Registry No.—*endo*-**1**, 22842-22-4; *endo*-**2**, 15507-07-0; 2,4-dinitrophenylhydrazone of *endo*-**2**, 22842-24-6; **5**, 22842-30-4; **6**, 22842-31-5; **7**, 22842-32-6; 2,4-dinitrophenylhydrazone of **7**, 22842-33-7; **8**, 22842-25-7; 2,4-dinitrophenylhydrazone of **8**, 22842-26-8; **11**, 22842-34-8; **12**, 22842-35-9.

Acknowledgments.—Financial support from the following agencies is gratefully acknowledged: Cities Service Co., Merck & Co., and the donors of the Petroleum Research Fund (1676-A1), administered by the American Chemical Society. We are grateful to Professors H. C. Brown and W. Kraus for spectral data.

Notes

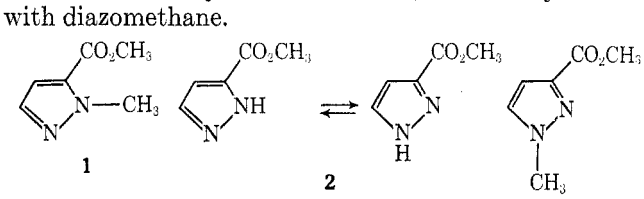
Pyrazole Product Ratio Analysis of the Reaction of Diazomethane with Methyl *cis*- and *trans*-β-Chloroacrylates

DONALD T. WITIAK AND BIRANDRA K. SINHA

Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received May 20, 1969

Carbomethoxypyrazoles **1**, **2**, and **3** are obtained upon reaction of appropriately substituted methyl acrylates (*i.e.*, **4** and **5**) with excess diazomethane in ether.[1,2] However, the mechanism of pyrazole formation remains obscure. To probe into the nature of the intermediates in pyrazole formation, we studied the reaction of methyl *cis*- and *trans*-β-chloroacrylates **6** with diazomethane.

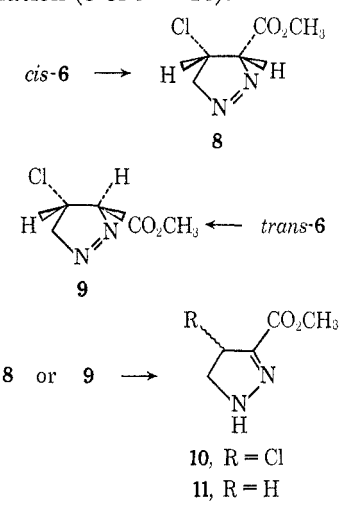


1 **2** **3**

X—CH=CH—CO_2R

4, X = AcS; R = CH_3
5, X = Br; R = CH_3
6, X = Cl; R = CH_3
7, X = Cl; R = H

Concerted addition of diazomethane to *cis*- and *trans*-**6** is expected to yield intermediate 1-pyrazolines **8** and **9**, respectively. This conclusion is supported by the observation that activated olefins containing a β substituent which is not a leaving group react with diazomethane to yield 1-pyrazolines with retention of geometrical configuration.[3] 1-Pyrazolines may readily isomerize to 2-pyrazolines.[4,5] This isomerization, which is apparently very fast,[6] would yield the 2-pyrazoline **10** as a common intermediate from either *cis*- or *trans*-**6**. Attempts, in our laboratories, to detect intermediate 1- or 2-pyrazolines spectrophotometrically failed. We therefore investigated the pyrazole product ratios, which we suspected would yield indirect evidence for the nature of the intermediates in pyrazole formation. If pyrazolines **8** and **9** are indeed formed during the reaction sequence, product analysis[1] should reflect the presence of these intermediates which are expected to eliminate HCl at different rates. Significant differences in pyrazole product ratio should only be observed if there are large differences in rates of elimination of HCl from intermediate stereoisomeric 1-pyrazolines and one of the elimination rates is faster than isomerization (**8** or **9** → **10**).



