mechanistic details of the net reaction are currently under investigation.

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Novel Synthetic Route to Heterocycles *via* Intramolecular Cycloaddition of Azalogs of Hexatriene. New Syntheses of Purines and Pyrazolo[3,4-*d*]pyrimidines

Sir:

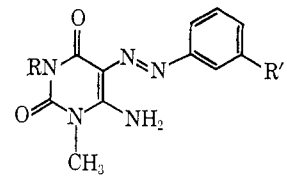
We would like to report a novel synthetic route to heterocycles which involves an intramolecular cycloaddition of azalogs of hexatriene and is of potential utility. This communication describes new syntheses of purines and pyrazolo[3,4-*d*]pyrimidines as typical examples of this route.

Refluxing 6-amino-1,3-dimethyl-5-phenylazouracil (Ia) in excess dimethylformamide dimethylacetal[1] for 5 hr gave 1,3-dimethyl-6-dimethylaminomethyleneamino-5-phenylazouracil (IIa) (mp 203°, 85%). Similarly, the 5-*m*-tolylazo analog (IIb) (mp 174°, 75%) was obtained from the condensation of 6-amino-1,3-dimethyl-5-*m*-tolylazouracil (Ib) (mp 257°) and dimethylformamide dimethylacetal. Fusion of IIa at 210–220° for 15 min under exclusion of moisture gave a mixture of 8-dimethylaminotheophylline (IIIa)[2] (mp >300°, 40%) and 1,3-dimethyl-7-dimethylamino-5-phenyl-5,6(or 5,8)-dihydro-6-azalumazine (IVa) (mp 251°, 42%) while releasing aniline (*ca.* 20%). Similarly, IIb gave a mixture of IIIa (45%) and the corresponding 5-*m*-tolyldihydro-6-azalumazine derivative (IVb) (mp 197°, 43%) together with *m*-toluidine (*ca.* 25%). In these reactions, lower melting 7-anilinotheophyllines (Va,b) (mp 170° dec) were isolated from the initial reaction mixtures. Although these compounds were isomeric with the starting materials (IIa,b) from their microanalyses and mass spectrometry, their ir spectra were quite different from those of IIa,b and showed similarity with the general pattern of ir spectra of 7-substituted theophyllines. Heating the isolated Va,b at 220° instantly gave IIIa and anilines. This conversion involves the thermal cleavage of the nitrogen–nitrogen bond of V to yield the theophylline and the respective nitrenes which abstract hydrogens probably from the substrate itself to give anilines. Therefore, Va and b are intermediates in the conversion of IIa and b to IIIa (Scheme I).

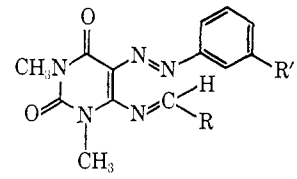
The structures of compounds IVa and b were ascertained by elemental analyses, molecular weight determination, and fragmentation study by mass spectrometry and from ir (the presence of NH absorption at 3270 cm^{-1}) and nmr spectra. Furthermore, the following transformation of IVa and b was carried out; reduction of IVa and b with sodium dithionite in formic acid gave 8-formylamino-7-phenyltheophylline (VIa) (mp 215°, 31%) and 8-formylamino-7-*m*-tolyltheophylline (VIb) (mp 208°, 32%).[3]

The heating of Ia with excess benzaldehyde at 220° for 3 hr, followed by cooling, caused to separate 8-phenyltheophylline (IIIc)[4] (mp >330°, 53%). From the filtrate, 1,3-dimethyl-5,7-diphenyl-5,6(or 5,8)-dihydro-6-azalumazine (IVc) (mp 248°, 25%) was isolated. Reduction of IVc with sodium dithionite in formic acid gave likewise 7,8-diphenyltheophylline (VIc)[5] (mp 223°, 25%). Similarly, the fusion of Ia with excess *p*-chlorobenzaldehyde gave 8-(*p*-chlorophenyl)-

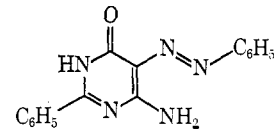
Scheme I



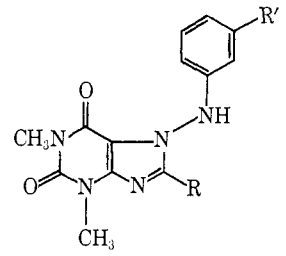
Ia, R = CH_3; R′ = H
b, R = CH_3; R′ = CH_3
c, R = H; R′ = H



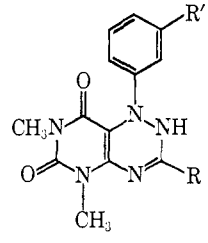
IIa, R = $(CH_3)_2N$; R′ = H
b, R = $(CH_3)_2N$; R′ = CH_3



