832. *Tetronic Acids and Related Compounds. Part IV.* Friedel–Crafts Reaction and Fries Rearrangement.*

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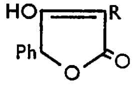
γ-Substituted tetronic acids undergo *C*-acylation with acetyl chloride in presence of Friedel–Crafts catalysts, and their enol acetates and benzoates are rearranged to α-acyl derivatives. These reactions are of value for the preparation of γγ-disubstituted α-acyltetronic acids.

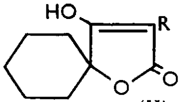
APPLICATIONS of the Friedel–Crafts reaction and the Fries rearrangement to tetronic acids have not previously been reported, but in view of the known susceptibility of tetronic acid to electrophilic substitution [1] it seemed that they might offer useful additions to existing methods [2,3] for the synthesis of α-acyltetronic acids.

The condensation of γ-phenyltetronic acid (I; R = H) with acetyl chloride in presence of aluminium, stannic, or zinc chloride was investigated under various conditions. The crude acid product was examined by paper chromatography, best with butan-1-ol–ammonia–pyridine–saturated aqueous sodium chloride;[4] tetronic acid derivatives were detected photographically by virtue of their ultraviolet absorption; this technique afforded rapid and convenient determination of the optimum conditions for acylation.

Acylation occurred with any of the three catalysts, the optimum conditions being to reflux γ-phenyltetronic acid with stannic chloride (1·3 mols.) in an excess of acetyl chloride for 4 hours. The α-acetyl-γ-phenyltetronic acid (I; R = Ac) isolated was identified by comparison with samples prepared from acetylmandelyl chloride and ethyl sodioacetoacetate or ethyl β-aminocrotonate (by Rebstock and Sell's modification [3] of Benary's method [2]). The separation of product from starting material required several



(I)



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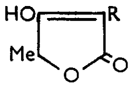

(III)

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* Part III, *J.*, 1956, 4556.

[1] Wolff and Schwabe, *Annalen*, 1896, **291**, 226; Wolff and Lüttringhaus, *ibid.*, 1900, **312**, 119.

[2] Benary, *Ber.*, 1909, **42**, 3912; Baker, Grice, and Jensen, *J.*, 1943, 241; Lecoq, *Compt. rend.*, 1946, **222**, 183; Reuter and Welch, *J. Proc. Roy. Soc. N.S.W.*, 1939, **72**, 120; Lacey, *J.*, 1954, 832; Haynes, Plimmer, and Stanners, *J.*, 1956, 4661.

[3] Rebstock and Sell, *J. Amer. Chem. Soc.*, 1952, **74**, 274.

[4] Bray, Lake, Thorpe, and White, *Biochem. J.*, 1950, **47**, 13.

recrystallisations, so the yield was poor, but better results were obtained with γγ-disubstituted tetronic acids: γγ-dimethyl- and γγ-diphenyl-tetronic acid gave (in about 50% yield) crude products which paper chromatography proved to be virtually pure α-acetyl derivatives. Surprisingly, *cyclo*hexane*spiro*-γ-tetronic acid (II; R = H) appeared not to undergo acylation. On acylation of γ-methyltetronic acid (III; R = H) there were indications of the formation of the α-acetyl derivative (III; R = Ac) but it could not be isolated. Nevertheless we treated γ-methyltetronic acid with 2-methoxycarbonylpropionyl chloride in the hope of obtaining carolinic acid (III; R = $CO\cdot[CH_2]_3\cdot CO_2H$): though paper chromatography showed the presence of a compound with the same R_F as carolinic acid yet this product could not be isolated.

Attempted alkylation of γ-phenyltetronic acid with ethyl bromide and stannic chloride or with benzyl chloride and aluminium chloride was unsuccessful, the acid being recovered.

