DIETHYLAMINE AND TRIETHYLAMINE AS SOURCES OF THE DIENOPHILE COMPONENT IN THE REVERSE AZADIENE SYNTHESIS WITH DIMETHYLPYRIMIDO[4,5-e]- AND -[5,4-e]-1,2,4-TRIAZINEDIONES AND 1,2,4,5-TETRAZINES*

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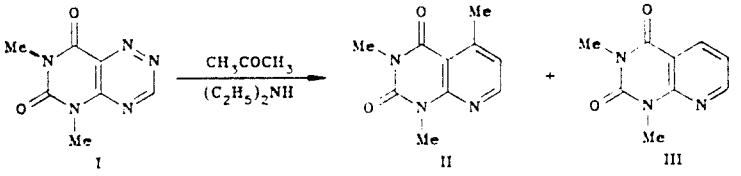
Diethylamine (DEA) and triethylamine (TEA) can function as sources for the two-carbon component in the reverse azadiene synthesis. Reaction of 5,7-dimethylpyrimido[4,5-e]-1,2,4-triazine-6,8-dione, 6,8-dimethylpyrimido-[5,4-e]-1,2,4-triazine-5,7-dione, or 1,2,4,5-tetrazine with an excess of DEA or TEA gives, respectively, the pyrido[2,3-d]pyrimidine-2,4-dione, pyrido[3,2-d]pyrimidine-2,4-dione, or pyridazine. The presence of an oxidant (atmospheric oxygen, MnO_2, or an electron-acceptor solvent) is required for the reaction to occur. Reaction of 5,7-dimethylpyrimido[4,5-e]-1,2,4-triazinedione with piperidine, morpholine, or under certain conditions DEA, results in opening of the triazine ring to give uracils with an amidine group in the 6-position.

It has been reported [3] that the reaction of 5,7-dimethylpyrimido-[4,5-e]-1,2,4-triazine-6,8-dione (isofervenulin, I) with acetone in the presence of excess diethylamine (DEA) gives, in addition to 1,3,5-trimethylpyrido[2,3-d]pyrimidine-2,4-dione (II), significant amounts of 1,3-dimethylpyrido[2,3-d]pyrimidine-2,4-dione (III). Both of these products arise by reverse azadiene synthesis, but although the formation of the trimethyl compound (II) is readily understood, that of the dimethyl compound (III) is most unexpected, since this requires a two-carbon dienophile component $CH_2 = CH–X$, where X can be OR or NR_2. The purpose of the present investigation was to establish a possible pathway for the formation of (III).



We have found that isofervenulin (I) does not react with pure acetone. Consequently, DEA is involved in the formation of (III). It was also found that (III) is the main product (85%), together with the amidine (V), when (I) is boiled with a 240-fold excess of DEA† (Table 1, experiment 1). The formation of (V) may be regarded as the result of addition of DEA to $C_{(3)}$ to (I), followed by ejection of nitrogen from the adduct (IV) (see scheme below).

The structures of (III) and (V) were assigned on the basis of their spectral data, and confirmed by x-ray diffraction analysis (Figs. 1 and 2). The geometric parameters of the dimethyluracil ring in (III) and (V) are similar to those found for fervenulin [4]. The bond lengths in the diethylamidine group in (V) indicate considerable π-electron delocalization in the $C_{(6)}–N_{(7)}–C_{(8)}–$

*For preliminary communication, see [1, 2].

†When smaller amounts of DEA are used, the isofervenulin does not dissolve completely.

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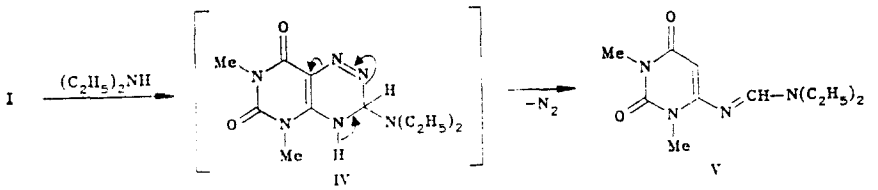


$N_{(9)}$ chain. The fragment $C_{(6)}N_{(7)}C_{(8)}N_{(9)}$ is not coplanar with the plane of the uracil ring, forming a dihedral angle with it of 22.6°. In turn, the plane passing through atoms $C_{(8)}N_{(9)}C_{(10)}C_{(12)}$ of the diethylamino group forms dihedral angles of 33.0° and 10.8° with the plane of the uracil ring and that in which atoms $C_{(6)}N_{(7)}C_{(8)}N_{(9)}$ of the amidine group lie, respectively. The torsion angle of $C_{(6)}N_{(7)}C_{(8)}N_{(9)}$ equals 169.0°.

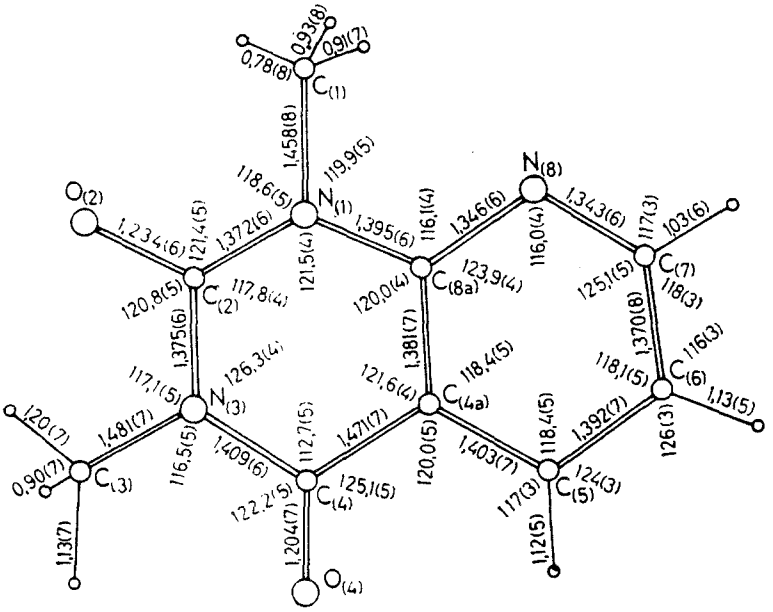


Fig. 1. Bond lengths and valence angles in (III).

