286. *Synthesis of Heterocyclic Compounds from δ-Unsaturated 1,3-Diketo-esters. Part II.*[1] *α-Substituted Styrylpyrazole- and Styrylisoxazole-carboxylic Esters.*

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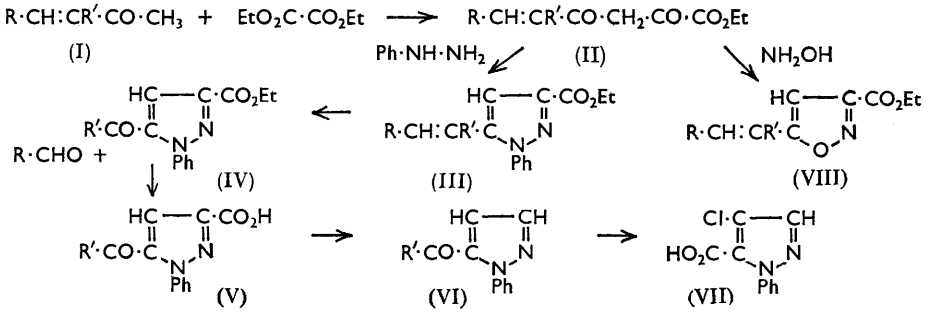
Several δ-unsaturated 1,3-diketo-esters (II) have been synthesised by the condensation of α-substituted styryl ketones (I) with ethyl oxalate. These were converted into the corresponding ethyl 1-phenyl-5-(α-substituted styryl)pyrazole-3-carboxylates (III), the structure of which has been determined by degradation to 5-benzoyl- and 5-acetyl-1-phenylpyrazole.

Analogous isoxazoles (VIII) have been prepared therefrom by the action of hydroxylamine.

In continuation of previous work,[1] we have prepared seven new δ-unsaturated 1,3-diketo-esters (II) by condensation of ethyl oxalate with α-methyl- and α-phenyl-styryl ketones (I; R′ = Me or Ph), of which two [I; R = 3,4-$(MeO)_2C_6H_3$, R′ = Me; and R = *p*-MeO·C_6H_4, R′ = Ph] are new.

These ethyl 2,4-dioxohexenoates as well as their methyl analogues failed to give crystalline dibromo-derivatives, and so 4-pyrones could not be prepared.[1]

On the other hand, they reacted readily with phenylhydrazine, giving ethyl 1-phenyl-5-(α-substituted styryl)pyrazole-3-carboxylates (III).



The positions of the ethoxycarbonyl and the styryl groups in these pyrazoles were established by degradation. Ozonolysis of ethyl 5-(α-phenylstyryl)-1-phenylpyrazole-3-carboxylate (III; R = R′ = Ph) gave benzaldehyde and ethyl 5-benzoyl-1-phenylpyrazole-3-carboxylate (IV; R′ = Ph), the latter yielding 5-benzoyl-1-phenylpyrazole [2] on hydrolysis and decarboxylation. Similarly, ethyl 5-(α-methylstyryl)-1-phenylpyrazole-3-carboxylate (III; R = Ph; R′ = Me) gave ethyl 5-acetyl-1-phenylpyrazole-3-carboxylate (IV; R′ = Me) and thence 5-acetyl-1-phenylpyrazole (VI; R′ = Me). The latter

[1] Part I, *J.*, 1956, 3663.
[2] Borsche and Hahn, *Annalen*, 1939, **537**, 219.

gave a phenylhydrazone, m. p. 136°, different from that, m. p. 182°, 3-acetyl-1-phenylpyrazole previously prepared by Diels and Petersen [3] by the action of phenylhydrazine on ethoxymethylenediacetyl.

Ozonolysis of the other styrylpyrazole carboxylic esteıs led to ethyl 5-acetyl- and 5-benzoyl-1-phenylpyrazole-3-carboxylates and the corresponding aromatic aldehydes.

