine to pyridine transformation (Fig. 8) we chose malonamide as the ambident reagent containing a carbon and a nitrogen nucleophilic center, and found that 1,3-dimethyluracil (8a) was converted smoothly into 2,6-dihydroxynicotinamide (17a).[30,31] Several 5-substituted 1,3-dimethyluracils (8) were also converted into 5-substituted 2,6-dihydroxynicotinamides (17b, d-g).[30,31] The ring transformation reaction proceeded more rapidly with dimethyluracils containing an electron withdrawing group at C5. The mechanism for this reaction is most probably S_n(ANRORC)[24] similar to the pyrimidine to pyrimidine transformation already discussed.[22,23] In this case, the initial step would be the formation of the Michael adduct [K] (Fig. 8) by reaction with the carbon nucleophile. The formation of the ring opened adduct [L] would be promoted by dissociation of the α-proton (most acidic) from [K]. Cyclization of [L] by attack of the amide nitrogen on the ureido carbonyl carbon with concommitant removal of 1,3-dimethylurea would furnish this pyrimidine to pyridine transformation. The fact that 2,4-dihydroxynicotinamide was not detected in the reaction mixture (initial attach is not by nitrogen) and methylmalonamide did not react with 8 to form the 5,5-disubstituted pyridine derivative (no α-proton in [L] lends support to this mechanism). 5-Nitro-1,3-dimethyluracil (8f) rapidly formed a very stable adduct with malonamide, but further transformation did not occur. 1,3,6-Trimethyluracil (8c) was recovered quantitatively from the

Fig. 7

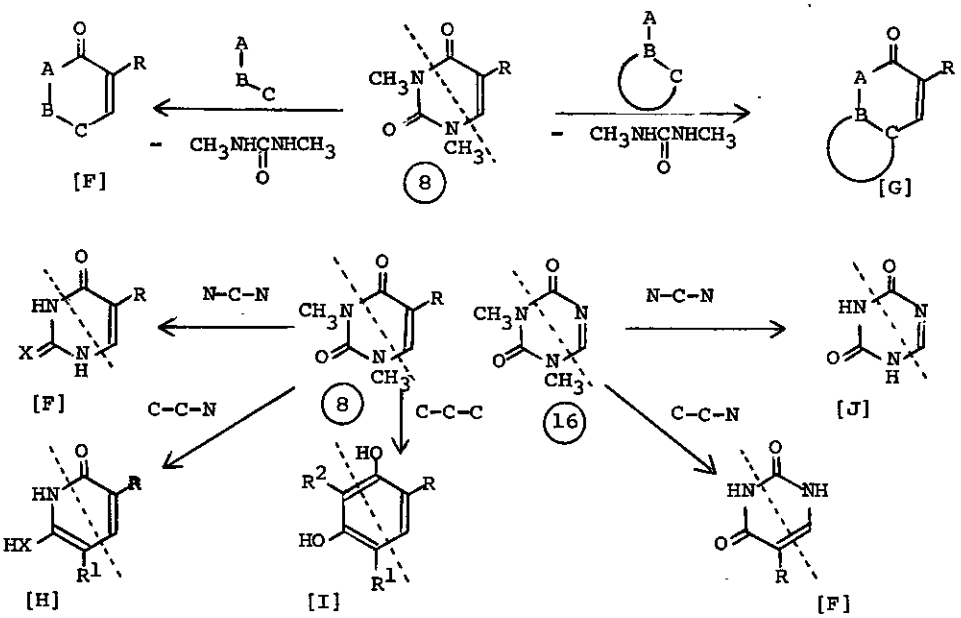
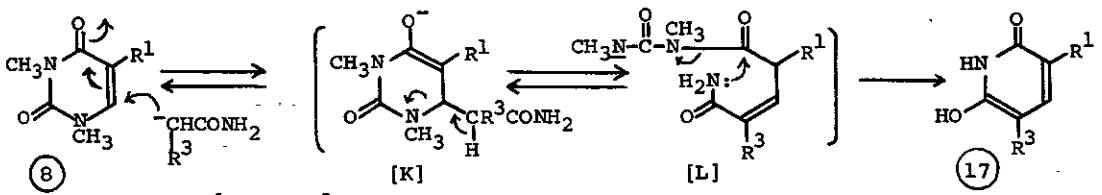
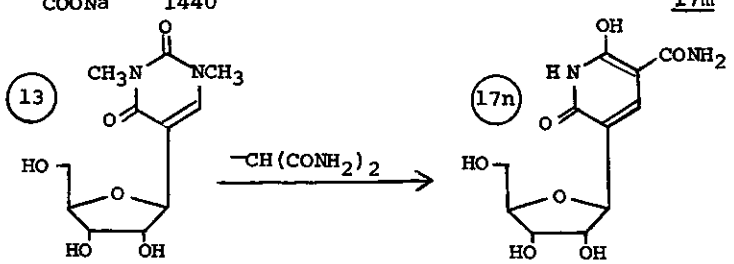


