Tetrahedron, 1962, Vol. 18, pp. 1381 to 1394. Pergamon Press Ltd. Printed in Northern Ireland

# THE REACTION OF DIAZOMETHANE WITH DOUBLE BONDS—I

## DIRECT METHYLATION OF TRISUBSTITUTED ETHYLENES*

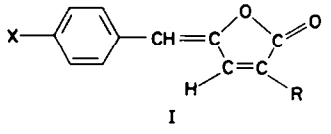
M. ALGUERÓ, J. BOSCH, J. CASTAÑER, J. CASTELLÁ, J. CASTELLS, R. MESTRES, J. PASCUAL† and F. SERRATOSA

Departamento de Química Orgánica de Barcelona. Patronato "Juan de la Cierva", de Investigación Tecnica. Consejo Superior de Investigaciones Científicas; Laboratorio de Química Orgánica de la Facultad de Ciencias. Universidad de Barcelona

(*Received* 12 *May* 1962)

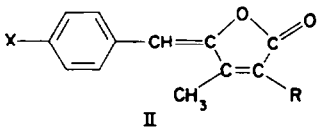
**Abstract**—The reaction of α-carbomethoxy-γ-benzylidenebutenolide with diazomethane has been studied, and the β-methylbutenolide structure of the resulting product established through degradative and synthetic work. Extension of this direct C-methylation to other related butenolides is presented. Hydrogenation of enol lactones is discussed in some detail.

WHEN α-carbomethoxy-γ-benzylidenebutenolide (Ic, X = H)[1] in dry ether suspension is treated with one mole of diazomethane in the same solvent, the crystalline aspect of the precipitate changes with simultaneous evolution of nitrogen. By recrystallization, a new ester $C_{14}H_{12}O_4$, m.p. 156–158°, is obtained (90% yield), which, upon hydrolysis, affords the corresponding acid, $C_{13}H_{10}O_4$, m.p. 190–192° (dec). Heating the acid *in vacuo* gives (50%) a decarboxylated product, $C_{12}H_{10}O_2$, m.p. 101–103°. The formulation of the ester, the acid, and the decarboxylated product as α-carbomethoxy-β-methyl- (IIc, X = H), α-carboxy-β-methyl- (IIb, X = H), and β-methyl-γ-benzylidene-butenolide (IIa, X = H), respectively, has been established by degradative and synthetic work.



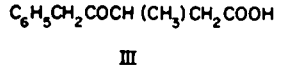
I

(a) R = H
(b) R = COOH

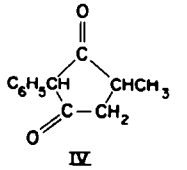


II

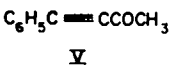
(c) R = $COOCH_3$
(d) R = CN



III



IV



V

* Abstracted in part from Ph.D. Thesis of M.A., J.B., J. Castañer, J. Castellá, and R. M.

† To whom reprints should be requested.

[1a] J. Castañer and J. Pascual, *J. Chem. Soc.* 3962 (1958); [b] C. Belil, J. Castellá, J. Castells, R. Mestres, J. Pascual and F. Serratosa, *Anales real Soc. Españ. fis. y quím., Madrid* **57B**, 617 (1961).

*Degradative work on* IIa (X = H). Treatment of the decarboxylated product IIa (X = H) with hydroiodic acid, at 160°, yields an acid $C_{12}H_{14}O_3$, m.p. 62–63° (semicarbazone, m.p. 171–173° dec), which has been identified (IR spectra, m.p.'s and mixed m.p.'s of parent substances and derivatives) as β-methyl-γ-oxo-δ-phenylvaleric acid (III), a new substance which we have prepared by acetoacetic synthesis (Chart I). A neutral product $C_{12}H_{12}O_2$, m.p. 181–183°, obtained by sodium hydride cyclization of the acid, is consequently given the structure of 4-methyl-2-phenylcyclopentane-1,3-dione (IV).

Chart 1

$$CH_3COCH_2COOC_2H_5 \xrightarrow{1} C_6H_5CH_2COCH(COCH_3)COOC_2H_5 \xrightarrow{2} C_6H_5CH_2COCH_2COOC_2H_5$$

$$\xrightarrow{3} C_6H_5CH_2COCH(CH_3)COOC_2H_5 \xrightarrow{4} C_6H_5CH_2COC(CH_3)(COOC_2H_5)CH_2COOC_2H_5 \xrightarrow{5} III$$

1. $(C_2H_5O)_2Mg$, $C_6H_5CH_2COCl$, 20% aq. $H_2SO_4$; 2. 10% aq. $NH_3$; 3. $C_2H_5ONa$, $ICH_3$;

4. $C_2H_5ONa$, $BrCH_2COOC_2H_5$, 10% aq. $H_2SO_4$; 5. 10% aq. KOH.

*Synthesis of* IIa (X = H) *and of* trans-*β-methyl-phenylpropargylideneacetic acid.* In the synthesis reported in this and the following section, 1-phenylbut-1-ynone (V) is used as starting material. None of the known methods for the preparation of this substance[2] is fully satisfactory and new routes to it were explored.

Since the reaction of acetylene Grignard derivatives with N-disubstituted amides to give acetylenic carbonyl compounds has been reported by different authors,[3] the reaction of phenylethynylmagnesium bromide with N-acetylpiperidine was carried out (Method 1). The primary reaction proceeds very smoothly and quantitatively. Hydrolysis with water and extraction with ether gives a product which IR spectrum shows to contain neither phenylacetylene nor N-acetylpiperidine, but on distillation it affords only these substances (cf. ref. 3*b*). Hydrolysis with dilute sulphuric acid leads to a mixture of these substances plus the desired ketone V, which can be isolated by distillation (10% yield).

Better results were obtained by oxidation of 1-phenylbut-1-yn-3-ol with chromic acid, whether in acetone or ether solution[4] (Method 2). However, the carbinol is unusually resistant to oxidation and pure ketone could be separated (25% overall yield) from the starting material only through its bisulphite derivative.

A third and much more convenient route to ketone V was the hydrolysis of the ethylketal (prepared[5] from phenylacetylene and ethyl orthoacetate) with aqueous tartaric, at room temperature (Method 3). The overall yield from phenylacetylene is 31% of pure ketone.

