# SOME $\gamma,\gamma$ -DIARYL- $\alpha,\beta$ -DIHALOGENOISOCROTONIC ACIDS\* \*\*

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Condensation of  $\beta$ -formyl- $\alpha$ ,  $\beta$ -dichloro (XXXI) or  $\beta$ -formyl- $\alpha$ ,  $\beta$ -dibromoacrylic acid (XXXII) with an appropriate aromatic compound in the presence of aluminium chloride resulted in  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogenoisocrotonic acids I, IV-XVII and XX. Analogous acids II, III, XVIII and XIX were prepared by a reaction of  $\gamma$ -phenyl- $\alpha$ ,  $\beta$ -dichloro,  $\gamma$ -phenyl- $\alpha$ ,  $\beta$ -dibromo,  $\gamma$ -4--fluorophenyl- $\alpha$ , $\beta$ -dibromo- $\Delta^{\alpha}$ , $\beta$ -crotonolactone or of an analogous  $\gamma$ -4-bromophenyl compound with the appropriate aromatic compound (AlCl<sub>3</sub>). Condensation of acid XXXII with p-xylene or condensation of XXXII and XXXI with mesitylene resulted solely in crotonolactone XXV, or XXVI and XXVII. Reductive dehalogenation of acids IV and V with sodium amalgam yielded 4,4-di-p-tolyl-2-butenic acid (XXXIV). The following products of oxidation of IV, V and VII by potassium permanganate were isolated or detected:  $\gamma, \gamma$ -di-*p*-tolyl- $\alpha, \beta$ -dihalogeno- $\Delta^{\alpha, \beta}$ -crotonolactone and di-*p*-tolylacetic acid, further  $\gamma,\gamma$ -bis(4-ethylphenyl)- $\alpha,\beta$ -dibromo- $\Delta^{\alpha},\beta$ -crotonolactone, 4,4'-diethyl-4, acetyl-4'-ethyl and 4,4'-diacetylbenzophenone, bis(4-ethylphenyl)acetic acid and oxalic acid. Applying the extended Hückel method it was computed that the difference in total energy of the cis and trans isomers of VII is small, the cis configuration being slightly favoured energetically. In an orientation test of I - XX for their antineoplastic effect on animals bearing transplanted tumours, acid VII appeared to be of special interest.

The present communication describes the preparation of  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogenoisocrotonic acids I-XX (Table I) and presents the results of informative testing of some of these compounds as to their therapeutical effect on animals with transplantable tumours. Attention was also paid to the oxidation products of  $\gamma,\gamma$ -di-*p*-tolyl-- $\alpha,\beta$ -dichloroisocrotonic acid (*IV*), its  $\alpha,\beta$ -dibromo analogue V and especially  $\gamma,\gamma$ --bis(4-ethylphenyl)- $\alpha,\beta$ -dibromoisocrotonic acid (*VII*). Acids *IV* and V were also subjected to reductive dehalogenation. The study of I-XX was stimulated by the earlier finding of a cytostatic effect with  $\gamma,\gamma$ -bis(4-chlorophenyl)- $\alpha,\beta$ -dichloroisocrotonic acid<sup>1</sup> and with the analogous acid described by Dunlop<sup>2</sup> which contains no halogen atoms at the benzene rings (see also ref.<sup>1</sup>) using tissue culture cells of sarcome 180 (ref.<sup>3</sup>). Of compounds of this type,  $\gamma$ -phenyl- $\gamma$ -4-chlorophenyl- $\alpha,\beta$ -dichloroisocrotonic acid was described before<sup>1</sup>.

- \* Part LV in the series Substances with Antineoplastic Activity; Part LIV: Česk. Farm. 22, 166 (1973).
- \*\* A part of this work is included in the thesis of Dr J. Hartl.