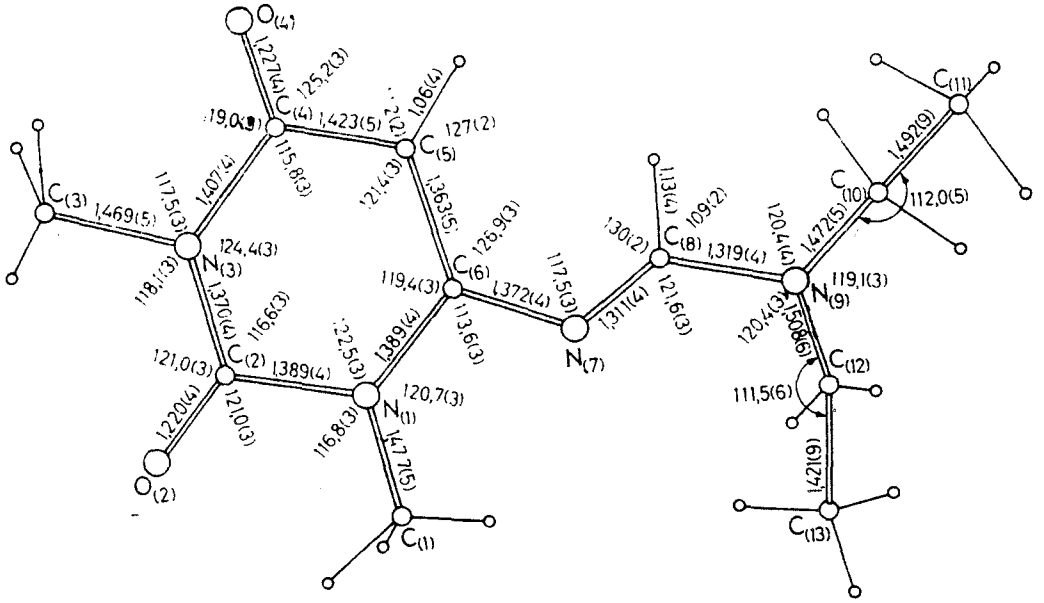


Fig. 2. Bond lengths and valence angles in (V).

TABLE 1. Reaction of Isofervenulin (I) with DEA *

Expt. No.	Solvent	Time, h	T, °C	Yield, %		Recovered (I), %
				III	V	
1	—	15	55...56	85	10	—
2	—	15	55...56	22	71	—
3**	—	15	100	34	66	—
4	—	85	55...56	32	68	—
5**	—	85	55...56	12	68	—
6	$CHCl_3$	28	61...62	70	Trace	—
7***	CCl_4	12	76...77	60	—	40
8***	CCl_4	12	76...77	75	—	—
9	C_6H_6	26	80...81	—	25	70
10	C_6H_6+γ-MnO_2	7	80...81	20	—	5
11	CH_3CN	26	81...82	—	45	40
12	CH_3OH	27	63...64	—	—	100
13	Dioxane	27	100...101	75	24	—

*Amounts of (I) of 0.2 g (1 mmole) were used in each experiment, except for Expts. 4 and 5, in which 8 mg (0.04 mmole) was used (the product ratios in Expts. 4 and 5 were determined from the PMR spectra). The DEA used was purified via its hydrochloride, apart from Expts. 1 and 3, in which redistilled DEA was used. Experiments 6-13 were carried out in 40 ml of dry solvent [(I):DEA ratio 107, except for Expt. 7, when the ratio was 49], and Expts. 1-5 were carried out without a solvent [(I):DEA ratio 243]. In Expt. 10, 0.5 g (5.7 mmoles) of γ-MnO_2 was added.

**The reaction mixture was placed in an ampule which was immersed in liquid nitrogen, frozen, and air pumped out (<1 mm) for 10 min. Degassing was repeated three times. The ampul was sealed, and the reaction carried out under the conditions given here.

***The solid which separated when the reaction was complete was filtered off. The filtrate was evaporated, then treated as described for Expt. 1.

All ten atoms of the condensed heterocycles in (III) are coplanar (the maximum departure from the mean plane is 0.018 Å), and the dihedral angle between the mean planes of both rings is 1.3°. There is little alternation of the lengths of the single and double bonds in the pyridine ring.

We have proposed two possible explanations for the formation of compound (III). The first is that commercial DEA contains impurities which react with (I) to give the pyridouracil (III). The second explanation requires that DEA be converted under the reaction conditions into an enamine, which by analogy with other enamines [3, 5-7] could function as a good dienophile.

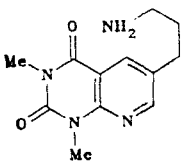
The nature and amounts of impurities in commercial DEA were determined by detailed GLC examination.

Impurities in Diethylamine. The twice-distilled DEA used here contained six impurities which in total amounted to 0.3% (by GLC). The principal impurities were ethylamine and TEA. Ethylamine does not participate in the reverse azadiene synthesis [8]. TEA, although it does react with (I) (see below), does not react so much more rapidly than DEA that the formation of significant amounts of (III) could be explained on this basis. Calculation shows that if other impurities were involved in the formation of the pyridouracil (III), the yield of the latter could not exceed 5%. In addition, when only a tenfold molar excess of DEA is used in the reaction (which was followed by PMR spectroscopy), the yield of (III) was 96%, and of (V) 4%. The formation of such large amounts of (III) requires the presence of around 10% of dienophilic impurities (!), which is not in accordance with the GLC results.

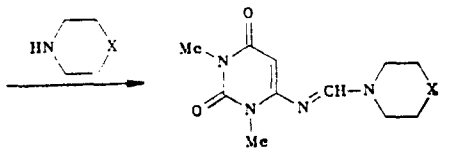
In order to eliminate the question of impurities, we carried out further purification of the DEA. Twice-recrystallized DEA hydrochloride was converted into the base, and distilled. This DEA, according to GLC, had impurity levels an order of magnitude less. On heating (I) with a 240-fold excess of this DEA, the yield of (III) decreased by a factor of four only (Table 1, Expts. 1 and 2). A similar experiment carried out in a sealed ampul and followed by PMR (Table 1, Expt. 4) showed an even higher yield of the azadiene synthesis product (32%). The decreased yield of (III) in Expt. 2, as compared with Expt. 4, is

clearly due to unavoidable losses of the dihydrouracil in the course of preparative isolation. These findings show conclusively that (III) is formed from DEA itself.

Use of Other Amines. In order to elucidate the mechanism of formation of the dienophile component and for the goal-directed synthesis of substituted pyridouracils, we examined the reactions of (I) with other amines. For example, reaction of (I) with piperidine would be expected to give the pyridouracil (VI) which has a γ-aminopropyl substituent in the pyridine ring. However, when (I) was reacted with an excess of piperidine in chloroform or in the absence of a solvent, near-quantitative yields of the amidine (VIIa) were obtained. Similarly, the reaction with morpholine gave the amidine (VIIb) exclusively.



VI

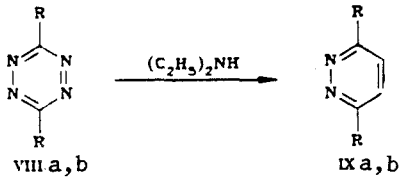


VII a X=CH_2, b X=O

Heating (I) with a 180-fold excess of twice-distilled TEA for 15 h gives (III) as the sole reaction product (80%). Under the same conditions, the use of TEA which had been purified by recrystallization of the hydrochloride followed by conversion to the base resulted in an extremely slow reaction, only 3-5% of (III) being formed after 15 h. TEA supplied by Fluka reacted with (I) at 50°C at 1/7 the rate of TEA which had not been specially purified.

