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SYNTHESIS OF HETEROCYCLES USING THE PRODUCTS OF THE ADDITION OF POLYHALOALKANES TO UNSATURATED SYSTEMS. 6.* TRANSFORMATION OF THE gem-TRICHLOROETHYL GROUP IN 2-METHYL-3-(2,2,2-TRICHLOROETHYL)-4-R-AMINOFURO[2,3-d]PYRIMIDINES, ISOMERIC STRUCTURES AND SEVERAL OF THEIR PRECURSORS

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A study was carried out on the conditions for the dehydrochlorination of 2-methyl-3-(2,2,2-trichloroethyl)-4-R-aminofuro[2,3-d]pyrimidines, isomeric structures, and several of their precursors. Dehydrochlorination by the action of sodium ethylate proceeds readily only for 2-methyl-3-(2,2,2-trichloroethyl)-4-imino-5-R-2,3-dihydrofuro[2,3-d]pyrimidines, which are converted in good yield into the corresponding 2,3-dichlorovinyl derivatives. These vinyl products readily undergo recyclization to give 2-methyl-3-(2,2-dichlorovinyl)-4-R-aminofuro[2,3-d]pyrimidines under conditions of the Dimroth rearrangement. Several substituted furo[2,3-d]pyrimidin-4-ones were also synthesized and studied.

Most of the investigators studying the radical addition of CCl_4 to unsaturated compounds have noted the feasibility and promise of the functionalization of the trichloromethyl group of the compounds obtained. However, a study of the literature has shown that the few methods discovered prior to the 1970's have not been further developed and are hardly used. The reported pathways for the functionalization of these compounds (see the review of Nesmeyanov et al. [2] and some later summaries [3, 4]) are based either on the hydrolysis of the trichloromethyl group or the dichloromethylene group obtained by dehydrochlorination to a carboxyl group, which proceeds in strongly acidic media such as concentrated sulfuric, nitric, and perchloric acids or Lewis acids, or upon oxidation by hydrogen peroxide or the conjugated oxidative chlorination of β,β-dichlorovinyl derivatives in acidic media to give α-chlorocarboxylic acids and the corresponding amino acids. The dichlorovinyl group, which is readily formed by the dehydrochlorination of the gem-trichloroethyl group, also holds independent interest since it is encountered in many biologically active compounds.

We have already described the transformations of available 3,5,5,5-tetrachloro-2-pentanone (I), which is the product of the addition of CCl_4 to methyl vinyl ketone [5], upon reaction with malonodinitrile through substituted 4-oxa-3-(2,2,2-trichloroethyl)-2-cyanovaleronitrile, leading to aminofuronitrile (III) [6].

Furylformamidines (IV) and isomeric furopyrimidines (V) and (VI) were obtained consecutively from aminonitrile III [6, 7].

*Communication 5, see ref. [1].

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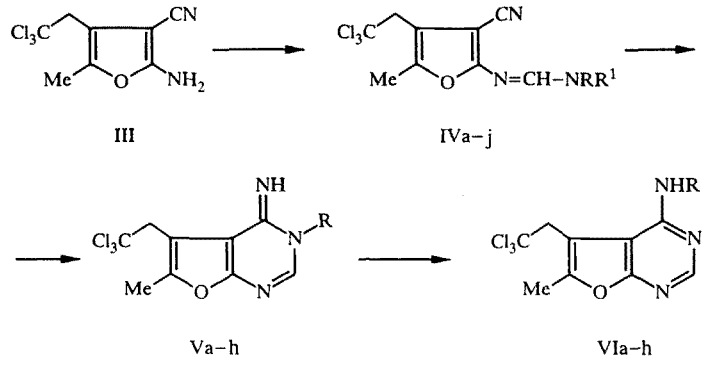
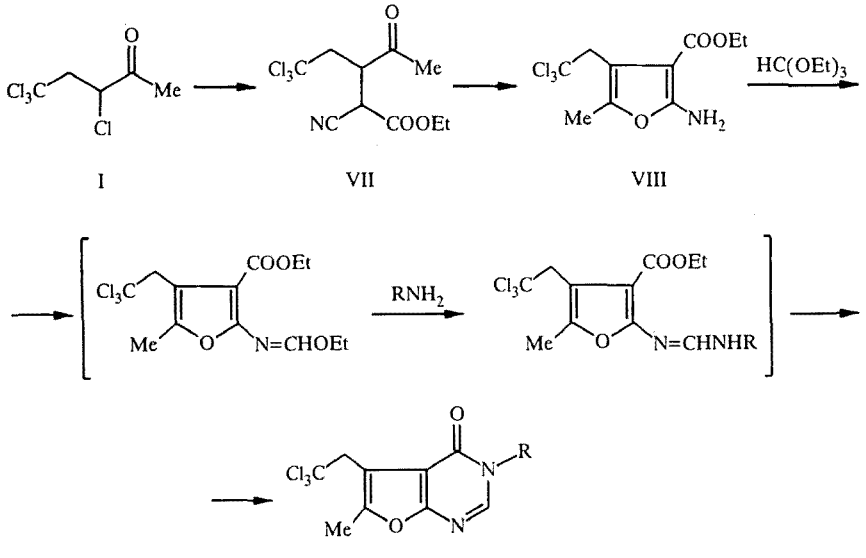