| $\begin{array}{llllllllllllllllllllllllllllllllllll$   | the section      | R <sup>3</sup><br>R <sup>4</sup> | Yield | M.p., °C                           | Formula  | Ö     | alculated/For | pun   |
|--|------------------|----------------------------------|-------|------------------------------------|--|-------|---------------|-------|
|  | R <sup>4</sup> % | %                                |       | (solvent)                          | (mol. wt.)   | % C   | Η%            | %     |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$  | · · · · ·        |                                  |       |                                    |  |       |               |       |
|  | Br.              | 01                               | 06    | 151-152.5                          | C <sub>16</sub> H <sub>21</sub> Br <sub>2</sub> O <sub>2</sub> | 48.51 | 3.05          | 40.35 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | br               |                                  |       | (CH3COUH)                          | (0.965)  | 48.67 | 3.19          | 40.23 |
|  | CI 52            | 52                               |       | 113-114.5                          | $C_{17}H_{14}Cl_2O_2$  | 63.57 | 4.39          | 22.08 |
|  | CI               |                                  |       | (CH <sub>3</sub> COOH)             | (321-2)  | 63.42 | 4.56          | 22.08 |
|  | Br 44            | 44                               |       | 141-143                            | $C_{17}H_{14}Br_2O_2$  | 49.79 | 3.43          | 38-97 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$  | Br               |                                  |       | (CH <sub>3</sub> COOH)             | (410.1)  | 49.79 | 3.49          | 38.71 |
|  | CI 96            | 96                               |       | 178-179.5                          | C18H16Cl2O2  | 64.49 | 4.81          | 21.16 |
|  | CI               |                                  |       | (CH <sub>3</sub> COOH)             | (335-2)  | 64.31 | 4.88          | 21.33 |
|  | Br 94            | 94                               |       | 167-169                            | $C_{18}H_{16}Br_{2}O_{2}$                                      | 50-97 | 3.80          | 37.69 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | Br               |                                  |       | (CH <sub>3</sub> OH)               | (424.1)  | 51.38 | 3.98          | 37-95 |
| $\begin{array}{cccc} (\mathrm{CH}_3\mathrm{COOH}) & (363\cdot2) & (66\cdot29 & 5\cdot72 & 19\cdot48 \\ 137-138 & \mathrm{C}_{20}\mathrm{H}_{20}\mathrm{Br}_2\mathrm{O}_2 & 53\cdot12 & 4\cdot46 & 35\cdot35 \\ (\mathrm{CHCl}_3) & (452\cdot2) & 52\cdot99 & 4\cdot35 & 35\cdot66 \\ 174\cdot5-176 & \mathrm{C}_{20}\mathrm{H}_{20}\mathrm{Cl}_2\mathrm{O}_2 & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ (\mathrm{CH}_3\mathrm{COOH}) & (365\cdot2) & 66\cdot17 & 5\cdot69 & 19\cdot74 \\ 206-208 & \mathrm{C}_{20}\mathrm{H}_{20}\mathrm{Br}_2\mathrm{O}_2 & 53\cdot12 & 4\cdot46 & 35\cdot35 \\ (\mathrm{C}_2\mathrm{H}_5\mathrm{OH}) & (452\cdot2) & 53\cdot12 & 4\cdot46 & 35\cdot35 \\ (\mathrm{C}_2\mathrm{H}_5\mathrm{OH}) & (452\cdot2) & 53\cdot12 & 4\cdot56 & 35\cdot12 \\ 191\cdot5-193\cdot5 & \mathrm{C}_{20}\mathrm{H}_{20}\mathrm{Cl}_2\mathrm{O}_2 & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ (\mathrm{CH}_3\mathrm{COOH}) & (365\cdot2) & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ (\mathrm{CH}_3\mathrm{COOH}) & (365\cdot2) & 65\cdot93 & 5\cdot62 & 19\cdot40 \\ \end{array}$ | CI 83            | 83                               |       | 133.5-135                          | $C_{20}H_{20}Cl_{2}O_{2}$                                      | 66.13 | 5.55          | 19-53 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | CI               |                                  |       | (CH <sub>3</sub> COOH)             | (363·2)  | 66.29 | 5.72          | 19-48 |
|  | Br 77            | LL                               |       | 137-138                            | $C_{20}H_{20}Br_{2}O_{2}$                                      | 53.12 | 4.46          | 35.35 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | Br               |                                  |       | (CHCl <sub>3</sub> )               | (452·2)  | 52-99 | 4.35          | 35.66 |
| $ \begin{array}{cccc} ({\rm CH}_3{\rm COOH}) & (363\cdot2) & 66\cdot17 & 5\cdot69 & 19\cdot74 \\ 206-208 & {\rm C}_{20}{\rm H}_{20}{\rm Br}_2{\rm O}_2 & 53\cdot12 & 4\cdot46 & 35\cdot35 \\ ({\rm C}_2{\rm H}_5{\rm OH}) & (452\cdot2) & 53\cdot12 & 4\cdot56 & 35\cdot12 \\ 191\cdot5-193\cdot5 & {\rm C}_{20}{\rm H}_{20}{\rm Cl}_2{\rm O}_2 & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ ({\rm CH}_3{\rm COOH}) & (363\cdot2) & 65\cdot93 & 5\cdot62 & 19\cdot40 \\ \end{array} $   | CI 93            | 93                               |       | 174.5-176                          | $C_{20}H_{20}Cl_{2}O_{2}$                                      | 66-13 | 5.55          | 19.53 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | CI               |                                  |       | (CH <sub>3</sub> COOH)             | (363·2)  | 66.17 | 5.69          | 19-74 |
| $ \begin{array}{cccc} (C_2H_5OH) & (452\cdot2) & 53\cdot12 & 4\cdot56 & 35\cdot12 \\ 191\cdot5-193\cdot5 & C_{20}H_{20}Cl_2O_2 & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ (CH_3COOH) & (363\cdot2) & 65\cdot93 & 5\cdot62 & 19\cdot40 \\ \end{array} $  | Br 86            | 86                               |       | 206-208                            | $C_{20}H_{20}Br_{2}O_{2}$                                      | 53.12 | 4.46          | 35.35 |
| $\begin{array}{cccccc} 191\cdot5-193\cdot5 & C_{20}H_{20}Cl_2O_2 & 66\cdot13 & 5\cdot55 & 19\cdot53 \\ (CH_3COOH) & (363\cdot2) & 65\cdot93 & 5\cdot62 & 19\cdot40 \\ \end{array}$   | Br               |                                  |       | (C <sub>2</sub> H <sub>5</sub> OH) | (452·2)  | 53.12 | 4.56          | 35.12 |
| (CH <sub>3</sub> COOH) (363·2) 65·93 5·62 19·40  | CI 94            | 94                               |       | 191.5-193.5                        | $C_{20}H_{20}Cl_{2}O_{2}$                                      | 66.13 | 5.55          | 19-53 |
|  | CI               |                                  |       | (CH <sub>3</sub> COOH)             | (363.2)  | 62.93 | 5.62          | 19-40 |

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TABLE I  $\gamma, -\gamma Diaryl - \alpha, \beta - dihalogenoisocrotonic Acids$ 