It has been shown by GLC that the total impurity levels in home-produced TEA are as much as 0.6%. The purified TEA, however, had figures similar to those of the Fluka sample (~0.09% DEA). Hence, as in the case of DEA, the impurities present in the TEA catalyze its conversion into the dienophile, and facilitate its participation in the reverse azadiene synthesis.

Use of Other Azadienes. It has been reported [9] that 3,6-diphenyltetrazine (VIIIa) reacts slowly with DEA, giving 15% of 3,6-diphenylpyridazine (IXa) after boiling the reaction mixture for a week. When reacted with TEA, however, (VIIIa) gave the compound (IXa) in trace amounts only.



VIII a,b IX a,b

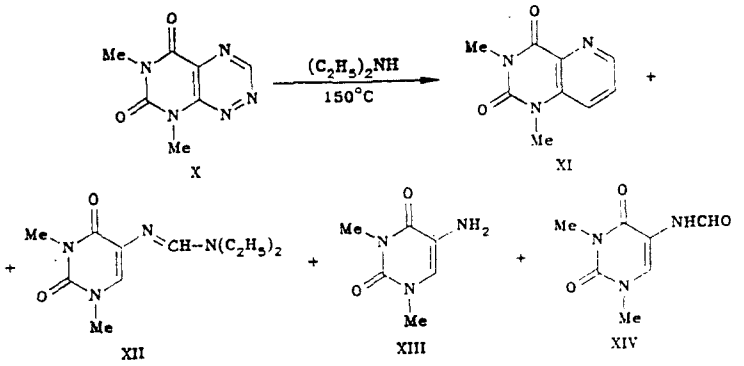
VIII, IX: a) R = C_6H_5; b) R = 2-pyridyl

We have found that impurities in DEA and TEA accelerate the reactions of the tetrazines (VIIIa, b) with amines, as in the case of isofervenulin described above. For example, on boiling the tetrazine (VIIIa) with a 240-fold excess of redistilled DEA for 50 h, the yield of the pyridazine (IXa) was 82%, whereas with purified DEA (such as was probably used by Haddadin et al. [9]) an 18% yield was obtained (Table 2, Expts. 1 and 2). Similar results were obtained with redistilled and further purified TEA (Table 2, Expts. 6 and 7). Using 3,6-di-(2-pyridyl)tetrazine (VIIIb) in this reaction gave 78% of the pyridazine (IXb).

6,8-Dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7-dione (fervenulin, X) did not give the reverse azadiene synthesis products with acetone in the presence of DEA under mild conditions [3]. Further experiments have shown that under severe conditions (sealed ampul, 150°C, 24 h) fervenulin reacts with DEA to give a mixture of compounds, from which have been isolated 1,3-dimethylpyrido-[3,2-d]pyrimidine-2,4-dione (XI, 11%), the amidine (XII) (9%), and 1,3-dimethyl-5-aminouracil (XIII, 3%) and its formyl derivative (XIV, 12%). It appears that the amidine (XII) is formed in a similar way to that proposed above for the amidine (V), while (XIII) and (XIV) are its hydrolytic cleavage products (see scheme below).

It is likely that the ability of DEA and TEA to function as sources of the dienophile component in the reverse azadiene synthesis is not limited to compound (I), but is of a general nature.

Effects of Solvents and Other Factors. The solvent used has a major effect on the azadiene synthesis with alkylamines. The reaction rate is greater in chloroform, and especially in CCl_4. This is well seen in the case of tetrazines (Table 2, Expts. 2-4). This rate increase is seen with both commercial and purified DEA. In the case of (I), acceleration of the reaction when chloroform or CCl_4 is used reduces almost to zero the formation of the amidine (V) as a by-product (Table 1, Expts.



6-8). It appears that, in addition to increasing the rate of the azadiene synthesis, when the reaction is carried out in chloroform or CCl_4 the formation of (V) is inhibited. Dioxane has a marked effect, and when purified DEA is used in this solvent the ratio of yields of amidine (V) to dihydrouracil (III) is changed considerably in favor of the latter (Table 1, Expt. 13). In benzene or acetonitrile, the reaction is extremely slow, and the sole product is the amidine (V) (Table 1, Expts. 9 and 11). When an oxidant (γ-MnO_2) is added to the reaction mixture, the azadiene synthesis product is also formed in benzene (Table 1, Expt. 10; Table 2, Expt. 5). In methanol, (I) failed to react (Table 1, Expt. 12).

Figure 3 shows the effects of the solvent on the rate of reaction of (I) with purified TEA, measured by PMR. The reaction rates of (I) and (III) decrease with respect to the solvent in the following order:

$$CCl_4 > HMPTA\text{-}D_{18} > DMSO\text{-}D_6 > C_5D_5N > CDCl_3 \gg C_6D_6 > CD_3CN.$$

Mechanism of Conversion of Alkylamines to the Dienophile. The DEA enamine exists predominantly as the Schiff base $C_2H_5N{=}CHCH_3$ [5, 10]. However, cycloaddition can occur in the presence of small amounts of the tautomeric enamine form, especially in view of the fact that enamines are highly reactive toward azadienes. The conversion of alkylamines into enamines requires the removal of two atoms of hydrogen, and the question arises as to the nature of the acceptor for them. In theory, the oxidant could be the azadiene itself, atmospheric oxygen, or other compounds present in the reaction mixture such as the solvent (see scheme on following page).

Haddadin et al. [9] consider that in the reaction of the tetrazine (VIIIa) with DEA, the former oxidizes the latter to the enamine $C_2H_5NH{-}CH{=}CH_2$, itself being converted into the dihydro-compound (XV).

The only evidence for this was the detection (by TLC) in the reaction mixture of a compound which was assumed to be 3,6-diphenyl-1,4-dihydrotetrazine (XV). The formation of (XV) in trace amounts was due to its rapid oxidation by

TABLE 2. Reaction of Tetrazine (VIIIa) with DEA and TEA*

Expt. No.	T/A**	Solvent	Time, h	T, °C	Yield (IXa), %	Recovered (VIIIa), %
1	243	—	50	55...56	82	3
2	214	—	50	55...56	18	80
3	107	$CHCl_3$	11	61...62	90	—
4***	107	CCl_4	3,5	76...77	90	—
5	107	C_6H_6+γ-MnO_2	17	80...81	90	—
6	243	—	45	89...90	42	42
7	243	—	45	89...90	17	67

*Expts. 1, 3-5 were carried out with 0.23 g (1 mmole) of (VIIIa), and Expts. 2, 6, and 7 with 0.12 g (0.5 mmole). In Expts. 1 and 6, redistilled alkylamines were used, and in the remaining experiments the amines were further purified via their hydrochlorides. Expts. 3-5 were carried out in 40 ml of dry solvent, and Expts. 1, 2, 6, and 7 in the absence of a solvent. Expts. 1-5 were carried out with DEA, and Expts. 6 and 7 with TEA. In Expt. 5, 0.45 g (5 mmoles) of γ-MnO_2 was added.