Phenylbutynone was condensed with carbomethoxymethylene-triphenylphosphorane to give the previously undescribed mixture of methyl-5-phenyl-3-methylpent-4-yn-2-enoates (VIa + VIb), b.p. 82–84° (0·01 mm) ($\lambda_{max}$ 297 mμ (16·600); $\nu\nu_{max}$ 2208 m

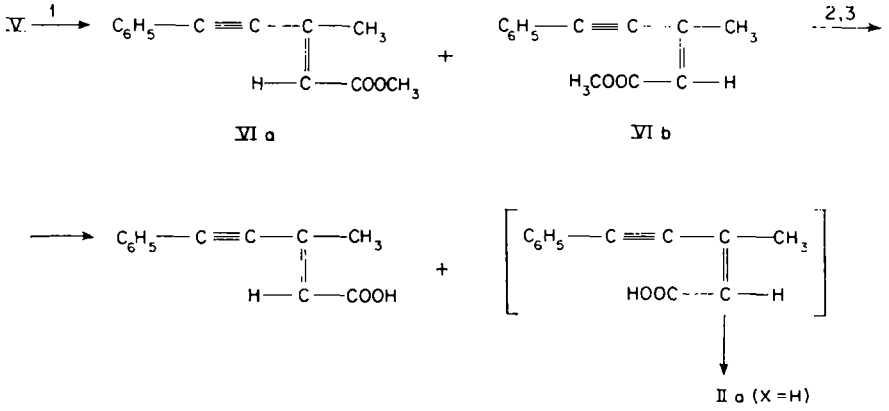
[2] J. W. Kroeger and J. A. Niewland, *J. Amer. Chem. Soc.* **58,** 1861 (1936); D. V. Nightingale and F. Wadsworth, *Ibid.* **67,** 416 (1945); G. Gamboni, V. Theus and H. Schinz, *Helv. Chim. Acta* **38,** 255 (1955).

[3a] E. R. H. Jones, L. Skattebøl and M. C. Whiting, *J. Chem. Soc.* 1054 (1958); [b] F. Serratosa, *Tetrahedron* **16,** 185 (1961).

[4] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.* **83,** 2952 (1961).

[5] B. W. Howk and J. C. Sauer, *J. Amer. Chem. Soc.* **80,** 4607 (1958).

(C≡C st), 1724s (C=O st), and 1613s $cm^{-1}$ (C=C st) in $CCl_4$). Hydrolysis of the esters affords the parent acids, the methanolic solution of which was treated with a catalytic amount of silver nitrate in order to induce the cyclization of the *cis*-isomer (cf. ref. 1*b* and 3*b*). Working up of the solution gives, as expected, an acid (15% yield) and a neutral substance (63%), the latter being identical (m.p., mixed m.p., UV and IR spectra) to the decarboxylated butenolide IIa (X = H). The acid, $C_{12}H_{10}O_2$, m.p. 131–133° ($\lambda_{max}$ 291 m$\mu$ (22·200); $\nu\nu_{max}$ 2215 m (C≡C st), and 1689s $cm^{-1}$ (C=O st), in $C_2Cl_4$) is, consequently, *trans*-5-phenyl-3-methylpent-4-yn-2-enoic acid (VII).




Wittig reactions in general are known to be non stereospecific,[6] the proportion of *cis*- to *trans*-isomer, formed depending, among other factors, on the relative volume of substituents; in this connection it is interesting to point out the substantial amount of *cis*-ester obtained in the above reaction, which must be related to the greater volume of a methyl than an ethynyl group. This result is in agreement with that reported by one of us in the description of the synthesis of patulin derivatives,[3b] where it was reported that the presence of a still bigger substituent (dimethoxymethyl) led almost exclusively to formation of a *cis*-isomer.[7]

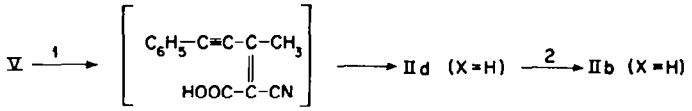
*Synthesis of* IIb (X = H). An attempted synthesis of (1-methyl-phenylpropargylidene) malonic acid (cyclization of which should give α-carboxy-β-methylbutenolide (cf. ref. 1)) by condensation of phenylbutynone and malonic acid gave a negative result. However, the ketone reacts easily with cyanoacetic acid,[8] affording a neutral compound, $C_{13}H_9NO_2$, m.p. 187–190°, to which the structure of α-cyano-β-methyl-γ-benzylidenebutenolide (IId, X = H) is given. This assignment follows from chemical analogy (cf. ref. 1), spectral evidence ($\lambda_{max}$ 360 m$\mu$ (33,200); $\nu\nu_{max}$ 2232m (C≡N st) and 1779s $cm^{-1}$ (lactone C=O st), in KBr), and identity of the compound with that prepared by diazomethane methylation of Id (X = H) (see later). Accordingly, it must be accepted that the reaction between phenylbutynone V and cyanacetic acid gives, as the primary condensation product, *cis*-(1-methyl-phenylpropargylidene)

[6] See, for example, U. Schöllkopf, *Angew. Chem.* **71**, 260 (1959).

[7] cf. S. Trippett in *Advances in Organic Chemistry*: *Methods and Results* Vol. I; p. 91. Interscience, New York (1960).

[8] cf. R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry* p. 54. John Wiley, New York (1953).

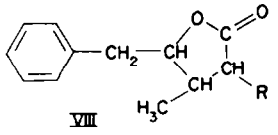
cyanoacetic acid, which then cyclizes to butenolide. Hydrolysis of IId (X = H) affords an acid identical to α-carboxy-β-methyl-γ-benzylidenebutenolide IIb (X = H).




1. $CNCH_2COOH$ ($CH_3COOH$); 2. $H^+$.

It is worth mentioning that the analogous condensation between phenylpropargylaldehyde and cyanoacetic acid[9] yields exclusively *trans*-phenylpropargylidenecyanoacetic acid; thus, in both cases, condensation leads to a *trans*-configuration of the two bulkier substituents.

*Catalytic hydrogenation of lactones* II. The β-methylbutenolide structure of the compounds which, for the sake of clearness, we have been already formulating since the beginning as II (X = H), has been also established by study of their hydrogenation derivatives VIII.




VIII

(a) R = H ; (b) R = COOH ; (c) $R = COOCH_3$

As preliminary work on the catalytic hydrogenation ($PtO_2$) of compounds II, had shown that reproducible results were difficult to obtain,* the carboxy-derivative IIb was selected for a series of well-controlled experiments. In these experiments, concentration, solvent, and amount of catalyst were kept constant, while alkalinity was changed over a considerable range; Fig. 1 shows the results obtained (see also Exp.). Under strong alkaline conditions (Exp. *g*) hydrogenation stops after 2·08 moles $H_2$ have been absorbed. In a neutral or weakly alkaline medium (Exp. *a–d*) nearly 6 moles $H_2$ are consumed.

