# PREPARATION OF ESTERS OF β-ACYLACRYLIC ACIDS BY THE WITTIG REACTION

M.KUCHAŘ, B.KAKÁČ and O.NĚMEČEK

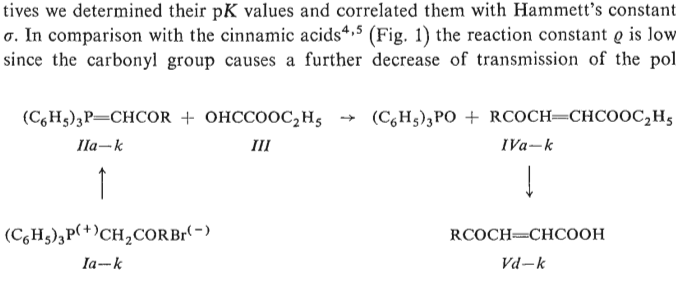
*Research Institute of Pharmacy and Biochemistry, Prague 3*

Received January 21st, 1972

Ethyl esters of β-acylacrylic acids (*IV*) were prepared by the Wittig reaction of β-ketoalkylidenephosphoranes (*II*) with the ethyl ester of glyoxylic acid which yielded the corresponding acids *V* by acidolysis. The p*K* values of the phosphoranes *II* and of the acids *V* were correlated with the aid of Hammett's function. The NMR spectra of phosphoranes *II* were measured and the character of P—C—H coupling is discussed.

In view of the antiviral activity of P-(1-adamantylcarbonyl)-acrylic acid[1] we prepared as reference compounds a series of β-acylacrylic acids and of their ethyl esters. For the preparation, the previously described reaction of β-ketoalkylidenephosphoranes (*II*) with the glyoxylic acid ester (*III*) was used[2]. The content of *IV* was determined from the absorbance of the maximum of the ester group in the IR spectrum (between 1710 and 1725 $cm^{-1}$) and from the absorbance of the maximum of the $\pi \rightarrow \pi^*$ transition of the double-bond conjugated system (between 270 and 320 nm) in the UV spectrum (Table I).

Esters *IV* underwent acidolysis with a mixture of acetic and hydrochloric acids (10 : 1) to obtain the corresponding β-acylacrylic acids (*V*). For the aromatic derivatives we determined their p*K* values and correlated them with Hammett's constants[3] $\sigma$. In comparison with the cinnamic acids[4,5] (Fig. 1) the reaction constant $\varrho$ is lower since the carbonyl group causes a further decrease of transmission of the polar




R: *a* $(CH_3)_3C$; *b* $CH_3$; *c* α-furyl; *d* *p*-$CH_3OC_6H_4$; *e* *p*-$CH_3C_6H_4$; *f* *p*-$C_2H_5C_6H_4$; *g* $C_6H_5$; *h* *p*-$ClC_6H_4$; *i* *p*-$BrC_6H_4$; *k* *p*-$NO_2C_6H_4$

SCHEME 1

effects of the substituents. The carbonyl group, at the same time, increases through its negative inductive and mesomeric effect the acidity of these acids.

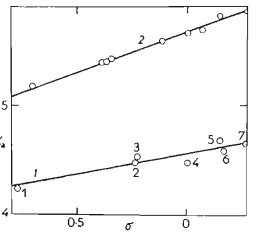



FIG. 1

Dependence of $pK_a$ on $\sigma$ for *1* β-Aroylacrylic Acids (*V*, R = X—$C_6H_4$) ($\varrho$ 0·34) and for *2* Cinnamic Acids (X—$C_6H_4$CH=CHCOOH) ($\varrho$ 0·68). X: *1* *p*-$NO_2$, *2* *p*-Br, *3* *p*-Cl, *4* H, *5* *p*-$C_2H_5$, *6* *p*-$CH_3$, *7* *p*-$CH_3O$.