**Molar ratio of tetrazine to alkylamine.

***The solid which had separated when the reaction was complete was filtered off, dissolved in 10 ml of water, and treated with 5% NaOH to pH 8-9. The solid which separated was filtered off to give 0.21 g (90%) of (IXa).

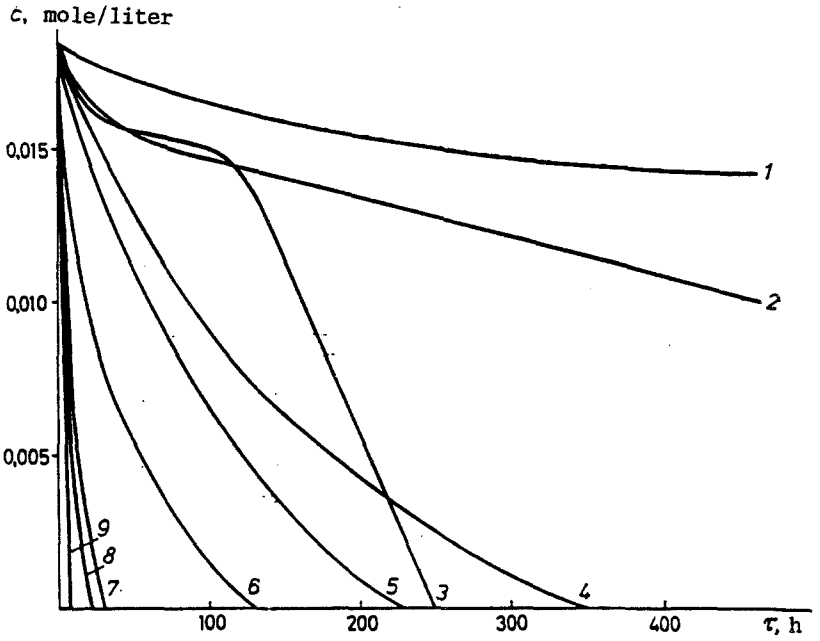
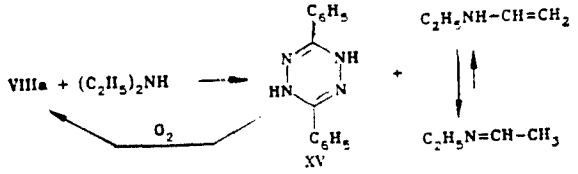


Fig. 3. Kinetic plots for the reaction of isofervenulin (I) ($c_0 = 1.85 \cdot 10^{-2}$ mole/liter) with a 100-fold molar excess of TEA at 50°C in different solvents: 1) in acetonitrile-D_3; 2) benzene-D_6; 3) chloroform-D; 4) pyridine-D_5; 5) DMSO-D_6; 6) DMSO-D_6 with the addition of $1.85 \cdot 10^{-2}$ mole/liter t-BuONa; 7) HMPTA-D_{18}; 8) CCl_4–benzene-D_6, 3:1; 9) HMPTA-D_{18} with the addition of $1.85 \cdot 10^{-2}$ mole/liter of t-BuONa.

TABLE 3. Cyclic Voltammogram Data for Azadienes (I), (VIIIa), and (X) (in acetonitrile)*

Compound	E_{pc}, V	I_{pc}, μA	E_{pa}, V	I_{pa}, μA
I	−0,98	108	−0,94	38
			−0,70	20
VIIIa	−0,72	106	−0,71	106
X	−0,75	112	−0,70	110
	−1,46	40	−1,28	20
Ferrocene	0,40	107	0,43	106

*Initial reduction steps for all the azadienes were one-electron, and fully reversible [except for (I), which was partially reversible]. E_{pc} and E_{pa} are the oxidation and reduction potentials, respectively; I_{pa} and I_{pc} are the maximum reduction and oxidation currents, respectively.



atmospheric oxygen to the starting tetrazine (VIIIa). Two arguments may be adduced against this mechanism. First, the oxidation of 1,4-dihydrotetrazines requires more severe conditions [11]. These compounds also undergo ring contraction, for example, to give 1,2,4-triazoles. However, no by-products arising from reactions of dihydrotetrazines have been detected either by Haddadi et al. [9] or by ourselves. On no occasion have we detected, either by TLC or PMR, either dihydro-compounds of isofervenulin, or their possible conversion products in the course of the reaction of (I) with DEA or TEA.

Second, if azadienes were to accept hydrogen directly from alkylamines, the rate of the azadiene synthesis would decrease in the sequence 1,2,4,5-tetrazines > (X) > (I), in accordance with the relative ease of polarographic reduction of these compounds (Table 3). However, quantitative measurements by PMR of the rate of reaction of (I) and (VIIIa) carried out by us have shown that the former compound reacts with TEA much more rapidly [experiments with DEA were less clear, since (I)

TABLE 4. PMR and Mass Spectra of (V), (VII), and (XI-XIV)

Compound	PMR spectrum (in $CDCl_3$), δ, ppm (J, Hz)*			Mass spectrum, (I ≥ 10%) m/z	HPMW, m/z	
	NCH_3 (s)	6-H	other		experimental	calculated (empirical composition)
V	3,34; 3,41	5,05** s	1,22 (t, J=7,2, $CCH_{3'}$); 1,28 (t, J=7,2, $CCH_{3''}$); 3,37 (q, J=7,2, $CH_{2'}$); 3,53 (q, J=7,2, $CH_{2''}$); 7,68 (c, —N=CH—)	239 (7), 238 (49), 209 (20), 140 (10), 97 (5), 82 (33), 72 (100), 58 (17), 57 (12), 56 (22), 55 (23)	238,1427 209,1034 140,0585	238,1429 ($C_{11}H_{18}N_4O_2$) 209,1038 ($C_9H_{13}N_4O_2$) 140,0585 ($C_6H_8N_2O_2$)
VIIa	3,22; 3,31	5,05** s	1,63 (m, β,γ-H piperidine); 3,40 (m, α-H); 3,63 (m, α-H); 7,70 (s, —N=CH—)	—	—	—
VIIb	3,20; 3,25	5,00** s	3,62 (m, CH_2); 7,65 (s, —N=CH—)	—	—	—
XI	3,35; 3,52	8,55 (dd, $J_{6,7}$=4,2; $J_{6,8}$=1,3)	7,75 (dd, $J_{7,8}$=8,9; $J_{6,7}$=4,2, 7-H); 7,96 (dd, $J_{7,8}$=8,9; $J_{6,8}$=1,3, 8,H)	192 (10), 191 (100), 162 (7), 134 (17), 107 (12), 106 (82), 105 (28), 79 (50), 78 (17), 64 (15), 58 (11), 52 (28), 51 (14)	191,0683	191,0894 ($C_9H_9N_3O_2$)
XII	3,37; 3,38	6,94 s	1,18 (t, J=7,2, CCH_3); 3,37 (q, J=7,2, CH_2); 8,39 (s, —N=CH—)	239 (14), 238 (100), 209 (51), 182 (39), 167 (52), 166 (66), 165 (16) 155 (74), 140 (11), 110 (21), 85 (22), 81 (13), 72 (63), 71 (69), 70 (46), 69 (20), 58 (81), 57 (32), 56 (46), 55 (16)	238,1420	238,1430 ($C_{11}H_{18}N_4O_2$)
XIII	3,34; 3,40	6,63 s	—	156 (7), 155 (94), 71 (6), 70 (100), 69 (35)	155,0698	155,0695 ($C_6H_9N_3O_2$)
XIV	3,41; 3,44	8,50 s	7,78 (br, NH); 8,38 (d, J=0,9, CHO)	183 (27), 155 (94), 70 (100), 69 (29)	183,0637	183,0644 ($C_7H_9N_3O_3$)

*The PMR spectrum of (XI) was obtained in DMSO-D_6.

