Aza-analogues of Pteridine. Part II.[1] The Novel Use of Silver Oxide in Transetherification of Alkoxy-1,2,4,6,8-penta-azanaphthalenes, Alkoxynitropyrimidines, and Related Systems

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Alkoxy-derivatives of 1,2,4,6,8-penta-azanaphthalene (pyrimido[5,4-*e*]-*as*-triazine) undergo transetherification when treated with boiling alcohols in the presence of silver oxide. Appropriate methoxy-compounds give 5-ethoxy-3-methyl-, 5-propoxy-3-methyl, and (more slowly) 5-isopropoxy-3-methyl-penta-azanaphthalene; also 5,7-diethoxy-, 5,7-dipropoxy-, 5,7-di-isopropoxy-, 5,7-diethoxy-3-methyl-, and 5-ethoxy-3,7-dimethyl-penta-azanaphthalene. Synthetic routes to the methoxy-substrates and to one of the products are reported; other structures are confirmed by u.v. and ^{1}H n.m.r. spectra.

4-Methoxypteridine undergoes transetherification similarly but simple alkoxypyrimidines and alkoxypyridines are resistant. However, the more highly activated 2-methoxy-5-nitro-, 4-methoxy-5-nitro-, and 2,4-dimethoxy-5-nitro-pyrimidine easily give their respective propoxy-homologues, and so does 2-methoxy-3,5-dinitropyridine. In contrast, 2,4-dimethoxy-6-methyl-5-nitropyrimidine gives only its 4-methoxy-2-propoxy-homologue, and both 4,6-dimethoxy-5-nitro- and 4-methoxy-2,6-dimethyl-5-nitro-pyrimidine remain unchanged.

The classical transetherification agent, ethanolic sodium ethoxide, reacts with 5,7-dimethoxypenta-azanaphthalene to give the 7-ethoxy-5-hydroxy-analogue. This was identified by spectral comparison with its 5-hydroxy-7-methoxy-homologue, itself synthesised by 5,6-addition of methanethiol to 7-methoxypenta-azanaphthalene followed by dehydrogenation and selective hydrolysis.

TRANSETHERIFICATION, the replacement of one alkoxy- or aryloxy-group by another, is recorded in a variety of aliphatic, carbocyclic, and heterocyclic series.[2] The process usually involves an ether group activated towards nucleophilic displacement by other substituents or by heteroatoms. As a rule,[3] the reagent is sodium alkoxide in the corresponding alcohol, but alcoholic solutions of acids or heavy-metal salts are used occasionally.[2]

We report here that silver oxide has proved to be an excellent catalyst for transetherification of certain alkoxy-1,2,4,6,8-penta-azanaphthalenes, alkoxypyrimidines, and related heterocyclic ethers by boiling alcohols; it could be used successfully when sodium alkoxide was ineffective or destructive. Silver acetate was useful

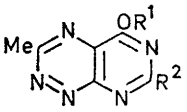
[1] Part I, M. E. C. Biffin, D. J. Brown, and T. Sugimoto, *J. Chem. Soc.* (*C*), 1970, 139.

[2] H. Meerwein in 'Methoden der Organischen Chemie (Houben-Weyl),' ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1965, vol. 6, part 3, p. 171 *et seq.*

[3] W. L. F. Armarego, 'Quinazolines,' Wiley, New York, 1967, p. 243; H. Yamanaka, *Chem. and Pharm. Bull.* (*Japan*), 1959, **4**, 505.

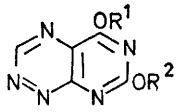
sometimes but no reactions occurred in the absence of catalyst.

Alkoxy-1,2,4,6,8-penta-azanaphthalenes.— 5-Methoxy-3-methylpenta-azanaphthalene [1] (1a) was converted into its n-alkoxy-homologues (1b and c) in good yield by boiling with silver oxide in ethanol or propanol respectively for 7—8 hr.; to obtain a comparable yield of the isopropoxy-homologue (1d) required about 100 hr., probably owing to steric interference with formation of a transition state; and no reaction could be detected on prolonged heating of the methoxy-compound (1a) with silver oxide in t-butyl alcohol. The structures (1b—d) were confirmed by the close similarity of the u.v. and ^{1}H n.m.r. spectra (Tables 1 and 2) to those of the starting material (1a).



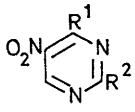
(1)

	R^1	R^2
a;	Me	H
b;	Et	H
c;	Pr	H
d;	Pr^i	H
e;	Me	Me
f;	Et	Me
g;	Me	OMe
h;	Et	OEt



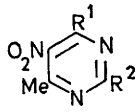
(2)

	R^1	R^2
a;	Me	Me
b;	Et	Et
c;	Pr	Pr
d;	Pr^i	Pr^i
e;	H	H
f;	Et	Me
g;	H	Et
h;	H	Me



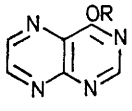
(3)

	R^1	R^2
a;	OMe	OMe
b;	$NH{\cdot}NH_2$	OMe
c;	NH·N:CH·OEt	OMe
d;	NH·N:CMe·OEt	OMe
e;	H	OMe
f;	OMe	H
g;	H	OPr
h;	OPr	H
i;	OPr	OPr
j;	OMe	$NH{\cdot}NH_2$



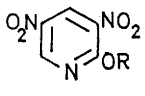
(4)