Fig. 8



	R^1	R^3	time (min)
8a	H	$CONH_2$	20
8b	CH_3	$CONH_2$	180
8d	F	$CONH_2$	10
8e	Br	$CONH_2$	30
8f	NO_2	$CONH_2$	10
8g	Cl	$CONH_2$	20
8h	CN	$CONH_2$	10
8a	H	CN	30
8a	H	$COCH_3$	300
8a	H	C_6H_5	420
8a	H	COONa	1440

	yield (%)
17a	80
17b	65
17d	38
17e	67
17f	0
17g	95
17h	68
17i	97
17j	51
17k	30
17m	14



reaction mixture.[30,31]

We also examined the suitability of acetamide derivatives as the C-C-N donors. Acetamide itself failed to react with 8a, probably because carbanion formation was not possible under these conditions. However, acetamide derivatives bearing an electron withdrawing group (at R^3) did react with 8 to afford the 3-substituted 2,6-dihydroxypyridines (17i-m) (Fig. 8). Recently we applied this transformation reaction to 1,3-dimethyl-ψ-uridine (13) and converted 13 into 5-β-D-ribofuranosyl-2,6-dihydroxynicotinamide (17n) (Fig. 8). As in the conversion of 13 into the pyrimidine C-nucleosides 6, 14 and 15 (Fig. 6), very little α,β-epimerization was observed during the 13 to 17n conversion.[32] However, prolonged treatment of 17n in base caused α,β-isomerization.[32]

Several pyrimidine to pyridine transformation reactions have been reported by others,[33-36] but these are not applicable to our uracil 2,4-dioxopyrimidine systems such as uracils (8).

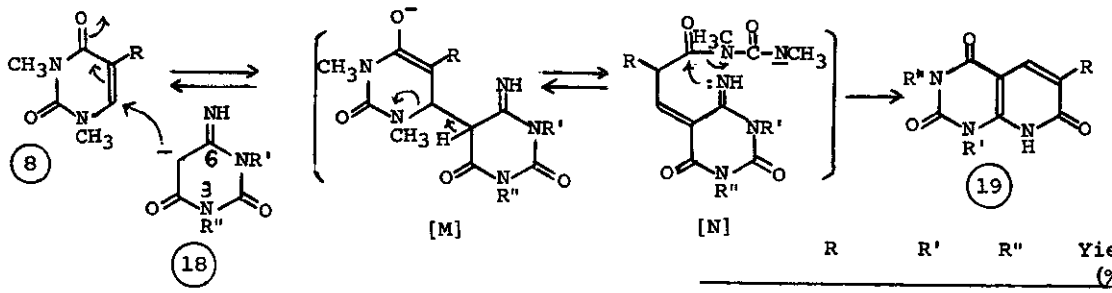
The synthesis of bicyclic compounds by exploitation of our ring transformation reaction was achieved using 6-amino-1,3-dimethyluracil (18a) as the cyclic 1,3-ambident reagent (Fig. 9). When a mixture of 8a and 18a was treated with base, 1,3-dimethylpyrido[2,3-d]pyrimidine-2,4,7(1H,3H, 8H)-trione (19a) was obtained in 33% yield. Several C6-substituted pyrido[2,3-d]pyrimidines (19b-e) were also prepared from 5-substituted 1,3-dimethyluracils (8f,h-j) with 18a. It is interesting to note that 5-nitro-1,3-dimethyluracil (8f) [which formed a stable Michael adduct with guanidine[23] or with malonamide[31] but failed to undergo the ring transformation reaction] afforded the 6-nitropyrido[2,3-d]pyrimidine (19b) by reaction with 18a.