**5-H.

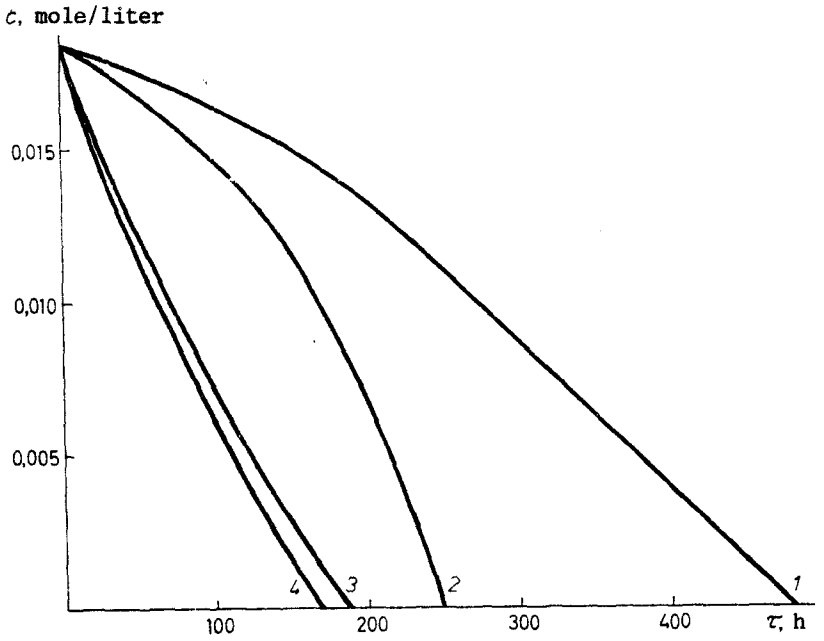


Fig. 4. Kinetic plots for the cycloaddition of azadienes (I) and (VIIIa) (c_0 = $1.85 \cdot 10^{-2}$ mole/liter) with a 100-fold molar excess of DEA or TEA in $CDCl_3$ at 50°C: 1) tetrazine (VIIIa) with DEA; 2) tetrazine (VIIIa) with TEA in the presence of isofervenulin (I) (see plot 3); 3) isofervenulin (I) with TEA in the presence of tetrazine (VIIIa) (see plot 2); 4) tetrazine (VIIIa) with TEA.

gives the amidine (V) as a second product in this case]. This is seen with special clarity when (I) and (VIIIa) react competitively (Fig. 4, plots 2 and 3). Hence, the true relative reactivities of azadienes in their reaction with alkylamines [(I) > 1,2,4,5-tetrazines » (X)] do not conform with their relative ease of reduction.

There remains one other possible mode of involvement of the azadiene in the oxidation of the alkylamine, in which the former functions as a carrier of electrons between the amine and oxygen. Such a mechanism may be represented as follows:

$$HetH + (C_2H_5)_2NH \rightleftharpoons HetH^{-\cdot} + (C_2H_5)_2NH^{+\cdot}$$

$$HetH^{-\cdot} + O_2 \rightleftharpoons HetH + O_2^{-\cdot}$$

$$C_2H_5\overset{+}{N}H\dot{C}HCH_3 \rightleftharpoons C_2H_5NH\dot{C}HCH_3 + H^+$$

$$C_2H_5NH\dot{C}HCH_3 + O_2^{-\cdot} \longrightarrow C_2H_5N{=}CHCH_3 + HO_2^-$$

$$\downarrow\uparrow$$

$$C_2H_5NH{-}CH{=}CH_2$$

In the first step, the alkylamine undergoes one-electron oxidation to give the azadiene anion-radical and the amine cation-radical. The anion-radical is in turn oxidized by atmospheric oxygen, resulting in regeneration of the azadiene and formation of the superoxide anion-radical. As is well known [12, 13], the C_α–H bond in the anion radicals of secondary and tertiary amines is easily broken either homo- or heterolytically. The neutral σ-radical formed by removal of a proton* reacts with the superoxide ion to give the HO_2^- anion and the azomethine, which is converted into the enamine.

Instances of the one-electron reduction of heterocycles by alkylamines have been reported. A necessary condition for the transfer of an electron to the heterocycle is that it should have a low reduction potential. For example, the antibiotic xanthotricin (1,6-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7-dione), which has a reduction potential 0.3 V below that of its iso-

*The enamine could also be formed by disproportionation of the σ-radical [14].

mer (X), reacts with DEA to give a deeply-colored anion-radical [15]. The ESR spectrum of the anion-radical has a typically well-resolved hyperfine structure [16]. On mixing (I) and (VIIIa), or (X), with DEA, the formation of anion-radicals was not observed. These experiments do not, however, rule out the possible formation of anion-radicals of the azadienes (I), (VIIIa), and (X) in small equilibrium amounts. However, the noncorrespondence between the relative ease of reduction of the azadienes (Table 3) and the observed reactivity with alkylamines shows that generation of their anion-radicals is not the main reaction pathway or limiting step of the reaction.

The most likely possibility is direct involvement of atmospheric oxygen in the oxidation of the amines. When the reactions were carried out in sealed ampuls from which air had been pumped out, the yields of the dihydrouracil (III) were substantially reduced, the yields of the amidine (V) being correspondingly increased (Table 1, Expts. 3 and 5). For example, when DEA was used the yield of (III) was reduced from 85 to 34%, and when purified DEA was used, from 32 to 12%. The formation of some of the pyridouracil (III) is probably due to the difficulty of removing oxygen from the DEA.

