[Contribution from the Research Laboratories, Parke, Davis & Company]

THE REACTION OF α,β-UNSATURATED ACID CHLORIDES WITH DIAZOMETHANE

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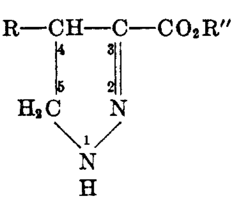
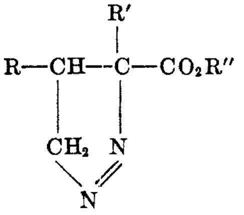
Although the formation of 3-carboxy or -acyl pyrazolines by the addition of diazomethane to α,β-unsaturated carbonyl compounds is a well-established preparative reaction (1), much less attention has been paid to the diazoacetyl pyrazolines which are obtained from unsaturated acid halides. In this and subsequent papers, the preparation, properties, and reactions of some members of this series will be described.

The structures of the pyrazolines which are obtained from olefinic esters were extensively studied by von Auwers and his school (2–5). It was established by optical exaltation measurements that when possible, the pyrazolines formed are conjugated, and the Δ^2 structure (I) was assigned. In cases in which migration of the double bond of the initially formed Δ^1 pyrazoline is blocked by a substituent in the α-position of the ester, the products were considered to be the Δ^1 isomers (II) (2). The latter compounds are converted to the more stable Δ^5 isomers (III) by treatment with acid (4).

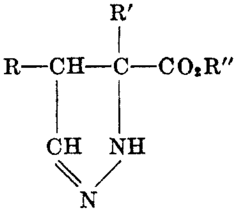
Smith and his students examined the addition of diazomethane to unsaturated ketones (6, 7). Unstable pyrazolines were isolated from both benzalacetone and benzalacetophenone; in the latter case this pyrazoline was purified and characterized. In both cases, the primary products were converted on warming to stable isomers; the unstable and stable isomers were assigned the Δ^1 and Δ^2 structures, respectively.[1] These considerations have also been applied to the structures of the pyrazolines obtained from unsaturated aldehydes (8).



I



II



III

The reaction of an α,β-unsaturated acid chloride with diazomethane was first described by Grundmann (9), who obtained a diazoacetylpyrazoline, m.p. 79°, from cinnamoyl chloride; the product was assigned, apparently arbitrarily, the improbable Δ^5 structure. Since the present work was begun, two further diazoacetylpyrazolines have been reported. From α-(p-chlorophenyl) cinnamoyl chloride, a product was obtained (10) which was tentatively formu-

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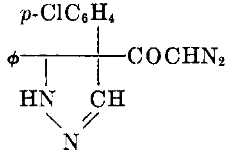
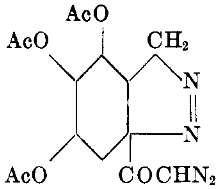
[1] The stable pyrazoline from benzalacetophenone is incorrectly pictured as the Δ^5-isomer in reference (1).

lated as a 4-diazoacetyl-Δ^2-pyrazoline (IV). The basis for assigning this structure was not presented; it seems likely that the product was the 3-diazoacetyl-Δ^1-pyrazoline. Grewe and Bokranz (11) have reported the formation of a pyrazoline from triacetylshikimyl chloride which was assigned the 3-acyl-Δ^1 structure (V).



