819. *Reactions of Hydroxymethylene Ketones. Part I. Synthesis of Isoxazoles and Pyrazoles from Cinnamoylacetaldehyde and its Derivatives.*

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The sodium salts of cinnamoylacetaldehyde and its α-methyl and α-phenyl derivative have been prepared and used in syntheses of 3- and 5-styrylisoxazoles and 1-phenyl-3- and 5-styrylpyrazoles. The structural formulæ of the intermediate monoximes (III), di-isoxazolinylhydroxylamines (IV), and 5-hydroxyaminoisoxazolines (V) are discussed. The isomeric styrylisoxazoles and pyrazoles have been differentiated by oxidation to acidic and ketonic derivatives.

IN his study of the reactivity of hydroxymethylene ketones, Claisen [1] prepared from benzoylacetaldehyde a monoxime and the so-called sesquioxime which was shown by von Auwers and Wunderling [2a] to be di-(3-phenyl-2-isoxazolin-5-yl)hydroxylamine.

From the sodium salt of cinnamoylacetaldehyde (I; R = H), Panizzi and Monti [3] prepared its condensation product (IIa; R = H) with aniline (see below) and then 5-styrylisoxazole by treatment of this product with hydroxylamine; yet they did not refer to the formation of oximes.

In this paper, we report preparation of the sodium and copper salts of this aldehyde and its α-methyl [4] and α-phenyl derivatives (I; R = Me and Ph) and their behaviour towards carbonyl reagents.

These three sodio-derivatives with aniline gave a vinylamine (IIb; R = Me) and two anils (IIa; R = H or Ph). The vinylamine is characterised by an infrared band at 3247 cm.$^{-1}$ attributable to the associated NH stretching frequency; [5a] the spectra of the two anils lack this band, whereas the C=N band, falling between 1629—1656 cm.$^{-1}$ for mono-conjugated aldimines,[6] is probably superimposed on the C=O band [5b] (see Table).

By the action of hydroxylamine on the sodio-derivatives we have prepared the monoximes (III; R = H, Me, or Ph) and the di-(3-styryl-2-isoxazolin-5-yl)hydroxylamines (IV; R = H, Me, or Ph), together with, in two cases, the 5-hydroxyamino-3-styryl-2-isoxazolines (V; R = H or Me).

The monoximes have reducing properties, give a green colour with ferric chloride, and appear to exhibit tautomerism (a $\rightleftharpoons$ b). Their spectra in solution indicate the presence of free OH and NH groups,[5c,d] whereas absorption in the region 3226—3268 cm.$^{-1}$ denotes associated OH [5c,7] and probably NH [5a] groups in the solid state; the C=N absorption appears to occur in a region slightly below that normal for non-conjugated monoximes.[6] The three hydroxylamines (IV) are characterised by a hydroxyl band in the region 3425—3448 cm.$^{-1}$ [5c] and by formation of monoacetates having strong ester-carbonyl absorption; [5e] they resemble di-(3-phenyl-2-isoxazolin-5-yl)hydroxylamine [2a] and the 3-methyl analogue [8] in undergoing acid-catalysed hydrolysis to 3-styrylisoxazoles (VI; R = H, Me, or Ph) by elimination of hydroxylamine and subsequent loss of water.

The relation between two monoacetates obtained from di-(3-α-methylstyryl-2-isoxazolin-5-yl)hydroxylamine has not been pursued; they give the same styrylisoxazole (VI; R = Me) on hydrolysis.

[1] Claisen, *Ber.*, 1891, **24**, 130.
[2] von Auwers and Wunderling, *Ber.*, 1934, **67**, (*a*) 638, (*b*) 1062.
[3] Panizzi and Monti, *Gazzetta*, 1947, **77**, 556.
[4] Panizzi and Benati, *Gazzetta*, 1946, **76**, 66.
[5] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1959, pp. (*a*) 253, (*b*) 132, (*c*) 96, (*d*) 249, (*e*) 179, (*f*) 268.
[6] Fabian, Legrand, and Poirier, *Bull. Soc. chim. France*, 1956, 1507.
[7] Palm and Werbin, *Canad. J. Chem.*, 1953, **31**, 1004.
[8] Justoni, *Gazzetta*, 1940, **70**, 796.

Infrared bands ($cm.^{-1}$) were measured on Perkin–Elmer model 137 spectrophotometer for a KBr disc. For solution spectra the thickness was 1 mm.