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| IX                       | 3,4-(CH <sub>3</sub> ) <sub>2</sub><br>3,4-(CH <sub>3</sub> ) <sub>2</sub>                      | 55          | 98            | 167·5-170<br>(CH <sub>3</sub> COOH)     | $C_{20}H_{20}Cl_2O_2$<br>(363-2)  | 66·13<br>65·99 | 5.55<br>5.51 | 19-53<br>19-62               |
|--------------------------|---|-------------|---------------|---|---|----------------|--------------|------------------------------|
| IIX                      | 3,4-(CH <sub>3</sub> ) <sub>2</sub><br>3,4-(CH <sub>3</sub> ) <sub>2</sub>                      | . Br<br>Br  | 92            | 191–193<br>(CH <sub>3</sub> COOH)       | $C_{20}H_{20}Br_2O_2$<br>(452·2)  | 53-12<br>53-19 | 4·46<br>4·42 | 35·35<br>35·55               |
| IIIX                     | $\begin{array}{c} 4\text{-}C_6H_{11}\text{-}cyclo\\ 4\text{-}C_6H_{11}\text{-}cyclo\end{array}$ | 55          | 87            | 163–165<br>(CH <sub>3</sub> COOH)       | C <sub>28</sub> H <sub>32</sub> Cl <sub>2</sub> O <sub>2</sub><br>(471·4) | 71-34<br>71-25 | 6.83<br>7.03 | 15-04<br>15-07               |
| AIX                      | $\begin{array}{l} 4\text{-}C_6H_{11}\text{-}cyclo\\ 4\text{-}C_6H_{11}\text{-}cyclo\end{array}$ | Br Br       | 19            | 144—146<br>(cyclohexane-<br>-hexane)    | C <sub>28</sub> H <sub>32</sub> Br <sub>2</sub> O <sub>2</sub><br>(560·3) | 60-02<br>60-19 | 5.75<br>5.98 | 28·52<br>28·69               |
| xV <sup>a</sup>          | 4-F<br>4-F  | 55          | 96            | 166–168<br>(CH <sub>3</sub> COOH)       | $C_{16}H_{10}Cl_2F_2O_2$<br>(343·1)                                       | 56-01<br>55-73 | 2.93<br>2.91 | 20-66<br>20-88               |
| IAX                      | 4-F<br>4-F  | Br<br>Br    | 83            | 161·5–164<br>(CH <sub>3</sub> COOH)     | $C_{16}H_{10}Br_2F_2O_2$<br>(432.0)                                       | 44·48<br>44·57 | 2·33<br>2·39 | 36.99                        |
| ПАХ                      | 4-F<br>4-F  | Br C        | 88            | 144·5-147·5<br>(benzene-<br>-hexane)    | C <sub>16</sub> H <sub>10</sub> BrClF <sub>2</sub><br>(387·6)             | 49-56<br>49-45 | 2.59<br>2.61 | 9·14 (20·62)<br>8·70 (20·50) |
| qIIIAX                   | 4-F<br>4-CH <sub>3</sub>  | Br<br>Br    | 48            | 112–114<br>(CHCl <sub>3</sub> )         | $C_{17}H_{13}Br_{2}FO_{2}$<br>(428.0)                                     | 47-69<br>47-73 | 3-05<br>3-25 | 37.33                        |
| XIXc                     | 4-F<br>4-Br   | Br<br>Br    | 83            | 147–149·5<br>(CHCl <sub>3</sub> )       | $C_{16}H_{10}Br_{3}FO_{2}$<br>(493.0)                                     | 38-98<br>38-75 | 2.04<br>2.09 | 48.62                        |
| XX                       | 4-Br<br>4-Br  | ច ច         | 97            | 181·5–183·5<br>(CH <sub>3</sub> COOH)   | $C_{16}H_{10}Br_2Cl_2O_2$<br>(465.0)                                      | 41·33<br>41·34 | 2.17<br>2.09 | 15.25 (34.37)                |
| <sup>a</sup> Calculated. | 11.07% F. found. 11.1   | 40/ F b C   | alculated. d  | .430/ F. found. 4.40                    | 0/ E Calculated: 3.850/   | E. found: 2.76 | 20/ E        |                              |
|                          | TTOIN TOTOT   | · · · · 0/1 | all unaiter a | 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - | 10 L. Calvulaton. J 0/10  | L'IOULU. J.V   | 0/0 F.       |                              |





Acids *IV*, *VI*, *VIII*, *X*, *XI*, *XIII*, *XV* and *XX* were prepared by condensation of  $\beta$ -formyl- $\alpha$ , $\beta$ -dichloroacrylic acid (*XXXI*) with excess aromatic component in the presence of aluminium chloride; acids *I*, *V*, *VII*, *IX*, *XII*, *XIV* and *XVI* were prepared analogously using  $\beta$ -formyl- $\alpha$ , $\beta$ -dibromoacrylic acid (*XXXII*) and acid *XVII* using  $\beta$ -formyl- $\beta$ -chloro- $\alpha$ -bromoacrylic acid (*XXXII*).

$$\begin{array}{c} X^{1} X^{2} \\ | & | \\ O = CH - C = C - COOH \\ XXXI, X^{1}, X^{2} = Cl; \quad XXXII, X^{1}, X^{2} = Br; \quad XXXIII, X^{1} = Cl, X^{2} = Br. \end{array}$$

In preparing acids XIII and XIV, the indifferent medium used consisted of cyclohexylbenzene and 1,2-dichloroethane. Hence, compounds I and IV-XX were prepared analogously to  $\gamma,\gamma$ -bis(4-chlorophenyl)- $\alpha,\beta$ -dichloroisocrotonic acid<sup>1</sup>. Acid XVI was also obtained by condensation of  $\gamma$ -4-fluorophenyl- $\alpha,\beta$ -dibromo- $\Delta^{\alpha,\beta}$ crotonolactone (XXI) (Table II) with fluorobenzene in the presence of aluminium chloride, excess fluorobenzene serving as the reaction medium (for analogy see<sup>1</sup>). Likewise, using  $\gamma$ -phenyl- $\alpha,\beta$ -dichloro<sup>1</sup> and  $\gamma$ -phenyl- $\alpha,\beta$ -dibromo<sup>1</sup> or  $\gamma$ -4-fluorophenyl- $\alpha,\beta$ -dibromo and  $\gamma$ -4-bromophenyl- $\alpha,\beta$ -dibromo- $\Delta^{\alpha,\beta}$ -crotonolactone (XXI and XXIII) (Table II) and an appropriate aromatic compound, acids II and III, and XVIII and XIX were prepared.

In the condensation of acids XXXI and XXXII with aromatic hydrocarbons and their halogen derivatives resulting in the above mentioned derivatives of isocrotonic acid, the primary reaction products are assumed to be the corresponding  $\gamma$ -aryl- $\alpha,\beta$ -dihalogeno- $\Delta^{\alpha,\beta}$ -crotonolactones. This is in agreement with the finding that XXXI and XXXII occur in the solutions of the aromatic components used as well as in chloroform and acetonitrile practically solely in the cyclic lactonol form (Table III, ref.<sup>4</sup>) which takes part in the Friedel–Crafts reaction *via* the secondary alcoholic group. Depending on the reaction conditions, mainly in dependence on temperature, amount of aluminium chloride used and the reactivity of the components, one can mostly control the reaction is either a derivative of isocrotonic acid or of crotonolactone<sup>1</sup>. Condensation of XXXI and XXXII with aromates is only a slightly exothermic reaction.