IV



V

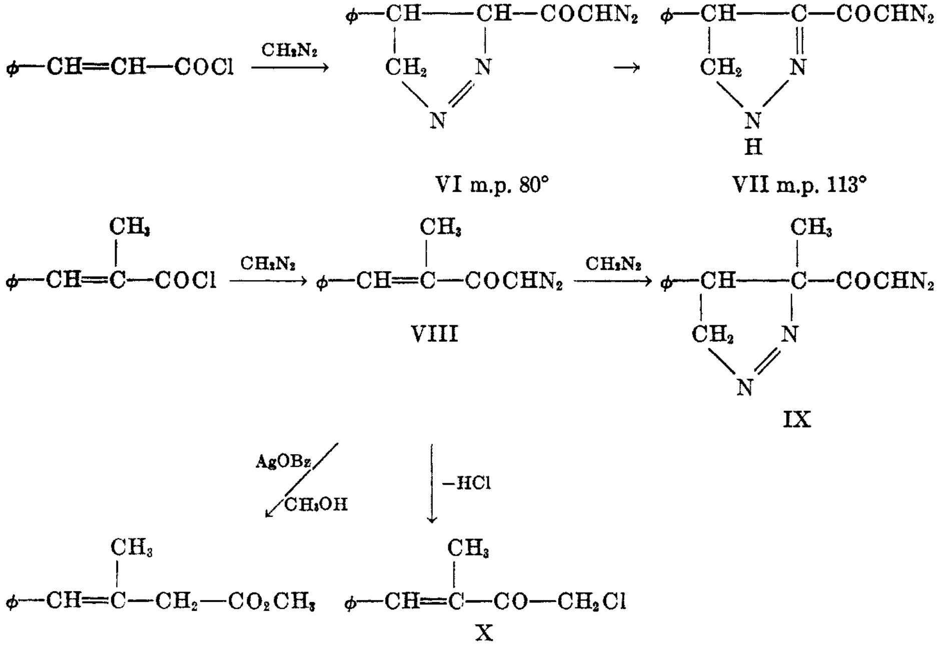
Quite recently, Wotiz and Buco (12) reinvestigated the reaction of cinnamoyl chloride with diazomethane. By using dilute solutions, the unsaturated diazoketone was obtained; under the usual conditions, a pyrazoline, m.p. 76°, was isolated. This product, presumably the same as that encountered previously (9), was assigned the Δ^1 structure (VI).

This reaction had been carried out some years ago in this laboratory, and a diazoacetyl pyrazoline, m.p. 113–114°, was obtained as the only product in 50 % yield. This preparation was repeated in the light of the confirmation of the early work, and in agreement with these reports a pyrazoline, m.p. 80°, was obtained when the reaction was processed promptly. When the reaction mixture was allowed to stand for 12 hours at 0°, however, the higher-melting product was isolated. It then was found that the primary product, m.p. 80°, was largely converted to the more stable (114°) isomer when the crystalline solid was stored at room temperature for one week. It appeared that this isomerism paralleled that described for simple ketones (7), and to confirm the structures of the compounds the spectra of these and some related pyrazolines and diazoketones were examined.

In order to obtain a Δ^1-diazoacetylpyrazoline of unambiguous structure, the reaction of α-methylcinnamoyl chloride with diazomethane was investigated. Under the usual conditions (excess diazomethane, 2–3 hours), the unsaturated diazoketone (VIII) was the preponderant product. Since only one other example of an α,β-unsaturated diazoketone was known (12), the opportunity was taken to examine some of the reactions of VIII. Wolf rearrangement with methanolic silver benzoate (13) followed by saponification gave 3-methyl-4-phenyl-3-butenoic acid; treatment with hydrochloric acid gave the chloroketone (X); and reaction with acetic acid gave the acetoxyketone. It thus appears that the conjugated double bond does not complicate the normal diazoketone reactions.

The diazomethyl α-methylstyryl ketone was converted to the pyrazoline (IX) in 55 % yield on prolonged treatment with diazomethane. This relatively slow addition, in contrast to the very rapid pyrazoline formation with the styryl ketone, parallels the behavior of the corresponding esters; methyl α-methylcinnamate reacts to a very limited extent even on long treatment with diazomethane (2). It has previously been observed (10) that pyrazoline formation is much more rapid with an α,β-unsaturated diazoketone than with the corresponding ester, presumably due to the more effective polarization of the double bond by the zwitterionic diazoacetyl group.