Formula	R	OH	NH	C=O	C=O	C=N	C=C	
Anils and vinylamine								
IIa	H	—	—	—	1631s	—	1613m	1560m
IIb	Me	—	3247m	—	1653s	—	1600s	—
IIa	Ph	—	—	—	1639s	—	1613m	1587m
Monoximes								
III	H	3268sb	—	—	1669s	1631m	1613sh	1587sh
III *	H	3676s	3333m	—	1672s	1653sh	1618s	1592sh
III	Me	3226sb	—	—	1672s	1631m	1610sh	1580sh
III †	Me	3663s	3401s	—	1678s	1634m	1613sh	1583w
III	Ph	3247sb	—	—	1695s	1613m	1600sh	1580sh
III *	Ph	3636s	3356s	—	1684s		1613sh	1592w
Oxazolines								
IV	H	3448s	—	—	—	—	1631w	1563m
IV	Me	3448s	—	—	—	—	1613w	1563m
IV	Ph	3425s	—	—	—	—	1608m	1563m
IV Acetate	H	—	—	1779s	—	—	1626w	1567w
IV Acetate A	Me	—	—	1779s	—	—	1613sh	1580w
IV Acetate B	Me	—	—	1776s	—	—	1610sh	1553w
IV Acetate	Ph	—	—	1786s	—	—	1613w	1575sh
V	H	3367s	3247s	—	—	—	1621sh	1563w
V †	H	3597s	3333s					
V	Me	3390s	3226s	—	—	—	1610w	1563w
V †	Me	3597s	3333s					
Isoxazoles								
VII	NH_2	—	3460, 3509s	1701s	—	1639s	1597sh	1563s
VIII	NH_2	—	3509s, 3330s	1701s	—	1653s	1621w	1580sh
VIII	OH		—	1754s	—	1676sh	1595s	1550w
VIII	OMe	—	—	1748s	—	1667sh	1597s	1563w
VIII	CH_3	—	—	—	1689s	1655sh	1600w	1567s

* In CCl_4. † In $CHCl_3$.

The 5-hydroxyamino-3-styryl-2-isoxazolines (V; R = H or Me) have reducing properties and are susceptible to acid-catalysed change to the bis-compounds (IV; R = H or Me), resembling 5-hydroxyamino-3-phenylisoxazoline which was studied by von Auwers and Wunderling.[2b] Their spectra show the associated NH and OH bands for the solids, and the free bands for their solutions (Table). The C=N absorption of these two heterocycles and of compounds (IV; R = H, Me, and Ph) appears to fall in the C=C absorption region owing to conjugation.[5f,6]

5-Styrylisoxazole (IX; R = H) was the sole product from the copper salt of cinnamoylacetaldehyde, its oxime (III; R = H), or the anil (IIa; R = H), whereas the hydroxylamine (IV; R = H) is the only source of 3-styrylisoxazole (VI; R = H). These two isomeric isoxazoles have been differentiated by oxidation to the isoxazolecarboxylic acids which were identified as amides.[9]

Analogously, 3-α-methylstyrylisoxazole (VI; R = Me) has been prepared from the hydroxylamine (IV; R = Me), and 5-α-methylstyrylisoxazole (IX; R = Me) from the other derivatives of the aldehyde (I; R = Me). Further, the occurrence of the 5-isomer in the reaction medium from which the hydroxylamine (IV; R = Me) was isolated indicates that the monoxime (III; R = Me) is primarily formed under these conditions. These isomeric isoxazoles were differentiated by oxidation to 3- (VII; R = Me) and 5-acetylisoxazole (VIII; R = Me). However, the ambiguity pertaining to these two ketones due to lengthy syntheses [10] led us to base the identifications on oxidation to the

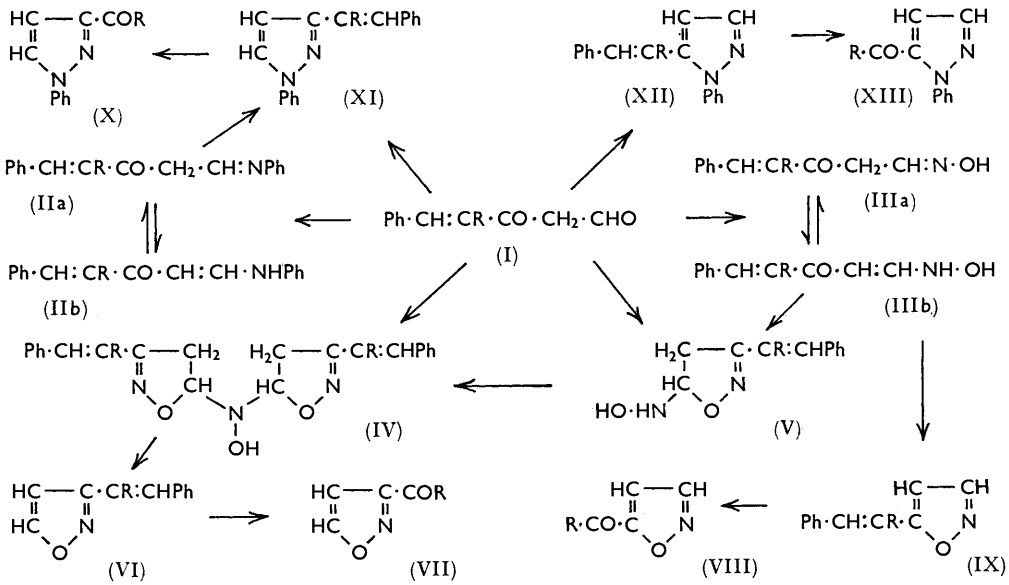
9 Quilico and Panizzi, *Gazzetta*, 1942, **72**, 458.

10 Quilico and Simonita, *Gazzetta*, 1947, **77**, 586; Quilico and Freri, *ibid.*, 1932, **62**, 436; Panizzi, *ibid.*, 1942, **72**, 475; Guadiano, Rieca, and Merlini, *ibid.*, 1959, **89**, 2466.

isoxazolecarboxylic acids. In this manner, we have demonstrated that previous assignments of the acetyl group in these two ketones were reversed.