Fries rearrangement of (enol) acetates and benzoates of a number of tetronic acids was also found to occur: again stannic chloride was a better catalyst than zinc or aluminium chloride, and better results were obtained with the γγ-disubstituted tetronic acids. The acetates of γγ-diphenyl- and γγ-dimethyl-tetronic acid gave a 63% and a 71% yield of the respective α-acetyl derivatives, identical with those obtained by Friedel–Crafts condensation. The benzoates of γγ-dimethyltetronic and *cyclo*hexane*spiro*-γ-tetronic acid gave the α-benzoyl derivatives in 77% and 71% yield respectively. Chromatography of the crude products from the rearrangement of the enol benzoates of γ-phenyl- and γγ-diphenyl-tetronic acids showed that a new substance had been formed in each case: the products however contained much benzoic and tetronic acids and the α-benzoyl compounds were not obtained pure.

EXPERIMENTAL

Light petroleum used had b. p. 60—80° unless otherwise stated.

α-Acetyl-γ-phenyltetronic Acid (I; R = Ac).—(*a*) Ethyl acetoacetate (13·0 g.) was added dropwise with stirring to sodium (2·3 g.) in dry ether (100 ml.) and the mixture set aside overnight. Acetylmandelyl chloride [5] (21·2 g.) in dry ether (50 ml.) was added dropwise with stirring and cooling in ice. The mixture was stirred for 3 hr. at room temperature, then shaken with ice (100 g.). The aqueous layer was separated and extracted twice with ether, and the combined ethereal extracts were washed with water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the ether left a yellow oil (40 g.). This product (6 g.) was treated in ethanol with aqueous 0·5N-sodium hydroxide (2 mols.) and set aside for 24 hr. at room temperature, then acidified with dilute sulphuric acid. α-Acetyl-γ-phenyltetronic acid was precipitated. After recrystallisation from light petroleum it (0·84 g., 26% based on acetylmandelyl chloride) had m. p. 102—104° (Lecoq [2] gives m. p. 104°).

(*b*) Ethyl β-aminocrotonate [6] (48·0 g.) in dry ether (175 ml.) and dry pyridine (32·8 g.) at −50° to −60° was treated with acetylmandelyl chloride [5] (88·3 g.) in dry ether (80 ml.) during 2 hr., then stirred overnight while it was allowed to come to room temperature. A colourless solid separated. The mixture was shaken with chloroform (80 ml.) and water (200 ml.), and the organic layer separated and dried (Na_2SO_4). Removal of the solvents gave a gum (72·0 g.) which crystallised on trituration with dry ether. Recrystallised from ether–light petroleum it had m. p. 86—89°. It (5·0 g.) was set aside with 10% aqueous sodium hydroxide at room temperature for 24 hr. Acidification with dilute hydrochloric acid and extraction gave α-acetyl-γ-phenyltetronic acid (2·4 g., 48%), m. p. 102—104° (from light petroleum). Hydrolysis with hot alkali or with acid at room temperature gave poorer yields. The acetyl compound gave a yellow precipitate with ferric chloride and a deep-red colour with sodium nitroprusside. It

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[5] Thayer, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 12.

[6] Mentzer, Billet, Molho, and Xuong, *Bull. Soc. chim. France*, 1945, **12**, 161; Tinker and Whatmough, *J. Amer. Chem. Soc.*, 1952, **74**, 5235.

formed an *oxime*, m. p. 162—164° [from ethyl acetate–light petroleum (b. p. 100—120°)] (Found: N, 5·8. $C_{12}H_{11}O_4N$ requires N, 6·0%).

cyclo*Hexane*spiro-*γ-tetronic Acid* (II; R = H) (with Dr. A. H. STANNERS).—A mixture of ethyl 1-hydroxy*cyclo*hexanecarboxylate [7] (34·4 g.), acetic anhydride (30 g.), and concentrated sulphuric acid (3 drops) was set aside for 5 hr., then refluxed for 15 min. Ether was added, and the solution washed with aqueous sodium hydrogen carbonate, then with water, and dried (Na_2SO_4). Distillation gave *ethyl* 1-*acetoxy*cyclo*hexanecarboxylate* (33·6 g., 77%), b. p. 117—121°/10 mm., n_D^{20} 1·4484 (Found: C, 62·1; H, 8·6. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