As starting compounds for the Wittig reaction we prepared β-ketoalkylidenephosphoranes *II* by dehydrohalogenation of the corresponding phosphonium salts *I*. When correlating the $pK_b$ values of the aromatic derivatives *IId–k* with Hammett's constants a linear relationship was found to exist with the negative value of the reaction constant $\varrho = -2{\cdot}56$. Measurement of the NMR spectra showed that the α-proton of all the phosphoranes *IIa–IIk* is characterized by a doublet. The splitting is apparently due to coupling with the atom of phosphorus and is characteristic for the P—C—H grouping. As it was found before[6,7] that the character of this doublet depends on temperature and can be converted to a singlet at a certain temperature this fact may account for the anomaly of the *p*-toluyl derivative *IIe*. Its temperature of doublet merging is apparently lower than with the other phosphoranes *II*. In the IR

TABLE I

Reaction of Phosphoranes *II* with Ethyl Glyoxylate *III*

| Phosphorane *II* | *a* | *b* | *c* | *d* | *e* | *f* | *g* | *h* | *i* | *k* |
|---|---|---|---|---|---|---|---|---|---|---|
| Content of *IV* in the crude product, IR[a], % | 90·9 | 99·7 | 93·4 | 87·1 | 90·4 | 97·9 | 93·1 | 83·8[b] | 89·1[c] | 95·0 |
| Content of *IV* in the crude product, UV, % | 94·6 | 95·2 | 96·0 | 84·7 | 95·3 | 95·7 | 91·6 | 84·0 | 93·1 | 94·6 |
| Yield of pure *IV*, % | 68·1 | 58·7 | 54·2 | 45·3 | 45·7 | 50·7 | 63·5 | 44·3 | 39·1 | 30·0 |

[a] According to $\varepsilon_{ester}$, within the experimental error limits (2%), identical with $\varepsilon_{CO}$; [b] according to content of Cl 87·7%; [c] according to content of Br 90·3%.

spectrum this group of phosphoranes is probably characterized by maxima at 1510 to 1540 $cm^{-1}$ (carbonyl group), at 1450 $cm^{-1}$ and 1110–1120 $cm^{-1}$ ($(C_6H_5)_3P$ grouping), at 880–900 $cm^{-1}$ (C—H bond in α-position with respect to P). Some of these wavenumbers were discussed before[8-10] (Table II).

TABLE II
Properties of β-Ketoalkylidenephosphoranes *II*

| Compound (yield, %) | M.p., °C (solvent) | $pK_b$ ($\sigma$) | $\nu$ ($cm^{-1}$) in KBr | $\delta$, p.p.m. $J$ (Hz) |
|---|---|---|---|---|
| *IIa* (75·0) | 183–184 (methanol–water 5 : 3) | 6·90 — | 890, 1 115, 1 398, 1 441, 1 530 | 3·75 (d) 28·0 |
| *IIb* (79·5) | 208·5–209·5[a] (methanol–water 5 : 3) | 7·20 — | 880 1 114, 1 390, 1 441, 1 540 | 3·70 (d) 28·0 |
| *IIc* (73·5) | 240·5–241·5 (ethanol) | 8·05 — | 887, 1 110, 1 392, 1 440, 1 531 | 4·42 (d) 24·0 |
| *IId* (65·3) | 157–157·5[c] (ethyl acetate) | 7·20 (−0·27) | 889, 1 120, 1 392, 1 441, 7 511 | 4·26 (d) 25·0 |
| *IIe* (75·2) | 185–186[d] (methanol–water 5 : 3) | 7·55 (−0·17) | 896, 1 110, 1 390, 1 440, 1 526 | 4·37 (b.s.) |
| *IIf* (44·1) | 190–191·5 (ethyl acetate–acetone 6 : 1) | 7·48 (−0·15) | 890, 1 106, 1 386, 1 437, 1 515 | 4·40 (d) 24·0 |
| *IIg* (74·2) | 185–185·5[e] (ethanol–water 5 : 1) | 7·95 (0) | 901, 1 110, 1 390, 1 441, 1 527 | 4·42 (d) 24·0 |
| *IIh* (68·9) | 198·5–199·5[f] (methanol) | 8·40 (0·227) | 874, 1 110, 1 395, 1 426, 1 470, 1 510 | 4·32 (d) 21·0 |
| *IIi* (67·2) | 199–200[g] (ethanol–water 3 : 1) | 8·45 (0·232) | 892, 1 113, 1 390, 1 440, 1 522 | 4·35 (d) 24·0 |
| *IIk* (73·5) | 160·5[h] (methanol–water 2 : 1) | 9·95 (0·78) | 884, 1 104, 1 392, 1 436, 1 525 | 4·50 (d) 24·5 |