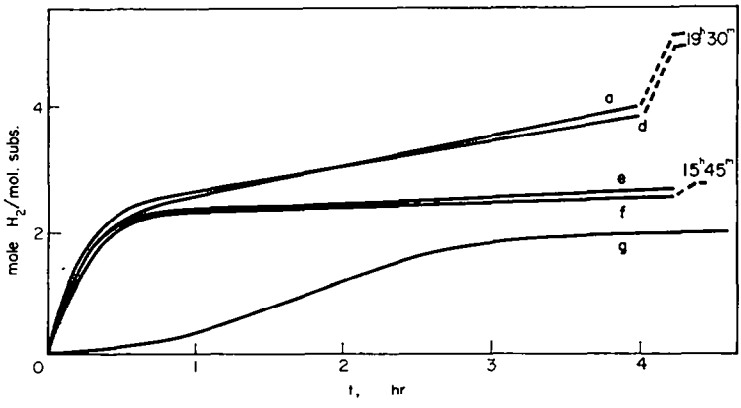



FIG. 1

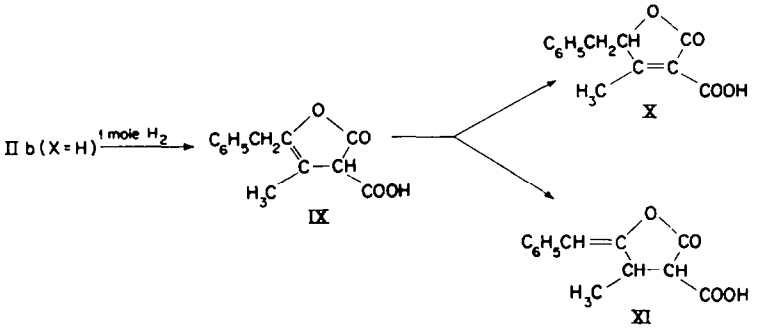
These results can be rationalized by accepting a 1,4-addition of the first mole of hydrogen, with formation of compound IX, which then isomerizes to X or XI, depending on the medium conditions. Compound X accepts only one additional mole

* This result is not unexpected in enol-lactones.[10]

[9] J. Bosch, J. Castells, and J. Pascual, *Anales real Soc. Españ. fís. y quím., Madrid* **57B**, 469 (1961).

[10] See for example, W. A. Jacobs and A. B. Scott, *J. Biol. Chem.* **93**, 139 (1931).

of hydrogen, while compound XI, being a vinylenolog of a phenol ester, can be hydrogenated in the benzene ring and suffer hydrogenolysis of the lactone bond.




Working up the product from Exp. *g* affords (45% yield) an acid, $C_{13}H_{14}O_4$, m.p. 123–127°, whose equivalent weight and IR spectrum ($\nu\nu_{max}$ 1783s (lactone C=O st) and 1721s $cm^{-1}$ (acid C=O st), in $HCCl_3$) agree with the structure of α-carboxy-β-methyl-γ-benzylbutanolide (VIIIb); there is obtained also a syrup (40%) which is considered to be (analysis, equivalent weight, IR spectrum) a stereoisomer of the crystalline acid, or a mixture of stereoisomeric acids.

Catalytic hydrogenation of IIc (X = H) was not studied as carefully as that of IIb but, eventually, a resin, b.p. 140° (0·01 mm) was isolated that analysed correctly for VIIIc and that, upon hydrolysis, yielded the crystalline acid, VIIIb.

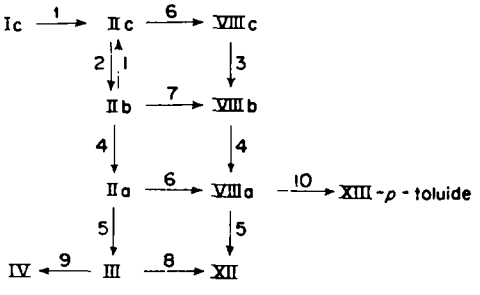
Decarboxylation of VIIIb gives β-methyl-γ-benzylbutanolide VIIIa, b.p. 130° (0·75 mm) ($\nu_{max}$ 1779s $cm^{-1}$ (lactone C=O st)); a compound with the same analytical figures is obtained by hydrogenation of IIa, but the possibility remains for this to be an isomeric mixture.

*Derivatives from β-methyl-γ-benzylbutanolide* VIIIa. Reduction of lactone VIIIa with hydroiodic acid gives a liquid acid, b.p. 210° (0·6 mm) (*p*-toluide, m.p. 107–108°; anilide, m.p. 109–111°), which has been identified (m.p.'s and mixed m.p.'s of the derivatives) with β-methyl-δ-phenylvaleric acid (XII), a known compound which we have prepared by a Wolff-Kishner reduction (Huang-Milon modification) of β-methyl-γ-oxo-δ-phenylvaleric acid.

Lactone VIIIa, treated with *p*-toluidinemagnesium bromide, affords a *p*-toluide, $C_{19}H_{23}NO_2$, m.p. 157–159°, that must be the *p*-toluide of β-methyl-γ-hydroxy-δ-phenylvaleric acid (XIII).

$C_6H_5CH_2CH_2CH(CH_3)CH_2COOH$ XII  $C_6H_5CH_2CH(OH)CH(CH_3)CH_2COOH$ XIII

Chart II summarizes all the correlations established on the degradative work with compounds II and VIII.

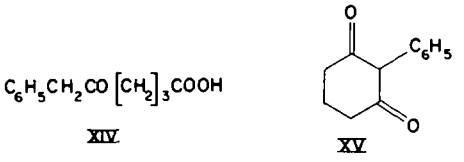


## Chart II

1. $CH_2N_2$; 2. $H^+$; 3. $OH^-$; 4. $\Delta$ (*in vacuo*); 5. HI ($CH_3COOH$);
6. $H_2$ ($PtO_2$); 7. $H_2$ ($PtO_2$, $OH^-$); 8. Wolff-Kishner reduction;
9. NaH-cyclization; 10. *p*-$CH_3C_6H_4NHMgBr$.

*Derivatives from ε-phenylcaproic acid.* At the beginning of the present work the fact that δ-oxo-ε-phenylcaproic acid (XIV), and its semicarbazone had m.p.'s practically identical[11] with those which later on were found to be possessed by β-methyl-γ-oxo-δ-phenylvaleric acid and its semicarbazone, suggested a possible identity of the former with the ketonic acid from HI-reduction of the decarboxylated lactone IIa (X = H). However, the reported m.p.'s of 2-phenylcyclohexane-1,3-dione[12] (XV) and of the anilide and *p*-toluide of ε-phenylcaproic acid[13] (XVI) were substantially different from those of compounds from degradative work which they were expected to duplicate.

For the sake of completeness and to clear up some inconsistences found in the literature,[14] the synthesis of compounds of the ε-phenylcaproic series (XIV and its semicarbazone; XVI; XVII and its *p*-toluide (these not previously described)) was repeated and the non-identity of all pairs of compounds was confirmed by direct comparison.