In an attempt to establish the position of the acetyl group in 5-acetyl-1-phenylpyrazole, by a different route, it was subjected to oxidation by Fuson's reagent.[4] This led to the isolation of 4-chloro-1-phenylpyrazole-5-carboxylic acid (VII) which was characterised by the formation of a methyl ester and decarboxylated to 4-chloro-1-phenylpyrazole.[5] Evidently, the formation of the carboxylate anion after the oxidation has rendered position 4 in the 1-phenylpyrazole nucleus the most favourable centre for electrophilic substitution.[6]

Analogously, these ethyl dioxohexenoates have been converted into 5-(α-substituted styryl)isoxazole-3-carboxylates to which are assigned formula (VIII). This conforms to our experience regarding the reactivity of the carbonyl group adjacent to the ethoxycarbonyl group towards the ordinary carbonyl reagents. It is also in agreement with Musante's views [7] regarding the positions assigned to the ethoxycarbonyl and the styryl groups in ethyl 5-styrylisoxazole-3-carboxylate.[1]

Experimental

Microanalyses were by Herr Alfred Bernhardt, Mulheim, Ruhr, W. Germany. Light petroleum used had b. p. 50—70°. *a*—*g* in formula numbers are defined in Table 1.

α-Methylstyryl Ketones.—3-Methyl-4-phenyl- [8] (I*a*), 3-methyl-4-*p*-methoxyphenyl- [9] (I*b*), 3-methyl-4-*o*-methoxyphenyl- [10] (I*c*), and 3-methyl-4-(3,4-methylenedioxyphenyl)-but-3-en-2-one [11] (I*d*) were prepared by condensation of butanone (2—3 mol.) with the corresponding aldehydes (1 mol.) in presence of dry hydrogen chloride at −5°, and working up as described in the literature. We record the following: *Oxime*, elongated plates (from ethanol), m. p. 112°, of (I*c*) (Found: C, 70·2; H, 7·3; N, 6·8. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4; N, 6·8%). The ketone (I*d*) yellowish-white prisms (from light petroleum), m. p. 97° (Found: C, 71·2; H, 6·15. Calc. for $C_{12}H_{12}O_3$: C, 70·6; H, 5·9%), and its oxime (from light petroleum) in plates, m. p. 119° (lit.,[11] m. p. 130°) (Found: C, 65·7; H, 5·9; N, 6·3. Calc. for $C_{12}H_{13}O_3N$: C, 65·7; H, 6·0; N, 6·4%). The ketone (I*d*) was contaminated with an unstable *chloro-compound*, m. p. 136°, yellowish-white needles (from light petroleum) (Found: Cl, 16·2. $C_{12}H_{13}O_3Cl$ requires Cl, 14·75%); Gheorghiu [10] described this compound as the styryl ketone.

3-Methyl-4-(3,4-dimethoxyphenyl)but-3-en-2-one (I*e*) was prepared by condensing veratraldehyde (22 g., 1 mol.) with butanone (40 g., 5 mol.) in presence of dry hydrogen chloride at −5°. After being kept at 0° for 48 hr., the mixture was worked up and the ketone purified by distillation at 200°/3 mm. (yield, 26 g.; m. p. 40°) (Found: C, 70·8; H, 7·15. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·2%). Its *oxime* crystallised from benzene–light petroleum in plates, m. p. 109° (Found: C, 66·8; H, 7·5; N, 6·0. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·3; N, 5·95%). Ichikawa [12] and Iwamoto [9] obtained a distyryl ketone as the sole product of acid-catalysed condensation of butanone with veratraldehyde.

4-p-Methoxyphenyl-3-phenylbut-3-en-2-one (I*g*) was prepared as described for 3,4-diphenylbut-3-en-2-one [13] (I*f*) from *p*-anisaldehyde (10 g., 1 mol.) and benzyl methyl ketone (15 g., 1·5 mol.). The oily product was vacuum-distilled, the excess of benzyl methyl ketone being

[3] Diels and Petersen, *Ber.*, 1922, **55**, 3449.
[4] Fuson and Bull, *Chem. Rev.*, 1934, **15**, 275.
[5] Severini, *Gazzetta*, 1893, **23**, I, 284; Wolff and Fertig, *Annalen*, 1900, **313**, 21; Dieckmann and Platz, *Ber.*, 1904, **37**, 4638.
[6] Elderfield, "Heterocyclic Compounds," John Wiley & Sons, Inc., New York, 1957, Vol. V, p. 97.
[7] Musante, *Gazzetta*, 1942, **72**, 134.
[8] Harries and Muller, *Ber.*, 1902, **35**, 966.
[9] Iwamoto, *Bull. Chem. Soc. Japan*, 1927, **2**, 51; Iwamoto and Kato, *Sci. Reports Tokyo Imp. Univ.*, 1930, **19**, 689.
[10] Gheorghiu, *Bull. Soc. chim. France*, 1933, **53**, 1442.
[11] O'Donoghue, Ryan, and Keane, *Proc. Roy. Irish Acad.*, 1927, **37**, *B*, 141.
[12] Ichikawa, *Sci. Reports Tokyo Imp. Univ.*, 1925, **14**, 127.
[13] Goldschmidt and Krczmar, *Monatsh.*, 1901, **22**, 659, 749.

recovered and the ketone (18 g.) collected at 220°/3 mm. It solidified and crystallised from light petroleum in rods, m. p. 62° (Found: C, 80·7; H, 6·4. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%). Its *oxime* crystallised from ethanol in elongated plates, m. p. 178° (Found: C, 76·1; H, 6·6; N, 5·3. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2%).

