DEHYDRATION OF 3- AND 4-ARYL- SUBSTITUTED 3-HYDROXY ACIDS IN ACETIC ANHYDRIDE IN PRESENCE OF ZINC CHLORIDE

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(Received in UK 22 January 1973; Accepted for publication 5 February 1973)

Abstract – The reaction of several di- and triaryl-substituted 3-aryl-3-hydroxy acids and a 4-aryl-3-hydroxy acid in acetic anhydride in the presence of anhydrous zinc chloride has been investigated. It has been shown that the reaction discovered with 3-(2'-thienyl)-substituted 3-hydroxy acids, namely, their conversion under the above stated conditions into α , β -unsaturated methyl ketones,^{1,2} occurs also with 3-aryl 3-hydroxy acids but to a smaller degree due to the concurrent cyclization reaction which leads to indene-1-ones. It has been established that the unsaturated methyl-ketones obtained, containing three aromatic substituted 3-hydroxy acid almost no unsaturated ketone is obtained, whereas instead the main product is a 2,3-disubstituted 1-naphthol which is acetylated under the conditions of the reaction. Its structure has been proved by its UV, IR and NMR spectra and confirmed by the mass spectrum of the compound.

In our previous papers we reported that in the experiments on the cyclization of 3-(2'-thienyl)-substituted 3-hydroxy acids to derivatives of 4H-cyclopenta/b) thiophene-4-one 1a-d in a 1:1 mixture of Ac₂O and glacial AcOH in the presence of anhydrous zinc chloride¹ no cyclization with the 3-carbon atoms of thiophene occurred, whereas α , β -unsaturated-4-(2'-thienyl)-substituted methylketones 2a-f

On the basis of the mechanism proposed, according to which the unsaturated methyl ketones are obtained from the intermediate⁴ mixed anhydrides of the corresponding acetoxy acids with acetic acid (**3a-d**), we changed the reaction conditions in view of the preliminary formation of **3**. On heating with zinc chloride, **3a-d** are decomposed mainly into unsaturated methyl ketones and thienylsubstituted stilbenes, while indene-1-ones (in case,



were obtained in a good yield^{2,3}. Cyclization proceeds in a small degree to indene-1-ones only when a phenyl substituent is available in a β -position of the initial hydroxy acid. In absence of zinc chloride only the compounds,^{4–6} normal for the dehydration in acetic anhydride were obtained, i.e. anhydrides of the corresponding cinnamic acids and thienylsubstituted stilbenes.³

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their formation is possible) are obtained only in trace amounts.

The purpose of the present investigation was to check whether this new reaction of hydroxy acids their conversion into unsaturated methyl-ketones proceeds only with thienyl-substituted acids or whether it has a general validity. Moreover, this method¹ has been proposed for the preparation of

2-Th-C(R)-CH-CO₂Ac
$$\xrightarrow{t^{\circ}}$$
 2-Th-C(R)=C-COMe + AcO ^{Θ} + CO₂
Ph Ph
3a-d 2a-f
3a: R = Me
3b: R = Et
3c: R = Ph
3d: R = 2-Th

indene-1-ones, and there are no data in the literature concerning the formation of other compounds under the reaction conditions.

The present paper reports the results of a study on the dehydration of 2,3-diphenyl-3-hydroxybutanoic acid (4a),2,3,3-triphenyl-3-hydroxypropanoic acid (4b) and 2,3-diphenyl-3-(2'-naphthyl)-3hydroxypropanoic acid (4c), as well as of 2,4diphenyl-3-methyl-3-hydroxybutanoic acid (5), not yet described, which cannot be cyclizated to an indene-1-one.

The acids were prepared from magnesosodium phenylacetate and aromatic ketones.⁷ The main isomer was isolated from the acid mixture by recrystallization. As it is known that the dehydration of aryl-substituted hydroxy acids does not take place stereospecifically,³⁻⁶ the configuration of the isolated acids has not been determined.

The dehydration of the hydroxy acids was carried out according to the Lit.¹ as well as by a method modified.³ The reaction mixture was treated as described previously:^{2,3} hydrolysis with water or conc hydrochloric acid, extraction of the organic products with ether, and isolation of the neutral compounds. The composition of the neutral products was measured by TLC and IR spectroscopy. The formation of methyl ketones was checked with the iodoform test.