$C_6H_5CH_2CO[CH_2]_3COOH$ XIV



XV

$C_6H_5[CH_2]_5COOH$ XVI

$C_6H_5CH_2CH(OH)[CH_2]_3COOH$ XVII

*Further examples of the methylation reaction and comments on the UV and IR spectra.* The availability of several benzylidenebutenolides I,[1,9] has allowed us to study the scope of the reported reaction with diazomethane.

Under similar experimental conditions, cyanobutenolide Id (X = H) gives α-cyano-β-methyl-γ-benzylidenebutenolide IId (X = H), identical to the compound prepared by reaction between phenylbutynone V and cyanoacetic acid. γ-(*p*-Methylbenzylidene)- (IIc, X = $CH_3$), m.p. 154–157°, γ-(*p*-chlorobenzylidene)- (IIc, X = Cl), m.p. 175–177·5°, and γ-(*p*-nitrobenzylidene)-α-carbomethoxy-β-methyl-butenolide (IIc, X = $NO_2$), m.p. 166–172° (dec), were prepared from the corresponding carbomethoxy-butenolides I; the structures are assigned on analogy grounds. The parent acids IIb were obtained by hydrolysis of the esters, except that from the nitroderivative.

In all cases, the preparation of carbomethoxy-β-methylbutenolides has been also effected by reaction of carboxybutenolides Ib with two moles of diazomethane.

It is important to point out that the only butenolide with no electron-attracting

[11] G. Soliman and A. Latif, *J. Chem. Soc.* 93 (1951).
[12] H. Born, R. Pappo and J. Szuszkovicz, *J. Chem. Soc.* 1779 (1953).
[13] S. Grateau, *C.R. Acad. Sci. Paris* **191**, 947 (1930).
[14] Ref. 12 gives 265° as the m.p. of δ-oxo-ε-phenylcaproic acid.

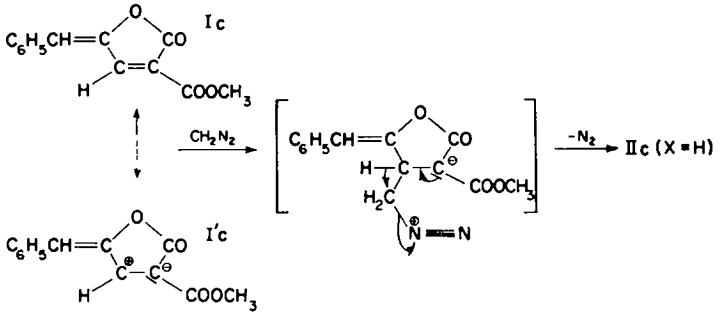
α-substituent that has been studied, γ-benzylidenebutenolide (Ia), *does not* react with diazomethane.

The UV and IR spectra of most of the compounds here described have been recorded. For the structural diagnosis the IR spectrum of IIa (X = H) is of interest because in it there is a band at 1387 $cm^{-1}$ (methyl sym. b.), which does not appear in the spectrum of Ia (X = H); the position (~1780 $cm^{-1}$) of the C=O st band of the lactone carbonyl in compounds II can be taken as further proof of the presence of an ylidenebutenolide structure.[1b]

With regard to the UV spectra (Table 1) we can offer no satisfactory explanation to the fact that methyl-butenolides II (even the compound in which R = H) absorb 5–10 mμ hypsochromically than the parent butenolides.[1b,9] Since in all these butenolides a *trans*-configuration of the *exo*cyclic double bond is most probable,[3b,15] any explanation in terms of resonance inhibition by steric interference between the methyl and phenyl groups is excluded.

*Reaction mechanism.* The reported reaction represents a direct methylation, with diazomethane, of an active trisubstituted double bond. The literature shows few examples of this type of reaction: we have found only the methylation in position 6- of 5-carbomethoxy-α-pyrone[16] and even this is not a strictly comparable example since the carbon atom to be methylated is bound to oxygen. In contrast to the carbomethoxy derivative, 5-methyl-α-pyrone does not react with diazomethane, in agreement with what is observed in the butenolide series.

The methylation of active ethylene could be interpreted by formation of a highly unstable intermediate pyrazoline which would be "pyrolized" completely and instantaneously during the course of the reaction; examples of partial denitrogenation while preparing pyrazolines have been reported.[17] Direct loss of $N_2$ from the intermediate betainic complex can be considered a limiting case of this interpretation.




However, this does not appear to be the correct explanation, because work from this Laboratory[18] shows that expectedly more unstable pyrazolines can be isolated under appropriate working conditions.

Presently, we consider more satisfactory to accept that the ethylene β-hydrogen of butenolides I, with an electron-attracting substituent (R = $COOCH_3$, CN), is acidic

[15] W. Parker, R. A. Raphael and D. I. Wilkinson, *J. Chem. Soc.* 2433 (1959).
[16] J. Fried and R. C. Elderfield, *J. Org. Chem.* **6**, 577 (1941).
[17] K. von Auwers and E. Cauer, *Leibigs Ann.* **470**, 284 (1929); L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.* **65**, 159 (1943).
[18] J. Bastús and J. Castells, *Proc. Chem. Soc.* 216 (1962).

