ESTERS OF 4,4-BIS(4-ETHYLPHENYL)-2,3-DIBROMO-2-BUTENOIC ACID AND 7-ETHYL-4-(4-ETHYLPHENYL)-2,3-DIBROMO-1-NAPHTHOL*

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Received September 7th, 1979

Chloride of 4,4-bis(4-ethylphenyl)-2,3-dibromo-2-butenoic acid (*VII*), prepared *in situ*, reacted with aliphatic alcohols and benzyl alcohol with the formation of esters *II*—*VI*. Reaction of the chloride *VII* with aromatic alcohols gave 7-ethyl-4-(4'-ethylphenyl)-2,3-dibromo-1-naphthol (*VIII*), whose structure was corroborated by IR and ^{1}H-NMR spectra. Compounds *II*—*VI* and *VIII* exhibited weaker antineoplastic effects than Edikron (*I*).

Out of the group of investigated 4,4-diaryl-2,3-dihalogeno-2-butenoic acids[1], 4,4-bis(4-ethylphenyl)-2,3-dibromo-2-butenoic acid, commercially known as Edikron, has proved to have the strongest inhibitory effect on growth of transplanted tumours and the strongest positive effect on survival of experimental animals with these tumours[1,2]. Edikron also inhibited the formation of coenzymes participating in biosynthesis of purine derivatives, inhibited incorporation of amino acids into proteins of tumour cells (*in vitro*) and synthesis of nucleic acids[2,3]. The pre-clinical development was completed and Edikron has entered the first stage of clinical examination.

The preceding paper of this series[4] describes syntheses of amides of the compound *I* and their preliminary evaluation for antineoplastic effect in animals with experimental tumours. The present communication deals with syntheses of several esters of Edikron (*II*–*VI*) and compares their antineoplastic action with that of Edikron.

The esters *II*–*VI* (Table I) were synthetized by the rewarding chloride method, consisting in the reaction of 4,4-bis(4-ethylphenyl)-2,3-dibromo-2-butenoic acid chloride (*VII*), prepared *in situ* by treatment of compound *I* with thionyl chloride in a chlorinated or aromatic solvent[4], with an excess of aliphatic alcohol or benzyl alcohol at the boiling point of the alcohol (compounds *II*–*IV*) or at 90°C (compounds *V* and *VI*).

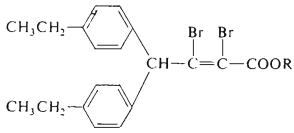
The structures of the esters *II*–*VI* were corroborated by spectral analyses of selected compounds. The IR spectra of the compounds exhibit, in keeping with the structures proposed, a single peak in the carbonyl region at 1725–1728 cm^{-1}, which can safely be assigned to the conjugated carbonyl of the esters. This indicates a double

* Part LXVII in the series Substances with Antineoplastic Activity; Part LXVI: This Journal *45*, 1410 (1980).

bond between the carbon atoms 2 and 3. In the ^{1}H-NMR spectrum the proton position on the carbon bound to the two aromatic rings is at 6·00 ppm, which accords with the earlier data for this group of compounds[1]. The course of the UV spectra, both in neutral methanol and in 0·1M sodium hydroxide in 50% methanol, is also a clear-cut proof that the double bond is not conjugated with aromatic rings; the compounds exhibit rather low peaks in the region of aromatic bonds (250–260 nm, $E^{1\%}_{1cm} = 60-80$, $\log \varepsilon = 3{\cdot}4-3{\cdot}6$).

The configuration of the double bond of the esters *II*–*VI* corresponds to the *Z*-isomer (in accordance with the quantum-chemical calculation of the total energy of isomers according to EHT) for the compound *I* (ref.[1]).

TABLE I



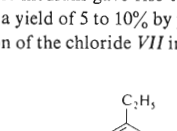
II – *VI*

I, R = H (EDIKRON)

Compound R	Formula (mol. mass)	M.p., °C (solvent)	Yield %	Calculated/Found % C	% H	% Br
II	$C_{21}H_{22}Br_2O_2$	29—30	63·1	54·11	4·75	34·28
CH_3	(466·2)	(hexane)		54·33	4·90	34·48
III	$C_{22}H_{24}Br_2O_2$	36—37	86·8	55·02	5·04	33·28
CH_2CH_3	(480·2)	(ethanol)		54·77	4·99	32·95
IV	$C_{23}H_{26}Br_2O_2$	82—83	73·5	55·89	5·30	32·33
$CH(CH_3)_2$	(494·2)	(hexane)		55·77	5·19	32·46
V	$C_{24}H_{28}Br_2O_2$	[a]	73·5	56·72	5·55	31·44
$(CH_2)_3CH_3$	(508·2)			56·46	5·41	31·15
VI	$C_{27}H_{26}Br_2O_2$	[b]	65·1	59·91	4·84	29·52
$CH_2—C_6H_5$	(542·3)			59·68	5·00	29·68

[a] n_D^{20} 1·5745; [b] n_D^{20} 1·6040.

Reaction of the chloride *VII* with phenol and/or 4-nitrophenol gave, instead of the expected esters, a derivative which has been identified by IR and ^{1}H-NMR spectra as 7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthol (*VIII*). The formation of this compound can be interpreted by intramolecular cyclization of the chloride *VII* by the midly acid phenol or 4-nitrophenol. The yields of this ring closure were 40–45%. However, a more rewarding synthesis of the compound *VIII* was melting the chloride *VII* with zinc chloride or its mixture with phosphorus pentoxide (10% w/w) at 60–80°C, which procedure raised the yield of the ring closure to *c.* 80% and simplified the working-up of the reaction mixture. Use of other condensation agents ($AlCl_3$, $TiCl_4$) in an inert medium gave rise to resin-like products. The compound *VIII* was also formed in a yield of 5 to 10% by prolonged action of Kieselgel 60 or gamma alumina on a solution of the chloride *VII* in tetrachloromethane.



