Tetrahedron Letters No. 17, pp 1475 - 1478, 1973. Pergamon Press. Printed in Great Britain.

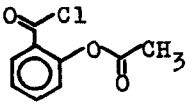
A NEW REACTION OF ACETYLSALICYLOYL CHLORIDE WITH 1,2-, 1,3- AND 1,4-DIOLS AND ALCOHOLS.

A.A.Akhrem, V.V.Zharkov, G.V.Zaitseva and I.A.Mikhailopulo[1]

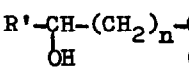
Department of Bioorganic Chemistry, Institute of Physical Organic Chemistry, Byelorussian SSR Academy of Sciences, Minsk, USSR

(Received in UK 25 January 1973; accepted for publication 15 March 1973)

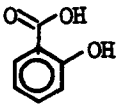
We have found acetylsalicyloyl chloride[2](1) to be reacting, in the absence of HCl acceptors, with 1,2-, 1,3- and 1,4-diols (2-7) to produce salicylic acid (14) and β-, γ- and δ-chloroalkyl acetates[3] (8-13), respectively.



1



2, n=0, R=R'=H	8, n=0, R=R'=H
3, n=0, R'=H, R=CH_3	9, n=0, a, R'=H, R=CH_3
	b, R'=CH_3, R=H
4, n=0, R'=R=CH_3	10, n=0, R'=R=CH_3
5, n=1, R'=H, R=CH_3	11, n=1, a, R'=H, R=CH_3
	b, R'=CH_3, R=H
6, n=1, R'=R=H	12, n=1, R'=R=H
7, n=2, R'=R=H	13, n=2, R'=R=H



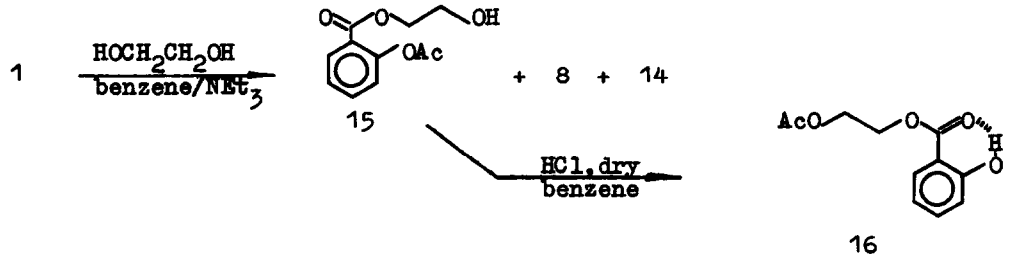
14

On mixing equimolar amounts of reagents in the absence of solvent a rapid exothermic reaction occured; in anhydrous pentane, benzene, methyl cyanide or dioxan, at 30 to 50 per cent concentrations of the reagents, completion period of the reaction was from 10 to 60 minutes, whereas in thinly dilute solutions (3 to 5%) this period was 12 to 36 hrs long and gave rise to formation of products in high yield (60-90%).

The reaction of 1,2-propanediol (3) with (1) in pentane at room temperature mainly gave β-chloroisopropyl acetate (9, a; pmr data[4]: δ 4,82 multiplet centre, 1H, AcO-C<u>H</u>; 3,40 d, 2H, Cl-C<u>H</u>$_2$, J=5Hz; 1,92 s, 3H, C<u>H</u>$_3$-CO; 1,20 d, 3H, C-C<u>H</u>$_3$, J=6Hz) along with small amounts (ca. 10% by glc

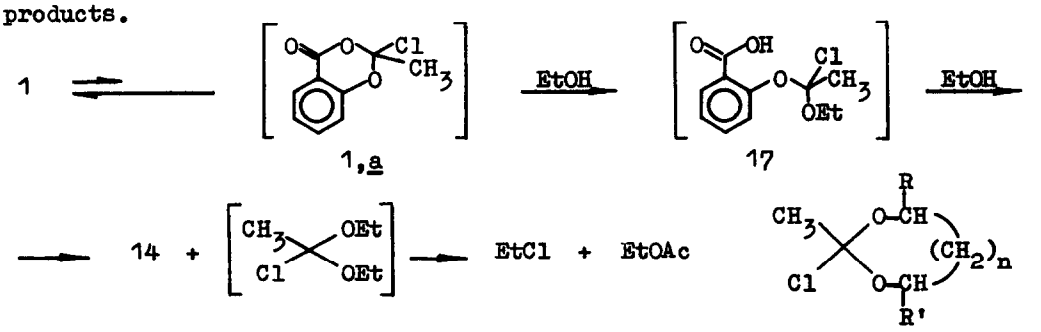
data) of β-chloropropyl acetate (9,b). Under similar conditions, the reaction of (1) with (5) resulted in a mixture of isomeric derivatives (11,a) and (11,b) in the ratio ca. 1:1. Furthermore, reactions of (1) with (4) and (5) were observed to produce diacetate derivatives of diols together with the main products (10) and (11), respectively.

