HETEROCYCLES, Vol. 7, No. 2, 1977

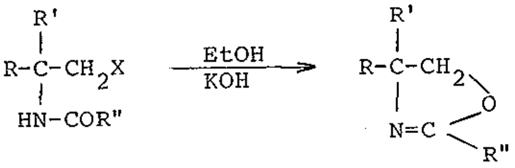
A NOVEL SYNTHESIS OF 4-HYDROXYPYRIMIDINE DERIVATIVES[1]

Edward Grochowski*
Institute of Organic Chemistry, Polish Academy of Sciences,
00-961 Warsaw, Poland
Zygmunt Eckstein
Institute of Organic Chemistry and Technology,
Polytechnical University, 00-662 Warsaw, Poland

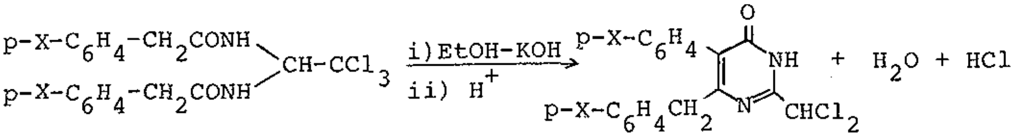
It was found that 2,2,2-trichloroethylidene-N,N'-bis-phenylacetamide derivatives in alcoholic potassium hydroxide undergo a cyclization to give 5-aryl-6-arymethyl-2-dichloromethyl-4-hydroxypyrimidines.

In our previous communication[2] on the reaction of nitriles with aldehydes, we have reported that 2,2,2-trichloroethylidene-N,N'-bis-phenylacetamides (I) react differently with alkaline reagents from other alkylidene-N,N'-bis-amides. Alkaline hydrolysis of the latter was described in details in the literatures[3] to produce the corresponding carboxylic acids. Under similar conditions, 2,2,2-trichloroethylidene-N,N'-bisbenzamide[4] are also hydrolysed to benzoic acid. Further, it is known that N-(2-halo-1-ethyl)-carboxamides in alcoholic potassium hydroxide, or on long storage, undergo cyclization to give 2-oxazolines.

$$\begin{matrix}\mathrm{RCONH}\\\mathrm{RCONH}\end{matrix}\!\!>\mathrm{CH{-}R'}\longrightarrow 2\mathrm{RCOOH}+\mathrm{R'CHO}$$



On the other hand, bisphenylacetamides (I) are not hydrolysed by alcoholic potassium hydroxide, but they eliminate one molecule of water and one molecule of hydrogen chloride to form the 4-pyrimidinol derivatives (II). In this paper we wish to report this transformation on 2,2,2-trichloroethylidene-N,N'-bisphenylacetamide, as the model compound, in details.



Ia-f

IIa-f

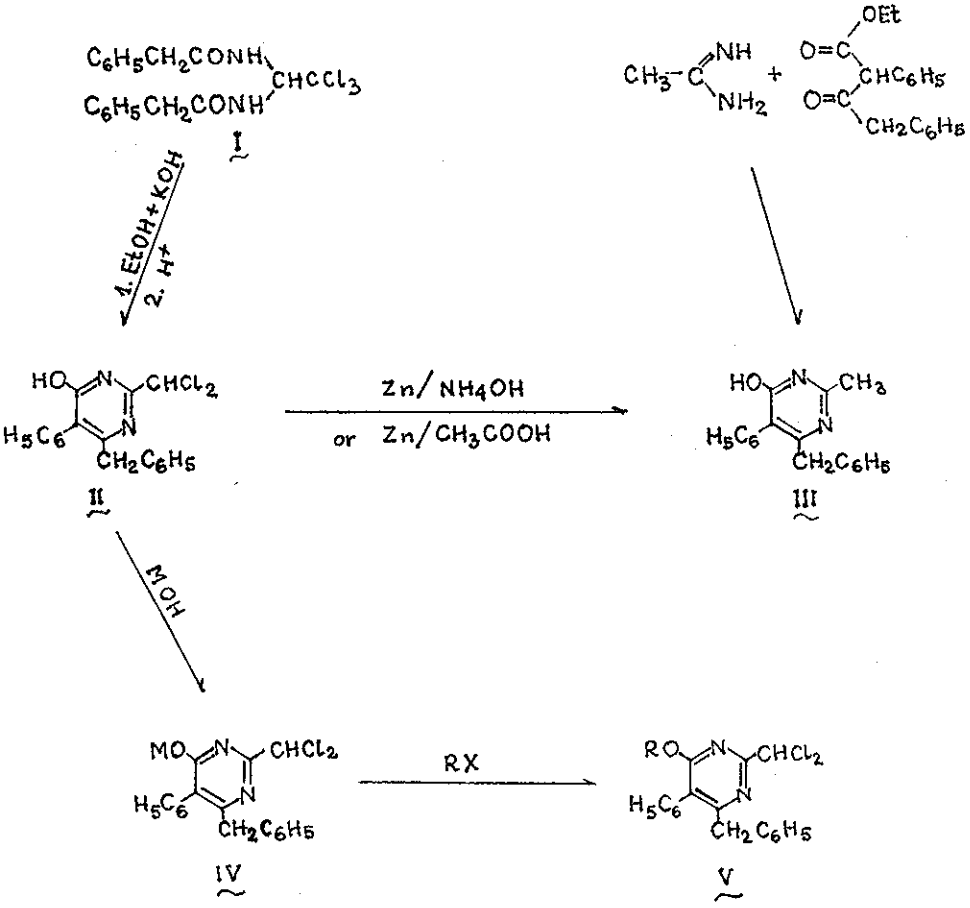
a, X=H, b, X=Cl, c, X=Br, d, X=I, e, X=F, f, X=CH_3O