cis-**6** → **8**

9 ← *trans*-**6**

8 or **9** → **10**, R = Cl; **11**, R = H

Results and Discussion

Methyl *cis*-β-chloroacrylate (**6**) was prepared by cuprous chloride catalyzed addition of HCl to propiolic acid followed by esterification in methanol.[7] The *trans* isomer **6** was prepared in a similar manner from *trans*-β-chloroacrylic acid (**7**) obtained by isomerization of *cis*-**7** in 6 *N* HCl.[7] A mixture of *cis* and *trans* isomers **6** could also be prepared by catalytic addition of HCl to methyl propiolate. Spinning-band distillation afforded pure *cis* and *trans* isomers in 60 and 5% yields, respectively. The purity of the geometrical β-chloro esters was confirmed by gas–liquid partition chromatography and by comparison with reported nmr spectra.[7]

Reaction of 10 m*M* *cis*-**6** in 36–43 m*M* distilled diazomethane–ether in a Dry Ice–acetone bath for 4 hr,

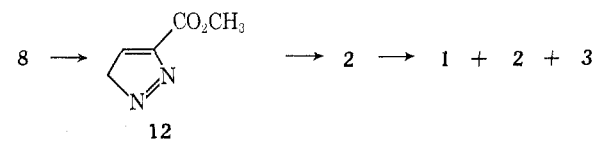
(1) D. T. Witiak and M. C. Lu, *J. Org. Chem.*, **33**, 4451 (1968).
(2) H. von Pechman and E. Burkard, *Ber.*, **33**, 3594 (1900).
(3) T. V. VanAuken and R. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962).
(4) L. I. Smith and W. Pings, *J. Org. Chem.*, **2**, 23 (1937).
(5) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 159 (1943).
(6) L. I. Smith and K. L. Howard, *ibid.*, **65**, 165 (1943).
(7) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

followed by standing at room temperature for 70 hr, affords, by gas–liquid partition chromatography, 1-methyl-5-carbomethoxypyrazole (**1**), 3-carbomethoxypyrazole (**2**), and 1-methyl-3-carbomethoxypyrazole (**3**) in a ratio of 2.20:1.34:1.00 (43.8, 36.5, and 19.7%, respectively). No starting material was detected. Reaction of 10 m*M* *trans*-**6** under identical conditions afforded only pyrazoles **1** and **2** in a ratio of 1.00:9.87 (9.2 and 90.8%, respectively). No starting material or 1-methyl-3-carbomethoxypyrazole (**3**) was detected. This difference in pyrazole product ratios, which is dependent upon the configuration of the starting β-chloro ester, is evidence for the lack of a common intermediate 2-pyrazoline **10** and/or an identical reaction pathway for the two geometrical isomers of **6**; the differences in pyrazole product ratios must be mainly a reflection of the ease of elimination of HCl from intermediate 1-pyrazolines **8** and **9**.

Support for this interpretation is derived from the following observations. Reaction of 10 m*M* 3-carbomethoxypyrazole (**2**) in 36–43 m*M* distilled diazomethane–ether under identical conditions described when *cis*- or *trans*-**6** served as starting material afforded pyrazoles **1**, **2**, and **3** in a ratio of 2.26:1.94:1.00 (43.5, 37.4, and 19.2%, respectively).[8] This ratio is nearly the same as the pyrazole product ratio observed when *cis*-**6** served as starting material. Under identical reaction conditions, but employing equimolar (10 m*M*) concentrations of 3-carbomethoxypyrazole (**2**) and diazomethane, the ratio obtained for **1**, **2**, and **3** was 1.53:6.90:1.00, respectively; *i.e.*, even at low concentrations of diazomethane, **3** was obtained as one of the products. When *trans*-**6** served as the reactant, no 1-methyl-3-carbomethoxypyrazole (**3**) was formed.