A plausible mechanism for this pyrido[2,3-d]pyrimidine formation is shown in Fig. 9. Attack by C5 of 18 on C6 of 8 would form the Michael adduct [M] which would undergo ring opening to produce [N]. Cyclization between the imino nitrogen and the ureido carbonyl carbon in [N] and subsequent release of 1,3-dimethylurea would complete the pyrido[2,3-d]pyrimidine transformation.[31] A somewhat similar pyrimidine to pyrido[2,3-d]pyrimidine transformation has been reported by Albert and Pendergast.[37]

1,3-Dimethyl-5-azauracil (16) was found to be extremely susceptible to ring transformation[38] (Fig. 10). Treatment of 16 with guanidine afforded 5-azacytosine (20). When 16 was treated with malonamide, uracil-5-carboxamide (21a) was obtained. Similar treatment with cyanoacetamide afforded 5-cyanouracil (21b).

The mechanisms for these s-triazine to s-triazine and s-triazine to pyrimidine transformations should be very similar to those we proposed for the pyrimidine to pyrimidine[23] and pyrimidine to pyridine[31] transformations discussed above. In the case of s-triazine to s-triazine conversion, the adduct [O] (Fig. 10) is not of the Michael type. In the case of s-triazine to pyrimidine transformation, attack of carbanion at C6 of 16 would occur to form the complex [P]. Proton transfer from the exocyclic α-position of structure [P] to N5 would give rise to carbanion [O]

Fig. 9



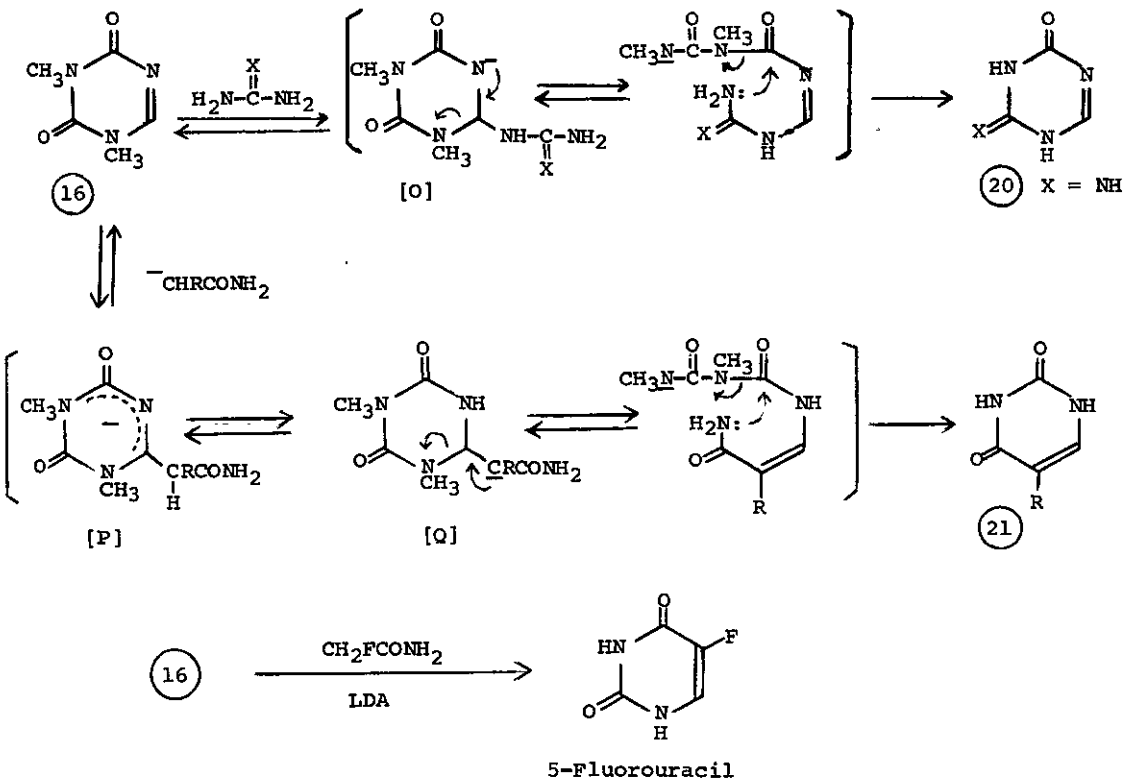
8a R = H
8f R = NO_2
8h R = CN
8i R = $COCH_3$
8j R = $CONH_2$