	R^1	R^2
a;	OMe	OMe
b;	OMe	OPr
c;	OMe	Me
d;	$NH{\cdot}NH_2$	OMe
e;	$NH{\cdot}NH_2$	OH
f;	$NH{\cdot}NH_2$	OPr



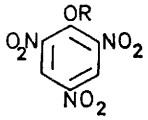
(5)

a; R = Me
b; R = Pr



(6)

a; R = Me
b; R = Pr



(7)

a; R = Me
b; R = Et

5,7-Dimethoxypenta-azanaphthalene (2a) was made from 2,4-dimethoxy-5-nitropyrimidine [4] (3a) *via* the hydrazinopyrimidine (3b) and its ethoxymethylene derivative (3c). Reductive cyclisation of the latter gave the (unisolated) 1,2-dihydro-7-methoxypenta-azanaphthalene which underwent the usual [5] 5-methoxylation during oxidation by silver oxide in methanol to yield the required product (2a). This was transformed easily by silver oxide in an appropriate alcohol to the homologues (2b—d); as before, the di-isopropoxy-compound (2d) was formed much more slowly than its di-n-propoxy-isomer (2c). The diethoxy-compound (2b) reverted into its dimethoxy-precursor (2a) on treatment with silver oxide in methanol. Structures (2a—d) were confirmed spectroscopically; also hydrolysis of the diethers (2a and c) gave the known [6] dihydroxy-analogue (2e). The diethoxy-compound (2b) was synthesised independently from the pyrimidine (3c) as for the homologue (2a) but by use of ethanol in the reductive cyclisation and subsequent oxidative steps; transetherification involving replacement of a 7-methoxy- by a 7-ethoxy-group is involved in this synthesis. This last change was avoided by using mercury(II) instead of silver oxide for the oxidative steps: the product was 5-ethoxy-7-methoxypenta-azanaphthalene (2f).

When the dimethoxy-compound (2a) was submitted to classical transetherification conditions (sodium ethoxide in ethanol), or when the diethoxy-compound (2b) underwent mild alkaline hydrolysis, an ethoxy-hydroxy analogue was formed. This was identified as the 7-ethoxy-5-hydroxy-compound (2g), because (*a*) acidic hydrolysis gave the 5,7-dihydroxy-analogue [6] (2e), and (*b*) the u.v. spectrum and the τ value for H-3 corresponded closely with the corresponding data for the 5-hydroxy-7-methoxy-homologue (2h), prepared by alkaline partial hydrolysis of the dimethyl ether (2a) and identified by comparison with material synthesised as follows. Reductive cyclisation of the ethoxymethylenehydrazinopyrimidine (3e) and subsequent oxidation gave a solution of 7-methoxypenta-azanaphthalene which was allowed to form a 5,6-adduct with methanethiol. This dihydro-compound was oxidised to 7-methoxy-5-methylthiopenta-azanaphthalene which underwent alkaline hydrolysis to give the required hydroxy-analogue (2h).

5,7-Dimethoxy-3-methylpenta-azanaphthalene (1g) was prepared like its lower homologue (2a) from the hydrazinopyrimidine (3b), but *via* the α-ethoxyethylidenehydrazino-derivative (3d). Transetherification by silver oxide in ethanol gave the diethoxy-compound (1h). In a similar way, 5-methoxy-3,7-dimethylpenta-azanaphthalene [1] (1e) gave its ethoxy-homologue (1f).

Alkoxypyrimidines.—Although 2-methoxypyrimidine and 2,4-dimethoxy-6-methylpyrimidine resisted transetherification, the activated methyl ethers [7,8] (3e) and (3f) were easily so converted into their respective propoxy-homologues (3g) and (3h). 2,4-Dimethoxy-5-nitropyrimidine [4] (3a) likewise gave its dipropoxy-homologue (3i), but 2,4-dimethoxy-6-methyl-5-nitro-

[4] D. J. Brown, *J. Appl. Chem.*, 1957, **7**, 109.
[5] M. E. C. Biffin and D. J. Brown, *Tetrahedron Letters*, 1968, 2503.
[6] C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1969, **34**, 2102.
[7] D. J. Brown and R. V. Foster, *Austral. J. Chem.*, 1966, **19**, 2321.
[8] M. E. C. Biffin, D. J. Brown, and T.-C. Lee, *Austral. J. Chem.*, 1967, **20**, 1041.