Titration indicated that the resulting compound II (colorless crystals, m.p. 153.5 - 154°C, 62 % yield) contains one acidic hydrogen. From a solution of the substance in aqueous sodium hydroxide, its stable salt could be isolated, but it did not dissolve in aqueous sodium carbonate. The reaction of the silver salt of II, prepared from sodium salt and silver nitrate, with ethyl iodide gave a monoethyl derivative Va, and the sodium, potassium or silver salt of II reacted with acetyl and benzoyl chloride to afford the corresponding monoacyl derivatives Vb and Vc respectively. The ir spectra of the derivatives Va-c do not exhibit the characteristic bands due to the lactam system which are observed in the spectrum of the starting material II (ν_{CO} = 1650 cm^{-1} and ν_{NH} = 3155 cm^{-1}). This fact proves that they are O-alkyl and O-acyl derivatives of II.

Reduction of II with zinc dust in acetic acid or with zinc dust in aqueous ammonia gave compound III, which did not contain chlorine any more and was still weakly acidic. Its ir spectrum indicated the presence of a lactam system, and its pmr spectrum showed signals at 7.40, 4.07 and 2.83 ppm with relative intensities 10:2:3, respectively. The singlet at 2.83 ppm (3H) indicates the presence of methyl group which located on the heteroaromatic ring. The signal at 4.07 ppm (2H, s) was assignable to benzylic protons and the multiplet at 7.40 ppm (10 H) to aromatic protons.

The above data show that the reaction product (II) has most probably the pyrimidine structure as shown in Scheme 1.

In order to prove this fact, we carried out an alternative synthesis of 6-benzyl-4-hydroxy-2-methyl-5-phenylpyrimidine according to Wajon and Arens[6] (Scheme 1), and the product obtained was identical with our compound III in all respects.



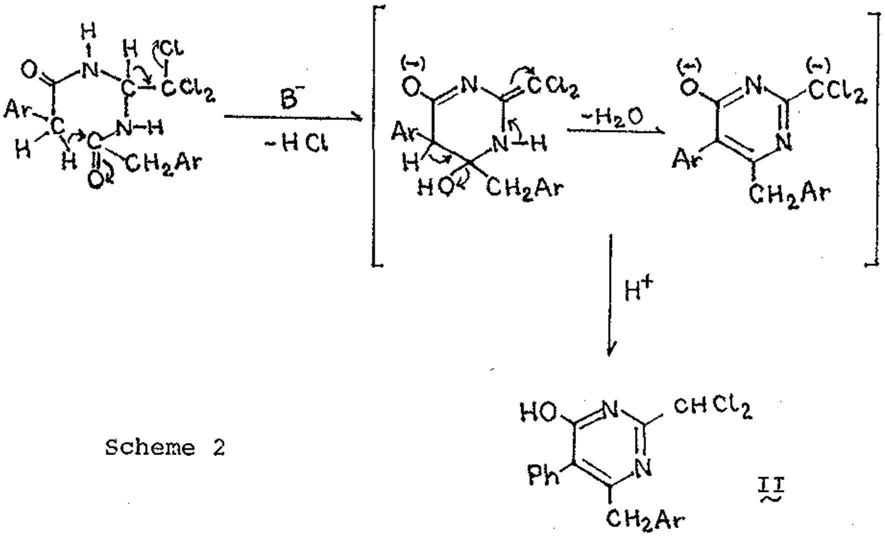
IVa : M = Na
IVb : M = K
IVc : M = Ag

Va : R = C_2H_5
Vb : R = CH_3CO
Vc : R = C_6H_5CO

Scheme 1

Similar transformations of other phenyl-substituted 2,2,2-trichloroethylidene-N,N'-bis-phenylacetamide (I) into pyrimidines were observed (Table 1).