18a R' = R" = CH_3
18b R' = R" = C_2H_5
18c R' = R = nC_3H_7
18d R' = nC_4H_9, R" = H

	R	R'	R"	Yield (%)*
19a	H	CH_3	CH_3	30
19b	NO_2	CH_3	CH_3	34(50)
19c	CN	CH_3	CH_3	52(63)
19d	$COCH_3$	CH_3	CH_3	(65)
19e	$CONH_2$	CH_3	CH_3	16(30)
19f	CN	C_2H_5	C_2H_5	65
19g	$COCH_3$	C_2H_5	C_2H_5	89(82)
19h	CN	nC_3H_7	nC_3H_7	63
19i	CN	nC_4H_9	H	24

*Yields in () when KOH was used.

Fig. 10



5-Fluorouracil

which would then undergo intramolecular reactions leading to pyrimidine 21.[38]

1,3-Dimethyl-5-azauracil (16) failed to react with fluoroacetamide in alcoholic alkoxide, the conditions which were employed for the s-triazine to pyrimidine transformation. It was found[39], however, that the transformation occurred smoothly in the presence of lithium isopropylamide in ether, and 5-fluorouracil was obtained in 88% yield after recrystallization (Fig. 10). This is probably the simplest and safest method of preparation of 5-fluorouracil which is one of the most extensively used drugs in the treatment of advanced solid cancers.[40]

In 1963, the first pyrimidine to benzene ring transformation reaction was discovered in our laboratory rather serendipitously. Attempts at recrystallization of crude 5-nitropyrimidine-2(1H)-one (22, Fig. 11) from acetone resulted in the quantitative formation of adduct (23a) which, upon treatment with sodium hydroxide, was converted into p-nitrophenol (24a)[41]. 1-Methyl-5-nitropyrimidin-2(1H)-one (25), when treated with acetone in the presence of acid, afforded two separable racemic adducts 26 and 27. Both were smoothly converted into 24a upon alkaline treatment (Fig. 11).[42] When 22 was treated with ethyl acetoacetate in acid, adduct 23b was formed, from which 5-nitrosalicyclic acid (24b) was obtained. Treatment of 22 with diethyl acetonedicarboxylate in the presence of acid afforded the bicyclic intermediate 28 which was converted into 2-hydroxy-5-nitroisophthalic acid (24c) by base treatment.[42]

Conversion of the ketone-nitropyrimidine adducts (23) into nitrophenols (24) may proceed by the following two mechanisms, depending upon the relative acidity of the α and γ, Path A (Fig. 12) should operate predominantly. Dissociation of the proton from the α-carbon would cause ring opening between N3 and C4 to form intermediate [R]. Dissociation of the proton at the γ position from [R] in base would result in the formation of carbanion [S]. Cyclization between the carbanion and C6 by assistance from the nitro group would lead to the formation of aci-nitro intermediate [T] from which p-nitrophenol products (24) would arise by simultaneous elimination of urea and aromatization.

If the proton on C$_\gamma$ is more labile than that on C$_\alpha$, path B should predominate. In this case, the initial step is abstraction of a proton from C$_\gamma$ of 23 to give the carbanion [T], which should then undergo intramolecular cyclization leading to formation of the bicyclic Michael adduct [U]. This intermediate [U] is structurally very similar to the bicyclic derivative 28, (Fig. 11) obtained by acid-catalyzed condensation of 22 with diethyl acetonedicarboxylate. Conversion of [U] into the p-nitrophenol product (24) would proceed via the aromatization of the ureido intermediate (Fig. 12) with loss of urea.