TABLE 1

U.v. spectra

Compd.[a]	$\lambda_{max.}$ (log ε) [b]
(1a) [c]	227 (4·30), *259* (*3·39*), 316 (3·69), 322 (3·70), 327 (3·71), *336* (*3·49*), 342 (3·35), 493 (2·46)
(1b)	229 (4·38), *254* (*3·65*), 319 (3·80), 324 (3·80), 332 (3·82), *338* (*3·68*), 347 (3·62), 495 (2·41)
(1c)	229 (4·39), 257 (3·65), 320 (3·83), 324 (3·83), 332 (3·85), *338* (*3·71*), 348 (3·64), 495 (2·56)
(1d)	231 (4·35), 255 (3·61), 321 (3·79), 326 (3·78), 334 (3·82), *341* (*3·64*), 349 (3·61), 488 (2·48)
(1e) [c]	229 (4·35), *255* (*3·43*), *323* (*3·69*), *327* (*3·71*), 334 (3·72), *347* (*3·52*), 495 (2·41)
(1f)	229 (4·38), *255* (*3·37*), *324* (*3·70*), 333 (3·73), *348* (*3·55*), 494 (2·59)
(1g)	231 (4·38), *251* (*3·79*), *268* (*2·52*), *334* (*3·66*), *341* (*3·69*), 344 (3·75), 354 (3·63), 362 (3·66), 486 (2·41)
(1h)	233 (4·40), *251* (*3·77*), *271* (*3·11*), *336* (*3·67*), *343* (*3·71*), 347 (3·78), *358* (*3·62*), 365 (3·70), 487 (2·66)
(2a)	230 (4·36), *250* (*3·63*), *270* (*3·11*), *328* (*3·69*), 334 (3·73), 339·5 (3·79), 349 (3·62), 356 (3·63), 486 (2·61)
(2b)	233 (4·42), *248* (*3·85*), 255 (3·82), *275* (*3·23*), *332* (*3·73*), *239* (*3·77*), 347 (3·82), *353* (*3·69*), 363 (3·64), 484 (2·42)
(2c)	233·5 (4·46), *248* (*3·92*), *255* (3·89), *273* (*3·38*), *333* (*3·77*), *338* (*3·80*), 348 (3·85), *357* (*3·71*), 365 (3·69), 484 (2·53)
(2d)	235·5 (4·42), *238* (*4·41*), *254* (*3·81*), *275* (*3·21*), *335* (*3·76*), *342* (*3·77*), 349 (3·83), *358* (*3·67*), 368 (3·64), 480 (2·54)
(2f)	233 (4·30), *250* (*3·55*), *272* (*2·81*), *329* (*3·62*), 338 (3·66), 342 (3·73), *350* (*3·60*), 358 (3·55), 484 (2·60)
(2g) [d] 3·0	237 (4·11), *260* (*3·90*), 341 (3·69)
9·0	252 (4·24), *295* (*3·19*), 365 (3·63)
(2h) [e] 3·0	234 (4·10), *260* (*3·80*), 336 (3·69)
9·0	249 (4·19), *295* (*3·00*), 365 (3·58)
MeS [f]	*223* (*4·18*), *255* (*3·81*), 259 (3·83), *263* (*3·81*), 301 (3·35), 312 (3·48), *358* (*3·83*), 369 (3·95), 382 (3·83), 388 (3·85), 494 (2·49)
(3a)	245 (3·86), *250* (*3·85*), 278 (3·85)
(3b) M	245 (4·09), 256 (4·10), 349 (3·80)
(3e) [g]	269 (4·08)
(3f) [h]	230 (3·68), 270 (3·10)
(3g)	271 (4·15)
(3h)	230 (3·85), 275 (3·54)
(3i)	246 (3·86), 252 (3·80), 280 (3·89)
(4a)	255 (3·66)
(4b)	264 (3·75)
(4d) M	223 (4·12), 235 (4·10), 240 (4·11), 346 (3·74)
(4f) M	222 (4·15), 243 (4·14), 350 (3·72)
[i]	*240* (*3·50*)
(5a) [j]	226 (4·17), 262 (3·46), 301 (3·84), 306 (3·90), 313 (3·76), 319 (3·74)
(5b)	227 (4·27), *253* (*2·43*), *285* (*2·81*), *290* (*3·23*), 297 (3·62), 303 (3·71), 308 (3·83), 315 (3·70), 320 (3·71)
M	225 (4·25), 262 (3·46), 303 (3·90)
(6a)	*233* (*3·88*), 274 (3·86), *295* (*3·78*)
(6b)	*235* (*3·88*), 278 (3·99), *300* (*3·86*)

[a] In cyclohexane except as indicated: M (methanol), or numeral (pH of aqueous buffer). [b] Inflections or shoulders in italics. [c] *Cf.* values in ethanol (ref. 1). [d] pK_a 5·86 ± 0·06 (spectrophotometric at 20°). [e] pK_a 5·93 ± 0·06 (spectrophotometric at 20°). [f] 5-Methylthio-analogue (2h). [g] *Cf.* values in water (ref. 7). [h] *Cf.* values in ethanol (ref. 8). [i] 4-Ethoxy-6-methoxy-5-nitropyrimidine; *cf.* 4,6-dimethoxy-homologue: 240 (3·47). [j] From ref. 11.