|                             | ound           | % Cl (Br)      | 47-57               | 47.88                | 10.06 (45.35)        |                        | 60.41              | 60.41                | 47.60                 | 47-41                  | 46.19                               | 46.46                  | 44.39                                 | 44.86                  | 26.16  | 26.24                | 21.28  | 21.51  | .37.86                | 37-81   | 35.49                           | 35.22             |
|-----------------------------|----------------|----------------|---------------------|----------------------|----------------------|------------------------|--------------------|----------------------|-----------------------|------------------------|-------------------------------------|------------------------|---------------------------------------|------------------------|--|----------------------|--|--|-----------------------|---|---------------------------------|-------------------|
|                             | Calculated/F   | Η%             | 1.50                | 1.54                 | 1.42                 | 1.53                   | 1.27               | 1.39                 | 1.35                  | 1.54                   | 2.91                                | 2.98                   | 3.36                                  | 3.37                   | 4.46   | 4.53                 | 4.23   | 4.16   | 3.34                  | 3.39  | 4.03                            | 4.15              |
|                             |                | % C            | 35.74               | 35.67                | 34.08                | 34.21                  | 30-26              | 30-41                | 40.31                 | 40.45                  | 41.66                               | 41.93                  | 43.36                                 | 43.55                  | 57.58  | 57.81                | 64.88  | 64.72  | 51.22                 | 51.41   | 53.34                           | 53.72             |
|                             | Formula        | (mol. wt.)     | $C_{10}H_5Br_2FO_2$ | (336.0)              | $C_{10}H_5Br_2CIO_2$ | (352.4)                | $C_{10}H_5Br_3O_2$ | (397-0)              | $C_{10}H_4Cl_4O_2$    | (298-0)                | $C_{12}H_{10}Br_2O_2$               | (346.0)                | $C_{13}H_{12}Br_{2}O_{2}$             | (360-0)                | C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>2</sub> | (271.1)              | C <sub>18</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub> | (333.2)  | $C_{18}H_{14}Br_2O_2$ | (422.1)   | $C_{20}H_{18}Br_2O_2$           | (450-4)           |
| onolactones                 | M.p., °C       | (solvent)      | 103-104             | (CHCl <sub>3</sub> ) | 109-111              | (CH <sub>3</sub> COOH) | 95-96.5            | (CHCl <sub>3</sub> ) | 110-112               | (CH <sub>3</sub> COOH) | 134.5-135.5                         | (CH <sub>3</sub> COOH) | 127-128                               | (CH <sub>3</sub> COOH) | 87.5-88.5  | (CHCl <sub>3</sub> ) | 131-132  | (hexane)   | 161-162               | (hexane)  | 65-66                           | (hexane)          |
| lo-∆ <sup>α,β</sup> -crot   | Yield          | %              | 75                  |                      | 69                   |                        | 90                 |                      | 85                    |                        | 85                                  |                        | 93                                    |                        | 02   |                      | 39   |  | 42                    |   |                                 | 15                |
| -Diaryl-α,β-dihaloger       | R <sup>1</sup> | R <sup>2</sup> | 4-F                 | Н                    | 4-CJ                 | Н                      | 4-Br               | Н                    | 3,4-(Cl) <sub>2</sub> | - H                    | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | н.                     | 2,4,6-(CH <sub>3</sub> ) <sub>3</sub> | Н                      | 2,4,6-(CH <sub>3</sub> ) <sub>3</sub>                          | Н                    | 4-(CH <sub>3</sub> )   | 4-(CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> ) | 4-CH <sub>3</sub>     | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> | 4-C <sub>2</sub> H <sub>5</sub> | $4-C_2H_5-C_6H_5$ |
| 1 ABLE 11<br>-Aryl and ץ,ץ- | Compound       | R <sup>3</sup> | xXI <sup>a</sup>    | Br                   | IIXX                 | Br                     | IIIXX              | Br                   | AIXX .                | CI                     | XXV                                 | Br                     | IAXX                                  | Br                     | HAXX   | CI                   | IIIAXX   | CI   | XIXX                  | Br  | XXX                             | Br                |

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<sup>a</sup> Calculated: 5.65% F; found: 5.56% F.

With the aim of preparing derivatives of isocrotonic acid, the condensation of XXXI and XXXII with benzene, its halogen derivatives, and with cyclohexylbenzene was carried out at 20-25°C and terminated at 70°C, using 1.5-2.8 equivalents of aluminium chloride per equivalent of acid. In the condensation of acid XXXII with fluorobenzene, carried out under the same conditions as in the case of analogous preparation of  $\gamma$ ,  $\gamma$ -bis(4-fluorophenyl)- $\alpha$ ,  $\beta$ -dichloroisocrotonic acid (XV), *i.e.* using 1.8 equivalent aluminium chloride, the main product isolated was  $\gamma$ -4-fluorophenyl-- $\alpha$ , $\beta$ -dibromo- $\Delta^{\alpha,\beta}$ -crotonolactone (XXI) together with a minor amount of acid VI. Under the same conditions, the use of chlorobenzene or bromobenzene as the

# TABLE III

Cyclic and Linear Forms of Acids XXXI and XXXII in Different Solvents (peaks in the IR region)

| Solvent                     | . X2             | <i>XXI</i>     | XXX                    | XII            |
|-----------------------------|------------------|----------------|------------------------|----------------|
| Concentration<br>of acid, % | cyclic form, %   | linear form, % | cyclic form, %         | linear form, % |
| Acetonitrile <sup>a</sup>   | 99·15            | 0·85           | 98·6                   | 1·35           |
| 1.0                         | (1 796)          | (1 710)        | (1 793)                | (1 712)        |
| Chloroform <sup>a</sup>     | 100·0            | 0              | 94·5                   | 5·5            |
| 1.0                         | (1 795)          |                | (1 790-1 803)          | (1 710)        |
| Benzene<br>1·0              | 100·0<br>(1 798) | 0              | 100·0<br>(1 793—1 808) | 0              |
| Toluene                     | 100·0            | 0              | 96·75                  | 3·25           |
| 1·0                         | (1 793)          |                | (1 775—1 793)          | (1 710)        |
| Ethylbenzene                | 97·7             | 2·3            | 97·9                   | 2·1            |
| 1.0                         | (1 792)          | (1 705)        | (1 778—1 796)          | (1 710)        |
| <i>m</i> -Xylene            | 99·35            | 0·65           | 99·15                  | 0·85           |
| 1.0                         | (1 798)          | (1 711)        | (1 793-1 802)          | (1 699)        |
| Mesitylene                  | 95·8             | 4·2            | 94·1                   | 5·9            |
| 0·5                         | 97·2             | 2·8            | 96·2                   | 3·8            |
| 1·0                         | 96·5             | 3·5            | 96·2                   | 3·8            |
| 5·0                         | (1 795)          | (1 695)        | (1 778-1 793)          | (1 695)        |
| Fluorobenzene               | 98·75            | 1·25           | . 94•8                 | 5·2            |
| 1.0                         | (1 796)          | (1 710)        | . (1 797)              | (1 708)        |
| Bromobenzene                | 95·6             | 4·4            | 95·4                   | 4.6            |
| 0·5                         | 94·9             | 5·1            | 94·5                   | 5.5            |
| 1·0                         | 91·4             | 8·6            | 92·8                   | 7.2            |
| 5·0                         | (1 793)          | (1 710)        | (1 779-1 793)          | (1 706)        |

<sup>a</sup> For comparison see ref.<sup>4</sup>.