III IVa–j

Va–h VIa–h

IV—VIa—h a R = H, b R = Me, c R = *i*-Pr, d R = CH_2Ph, e R = cyclo-C_6H_{11}, f R = Bu, g R = *i*-Bu, h R = *p*-ClC_6H_4, IV i R = *t*-Bu; IVa—i R^1 = H, IVj R + R^1 = $-CH_2CH_2OCH_2CH_2-$

In the present work, an ester derivative of 2-aminofuran-3-carboxylic acid (VIII) was obtained from ketone I without isolation of the intermediate product of its condensation with ethyl cyanoacetate and ketonitrile (VII).

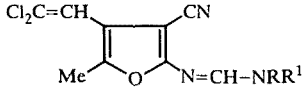


I VII VIII

IXa, b

IX a R = H, b R = Me

Aminofuran derivatives III and VIII are obtained in basic media and do not undergo dehydrochlorination upon heating in ethanolic sodium ethylate or potassium hydroxide at reflux. The feasibility of the dehydrochlorination of furylformamidines IV was studied in the case of IVi and IVj, which do not undergo cyclization under base catalysis conditions. The corresponding divinyl derivatives (Xa) and (Xb) could not be isolated even upon prolonged heating with sodium ethylate in ethanol at reflux. The PMR spectrum of the reaction mixture indicates that the reaction nevertheless proceeds and the ratio of product X to the starting compound is 1:2 for IVi and 1:3 for IVj.

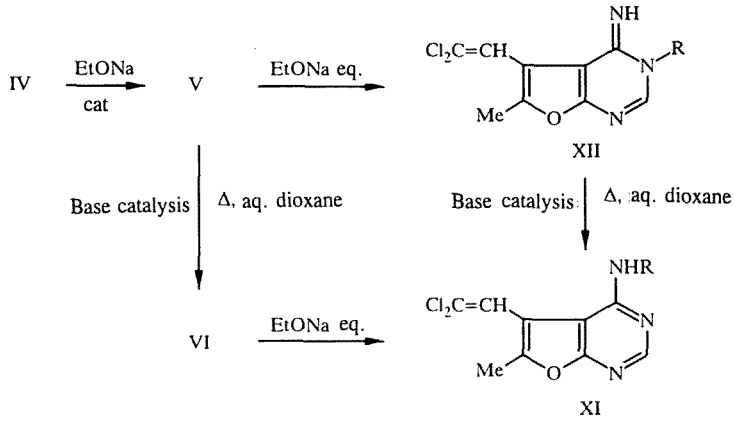


Xa, b

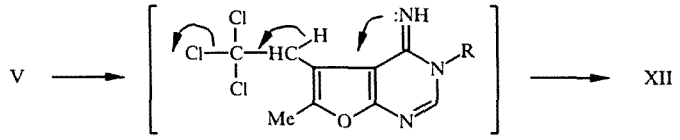
X a R = *t*-Bu, R^1 = H; b R + R^1 = $-(CH_2)_2O(CH_2)_2-$

The dehydrochlorination of furopyrimidines VI also requires vigorous conditions. Prolonged heating in a solution containing an equimolar amount of sodium ethylate or alkali at reflux leads to mixtures of the starting furopyrimidine and its dichlorovinyl derivative (XI), which could not be isolated. In the case of IVa, partial dehydrochlorination proceeds upon prolonged heating in pyridine at reflux or upon sublimation. However, the reaction does not proceed to completion even upon repeated sublimation in the presence of BaO. The corresponding divinyl derivative XIa (R = H) was obtained in 10% yield upon heating the starting aminofuronitrile in formamide at reflux with subsequent sublimation and also upon heating XIc (R = i-Pr) in concentrated sulfuric acid.