The interaction that occurs between (1) and (2) in anhydrous benzene at 20°C in the presence of NEt_3 (with a 5% excess) predominantly gave β-oxyethyl acetylsalicylate (15)(an oil-like product, 80% yield, ν C=O 1720 cm^{-1} Ar-C=O; ν C=O 1770 cm^{-1} Ac-OAr; ν OH 3520 cm^{-1}), as well as β-chloroethyl acetate (8)(ca. 5% yield as estimated by glc and ir analyses: ν C=O 1740 cm^{-1}) and (14). A 6-hours' treatment of the benzene solution (15) with dry HCl at 20°C resulted in the formation of mixture (15) with β-acetoxyethyl salicylate (16)(ν C=O 1740 cm^{-1} Ac-OAlk; ν C=O 1680 cm^{-1} Ar-C=O; ν OH 3200 cm^{-1}, the intensity not changing in ultimately diluted CCl_4 solutions[5]); no formation of (8) took place under these conditions, and (15) was not, therefore, any intermediate product of the (2) to (8) transformation, resulting from the interaction of (1) with (2) in the absence of HCl acceptor. Moreover, (8) is formed in the course of formation of (15), most probably, as a result of a concurrent reaction not linked with the disengagement of free HCl.



Alcohols (EtOH, isoamyl alcohol) reacted with (1)(molar ratio of reactants - 2:1) in the absence of HCl acceptors to give respective alkyl chlorides and acetates in a yield ratio of about 1:1,2 (total yield 80% based on alcohol) and (14). To ascertain the process of this reaction, we have analysed the reaction of(1) with $Et^{18}OH$ (11,8% enrichment), as a result of which EtOAc, EtCl and (14) have been separated. The mass spectrum of (14) was found to contain no ^{18}O-ions, whereas that of EtOAc clearly showed the following ions:

M/e 90 ($CH_3C^{18}OOEt$ + $CH_3CO^{18}OEt$, 19% of the total peak intensity at M/e 88, 90 and 92), M/e 92 ($CH_3C^{18}O^{18}OEt$, 1%), M/e 75 ($C^{18}OOEt$ + $CO^{18}OEt$, 18%), M/e 63 ($CH_3C^{18}OOH_2$ + $CH_3CO^{18}OH_2$, 18%). The ^{18}O-incorporations of carbonyl and alcoholic oxygens (ca.6% and ca.10% respectively) in ethylacetate were estimated by comparing the intensity of their peaks in the product mass spectrum with that of ordinary EtOAc. If (1) is assumed to exist as an equilibrium mixture with the cyclic structure (1,a), the reaction must be represented by the following scheme which agrees with the ^{18}O-distribution in the reaction products.



1,a 17 18 19

We have failed to detect any cyclic structure (1,a) in (1) by means of ir-spectroscopy; however, this does not preclude the probability of its existence in low concentrations. If so, (1,a) ought to offer a very intense reactivity to nucleophiles. The proposed scheme is in good agreement with the mass-spectrometric analysis data: (i) absence of ^{18}O in (14); (ii) there is a good agreement between the data obtained in the analysis and the ^{18}O distribution in EtOAc as calculated from the proposed reaction scheme in case 11,8% ^{18}O-enriched ethanol is used: M/e 88 - 79,5%, M/e 90 - 19,5% and M/e 92 - 1%; the overestimated percentage of $^{18}O\overset{+}{E}t$-fragment, as compared with $\overset{+}{C}H_3C^{18}O$, in the mass spectrum of the tracer-tagged EtOAc can be accounted for by a measurement error due to overlapping by normal peaks in this region. In no way do these data exclude the probability of another way of the formation of the final products of the reaction of (1) with EtOH, viz., disintegration of the intermediate compound (17) into EtCl and acetylsalicylic acid with subsequent migration of the acetyl group from the latter to EtOH. The available information does not enable one to put forward an exact scheme of

the reaction of alcohols with (1); in the case of diols, however, at least of (2),(6) and (7), the reaction with (1) involves, in the main, formation of (19) as the most probable intermediate product, this being evidenced by the absence of detectable amounts of diacetyl or/and dichloro derivatives of diols in the products of the reaction. The unstable intermediates (18) and (19) had been expected earlier in other reactions with similar end-products[6].

The rearrangement of (19) into the end-products is likely to involve S_{ni} mechanism or a tight ion-pair, without establishing equilibrium with the solvent. This assumption is proved by the formation of (8) in the reaction of (1) with (2) in the presence of triethylamine as well as by the experiment with 91% DO-enriched ethylene glycol where we found no deuterium incorporation into (8).

We have successfully applied the reaction to synthesize chlorodeoxy sugars and -nucleosides, which will be reported on elsewhere.

Acknowledgements: We wish to thank Dr. S.I.Zavialov (N.D.Zelinsky Institute of Organic Chemistry, USSR Academy of Sciences, Moscow) for helpful advices and discussions. We thank Dr. D.A.Fesenko and Mr. O.A.Strelchonok (this Institute) for recording the nmr and mass spectra.

References

1. Author to whom inquiries may be addressed.
2. H.Schonenberger, J.Holzheu-Eckardt, E.Bamann, Arzneimittel-Forsch., 14, 324 (1964).
3. All compounds gave satisfactory elemental analyses.
4. PMR spectra were obtained on a Carl Zeiss (DDR) Modell ZKR-60 spectrometer. GLC analyses were carried out on a Chrom-3 (CSSR) gas chromatograph, using the 1,3 m stainless steel column of 20% E-301 on Chromosorb W. IR spectra were taken on a Carl Zeiss (DDR) Modell UR-20 spectrophotometer. Mass spectra were determined on a MX-1303(USSR) spectrometer.
5. N.Mori, Y.Asano, Y.Tsuzuki, Bull. Chem. Soc., Japan, 42, 488 (1969).
6. M.S.Newman, C.H.Chen, J. Amer. Chem. Soc., 94, 2149 (1972) and references cited therein.