TABLE 1

| Compound | Formula | | C | H | Cl | N | Acid equiv | m.p. | $\lambda\lambda_{max}$ in m$\mu$ ($\varepsilon$)* |
|---|---|---|---|---|---|---|---|---|---|
| IIa, X = H | $C_{12}H_{10}O_2$ | Calc | 77·40 | 5·41 | | | | 101–103° | 226(9150), 240(7960), |
| | | Found | 77·32 | 5·42 | | | | | 324(20490) |
| IIb, X = H | $C_{12}H_{10}O_4$ | | 67·82 | 4·38 | | | | 190–192° dec | 202(11300), 231(7800), |
| | | | 67·96 | 4·71 | | | | | 344(26400) |
| IIb, X = $CH_3$ | $C_{14}H_{12}O_4$ | | 68·84 | 4·96 | | | 244 | 202–210° dec | 204(16700), 233(10130), |
| | | | 68·85 | 5·39 | | | 250 | | 351–3(27900). |
| IIb, X = Cl | $C_{12}H_9ClO_4$ | | 58·99 | 3·43 | 13·40 | | 265 | 208–218° dec | 202(12330), 234(12500), |
| | | | 58·68 | 3·79 | 13·40 | | 266 | | 342–3(32700). |
| IIc, X = H | $C_{14}H_{12}O_4$ | | 68·84 | 4·96 | | | | 156–158° | 202(14500), 227(7180), |
| | | | 69·04 | 5·04 | | | | | 245(6720), 355(25150). |
| IIc, X = $CH_3$ | $C_{15}H_{14}O_4$ | | 69·76 | 5·47 | | | | 154–157° | 233–6(8180), 366(28000) |
| | | | 70·02 | 5·72 | | | | | |
| IIc, X = Cl | $C_{14}H_{11}ClO_4$ | | 60·34 | 3·98 | 12·72 | | | 175–177·5° | 237(9140), 361(29200) |
| | | | 60·64 | 4·42 | 12·75 | | | | |
| IIc, X = $NO_2$ | $C_{14}H_{11}NO_6$ | | 58·13 | 3·84 | | 4·85 | | 166–172° dec | |
| | | | 58·51 | 3·89 | | 5·11 | | | |
| IId, X = H | $C_{13}H_9NO_2$ | | 73·92 | 4·29 | | 6·63 | | 187–190° | 202(10300), 230(7050) |
| | | | 73·65 | 4·43 | | 6·86 | | | 246(6800), 360(33200), |
| III | $C_{12}H_{14}O_2$ | | 69·87 | 6·84 | | | 206 | 62–63° | |
| | | | 69·82 | 6·89 | | | 204 | | |
| III-semi-carbazone | $C_{13}H_{17}N_3O_3$ | | 59·30 | 6·51 | | 15·96 | | 171–173° dec | |
| | | | 59·40 | 6·62 | | 15·78 | | | |
| IV | $C_{12}H_{12}O_2$ | | 76·57 | 6·42 | | | | 181–183° | |
| | | | 77·07 | 6·67 | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| V† | $C_{10}H_8O$ | 83·31 | 5·59 | | | $b_{0.01}$ 44·5° | 212(12520), 216(13500), 236(7100), 259(13250), 270(17450), 283(13550), (in cyclohexane) |
| | | 83·18 | 5·98 | | | | |
| VIa, b | $C_{12}H_{12}O_2$ | 77·98 | 6·04 | | | $b_{0.01}$ 82–84° | 220(15900), 240(9150), 251(9750), 297(16600) |
| | | 77·54 | 6·33 | | | | |
| VII | $C_{12}H_{10}O_2$ | 77·40 | 5·41 | | 186 | 131–133° | 202(20100), 220sh, (13200), 291–2(22200) |
| | | 77·40 | 5·72 | | 183 | | |
| VIIIa | $C_{12}H_{14}O_2$ | 75·76 | 7·42 | | | $b_{0.75}$ 135° | |
| | | 75·30 | 7·60 | | | | |
| VIIIb | $C_{13}H_{14}O_4$ | 66·66 | 6·03 | | 234 | 123–127° | |
| | | 66·88 | 6·13 | | 241 | | |
| VIIIc | $C_{14}H_{16}O_4$ | 67·73 | 6·50 | | | $b_{0.05}$ 140° | |
| | | 67·76 | 6·92 | | | | |
| XII† | $C_{12}H_{16}O_2$ | 74·96 | 8·39 | | 192 | $b_{0.8}$ 210° | |
| | | 74·87 | 8·66 | | 194 | | |
| XII-anilide† | $C_{18}H_{21}NO$ | 80·86 | 7·92 | 5·24 | | 109–111° | |
| | | 80·82 | 8·13 | 5·28 | | | |
| XII-*p*-toluide | $C_{19}H_{23}NO$ | 81·10 | 8·24 | 4·98 | | 107–108° | |
| | | 80·84 | 8·23 | 5·14 | | | |
| XIII-*p*-toluide | $C_{19}H_{23}NO_2$ | 76·76 | 7·80 | 4·72 | | 157–159° | |
| | | 76·69 | 7·98 | 5·07 | | | |
| XVII-*p*-toluide | $C_{19}H_{23}NO_2$ | 76·76 | 7·80 | 4·72 | | 129–230° | |
| | | 76·87 | 7·70 | 5·07 | | | |

* In alcohol.
† Known compound.

enough (cf. Ic) to give rise to a direct C-methylation similar to esterification of acids with diazomethane. In this way, the exclusive formation of methyl derivatives is justified (no cyclopropane derivatives have been isolated).

Further examples of C-methylation by diazomethane, and $pK_a$ measurements of the reactants will be published elsewhere.*

## EXPERIMENTAL

In Table 1, m.p.s (Kofler microscope), analyses, and UV spectra (Uvispek, Hilger Spectrophotometer) of the new compounds are summarized. Significant bands of IR spectra (Infracord 137, and 137-G, Perkin-Elmer Spectrophotometers) are given when not previously mentioned in the theoretical part.

*α-Carbomethoxy-β-methyl-γ-benzylidenebutenolides* IIc

(a) α-Carboxy-γ-benzylidenebutenolide (4·0 g) in ether (15 ml) was treated, at room temp, with a slight excess of diazomethane in ether (2·2–2·4 moles); the product dissolved slowly and a yellow precipitate appeared. The precipitate was filtered off after some hours (the concentrated mother liquors gave more product). Recrystallization of the product from ether (or ethyl acetate) gave the *α-carbomethoxy-β-methyl-γ-benzylidenebutenolide* IIc (X = H; 3·8 g) as yellow needles, m.p. 156–158°, $\nu\nu_{max}$ 1786s (lactone C=O st), and 1726s $cm^{-1}$ (ester C=O st), in $CCl_4$.

(b) α-Carbomethoxy-γ-benzylidenebutenolide (0·3 g) in ether was treated with a slight excess of diazomethane in ether (1·2–1·4 moles) as above. The same β-methylbutenolide (0·3 g), m.p. and mixed m.p. 156–158°, was obtained.

(c) The β-methyl-γ-benzylidenebutenolides IId (X = H) and IIc (X = $CH_3$, Cl, $NO_2$) were prepared by identical procedures.

*Attempted reaction of γ-benzylidenebutenolide with diazomethane*

γ-Benzylidenebutenolide (0·2 g) was treated with an excess of ethereal diazomethane. After some hours the ether was evaporated. The residue was recrystallized from ether, giving white prisms (0·2 g), m.p. 86–87°, which showed no depression on admixture with the starting material.

*α-Carboxy-β-methyl-γ-benzylidenebutenolides*, IIb

(a) α-Carbomethoxy-β-methyl-γ-benzylidenebutenolide (7·23 g), dioxane (200 ml), and conc HCl (80 ml) were heated at 100° for 10 hr, under an atmosphere of $N_2$. The yellow precipitate was collected, washed with alcohol and water, and recrystallized from dioxane to give *α-carboxy-β-methyl-γ-benzylidenebutenolide* IIb (X = H; 5·22 g), m.p. 190–192° (dec), $\nu\nu_{max}$ 1757s (lactone C=O st) and 1724s $cm^{-1}$ (acid C=O st) in $HCCl_3$.

Acid IIb (X = H) was reconverted into its methyl ester: acid (196 mg), methanol (12 ml), and conc HCl (0·2 ml) were refluxed for 13 hr; ethyl acetate was added to insolubilize some of the unreacted acid. The solution was washed with 2N aq. $K_2CO_3$ and water, dried and columned through alumina. Removal of solvents and recrystallization from alcohol afforded ester IIc (X = H). Treatment of the acid with diazomethane afforded also the methyl ester.