The ultraviolet and infrared spectra of 3-diazoacetyl-3-methyl-4-phenyl-Δ^1-pyrazoline (IX) and the unstable 80° m.p. isomer of 3-diazoacetyl-4-phenylpyrazoline were very similar, and the latter is clearly the Δ^1 isomer (VI). The ultraviolet maxima, at 273 and 277 mμ, respectively, are in the region expected for an unconjugated diazoketone; a low maximum at 315 mμ in the spectrum of VI most probably arises from a small amount of VII. The infrared spectra of VI and IX were characterized by the absence of a band in the 2.9–3.0 μ (N—H) region, and the presence of strong bands at 4.66 μ (diazo), 6.08–6.10 μ (diazocarbonyl),[2] and 6.43 and 6.44 μ (N=N). The spectra of the stable isomer, VII, support the conjugated Δ^2 structure, with λ_{max} 336 mμ; strong infrared bands were present at 2.89 μ (N—H), 4.69 μ, 6.19 μ (conjugated diazocarbonyl), and 6.43 μ. This 6.43 μ band is presumably due to the conjugated C=N linkage in VII; the shift from the usual C=N position of 5.95–6.15 μ (14) is greater than



VI m.p. 80°

VII m.p. 113°

VIII

IX

X

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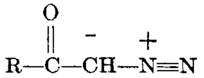
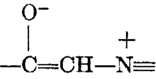
[2] The strong, sharp band in the 6.05–6.15 μ region of the infrared spectra of diazoketones (6.15–6.25 μ for conjugated diazoketones, *e.g.* VII and VIII) must be associated with the diazocarbonyl system. The large displacement of these bands from normal carbonyl positions is clear evidence that the simple representation  $R{-}\overset{\overset{O}{\|}}{C}{-}\overset{-}{C}H{-}\overset{+}{N}{\equiv}N$ is inadequate; a resonance hybrid including the structure  $R{-}\overset{\overset{O^-}{|}}{C}{=}CH{-}\overset{+}{N}{\equiv}N$ has been suggested (ref. 1, p. 538).

might be expected, and it is evident that a band at this position cannot be used to distinguish between the conjugated C=N and the N=N groups.

Few spectral data on pyrazolines have been published, and in order to confirm some of the assignments made in the foregoing discussion, the spectra of some pyrazolines uncomplicated by the diazoacetyl chromophore were obtained. 3-Carbomethoxy-4-phenyl- Δ^2-pyrazoline (3) (I; $R = C_6H_5$, $R'' = CH_3$) was found to have $\lambda_{\max}^{\text{EtOH}}$ 296 mμ; the infrared spectrum had bands at 2.87 μ (N—H), 5.81 μ (ester carbonyl), and 6.37 μ (C=N). The surprisingly long wave length of the ultraviolet maximum led to the consideration of a Δ^3 or cinnamoyl structure for this compound. To test this possibility, 3-carbomethoxy-Δ^2-pyrazoline (5) (I; R = H, $R'' = CH_3$) was examined, since a Δ^3 structure for this compound would not furnish a cinnamoyl chromophore. The spectra, $\lambda_{\max}^{\text{EtOH}}$ 293 mμ, infrared bands at 2.87 μ, 5.82 μ, and 6.37 μ, were strikingly similar to those of the 4-phenyl member, clearly requiring identical chromophores in the two compounds. There thus seems to be no reason to revise the accepted Δ^2 structure for these pyrazolines. The bathochromic shift of the ultraviolet maxima must arise in part by participation of the free electron pair on the adjacent nitrogen atom. The 6.4 μ band is evidently characteristic for 3-carboxy- or -acyl-Δ^2-pyrazolines, and it appears that it must be associated with the C=N group.

Acknowledgments. The microanalyses were performed by Mr. C. E. Childs and his staff; the ultraviolet spectra were determined by Dr. J. M. Vandenbelt and his staff, and the infrared spectra by Mr. R. B. Scott and Mr. E. Schoeb.