On identical lines, (VI; R = Ph) and 5-α-phenylstyrylisoxazole (IX; R = Ph) have been prepared and oxidised to 3- [10] (VII; R = Ph) and 5-benzoylisoxazole (VIII; R = Ph).

The degradation products of the styrylisoxazoles have been further characterised by the infrared spectral data recorded in the Table, including the nuclear C=N absorptions.



With phenylhydrazine, benzoylacetaldehyde gave 1,3- and 1,5-diphenylpyrazole.[11] We have similarly obtained 1-phenyl-3- (XI; R = H) and 1-phenyl-5-styrylpyrazole (XII; R = H) from the sodium or copper salt of cinnamoylacetaldehyde. However, the 5-isomer was the exclusive product from the anil (IIa; R = H).

Panizzi and Monti [3] described as 1-phenyl-5-styrylpyrazole a pyrazole which they prepared by the action of phenylhydrazine on 5-styrylisoxazole. However, this is not in harmony with what is known [12] about the transformation of 5-substituted isoxazoles into 3-substituted pyrazoles, and it is contrary to our present experience of identification by ozonolysis. By ozonolysis we obtained 3-formyl-1-phenylpyrazole (X; R = H) and 1-phenylpyrazole-3-carboxylic acid [13] from this pyrazole which thus has structure (XI; R = H). Further, the 5-isomer (XII; R = H) yielded 5-formyl-1-phenylpyrazole [14] (XIII; R = H) and 1-phenylpyrazole-5-carboxylic acid,[15] the latter being identified by conversion into 4-chloro-1-phenylpyrazole-5-carboxylic acid.[16]

Analogously, 3- (XI; R = Me) and 5-α-methylstyryl-1-phenylpyrazole (XII; R = Me) have been prepared from the sodium or copper salt of the keto-aldehyde (I; R = Me), and are oxidised to 3- (X; R = Me) and 5-acetyl-1-phenylpyrazole [16] (XIII; R = Me), respectively.

[11] von Auwers and Schmidt, *Ber.*, 1925, **58**, 528; von Auwers and Mauss, *Annalen*, 1927, **452**, 182.
[12] Elderfield, " Heterocyclic Compounds," John Wiley & Sons, Inc., New York, 1957, Vol. V, pp. 86, 465.
[13] Claisen and Roosen, *Ber.*, 1891, **24**, 1888; Soliman and Rateb ,*J.* ,1956, 3663.
[14] Rojahn and Seitz, *Annalen*, 1924, **437**, 297.
[15] Claisen, *Annalen*, 1893, **278**, 261.
[16] Rateb and Soliman, *J.*, 1960, 1426.

1-Phenyl-5-α-phenylstyrylpyrazole (XII; R = Ph) is the only isomer which we have obtained from the α-phenyl derivative (I; R = Ph) and it was oxidised to 5-benzoyl-1-phenylpyrazole (XIII; R = Ph).[16,17]

Experimental

Light petroleum used had b. p. 50—70°.

Cinnamoylacetaldehyde Salts.[3]—Methyl styryl ketone (14 g., 1 mol.) and ethyl formate (29·5 g., 4 mol.) were added to an ice-cold suspension of sodium ethoxide (6·8 g., 1 mol.) in dry ether (200 ml.). The mixture was kept overnight at room temperature, and the sodium salt (14·5 g.) was separated, washed with ether, and dried. The ethereal solution yielded a yellow resin (8·5 g.), sparingly soluble in ethanol, its alcoholic solution giving a brown colour with ferric chloride and a deep-red colour with potassium hydroxide.

The copper salt was obtained when a solution of the sodium salt (8 g.) in water (200 ml.) was mixed with saturated aqueous copper acetate (40 ml.). The green precipitate (7 g.), m. p. 205°, crystallised from benzene in dark green plates, m. p. 226°.

The anil (IIa; R = H) crystallised from methanol in yellow rods, m. p. 152°, which gave a pale brown colour with ferric chloride (Found: C, 81·45; H, 6·4; N, 5·5. Calc. for $C_{17}H_{15}NO$: C, 81·9; H, 6·1; N, 5·6%).

Cinnamoylacetaldehyde Monoxime (III; R = H).—Hydroxylamine hydrochloride (1·5 g., 1 mol.) was shaken with the above sodium salt (4 g., 1 mol.) in water (300 ml.). The sticky product yielded the *oxime* (1 g.), m. p. 98°, on treatment with cold benzene. It crystallised from benzene in yellowish-white needles, m. p. 105°, which gave a green colour with ferric chloride and reduced Fehling's solution and silver nitrate (Found: C, 69·3; H, 5·6; N, 7·6. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·8; N, 7·4%).

5-Hydroxyamino-3-styryl-2-isoxazoline (V; R = H) separated when the mother-liquor of the foregoing reaction was kept overnight at room temperature, and crystallised from water in plates (1·1 g.), m. p. 138° (Found: C, 64·7; H, 5·9; N, 14·0. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%). It was also prepared when a suspension of the monoxime (0·9 g.) in a solution of hydroxylamine hydrochloride (0·5 g., 1 mol.) in water (20 ml.) was shaken for about 12 hr. It gave a negative test with ferric chloride but reduced Fehling's solution and silver nitrate.