The dehydration of 4a-c proceeds with the formation mainly of the corresponding indene-1-ones and stilbenes. In addition, compounds in a low vield (8-10%) were also obtained, which, according to their chromatographic behaviour and characteristic IR spectra, represented the respective α,β unsaturated methyl ketones. When conditions for the preliminary formation of mixed anhydrides of type 3 were provided, (i.e. heating the hydroxy acids for 4-5 hr in Ac₂O at 65-70°), followed by a temperature increase to the b.p. of the reaction mixture in the presence of zinc chloride,3 the composition of the neutral products was altered. That means, the amount of indene-1-ones was sharply decreased, whereas the formation of the corresponding unsaturated methyl ketones increased.

From the mixture of neutral products, obtained by dehydration of 4a,³ were isolated by preparative TLC, besides the known *trans*-1,2-diphenyl-prop-1-ene and 2-phenyl-3-methyl-indene-1-one, also a pale yellow non-crystalline substance which under UV light proved to be a mixture of two products. By rechromatography yellow needle-like crystals and a pale yellow non-crystalline product was obtained. On the basis of the 1R, UV, and NMR spectra, and the iodoform test, these compounds were assigned the structures of the geometrically isomeric 3,4-diphenyl-pent-3-ene-2-ones 6a, b. The type of the aromatic multiplets in the NMR spectra as well as some physical constants indicated that the crystalline substance was the *trans*-diphenyl isomer **6a**, while the non-crystalline product was the *cis*-diphenyl isomer **6b**.



The experiments on 4b, led to analogous results. The amount of the 2,3-diphenyl-indene-1-one formed decreased from 30% to 3-4% on dehydration,³ whereas the yield of the unsaturated methyl ketone increased from 7% to 32%. In all experiments carried out triphenylethylene and benzophenone were also isolated, the latter being formed from the decomposition of part of the initial hydroxy acid. We assigned the structure 3,4,4triphenyl-but-3-ene-2-one (6c) to the unsaturated ketone isolated on the basis of its 1R, UV, and NMR spectra and the iodoform test.

Contrary to the IR spectra of 6a, b and of thienylsubstituted ketones of the same group,^{2,3} in the IR spectrum of 6c the frequency of the CO absorption is relatively high for unsaturated ketones. 1692 cm⁻¹, while its intensity can be compared with that of the C==C group at 1605 cm⁻¹. These intensities as well as the great distance between the two absorption bands is, as is well known, an analytical indication of the presence of s-cis-(C==C, C==O)conformation.⁸⁻¹⁰ The decreased intensity of the maxima, characteristic of α,β -unsaturated carbonyl compounds in the UV spectrum of this compound. is in agreement with the data from the IR spectrum.^{11, 12} The Dreiding model of the molecule also shows that this conformation seems to be sterically more favourable.



When 4c was dehydrated, in all experiments carried out mainly stilbenes and the isomeric 2-phenyl-3-(2'-naphthyl)- indene-1-one and 2,3-diphenylbenz (6,7) indene-1-one were obtained. The formation of an unsaturated methyl ketone was impeded, presumably due to steric reasons. The yield of the 3,4-diphenyl-4-(2'-naphthyl)-but-3-ene-2-one (6d) isolated was 5-15%. The intensity and the position of the bands for the C=C and C=O groups in the IR spectrum of the compound indicate, in agreement with the sterical model of the molecule, that this ketone too, exists in a s-cis-(C=C, C=O)-conformation.

These results show that the interaction between di- and triaryl-substituted hydroxy acids and Ac₂O in the presence of zinc chloride proceeds with the formation of a large number of neutral compounds: unsaturated methyl ketones, stilbenes, cyclic ketones, and it is additionally complicated especially in the case of triaryl-substituted acids, by their decomposition into the initial ketone and phenylacetic acid. The formation of unsaturated methyl ketones with the acids 4a-c proceeds with greater difficulty and gives a lower yield, as compared with analogous 3-(2'-thienyl)-substituted 3-hvdroxy acids. Here, however, a cyclization reaction leading to the corresponding inden-1-ones occurs (with a phenyl substituent at β -position in the hydroxy acid), whereas under the same conditions analogous thienyl-substituted hydroxy acids are not cyclizated to the derivatives of 4H-cyclopenta (b) thiophene-4-one 1. The reason for this lies in the higher reactivity of the o-carbon atoms of the phenyl nucleus, in contrast to the 3-carbon atoms of the thienyl nucleus towards electrophilic reagents. such as the acyl complexes with zinc chloride are and mainly in the lower formation energy of the indenone system, as compared to that of 4Hcyclopenta (b) thiophene-4-one. The yield of unsaturated methyl ketones increased considerably as shown above, by the preliminary preparation of mixed anhydrides of the respective acetoxy-acids with acetic acid, which confirms the mechanism assumed for their formation from these anhydrides,