[a] Ref.[11] m.p. 205–206°C; [b] ref.[12] m.p. 239–239·5°C; [c] ref.[13] m.p. 142·5–143·5°C; [d] ref.[13] m.p. 179–180°C; [e] ref.[13] m.p. 181–182°C; [f] ref.[13] m.p. 199°C; [g] ref.[13] m.p. 201–201·5°C; [h] ref.[13] m.p. 147·5–148·5°C.

## EXPERIMENTAL

### Methods

The IR spectra between 400 and 4000 $cm^{-1}$ of *IV* and *V* were measured in a 3% solution in chloroform; those of phosphoranes *II* in a KBr pellet in a Ur-10 (Zeiss, Jena) spectrophotometer. The UV absorption spectra of esters *IV* between 200 and 400 nm were measured in a methanol

solution in a 1 cm quartz cuvette using an Optica Milano CF-4R spectrophotometer. The NMR spectra of phosphoranes *II* were recorded in a ZKR 60 (Zeiss, Jena) spectrometer using a 6% solution in deuteriochloroform. Hexamethyldisiloxane was used as internal standard and the values obtained were compared with tetramethylsilane. The p*K* values of phosphoranes *II* were estimated in methanol, those of acids *V* in 50% aqueous ethanol using the Titrigraph (Radiometer) potentiometer of type SBR 2c. Chromatographic estimation of esters *UV* and acids *V* is based on quench ing the light of a low-pressure mercury-discharge tube (Chromatolite). For the esters, Whatman No 1 impregnated with kerosene in n-hexane was used, developed in 70% aqueous 2-propanol. For acids *V*, Whatman No 1 impregnated with 40% formamide and 5% ammonium formate was used, developing with chloroform. All the compounds were identified also by elementary analysis. The melting points were determined in a Boëtius M block and are not corrected.

Triphenyl-β-ketoalkylphosphonium Bromides (*I*)

These were prepared by conventional methods[10,13] from equimolar amounts of triphenylphosphine and bromomethyl ketone in benzene by 2 h of boiling and subsequent 24 h of stirring at room temperature. The precipitated product was filtered, washed with benzene and, after crystallization, processed to the corresponding phosphorane.

*Ia*: $C_{24}H_{26}BrOP.H_2O$, m.p. 235–237°C (water), yield 56·5%. *Ib*: m.p. 230–232°C (chloroform–ether) (ref.[17] 234–237°C), yield 65·0%. *Ic*: m.p. 282–283°C (ethanol) (ref.[11] 275–276°C), yield 61·7%. *Id*: m.p. 228–230°C (water) (ref.[11] 222°C), yield 48·0%. *Ie*: m.p. 282–283·5°C (water–ethanol) (ref.[11] 253–254°C), yield 66·7%. *If*: $C_{28}H_{26}BrOP.H_2O$, m.p. 112–114°C (water–methanol 5 : 2), yield 66·9%. *Ig*: m.p. 299–300°C (water–ethanol 3 : 1) (ref.[11] 276–277°C) yield 69·4%. *Ih*: $C_{26}H_{21}BrClOP.H_2O$, m.p. 263–264°C (methanol–water 1 : 1) (ref.[11] 264 to 264·5°C), yield 68·7%. *Ii*: m.p. 234–236°C (water-ethanol 1 : 1) (ref.[11] 239–239·5°C), yield 77·5%. *Ik*: m.p. 148°C under decomposition (methanol–water 4 : 1) (ref.[11] 150°C under decomposition), yield 83·0%.