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reaction component (lactones XXII and XXIII – Table II) resulted in the formation of lactones. Likewise, when o-dichlorobenzene was used in an analogous reaction with acid XXXI, with the mixture of excess o-dichlorobenzene and 1,2-dichloro-ethane serving as the reaction medium, a lactone was formed (XXIV – Table II). Acid XVI was obtained as the main product only on using 2.8 equivalents aluminium chloride as condensing agent.

The reaction of mono- and dialkylbenzenes with acids XXXI and XXXII, aiming at the synthesis of isocrotonic acid derivatives, was carried out at  $20-25^{\circ}$ C, using 1.5 equivalent aluminium chloride. Somewhat different was the reaction of acid XXXII with *p*-xylene and the condensation of the same acid and of acid XXXIwith mesitylene under the same conditions; the reaction products here were crotonolactones XXV, XXVI and XXVII (Table II). Attempts at preparing the corresponding derivatives of isocrotonic acid, again using lactones XXV-XXVII as the starting compounds, were unsuccessful. The more drastic reaction conditions, a higher temperature or application of a larger amount of aluminium chloride, resulted in a varied mixture of compounds.

In the case of acid *VII* which was selected for preclinical research and which had to be prepared in a larger amount, it was found useful to carry out the condensation at first at  $10-13^{\circ}$ C, then at  $20-25^{\circ}$ C (using 1.5 equivalents of aluminium chloride), with the aim of curbing the disproportionation reaction of ethyl benzene with the aid of aluminium chloride. Application of homologous alkylbenzenes (n-propyl to n-hexyl derivatives) for the reaction with acids *XXXI* and *XXXII* did not result in homogeneous products apparently due to the occurrence of the disproportionation reactions of the alkyl benzenes. The use of stannic chloride for the condensation of acid *XXXI* with n-butyl benzene resulted merely in the previously described bis(2-oxo-3,4-dichloro-2,5-dihydrofuryl) ether<sup>5</sup>. Condensation of  $\gamma$ -phenyl- $\alpha$ , $\beta$ -dichloro, $\gamma$ -phenyl- $\alpha$ , $\beta$ -dibromo- $\Delta^{\alpha,\beta}$ -crotonolactone and lactone *XXI* with toluene and condensation of lactone *XXIII* with fluorobenzene, resulting in derivatives of isocrotonic acid *II*, *III*, *XVIIII* and *XIX*, was carried out first at  $20-25^{\circ}$ C, then at  $70-75^{\circ}$ C, using 1.8 equivalent aluminium chloride for *XVIII*, and 1.5 equivalent in the case of other acids.

The position of the substituent or substituents at the benzene rings of the substituted  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogenoisocrotonic acids or of the analogously substituted  $\gamma$ -aryl- $\alpha,\beta$ -dihalogeno- $\Delta^{\alpha,\beta}$ -crotonolactones, was estimated on the basis of previously published evidence of structure of analogous compounds<sup>1,6,7</sup> and on the basis of known substitution rules. The structure of  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogenoisocrotonic acids is in agreement with the results of their IR spectra (Table IV) and the NMR spectrum of acid XVII taken as representative of the whole group. The structure of acids I-XX also agrees with the structure of the product of reductive dehalogenation of acids IV and V with sodium amalgam. In both cases the reaction product is 4,4-di(p-tolyl)-2-butenoic acid (XXXIV). The structure of this compound agrees

with the results of spectral studies (IR, NMR); the shift of the double bond from position  $\alpha,\beta$  of the starting derivative of isocrotonic acid into position  $\beta,\gamma$  of the product is in agreement with the aromatic substitution at the  $\gamma$ -carbon of the dehalogenated product, increasing the mesomeric energy of conjugation of the newly formed propene bond with the aryl groups<sup>8,9</sup>.

The oxidation products of acids IV, V and VII were of interest as potential metabolites with an antineoplastic effect. The oxidation products of acid VII were taken up in more detail. The oxidation of the acids was done at pH 7.5 at 20°C, using equimolar amounts of potassium permanganate. In the case of IV or V, the reaction products contained, besides di-*p*-tolylacetic acid, also  $\gamma,\gamma$ -di-*p*-tolyl- $\alpha,\beta$ -dichloro-

# TABLE IV

Characteristic of  $\gamma, \gamma$ -Diaryl- $\alpha, \beta$ -dihalogenoisocrotonic Acids in the IR Region (peaks at cm<sup>-1</sup>)

| Compound               | OH<br>(COOH)   | CO<br>(COOH) | -C    | C00(-) | Phenyl                  | соон                    | Ľ,    | Substituted<br>phenyl |
|------------------------|----------------|--------------|-------|--------|-------------------------|-------------------------|-------|-----------------------|
| I                      | 2 635          | 1 698        | 1 600 | 1 555  | 1 498                   | 1 420<br>1 260          | -     |                       |
| II, III                | 2 670<br>2 520 | 1 705        | -     | -      | 1 508<br>1 520<br>1 500 | 1 410<br>1 260          | -     | 820                   |
| * <i>IV</i> , <i>V</i> | 2 640<br>2 520 | 1 701        | 1 668 | 1 565  | 1 520                   | 1 418<br>1 262          | -     | 823                   |
| VI, VII                | 2 660<br>2 530 | 1 710        | 1 665 | 1 570  | 1 520                   | 1 422<br>1 265          | -     | 840                   |
| VIII                   | 2 650<br>2 520 | 1 698        | 1 660 | 1 560  | 1 620<br>1 506          | 1 420<br>1 265          | —·    | 825                   |
| IX <sup>a</sup>        | 2 660<br>2 530 | 1 711        | 1 670 | -      | 1 620<br>1 500          | 1 420<br>1 295<br>1 240 | -     | 825                   |
| X                      | 3 510<br>2 650 | 1 708        | 1 620 | 1 550  | 1 500                   | 1 410<br>1 260          | -     | 820                   |
| XVII                   | 3 500<br>2 650 | 1 700        | 1 610 | 1 560  | 1 510                   | 1 412<br>1 240          | 1 022 | 835                   |
| <br>XVIII              | 3 500<br>2 650 | 1 698        | 1 610 | -      | 1 510                   | 1 420<br>1 240          | 1 022 | 835<br>815            |
|                        |                |              |       |        |                         |                         |       |                       |

<sup>a</sup> In KBr pellet.