On the other hand, furopyrimidinonimines V are readily converted to the corresponding divinyl derivatives (XII) in good yields by the action of an equivalent amount of sodium ethylate in the cold. An excess of base or increase in the temperature also lead to products VI and XI, which arise as a result of the Dimroth rearrangement, which proceeds much more slowly than dehydrochlorination under these conditions. Heating of furopyrimidines XII in aqueous dioxane at reflux proved most convenient for the preparative synthesis of XI. Furopyrimidines XII may be used without isolation from the reaction medium.



Let us examine the following factors in order to understand the unusual ease for the dehydrochlorination of the trichloroethyl group of imines V in comparison with the isomeric amidines IV and aminofuropyrimidines VI. Products IV-VI are found in equilibrium with a form obtained by their deprotonation at the amino or imino group in the presence of sodium ethylate. The structures of IV and VI permit mesomeric distribution of negative charge throughout the entire heteroaromatic residue. There is no such possibility for imines V and the charge will be localized in these compounds on the exocyclic nitrogen atom, which should facilitate proton transfer from the methylene group. In the case of V, we may also propose participation of the highly basic imino group of the furopyrimidine fragment in the reaction. The steric propinquity of the furopyrimidine fragment may facilitate removal of the methylene proton:



Such activation is impossible for formamidine IV and should be significantly less for aminofuropyrimidine VI. The same factors should be relevant for aminofuronitrile III. In the case of oxofuropyrimidines IX, the lower basicity of the oxo group in comparison with the imino group does not facilitate dehydrochlorination, which proceeds only partially (the ratio of dehydrochlorination product XIII to starting IXb is 7:2).

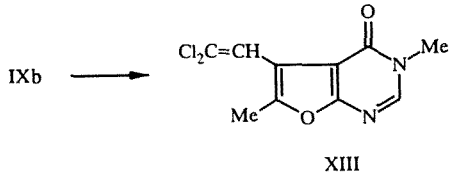


TABLE 1. PMR Spectra of Dichlorovinyl Derivatives XI-XIII (in DMSO-d_6)

Compound	Chemical shifts, ppm				
	$Cl_2C=CH$	H in pyrimidine ring	Me in furan ring	NH	R
XIIb	7,31 s	8,03 s	2,25 s	6,70 br	Me: 3,35 d
XIIc	7,37 s	8,10 s	2,25 s	6,78 br	*i*-Pr: 5,20 br (1H), 1,37 d (6H), J = 6,7 Hz
XIId	7,31 s	8,25 s	2,27 s	6,78 br	$PhCH_2$: 7,22...7,38 m (5H), 5,19 s (2H)
XIIe	7,45 s	8,17 s	2,40 s	7,10 br	*cyclo*-C_6H_{11}: 4,8 t (1H), 1,60...1,90 m (4H); 1,15...1,40 m (6H)
XIIg	7,32 s	7,90 s	2,25 s	6,75 br	*i*-Bu: 3,75 d (2H), 2,10...2,25 m (1H), 0,85 d (6H), J = 7,5 Hz
XIa	7,34 s	8,13 s	2,32 s	7,10 br (2H)	
XIb	7,30 s	8,23 s	2,30 s	6,92 q	Me: 2,94 d, J = 6,0 Hz
XIc	7,47 s	8,20 s	2,30 s	6,25 d	*i*-Pr: 4,35 m (1H), 2,21 d (6H), J = 6,5 Hz
XId	7,38 s	8,20 s	2,33 s	7,50 t	$PhCH_2$: 4,72 d (2H), J = =6,0 Hz, 7,18...7,33m (5H)
XIe	7,50 s	8,20 s	2,30 s	6,23 d	*cyclo*-C_6H_{11}: 4,05 br (1H), 1,87...1,97 m (4H), 1,58...1,80 m (4H), 1,15...1,42m (2H)
XIf	7,33 s	8,20 s	2,31 s	6,87 t	Bu: 3,8 m (2H), 1,50...1,62 (2H), 1,27...1,40 m (2H), 0,92 br . t, J = 7 Hz
XIh	7,42 s	8,38 s	2,40 s	8,78 s	*p*-ClC_6H_4: 7,37...7,70 dd
XIII	7,05 s	8,39 s	2,32 s	—	Me: 3,48 s (3H)