This ester (16·1 g.) in dry ether (25 ml.) was added during 30 min. to an ethereal suspension of di*iso*propylaminomagnesium bromide [8] (from magnesium 2·43 g., ethyl bromide 10·9 g. and di*iso*propylamine 10·1 g.); a light green sticky mass separated. The mixture was refluxed for another 1 hr. and set aside overnight. Ice-cold 3N-hydrochloric acid (100 ml.) was added, and the aqueous layer separated, saturated with sodium chloride, and extracted with ether. The combined ether solutions were extracted with aqueous sodium hydrogen carbonate, and the alkaline extract acidified, to give a *cyclo*hexane*spiro*-γ-tetronic acid. Extraction with ethyl acetate gave a total yield of 5·6 g. (45%), prisms (from aqueous ethanol), m. p. 195—196° (Jones and Whiting [9] give m. p. 198°). It gave a light purple colour with aqueous sodium nitrite.

Friedel–Crafts Reactions.—In acetylations, the most effective procedure was to mix the tetronic acid with some excess of acetyl chloride, to add stannic chloride (1·3 mol.), and to heat the red solution under reflux for 3—4 hr. The mixture was poured into ice-cold 5N-hydrochloric acid and set aside until it came to room temperature, then filtered and extracted with chloroform, and the extract shaken with concentrated aqueous sodium hydrogen carbonate. (At this stage, much inorganic material was removed with difficulty by filtration.) Acidification of the carbonate layer with concentrated hydrochloric acid produced a white opacity. The mixture was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated at reduced pressure. The extent of acylation was then estimated by paper chromatography of this crude residue, with butan-1-ol–ammonia (*d* 0·880)–pyridine–saturated aqueous sodium chloride (40 : 30 : 80 : 50 v/v).[4] Spots were located by making contact prints of the chromatograms by exposure (3—4 sec.) to ultraviolet light.

In this way γ-phenyltetronic acid (13·2 g.) gave a crude semicrystalline product which after five recrystallisations from light petroleum gave chromatographically pure α-acetyl-γ-phenyltetronic acid (3·2 g., 20%), m. p. 101—104° (mixed m. p. 100—102°) (Found: C, 66·5; H, 4·7. Calc. for $C_{12}H_{10}O_4$: C, 66·1; H, 4·6%).

γγ-Diphenyltetronic acid (2·0 g.) gave virtually pure α-acetyl-γγ-diphenyltetronic acid (1·3 g., 56%) which, crystallised readily from light petroleum (b. p. 60—80°), had m. p. 99—101° (Lacey [2] gives m. p. 102°).

γγ-Dimethyltetronic acid (2·6 g.) gave a crystalline crude product (2·0 g., 58%) which, recrystallised from light petroleum (b. p. 80—100°), gave pure α-acetyl-γγ-dimethyltetronic acid, m. p. 64° (Lacey [2] gives m. p. 64—65°).

Attempts at benzoylation, using benzoyl chloride and stannic chloride, were unsuccessful owing partly to the amount of benzoic acid produced in the working up; some conversion was, however, detectable chromatographically.

Preparation of Enol Esters.—Enol acetates were prepared by mixing the tetronic acid with a small excess of acetic anhydride and adding a few drops of concentrated sulphuric acid. The solution was kept at room temperature for a few hours, then diluted with chloroform. The solution was washed with saturated sodium hydrogen carbonate solution, from which a little unchanged tetronic acid was recovered by acidification. The chloroform solution was dried (Na_2SO_4) and solvent removed at reduced pressure. The residue then crystallised from light petroleum.