(b) *α-Carboxy-β-methyl-γ-benzylidenebutenolides* IIb, X = $CH_3$ and X = Cl, were prepared by identical procedure.

*β-Methyl-γ-benzylidenebutenolide* IIa (X = H)

α-Carboxy-β-methyl-γ-benzylidenebutenolide (2·0 g) was heated *in vacuo* at 250°. A yellow oil, that solidified easily, distilled at 210°/18 mm. The solid was recrystallized from ether (or pet ether) to give *β-methyl-γ-benzylidenebutenolide* (0·8 g), as white prisms, m.p. 101–103°, $\nu\nu_{max}$ 1786s (lactone C=O st) and 1387w $cm^{-1}$ ($CH_3$ sym. b.), in $CCl_4$.

*Reduction with hydroiodic acid of β-methyl-γ-benzylidenebutenolide*

A mixture of β-methyl-γ-benzylidenebutenolide (1·0 g), 40% HI (20 ml) and acetic acid (20 ml), was heated at 160° in a sealed tube for 6 hr. The mixture was diluted with water, a few drops of conc $NaHSO_3$ solution were added, and the solution was treated several times with ether. The combined

* *Note added in proof*—Recently we have been acquainted with the paper by F. D. Popp and A. Catala (*J. Org. Chem.* **26**, 2738 (1961)) where examples of direct C-methylation are reported.

ether solutions were extracted with aq. $Na_2CO_3$. The alkaline solution was acidified (2N HCl) and re-extracted with ether; the dried ether solution was evaporated *in vacuo*, and white residue was recrystallized from petrol ether, to give *β-methyl-γ-oxo-δ-phenylvaleric acid* (0·96 g), m.p. and mixed m.p. with an authentic sample (*vide infra*) 62–63°. *Semicarbazone:* white crystals, m.p. and mixed m.p. with an authentic sample (*vide infra*), 171–173° (dec).

*4-Methyl-2-phenylcyclopentane-1,3-dione* IV

Methyl β-methyl-γ-oxo-δ-phenylvalerate (1·3 g) (from the above acid and diazomethane), sodium hydride (0·28 g), and ether (20 ml) were refluxed for 6 hr. The mixture was diluted with ether (40 ml), acidified, washed with water, dried and evaporated to dryness. Recrystallization of the residue from benzene gave *4-methyl-2-phenylcyclopentane-1,3-dione* (0·6 g) as a white solid, m.p. 181–183°.

*β-Methyl-γ-oxo-δ-phenylvaleric acid* III

A solution of ethyl α-methyl-β-oxo-γ-phenylbutyrate[19] (10·0 g) in benzene (35 ml) was allowed to react with sodium alcoholate (from 1·15 g of Na in 15 ml of alcohol), and the benzene was distilled off to remove all traces of alcohol. Ethyl bromoacetate (8·25 g) in benzene (10 ml) was added and the mixture was refluxed for 9 hr. The reaction mixture was acidified with 2N $H_2SO_4$, the benzene layer separated and washed with M/2 $NaHCO_3$ solution and water. Distillation *in high vacuo* gave ethyl β-methyl-β-carbethoxy-γ-oxo-δ-phenylvalerate as a colourless oil (6·2 g), b.p. 131–132° (0·1 mm) $n_D^{22}$ 1·4960.

Without further purification, the product (8·18 g) was shaken for 24 hr with 10% aq. KOH in dioxane (8·18 ml), washed with ether and acidified with 2N HCl. Extraction with ether and evaporation yielded a crystalline product (4·17 g) which was recrystallized from ether–pet ether (1:3) to give *β-methyl-γ-oxo-δ-phenylvaleric acid* (1·34 g), m.p. 62–63°.

*Semicarbazone:* m.p. 171–173° (dec).

*β-Methyl-δ-phenylvaleric acid* XII

A mixture of β-methyl-γ-oxo-δ-phenylvaleric acid* (0·44 g), diethylenglycol (5 ml), 80% hydrazine hydrate (2·5 ml) and KOH (2·9 g) was refluxed for 1 hr and then slowly distilled until the inside temperature had risen to 175°. At this point the mixture was refluxed again for 7 hr, water was added and the solution was washed with ether. The aqueous solution was acidified with 6N HCl and extracted with ether. The combined ether extracts were washed twice with water and dried; evaporation of the solvent gave a yellow oil (0·34 g), which was dissolved in benzene and columned through silica-gel. The benzene–ether (100:5) eluate gave the β-methyl-δ-phenylvaleric acid (0·34 g) as a colourless oil. Anilide, m.p. 109–111°; p-*toluide*, m.p. 107–108°.

*1-Phenylbut-1-ynone* V

*Method* 1. Under an atmosphere of purified nitrogen, a solution of phenylacetylene (11·2 g) in dry benzene (20 ml) was added dropwise to a stirred solution of ethylmagnesium bromide (prepared from 2·43 g Mg) in ether (80 ml). The mixture was refluxed for 2 hr, then cooled at room temp and a solution of N-acetylpiperidine (12·7 g) in dry benzene (50 ml) was added dropwise. After stirring for further 17 hr, the mixture was cooled with ice and 2N $H_2SO_4$ (200 ml) was added and the mixture was shaken for 24 hr. The mixture was extracted with ether (3 × 100 ml) and the combined ether extracts were washed with 0·6M $NaHCO_3$ solution and water, and dried. On distillation *in vacuo* phenylacetylene (3·25 g), b.p. 52–53° (15 mm) was obtained, and the residue was distilled at high vacuum affording N-acetylpiperidine (1·96 g), b.p. 67–70° (0·8 mm) and 1-phenylbut-1-ynone (1·20 g), b.p. 75–76° (0·8 mm) $\nu\nu_{max}$ 2208s (C≡C st) and 1681s $cm^{-1}$ (C=O st), in $CCl_4$.

*Method* 2. (a) *1-Phenylbutyn-3-ol*[20]. To a stirred ice-cooled solution of phenylmagnesium bromide (from 12·0 g phenylacetylene), prepared as described in Method 1, a solution of freshly distilled acetaldehyde (6·16 g) in dry benzene (40 ml) was added dropwise, and the mixture stirred for 17 hr at room temp, and, finally, heated under reflux for 0·5 hr. The reaction mixture was hydrolyzed with 2N $H_2SO_4$ (100 ml) and worked up as usual. Solvents were removed and the remaining

* This experiment has also been carried out with a sample of the acid from HI-reduction of β-methyl-γ-benzylidenebutenolide.

[19] G. Soliman and R. W. West, *J. Chem. Soc.* 5355 (1944).

