FRIEDEL–CRAFTS REACTION OF γ-PHENYL-β-BROMO-$\Delta^{\alpha,\beta}$-CROTONOLACTONE AND ITS 4-METHOXYPHENYL ANALOGUE WITH BENZENE

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Reaction of γ-phenyl-β-bromo-$\Delta^{\alpha,\beta}$-crotonolactone (*I*) with benzene ($AlCl_3$) yielded 4,4-diphenyl-3-bromo-2-butenoic acid (*II*), lactone of 3,4,4-triphenyl-4-hydroxybutanoic acid (*IV*) and 3,4,4-triphenyl-3-butenoic acid (*V*). Analogously, reaction of the 4-methoxyphenyl analogue of lactone *I* with benzene yielded the 4-phenyl-4-*p*-methoxyphenyl analogue of acid *II*. Lactone *I* was prepared by a reduction of β-benzoyl-β-bromoacrylic acid with sodium borohydride. In animals with transplanted tumours acids *II* and *III* were ineffective upon application per os; acid *II* required for its efficiency the presence of another bromine atom at $C_{(2)}$ of the molecule.

The Friedel–Crafts reaction of γ-phenyl-β-bromo-$\Delta^{\alpha,\beta}$-crotonolactone (*I*) and its 4-methoxyphenyl analogue with benzene ($AlCl_3$) was taken up with the aim of obtaining 4,4-diphenyl-3-bromo-2-butenoic acid (*II*) and its 4-phenyl-4-*p*-methoxyphenyl analogue *III*. It was of interest to compare the possible antineoplastic effect of acids *II* and *III* with the same effect of γ,γ-diphenyl-α,β-dibromoisocrotonic acid as demonstrated in animals with some transplanted tumours[1], hence basically to establish the effect of the reactive bromine atom at C_α of the last-named acid on its cytostatic effect.

The starting γ-4-methoxyphenyl-β-bromo-$\Delta^{\alpha,\beta}$-crotonolactone was prepared before by a reduction of β-4-methoxybenzoyl-β-bromoacrylic acid with sodium borohydride[2]. Lactone *I* was now prepared from β-benzoyl-β-bromoacrylic acid in the same way. The reaction of the two crotonolactones with benzene ($AlCl_3$) represents an analogy with the reaction of γ-aryl-α,β-dihalogeno-$\Delta^{\alpha,\beta}$-crotonolactones with benzene and its derivatives[1,3].

Proceeding from the crude product of the reaction of lactone *I* with excess benzene ($AlCl_3$) done at the boiling point of the reaction mixture, we obtained (by column chromatography on silica gel and crystallization) acid *II* and two further compounds which were identified as lactone of 3,4,4-triphenyl-4-hydroxybutanoic acid (*IV*) and

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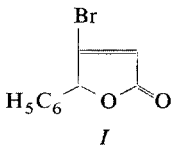
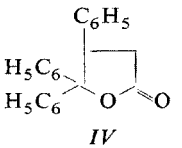
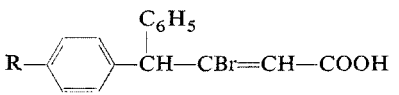
3,4,4-triphenyl-3-butenoic acid (*V*). Lactone *IV* was prepared by Purdie and Arup[4] in a reaction of methoxysuccinic ester with phenylmagnesium bromide, and by Scholtis[5] as a by-product of a reaction of phenyllithium with the diethyl ester of fumaric acid or malic acid. By applying a mineral acid, the authors[4,5] obtained acid *V* from lactone *IV*.



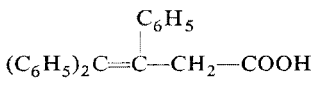
I



IV



II, R = H
III, R = OCH_3



V

Lactone *IV* is assumed to arise from lactone *I* by a shift of the double bond from position α,β to position β,γ and by a subsequent addition of benzene to this double bond and by replacing the bromine with a benzene residue. By opening up the lactone ring of *IV* and by splitting off water, acid *V* is then formed (ref.[4,5]).

In the case of acid *II* the absorption maximum at 1696 cm^{-1} confirms that the carbonyl group of the carboxyl is conjugated with the carbon double bond. On the other hand, the presence of the double bond in position β, γ of *V* causes a shift of the carbonyl maximum to higher wavenumbers (1712 cm^{-1}). The NMR spectrum of *II* documents the presence of the two protons at $C_{(2)}$ and $C_{(4)}$ (2 singlets at 6·87 and 6·60 p.p.m.); the spectrum of *V* lacks the olefinic proton bands.

Acid *III* was prepared in analogy to acid *II*. The acid exhibited a practically identical IR and NMR spectrum as compound *II*. In the IR region of the spectrum, *III* showed a maximum at 1692 cm^{-1} characterizing its molecule, much as the maximum at 1696 cm^{-1} for compound *II*, and additional sharp peaks at 2480 and 1185 cm^{-1} characteristic for the methoxy group at the aromatic ring. The three protons of the methoxy group appear in the NMR spectrum as a clear singlet at 3·73 p.p.m. A *para*-substitution of the benzene cycle is documented by the peak at 822 cm^{-1}, by the doubling of two pairs of aromatic protons which are apparent at 7·23 and 6·85 p.p.m. (J = 9·0 Hz) in the NMR spectrum.