Di-(3-styryl-2-isoxazolin-5-yl)hydroxylamine (IV; R = H).—A suspension of cinnamoylacetaldehyde sodium salt (7·85 g., 1 mol.) in ethanol (100 ml.) was mixed with powdered hydroxylamine hydrochloride (4·2 g., 1·7 mol.) and kept at 40° for 20 min. The *product* (7·5 g.) was separated, washed with water, and crystallised from dioxan–ethanol in plates, m. p. 214° (Found: C, 70·3; H, 5·7; N, 11·2. $C_{22}H_{21}N_3O_3$ requires C, 70·4; H, 5·65; N, 11·2%). It was also prepared when 5-hydroxyamino-3-styryl-2-isoxazoline (0·1 g.) in ethanol (5 ml.) was warmed with a drop of hydrochloric acid. Its *acetate* (prepared in pyridine–acetic anhydride at 40°) crystallised from benzene in needles, m. p. 205° (Found: C, 69·2; H, 5·5; N, 10·1; OAc, 11·2. $C_{24}H_{23}N_3O_4$ requires C, 69·1; H, 5·5; N, 10·1; OAc, 10·3%).

3-Styrylisoxazole (VI; R = H).—The hydroxylamine (IV; R = H) (3 g.) was refluxed with 18% hydrochloric acid (50 ml.) for 30 min. during which the solid became oily. The *isoxazole* was recovered by extraction with ether and crystallised from light petroleum in plates, m. p. 59° (Found: C, 77·1; H, 5·3; N, 8·35. $C_{11}H_9NO$ requires C, 77·2; H, 5·3; N, 8·2%). The residue recovered by evaporation of the aqueous solution gave a positive test for hydroxylamine.[18]

This isoxazole was also prepared by heating 5-hydroxyamino-3-styryl-2-isoxazoline (1 g.) with 18% hydrochloric acid (10 ml.) for 30 min.

Isoxazole-3-carboxylic Acid.—Powdered potassium permanganate (4·7 g.) was gradually added to a solution of 3-styrylisoxazole (1·7 g.) in acetone (75 ml.). The potassium salts and manganese dioxide were then separated and digested with warm water. Acidification of the aqueous solution gave benzoic acid (0·9 g.). The mother-liquor was repeatedly extracted with ether, the ethereal solution evaporated to dryness, and the residual isoxazole-3-carboxylic acid (1 g.) washed with light petroleum. It crystallised from benzene containing a trace of methanol

[17] Borsche and Hahn, *Annalen*, 1939, **537**, 219.
[18] Feigl, " Spot Tests. Part II. Organic Applications," Elsevier, Amsterdam, 1959, p. 161.

in elongated plates, m. p. 147—148°. Its methyl ester, prepared by diazomethane, was converted into the *amide* which crystallised from ethyl acetate in elongated plates, m. p. 143° (Found: N, 25·0. Calc. for $C_4H_4N_2O_2$: N, 25·0%).

5-*Styrylisoxazole* (IX; R = H).[3]—The copper salt of cinnamoylacetaldehyde (10 g., 1 mol.) in methanol (70 ml.) was refluxed with hydroxylamine hydrochloride (3·6 g., 1 mol.) in water (3 ml.) for 30 min. The mixture was then concentrated, diluted, and extracted with ether. The isoxazole (7·4 g.) recovered from the ethereal solution was purified by steam-distillation and crystallised from light petroleum in prismatic needles, m. p. 45° (Found: C, 76·7; H, 5·2; N, 8·55. Calc. for $C_{11}H_9NO$: C, 77·2; H, 5·3; N, 8·2%). It was also prepared by heating the monoxime (III; R = H) (2 g.) in methanol (15 ml.) containing 2 drops of hydrochloric acid for 3 hr., and by heating the anil (IIa; R = H) (3·3 g.) with hydroxylamine hydrochloride (1·2 g.) in ethanol for 3 hr.

Isoxazole-5-carboxylic acid was obtained on oxidation of this isoxazole (2·5 g.) with powdered potassium permanganate (7 g.) in acetone (100 ml.). The acid (1·7 g.) was recovered as described above and crystallised from benzene–methanol in plates, m. p. 147—148° (Found: C, 42·8; H, 2·6; N, 12·5. Calc. for $C_4H_3NO_3$: C, 42·5; H, 2·7; N, 12·4%). Its methyl ester, prepared by diazomethane, crystallised from light petroleum in cubes, m. p. 50° (Found: C, 47·5; H, 4·2; N, 10·7. Calc. for $C_5H_5NO_3$: C, 47·25; H, 4·0; N, 11·0%). Its amide, prepared from the ester, crystallised from ethyl acetate in plates, m. p. 178° (lit.,[9] 174°) (Found: N, 25·0. Calc. for $C_4H_4N_2O_2$: N, 25·0%).