EXPERIMENTAL

3-Diazoacetyl-4-phenyl-Δ^2-pyrazoline (VII). An ether solution of 16 g. (0.1 mole) of cinnamoyl chloride was added rapidly to diazomethane prepared from 50 g. of nitrosomethylurea. The solution was placed in the refrigerator overnight and then was concentrated *in vacuo*. Bright yellow crystals separated at a small volume; these were filtered and washed with ether, 8.5 g., m.p. 113–114°. A sample was recrystallized from methanol-water (the compound decomposes rapidly when warmed in solution), giving bright yellow plates, m.p. 114–115°; $\lambda_{\max}^{\text{EtOH}}$ 336 mμ (ϵ 16,100), $\lambda_{\min}$ 262 mμ, $\lambda_{\text{infl.}}$ 235 mμ, 292 mμ; I.R. ($CHCl_3$) (μ) 2.89 (m), 3.27 (w), 4.69 (s), 6.19 (s), 6.43 (m), 6.68 (m), 7.07, 7.23 (s), 7.68 (s).

Anal. Calc'd for $C_{11}H_{10}N_4O$ (214.2): C, 61.67; H, 4.71; N, 26.16.

Found: C, 61.83; H, 4.79; N, 25.82.

3-Diazoacetyl-4-phenyl-Δ^1-pyrazoline (VI). A solution of 3.33 g. (0.02 mole) of recrystallized cinnamoyl chloride in ether was added at 5° to 0.07 mole of diazomethane. After one hour the reaction mixture was concentrated *in vacuo* and pale yellow needles separated. The crystals, 2.25 g., m.p. 77–79°, were recrystallized from ether, giving pale yellow prisms, m.p. 80–81°; $\lambda_{\max}^{\text{EtOH}}$ 276 mμ (ϵ 10,400), 329 mμ (1,050), (shoulder 255 mμ, ϵ 9,000); I.R. ($CHCl_3$) (μ) 3.35 (w), 4.67 (s), 6.08 (s), 6.44 (m), 6.68 (m), 7.38 (s), 8.73 (s). After standing for 10 days in a dark bottle at room temperature, the crystals had become dark orange in color, m.p. 104–107°. Recrystallization from methanol-water gave yellow plates, m.p. 109–111°, $\lambda_{\max}^{\text{EtOH}}$ 335 mμ (ϵ 15,000), mixture m.p. with pure Δ^2 isomer (m.p. 113°) was 109–113°.

Diazomethyl α-methylstyryl ketone (VIII). A solution of 62 g. (0.34 mole) of α-methylcinnamoyl chloride, m.p. 49–50°, in 300 ml. of ether was added during 1.5 hrs. to a well-stirred solution of 0.88 mole of diazomethane in 2.5 l. of ether at 10°. The solution was allowed to warm to room temperature and then was filtered, concentrated *in vacuo*, and diluted with 500 cc. of heptane. On cooling, long lemon-yellow prisms of the unsaturated diazoketone, 43 g., m.p. 82–84°, were obtained. The mother liquor furnished an additional

2 g. of VIII; on further standing, heavy, colorless prisms crystallized. These prisms were recrystallized from methanol, furnishing 5.5 g. of pyrazoline (IX), m.p. 88–91°.

A sample of the unsaturated diazoketone was recrystallized twice from alcohol-water. pale lemon spears, m.p. 88–89°; $\lambda_{\max}^{\mathrm{EtOH}}$ 304 mμ (ε 18,500) (shoulder 276 mμ, ε 16,000); I.R, ($CHCl_3$)(μ): 3.25 (w), 4.68 (s), 6.21 (s), 6.69 (w), 6.91 (m), 7.17 (m), 7.35 (s).

Anal. Calc'd for $C_{11}H_{10}N_2O$ (196.21): C, 70.95; H, 5.41; N, 15.05.

Found: C, 70.92; H, 5.52; N, 14.08, 14.06.