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 $-\Delta^{\alpha,\beta}$ -crotonolactone (XXVIII) or the analogous  $\alpha,\beta$ -dibromolactone XXIX (Table II). Among the oxidation products of VII it was possible to isolate  $\gamma$ ,  $\gamma$ -bis(4-ethylphenyl)- $\alpha$ ,  $\beta$ -dibromo- $\Delta^{\alpha,\beta}$ -crotonolactone (XXX) (Table II), 4,4'-diacetylbenzophenone, 4,4'-diethylbenzophenone, 4-acetyl-4'-ethylbenzophenone and oxalic acid; the presence of bis(4-ethylphenyl)acetic acid in the reaction mixture was demonstrated by thin-layer chromatography using an authentic preparation synthesized according to Brault<sup>10</sup>. Lactones XXVIII-XXX are formed from the corresponding acids by hydroxylation of the tertiary carbon atom in position  $\gamma$  and subsequent lactonization of the  $\gamma$ -hydroxy acid formed<sup>11,12</sup>. Oxidative cleavage of the double bond of lactone XXX in position  $\alpha,\beta$  apparently gives rise to bis(4-ethylphenyl)glycollic acid and oxalic acid. The glycollic acid derivative is then oxidized to 4,4'-diethylbenzophenone (for analogy see e.g.<sup>13</sup>), the methylene groups of which, activated by the aromatic ring, are oxidized to 4-acetyl-4'-ethylbenzophenone and 4,4'-diacetylbenzophenone<sup>14,15</sup>. On increasing the amount of potassium permanganate used and raising the temperature to 45°C, the yield of 4,4'-diacetylbenzophenone was increased. Di-p-tolylacetic acid is formed from acids IV and V, and bis(4-ethylphenyl)acetic acid is formed from acid VII by oxidation of the double bond in position  $\alpha$ ,  $\beta$  of the starting acids. The structure of lactones XXVIII-XXX and of oxidation products of the benzophenone type agrees with the results of their IR spectroscopy.



## FIG. 1

Molecular Diagram of *cis* and *trans* Isomers of  $\gamma, \gamma$ -Diphenyl- $\alpha, \beta$ -dibromoisocrotonic Acid The overlapping populations of electrons are shown at the connecting lines between atoms. The values of total charge are shown underlined at the individual atoms.

The formation of  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogeno- $\Delta^{\alpha,\beta}$ -crotonolactones from acids IV, Vand VII and the formation of  $\gamma,\gamma$ -diaryl- $\alpha,\beta$ -dihalogenoisocrotonic acids from the corresponding  $\gamma$ -aryl- $\alpha,\beta$ -dihalogeno- $\Delta^{\alpha,\beta}$ -crotonolactones led to the assumption that acids I-XX are in the *cis* configuration, *i.e.* that they are derivatives of isocrotonic acid.

This assumption was supported by a quantum-chemical calculation of the total energy of VII and its *trans* isomer, using the extended Hückel theory (EHT) (refs<sup>16,17</sup>). The total calculated energies of both isomers, using the permitted approximation of aryl groups by hydrogen atoms (*cis*: 822·170 eV; *trans*: 822·224 eV) indicate that the *cis*-configuration is energetically favoured. It follows from a calculation of total charges and so-called electron populations that with both isomers, the bromine atom at C( $\beta$ ) is bound more firmly (Fig. 1).

An orientation study of acids I - XX with respect to their therapeutical effect on animals with transplanted tumours was done by Dr H. Veselá, using H strain mice with a mammary gland adenocarcinome (HK tumour), Ehrlich ascites carcinome (ATE), ascites sarcome S 37, Krebs ascites carcinome (Kr 2), and Wistar rats with a Yoshida ascites sarcome (Y). In the case of VII, the spectrum of animals with transplanted tumours was extended to include H strain mice with a melanome of Harding and Passey (MHP) and C3H mice with an ascites lymphosarcome of Gardner (LSG) and with an ascites lymphome of Németh and Kellner (NK). The method of testing was described earlier<sup>18,19</sup>. The compounds were applied per os. In animals with solid tumours, the application began on the 5th day, in those with ascitic tumours 24 h after tumour transplantation. The most interesting compound<sup>20</sup> in this respect is VII which, using a single daily dose of 100 mg/kg, applied for 12 days, caused a 26% longer survival of ATE animals with a simultaneous decrease in tumour size (by weighing) by 30% as compared with the controls. In the case of HK animals the compound increased survival by 56% but had no effect on tumour size. With a daily dose of 50 mg/kg, survival of S37 animals was extended by 28%, the tumour size was only insignificantly decreased; with animals bearing a Kr 2 tumour, survival was prolonged by 42% and the tumour size was decreased by 36%; with the NK animals, survival was prolonged by 22% (because of the metastatic character of the tumour its size could not be estimated). Compound VII had no effect on the survival of animals with other tumours, if applied at a daily dose of 100 mg/kg.

The acute  $LD_{50}$  of VII, applied p.o. to H mice, was about 800 mg/kg. In the case of I, tumour growth was inhibited in animals bearing HK, ATE and Kr 2 tumours by 20%, 27% and 38%, respectively, there being no practical effect on the survival of the experimental animals (a daily dose of 100 mg/kg throughout). In the case of mice with a S37 tumour, application of 50 mg I/kg per day inhibited tumour growth by 20% and increased survival by 41%.

#### EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for elementary analysis were dried at a temperature proportional to their melting point at 0.2 Torr over phosphorus pentoxide. The homogeneity of the compounds as well as the composition of the reaction mixtures were checked by thin-layer chromatography on Silufol UV<sub>254</sub> mostly impregnated with a solution of formamide (10%) or formic acid (0.5%) in acetone or on KF<sub>254</sub> Fertigplatten of Merck. The thin layers were developed in benzene, benzene-chloroform (3 : 2) or benzenemethanol-acetic acid (90 : 10 : 1). The compounds were detected by quenching of fluorscence due to UV light at 254 nm. The IR spectra of selected compounds were measured in a UR-10 Zeiss spectrophotometer in 5% chloroform (unless stated otherwise) in a 0.1 mm NaCl cuvette. The NMR spectra were recorded in a ZKR 60 Zeiss spectrometer using a 6% solution in deuteriochloroform with tetramethyl silane as internal standard. The reaction components used were practically anhydrous, aluminium chloride was coarsely granulated; all the reactions carried out in its presence were done in the absence of air moisture.