In this way were prepared: 3-*acetoxy*-2 : 5-*dihydro*-5-*oxo*-2 : 2-*diphenylfuran* (68%), m. p. 105° (Found: C, 73·6; H, 4·7. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%); 3-*acetoxy*-2 : 5-*dihydro*-2 : 2-*dimethyl*-5-*oxofuran* (79%), m. p. 59—60° (Found: C, 56·7; H, 6·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%); and cyclo*hexane*spiro-2-(2 : 5-*dihydro*-5-*oxofuran*) (74%), m. p. 93° (Found: C, 63·1; H, 6·8. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

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[7] Billimoria and Maclagan, *J.*, 1951, 3069.
[8] Haynes and Stanners, *J.*, 1956, 4103.
[9] Jones and Whiting, *J.*, 1949, 1421.

Enol benzoates were prepared by the Schotten–Baumann method. The tetronic acid in sodium carbonate solution was shaken for 5—10 min. with 1 mol. of benzoyl chloride and kept for 2—3 days at room temperature. The brown resin which resulted was washed by suspension in sodium carbonate solution, then recovered and dried. Crystallisation from light petroleum gave the pure enol benzoate.

In this way were prepared: 3-*benzoyloxy*-2 : 5-*dihydro*-5-*oxo*-2-*phenylfuran* (69%), m. p. 93° (Found: C, 73·2; H, 4·6. $C_{17}H_{12}O_4$ requires C, 72·8; H, 4·3%), and -2 : 2-*diphenylfuran* (76%), m. p. 165° (Found: C, 77·6; H, 4·8. $C_{23}H_{16}O_4$ requires C, 77·5; H, 4·5%); 3-*benzoyloxy*-2 : 5-*dihydro*-2-*methyl*- (62%), m. p. 39—43° (Found: C, 65·9; H, 4·5. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%), and -2 : 2-*dimethyl*-5-*oxofuran* (73%), m. p. 130—131° (Found: C, 66·9; H, 5·0. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%); and cyclo*hexane*spiro-2-(3-*benzoyloxy*-2 : 5-*dihydro*-5-*oxofuran*) (82%), m. p. 125—128° (Found: C, 71·0; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·5; H, 5·9%).

Fries Rearrangements.—For acetates the best method was to suspend the ester (0·01 mol.) in dry nitrobenzene, add the catalyst (0·013 mol.), and heat the whole at 100° for 2—3 hr. After working up as for the Friedel–Crafts reactions, the extent of conversion was estimated chromatographically.

With zinc chloride as catalyst, γ-phenyltetronic acid acetate (Haynes *et al.*[2]) gave crude α-acetyl-γ-phenyltetronic acid containing about 10% of γ-phenyltetronic acid, inseparable by crystallisation. Ten chromatograms on 3MM. Whatman No. 1 paper, the pure acetyl compound being recovered by spraying the papers with dilute hydrochloric acid and eluting the appropriate areas with ethanol, gave the α-acetyl compound, m. p. and mixed m. p. 104—105° (from light petroleum).

With stannic chloride as catalyst, γγ-diphenyltetronic acid acetate gave α-acetyl-γγ-diphenyltetronic acid (63%) which after one crystallisation from light petroleum (b. p. 80—100°) was chromatographically pure and had m. p. and mixed m. p. 64° (Found: C, 56·9; H, 6·1. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%). The *spiro*-acid acetate did not rearrange. γ-Methyltetronic acid acetate gave a mixture of about equal parts of α-acetyl-γ-methyl- and γ-methyltetronic acid, which with phenylhydrazine in boiling benzene gave yellow α-acetyl-γ-methyltetronic acid phenylhydrazone, m. p. 163—165° (Lacey [2] gives m. p. 165°).

For rearrangements of the benzoates, similar conditions were used, save that heating was usually for 4 hr. γγ-Dimethyltetronic acid benzoate gave 4-*benzoyl*-2 : 5-*dihydro*-2 : 2-*dimethylfuran* (77%), m. p. 77°, chromatographically pure after recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 67·2; H, 5·2. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). The *spiro*-acid benzoate similarly gave cyclo*hexane*spiro-2-(4-*benzoyl*-2 : 5-*dihydro*-5-*oxofuran*) (71%), m. p. 119° [from ethyl acetate–light petroleum (b. p. 80—100°)] (Found: C, 70·8; H, 6·3. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

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