The following reaction mechanism for the formation of the pyrimidine ring from 2,2,2-trichloroethylidene-N,N'-bis-arylacetamides (I) is shown in Scheme 2.



Scheme 2

Further studies on the pyrimidone-pyrimidinol tautomerism of compound II concerned its spectral properties. The ir spectrum of its 0.0025 M solution in tetrachloromethane was investigated in the region characteristic of valency vibrations of the NH and OH groups. Thus in the region 4000-3000 cm^{-1}, compound II has two sharp absorption bands at 3563 cm^{-1} (low intensity) and at 3396 cm^{-1} (high intensity). The former band at 3563 cm^{-1} could be assigned to the valence vibration of the free OH group, which might indicate the presence of the hydroxy form in dilute solution, whereas the band 3396 cm^{-1} is clearly due to NH stretching vibrations.

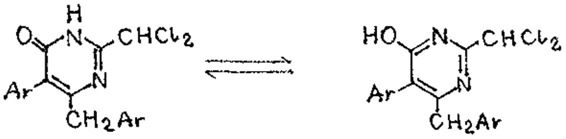
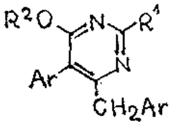


Table 1 shows a list of some pyrimidines newly obtained. All the new compounds therein gave satisfactory microanalyses, and their spectral data (ir and pmr) confirmed the proposed structures.

Table 1. 4-Hydroxypyrimidines.



No	Ar	R^1	R^2	yield %	mp
II	C_6H_5	$CHCl_2$	H	62	153.5-154.5
III	$C_6H\ _5$	CH_3	H	68	229-230
Va	C_6H_5	$CHCl_2$	C_2H_5	90	92-93
Vb	C_6H_5	$CHCl_2$	CH_3CO	92	81-82
Vc	C_6H_5	$CHCl_2$	C_6H_5CO	96	137-138.5
VI	$pF{-}C_6H_4$	$CHCl_2$	H	68	175-176
VII	$mCl{-}C_6H_4$	$CHCl_2$	H	70	158-159
VIII	$pCl{-}C_6H_4$	$CHCl_2$	H	73	195-196
IX	$pBr{-}C_6H_4$	$CHCl_2$	H	60	206.5-207.5
X	$pJ{-}C_6H_4$	$CHCl_2$	H	58	227-228
XI	$pCH_3O{-}C_6H_4$	$CHCl_2$	H	63	192-194

The reaction described above presents a new facile method for the synthesis of 4-hydroxypyrimidine derivatives.

General procedure for the preparation of 5-aryl-6-arylmethyl-2-dichloromethyl-4-hydroxypyrimidines is as follows: A mixture of 0.1 mole of 2,2,2-trichloroethylidene-N,N'-bis-arylacetamide,[7] 0.3 mole of potassium hydroxide and 300 ml of ethanol was refluxed for 2 - 3 hr. After the reaction, most of ethanol was removed *in vacuo* and the residue was then diluted with 300 ml of water. The resulting aqueous solution was treated with charcoal, heated under boiling, and filtered. The filtrate was cooled and acidified with acetic acid. The precipitates were collected and recrystallized from acetone, alcohol or chloroform. The yields are given in Table 1.

ACKNOWLEDGEMENT

We are very much indebted to Professor M. Kocór for his helpful discussion.

REFERENCES

1. This paper forms Part IV in the series of "Electrophilic Reactions of the Cyano Group", Part III, see Ref. 7, Part V, *Bull. Acad. Polon. Sci., Sér. Sci. chim.*, 1971, **19**, 371.
2. Z. Eckstein and E. Grochowski, *Przemysl Chem.*, 1959, **38**, 693.
3. E. Hepp and G. Spiess, *Ber.*, 1867, **9**, 1424.
4. R. F. Batt and D. Woodcock, *J. Chem. Soc.*, 1948, 2322.
5. R. M. Luskin and J. J. Ritter, *J. Amer. Chem. Soc.*, 1950, **72**, 5577.

6. J. F. Wajon and J. F. Arens, *Rec. Trav. chim.*, 1956, **76**, 79.

7. E. Grochowski and Z. Eckstein, *Roczniki Chem.*, 1970, **44**, 2173.

Received, 5th August, 1977