TABLE 2. Characteristics for IX and XI-XII

Compound	Chemical formula	M^+	mp, °C	Yield, %
IXa	$C_9H_7Cl_3N_2O_2$	279	238...239	76
IXb	$C_{10}H_9Cl_3N_2O_2$	284	200...202	85
XIa	$C_9H_7Cl_2N_3O$	243	225...226	73*[2]
XIb	$C_{10}H_9Cl_2N_3O$	257	157...160	87
XIc	$C_{12}H_{13}Cl_2N_3O$	283	158...160	97
XId	$C_{16}H_{13}Cl_2N_3O$	333	131...133	95
XIe	$C_{15}H_{17}Cl_2N_3O$	325	115...117	62
XIf	$C_{13}H_{15}Cl_2N_3O$	299	98...99	80
XIh	$C_{15}H_{10}Cl_3N_3O$	353	155...156	20
XIIb	$C_{10}H_9Cl_2N_3O$	257	152...153	90
XIIc	$C_{12}H_{13}Cl_2N_3O$	283	105...108	56
XIId	$C_{16}H_{13}Cl_2N_3O$	333	149...150	81
XIIe	$C_{15}H_{17}Cl_2N_3O$	325	148...150	36
XIIg	$C_{13}H_{15}Cl_2N_3O$	299	109...110	40
XIII	$C_{10}H_8Cl_2N_2O_2$	258	180...184	32

*The values for M^+ correspond to the ^{35}Cl isotope.

*[2]The yield for procedure B is given, the yield using procedure A is 10%.

The IR spectra of dichlorovinyl derivatives XI have bands at 1584-1596 and 1488-1512 cm^{-1} characteristic for the pyrimidine fragment, while the spectrum of XII has a strong band for the exocyclic imino group at 1630-1650 cm^{-1}. These bands were also found in the spectra of starting amines VI and imines V [7]. Products XI and XII also have bands at 880-915 and 590-610 cm^{-1}, which are characteristic for the dichlorovinyl C–Cl bond [8]. However, bands for the trichloromethyl group of starting compounds V and VI are found in the same spectral regions. Some difficulties also arise in assigning the bands at 1610-1630 cm^{-1} since XI and XII have heterocyclic C=C and C=N bonds in addition to the C=C bond of the dichlorovinyl group. Thus, IR spectroscopy cannot be used for unequivocal confirmation of the structural changes described.

The structures of these compounds were also indicated by PMR spectroscopy (see Table 1), mass spectrometry (see Table 2), and elemental analysis.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz in DMSO-d_6. The IR spectra were taken on Perkin–Elmer 577 and Specord M-80 spectrometers for KBr pellets or chloroform solutions. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer with direct inlet of the sample into the ion source. The ionizing voltage was 70 eV and the emission current was 100 μA.

The elemental analysis data of these products for C, H, N, and Cl correspond to the calculated data.

Ethyl Ester of 2-Amino-5-methyl-4-(2,2,2-trichloroethyl)furan-3-carboxylic acid (VIII, $C_{10}H_{12}Cl_3NO_3$). A sample of 1.05 g sodium was dissolved in 10 ml abs. ethanol, 5.1 g ethyl cyanoacetate was added, and the mixture was heated until the sodium derivative was dissolved. A sample of 10 g chloroketone I was added to the warm solution and maintained at 70°C until completion of the reaction. (Thin-layer chromatography was carried out on Silufol plates with 1:3 ethyl acetate–hexane as the eluent, R_f of the product was 0.64). Ester VIII was precipitated by adding water, filtered off, and recrystallized from aqueous ethanol, mp 82-84°C. The yield of VIII was 8.82 g (65.7%).