Ethyl 5-Methyl-2,4-dioxo-6-phenylhex-5-enoate (II*a*).—The ketone [8] (I*a*) (16 g., 1 mol.) and ethyl oxalate (14 g., 1 mol.) were added to an ice-cold suspension of sodium ethoxide (6·6 g., 1 mol.) in dry ether (100 ml.). The mixture was kept overnight at room temperature and the sodium salt was separated and acidified with dilute sulphuric acid. The recovered ester (26 g.) crystallised from methanol in lemon-yellow plates, m. p. 66° (lit.,[14] m. p. 50—53°) (Found: C, 68·7; H, 6·3; OEt, 17·2. Calc. for $C_{15}H_{16}O_4$: C, 69·2; H, 6·2; OEt, 17·3%).

When the ethyl ester (1 g.) was refluxed in methanol (5 ml.) containing one drop of concentrated sulphuric acid for 1 hr. it gave the *methyl ester*, m. p. 131—133° (from light petroleum), pale-yellow plates (Found: C, 68·35; H, 5·7; OMe, 12·55. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7; OMe, 12·6%).

Both esters gave an intense red colour with ferric chloride, but with 5% titanium trichloride they gave a reddish-violet colour which changed into dark-red ⟶ reddish-brown ⟶ colourless.

The ethyl 2,4-dioxohexenoates (II*b*—*g*) given in Table 1 were prepared from the ketones (I*b*—*g*) in 84—97% yields and crystallised from ethanol. Therefrom, the analogous methyl esters have been obtained by methanolysis and crystallised from methanol.

These esters gave reddish-brown or brown colours with ferric chloride and initial reddish-violet or violet colours with 5% titanium trichloride.

Ethyl 5-Benzoyl-1-phenylpyrazole-3-carboxylate.—A chloroform solution of ethyl 1-phenyl-5-(α-phenylstyryl)pyrazole-3-carboxylate (3 g.) was treated with ozonised oxygen and, after

TABLE 1. *Esters*, R·CH:CR′·CO·CH_2·CO·CO_2Alkyl.

				Found (%)				Required (%)		
R	R′	M. p.	Appearance	C	H	OEt	Formula	C	H	OEt
Ethyl esters										
b *p*-MeO·C_6H_4	Me	68°	Orange *	66·4	6·2	15·4	$C_{16}H_{18}O_5$	66·2	6·25	15·5
c *o*-MeO·C_6H_4	Me	102	Yellow *	66·1	6·3	15·3	$C_{16}H_{18}O_5$	66·2	6·25	15·5
d 3,4-CH_2O_2:C_6H_3	Me	92	Yellow †	62·7	5·3	—	$C_{16}H_{16}O_6$	63·1	5·3	—
e 3,4-$(MeO)_2C_6H_3$	Me	82	Orange †	63·7	6·2	13·9	$C_{17}H_{20}O_6$	63·7	6·3	14·1
f Ph	Ph	98	Yellow †	74·4	5·8	14·6	$C_{20}H_{18}O_4$	74·5	5·6	14·0
g *p*-MeO·C_6H_4	Ph	112	Orange *	71·5	5·7	12·5	$C_{21}H_{20}O_5$	71·6	5·7	12·7
Methyl esters						OMe				OMe
p-MeO·C_6H_4	Me	76	Orange *	65·15	6·0	22·5	$C_{15}H_{16}O_5$	65·2	5·8	22·5
o-MeO·C_6H_4	Me	87	Yellow †	65·2	5·7	21·8	$C_{15}H_{16}O_5$	65·2	5·8	22·5
3,4-CH_2O_2:C_6H_3	Me	115	Yellow ‡	62·2	4·9	10·4	$C_{15}H_{14}O_6$	62·1	4·9	10·7
3,4-$(MeO)_2C_6H_3$	Me	97	Yellow †	62·6	6·0	30·5	$C_{16}H_{18}O_6$	62·7	5·9	30·4
Ph	Ph	118	Yellow *	73·9	5·4	10·1	$C_{19}H_{16}O_4$	74·0	5·2	10·1
p-MeO·C_6H_4	Ph	155	Yellow †	70·7	5·4	18·2	$C_{20}H_{18}O_5$	71·0	5·4	18·3

* Plates. † Needles. ‡ Rods.