The marked increase in the rate of the azadiene synthesis reaction in chloroform and, especially in CCl_4, indicates that the generation of enamines could involve the solvent if it has a suitable redox potential. The half-wave reduction potentials of chloroform and CCl_4 in acetonitrile are –1.32 and –0.25 V, respectively [17]. The reaction in CCl_4 is accompanied by the formation of large amounts of HCl, which is bound by the alkylamine. In addition, when (I) is reacted with DEA in CCl_4, the formation of chloroform is detected by PMR. This chloroform is formed at the same rate in a control experiment without isofervenulin (I), thus excluding the participation of the azadienes in the oxidation of alkylamines. In accordance with these observations, the mode of formation of the enamine in the presence of CCl_4 may be represented as follows:

$$(C_2H_5)_2NH + CCl_4 \rightleftharpoons (C_2H_5)_2NH^{+\cdot} + CCl_4^{-\cdot}$$

$$(C_2H_5)_2NH^{+\cdot} \rightleftharpoons C_2H_5NH\dot{C}HCH_3 + H^+$$

$$CCl_4^{-\cdot} \longrightarrow CCl_3^{\cdot} + Cl^-$$

$$C_2H_5NH\dot{C}HCH_3 + CCl_3^{\cdot} \longrightarrow C_2H_5N{=}CHCH_3 + CHCl_3$$

$$(C_2H_5)_2NH + CCl_4 \longrightarrow C_2H_5N{=}CHCH_3 + CHCl_3 + HCl$$

The high rate of the azadiene synthesis in dipolar aprotic solvents (DMSO-D_6 and HMPTA-D_{18}; Fig. 3, plots 5 and 7) is in accordance with their ability to stabilize ion-radical species [18]. On the other hand, in benzene, which does not show this ability, the reaction fails to proceed, and only in the presence of a strong oxidant such as activated MnO_2 does the formation of the azadiene synthesis product take place.

Dioxane, which is not as strong an oxidizing agent as CCl_4, but forms peroxides in air, accelerates the cycloaddition (Table 1, Expt. 13). It is natural to assume that it is these dioxane peroxides which catalyze the oxidation of alkylamines to enamines. The significant acceleration of the azadiene synthesis when home-produced commercial DEA or TEA is used is also due to the presence therein of peroxidic impurities. The latter are known to initiate the autooxidation of alkylamines, which in this instance proceeds by a chain radical mechanism [12, 19, 20].

$$RO_2^{\cdot} + (C_2H_5)_2NH \longrightarrow C_2H_5HN\dot{C}HCH_3 + RO_2H \quad \text{(chain initiation)}$$

$$C_2H_5HN\dot{C}HCH_3 + O_2 \longrightarrow C_2H_5HN{-}\underset{\displaystyle O-O^{\cdot}}{CH}{-}CH_3$$

$$C_2H_5HN{-}\underset{\displaystyle O-O^{\cdot}}{CH}{-}CH_3 \longrightarrow C_2H_5N{=}CH{-}CH_3 + HO_2^{\cdot}$$

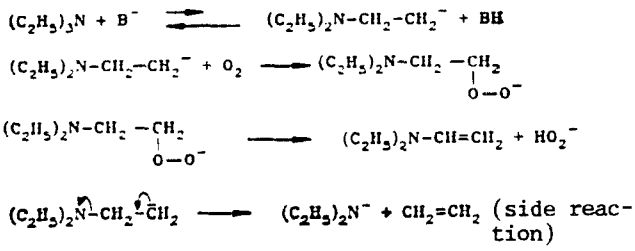
$$(C_2H_5)_2NH + HO_2^{\cdot} \longrightarrow C_2H_5HN\dot{C}HCH_3 + H_2O_2 \text{ etc.}$$

From this point of view, it becomes understandable why acetonitrile, which is a trap for peroxide radicals [21], strongly retards the reaction. As investigations of the autooxidation of N-butylisoindoline have shown [19], this retardation occurs at the stage of formation of the enamine rather than the cycloaddition step. Since proton-donor solvents normally facilitate the Diels–Alder reaction [3, 22], inhibition of the reaction in methanol in the present case is also due to retardation of the oxidation of the alkylamines.

As will be seen from Table 4 (plots 1 and 4), TEA reacts with tetrazine (VIIIa) in deuterochloroform at 50°C approximately 3.5 times as fast as DEA. This is in accordance with the lower oxidation potential of $(C_2H_5)_3N$ (0.66 V) as

compared with $(C_2H_5)_2NH$ (1.11 V) [23]. However, piperidine and morpholine, which have approximately the same oxidation potentials as those mentioned above, fail to give azadiene synthesis products. According to literature reports [23, 24], this could be due to the difficulty of deprotonation of the cation-radicals of the cyclic amines. Since the C_α–H bond therein is sited almost perpendicularly to the charge-bearing orbitals of the aminium nitrogen, the radical formed is insufficiently stabilized. Taken together, these observations lead to the conclusion that the formation of the enamine is the limiting step in the reaction of alkylamines with (I). In the case of tetrazines, the rates of both stages are probably comparable, although the formation of the enamine is somewhat slower than the subsequent cycloaddition. In the case of compound (X), however, the limiting stage is the second step, and the azadiene product is formed under very severe conditions and in low yield.

In dipolar aprotic solvents (DMSO-D_6 and HMPTA-D_{18}), the reaction is markedly accelerated in the presence of a strong base. For example, the half-conversion time of isofervenulin (I) to the pyridouracil (III) in the presence of a 100-fold excess of TEA in DMSO-D_6 is ~70 h, whereas in the presence of sodium tert-butoxide it is reduced to ~22 h (Fig. 3, plots 5 and 6). From an earlier report [24], it seems that the formation of the enamine in this case occurs by oxidation of the TEA carbanion formed in equilibrium amounts. This interpretation is supported by the formation in the reaction mixture of ethylene (δ 5.4 ppm) as a result of E_2 elimination [25], as shown by PMR. Catalysis by base may be represented as follows:



Consequently, the formation of enamines from alkylamines occurs by different mechanisms depending on the solvent and additives (cf. [12]).

This investigation has shown that DEA and TEA are convenient synthetic equivalents for their unstable enamines. The use of such alkylamines in the reverse azadiene synthesis is obviously of preparative value.

EXPERIMENTAL

IR spectra were obtained on a UR-20 in chloroform, and UV spectra on a Pye–Unicam SP 8-100. The PMR spectra of (VIIa, b) were obtained on a Tesla BS-487 (80 MHz), internal standard HMDS, and the remaining compounds on a Bruker WH-90 spectrometer (90 MHz), internal standard TMS. The ^{13}C NMR spectrum of (V) was obtained on a WH-90 spectrometer (22.62 MHz), chemical shifts being measured relative to $CDCl_3$ (δ 77.0 ppm). Mass spectra (for which the authors thank N. A. Klyuev and V. G. Zhil'nikov) were obtained on a Varian MAT-311A by direct introduction of the sample into the ion source (accelerating voltage 3.0 kV, ionizing voltage 70 eV, cathode emission current 1.0 mA, ionization chamber temperature 70-150°C). Voltammograms (obtained by A. A. Bumber, to whom the authors express their thanks) were obtained on an IP-50-1 pulse potentiostat with a platinum disk of diameter 2 mm and a potential inversion rate of 0.5 V/sec. The solvent was dry acetonitrile containing 0.1 mole/liter of tetraethylammonium perchlorate. The measurements were made relative to a saturated calomel electrode. The reactions were followed and the purity of the products established by TLC on silica gel L 40/100, eluent ethyl acetate, and on Brockman grade III alumina, eluent chloroform. The developer was iodine vapor.