2-Methyl-3-(2,2,2-trichloroethyl)furo[2,3-d]pyrimidin-4-one (IXa). Ester VIII was heated in excess ethyl orthoformate at reflux for 4-5 h. The completion of the reaction was determined by thin-layer chromatography on Silufol plates using 1:3 ethyl acetate–hexane as the eluent. R_f of the starting compound was 0.5 and of the reaction product 0.8. The reaction mixture was evaporated and the residual dark brown oil containing the intermediate iminoester was dissolved without further purification in ether. A stream of ammonia was introduced into this solution to precipitate N^1-[5-methyl-4-(2,2,2-trichloroethyl)-3-ethoxycarbonyl-2-furyl]-N^2-formamidine, which was filtered off, mp 131-132°C (from ethanol). PMR spectrum: 7.90 (1H, d.d, $CH_{amidine}$), 7.62 (1H, d.d, NH), 7.38 (1H, d.d, J = 14.5 and ~2.5 Hz, NH), 4.11 (2H, s, CH_2), 4.08 (2H, q, OCH_2), 2.22 (3H, s, Me_{Ar}), 1.20 (3H, t, J_{CH_2,CH_3} = 7 Hz, CH_2CH_3). The yield of this formamidine was 70%.

The action of an equimolar amount of sodium ethylate in absolute ethanol on this formamidine at ~20°C for 10-15 h, subsequent precipitation by the addition of water, and recrystallization from aqueous ethanol gave IXa. IR spectrum: 3500, 2900 (NH), 1670, 1554 cm^{-1} (C=O, C=N). PMR spectrum: 12.5 (1H, br, NH), 8.08 (1H, s, CH_{Ar}), 4.20 (2H, s, CH_2), 2.45 (3H, s, Me).

2,5-Dimethyl-3-(2,2,2-trichloroethyl)furo[2,3-d]pyrimidin-4-one (IXb) was obtained similarly to IXa except that a double molar amount of methylamine was added to the ethereal solution of the iminoester and left for 8-10 h at room temperature. The precipitate formed was recrystallized from aqueous ethanol. IR spectrum: 1700, 1680, 1532 cm^{-2} (C=O, C=N).

4-Imino-2-methyl-3-(2,2-dichlorovinyl)-5-R-4,5-dihydrofuro[2,3-d]pyrimidines (XIIb-XIIe, XIIh). An equimolar amount of sodium ethylate was added to a solution of the corresponding derivative V in a minimal amount of absolute ethanol. The reaction mixture was left overnight at 4°C. The completion of the reaction was monitored by thin-layer chromatography with ethyl acetate as the eluent. The product was precipitated by adding water, washed with water, and recrystallized from aqueous methanol.

4-R-Amino-2-methyl-3-(2,2-dichlorovinyl)furo[2,3-d]pyrimidines (XIb-XIe). An aqueous dioxane solution of XII of solution of the corresponding derivative V with an equimolar amount of sodium ethylate in absolute ethanol diluted with a double volume of aqueous dioxane maintained for 10 h at room temperature was heated at reflux for 20 h. The product was precipitated by the addition and recrystallized from aqueous methanol or dioxane.

2-Methyl-4-(p-chloranilino)-3-(2,2-dichlorovinyl)furo[2,3-d]pyrimidine (XIg). A solution of amidine IV with a slight excess of sodium ethylate was left for five days at room temperature. A precipitate of the product formed. An additional amount of product was obtained by precipitation upon the addition of water.

4-Amino-2-methyl-3-(2,2-dichlorovinyl)furo[2,3-d]pyrimidine (XIa). A. Aminonitrile III was heated in formamide at reflux for 20 h in the presence of a catalytic amount of acetic anhydride. Evaporation and sublimation of the tarry residue gave XIa.

B. 4-Isopropylamino-2-methyl-3-(2,2-dichlorovinyl)furo[2,3-d]pyrimidine XIc was maintained at ~100°C for 12 h in 93% sulfuric acid. The solution was diluted with water and neutralized by the addition of aqueous NaOH to give XIa as a crystalline precipitate in 60% yield. Extraction of the filtrate with chloroform gave an additional ~20% product XIa.

C. Heating amiznofuropyrimidine VIa in pyridine at reflux led to a 2:1 mixture of the starting compound and dehydrochlorination product XIa. Repeated sublimation of VIa in the presence of BaO or CaO gave a mixture of these compounds; the VIa:XIa ratio was 1:2.

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