TABLE 2. *Pyrazole esters* (III).

					Found (%)				Required (%)		
	R	R′	M. p.	Appearance	C	H	N	Formula	C	H	N
a	Ph	Me	66°	Plates	75·9	6·0	8·4	$C_{21}H_{20}O_2N_2$	75·9	6·1	8·4
b	*p*-MeO·C_6H_4	Me	110	Plates	73·0	6·2	7·6	$C_{22}H_{22}O_3N_2$	72·9	6·1	7·7
c	*o*-MeO·C_6H_4	Me	110	Plates	72·45	6·1	7·7	$C_{22}H_{22}O_3N_2$	72·9	6·1	7·7
d	3,4-CH_2O_2:C_6H_3	Me	110	Plates	70·5	5·3	7·4	$C_{22}H_{20}O_4N_2$	70·2	5·4	7·4
e	3,4-$(MeO)_2C_6H_3$ *	Me	132	Plates	69·7	5·5	7·5	$C_{22}H_{22}O_4N_2$	69·8	5·7	7·4
f	Ph	Ph	105	Needles	79·0	5·7	7·25	$C_{26}H_{22}O_2N_2$	79·15	5·6	7·1
g	*p*-MeO·C_6H_4	Ph	139	Needles	76·75	5·75	6·7	$C_{27}H_{24}O_3N_2$	76·4	5·7	6·6

* This pyrazole was prepared by heating the methyl ester for 3 hr., being recovered from the reaction mixture by extraction with ether and crystallisation from methanol.

removal of the solvent, the ozonide was decomposed and distilled with steam until benzaldehyde ceased to pass over. The non-volatile residue was extracted with ether, and the ethereal

[14] Panizzi and Benati, *Gazzetta*, 1946, **76**, 66.

solution shaken with sodium hydrogen carbonate. The *keto-ester* (2·3 g.) was recovered from the neutral ethereal solution and crystallised from light petroleum in plates, m. p. 112° (Found: C, 71·1; H, 5·0; N, 8·8. $C_{19}H_{16}O_3N_2$ requires C, 71·2; H, 5·0; N, 8·8%). It failed to give an oxime.

Ozonolysis of ethyl 5-(4-methoxy-α-phenylstyryl)-1-phenylpyrazole-3-carboxylate gave the same keto-pyrazole ester, *p*-anisaldehyde, and *p*-anisic acid.

5-Benzoyl-1-phenylpyrazole-3-carboxylic Acid.—This *acid* was prepared by refluxing the foregoing ester (1 g.) with dilute hydrochloric acid (1 : 1) for 2 hr. It crystallised from boiling water in needles, m. p. 170° (Found: C, 70·2; H, 4·3; N, 9·75. $C_{17}H_{12}O_3N_2$ requires C, 69·85; H, 4·1; N, 9·6%).

5-Benzoyl-1-phenylpyrazole.—This was prepared by decarboxylation of 5-benzoyl-1-phenylpyrazole-3-carboxylic acid (0·8 g.) with freshly precipitated copper powder (0·8 g.) at 190° in 45 min. The ketone was extracted with ethanol, and the solution concentrated, diluted with water, and extracted with ether. The ethereal solution was then shaken with sodium hydrogen carbonate, dried, and distilled. The recovered ketone (0·3 g.) crystallised from light petroleum in plates, m. p. 119—120° (Found: C, 77·5; H, 4·7; N, 11·5. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·9; N, 11·3%). It gave a 2,4-dinitrophenylhydrazone which crystallised from dilute ethanol in orange needles,[2] m. p. 195°.

Ethyl 5-Acetyl-1-phenylpyrazole-3-carboxylate.—This ester was prepared by ozonolysis of ethyl 5-(α-methylstyryl)-1-phenylpyrazole-3-carboxylate (4 g.) as described before and the recovered *keto-pyrazole ester* (3 g.) crystallised from light petroleum in needles, m. p. 112° (Found: C, 65·0; H, 5·5; N, 10·8. $C_{14}H_{14}O_3N_2$ requires C, 65·1; H, 5·5; N, 10·85%). Its *oxime* crystallised from ethanol in plates, m. p. 118° (Found: N, 15·4. $C_{14}H_{15}O_3N_3$ requires N, 15·4%).