To determine whether intermediate 1- or 2-pyrazolines could undergo such methylation, we subjected methyl acrylate to identical reaction conditions, removed the solvent under reduced pressure, and converted the residual pyrazolines into pyrazoles by bromination followed by elimination of HBr.[2] Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (**1**) and 3-carbomethoxypyrazole (**2**) to be present in 11.6 and 76.8% yield, respectively. No 1-methyl-3-carbomethoxypyrazole (**3**) was detected; therefore, the 1-pyrazoline does not yield **3**. 3-Carbomethoxy-2-pyrazoline (**11**) was also prepared in pure form and subjected to methylation under the same conditions. After removal of the solvent, the residual pyrazolines were similarly converted into pyrazoles. Product ratio analysis again revealed the absence of **3** and the presence of **1** and **2** in 7.6 and 86.6% yield, respectively. The product ratios when **11** served as starting material were similar to the ratios observed when *trans*-**6** served as starting material. Since **3** is not obtained from intermediate 1- or 2-pyrazolines, it must result from methylation of pyrazole **2** when *cis*-**6** serves as the reactant.

Cromwell and coworkers have evidence suggesting that *trans* elimination (under acidic conditions) of appropriately substituted 4-aminopyrazolines is more rapid than *cis* elimination.[9] When methyl β-(acetylthio)acrylates were employed as starting material, product ratio analysis suggested *cis* elimination of thiolacetic acid from the intermediate 1-pyrazoline to be the more facile process.[1] Since large differences in pyrazole product ratio were not observed when stereoisomeric methyl β-(acetylthio)acrylates served as the reactant, but were observed when the acetylthio group was replaced by chloride, it seems that *trans* elimination of the acetylthio group also takes place readily. With the β-chloroacrylates, results obtained are consistent with the proposal that the 1-pyrazoline **8**, derived from *cis*-**6**, undergoes a relatively rapid *trans* elimination of HCl, affording, after rapid isomerization of intermediate **12**, 3-carbomethoxypyrazole (**2**). The intermediate 1-pyrazoline **8** is methylated to the same extent (*via* **3**) as when **3** itself serves as the reactant. Such *trans* elimination of HCl is apparently faster than isomerization (**8** → **10**) and involves the more acidic proton α to the carbomethoxy group, since the relative configuration of this proton represents the only difference between intermediates **8** and **9**. With intermediate **9**, derived from *trans*-**6**, elimination of HCl is considerably slower and most likely takes place during solvent (and diazomethane) removal, since pyrazole **3** was not detected as one of the reaction products. The elimination of HCl may in fact occur during or after isomerization (**9** → **10**).



Experimental Section

***cis*-β-Chloroacrylic acid** (**7**) was prepared by cuprous chloride catalyzed addition of HCl to propiolic acid according to a published method: mp 59–60° (lit.[7] mp 60.8–61.4°).

***trans*-β-Chloroacrylic acid** (**7**) was prepared from *cis*-**7** by heating in 6 *N* HCl for 6 hr: mp 85–86.5° (lit.[7] mp 85–86°).

Methyl *cis*-β-chloroacrylate (**6**) was prepared by heating *cis*-**7** in methanol containing a few drops of concentrated H_2SO_4: bp 85–86° (90 mm) [lit.[7] bp 79–83° (78 mm)]. Alternatively, methyl *cis*-β-chloroacrylate (**6**) may be prepared from methyl propiolate. To a solution of 2.0 g of CuCl in 40 ml of concentrated HCl was added 15.0 g (0.19 mol) of methyl propiolate during 15 min with constant stirring at a temperature of 8–12°. After standing at 0° overnight, the mixture was extracted with chloroform, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (14.0 g) was distilled using a spinning-band column, affording 13.0 g (62%) of pure *cis*-**6** and 1.0 g (4.5%) of *trans*-**6**.

Methyl *trans*-β-chloroacrylate (**6**) was prepared from *trans*-**7** in a manner similar to the preparation of the *cis* isomer **6**: bp 60–62° (100 mm) [lit.[7] bp 74–75° (131 mm)].