1,3-Dimethyluracil (8a) did not undergo adduct formation with ketonic reagents in alcoholic sodium alkoxide. The 5-nitro analog (8f), however, was found to form a Michael adduct (29) (Fig. 13) in base with diethyl acetonedicarboxylate. Prolonged base treatment of 29 afforded (5,6-di-

Fig. 11

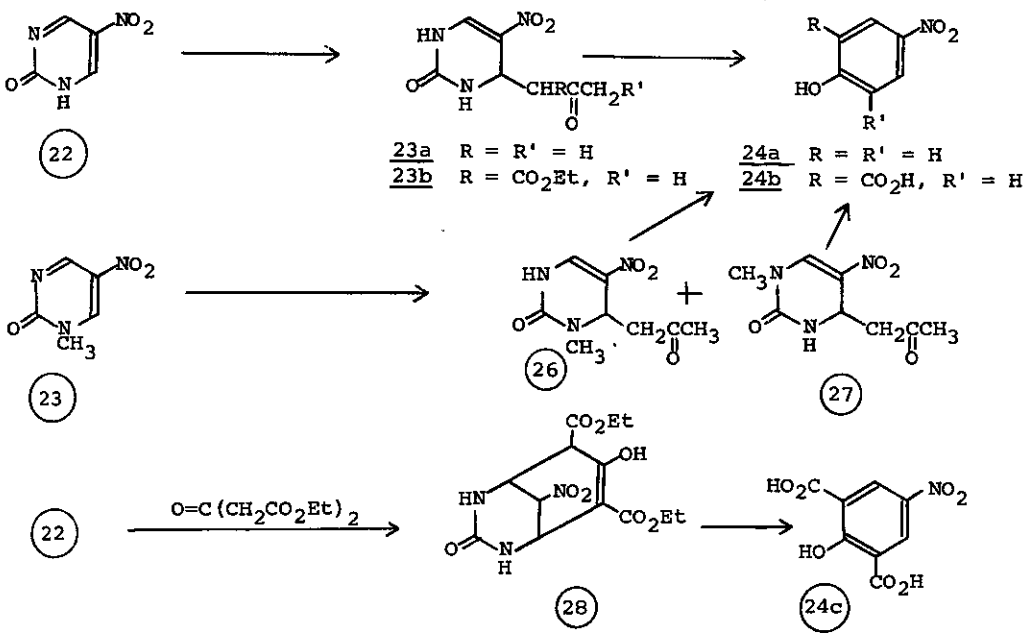
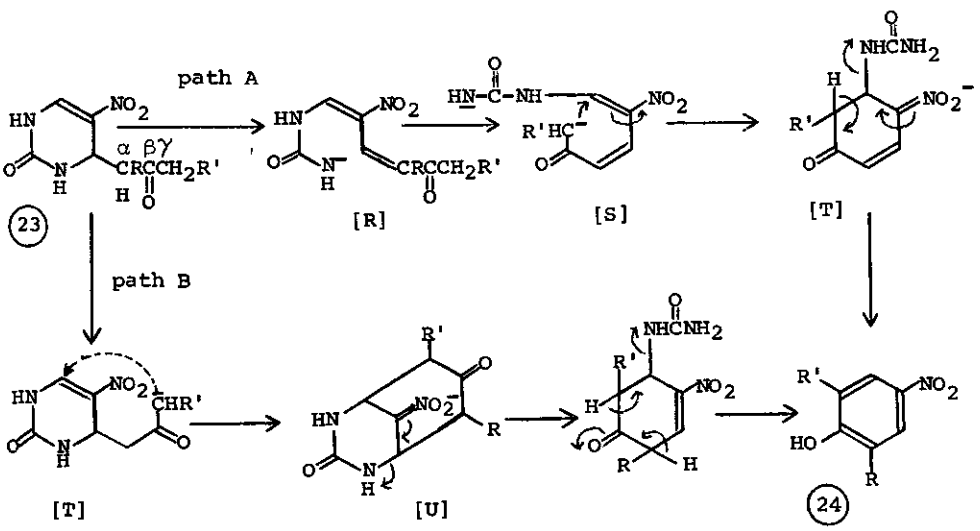

22
23a R = R' = H
23b R = CO2Et, R' = H
24a R = R' = H
24b R = CO2H, R' = H
23
26
27
22
O=C(CH2CO2Et)2
28
24c