TABLE 2

^{1}H N.m.r. spectra

Compd.[a]	τ Values [b]
(1a) [c]	Me: 6·77; MeO: 5·68; 7-H: 0·92
(1b)	EtO: 8·43 (t, *J* 7), 5·13 (q, *J* 7); Me: 6·77; 7-H: 0·89
(1c)	PrO: 8·89 (t, *J* 7), 8·6—7·6 (m, H_2), 5·26 (t, *J* 7); Me: 6·74; 7-H: 0·84
(1d)	Pr^{i}O: 8·45 (d, *J* 6), 4·29 (septet, *J* 6); Me: 6·79; 7-H: 0·93
(1e) [c]	7-Me: 7·14; 3-Me: 6·8; MeO: 5·69
(1f)	EtO: 8·42 (t, *J* 7), 5·17 (q, *J* 7); 7-Me: 7·14; 3-Me: 6·79
(1g)	Me: 6·81; 5,7-$(MeO)_2$: 5·71, 5·66.
(1h)	5,7-$(EtO)_2$: 8·46 (t, *J* 7), 8·42 (t, *J* 7), 5·24 (q, *J* 7), 5·17 (q, *J* 7); Me: 6·84
(2a)	5,7-$(MeO)_2$: 5·71, 5·68; 3-H: −0·04
(2b)	5,7-$(EtO)_2$: 8·43 (t, *J* 7), 8·35 (t, *J* 7), 5·23 (q, *J* 7), 5·15 (q, *J* 7); 3-H: −0·04
(2c)	5,7-$(PrO)_2$: 8·89 (t, *J* 7, H_6), 8·5—7·7 (m, H_4), 5·32 (t, *J* 7), 5·28 (t, *J* 7); 3-H: −0·06
(2d)	5,7-$(Pr^iO)_2$: 8·48 (d, *J* 6), 8·45 (d, *J* 6), 4·6—3·8 (m, H_2); 3-H: −0·01
(2f)	EtO: 8·40 (t, *J* 7), 5·17 (q, *J* 7); MeO: 5·70; 3-H: −0·06
(2g) [d]	EtO: 8·60 (t, *J* 7), 5·39 (q, *J* 7); 3-H: 0·05
(2h) [d]	MeO: 5·86; 3-H: 0·00
MeS [e]	MeS: 7·26; MeO: 5·68; 3-H: −0·01
(3a)	$(MeO)_2$: 5·88, 5·80; 6-H: 0·74
(3b) [f]	MeO: 5·49; 6-H: 0·62
(3e)	MeO: 5·80; 4,6-H_2: 0·48
(3f)	MeO: 5·73; 2-H: 0·90; 6-H: 0·66
(3g)	PrO: 8·96 (t, *J* 7), 8·6—7·7 (m, H_2), 5·50 (t, *J* 7); 4,6-H_2: 0·64
(3h)	PrO: 8·94 (t, *J* 7), 8·6—7·7 (m, H_2), 5·43 (t, *J* 7); 2-H: 1·04; 6-H: 0·82
(3i)	2,4-$(PrO)_2$: 8·94 (t, *J* 7, H_6), 8·6—7·7 (m, H_4), 5·53 (t, *J* 7), 5·43 (t, *J* 7); 6-H: 0·85
(4a)	Me: 7·45; 2,4-$(MeO)_2$: 5·93, 5·89
(4b)	PrO: 8·99 (t, *J* 7), 8·6—7·8 (m, H_2), 5·85 (t, *J* 7); Me: 7·56; MeO: 5·94
(4d) [f]	Me: 6·93; MeO: 5·52
(4f) [f]	PrO: 8·90 (t, *J* 7), 8·4—7·7 (m, H_2), 5·17 (t, *J* 7); Me: 6·95 EtO: 8·64 (t, *J* 7), 5·46 (q, *J* 7); MeO: 5·93; 2-H: 1·50 4,6-$(MeO)_2$: 5·90; 2-H: 1·48
(5a)	MeO: 5·67; 6-H: 0·95 (d, *J* 1·7); 2-H: 0·84; 7-H: 0·73 (d, *J* 1·7)
(5b)	PrO: 8·91 (t, *J* 7), 8·5—7·7 (m, H_2), 5·28 (t, *J* 7); 6-H: 0·94 (d, *J* 1·7); 2-H: 0·87; 7-H: 0·74 (d, *J* 1·7)
(6a)	MeO: 5·70; 6-H: 0·83 (d, *J* 2·6); 4-H: 0·58 (d, *J* 2·6)
(6b)	PrO: 8·92 (t, *J* 7), 8·6—7·7 (m, H_2), 5·35 (t, *J* 7); 4-H: 0·88 (d, *J* 2·6); 6-H: 0·64 (d, *J* 2·6)

[a] In $CDCl_3$ except where otherwise indicated. [b] Relative to Me_4Si; singlet unless otherwise indicated; *J* in Hz. [c] From ref. 1. [d] In $(CD_3)_2SO$. [e] 5-Methylthio-analogue of (2h). [f] In $F_3C{\cdot}CO_2H$. [g] From ref. 8. [h] 4-Ethoxy-6-methoxy-5-nitropyrimidine. [i] 4,6-Dimethoxy-5-nitropyrimidine.

pyrimidine [9] (4a) underwent only mono-transetherification to 4-methoxy-6-methyl-5-nitro-2-propoxypyrimidine (4b) (see later), and both 4,6-dimethoxy-5-nitropyrimidine and 4-methoxy-2,6-dimethyl-5-nitropyrimidine (4c) were unaffected; moreover, 4-chloro-6-methoxy-5-nitropyrimidine,[10] in which the methoxy-group is activated by the chloro-substituent rather than slightly deactivated by methyl groups, suffered no transetherification but only a slow nucleophilic displacement of chlorine to yield 4-ethoxy-6-methoxy-5-nitropyrimidine.

Compound (4b) was independently synthesised as follows. Monohydrazinolysis of the 2,4-dimethoxypyrimidine (4a) gave the 4-hydrazino-2-methoxypyrimidine (4d). The orientation of the substituents was confirmed by the close similarity of the u.v. spectrum of (4d) to that of the lower homologue (3b), which was distinguished from its isomer (3j) by (*a*) conversion (see before) into penta-azanaphthalenes, and (*b*) oxidation to the known [7] 2-methoxy-5-nitropyrimidine (3e). Gentle hydrolysis of the ether (4d) gave the corresponding hydrazinohydroxypyrimidine (4e), which was also formed from the pyrimidine (4b) *via* the 4-hydrazino-2-propoxypyrimidine (4f).