The purity of the alkylamines was checked by GLC on a Tsvet 101 instrument with a flame ionization detector, column 300 × 3 mm, 15% Apiezon L on Inerton AW DMCS, grain size 0.125-0.160 mm with 4% KOH. The flow rate of the helium carrier gas was 3, hydrogen 25, and air 300 ml/min. The temperature of the column was 100, evaporator 110, and detector 190°C. In twice-distilled commercial DEA, six impurities were found in amounts of 0.001-0.300% of the principal component, having retention indices of 353, 438 (ethylamine), 485, 509, 678, and 728 (TEA). Twice-distilled commercial TEA contained five impurities in amounts of 0.02-0.60% of the main component, retention indices 433 (ethylamine), 490, 559 (DEA), 604, and 753.

The kinetics of the cycloaddition of azadienes (I) and (VIIIa) were measured by PMR spectroscopy on a WH-90 instrument. The DEA and TEA used were purified via their hydrochlorides. The instant concentrations (c) of the azadienes (I) and (VIIIa) were calculated using the equation $c = \chi c_0$, where c_0 is the initial concentration. The proportion of starting material in the reaction mixtures in admixture with products (III) and (IXa) in the course of the reaction (χ) was determined from the integral intensities of the signals for the o-protons of the phenyl substituents for tetrazine (VIIIa), and from the differential spectra by deduction of the signals for the N-methyl protons in the case of isofervenulin (I); for the method of quantitative estimation by differential PMR spectra, see [26].

X-Ray Diffraction Analysis. The monoclinic crystals of (III), $C_9H_9N_3O_2$, were grown from ethyl acetate, a = 9.069(6), b = 12.933(8), c = 7.336(4) Å, β = 94.15(4)°, V = 858.2(9) Å^3, Z = 4, space group $P2_1/C$. Triclinic crystals of (V), $C_{11}H_{18}N_4O_2$, were grown from ethyl acetate, a = 5.147(4), b = 12.467(9), c = 10.780(6) Å, α = 109.95(5), β = 97.79(5), γ = 95.10(5)°, V = 637.4(8) Å^3, Z = 2, space group $P\bar{1}$.

The x-ray examination was carried out on a Syntex-$P\bar{1}$ diffractometer; λ_{MoK_α}, graphite monochromator, $\theta/2\theta$ scanning, $3 \leq 2\theta < 50°$. The structures of (III) and (V) were calculated directly, and refined by least squares in full-matrix anisotropic approximation (H atoms, located by difference syntheses, were refined in isotropic approximation) to R = 0.095 (R_w = 0.097) for 1123 reflections with $F^2 \geq 2\sigma$ for (III) and R = 0.075 (R_w = 0.090) for 1536 reflections with $F^2 \geq 2\sigma$ for (V). The atom coordinates and temperature factors may be obtained from the authors.

Home-produced commercial DEA and TEA were twice distilled at 55-56°C and 89-90°C, respectively. In order to obtain more highly purified samples of DEA and TEA, their hydrochlorides were twice recrystallized from butanol, then treated with KOH in a small amount of water, and the alkylamines distilled off. The DEA and TEA were then redistilled over KOH, collecting the fractions boiling at 55-56 and 89-90°C, respectively.

The spectral characteristics of (V), (VII), and (XI-XIV) are given in Table 4. The elemental analyses of (V), (VIIa, b), and (IXb) for C, H, and N were in agreement with the calculated values.

Reaction of Isofervenulin (I) with DEA (Table 1, Expt. 1). A mixture of 0.2 g (1 mmole) of (I) and 25 ml (243 mmoles) of twice-distilled DEA was boiled for 15 h, evaporated to dryness, and the residue dissolved in 2 ml of chloroform and chromatographed on a column of silica gel (25 × 2 cm). First eluted was **1,3-dimethylpyrido[2,3-d]pyrimidine-2,4-dione (III)** with ethyl acetate (R_f 0.9), yield 0.17 g (85%), mp 163-164°C (from alcohol), in agreement with literature values [27]. Alcohol then eluted **1,3-dimethyl-6-(diethylaminomethyleneamino)-pyrimidine-2,4-dione (V, $C_{11}H_{18}N_4O_2$)**, yield 0.025 g (10%), R_f 0.25 (silica gel, ethyl acetate). Colorless needles, mp 127-128°C (from octane). IR spectrum: 1578, 1602 (ring), 1638, 1685 cm^{-1} (C=O). UV spectrum (methanol), λ_{max} (log ε): 240 (4.05), 304 nm (4.18). ^{13}C NMR spectrum ($CDCl_3$): 12.12 (q.t, ^1J = 127.3; $^2J_{C,CH_2}$ = 3.2 Hz, CCH_3·); 14.72 (q.t, ^1J = 127.6, $^2J_{C,CH_2}$ = 2.9 Hz, CCH_3·); 27.65 (q, ^1J = 141.3 Hz, 1-CH_3); 30.01 (q, ^1J = 141.6 Hz, 3-CH_3); 40.61 (t.m, ^1J = 139.1 Hz, CH_2·); 46.52 (t.m, ^1J = 137.5 Hz, CH_2·); 83.08 (d, ^1J = 169.9 Hz, $C_{(5)}$); 152.80 (m, $C_{(6)}$), 153.04 (d.m, ^1J = 173.8 Hz, –N=CH–); 159.77 (m, $C_{(2)}$); 163.90 ppm (q, $^3J_{C,CH_3}$ = 2.8 Hz, $C_{(4)}$).

Experiments 2-13 were carried out similarly (for conditions, see Table 1).

Reaction of Isofervenulin (I) with TEA. A. A solution of 0.1 g (0.5 mmole) of (I) in 13 ml (90 mmoles) of twice-distilled TEA was boiled for 15 h, then the mixture was evaporated to dryness. The residue was dissolved in 2 ml of chloroform, and chromatographed on a column of silica gel (25 × 2 cm), eluent ethyl acetate. The yield of the product (III) was 0.08 g (80%), colorless needles, mp 162-163°C (from alcohol).

B. A mixture of 0.2 g (1 mmole) of (I), 0.5 g (5.7 mmoles) of γ-MnO_2, and 13 ml (90 mmoles) of TEA purified via its hydrochloride in 40 ml of dry benzene was boiled with stirring for 7 h, then evaporated to dryness. The residue was dissolved in 2 ml of chloroform, and chromatographed on a column of alumina (15 × 3 cm), eluent chloroform. The colorless fraction with R_f 0.80 was collected. The yield of (III) was 0.1 g (50%), colorless needles, mp 162-163°C (from alcohol). Ten mg (5%) of (I) was recovered.