α-*Methylcinnamoylacetaldehyde Derivatives.*—A mixture of 3-methyl-4-phenylbut-3-en-2-one [19] (14 g., 1 mol.) and ethyl formate (13 g., 2 mol.) was added to an ice-cold suspension of sodium ethoxide (6 g., 1 mol.) in dry ether. The mixture was kept overnight at room temperature, washed with ether, and dried. The neutral ethereal solution yielded a brown oil (3·5 g.) from which the ketone, m. p. and mixed m. p. 39°, was recovered after washing with sodium hydroxide. Its copper salt was prepared as in the previous case and crystallised from benzene in dark green plates, m. p. 152° (Found: C, 65·7; H, 5·2. Calc. for $C_{24}H_{22}CuO_4$: C, 65·8; H, 5·1%).

5-*Anilino*-2-*methyl*-1-*phenylpenta*-1,4-*dien*-3-*one* (IIb; R = Me) was obtained when an aqueous solution of the sodium salt (2 g.) was treated with aniline (1·2 g.) in acetic acid (2 ml.). It crystallised from methanol in yellow needles, m. p. 163—164°, which gave a pale reddish-brown colour with ferric chloride (Found: C, 82·05; H, 6·5; N, 5·4. $C_{18}H_{17}NO$ requires C, 82·1; H, 6·5; N, 5·3%).

α-*Methylcinnamoylacetaldehyde monoxime* (III; R = Me) was formed from the sodium salt (3 g., 1 mol.) and hydroxylamine hydrochloride (1 g., 1 mol.) in water (360 ml.). The oxime (2·2 g.) which gradually separated, crystallised from benzene–light petroleum in needles, m. p. 80°, which gave a green colour with ferric chloride and reduced Fehling's solution and silver nitrate (Found: C, 70·9; H, 6·3; N, 7·0. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·4; N, 6·9%). 5-*Hydroxyamino*-3-α-*methylstyryl*-2-*isoxazoline* (V; R = Me) was recovered in traces (0·15 g.) from the mother-liquor from this reaction when kept overnight; it crystallised from water in needles, m. p. 145—146° (Found: C, 65·9; H, 6·4; N, 12·8. $C_{12}H_{14}N_2O_2$ requires C, 66·05; H, 6·4; N, 12·8%), that reduce Fehling's solution and silver nitrate.

Di-(3-α-*methylstyryl*-2-*isoxazolin*-5-*yl*)*hydroxylamine* (IV; R = Me).—A suspension of α-methylcinnamoylacetaldehyde sodium salt (9 g.) in ethanol (100 ml.) was warmed with hydroxylamine hydrochloride (4·7 g., 1·6 mol.) in ethanol (100 ml.), and the precipitated sodium chloride separated. The filtrate yielded, on concentration and cooling, the desired *compound* (4·5 g.), that crystallised from ethanol in needles, m. p. 203° (Found: C, 71·5; H, 6·1; N, 10·5. $C_{24}H_{25}N_3O_3$ requires C, 71·45; H, 6·25; N, 10·4%). The reaction mother-liquor yielded on evaporation a sticky residue from which 5-α-methylstyrylisoxazole (3 g.), m. p. and mixed m. p. 47°, was recovered by extraction with light petroleum.

The hydroxylamine (IV; R = Me) was also prepared when the vinylamine (IIb; R = Me) (0·5 g.) was gently warmed with hydroxylamine hydrochloride (0·2 g.) in ethanol (20 ml.), or when 5-hydroxyamino-3-α-methylstyryl-2-isoxazoline (0·1 g.) in ethanol (5 ml.) containing a drop of hydrochloric acid was warmed.

The foregoing product (1 g.) was kept in acetic anhydride (10 ml.) and pyridine (10 ml.) at 40° for 6 hr., then overnight at room temperature, and the acetates were obtained by treatment with water. On crystallisation of this product from ethyl acetate and then from

[19] Harris and Muller, *Ber.*, 1902, **35**, 966.

methanol, a *monoacetate "A"* was obtained in needles, m. p. 169—170° (Found: C, 69·7; H, 6·3; N, 9·7. $C_{26}H_{27}N_3O_4$ requires C, 70·1; H, 6·1; N, 9·4%). The ethyl acetate mother-liquor yielded, on concentration, a *monoacetate "B"* which crystallised from methanol in plates, m. p. 147° (Found: C, 70·05; H, 6·0; N, 9·4; OAc, 8·9. $C_{26}H_{27}N_3O_4$ requires C, 70·1; H, 6·1; N, 9·4; OAc, 9·7%). These two acetates were converted into 3-α-methylstyrylisoxazole (VI; R = Me) by boiling 18% hydrochloric acid in 30 min.

3-α-*Methylstyrylisoxazole* (VI; R = Me).—This *isoxazole* was prepared quantitatively when di-(3-α-methylstyryl-2-isoxazolin-5-yl)hydroxylamine (3 g.) was heated in 18% hydrochloric acid (30 ml.) for 30 min. It was recovered by extraction with ether and crystallised from light petroleum in needles, m. p. 60° (Found: C, 78·35; H, 5·95; N, 7·6. $C_{12}H_{11}NO$ requires C, 78·0; H, 6·0; N, 7·6%). The acidic mother-liquor gave a positive test for hydroxylamine.[18]

3-*Acetylisoxazole* (VII; R = Me).—3-α-Methylstyrylisoxazole (2·8 g.) in acetone (200 ml.) was oxidised with potassium permanganate (6·5 g.) overnight at room temperature; an oily residue (0·6 g.) was recovered from the acetone solution. On treatment with light petroleum, this yielded the *ketone* which recrystallised in plates, m. p. 53° (Found: C, 54·5; H, 4·4; N, 12·4. $C_5H_5NO_2$ requires C, 54·1; H, 4·5; N, 12·6%). Its *p*-nitrophenylhydrazone crystallised from acetic acid in yellow needles, m. p. 214° [10] (Found: N, 22·6. Calc. for $C_{11}H_{10}N_4O_3$; N, 22·8%).