VIII

Preliminary tests for antineoplastic action of compounds *II–VI* and *VIII* on animals with transplanted tumours were performed by Dr K. Řežábek and coworkers of the Pharmacological Department of our Institute. The compounds *II–VI* exhibited a specific antineoplastic action, but this, however, was less than that of Edikron. Thus compound *III* extended the survival time of animals with mammary adenocarcinoma HK by 56% and with sarcoma S 180 by 54% in the daily dosage of 100 mg/kg, administered orally during 12 days. In the same dosage it reduced the tumour size in animals with ascites sarcoma S 37 by 40% (*cf.*[1]). The compound *VIII*, as representative of a new group of compounds, in an analogous scheme of evaluation, extended survival of animals with sarcoma S 180 by 33%, at the same time reducing the mass of the tumour by 20%. The methods of testing the compounds and evaluation of the results are described elsewhere[5,6].

EXPERIMENTAL

The melting points of the compounds were determined on the Kofler block and were not corrected. Samples for elemental analyses were dried at 20—25°C over phosphorus pentoxide at a pressure of 70 Pa. Homogeneity of the samples and composition of the reaction mixtures

were monitored by TLC on Silufol reflex plates UV_{254} (Kavalier) by means of quenching of UV light at 254 nm. ^{1}H-NMR spectra were measured with a spectrometer Tesla BS 487 C; 10% solutions in deuteriochloroform and tetramethylsilane as internal standard were used. The IR spectra were recorded with a spectrometer Infrascan (Hilger); 5% solutions in chloroform and 0·1 mm KBr cells were used. The UV spectra were measured with an apparatus Optica Milano.

All the reaction components were anhydrous and the reactions were conducted in a way excluding contact with the aerial moisture.

Esters of 4,4-Bis(4-ethylphenyl)-2,3-dibromo-2-butenoic Acid (*II*—*VI*)

To the chloride *VII*, prepared from 9·04 g (20 mmol) of compound *I* according to ref.[4], was added an excess (*c.* 30 ml) of a corresponding alcohol and the mixture was refluxed for 2 h (in preparing compounds *II*—*IV*) or heated for 6 h to 90°C (compounds *V* and *VI*). The volatile components were distilled off *in vacuo* and the residue was dissolved in chloroform. The solution was shaken with aqueous sodium hydrogen carbonate (2—3% solution) and water. After drying up the chloroform layer and concentration the separated compounds *II*—*IV* were recrystallized from suitable solvents (Table I), whereas compounds *V* and *VI* were purified by chromatography on a column of alumina (Reanal, activity degree III), using benzene as eluant. The combined fractions were dried to constant weights; for yields see Table I.

Ethyl ester III: ^{1}H-NMR spectrum: ($CDCl_3$) δ 7·15 (s, 8 H, Ar—H), 6·00 (s, 1 H, ArCHAr), 4·22 (q, J = 7·0 Hz, 2 H, OCH_2), 2·62 (q, J = 7·0 Hz, 4 H, $ArCH_2$), 1·30 (t, J = 7·0 Hz, ester CH_3), 1·23 (t, J = 7·0 Hz, 6 H, $ArCH_2CH_3$).

Isopropyl ester IV: H^1-NMR spectrum: ($CDCl_3$) δ 7·15 (s, 8 H, Ar—H), 6·00 (s, 1 H, ArCH), 5·08 (m, 1 H, OCH), 2·62 (q, J = 7·0 Hz, 4 H, $ArCH_2$), 1·28 (d, J = 6·0 Hz, 6 H, isopropyl CH_3), 1·24 (t, J = 7·0 Hz, 6 H, $ArCH_2CH_3$).

7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthol (*VIII*)

a) To a solution of compound *VII*, prepared from 9·04 g (20 mmol) of compound *I*, in 25 ml of tetrachloromethane was added 2·8 g (30 mmol) of phenol and the mixture was refluxed for 3 h. After cooling, distilling off the volatile components *in vacuo*, and cooling to —5°C the separated product was collected on a filter and washed with hot water and methanol; yield 3·6 g (41·5%). Recrystallization from a chloroform–methanol mixture (1 : 5) gave a sample melting at 115 to 117°C.

b) To the chloride *VII*, prepared from 90·4 g (0·2 mol) of compound *I*, was added 40·8 g (0·3 mol) of anhydrous zinc chloride and 4 g of phosphorus pentoxide. The mixture was stirred and heated to 60°C until the reaction started, then to 80°C for 2 h. The melt was cooled down, decomposed with water and extracted with chloroform. After concentration the crude product was purified by crystallization from a chloroform–methanol mixture (1 : 5); yield 70·2 g (81%). Recrystallization from the same system gave a sample melting at 115—117°C. For $C_{20}H_{18}Br_2O$ (434·2) calculated: 55·72% C, 4·15% H, 36·85% Br; found: 55·47% C, 4·33% H, 36·80% Br, H^1-NMR spectrum: ($CDCl_3$) δ 8·03 (bs, 1 H, ArC_8H), 7·00—7·40 (m, 6 H, ArH), 6·14 (s, 1 H. phenol OH), 2·80 (bq, J = 7·0 Hz, 4 H, $ArCH_2$), 1·33, 1·30 (t, J = 7·0 Hz, 6 H, $ArCH_2CH_3$).

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Translated by J. Salák.