3-Methyl-4-phenyl-3-butenoic acid from VIII. A solution of 1.86 g. (0.01 mole) of the unsaturated diazoketone in 30 ml. of absolute methanol was placed in a three-neck flask fitted with a stirrer and dropping-funnel. A solution of 0.26 g. of silver benzoate in 4 ml. of triethylamine was added with stirring at room temperature. The reaction mixture became black, and nitrogen was evolved steadily. Gas evolution ceased after one hour. After warming for a short time, the reaction mixture was treated with charcoal, filtered, and concentrated *in vacuo*. The residue was taken up in ether, and the solution was washed with bicarbonate, dilute acid, and water. The solution then was dried and evaporated, furnishing 1.70 g. of light yellow, sweet-smelling methyl ester. A portion of this ester was saponified overnight at room temperature with 16% methanolic potassium hydroxide. The methanol was removed, and the residue was taken up in water, extracted with ether, and acidified; the crystalline acid which separated was filtered, dried and recrystallized from aqueous acetone as white plates, m.p. 112–113° [lit. (15): 113°]; $\lambda_{\max}^{\mathrm{EtOH}}$ 245 mμ (ε 14,600); pK'_A 5.35; mol. wt. (titration): 178; calc'd for $C_{11}H_{12}O_2$: 176.2.

α-Methylstyryl chloromethyl ketone (X). A solution of 1.00 g. of VIII in methanol was treated dropwise with 0.5 cc. of conc'd hydrochloric acid. Vigorous gas evolution occurred and the original yellow color of the solution became very pale. After dilution of the reaction solution with a little more water, shining white laths separated, 770 mg., m.p. 64–66°. The chloroketone was crystallized twice from methanol-water as fine white needles, m.p. 71–71.5°; $\lambda_{\max}^{\mathrm{EtOH}}$ 220 mμ (ε 8,200), 284 mμ (ε 18,400); I.R. (Nujol) (μ): 5.97 (s), 6.17 (m), 6.71 (w), 7.31 (m), 7.55, 7.72 (w), 8.29 (s), 9.43 (s).

Anal. Calc'd for $C_{11}H_{11}ClO$ (194.67): C, 67.86; H, 5.70.

Found: C, 68.21; H, 6.13.

This chloroketone furnished an *oxime* by the usual procedure which crystallized in needles from methanol-water, m.p. 106–108°.

Acetate of 1-hydroxy-3-methyl-4-phenyl-3-buten-2-one. A solution of 500 mg. of VIII in 2 cc. of glacial acetic acid was warmed for 10 min. on the steam-bath. Most of the solvent was removed in a stream of air and the residue was dissolved in ether; the ether solution was washed with water and bicarbonate solution, dried, and evaporated. The orange oil could not be crystallized; a portion of the material was distilled in a sublimation apparatus at 100° (bath). The colorless oil had $\lambda_{\max}^{\mathrm{EtOH}}$ 220 mμ (ε 9,000), 281 mμ (ε 19,900); I.R. (liquid film) (μ): 3.34 (w), 5.71 (s), 5.92 (s), 6.15 (m), 6.70 (w), 6.94–6.98 (m), 7.28 (m-s), 8.05, 8.23 (s), 10.56 (s).

About 80 mg. of the crude acetoxy ketone was treated with a solution of 100 mg. of 2,4-dinitrophenylhydrazine in ethanol containing several drops of conc'd hydrochloric acid and 0.5 cc. of acetic acid. A hydrazone separated from the warm solution in orange-red prisms, m.p. 163–165°, 85 mg. Rapid recrystallization from ethanol gave tiny orange needles which became red at 130°, m.p. 166–169°.

Anal. Calc'd for $C_{19}H_{18}N_4O_6$ (398.4): C, 57.28; H, 4.55; N, 14.07.

Found: C, 57.32; H, 4.74; N, 14.05.