5-Acetyl-1-phenylpyrazole-3-carboxylic Acid.—This *acid* was prepared by hydrolysis of the ester (3 g.) in boiling dilute hydrochloric acid (1 : 1) (30 ml.) for 3 hr. It crystallised from boiling water in needles, m. p. 212° (Found: C, 62·2; H, 4·7; N, 12·3. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%).

5-Acetyl-1-phenylpyrazole.—This *ketone* was prepared by decarboxylation of the above-mentioned acid (2 g.) with freshly precipitated copper powder (2 g.) at 190° in 45 min. The recovered ketone (0·9 g.) crystallised from light petroleum in plates, m. p. 83° (Found: C, 70·85; H, 5·6; N, 15·0. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%). Its *oxime* crystallised from light petroleum in plates, m. p. 108° (Found: N, 20·6. $C_{11}H_{11}ON_3$ requires N, 21·0%). Its *phenylhydrazone* crystallised from light petroleum in plates, m. p. 136° (Found: N, 20·25. $C_{17}H_{16}N_4$ requires N, 20·3%).

4-Chloro-1-phenylpyrazole-5-carboxylic Acid.—A mixture of 5-acetyl-1-phenylpyrazole (0·5 g.), dioxan (15 ml.), and potassium iodide (1·5 g.) in water (5 ml.) was treated with freshly prepared 2N-sodium hypochlorite (25 ml.). The mixture was kept for 1 hr., the iodoform separated, and the alkaline solution extracted with ether. On acidification and extraction with ether, the *chloro-acid* (0·3 g.), m. p. 176°, was recovered and crystallised from boiling water, forming needles, m. p. 185° (Found: C, 53·6; H, 3·05; N, 12·0; Cl, 15·7. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·2; N, 12·6; Cl, 15·9%). Its *methyl ester*, prepared by diazomethane, crystallised from light petroleum in needles, m. p. 62° (Found: C, 55·7; H, 3·7; N, 11·6; Cl, 14·85. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·8; Cl, 15·0%).

4-Chloro-1-phenylpyrazole.—When 4-chloro-1-phenylpyrazole-5-carboxylic acid was heated at 215° it readily lost carbon dioxide and 4-chloro-1-phenylpyrazole was obtained as a colourless sublimate, m. p. 74°, which crystallised from dilute ethanol in needles, m. p. 75°.

TABLE 3. *Styrylisoxazoles* (VIII).

					Solv. for	Found (%)				Required (%)		
	R	R′	M. p.	Appearance	crystn.	C	H	N	Formula	C	H	N
a	Ph	Me	67°	Plates	EtOH	69·8	5·8	5·4	$C_{15}H_{15}O_3N$	70·0	5·9	5·4
b	*p*-MeO·C_6H_4	Me	82	Pale violet plates	EtOH	66·8	6·0	4·8	$C_{16}H_{17}O_4N$	66·9	6·0	4·9
c	*o*-MeO·C_6H_4	Me	101	Plates	Light petroleum	67·2	6·2	5·0	$C_{16}H_{17}O_4N$	66·9	6·0	4·9
d	3,4-CH_2O_2:C_6H_3	Me	97	Pale violet needles	EtOH	64·0	5·0	4·8	$C_{16}H_{15}O_5N$	63·8	5·0	4·65
e	3,4-$(MeO)_2C_6H_3$	Me	94	Plates	EtOH	64·5	6·0	4·6	$C_{17}H_{19}O_5N$	64·3	6·0	4·4
f	Ph	Ph	82	Needles	Aq. EtOH	74·9	5·4	4·45	$C_{20}H_{17}O_3N$	75·2	5·4	4·4
g	*p*-MeO·C_6H_4	Ph	114	Needles	Aq. EtOH	72·55	5·5	4·0	$C_{21}H_{19}O_4N$	72·2	5·5	4·0

Styrylisoxazoles.—The *styrylisoxazoles* (VIII*a*—*g*) reported in Table 3 were prepared from the appropriate ethyl 2,4-dioxohexenoates (II) and hydroxylamine. They gave a yellow, orange, or brown colour with concentrated sulphuric acid.

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