Reaction of Methyl *cis*-β-Chloroacrylate (6) with Distilled Diazomethane in Ether.—To 200 ml of the distilled ether–diazomethane ($3.6–4.3 \times 10^{-2}$ mol) solution[10] was added 1.2 g (1.0×10^{-2} mol) of methyl *cis*-β-chloroacrylate (**6**) in 100 ml of dry ether. The flask containing *cis*-**6** was washed with 50 ml of dry ether and added to the reaction flask to make 350 ml. The reaction mixture was kept in a Dry Ice–acetone bath for 4 hr and then allowed to stand at room temperature for 70 hr. The solvent was removed under reduced pressure and the residue was dissolved in 25 ml of dry chloroform. The chloroform solution was analyzed by gas–liquid partition chromatography on silicone gum rubber (UC-W98) on Chromosorb W (80–100 mesh) with a 4 ft × 0.25 in. glass column with column temperature of 120°, detector temperature of 240°, injection port temperature of 250°, inlet pressure of 35 psi, and carrier gas (He)

(8) This pyrazole product ratio is dependent upon the concentration of diazomethane and the reaction conditions employed. Under somewhat different conditions (see ref 1), other ratios are obtained.

(9) N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J. Vanderhorst, F. W. Olson, and J. H. Anglin, Jr., *J. Amer. Chem. Soc.*, **73**, 1044 (1951).

(10) H. A. Blatt, Ed., "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1955, p 165.

flow rate of 45 ml/min. Retention times of 0.90 min for 1-methyl-5-carbomethoxypyrazole (1), 1.5 min for 3-carbomethoxypyrazole (2), and 2.30 min for 1-methyl-3-carbomethoxypyrazole (3) were obtained. These retention times are similar to those previously reported.[1] The peak ratio for 1/2/3 was 2.2:1.34:1.0 (43.8:36.5:19.7%), respectively.

Reaction of Methyl *trans*-β-Chloroacrylate (6) with Distilled Diazomethane in Ether.—Reaction conditions employed were the same as in the reaction of *cis*-6 with distilled ether–diazomethane. Gas–liquid partition chromatography under identical conditions afforded 1-methyl-5-carbomethoxypyrazole (1) and 3-carbomethoxypyrazole (2) in a ratio of 9.87:1.00 (90.8:9.2%), respectively. No 1-methyl-3-carbomethoxypyrazole (3) was detected.

Pyrazoline and Pyrazole Formation When Methyl Acrylate Served as Starting Material.—One gram (1.1×10^{-2} mol) of methyl acrylate was treated with distilled ether–diazomethane ($3.6\text{–}4.3 \times 10^{-2}$ mol) under conditions identical with those described for the reaction of methyl *cis*-β-chloroacrylate (6) with distilled diazomethane in ether. The solvent was removed under reduced pressure and the residue containing pyrazolines was brominated by dropwise addition of 1.0 g (0.55×10^{-2} mol) of Br_2 in 10 ml of dry CCl_4 according to the method of Pechman and Burkard.[2] The reaction temperature was maintained at 0° for 0.5 hr and then the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 25 ml of dry chloroform. Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (1), 11.6%, and 3-carbomethoxypyrazole (2), 76.8%. No 1-methyl-3-carbomethoxypyrazole (3) was detected. Uncharacterized compounds represented a total of 11.6% of the reaction mixture.