Other Ethers.—4-Methoxypteridine (5a) [11] was converted easily into its propoxy-homologue (5b) by silver oxide in propanol; similar treatment of 2- and 6-methoxypteridine gave unidentified products.

Although 2- and 4-methoxy-5-nitropyridine proved resistent to transetherification, the more activated ether, 2-methoxy-3,5-dinitropyridine (6a),[12] gave its propoxy-analogue (6b) in good yield. Similarly, 2,4- and 2,6-dinitroanisole resisted transetherification but 2,4-6-trinitroanisole (7a) is known [13] to change partly into the corresponding phenetole (7b) even during recrystallisation from ethanol.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff. ^{1}H N.m.r. spectra were recorded by Mr. S. E. Brown (60 MHz; 33°) and u.v. spectra were measured with a Shimadzu RS27 recording spectrophotometer; $\lambda_{max.}$ and $\varepsilon_{max.}$ values were confirmed with an Optica manual instrument.

Transetherification of 5-Methoxy-3-methylpyrimido[5,4-e]-as-*triazine.*—The methoxy-compound [1] (0·30 g.) and silver oxide (1·5 g.) were stirred under reflux in boiling propanol for 7 hr. The filtered mixture was evaporated to dryness under reduced pressure. Sublimation (100°/0·05 mm.) of the residue and subsequent recrystallisation from light petroleum (b.p. 60—80°) gave red needles of the *propoxy-homologue* (82%), m.p. 45—46° (Found: C, 52·7; H, 5·6; N, 33·7. $C_9H_{11}N_5O$ requires C, 52·7; H, 5·4; N, 34·1%); use of silver acetate (1·8 g.) in boiling propanol for 2 hr. led to the same product in 80% yield.

The methoxy-compound and silver oxide in boiling ethanol for 8 hr. gave the *ethoxy-homologue* (81%), m.p. 118—119° (Found: C, 50·7; H, 5·2; N, 37·1. $C_8H_9N_5O$ requires C, 50·25; H, 4·7; N, 36·6%) which, on similar treatment in methanol, reverted into the methoxy-homologue, m.p. 168—169° (lit.,[1] 168°) (Found: C, 47·4; H, 3·9; N, 39·3. Calc. for $C_7H_7N_5O$: C, 47·45; H, 4·0; N, 39·5%). The *isopropoxy-homologue* (82%), m.p. 117—119°, was formed by boiling the methoxy-compound and silver oxide in propan-2-ol for 4 days (Found: C, 52·7; H, 5·6; N, 34·4. $C_9H_{11}N_5O$ requires C, 52·7; H, 5·4; N, 34·1%); the substrate was recovered (>80%) after similar treatment in t-butyl alcohol.

5,7-Dimethoxypyrimido[5,4-e]-as-*triazine.*— 2,4-Dimethoxy-5-nitropyrimidine [4] (13·0 g.), hydrazine hydrate (3·7 g.), and ethanol (800 ml.) were boiled under reflux for 4 hr. The cooled solution was filtered and evaporated to *ca.* 50 ml. *in vacuo*. Refrigeration gave orange *4-hydrazino-2-methoxy-5-nitropyrimidine* (10·8 g.), m.p. 135—136° (from methanol) (Found: C, 32·4; H, 4·05; N, 37·8. $C_5H_7N_5O_3$ requires C, 32·4; H, 3·8; N, 37·8%). [Structural confirmation: the hydrazinopyrimidine (4·0 g.), silver oxide (12 g.), and methanol (300 ml.) were boiled with stirring under reflux for 20 hr. Filtration, evaporation, and sublimation (65°/0·05 mm.) gave 2-methoxy-5-nitropyrimidine (52%), identical with authentic material [7] (mixed m.p. 69—70°; and i.r. spectra)].

The hydrazinopyrimidine (4·0 g.) triethyl orthoformate (40 ml.), and ethanol (50 ml.) were heated under reflux for 1 hr. The chilled solution deposited yellow *4-ethoxymethylenehydrazino-2-methoxy-5-nitropyrimidine* (4·6 g.), m.p. 151—152° (Found: C, 39·5; H, 4·55; N, 28·9. $C_8H_{11}N_5O_4$ requires C, 39·8; H, 4·6; N, 29·0%). The ethoxymethylene compound (2·0 g.) was hydrogenated (20°/760 mm.) over palladium–charcoal (10%; 0·3 g.) in methanol (150 ml.) during 40 min. The filtered solution was stirred with anhydrous sodium sulphate (20 g.) at *ca.* 20° for 2 hr. Then the mixture was stirred under reflux with silver oxide (5·0 g.) for 3 hr. Solids were removed; sublimation (120°/0·5 mm.) of the residue from evaporation gave the yellow *5,7-dimethoxypyrimidotriazine* (64%), m.p. 155—156° (from ethanol) (Found: C, 43·2; H, 3·6; N, 36·7. $C_7H_7N_5O_2$ requires C, 43·5; H, 3·65; N, 36·3%).