3-Diazoacetyl-3-methyl-4-phenyl-Δ¹-pyrazoline (IX). A solution of 28.5 g. of α-methylcinnamoyl chloride in ether was added with stirring to a cold solution of diazomethane prepared from 110 g. (one mole) of nitrosomethylurea. The solution was stored 16 hrs. at 8° and then was concentrated to 250-cc. volume *in vacuo*. A total of 22 g. of yellow crystals, m.p. 75–79°, was obtained in several crops. All of the product, including the mother liquors, then was redissolved in an ethereal solution of diazomethane prepared from 50 g. of nitrosomethylurea and the solution was allowed to stand at 26° for 20 hours. Some amorphous brown solid was filtered off and the solution then was concentrated *in vacuo* and crystallized. Cream-colored prisms of the pyrazoline (IX), m.p. 85–87°, 14.1 g., were obtained; the mother liquor deposited yellow needles of (VIII). Further treatment of the mother liquors with diazomethane gave an additional 5.1 g. of pyrazoline. In subsequent preparations, difficulties in isolation and lower yields were sometimes encountered when crude styryl ketone was used or when the acid chloride was added to a larger amount of diazomethane and the steps were combined. Impurities carried over appeared to catalyze decomposition, and in larger runs, only purified VIII was used.

The diazoacetylpyrazoline was recrystallized from methanol-ether and finally from methanol as colorless, stout prisms, m.p. 92–93°; mixture m.p. with the unsaturated diazoketone, 72–80°. The pure pyrazoline was much less soluble in ether than was pure VIII; λ_{max}^{EtOH} 273 mμ (ϵ 10,500); I.R. ($CHCl_3$) (μ): 3.23 (w), 4.66 (s), 6.10 (s), 6.43 (m), 6.67 (m), 6.89 (m), 7.40 (s).

Anal. Calc'd for $C_{12}H_{12}N_4O$ (228.25): C, 63.14; H, 5.30; N, 24.55.
Found: C, 63.34; H, 5.09; N, 24.50.

3-Carbomethoxy-4-phenyl-Δ²-pyrazoline was prepared from 1.0 g. of cinnamic acid by the addition of excess diazomethane. After standing overnight, the solution gave 1.27 g. of white prisms, m.p. 126–126.5° [lit. (16): 128°]; λ_{max}^{EtOH} 296 mμ (9,600) (unchanged by addition of acid or alk.); I.R. ($CHCl_3$) (μ) 2.87 (m), 3.25 (m), 5.81 (s), 6.37 (m), 6.68 (w), 6.91 (s), 7.09 (m), 7.35, 7.44 (m), 8.12 (s), 8.84 (s).

3-Carbomethoxy-Δ²-pyrazoline was prepared from 2.4 g. of glacial acrylic acid and excess diazomethane in ether solution at −5°. The reaction was complete within 10 minutes. The solution was filtered and concentrated *in vacuo*, a total of 3.46 g. of pyrazoline was obtained in 3 crops, m.p. 65–66° [lit. (5): m.p. 66–67°]; λ_{max}^{EtOH} 292 mμ (10,200), $\lambda_{max}^{.1\,N\,HCl}$ 288 mμ (5,400), $\lambda_{max}^{H_2O}$ 288 mμ (8,400); I.R. ($CHCl_3$) (μ) 2.87 (m), 3.26 (m); 3.41 (sh), 5.82 (s), 6.37 (m), 6.90 (s), 7.09 (s), 7.31, 7.40 (m), 7.57 (m), 7.85 (s), 8.30 (s), 8.85 (s).

SUMMARY

Cinnamoyl chloride has been shown to react with diazomethane to give initially a 3-diazoacetyl-Δ¹-pyrazoline which is rapidly converted to the stable Δ² isomer. An α,β-unsaturated diazoketone can be prepared from α-methyl cinnamoyl chloride; this compound undergoes normal diazoketone reactions and furnishes a pyrazoline on further reaction with diazomethane. Some spectral characteristics of 3-substituted pyrazolines are discussed.

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