3-hydroxybutanoic acid (5) were carried out. Because of the impossibility of cyclization to indene-1one, the primarily formation of an unsaturated ketone could be expected. When 5 was dehydrated according to both methods,^{1,3} only traces of such ketone were formed, whereas the main product of the reaction, obtained in a high yield (51%), represented a colourless crystalline substance which gave no reactions, characteristic of unsaturated methyl ketones (the iodoform test and the specific colouration with conc sulphuric acid). In its IR spectrum two intensive absorption bands appeared at 1775 cm⁻¹ and 1205 cm⁻¹ (the latter being split and having higher intensity), as well as a moderately intensive absorption at 1370 cm⁻¹, indicating the presence of an acetate group in the molecule. The specific "acetate bands" were shifted, as seen towards the respective higher and lower frequencies. which indicated that the AcO- group is connected with an sp²-hybridized C atom. The UV spectrum showed the multiplet structure, characteristic of naphthalene derivatives. the longest-wavemaximum being positioned at 320 nm. In the NMR spectrum two singlet signals appeared for Me groups, at 1.93 ppm and 2.16 ppm (δ -units), for an acetate and an aromatic-bound Me group. The data suggested that the compound obtained represented 2-phenyl-3-methyl-1-acetoxy-naphthalene (7), formed according to the following scheme:



most probably bound in complexes with zinc chloride, by a subsequent or a synchronous elimination of AcO^- and $CO_2^{2,2,3}$

Nevertheless, in comparison with the formation of analogous 4-(2'-thienyl)-substituted methyl ketones,^{2,3} the yield was considerably lower in this case. It is evident, that the presence of a 2-thienyl group in the initial hydroxy acid is favourable for the formation of these ketones. At the present stage, it is difficult to explain this influence precisely. Probably the effect is to facilitate the decarboxylation of either the anhydrides or their complexes with zinc chloride. Naturally, it can be presumed that the more difficult formation of unsaturated methyl ketones may be due to steric factors acting during the transitional state.

Further experiments with 2,4-diphenyl-3-methyl-

This structure was confirmed by the mass spectrum of the compound. The molecular peak had m/e 276, confirming the molecular formula $C_{19}H_{16}O_2$, while the most intensive peaks were at m/e 234 (78%) and m/e 233 (100%), due to the formation of the A(M-43), and B(M-42) ions.

The too high intensity of the peak with m/e 233 was presumably due to the superposition with the peaks of other fragments, obtained from the molecular ion by the loss of m/e 42 and hydrogen or from A by elimination of hydrogen (from the methyl group or from the ring) with the following formation of the hydroxybenztropylium ion C (fragmentation, characteristic of alkylated naphthalenes and cresols),^{13, 14} from which via hydrogen elimination the troponium ion D (m/e 232) originated. With the fragmentation of the latter, characteristic of tropone

derivatives, the expulsion of CO (cf Ref 15) we could explain the presence of peaks with m/e 204, 127, and 128, which presumably represent phenylnaphthalene and naphthalene ions. The appearance of ions with m/e 217 and 216 could be explained by the elimination of OH or H₂O from ion A. Such a process was observed with some alkylated phenols. Most probably the phenyltropylium ion E was produced from which by loss of a fragment with m/e 26 (acetylene) the ion with m/e 191 (presumably 2-phenylindenyl cation) was formed.

EXPERIMENTAL

1. Dehydration of 2,3-diphenyl-3-hydroxybutanoic acid

A. The hydroxy acid (1.01 g) was heated in 20 ml 1:1 mixture of Ac₂O and glacial AcOH and 0.3 g anhyd ZnCl₂ for 30-40 min at the b.p. of the reaction mixture. Water was then added and organic products were extracted with ether. The ether soln was treated with Na₂CO₃aq (to extract the carboxylic acids), washed with water and dried (Na₂SO₄). After distillation of the ether 0.78 g mixture of neutral products was obtained.