Fig. 12


path A
23
[R]
[S]
[T]
path B
[T]
[U]
24

hydro-1,3-dimethyl-5-nitrouracil-6-yl)acetic acid (30), which obviously arose by a retro-Claisen reaction from 29.[43] Compound 8f forms adducts (31) with other ketonic reagents (such as ethyl acetoacetate, acetone or butanone) as isolable crystalline products. Prolonged heating of 31 in base afforded the nitroresorcinol derivatives (32)[43] (Fig. 13). This 5-nitrouracil (8f) to nitroresorcinol (32) transformation may proceed via an open-chain intermediate by mechanisms similar to the 5-nitropyrimidinone (22) to p-nitrophenol (24) conversion (Fig. 12).

The above experiments indicate the importance of the susceptibility of C6 of 1,3-dimethyluracil (8) to nucleophilic attack by ketonic reagents in the pyrimidine to benzene ring transformation. 5-Cyano-1,3-dimethyluracil (8h) is highly susceptible to nucleophilic attack at C6 due to the electron-withdrawing effect of the cyano substituent at C5. When 8h was treated with acetone in base, two products were obtained, one of which was 1,3-dimethyluracil-5-carboxamide (33) (Fig. 14), and the other 1,3,7-trimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (34). The former arose by hydrolysis of the nitrile 8h. For the formation of the latter, apparently, the Michael adduct [V] (Fig. 14) was converted into the open-chain intermediate [W] which underwent cyclization by a mechanism involving attack by the terminal urea nitrogen on the cyano group to afford the 6-aminouracil [X]. Intramolecular condensation of the amino group with the neighboring ketone would furnish the formation of 34.[44]

The above mechanism suggests that an activated acetonitrile, such as malononitrile or ethyl cyanoacetate, should form the Michael adduct (35) more readily (Fig. 14), since such reagent is a better nucleophile than a ketone. The adduct 35 should be converted more readily into the open-chain intermediate [Y] since the α-proton of 35 is more acidic than that in [V]. Cyclization to the 6-aminouracil intermediate [Z] and subsequent formation of the bicyclic product 36 should also occur readily. Actually, when 8h was treated with these reagents, 7-amino-6-cyano-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (36a) and 7-amino-6-ethoxycarbonyl-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (36b), respectively, were obtained.

Application of this new reaction to the 5-cyanouridine derivative (39, Fig. 15) which was prepared in two-steps from the known 5-bromouridine (37) yielded the protected nucleosides (40-42) in excellent yield. After hydrogenolysis of the benzyloxymethyl group followed by acid hydrolysis, compounds 40 and 42 gave the corresponding novel type of bicyclic nucleosides 43 and 45, respectively. The 6-cyano derivative (44) was not obtained directly from 41, but it was prepared from the 6-carboxamide intermediate (40).[45] Some 1-ribosylpyrido[2,3-d]pyrimidines have been synthesized by condensation of the silylated base with a ribosyl halide as potential antitumor agents.[46] Somewhat similar nucleosides, 8-ribosylpteridines, have also been synthesized by rather elaborate procedures.[47]