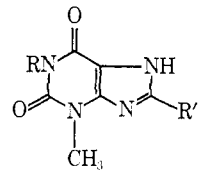
Id



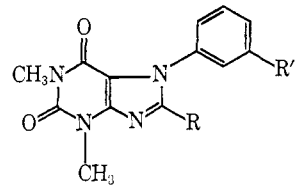
Va, R = $(CH_3)_2N$; R′ = H
b, R = $(CH_3)_2N$; R′ = CH_3



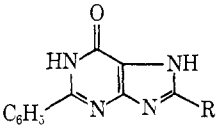
IVa, R = $(CH_3)_2N$; R′ = H
b, R = $(CH_3)_2N$; R′ = CH_3
c, R = C_6H_5; R′ = H
d, R = *p*-ClC_6H_4; R′ = H



IIIa, R = CH_3; R′ = $(CH_3)_2N$
c, R = CH_3; R′ = C_6H_5
d, R = CH_3; R′ = *p*-ClC_6H_4
e, R = H; R′ = C_6H_5
f, R = H; R′ = *p*-ClC_6H_4
g, R = H; R′ = 3,4-$Cl_2C_6H_3$
h, R = H; R′ = *p*-$CH_3OC_6H_4$
i, R = H; R′ = *p*-$(CH_3)_2NC_6H_4$



VIa, R = NHCHO; R′ = H
b, R = NHCHO; R′ = CH_3
c, R = C_6H_5; R′ = H



IIIj, R = C_6H_5
k, R = 3,4-$Cl_2C_6H_3$

(1) H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann, and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).
(2) (a) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1347 (1968); (b) F. Yoneda, M. Higuchi, T. Matsumura, and K. Senga, *Bull. Chem. Soc. Jap.*, **46**, 1836 (1973).
(3) This is best rationalized by assuming initial reductive nitrogen–nitrogen bond cleavage to a 5-anilino-6-amidinouracil derivative, followed by formylation and intramolecular cyclization with elimination of dimethylamine. An analogous ring contraction was observed by the reduction of other 6-azalumazine derivatives. F. Yoneda, Y. Sakuma, M. Ueno, and S. Nishigaki, *Chem. Pharm. Bull.*, **21**, 926 (1973).
(4) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, **86**, 4721 (1964).
(5) E. C. Taylor and F. Yoneda, *J. Org. Chem.*, **37**, 4464 (1972).

Table I. Purine Synthesis from 6-Amino-5-phenylazopyrimidines and Aryl Aldehydes

Starting material	Aryl aldehyde	Product[a]	Yield (%)
Ic	Benzaldehyde	IIIe	70
Ic	*p*-Chlorobenzaldehyde	IIIf	83
Ic	3,4-Dichlorobenzaldehyde	IIIg	95
Ic	*p*-Anisaldehyde	IIIh	78
Ic	*p*-Dimethylaminobenzaldehyde	IIIi	93
Id	Benzaldehyde	IIIj	70
Id	3,4-Dichlorobenzaldehyde	IIIk	78

[a] None of products melted below 330°.

Table II. Pyrazolo[3,4-*d*]pyrimidine Synthesis from 6-(Benzylidenehydrazino)-1,3-dimethyluracil and Aryl Aldehydes

Starting material	Aryl aldehyde	Product	Mp, °C	Yield (%)
VIIa	Benzaldehyde	VIIIa	193	83
VIIb	*p*-Chlorobenzaldehyde	VIIIb	181	87
VIIc	3,4-Dichlorobenzaldehyde	VIIIc	194	85
VIId	*p*-Anisaldehyde	VIIId	160	84
VIId	*p*-Chlorobenzaldehyde	VIIIe	173	75
VIIe	Benzaldehyde	VIIIf	326	67

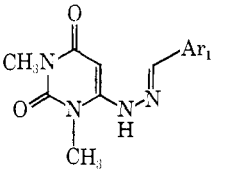
theophylline (IIId) (mp >330°, 60%) and 7-(*p*-chlorophenyl)-1,3-dimethyl-5-phenyl-5,6-dihydro-6-azalumazine (IVd) (mp 250°, 15%).

This new purine synthesis appears to be general and is equally applicable to other 6-amino-5-phenylazopyrimidines. Namely, fusion of 6-amino-1-methyl-5-phenylazouracil (Ic) and 6-amino-4-hydroxy-2-phenyl-5-phenylazopyrimidine (Id) with excess aryl aldehydes under the same conditions gave the corresponding purine derivatives (IIIe–k) in good yields (see Table I). In these cases, the corresponding 6-azalumazine derivatives were not obtained.