When this ketone (0·3 g.) was oxidised with boiling potassium dichromate (0·9 g.) in 20% sulphuric acid (60 ml.) for 2 hr., isoxazole-3-carboxylic acid (0·2 g.) was obtained. It was recovered by continuous extraction with ether and converted into the amide, m. p. and mixed m. p. 143°.

5-α-*Methylstyrylisoxazole* (IX; R = Me).—α-Methylcinnamoylacetaldehyde copper salt (5 g., 1 mol.) in methanol (50 ml.) was refluxed with hydroxylamine hydrochloride (1·7 g., 1 mol.) in water (3 ml.) for 30 min. After concentration, dilution with water, and extraction with ether, the *isoxazole* (3·7 g.), m. p. 37—42°, was recovered and purified by steam-distillation and recrystallised from light petroleum in needles, m. p. 46° (Found: C, 78·0; H, 5·8; N, 7·6. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0; N, 7·6%). This isoxazole (2 g.) was also prepared from (*a*) the monoxime (2 g.) when refluxed in 50% ethanol (10 ml.) containing 2 drops of hydrochloric acid for 30 min., (*b*) the vinylamine (1 g.) when refluxed with hydroxylamine hydrochloride (0·3 g.) in methanol for 3 hr., and (*c*) as an appreciable by-product during the preparation of the hydroxylamine (IV; R = Me).

5-*Acetylisoxazole* (VIII; R = Me).—This *ketone* (0·7 g.) was obtained on oxidation of 5-α-methylstyrylisoxazole (2·8 g.) with potassium permanganate (6·5 g.) in acetone (200 ml.) and crystallised from light petroleum in elongated plates, m. p. 56° (Found: C, 54·4; H, 4·5. $C_5H_5NO_2$ requires C, 54·1; H, 4·5%). Its *p*-nitrophenylhydrazone crystallised from acetic acid in yellow needles, m. p. 221° [10] (Found: N, 22·6%. Calc. for $C_{11}H_{10}N_4O_3$: N, 22·8%).

Oxidation of this ketone (0·2 g.) by dichromate led to isoxazole-5-carboxylic acid (0·2 g.) which yielded the amide, m. p. and mixed m. p. 178°.

α-*Phenylcinnamoylacetaldehyde Derivatives*.—The keto-aldehyde (I; R = Ph) was formed when an ethereal solution of 3,4-diphenylbut-3-en-2-one [20] (9·65 g., 1 mol.) and ethyl formate (6·5 g., 2 mol.) was rapidly added to sodium ethoxide (2·95 g., 1 mol.) in dry ether. The mixture rapidly acquired a buff colour having a faint violet fluorescence and yielded the sodium salt which gave a deep-red colour with ferric chloride. The neutral ethereal solution yielded a brown viscous oil (4 g.) from which a white substance (1·3 g.) was obtained on treatment with methanol. It crystallised from benzene–methanol in plates, m. p. 161° [Found: C, 88·8; H, 6·4%; *M* (Rast), 324], and gave an oxime, needles (from ethyl acetate), m. p. 263° (Found: C, 78·2; H, 6·0; N, 3·3%).

α-*Phenylcinnamoylacetaldehyde copper salt* was prepared from the sodium salt and crystallised from benzene–methanol in green plates, m. p. 217—218° (Found: C, 72·9; H, 4·9. $C_{34}H_{26}CuO_4$ requires C, 72·6; H, 4·7%).

The *anil*, obtained from the sodium salt (1·2 g.) and aniline (0·6 g.) in aqueous acetic acid, crystallised from methanol in yellow needles, m. p. 110—111°, which gave a yellowish-brown colour with ferric chloride (Found: C, 85·1; H, 5·0; N, 4·3. $C_{23}H_{19}NO$ requires C, 84·9; H, 4·9; N, 4·3%).

[20] Goldschmidt and Krcymar, *Monatsh.*, 1901, **22**, 659.

The *monoxime* (III; R = Ph), prepared from the sodium salt (1·5 g.) and hydroxylamine hydrochloride (0·5 g.) in water, crystallised from ether–light petroleum in yellow needles, m. p. 105°, which gave a green colour with ferric chloride (Found: C, 76·8; H, 5·9; N, 5·1. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%).

Di-(3-α-phenylstyryl-2-isoxazolin-5-yl)hydroxylamine (IV; R = Ph).—The last-mentioned sodium salt (2 g., 1 mol.) in methanol (30 ml.) was refluxed with hydroxylamine hydrochloride (0·75 g., 1·5 mol.) for 1 hr. The solvent was then distilled off, the residue washed with water, and the insoluble *hydroxylamine* crystallised from dioxan–ethanol in rods, m. p. 212° (Found: C, 76·8; H, 5·7; N, 8·0. $C_{34}H_{29}N_3O_3$ requires C, 77·4; H, 5·5; N, 8·0%). Its *acetate* crystallised from ethyl acetate in plates, m. p. 200° (Found: C, 76·2; H, 5·4; N, 7·4; OAc, 8·3. $C_{36}H_{31}N_3O_4$ requires C, 75·9, H, 5·5, N, 7·4, OAc, 7·6%).