TABLE III

Properties of β-Acylacrylic Acid Esters *IV*

| *IV* | M.p. (ethanol) or b.p. | $\nu$ ($cm^{-1}$) in $CHCl_3$ | $\lambda$ nm | $E_1^1$ | $R_F$[a] |
|---|---|---|---|---|---|
| *a* | 84°C/3 Torr | 978, 1 635, 1 691 1 717 | 223 | 847 | 0·78 |
| *b* | 89–90°C/13 Torr[b] | 985, 1 646, 1 688–1 704, 1 724 | 219, 5 | 1 142 | 0·86 |
| *c* | 59–60·5°C[c] | 982, 1 640, 1 678, 1 726 | 239, 313 | 544, 702 | 0·65 |
| *d* | 37–38°C[d] | 985, 1 635, 1 668, 1 721 | 234, 320 | 620, 488 | 0·63 |
| *e* | 147°C/1·0 Torr | 985, 1 635, 1 670, 1 721 | 230, 292 | 658, 526 | 0·73 |
| *f* | 162·5°C/1·6 Torr | 981, 1 635, 1 671, 1 724 | 231, 293 | 627, 513 | 0·57 |
| *g* | 131°C/1·0 Torr[e] | 977, 1 635, 1 670, 1 722 | 231, 274 | 664, 495 | 0·78 |
| *h* | 64–65°C | 981, 1 638, 1 675, 1 724 | 221, 285 | 570, 533 | 0·57 |
| *i* | 61·5–62·5°C | 982, 1 640, 1 678, 1 726 | 289 | 494, 5 | 0·53 |
| *k* | 71–72°C | 981, 1 640, 1 681, 1 726 | 273 | 705 | 0·63 |

[a] System described in the Experimental part; [b] ref.[14] b.p. 78–80°3/8 Torr; [c] light petroleum–ether 1 : 1; [d] ref.[15] m.p. 42–43°C; [e] ref.[17] b.p. 130°C/1 Torr; [f] ethanol.

β-Ketoalkylidenephosphoranes (*II*)

*Method* A: A solution of 0·15 mol $K_2CO_3$ in 200 ml water was added to a suspension of 0·1M phosphonium salt *I* in 550 ml benzene and 250 ml water. After dissolving of the phosphonium salt the benzene layer was separated, washed twice with 100 ml water and, after drying with calcium chloride and filtration with charcoal, the filtrate was condensed *in vacuo* to a volume of about 75 ml. After dilution with 100 ml light petroleum, the precipitated product was filtered, washed with light petroleum and crystallized. (This method was used for the preparation of *IIa*, *IIb* and *IIg*.)

*Method* B: 50·0 mmol phosphonium salt *I* was added to a solution of sodium ethylate (from 1·5 g sodium in 40 ml ethanol) and, after 10 min, the suspension was dissolved by adding 300 ml chloroform. After 1 h, the precipitated sodium bromide was filtered, the filtrate concentrated to dryness and the residue crystallized. (This was used for the preparation of the other phosphoranes.)

Ethyl Esters of β-Acylacrylic Acids (*IV*)

A solution of phosphorane *II* (20·0 mmol/100 ml benzene) was added to a solution of 20·0 mmol *III* in 20 ml benzene and the reaction mixture was heated under stirring in an atmosphere of nitrogen. On the next day, the clear solution was evaporated to dryness *in vacuo* and the residue extracted with a mixture of light petroleum and ether (at a ratio of 9 : 1 for *IVa*, 8 : 1 for *IVc,e,f,i*, 4 : 1 for *IVd,h* and 2 : 1 for *IVk*). After filtration of the nondissolved fraction, the filtrate was evaporated and the crude product was purified by chromatography on a column of silica gel by elution with a mixture of light petroleum and ether by subsequent distillation or crystallization (Table III).