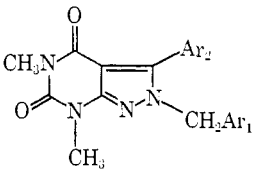
Next, we have used 5-benzylidene derivatives of 6-(benzylidenehydrazino)uracils for this reaction. The refluxing of 6-(benzylidenehydrazino)-1,3-dimethyluracil (VIIa)[6] with a slight excess of benzaldehyde in dimethylformamide for 3 hr gave exclusively 2-benzyl-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (VIIIa) in excellent yield. Similarly, the heating of other 6-(benzylidenehydrazino)-1,3-dimethyluracil derivatives (VIIb–e)[6] with several aryl aldehydes in dimethylformamide gave the corresponding 3-aryl-2-benzylpyrazolo[3,4-*d*]pyrimidine derivatives (VIIIb–f) (see Table II). The structures of VIII were established by comparison with authentic samples prepared by the benzylation[7] of 3-aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones[6] with the corresponding benzyl halides in dimethylformamide in the presence of potassium carbonate. Although we did not detect any other compounds in the reactions, the possible intermediates must be 5-benzylidene derivatives (IX)[8] of VII in consideration of the products and of the next reaction described below.

5-Benzylidene-6-(benzylidenehydrazino)-3-methyluracil (Xa) (mp 277–278°) and 5-(*p*-chlorobenzylidene)-6-(*p*-chlorobenzylidenehydrazino)-3-methyluracil (Xb) (mp 298°), which were prepared by the condensation of the corresponding 6-(benzylidenehydrazino)-3-methyluracils and aryl aldehydes in ethanol at 90°, were heated under reflux in dimethylformamide for 8 hr; dilution with ethanol caused separation of 2-benzyl-5-methyl-3-phenyl- (XIa) (mp 229–230°, 68%) and 2-(*p*-chlorobenzyl)-3-(*p*-chlorophenyl)-5-methyl-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (XIb) (mp 267°, 72%), respectively. Their structures were confirmed by the transformation of XIa and XIb into VIIIa and VIIIb by the methylation with methyl iodide in dimethylformamide in the presence of potassium carbonate. The refluxing of the 6-(benzylidenehydrazino)-3-methyluracils with aryl aldehydes in dimethylformamide gave directly XI (Scheme II).

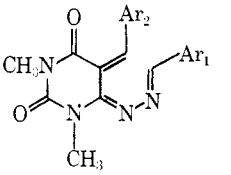
Scheme II



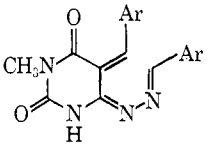
VIIa, $Ar_1 = C_6H_5$
b, $Ar_1 = p\text{-}ClC_6H_4$
c, $Ar_1 = 3,4\text{-}Cl_2C_6H_3$
d, $Ar_1 = p\text{-}CH_3OC_6H_4$
e, $Ar_1 = p\text{-}(CH_3)_2NC_6H_4$



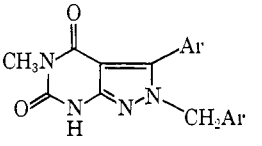
VIIIa, $Ar_1 = C_6H_5$; $Ar_2 = C_6H_5$
b, $Ar_1 = p\text{-}Cl\text{-}C_6H_4$; $Ar_2 = p\text{-}ClC_6H_4$
c, $Ar_1 = 3,4\text{-}Cl_2\text{-}C_6H_3$; $Ar_2 = 3,4\text{-}Cl_2C_6H_3$
d, $Ar_1 = p\text{-}CH_3O\text{-}C_6H_4$; $Ar_2 = p\text{-}CH_3OC_6H_4$
e, $Ar_1 = p\text{-}CH_3OC_6H_4$; $Ar_2 = p\text{-}ClC_6H_4$
f, $Ar_1 = p\text{-}(CH_3)_2N\text{-}C_6H_4$; $Ar_2 = C_6H_5$



IX



Xa, Ar = C_6H_5
b, Ar = $p\text{-}ClC_6H_4$



XIa, Ar = C_6H_5
XIb, Ar = $p\text{-}ClC_6H_4$

These new cyclizations may involve a possible [$\pi 4 + \pi 2$] cycloaddition of azalogs of hexatriene, followed by thermal 1,5 shift of a hydrogen atom to give the respective heterocycles. The syntheses of other heterocycles by this route are currently under investigation.

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(6) F. Yoneda and T. Nagamatsu, *Synthesis*, 300 (1973).
(7) In the benzylation, the isomeric 1-benzylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives were obtained as the minor products
(8) Attempts to obtain IX by the condensation of VII with aryl aldehydes at lower temperatures were unsuccessful, with the starting materials being recovered.

Tight Binding of Hydroxyl Protons in *gem*-Diols and Hemiacetals

Sir:

The hydroxyl protons of *gem*-diols and hemiacetals are located in a tighter binding potential than are