Transetherification of 5,7-Dimethoxypyrimido[5,4-e]as-*triazine.*—The dimethoxy-compound (0·6 g.), silver oxide (2·1 g.), and propanol (100 ml.) were boiled under reflux with stirring for 2·5 hr. The filtered solution was evaporated to dryness. The residue gave orange needles (73%) of the *5,7-dipropoxy-homologue*, m.p. 87—88° [from light petroleum (b.p. 60—80°)] (Found: C, 52·5; H, 6·2; N, 27·9. $C_{11}H_{15}N_5O_2$ requires C, 53·0; H, 6·1; N, 28·1%). Its *5,7-di-isopropoxy-isomer* (83%), m.p. 118—120°, was made similarly by boiling in propan-2-ol for 5 days (Found: C, 52·6; H, 6·4; N, 27·95%); the *5,7-diethoxy-homologue* (96%), m.p. 141—142°, was formed in boiling ethanol (7 hr.) (Found: C, 48·5; H, 5·3; N, 32·0. $C_9H_{11}N_5O_2$ requires C, 48·9; H, 5·0; N, 31·7%). The last compound was also prepared (60%) from 4-ethoxymethylenehydrazino-2-methoxy-5-nitropyrimidine as for the dimethoxy-homologue but with ethanol in place of methanol throughout the reactions. Reversion of the diethoxy- to the dimethoxy-homologue (40%; identified by mixed m.p.

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and i.r. spectra) occurred on treatment with silver oxide in boiling methanol for 14 hr.

The dimethoxy-compound (0·20 g.) and ethanolic sodium ethoxide [sodium (0·12 g.) in ethanol (200 ml.)] were stirred at 20° for 15 hr. The solution was adjusted to pH 4 with ethanolic hydrogen chloride, filtered, and evaporated under reduced pressure. The residual *7-ethoxy-5-hydroxypyrimidotriazine* (0·08 g.) had m.p. 186° (from water) (Found: C, 43·7; H, 3·8; N, 36·7. $C_7H_7N_5O_2$ requires C, 43·5; H, 3·65; N, 36·3%). The same product (60%) resulted from alkaline hydrolysis of 5,7-diethoxypyrimidotriazine as described later for the 5-hydroxy-7-methoxy-analogue.

5-Ethoxy-7-methoxypyrimido[5,4-e]-as-*triazine*.— 4-Ethoxymethylenehydrazino-2-methoxy-5-nitropyrimidine (1·0 g.) was hydrogenated in ethanol (150 ml.) as already described. The filtered solution and yellow mercury(II) oxide (7·0 g.) were stirred and boiled under reflux for 8 hr. Solids were removed and the solution was evaporated to dryness. Extraction with ether (2 × 300 ml.) and evaporation gave a residue which sublimed (120°/0·4 mm.) to give orange needles (0·07 g.) of the *5-ethoxy-7-methoxy-derivative*, m.p. 145—146° (from ether) (Found: C, 46·7; H, 4·7; N, 34·1. $C_8H_9N_5O_2$ requires C, 46·4; H, 4·4; N, 33·8%).

5,7-Dimethoxy- (*and Diethoxy-*) *3-methylpyrimido*[5,4-e]-as-*triazine*.— 4-Hydrazino-2-methoxy-5-nitropyrimidine (5·0 g.), triethyl orthoacetate (30 ml.), and ethanol (80 ml.) were boiled under reflux for 1 hr. Concentration gave *4-α-ethoxyethylidenehydrazino-2-methoxy-5-nitropyrimidine* (5·3 g.), m.p. 103—104° (from ethanol–ether) (Found: N, 27·6. $C_9H_{13}N_5O_4$ requires N, 27·4%). The ethoxyethylidene compound (0·8 g.) was hydrogenated over palladium–charcoal in anhydrous tetrahydrofuran (250 ml.) for 5 hr. at 20°/760 mm. The mixture was stirred with barium oxide (15 g.) and silver oxide (10 g.) at 20° for 12 hr. The filtrate, methanol (50 ml.), and fresh silver oxide (3 g.) were stirred at 20° for 24 hr. Evaporation of the filtered solution and sublimation (105°/0·1 mm.) of the residue gave the slightly hygroscopic *dimethoxy-3-methylpyrimidotriazine* (0·25 g.), m.p. 160° (Found: C, 46·1; H, 4·25; N, 33·4. $C_8H_9N_5O_2$ requires C, 46·4; H, 4·4; N, 33·8%). Transetherification (ethanol; 15 hr.) as for the 3-demethyl homologue and final sublimation (110°/0·4 mm.) gave the *diethoxy-3-methylpyrimidotriazine* (75%), m.p. 140—141° (from light petroleum) (Found: C, 51·0; H, 5·7; N, 29·3. $C_{10}H_{13}N_5O_2$ requires C, 51·05; H, 5·6; N, 29·8%).

5-Ethoxy-3,7-dimethylpyrimido[5,4-e]-as-*triazine*.— 5-Methoxy-3,7-dimethylpyrimidotriazine [1] (0·1 g.), silver oxide (0·4 g.), and ethanol (40 ml.) similarly gave in 11 hr. the orange *5-ethoxy-homologue* (0·07 g.), m.p. 148—150° (from light petroleum) (Found: C, 52·4; H, 5·4; N, 33·8. $C_9H_{11}N_5O$ requires C, 52·7; H, 5·4; N, 34·1%).