B. The hydroxy acid (1.00 g) was heated in 15 ml Ac₂O for 5 hr at 60-65°. Then 0.4 g anhyd ZnCl₂ was added and



the temp was increased. At the b.p. of the mixture a vigorous evolution of CO_2 (precipitated as BaCO₃) was observed, which ceased after 3-4 min. The mixture was hydrolysed and treated as described in IA. The mixture (0-80 g) of neutral products was subjected to preparative TLC* (light petroleum: benzene = 2.5:1). The isolated products were 0-18 g trans-1,2-diphenyl-prop-2-ene, 0-04 g 2-phenyl-3-methyl-indene-1-one, and 0-36 g mixture of yellow substances which was again subjected to chromatography (solvent system, light petroleum: acetone = $50:1\cdot2$). After rechromatography 0-20 g (25%) yellow crystals with m.p. $111-112^{\circ}$ (from EtOH) 6a, and 0-10 g (11%) yellow non-crystalline substance 6b were obtained. Both these compounds gave a positive iodoform test and a yellow-orange colouration with conc H₂SQ₄.

IR spectrum C=O: 1689 cm⁻¹(s); C=C: 1628 cm⁻¹ (w); Ac: 1360 cm⁻¹ (m) Me: 2930 cm⁻¹(m), 2860 cm⁻¹(w), 1475 cm⁻¹(m) and 1386 cm⁻¹(w); UV spectrum: λ max at 265 nm (ϵ = 11,300) and 317 nm (ϵ = 8,900); NMR spectrum: MeC=C: 2.64 ppm (s, 3H); Ac: 2.72 ppm (s, 3H); aromatic protons: 7.18–7.92 ppm (m, 10H). (Found: C, 86-22; H, 7.03; Calc for C₁₇H₁₆O: C, 86-44; H, 6.85%). The semicarbazone (obtained by the conventional method): pale yellow crystals with m.p. 185–186° (from EtOH).

Yellow non-crystalline substance. IR spectrum: C==O: 1688 cm⁻¹(s); C==C: 1624 cm⁻¹(w); Ac; 1355 cm⁻¹(m); Me: 2928 cm⁻¹(m), 2855 cm⁻¹(w), 1465 cm⁻¹(m), 1379 cm⁻¹(w); UV spectrum: λ max at 257 nm (ϵ = 10,100) and 310 nm (ϵ = 9,200); NMR spectrum: MeC==C: 2.69 ppm (s, 3H); Ac: 2.71 ppm (s, 3H); aromatic protons 7.10-7.40 ppm (m, 10H). The semicarbazone: pale yellow crystals with m.p. 169-170° (from EtOH). (Found: C, 73.68; H, 6-90; N, 13.95; Calc for C₁₈H₁₉ON₃: C, 73.72; H, 6.72; N, 14.22).

2. Dehydration of 2,3,3-triphenyl-3-hydroxypropanoic acid

A. According to procedure 1A, from 1.01 g hydroxy acid, a mixture of 0.83 g of neutral products was obtained, which contained 2,3-diphenyl-indene-1-one, diphenyl ketone and small quantity of a carbonyl compound with m.p. $132-133^{\circ}$.

B. According to procedure 1B, from 1-00 g hydroxy acid, a mixture of 0-8 g of neutral products was subjected to preparative TLC (light petroleum: acetone: EtOAc = 50:1-2:1-5) yielding: 0-18 g triphenyl-ethylene, 0-07 g (3.1-2) yielding: 0-18 g triphenyl-ethylene, 0-07 g (3.1-2) yielding: 0-18 g triphenyl-thylene, 0-07 g (3.1-2) yielding: 0-29 g (3.1-2) yielding: 0-18 g triphenyl-thylene, 0-07 g (3.1-2) yielding: 0-29 g (3.1-2) yieldin

3. Dehydration of 2,3-diphenyl-3-(2'-naphthyl)-3-hydroxypropanoic acid

According to 1B, 1.03 g of hydroxy acid gave 0.84 g mixture of neutral products which when subjected to pre-

parative TLC (light petroleum: benzene: acetone = 45:7:1), gave 0.12 g stilbenes, 0.15 g 2-phenyl-3-(2'-naphthyl)-indene-1-one, 0.30 g of 2,3-diphenyl-benz (6,7) indene-1-one, 0.09 g phenyl-2-naphthyl ketone, and 0.1068 g (11%) of a pale-yellow crystalline substance with a m.p. 118-119° (from MeOH), which gave a positive iodoform test and a yellow-orange colouration with conc H₂SO₄.

IR spectrum: C=O: 1688 cm⁻¹(s); C=C: 1600 cm⁻¹ (s); Ac: 1362 cm⁻¹(m), NMR spectrum: Ac: 2.41 ppm (s, 3H); aromatic protons: 7.07-8.20 ppm (m, 17H). (Found: C, 89.57; H, 5.90; Calc for $C_{26}H_{20}O$: C, 89.69; H, 5.78).