#### Acids I, IV-XVII, XX and Lactones XXI-XXVII

A suspension of 20.5 g (0.154 mol) aluminium chloride in 0.917 mol of the appropriate aromate was combined under stirring at  $20-25^{\circ}$ C (over a period of 20 min) with 0.1 mol of the corresponding acid XXXI or XXXII. After 1 h of stirring at  $20-25^{\circ}$ C and after standing for 12 h at room temperature, the mixture was introduced into 130 g crushed ice and 40 ml concentrated hydrochloric acid. After shaking the mixture, the organic layer was separated, washed with water, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* of a water pump. The precipitated product was purified by crystallization (the solvents used and yields are found in Table I and II). There were some differences in the working procedure with certain compounds, thus:

Acid I: 24.7 g (0.185 mol) aluminium chloride was used. After cessation of the exothermic reaction the mixture was left to stand for 30 min at  $20-25^{\circ}$ C, then for 2.5 h it was heated to  $70-75^{\circ}$ C, cooled and then processed.

Acid VII: acid XXXII was introduced into the mixture of aluminium chloride and ethyl benzene at  $10-13^{\circ}$ C, the mixture was maintained at this temperature for 2 h, temperature was then permitted to rise within 1 h to 20°C, was kept for 2 h at  $20-25^{\circ}$ C and then left to stand at room temperature for 20 h.

Acids XIII and XIV: mixture of cyclohexylbenzene and aluminium chloride was combined with 25 ml 1,2-dichloroethane. After cessation of the reaction at  $20-25^{\circ}$ C, the mixture was kept for 2.5 h at  $70-75^{\circ}$ C and left to stand for 24 h at room temperature. The acid was isolated by column chromatography on silica gel using benzene for elution.

Acids XV, XVI, XX lactones XXI-XXIV: 24 g (0.18 mol) aluminium chloride and 0.615 mol halogenated aromatic hydrocarbon were used. After combination of the mixture with acid XXXI or XXXII at  $20-25^{\circ}$ C the mixture was slowly heated (over 60 min) to  $70-75^{\circ}$ C and maintained at that temperature for 2.5 h. Suspension of the product obtained by shaking the reaction mixture with ice and with hydrochloric acid was filtered, washed with light petroleum and crystallized (Tables I and II). Another fraction of lactone XXI was obtained by extracting the residue of the organic phase of the filtrate with boiling methanol and leaving the solution at 6°C. The combined residues of the methanolic mother liquor and the chloroform mother liquor after crystallization of lactone XXI were extracted with a small amount of boiling chloroform and the crude acid XVI (about 1.4%) precipitated after cooling of the extract, was purified by repeated crystallization from acetic acid (the properties of the compound are shown in Table I).

Acid XVI: To suppress the formation of lactone XXI, 37.6 g (0.282 mol) aluminium chloride was used for the reaction.

Acid XVII. A suspension of 1.25 g (9.2 mmol) aluminium chloride in 5.0 g (50 mmol) fluorobenzene was combined with 1.03 g (4.8 mmol) acid XXXIII (ref.<sup>21</sup>). After termination of the exothermic reaction, the mixture was left to stand for 30 min at 20–25°C, then heated for 2.5 h to 70–75°C and, after cooling, immediately processed. The NMR spectrum of the compound contains a singlet of 1 H at  $\delta$  10.55 which disappears after deuterization (—COOH), a multiplet of 8 protons (substituted phenyl rings) at  $\delta$  6.80–7.50 and a singlet of 1 H (CH—C=C) at  $\delta$  6.46.

Lactones XXV-XXVII: The reaction mixture was left to stand for 24 h at room temperature, mixed with ice and hydrochloric acid and combined with 250 ml benzene. After shaking the mixture, the organic phase was washed with water, dtied with  $Na_2SO_4$  and the volatile fractions were removed *in vacuo* of a water pump. For the preparation of lactone XXV the residue was dissolved in boiling methanol, for the other two lactones in boiling chloroform. The precipitate was purified by crystallization (Table II).

## Acids II and III

20.0 g (0.15 mol) aluminium chloride was added at  $20-25^{\circ}\text{C}$  to a mixture of 22.9 g (0.1 mol)  $\gamma$ -phenyl- $\alpha$ , $\beta$ -dichloro- $\Delta^{\alpha}$ , $\beta$ -crotonolactone<sup>1</sup> (for the preparation of *II*) or 31.7 g (0.1 mol) analogous  $\alpha$ , $\beta$ -dibromocrotonolactone (for the preparation of *III*) and 350 g (3.8 mol) toluene. The mixture was kept for 2.5 h at 70-75°C, cooled, combined with 130 g crushed ice and 40 ml concentrated hydrochloric acid. The organic layer was separated, washed with water, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated at a water pump. The precipitated acid was recrystallized (Table I).

## Acids XVI (from lactone XXI), XVIII and XIX

33.4 g (0.1 mol) lactone XXI (for acids XVI and XVIII) or 39.2 g (0.1 mol) lactone XXIII was added under stirring over 20 min to a suspension of 25.0 g (0.18 mol) aluminium chloride in 190 ml (2.0 mol) fluorobenzene (for acid XVI) or 184 g (2 mol) toluene (for acid XVIII) or 20.0 g (0.15 mol) aluminium chloride and 190 g (2.0 mol) fluorobenzene (for acid XIX). After the exothermic reaction was over, the mixture was left to stand for 30 min at  $20-25^{\circ}$ C, then heated for 2.5 h to  $70-75^{\circ}$ C and processed in the same way as in the preparation of acids II and III. The products were purified by crystallization (Table I). Acid XVI was obtained in a 52% yield; m.p.  $161.5-164^{\circ}$ C. Its mixed melting point with the same compound prepared by direct condensation of acid XXXII with fluorobenzene showed no depression.