Transetherification of 4-Methoxypteridine.—4-Methoxypteridine [11] (0·14 g.), silver oxide (0·7 g.), and propanol (40 ml.) were boiled for 3 hr. Filtration, evaporation, and sublimation (60°/0·5 mm.) gave *4-propoxypteridine* (88%), m.p. 66—67·5° (from ether) (Found: C, 56·95; H, 5·6; N, 29·3. $C_9H_{10}N_4O$ requires C, 56·8; H, 5·3; N, 29·5%).

Under similar conditions, 2-methoxypteridine [11] gave a deep violet product which resisted sublimation, and 6-methoxypteridine [14] gave only unidentified materials bearing no propyl group (¹H n.m.r. spectrum).

Transetherification of Methoxypyrimidines.—2-Methoxy-5-nitropyrimidine [7] (1·4 g.), silver oxide (4·0 g.), and propanol (30 ml.) were boiled under reflux for 16 hr. Removal of solvent from the filtered solution gave a residue which was extracted with ether (300 ml.). The extract, washed with aqueous sodium hydrogen carbonate and then with water, was dried over barium oxide and later phosphorus pentoxide. Evaporation and distillation gave *5-nitro-2-propoxypyrimidine* (0·92 g.), b.p. 91°/0·4 mm., m.p. 37—38° (Found: C, 45·8; H, 5·0; N, 22·7. $C_7H_9N_3O_3$ requires C, 45·9; H, 5·0; N, 22·9%). 4-Methoxy-5-nitropyrimidine [8] similarly gave *5-nitro-4-propoxypyrimidine* (58%), b.p. 116°/5 mm., m.p. *ca.* 20° (Found: C, 46·1; H, 5·5; N, 22·5. $C_7H_9N_3O_3$ requires C, 45·9; H, 5·0; N, 22·9%); 2,4-dimethoxy-5-nitropyrimidine [4] gave (in 20 hr.) *5-nitro-2,4-dipropoxypyrimidine* (30%), b.p. 115—117°/0·25 mm. (Found: C, 49·8; H, 6·6; N, 17·8. $C_{10}H_{15}N_3O_4$ requires C, 49·8; H, 6·3; N, 17·4%); and 2,4-dimethoxy-6-methyl-5-nitropyrimidine [9] gave (in 17 hr.) *4-methoxy-6-methyl-5-nitro-2-propoxypyrimidine* (81%), b.p. 104—106°/0·3 mm. (Found: C, 47·9; H, 6·1; N, 18·7. $C_9H_{13}N_3O_4$ requires C, 47·6; H, 5·8; N, 18·5%).

4-Chloro-6-methoxy-5-nitropyrimidine [10] (1·0 g.), silver oxide (2 g.), and ethanol (50 ml.) were boiled under reflux for 36 hr. Filtration and evaporation gave *4-ethoxy-6-methoxy-5-nitropyrimidine* (0·8 g.), m.p. 69—71° (from ether) (Found: C, 42·0; H, 4·7; N, 21·15. $C_7H_9N_3O_4$ requires C, 42·2; H, 4·55; N, 21·1%).

The following methoxypyrimidines were unchanged by silver oxide–alkanol under the conditions indicated: 2-methoxypyrimidine [15] (ethanol; 120°; 62 hr.); 2,4-dimethoxy-6-methylpyrimidine [16] (boiling ethanol; 5 hr.); 4,6-dimethoxy-5-nitropyrimidine [17] (boiling propanol; 22 hr.); 4-methoxy-2,6-dimethyl-5-nitropyrimidine [18] (boiling propanol; 60 hr.).

3,5-Dinitro-2-propoxypyridine.— 2-Methoxy-3,5-dinitropyridine [12] (1·7 g.) underwent transetherification when boiled with silver oxide (4·0 g.) in propanol (50 ml.) for 100 hr. The residue from evaporation of the filtered solution was extracted with ether (200 ml.). The extract, washed with aqueous sodium hydrogen carbonate and with water, was dried successively over barium oxide and phosphorus pentoxide. Distillation gave the propoxypyridine [12] (1·1 g.), b.p. 113—115°/0·01 mm. (Found: C, 42·0; H, 4·2; N, 18·3. Calc. for $C_8H_9N_3O_5$: C, 42·3; H, 4·0; N, 18·5%).

Transetherification of the following compounds was unsuccessful in boiling propanol: 2-methoxy-5-nitropyridine [19] (38 hr.; gave a little 1,2-dihydro-1-methyl-5-nitro-2-oxopyridine [20]); 4-methoxy-3-nitropyridine [21] (26 hr.); 2,4-dinitroanisole [22] (24 hr.); and 2,6-dinitroanisole [22] (70 hr.).

5-Hydroxy-7-methoxypyrimido[5,4-e]-as-*triazine*.—(*a*) 5,7-Dimethoxypyrimido[5,4-*e*]-*as*-triazine (0·45 g.) was stirred in 0·3N-sodium hydroxide at 20° for 24 hr. The solution

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was adjusted to pH 2 with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was extracted with boiling acetone (2 × 100 ml.). Concentration of the extracts to 50 ml. and refrigeration gave the yellow 5-*hydroxy*-7-*methoxypyrimidotriazine* (0·4 g.), m.p. 185° (decomp.) (from methanol) (Found: C, 40·0; H, 3·0; N, 39·05. $C_6H_5N_5O_2$ requires C, 40·2; H, 2·8; N, 39·1%).