3-α-*Phenylstyrylisoxazole* (VI; R = Ph).—The hydroxylamine (IV; R = Ph) (3 g.) was refluxed with 18% hydrochloric acid (100 ml.) for 3 hr., and the oily *product* extracted with ether and purified by steam-distillation. It crystallised from light petroleum in needles, m. p. 82—83° (Found: C, 82·3; H, 5·2; N, 5·8. $C_{17}H_{13}NO$ requires C, 82·5; H, 5·3; N, 5·7%).

3-Benzoylisoxazole (VII; R = Ph) was formed when this compound (3·1 g.) in acetone (100 ml.) was oxidised with potassium permanganate (5 g.) overnight at room temperature. The oily ketone (1·9 g.), recovered from the acetone solution, gave a semicarbazone which crystallised from benzene in plates,[10] m. p. 173°.

5-α-*Phenylstyrylisoxazole* (IX; R = Ph).—The anil (IIa; R = Ph) (2·2 g., 1 mol.) was refluxed with hydroxylamine hydrochloride (0·6 g., 1 mol.) for 3 hr. After concentration, addition of water, and extraction with ether, this *isoxazole* (1·8 g.) was recovered and purified by steam-distillation. It crystallised from light petroleum in needles, m. p. 60—61° (Found: C, 82·2; H, 5·3; N, 5·8. $C_{17}H_{13}NO$ requires C, 82·5; H, 5·3; N, 5·7%). It was also obtained (2 g.) when the monoxime (2 g.) was heated in methanol (30 ml.) containing 2 drops of hydrochloric acid, or (3·9 g.) when the copper salt (5 g.) was heated with hydroxylamine hydrochloride (1·3 g.) in methanol (30 ml.) for 30 min.

5-*Benzoylisoxazole* (VIII; R = Ph).—A solution of the foregoing isoxazole (3·1 g.) in acetone (100 ml.) was oxidised with potassium permanganate (5 g.), and the *ketone* (1·7 g.) recovered from the acetone solution. It crystallised from light petroleum in elongated plates, m. p. 51° (Found: C, 68·8; H, 4·2; N, 8·2. $C_{10}H_7NO_2$ requires C, 69·4; H, 4·1; N, 8·1%). Its p-*nitrophenylhydrazone*, prepared in glacial acetic acid, crystallised from ethyl acetate in yellow prisms, m. p. 198° (Found: N, 18·3. $C_{16}H_{12}N_4O_3$ requires N, 18·2%). Its *semicarbazone*, m. p. 190°, crystallised from ethyl acetate in needles (Found: N, 24·5. $C_{11}H_{10}N_4O_2$ requires N, 24·35%).

1-*Phenyl-5-styrylpyrazole* (XII; R = H).—A mixture of the anil (IIa; R = H) (1·8 g., 1 mol.) and phenylhydrazine hydrochloride (1·2 g., 1 mol.) was refluxed in methanol (30 ml.) for 6 hr., and the *pyrazole* (1·8 g.) was recovered by concentration, dilution, and extraction with ether. It crystallised from light petroleum in yellowish needles, m. p. 66° (Found: C, 83·2; H, 5·8; N, 11·5. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

Ozonised oxygen was bubbled through an ice-cold solution of this pyrazole (5 g.) in chloroform. The oily residue obtained on evaporation of the solvent and decomposition of the ozonide was distilled with steam until benzaldehyde ceased to pass over. The non-volatile residue was extracted with ether, and the ethereal solution was shaken with sodium hydrogen carbonate. On acidification of the latter extract, 1-phenylpyrazole-5-carboxylic acid (0·9 g.) was obtained; it crystallised from water in needles,[15] m. p. 184°. This acid gave 4-chloro-1-phenylpyrazole-5-carboxylic acid,[16] m. p. and mixed m. p. 188°, on treatment with sodium hypochlorite. The neutral ethereal solution yielded 5-formyl-1-phenylpyrazole (1·7 g.) (oxime,[14] m. p. 177°, needles from benzene), which with potassium permanganate in acetone gave 1-phenylpyrazole-5-carboxylic acid.

1-*Phenyl-3-styrylpyrazole* (XI; R = H).—A mixture of cinnamoylacetaldehyde copper salt (4 g.) and phenylhydrazine hydrochloride (6 g.) was refluxed in methanol (100 ml.) for 30 min. On concentration, dilution, extraction with ether, and evaporation, treatment of the brown oily residue (4·5 g.) with cold methanol yielded the *pyrazole* (1·5 g.), m. p. 125°. This crystallised from methanol in pale yellow needles, m. p. 127° (Found: C, 82·95; H, 5·6; N, 11·45%). The mother-liquor yielded the 5-isomer (2·5 g.), m. p. and mixed m. p. 66°, on fractional crystallisation.