[20] E. A. Braude and J. A. Coles, *J. Chem. Soc.* 2085 (1951).

oil was distilled giving unreacted phenylacetylene (2·37 g), b.p. 45° (20 mm) and 1-phenylbutyn-3-ol (11·13 g), b.p. 140–141° (20 mm), $n_D^{31}$ 1·5634; $\nu\nu_{max}$ 3333s (bonded OH st), and 2237m and 2208m $cm^{-1}$ (C≡C st) liquid film.

(b) *Oxidation.*[4] To a stirred solution of 1-phenylbutyn-3-ol (11·2 g) in ether (33·5 ml), cooled at −15°, a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (7·67 g) and conc $H_2SO_4$ (5·76 ml) in water (up to a volume of 38·5 ml) was added dropwise, in such a rate that the temp was kept below 25°. The mixture was stirred for a further 4 hr at room temp, the ether layer was separated, and the aqueous solution extracted twice with ether (2 × 15 ml). The combined ether extracts were washed with $NaHCO_3$ solution, with water, and dried. On distillation, impure 1-phenylbut-1-ynone (7·78 g) was obtained, b.p. 61–65° (0·15 mm) the IR spectrum showed the presence of some starting carbinol.

The more conventional oxidation with $CrO_3$ in acetone afforded a lower yield of equally impure ketone.

(c) *Purification.* The above impure 1-phenylbut-1-ynone (6·95 g) was treated with an excess of 45% $NaHSO_3$ solution (16 g) and the mixture was shaken for 17 hr. The precipitate formed was filtered off, washed with ether, dried (5·02 g), and then hydrolysed with saturated $Na_2CO_3$ solution (35 ml). The aqueous solution was extracted with ether to give pure ketone (2·6 g); distillation yielded the ketone (2·48 g) as a colourless liquid, b.p. 44–45° (0·01 mm) with an identical IR spectrum than the undistilled product.

*Method* 3. (a) *1-Phenylbut-1-ynone diethylketal.*[5] In a distillation flask, fitted with a column packed with Fenske helices, a mixture of phenylacetylene (10·2 g), ethyl orthoacetate (21·1 g) and freshly fused $ZnCl_2$ (1·0 g) was heated slowly up to 180° (8 hr), the alcohol formed being removed (4·6 g). The reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with water, dried and distilled; the fraction b.p. 61–63° (0·01 mm) (9·21 g) was collected. The IR spectrum showed carbonyl by-products to be present (band at 1710 $cm^{-1}$); these were removed by sublimation at 0·01 mm and 75° (bath temp). After changing the distillation head, the remaining product was distilled to give pure 1-phenylbut-1-ynone diethylketal, b.p. 60° (0·01 mm) (6·77 g).

(b) *Hydrolysis.* A mixture of 1-phenylbut-1-ynone diethylketal (6·67 g) and 30% tartaric acid solution (55 ml) was shaken for 7 days at room temp. Extraction with ether and evaporation gave the ketone (4·52 g); distillation afforded pure 1-phenylbut-1-ynone (3·75 g) as a colourless liquid, b.p. 43° (0·01 mm) the IR spectra of both, crude and distilled product, being identical.

*Methyl 5-phenyl-3-methylpent-4-yn-2-enoate* (VIa + VIb)

Under an atmosphere of $N_2$, a solution of 1-phenylbut-1-ynone (1·0 g) and carbomethoxymethylen-triphenylphosphorane[21] (2·9 g) in dry benzene (47 ml) was refluxed for 24 hr. The benzene evaporated *in vacuo* and the residue was dissolved in ether: most of the triphenylphosphine oxide crystallized out, was filtered off. The ether was removed and the residue thoroughly extracted with hot pet ether. The pet ether solution was kept in the refrigerator, and slowly more triphenylphosphine oxide crystallized out. The solution was evaporated once again and the oily residue was distilled at high vacuum to give the mixture of *methyl 5-phenyl-3-methylpent-4-yn-2-enoate* (0·92 g), b.p. 82–84° (0·01 mm).

*Synthesis of β-methyl-γ-benzylidenebutenolide* IIa (X = H)

Methyl ester VI (2·0 g) in dioxane (16 ml) was vigorously shaken for 2 hr with 0·5N NaOH solution (24 ml), and then set aside overnight. The solution was washed with ether (4 × 15 ml), acidified with 2N HCl (23 ml), and extracted with ether. The combined ether extracts were washed with water, and dried. A crude mixture of *cis*- and *trans*-acid (1·85 g) was obtained as a yellow oil after removal of the ether *in vacuo*. The mixture was dissolved in methanol (10 ml) and 4 drops of 1% silver nitrate solution were added. An exothermic reaction ensued and the mixture was then left 1·5 hr at room temp. The methanol was removed and the oily residue was taken up with ether. The ether solution was washed with 0·5M $NaHCO_3$ solution (sol. A), dried and evaporated, affording *β-methyl-γ-benzylidenebutenolide* (0·82 g) as yellow crystals. The recrystallized product was identical, in all respects, with the substance from diazomethane reaction (see p. 20).

[21] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta* **40**, 1242 (1957).

When the above $NaHCO_3$ solution (sol. A) was acidified and extracted with ether, a solid (0·75 g) with unsharp m.p. (67–129°) was obtained. The benzene solution of the crude acid was chromatographed over silica-gel, the benzene–ether eluates affording pure trans-*5-phenyl-3-methylpent-4-yn-2-enoic acid* (0·27 g), m.p. 131–133°, methylbutenolide IIa (0·36 g) and a mixture of both products (0·10 g).

*Attempted condensation of 1-phenylbut-1-ynone with malonic acid*

A mixture of 1-phenylbut-1-ynone (0·39 g), malonic acid (0·39 g), and acetic acid (3 ml) was refluxed for 18 hr (atm of $N_2$). Dilution with water (5 ml) afforded an oily product from which no definite compound was isolated.

*Synthesis of α-carboxy-β-methyl-γ-benzylidenebutenolide* IIb (X = H)

A mixture of 1-phenylbut-1-ynone (0·38 g), cyanoacetic acid (0·67 g) and acetic acid (2 ml) was heated at 100° for 82 hr (atm of $N_2$). Water (3 ml) and pet ether (3 ml) were added; the solid residue was filtered off, washed again with water and pet ether, and recrystallized from benzene to give *α-cyano-β-methyl-γ-benzylidenebutenolide* (0·15 g), yellow prisms, m.p. 187–190°. From the combined pet ether solutions, after washing with 0·6M $NaHCO_3$, with water and drying, some (0·14 g) 1-phenylbut-1-ynone was recovered.

*Hydrolysis.* A mixture of α-cyano-β-methyl-γ-benzylidenebutenolide (0·10 g), acetic acid (2·5 ml) and 60% $H_2SO_4$ (3 ml) was heated for 3 hr at 100°. After cooling, water (5 ml) was added and the precipitate was filtered off and recrystallized from alcohol to give a substance identical in all respects with the substance from diazomethane reaction (see p. 20).