### Bis(3,4-dichloro-2-oxo-2,5-dihydrofuryl) Ether

6.2 g (0.023 mol) stannic chloride was added dropwise under stirring over a period of 10 min to a suspension of 3.6 g (0.02 mol) acid XXXI in 10.0 g (0.07 mol) butyl benzene at  $100-105^{\circ}$ C in the absence of air moisture. The mixture was stirred further at the same temperature for 5.5 h. After 24 h of standing at  $20-25^{\circ}$ C, 40 ml hydrochloric acid (1 : 1) was added dropwise under stirring to the mixture and stirred for further 20 min. After adding 30 ml benzene and shaking, the organic phase was separated, repeatedly shaken with dilute hydrochloric acid and water and dried with Na<sub>2</sub>SO<sub>4</sub>. Then it was evaporated at a water pump. The residue (1.53 g) was repeatedly crystallized from acetic acid to yield a compound melting at  $142-143^{\circ}$ C (ref.<sup>5</sup> reports a m.p. of  $141-143^{\circ}$ C).

## Oxidative Cleavage of Acids IV, V and VII

A solution of 2.45 g (0.016 mol) potassium permanganate in 100 ml water was added in parts under stirring over a period of 1 h to a solution of 5.0 g (0.014 mol) acid *IV* in 200 ml water and 0.85 g (0.0016 mol) potassium hydroxide and the mixture was left to stand for 24 h at  $20-25^{\circ}$ C. Its pH was then adjusted with 0.1M sodium hydroxide to 10, the mixture was saturated with sodium chloride and the organic fraction was extracted with 3 . 200 ml ether. Chromatography of the residue (4.45 g) of the ether extract on a column of silica gel (250 . 25 mm) using benzene for solution and elution, yielded 1.95 g (39%) lactone *XXVIII* and 0.75 g di-*p*-tolylacetic acid which, after crystallization from hexane, showed a m.p. of 141.5-143°C (ref.<sup>22</sup> reports a m.p. of 143 to 144°C). Lactone *XXVIII* was purified by crystallization (Table II).

Oxidative cleavage of acid V was done in the same way. The yield of lactone XXIX and some of its properties are shown in Table II. In the IR region of the spectrum, lactone XXIX shows characteristic absorption at  $1789 \text{ cm}^{-1}$ , corresponding to the lactone-linked carbonyl group, the peaks at 1243 and 1210 cm<sup>-1</sup> belonging to the C—O bond in C—O—C—O and those at 1612, 1520 and 825 cm<sup>-1</sup> to the aromatic rings.

Oxidative cleavage of acid VII yielded lactone XXX (15%), 4,4'-diethylbenzophenone (10%), 4-acetyl-4'-ethylbenzophenone (5%), 4,4'-diacetylbenzophenone (3%), di(4-ethylphenyl)acetic acid (trace amounts) and some 50% of the starting acid VII. Using the aqueous phase, after extraction with ether, acidification with hydrochloric acid and separation of inorganic fractions by repeated crystallization, it was possible to isolate oxalic acid and detect it by a colour reaction<sup>23</sup>. The presence of di(4-ethylphenyl)acetic acid in the reaction mixture was demonstrated by thinlayer chromatography by comparing with a standard of di(4-ethylphenyl)acetic acid, prepared according to ref.<sup>10</sup>. Combined fractions of lactone XXX were crystallized (Table II). The IR spectrum of the compound shows a characteristic absorption at 1776 cm<sup>-1</sup>, corresponding to the carbonyl group of the lactone, the sharp bands at 1600–1506 cm<sup>-1</sup> characterizing aromatic substitution of the lactone cycle and the band at 830 cm<sup>-1</sup> corresponding to a *p*-substituted aromatic ring.

4,4'-Diethylbenzophenone: Combined fractions from the chromatography of the crude product were purified by crystallization from hexane; m.p.  $46^{\circ}$ C (ref.<sup>24</sup> reports 47°C). The IR spectrum of the compound (using a KBr pellet) shows a band at 1650 cm<sup>-1</sup> corresponding to the carbonyl group of benzophenone.

4-Acetyl-4'-ethylbenzophenone: Fraction from column chromatography was crystallized from hexane; m.p. 72°C. The IR spectrum shows a band at 1650 cm<sup>-1</sup> (carbonyl group of benzophenone) and a band at 1685 cm<sup>-1</sup> (acetyl group bound to an aromatic ring). For  $C_{17}H_{16}O_2$  (252-3) calculated 80.91% C, 6.39% H; found: 80.68% C, 6.51% H.

4,4'-Diacetylbenzophenone: The corresponding fraction from column chromatography was crystallized from chloroform; m.p. 156–157°C. The IR spectrum shows an absorption band at 1640 cm<sup>-1</sup> (carbonyl group of benzophenone) and at 1684 cm<sup>-1</sup> (acetyl groups bound to a benzene ring). For  $C_{17}H_{14}O_3$  (266·3) calculated: 76·68% C, 5·30% H; found: 76·75% C, 5·45% H.

## Reductive Dehalogenation of Acids IV and V

4% sodium amalgam (150 g) was added in parts under agitation to a solution of 1·1 g (3·28 mmol) acid IV in 3% NaOH. After 15 min at 80°C, the aqueous phase was acidified with hydrochloric acid and the precipitated product was filtered and washed with water (0·62 g, 72%). Repeated crystallization from aqueous methanol resulted in a product melting at 144–146°C. The same

product, practically at the same yield, was obtained by a similar processing of 1.39 g (3.28 mmol) acid V. For  $C_{18}H_{18}O_2$  (266.3) calculated 81.17% C, 6.83% H, found 81.17% C, 6.81% H. IR spectrum: 2640 and 2570 cm<sup>-1</sup> (OH in carboxyl), 1718 cm<sup>-1</sup> (nonconjugated carbonyl group in COOH), 1672 cm<sup>-1</sup> (—CH—CH— aromatic), 1620 and 1525 cm<sup>-1</sup> (benzene rings), 1425, 1290 and 1245 cm<sup>-1</sup> (COOH) and 830 cm<sup>-1</sup> (*para*-substituted phenyl). NMR spectrum:  $\delta 9.6$  (s, COOH), 7.03 (s with fine structure of 8 protons; *p*-tolyl, 2 x), 6.07 (t, J = 8.0 Hz, C—CH), 3.11 (d, J = 8.0 Hz, C—CH—CH<sub>2</sub>) and 2.23 and 2.28 (ss, CH<sub>3</sub> at phenyl, 2 x).

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