β-Acylacrylic Acids (*V*)

Ester *IV* (25·0 mmol) was combined with 50 ml of a mixture of acetic acid and hydrochloric acid (10 : 1) and boiled for 1 h. The reaction mixture was then poured into a five-fold volume of water

TABLE IV

Properties of β-Acylacrylic Acids *V*

| *V* | M.p., °C (solvent) | p$K_a$ | $\nu$ (cm$^{-1}$) in $CHCl_3$ | $R_F$[a] | Yield[b] of acidolysis, % |
|---|---|---|---|---|---|
| *d* | 126·5° ($CH_3OH$—$H_2O$ 1 : 2) | 4·67 | 980, 1 640, 1 671, 1 709 | 0·10 | 41·5 |
| *e* | 137—138[d] ($C_6H_6$) | 4·60 | 980, 1 638, 1 675, 1 702 | 0·18 | 45·4 |
| *f* | 105—106 ($C_6H_6$) | 4·70 | 980, 1 638, 1 671, 1 708 | 0·26 | 29·2 |
| *g* | 95—96[e] ($C_2H_5OH$—$H_2O$ 1 : 2) | 4·40 | 983, 1 647, 1 680, 1 715 | 0·07 | 38·0 |
| *h* | 155—156[f] ($C_6H_6$) | 4·55 | 981, 1 641, 1 678, 1 711 | 0·07 | 35·6 |
| *i* | 160—161[g] ($C_6H_6$) | 4·50 | 979, 1 625, 1 676, 1 711 | 0·11 | 35·8 |
| *k* | 163 ($CH_3OH$—$H_2O$ 1 : 1) | 4·25 | 985, 1 643, 1 676, 1 700 | 0·0 | 40·3 |

[a] The system as in the Experimental part; [b] product after crystallization; [c] ref.[15] m.p. 138—139°C; [d] ref.[15] m.p. 137·5—138·5°C; [e] ref.[15] m.p. 98—99°C; [f] ref.[15] m.p. 154—155°C; [g] ref.[15] m.p. 159—160°C.

and the separated oil which usually crystallized on standing was purified *via* the sodium salt (by dissolving in 5% $Na_2CO_3$) and subsequent crystallization (Table IV).

*The analyses were done at the analytical departments, Research Institute of Pharmacy and Biochemistry. The IR spectra were recorded by Mrs P. Vejdělková, the chromatographic separations were done by Mrs M. Jelínková.*

REFERENCES

1. Šmejkal F., Buděšínský Z., Sluka J., Kuchař M.: VIIth Internat. Chemotherap. Congr., Prague 1971. Abstract vol. I, No, A-5/15.
2. Kuchař M.: This Journal *33*, 880 (1968).
3. Jaffé H. H.: Chem. Rev. *53*, 191 (1953).
4. Fuchs R., Bloomfield J. J.: J. Org. Chem. *31*, 3423 (1966).
5. Kuchař M., Němeček O., Roubal Z., Grimová J., Kakáč B.: Českoslov. farm., in press.
6. Bestmann H. J., Joachim G., Lengyel I., Oth S. F. M., Mereny J., Weitkamp J.: Tetrahedron Letters *1956*, 3335.
7. Bestmann H. J., Snyder J. P.: J. Am. Chem. Soc. *89*, 3936 (1967).
8. Bestmann H. J., Arnason B.: Chem. Ber. *95*, 1513 (1962).
9. Speziale A. J., Ratts K. W.: J. Org. Chem. *28*, 465 (1963).
10. Witschard G., Griffin C. E.: Spectrochim. Acta *19*, 1905 (1963).
11. Ramirez F., Derzhowitz S.: J. Org. Chem. *22*, 41 (1957).
12. Ševčuk M. J., Dombrovskij A. V.: Ž. Obšč. Chim. *34*, 916 (1964).
13. Dombrovskij A. V., Ševčuk M. J.: Ž. Obšč. Chim. *33*, 1263 (1963).
14. Dahlen M., Frisell C.: Acta Chem. Scand. *16*, 1191 (1962).
15. Papa D., Schwenk E., Villani F., Klingsberg E.: J. Am. Chem. Soc. *70*, 3356 (1948).
16. Scarpatti R., Graziano M. L., Nicolaus R. A.: Gazz. Chim. Ital. *97*, 1317 (1967).
17. Wittig G., Geisler G.: Ann. Chem. *580*, 44 (1953).

Translated by A. Kotyk.