*Catalytic hydrogenation of α-carboxy-β-methyl-γ-benzylidenebutenolide* (Fig. 1)

*Experiment g.* A mixture of α-carboxy-β-methyl-γ-benzylidenebutenolide (200 mg), $PtO_2$ (33 mg), KOH (75 mg), water (2 ml), and absolute alcohol (33 ml) was hydrogenated at atm press. (752 mm) and room temp (14°). Absorption of hydrogen stopped after 50·8 ml of $H_2$ (2·08 moles $H_2$/mol substance) had been taken up. 2N HCl (0·22 ml) was added and the solvent was removed *in vacuo*; the residue was treated with water (30 ml), acidified with 2N HCl and extracted with chloroform–ether (1:10). The organic solution was worked up as usual giving an oily product which was treated with ether to afford *α-carboxy-β-methyl-γ-benzylbutanolide*, VIIIb (90 mg), white plates, m.p. 123–127°. The resulting ether solution was extracted with $NaHCO_3$ solution and this was again acidified and extracted with ether; removing of the solvent gave a syrup (83 mg) which was purified by columning through silica-gel (Found C, 66·47, H, 6·69. $C_{13}H_{14}O_4$ requires: C, 66·66, H, 6·03%. Acid equiv. Found, 234; Calc. 234) (IR spectrum different but very similar to that of the crystalline isomer).

*Other experiments.* Six further hydrogenation experiments were carried out using the following amounts of reactants (given in this order: IIb, R = H (mg); $PtO_2$ (mg); absolute alcohol (ml); KOH (mg); water (ml)):
(a) 200, 33, 33, 0, 0; (b) 229, 25, 40, 0, 0; (c) 202, 26, 40, 0, 0; (d) 200, 33, 33, 2, 1; (e) 200, 33, 33, 14, 7; (f) 200, 33, 33, 34, 17.

Hydrogenations *a*, *d*, *e*, and *f* were pursued, as experiment *g*, until no more hydrogen was being taken up; experiments *b* and *c* were discontinued after absorption of 2·1 and 3·2 moles of $H_2$, respectively. Working up of the product from experiment *c* afforded some α-carboxy-β-methyl-γ-benzylbutanolide (73 mg).

*α-Carbomethoxy-β-methyl-γ-benzylbutanolide* VIIIc

α-Carbomethoxy-β-methyl-γ-benzylidenebutenolide (2·0 g) in alcohol (75 ml) was hydrogenated over $PtO_2$ (0·1 g) at atm press and room temp. The residue obtained after filtration and evaporation was an oil, which was distilled to give *α-carbomethoxy-β-methyl-γ-benzylbutanolide* as a colourless fluid resin, b.p. 140° (0·01 mm).

*Saponification.* α-Carbomethoxy-β-methyl-γ-benzylbutanolide (2·0 g), KOH (2·0 g) and alcohol (20 ml) were refluxed for 1 hr; the potassium salt which precipitated on cooling was filtered off, dissolved in water and acidified with 2N HCl. A resin, which crystallized sometimes, precipitated; recrystallization from ether gave α-carboxy-β-methyl-γ-benzylbutanolide (0·9 g), identical with the compound prepared by hydrogenation of IIb (X = H).

*β-Methyl-γ-benzylbutanolide* VIIIa

(a) α-Carboxy-β-methyl-γ-benzylbutanolide (2·0 g) was heated at 140° *in vacuo* for 30 min and afterwards distilled to give *β-methyl-γ-benzylbutanolide* (0·8 g), b.p. 130° (0·75 mm), as a colourless oil.

(b) β-Methyl-γ-benzylidenebutenolide (1·0 g), in alcohol (50 ml) was hydrogenated over $PtO_2$ (60 mg). After filtration and evaporation, the residue was distilled giving a colourless oil, b.p. 130° (0·75 mm) which had the same characteristics and behaviour as the substance prepared in (a).

*Reduction with hydroiodic acid of β-methyl-γ-benzylbutanolide*

A mixture of β-methyl-γ-benzylbutanolide (2·0 g), 40% HI (40 ml), and acetic acid (40 ml), was heated at 160° in a sealed tube for 6 hr. The product was treated as in the reduction of β-methyl-γ-benzylidenebutenolide. The dried ether solution was evaporated and the resulting oil was distilled to give β-methyl-δ-phenylvaleric acid XII, as a colourless oil, b.p. 210° (0·6 mm). This acid (after esterification with diazomethane) was converted, by reaction with aniline and *p*-toluidine-magnesium bromide, into its anilide, m.p. 109–111° and *p*-toluide, m.p. 107–108°, which gave no depression on admixture with authentic specimens.

p-*Toluide of β-methyl-γ-hydroxy-δ-phenylvaleric acid* XIII

β-Methyl-γ-benzylbutanolide (1·90 g) in ether (20 ml) was added to an excess of a Grignard reagent prepared by adding *p*-toluide to ethereal ethyl magnesium bromide. After 30 min refluxing, more ether (70 ml) was added, and the cold solution was washed several times with 2N HCl and then with water. The dried ether solution was evaporated and the residue was recrystallized from ether to give the p-*toluide of β-methyl-γ-hydroxy-δ-phenylvaleric acid* (1·30 g), as white needles, m.p. 157–159°.

*Derivatives of ε-phenylcaproic acid*

δ-Oxo-ε-phenylcaproic acid XIV (prepared by a modification of the method of Soliman and Latif[11]) showed m.p. 59–61°; semicarbazone, m.p. 172–173° (dec). ε-Phenylcaproic acid XVI, b.p. 132° (0·6 mm), was obtained by Wolff-Kishner reduction (Huang-Milon modification) of δ-oxo-ε-phenylcaproic acid. IR spectrum different but very similar to that of β-methyl-δ-phenylvaleric acid.

The p-*toluide of δ-hydroxy-ε-phenylcaproic acid* XVII, was prepared as follows: δ-Oxo-ε-phenylcaproic acid (0·50 g) in absolute alcohol (10 ml) was hydrogenated at atm press in the presence of Adams' catalyst (0·025 g). Working up as usual a heavy oil (0·50 g) was obtained, which was dissolved in ether and added to a Grignard reagent prepared by adding *p*-toluidine to ethereal ethylmagnesium bromide (from 0·10 g Mg in 25 ml ether); the mixture was refluxed for 0·5 hr. More ether was added and the ether solution was washed with 2N HCl and water. Evaporation of the dried ether solution gave the *p*-toluide of XVII, m.p. 129–130°.

*Acknowledgements*—The authors wish to acknowledge their indebtedness to Dr. J. Estevan and his associates, of this Department, for the analysis, and to "Fundacion Juan March" for financial support (Ayuda a la Investigación de Ciencias, 1958), and a fellowship (Beca de Estudios de Ciencias, 1960) to one of us (R. M.).