Fig. 13

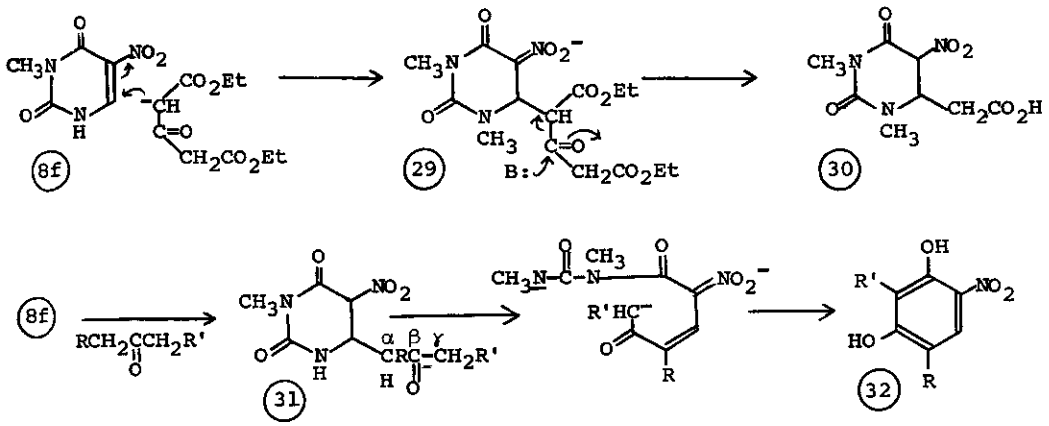


Fig. 14

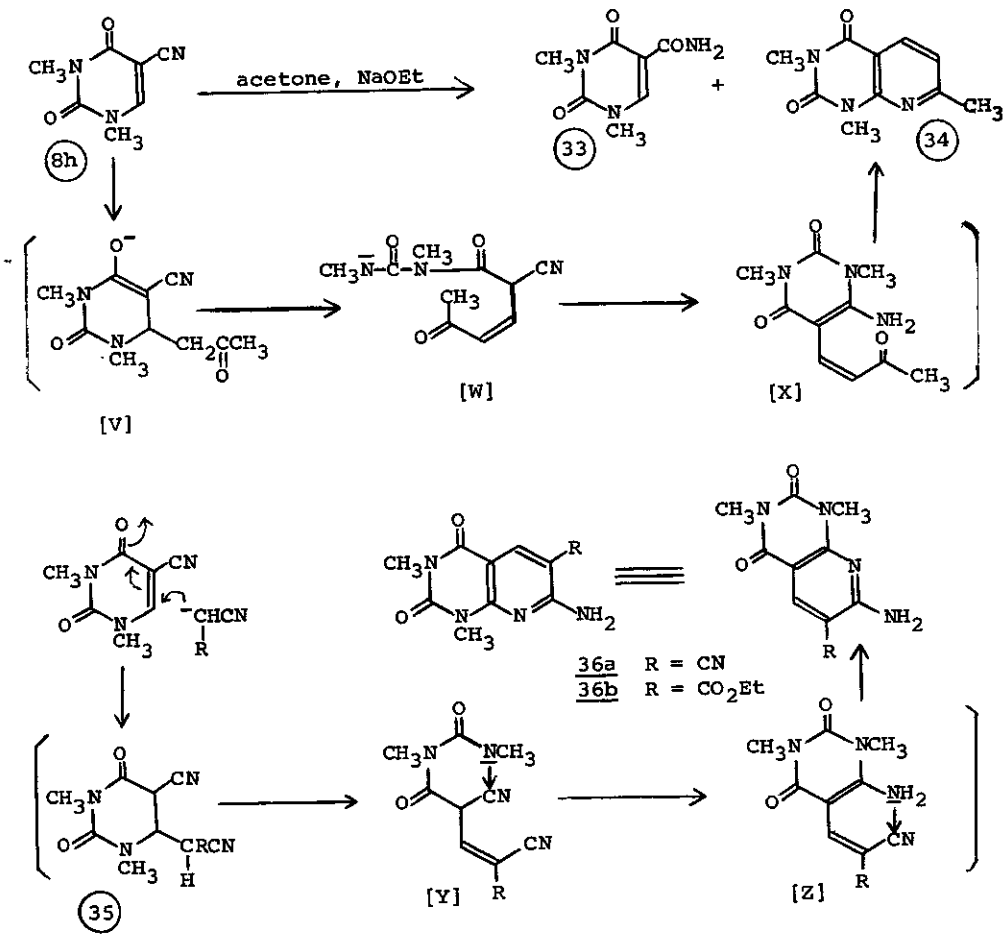
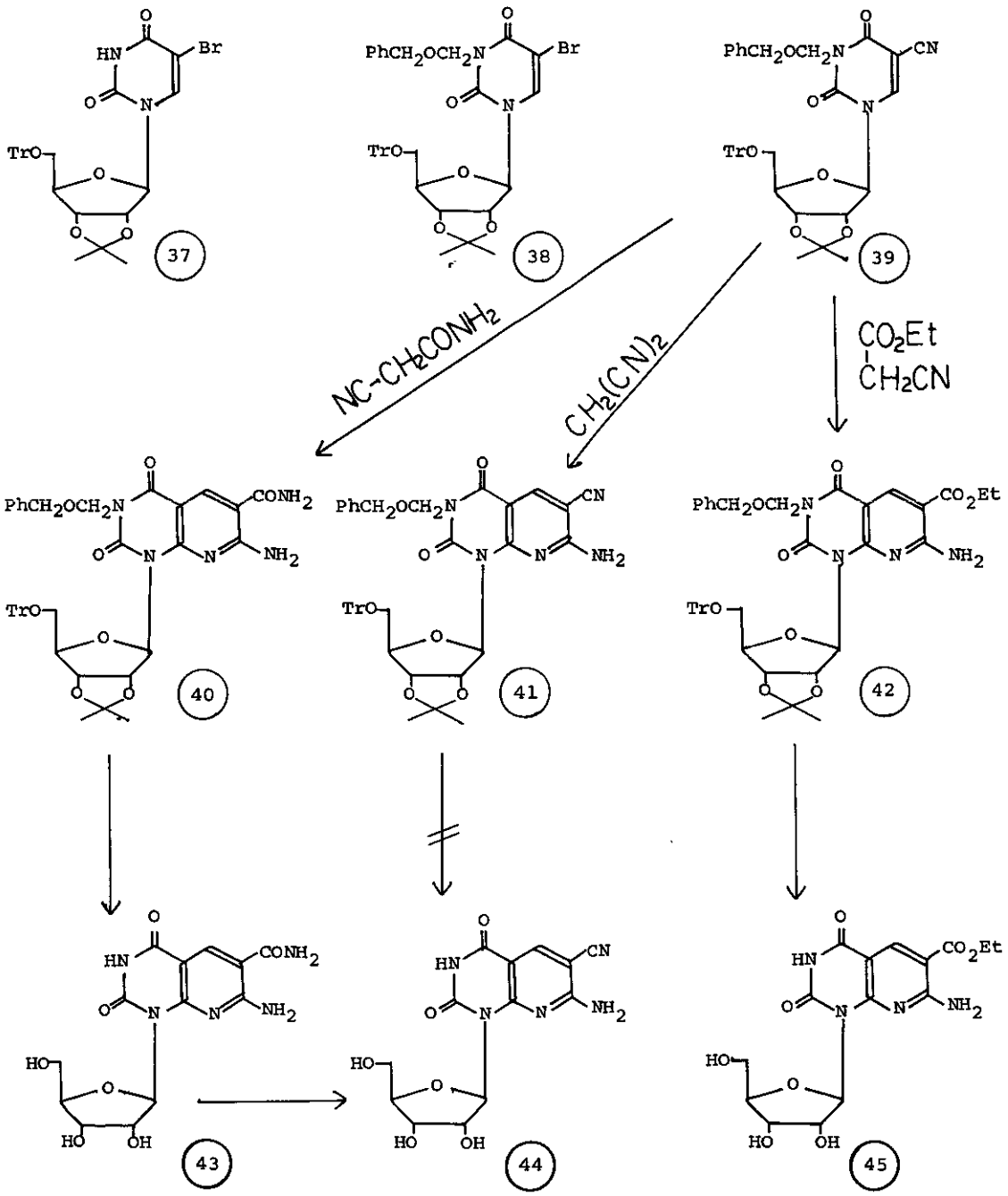


Fig. 15


Br
PhCH2OCH2N
CN
TrO
37
38
39
NC-CH2CONH2
CH2(CN)2
CO2Et
CH2CN
CONH2
NH2
40
41
42
HO
OH
43
44
45

The pyrido[2,3-d]pyrimidine ring system is found in a number of biologically active compounds,[48] including antitumor,[49] antibacterial,[50] antimalarial,[51] antihypertensive,[52] antiallergic,[53] analgesic,[54] antiphlogistic,[54] antipyretic,[54] and anticonvulsive[54] activities. We now have easy assess to this important ring system

It is clear that these novel heterocyclic ring transformation reactions have opened up new possibilities for the facile syntheses of many specifically-substituted heterocycles and phenols which are not readily accessible by other procedures. Further investigations into this fruitful area are underway in our laboratory.

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