An informative evaluation of acids *II* and *III* as to their therapeutical effect in animals with transplanted tumours was done by Dr H. Veselá of this institute, using the same tumours, the same technique, and application regime as was done with

γ,γ-diphenyl-α,β-dibromoisocrotonic acid[1]. At a daily dose of 50 and 100 mg/kg *p.o.* both compounds were therapeutically uninteresting. *E.g.*, acid *II* at a dose of 50 mg/kg per day applied to H mice with a S 37 ascitic sarcome had no effect on the tumour size or on the time of survival of the animals, as compared with the control group of untreated animals. In view of the fact that γ,γ-diphenyl-α,β-dibromoisocrotonic acid influenced at the same does both parameters investigated rather favourably[1] it would indicate that the elimination of bromine at C_α of this acid is accompanied by a loss of its therapeutical effect.

EXPERIMENTAL

The melting points of the compounds were determined in Kofler's block and are not corrected. Samples for analysis were dried at 0·1 Torr at a temperature raised in proportion to their melting point. The IR spectra were recorded in KBr pellets (2 mg/600 mg KBr) in a UR-20 spectrophotometer (C. Zeiss, Jena). The NMR spectra were recorded in $CDCl_3$ (6%), using tetramethylsilane as internal standard in a ZKR-60 (Zeiss-Jena) spectrometer. The compounds were evaluated in a thin layer of silica gel with fluorescein, using the system of benzene–methanol (8 : 2) in the case of *II*, *IV* and *V* and the system of benzene–methanol–acetic acid (80 : 20 : 1) for *III*. The compounds were detected on the basis of their ability to quench fluorescence brought about by UV light at 254 nm.

γ-Phenyl-β-bromo-$\Delta^{\alpha,\beta}$-crotonolactone (*I*)

A solution of 0·4 g NaOH in 2 ml water was added to a solution of 2·55 g (0·01 mol) β-benzoyl-β-bromoacrylic acid[6] in 40 ml methanol. This was followed by an addition of 0·2 g sodium borohydride and the mixture was stirred for 3 h at 40°C. After adding further 0·2 g sodium borohydride, the mixture was left to stand overnight at room temperature, was diluted with 80 ml water and filtered. The filtrate was made acid with hydrochloric acid and left to stand overnight at 5°C. The precipitated product (2·15 g, 90%; m.p. 88—89°C) was recrystallized from methanol, m.p. 89—90°C. For $C_{10}H_7BrO_2$ (239·0) calculated: 50·24% C, 2·95% H, 33·43% Br; found: 50·09% C, 2·94% H, 33·34% Br.

Condensation of Lactone *I* with Benzene

A mixture of 48 g (0·21 mol) lactone *I*, 56 g (0·42 mol) anhydrous aluminium chloride and 600 ml benzene was refluxed for 2 h with stirring under exclusion of air humidity. After 12 h of standing at 20°C, the mixture was combined under stirring with crushed ice and with 100 ml concentrated hydrochloric acid. The separated aqueous phase was extracted with benzene (2 × 500 ml) and the combined benzene fractions were dried (Na_2SO_4) and freed of benzene by distillation. The solution of the residue in 40 ml acetic acid was mixed with 300 ml water to precipitate the crude product which was dissolved in 30 ml methanol and reprecipitated by adding 300 ml water. After drying at 40°C/1 Torr the product was chromatographed on a column of silica gel (200 g), using benzene as elution agent. The pooled fractions containing *II*, *IV* and *V* (53 g) were successively crystallized from ethanol (60 ml), acetic acid (30 ml) and methanol (90 ml) to obtain fraction A (6·8 g) containing compounds *IV* and *V* in a ratio of about 1 : 1 (semiquantitatively by thin-layer chromatography). The mixture was separated on a column of silica gel (100 g) using chloroform for elution. The pooled fractions of the faster travelling lactone *IV* were crystallized from methanol;

m.p. 160—162°C (ref.[5] reports a m.p. of 162·5—163·5°C). The pooled fractions containing acid *V* yielded on crystallization from methanol a product melting at 199—200°C (ref.[5] reports 198 to 200°C).

The mother liquors after fraction A were evaporated in water-pump vacuum and the residues were crystallized from 25 ml acetic acid. The precipitated product (8·8 g) contains compounds *II* and *V* at a ratio of about 1 : 1. The mixture was separated in the same manner as in the case of fraction A. Pooled fractions of acid *V* or of acid *II* were purified by crystallization from methanol (2 g and 4 g, respectively). The m.p. of *II* was 157—158°C. For $C_{16}H_{13}BrO_2$ (317·2) calculated: 60·58% C, 4·13% H, 25·19% Br; found: 60·35% C, 4·09% H, 25·10% Br.

4-Phenyl-4-*p*-methoxyphenyl-3-bromo-2-butenoic Acid (*III*)

A mixture of 27·0 g (0·1 mol) γ-4-methoxyphenyl-β-bromo-$\Delta^{\alpha,\beta}$-crotonolactone[2], 28·0 g (0·21 mol) anhydrous aluminium chloride and 300 ml benzene was refluxed for 2 h under exclusion of air moisture, left to stand overnight at room temperature and decomposed by an addition of crushed ice and 50 ml concentrated hydrochloric acid. After adding 600 ml benzene and shaking the aqueous layer was extracted with further 300 ml of the same solvent. The pooled benzene fractions were dried (Na_2SO_4) and evaporated in oil-pump vacuum. The residue was treated by column chromatography on silica gel (200 g) using benzene, and benzene with 10% ethanol, for elution. The middle fractions (21·0 g) containing *III* were crystallized from a mixture of benzene with hexane; m.p. 100—101°C (14·0 g). For $C_{17}H_{15}BrO_3$ (347·2) calculated: 58·81% C, 4·35% H, 23·01% Br; found: 58·97% C, 4·39% H, 23·03% Br.

The analyses were done by Mrs J. Komancová (under the direction of Dr J. Körbl) in the analytical department of this institute; chromatography of the compounds was done ba Mrs M. Jelínková, also from this institute.

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