A mixture of 1-phenyl-3- (1 g.) and 1-phenyl-5-styrylpyrazole (5·8 g.) was also obtained

by the action of phenylhydrazine hydrochloride (6 g.) on cinnamoylacetaldehyde sodium salt (7·9 g.).

1-Phenylpyrazole-3-carboxylic acid (X; R = OH) was formed by ozonolysis of 1-phenyl-3-styrylpyrazole (2 g.) as described for the 5-isomer. The acid (0·3 g.) was recovered from the sodium hydrogen carbonate extract and crystallised from water in needles,[13] m. p. 143°.

The neutral ethereal solution yielded 3-formyl-1-phenylpyrazole (X; R = H) (0·7 g.) [*oxime*, m. p. 169°, plates from benzene (Found: C, 64·1; H, 5·1; N, 22·5. $C_{10}H_9N_3O$ requires C, 64·2; H, 4·85; N, 22·5%)], which with potassium permanganate in acetone gave 1-phenylpyrazole-3-carboxylic acid.

3-α-*Methylstyryl*-1-*phenylpyrazole* (XI; R = Me).—α-Methylcinnamoylacetaldehyde copper salt (4 g., 1 mol.) and phenylhydrazine hydrochloride (2·9 g., 1 mol.) were refluxed in ethanol (40 ml.) for 30 min. On concentration, dilution, and extraction with ether, the *pyrazole* (4·5 g.) was obtained; it crystallised from methanol in plates, m. p. 88° (Found: C, 82·8; H, 6·2; N, 11·2. $C_{18}H_{16}N_2$ requires C, 83·0; H, 6·2; N, 10·8%).

3-*Acetyl*-1-*phenylpyrazole* (X; R = Me) was formed on oxidation of the foregoing styrylpyrazole (2·2 g.) with potassium permanganate (4 g.) in acetone (75 ml.). The ketone (1·2 g.), m. p. 57°, recovered from the acetone solution, crystallised from light petroleum in plates, m. p. 58° (Found: C, 70·95; H, 5·3; N, 15·0. $C_{11}H_{10}N_2O$ requires C, 71·0; H, 5·4; N, 15·1%). Its *oxime* crystallised from benzene–light petroleum in needles, m. p. 141—142° (Found: C, 65·7; H, 5·5; N, 20·6. $C_{11}H_{11}N_3O$ requires C, 65·7; H, 5·5; N, 20·9%). Its phenylhydrazone crystallised from ethanol in elongated plates, m. p. 174°, not raised to 182°, recorded in literature [21] (Found: C, 74·3; H, 6·0; N, 19·8. Calc. for $C_{17}H_{16}N_4$: C, 73·9; H, 5·8; N, 20·3%).

5-α-*Methylstyryl*-1-*phenylpyrazole* (XII; R = Me).—The sodium salt of α-methylcinnamoylacetaldehyde (4 g., 1 mol.) and phenylhydrazine hydrochloride (2·9 g., 1 mol.) were refluxed in 80% ethanol (50 ml.) for 30 min. The *pyrazole* was extracted with ether and crystallised from methanol in plates, m. p. 76° (Found: C, 83·0; H, 6·15; N, 10·8. $C_{18}H_{16}N_2$ requires C, 83·0; H, 6·2; N, 10·8%). It was also obtained when the vinylamine (IIb; R = Me) (0·3 g., 1 mol.) and phenylhydrazine hydrochloride (0·2 g., 1 mol.) in ethanol (10 ml.) were refluxed for 45 min. and the mixture was diluted with water and extracted with ether.

5-Acetyl-1-phenylpyrazole was obtained on ozonolysis of this pyrazole in chloroform and crystallised from light petroleum in plates,[16] m. p. 83°. Its oxime crystallised from benzene–light petroleum in plates, m. p. 108°.

1-*Phenyl*-5-α-*phenylstyrylpyrazole* (XII; R = Ph).—α-Phenylcinnamoylaldehyde copper salt (2 g., 1 mol.) and phenylhydrazine hydrochloride (1·5 g., 1 mol.) in methanol (40 ml.) were refluxed for 30 min. The *pyrazole* (2 g.) was recovered by concentration, dilution, and extraction with ether, and crystallised from methanol in plates, m. p. 121—122° (Found: C, 85·8; H, 5·6; N, 8·8. $C_{23}H_{18}N_2$ requires C, 85·7; H, 5·6; N, 8·7%). It was also prepared when the sodium salt or the anil (IIa; R = Ph) (1·5 g., 1 mol.) was heated with phenylhydrazine hydrochloride (0·8 g., 1 mol.) in ethanol (40 ml.) for 5 hr.

5-Benzoyl-1-phenylpyrazole [16,17] was formed on ozonolysis of the foregoing pyrazole (2·6 g.) in chloroform and crystallised from light petroleum in cubes, m. p. 121° (Found: C, 77·2; H, 4·9; N, 11·3. Calc. for $C_{16}H_{12}N_2O$: C, 77·4; H, 4·9; N, 11·3%). Its 2,4-dinitrophenylhydrazone crystallised from ethanol in orange needles, m. p. 205° (cf. refs. 16 and 17) (Found: N, 19·6. Calc. for $C_{22}H_{16}N_6O_4$: N, 19·6%).

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[21] Diels and Petersen, *Ber.*, 1922, **55**, 3449.