4. Dehydration of 2,4-diphenyl-3-methyl-3-hydroxybutanoic acid

A. According to 1A, from 1.00 g hydroxy acid, the reaction yielded 0.84 g neutral products. Preparative TLC (light petroleum: benzene = 2.5:1) yielded: 0.18 g stilbenes, 0.41 g colourless crystals with m.p. $81-82^{\circ}$ (from EtOH), as well as a small quantity of other substances.

B. According to 1B, 1.00 g hydroxy acid yielded 0.85 g mixture of neutral products, which when subjected to preparative TLC (light petroleum: benzene = 2.2:1), gave: 0.17 g of stilbenes, 0.49 g (48.70%) of a product with m.p. 82°, 0.095 g of a mixture, composed of a substance with m.p. 82° and a substance which had an intensive blue fluorescence (under UV light), as well as a complex mixture of several, more polar products. From the mixture of these two substances by rechromatography (light petroleum: acetone = 50:1.5) were isolated 0.054 g of a substance which gave a positive iodoform test and a specific colouration with conc H₂SO₄.

Non-crystalline substance. IR spectrum: C=O: 1687 cm⁻¹(s); C=C: 1635 cm⁻¹; Ac: 1362 cm⁻¹(m). Substance with m.p. $81-82^{\circ}$. (Found: C, 82.43; H, 5.94; Calc for C₁₉H₁₆O₂: C, 82.58; H, 5.84.)

IR spectrum: -O.Ac: C=O: 1775 cm⁻¹(s); =C-O-C: 1205 cm⁻¹(vs) and 1030 cm⁻¹(m); Ac: 1370 cm⁻¹(s); Me: 2980 cm⁻¹(w), 2930 cm⁻¹(m), 2860 cm⁻¹(w), 1465 cm⁻¹(w) and 1381 cm⁻¹(w); aromatic ring: 3075 cm⁻¹(m), 3030 cm⁻¹(w), 1605 cm⁻¹(w), 1500 cm⁻¹(m), 1448 cm⁻¹ (m), 1068 cm⁻¹(s), 900 cm⁻¹(m), 882 cm⁻¹(m), 850 cm⁻¹ (m), 705 cm⁻¹(s) and 680 cm⁻¹(w).

NMR spectrum: Me: 2·16 ppm (s, 3H); O.Ac: 1·93 ppm (s, 3H); aromatic protons: 7·14–7·78 ppm (m, 10H).

Mass spectrum: M=276 (25·8%); m/e 234 (78·0), 233 (100%), 232 (18·9%), 231 (10·6%), 230 (9·2%), 218 (6·0%), 217 (17·2%), 216 (2·6%), 215 (4·8%), 214 (10·8%), 204 (11·5%), 203 (4·8%), 202 (11·4%), 201 (17·1%), 200 (3·5%), 199 (2·9%), 191 (11·0%), 190 (4·6%), 189 (10·0%), 178 (3·1%), 165 (3·8%), 128 (6·9%), 127 (5·5%), 116 (3·2%), 110 (2·3%), 102 (8·3%), 101 (1·7%), 91 (8·2%), 89 (3·6%) 77 (8·3%), 76 (3·0%), 63 (4·2%), 51 (4·0%), 43 (21·0%), 42 (10·0%), 39 (4·0%), 28 (15·0%).

The 1R spectra were recorded on a 1R-10 Zeiss (1958) spectrometer. Solutions of the substances in CCl₄ (1% w/v) in a 1 mm NaCl cell were used.

The UV spectra were taken on a Perkin-Elmer, Model UV-137, selfrecording spectrophotometer. Solns of the samples in EtOH $(1.5 \times 10^{-6} \text{ g})$ were used.

The NMR spectra were taken on a HA-100-Varian spectrometer, operating at a frequency of 100 MHz, at room temp. Solns of the substances (12% w/v) in CDCl₃, containing 1% HMSO as internal standard were used. The chemical shift values are given in ppm (δ -units).

^{*}For TLC Silica Gel Merck (type 60) has been used.

[†]All melting points (uncorrected) were taken on a Koffler apparatus.

Acknowledgment – The authors wish to thank Dr. A. U. Stepanjantz of the Laboratory of NMR Spectroscopy, Institute of Chemical Physics, USSR Academy of Sciences, for taking the NMR spectra and the Laboratory of Mass Spectroscopy, The Moscow State University, for taking and calculating the mass spectrum. The authors are also indebted to Dr. S. Popov, Institute of Organic Chemistry, Bulgarian Academy of Sciences for helping them in the interpretation of the mass-spectrum.

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