1,3-Dimethyl-6-(piperidinomethyleneamino)pyrimidine-2,4-dione (VIIa, $C_{12}H_{18}N_4O_2$). A. A solution of 0.2 g (1 mmole) of (I) in 10 ml (102 mmoles) of freshly distilled piperidine was boiled for 2 h. The mixture was then evaporated to dryness, and the residue dissolved in 5 ml of chloroform and chromatographed on a column of alumina (15 × 3 cm), the first fraction being eluted with chloroform, yield 0.21 g (84%), colorless prisms, mp 192-193°C (from benzene–octane). IR spectrum: 1575, 1605 (ring), 1635, 1685 cm^{-1} (C=O).

B. A solution of 0.2 g (1 mmole) of (I) and 10.5 ml (107 mmoles) of freshly-distilled piperidine in 40 ml of chloroform was boiled for 26 h. The mixture was then evaporated to dryness, and the residue dissolved in 5 ml of chloroform and chromatographed on a column of silica gel (25 × 2 cm), the amidine (VIIa) being eluted with alcohol in 0.25 g yield (quant.),

R_f 0.15 (silica gel, ethyl acetate). The material obtained was identical to that obtained by method A in its melting point and IR spectrum.

1,3-Dimethyl-6-(morpholinomethyleneamino)pyrimidine-2,4-dione (VIIIb, $C_{11}H_{16}N_4O_3$). This was obtained as for (VIIa) (method B) from 0.2 g (1 mmole) of (I) and 9.3 ml (107 mmoles) of freshly-distilled morpholine in 40 ml of chloroform, reaction time 14 h. The yield of the product (VIIb) was 0.2 g (84%), R_f 0.09 (silica gel, ethyl acetate), colorless needles, mp 204-205°C (from methanol). IR spectrum: 1575, 1605 (ring), 1633, 1680 cm^{-1} (C=O).

3,6-Diphenylpyridazine (IXa) (Table 2, Expt. 1). A. A solution of 0.23 g (1 mmole) of the tetrazine (VIIIa) in 25 ml (243 mmoles) of redistilled TEA was boiled for 50 h. The color of the mixture changed from bright crimson to pale pink. The mixture was evaporated to dryness, and the residue dissolved in 5 ml of chloroform and chromatographed on a column of alumina (15 × 3 cm), eluent chloroform. The first crimson fraction (8 mg, 3%) of starting (VIIIa), R_f 0.9, was discarded. There was then eluted a colorless fraction (IXa), R_f 0.7, yield 0.19 g (82%), mp 220-222°C (from alcohol), in agreement with the literature value [28].

Experiments 2-7 were carried out similarly (for conditions, see Table 2).

B. A mixture of 0.23 g (1 mmole) of the tetrazine (VIIIa), 0.52 ml (2 mmoles) of redistilled DEA, and 8 ml (83 mmoles) of vinyl ethyl ether in 5 ml of methanol was boiled for 8 h. The mixture was then evaporated to dryness, and the product (IXa) isolated as in method A. Yield 0.22 g (95%). (This experiment was carried out to obtain an authentic sample of (IXa) [3].)

3,6-Di-(2-pyridyl)pyridazine (IX, $C_{14}H_{10}N_4$). A solution of 1.24 g (1 mmole) of (VIIIb) in 11 ml (107 mmoles) of DEA, purified via its hydrochloride, and 40 ml of dry CCl_4 was boiled for 1 h. The mixture was evaporated to dryness, and the residue dissolved in 5 ml of chloroform and chromatographed on a column (15 × 3 cm) of alumina, eluent chloroform. The fraction with R_f 0.8 was collected. Yield 0.19 g (78%). Pale yellow needles, mp 178-180°C (from ethanol).

Reaction of Fervenulin (X) with DEA. A suspension of 0.19 g (1 mmole) of (X) in 10 ml (97 mmoles) of redistilled DEA was heated for 24 h at 150°C in a sealed ampul. The solid which separated on cooling was filtered off, washed with DEA (4 × 0.5 ml), and air-dried. The solid was dissolved in 1 ml of chloroform and chromatographed on a column (45 × 18 mm) of Silpearl, eluent chloroform. First eluted was **1,3-dimethylpyrido[2,3-di]pyrimidine-2,4-dione (XI),** yield 21 mg (11%), R_f 0.33 (chloroform–methanol, 20:1), mp 239.5-241°C (from chloroform). UV spectrum (methanol), λ_{max} (log ε): 208 (4.34), 244 pl (3.89), 314 nm (3.68). This was followed by **5-amino-1,3-dimethylpyrimidine-2,4-dione (XIII),** yield 4 mg (3%), R_f 0.2 (chloroform–methanol, 20:1), mp 112-114°C (from chloroform).

The filtrate was evaporated to dryness, and the residue dissolved in 2 ml of methanol and chromatographed on alumina plates, eluent chloroform. The zones with R_f 0.6 contained, according to PMR, two compounds. These were separated by column chromatography (100 × 18 mm) on Silpearl. First eluted, with chloroform, was **1,3-dimethyl-5-formylaminopyrimidine-2,4-dione (XIV),** 22 mg (12%), mp 203-204°C (from ethyl acetate). UV spectrum (methanol), λ_{max} (log ε): 232 (3.94), 287 nm (3.82), followed by (eluent methanol–chloroform, 5:1) **1,3-dimethyl-5-(diethylaminomethyleneamino))pyrimidine-2,4-dione (XII),** 21 mg (9%), mp 91-93°C (from chloroform–methanol). UV spectrum, λ_{max} (log ε): 201 (4.05), 256 (3.94), 288 nm (3.88).

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5-SUBSTITUTED 2-BENZYLOXAZOLIDINES

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The reaction of N-benzylhydroxylamine with α,β-unsaturated carbonyl compounds provides a method of synthesis of 5-hydroxy-2-benzyloxazolidines, nucleophilic replacement of the hydroxyl group in which gives the corresponding 5-amino- and 5-hydrazinoisoxazolidines.

The reaction of α,β-unsaturated aldehydes [1] and ketones [2] with N-substituted hydroxylamines constitutes a method for the preparation of hydroxyisoxazolidines, from which alkoxy-, amino-, and hydrazinoisoxazolidines may be obtained [3]. The course of the cyclization is sensitive to the substituent at nitrogen, arylhydroxylamines giving 5-hydroxy-, while hydroxamic acids give both 3-hydroxy- and (or) 5-hydroxyisoxazolidines. There have been no reports of the structures of products from hydroxylamines with donor substituents. For this reason, as well as to further examine the preparative potential of this reaction, we have studied the reaction of the α,β-unsaturated carbonyl compounds (Ia-d) with N-benzylhydroxylamine (see scheme on page 1304).

The reaction proceeds rapidly and smoothly, the sole products being the 5-hydroxyisoxazolidines (IIIa-d) (Table 1). The use of solid-phase synthesis on adsorbents of different types (silica gel and alumina) and prolonged heating of the reaction mixtures at 100°C in the presence of added acid catalysts had no effect whatsoever on the structures of the products. Proof of the location of the hydroxyl group was based on reliable criteria [1], the positions of the chemical shifts for $C_{(5)}$ being in the range ~100 ppm, indicating its O–C–O environment. The remaining features of the proton and carbon spectra were in full agreement with the proposed structure (Table 1).

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