(*b*) 4-Ethoxymethylenehydrazino-2-methoxy-5-nitropyrimidine (2·0 g.) was hydrogenated at 20°/760 mm. over palladium–charcoal (10%; 0·5 g.) in anhydrous tetrahydrofuran for 15 hr. The mixture was stirred with silver oxide (4·0 g.) and barium oxide (10 g.) at 20° for 12 hr. The filtrate was mixed with methanethiol (2·0 g.), kept at 20° for 15 hr., then boiled briefly to remove the excess of methanethiol, stirred at 20° with silver oxide (5·0 g.) for 12 hr., and filtered while boiling. The residue from evaporating the filtrate gave orange needles of 7-*methoxy*-5-*methylthiopyrimido*[5,4-e]-as-*triazine* (0·80 g.), m.p. 185—186° (from ether) (Found: C, 39·9; H, 3·4; N, 33·45. $C_7H_7N_5OS$ requires C, 40·2; H, 3·4; N, 33·5%). This thioether (0·27 g.) was stirred in 0·03N-sodium hydroxide (60 ml.) at 20° for 15 hr. The solution was adjusted with hydrochloric acid to pH 2 and evaporated under reduced pressure. The residue crystallised from water to give the 5-hydroxy-7-methylpyrimidotriazine (0·19 g.), identified by mixed m.p. and i.r. spectra.

5,7-*Dihydroxypyrimido*[5,4-e]-as-*triazine*.—(*a*) 5-Hydroxy-7-methoxypyrimido[5,4-*e*]-*as*-triazine (0·20 g.) or an equivalent amount of its 7-ethoxy-homologue and 5N-hydrochloric acid (25 ml.) were kept at 20° for 12 hr. The residue from evaporation crystallised from methanol to give the dihydroxypyrimidotriazine (0·16 g.), m.p. *ca.* 340° (decomp.), identical with authentic material [6] (u.v., i.r., and ^{1}H n.m.r. spectra) (Found: C, 36·3; H, 2·1; N, 42·75. Calc. for $C_5H_3N_5O_2$: C, 36·4; H, 1·8; N, 42·4%).

(*b*) 5,7-Dimethoxypyrimido[5,4-*e*]-*as*-triazine (0·10 g.) or its dipropoxy-homologue (0·11 g.), methanol (5 ml.), and 5N-hydrochloric acid (10 ml.) were kept at 20° for 24 hr. Evaporation and crystallisation of the residue from ethanol gave the dihydroxy-compound (0·05 g.).

4-*Hydrazino*-2-*hydroxy*-6-*methyl*-5-*nitropyrimidine*.—(*a*) 2,4-Dimethoxy-6-methyl-5-nitropyrimidine [9] (25 g.), hydrazine hydrate (7·0 g.), and ethanol (800 ml.) were boiled under reflux for 2 hr. After treatment with charcoal, the solution was concentrated to *ca.* 300 ml. and chilled. Yellow 2,4-*dihydrazino*-6-*methyl*-5-*nitropyrimidine* (1·0 g), m.p. 198° (decomp.) (from methanol) (Found: C, 30·0; H, 4·6; N, 48·6. $C_5H_9N_5O_2$ requires C, 30·15; H, 4·55; N, 49·2%) was filtered off. Evaporation of the filtrate under reduced pressure gave 4-*hydrazino*-2-*methoxy*-6-*methyl*-5-*nitropyrimidine* (13 g.) m.p. 136—138° (from methanol) (Found: C, 35·3; H, 4·5. $C_6H_9N_5O_3$,0·25H_2O requires C, 35·4; H, 4·7%). A solution of this compound (0·50 g.) in 2·5N-hydrochloric acid (20 ml.) was kept at 20° for 48 hr. and then evaporated to dryness. The residual hydrochloride was recrystallised from dilute aqueous sodium hydrogen carbonate to give 4-*hydrazino*-2-*hydroxy*-6-*methyl*-5-*nitropyrimidine* (0·4 g.), m.p. 228—229° (from water) (Found: C, 32·3; H, 3·7; N, 37·9. $C_7H_7N_5O_3$ requires C, 32·4; H, 3·8; N, 37·8%). Alternatively, the hydrazinomethoxy-compound (5·0 g.), sodium iodide (4·0 g.), and acetic acid (70 ml.) were boiled under reflux for 30 min. The residue from evaporation was triturated with boiling methanol (50 ml.). The whole mixture was allowed to cool and the solid hydriodide was collected. Recrystallisation from aqueous sodium hydrogen carbonate gave the same hydroxypyrimidine (3·0 g.). Hydrolysis of the same substrate in boiling 5N-hydrochloric acid gave 6-methyl-5-nitrouracil [23] (>95%), identified by mixed m.p. (*ca.* 290°) and i.r. spectra.

(*b*) 4-Methoxy-6-methyl-5-nitro-2-propoxypyrimidine (0·9 g.), hydrazine hydrate (0·2 g.), and ethanol (30 ml.) were boiled under reflux for 5 hr. Clarification and concentration to 10 ml. gave 4-*hydrazino*-6-*methyl*-5-*nitro*-2-*propoxypyrimidine* (0·63 g.), m.p. 107—109° (from ethanol) (Found: C, 42·2; H, 6·05; N, 31·3. $C_8H_{13}N_5O_3$ requires C, 42·3; H, 5·8; N, 30·8%). Hydrolysis with 2·5N-hydrochloric acid as for the 2-methoxy-homologue gave the 2-hydroxy-compound (60%), identical with that prepared by route (*a*).

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