Pyrazole Formation When 3-Carbomethoxy-2-pyrazoline (11) Served as Starting Material.—3-Carbomethoxy-2-pyrazoline was prepared from 2.1 g (2.4×10^{-2} mol) of methyl acrylate under the same reaction conditions as described previously. The solvent was removed under reduced pressure and the residue was crystallized from 95% ethanol, affording 1.8 g (60%) of 3-carbomethoxy-2-pyrazoline (11), mp 61–63° (lit.[2] mp 63–66°). One gram (7.9×10^{-3} mol) of 3-carbomethoxy-2-pyrazoline (11) was treated in distilled ether–diazomethane (2.5×10^{-2} mol) under conditions identical with the reaction conditions described for *cis*-6 with distilled diazomethane in ether. The solvent was removed under reduced pressure and the residue was brominated by addition of 1.0 g (0.55×10^{-2} mol) of Br_2 in 10 ml of dry CCl_4 as above. Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (1), 7.6%, and 3-carbomethoxypyrazole (2), 89.6%. No 1-methyl-3-carbomethoxypyrazole was detected. Uncharacterized compounds represented a total of 2.8% of the reaction mixture.

Registry No.—Diazomethane, 334-88-3; *cis*-6, 3510-44-9; *trans*-6, 5135-18-2.

Acknowledgment.—We are grateful to the Environmental Control Administration, National Institutes of Health, Rockville, Md., for support of this work through Grant EC-00115.

Isomeric Transition Metal Complexes of *trans*-2-(2′-Quinolyl)-methylene-3-quinuclidinones[1]

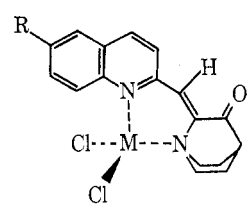
D. L. COFFEN AND T. E. MCENTEE, JR.

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

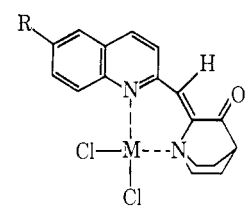
Received April 14, 1969

Tetrahedral–square-planar equilibria have been identified and studied with a variety of tetracoordinate nickel(II) complexes in solution.[2] In comparatively fewer instances, both isomers of a given complex have been isolated in pure form.[3] This has been accomplished with bis(alkyldiphenylphosphine)nickel(II) dihalides. It has now been observed that both the tetrahedral and square planar nickel(II) dichloride complexes of the bidendate ligand *trans*-2-(2′-quinolyl)methylene-3-quinuclidinone and of its 6′-methoxy derivative are very easily prepared in pure crystalline form.

2-(6′-Methoxy-2′-quinolyl)methylene-3-quinuclidinone was synthesized in the course of a project concerned with antimalarials of the quinolinemethanol class by the base-catalyzed condensation of 6-methoxyquinoline-2-carboxaldehyde[4] with 3-quinuclidinone. In order to prove the anticipated *trans* stereochemistry of the product, its cobalt, nickel, and copper dichloride complexes were prepared. Since these exhibit normal (1710–1720 cm^{-1}) carbonyl stretching frequencies in their infrared spectra, both nitrogen atoms and not the carbonyl oxygen are involved in coordination, whence the *trans* geometry must obtain.



1, M = CO; R = OCH_3
2, M = Ni; R = OCH_3
5, M = CO; R = H
6, M = Ni; R = H



3, M = Cu; R = OCH_3
4, M = Ni; R = OCH_3
7, M = Cu; R = H
8, M = Ni; R = H

The complexes were prepared by combining ethanol solutions of the metal dichlorides with solutions of the ligand. They crystallized out immediately. The cobalt complex 1 is deep green and may be recrystallized without change from chloroform–ethanol. The nickel complex 2 is maroon and has an infrared spectrum (Nujol) identical with that of the cobalt complex. The copper complex 3 is brown-yellow and has an entirely different infrared spectrum from those of complexes 1 and 2. Given the propensity of cobalt(II) to form tetrahedral complexes and of copper(II) to form square-planar complexes,[5] tetrahedral stereochemistry can be assigned to complexes 1 and 2 and square-planar stereochemistry to complex 3. When the maroon nickel complex 2 is recrystallized from methylene chloride–ethanol, it changes color and yields yellow-brown crystals of a complex having an infrared spectrum virtually identical with that of the copper complex 3. On this basis it is assigned the square-planar structure 4.

The isomerization of 2 to 4 is irreversible, the latter evidently being the more stable isomer, and the successful preparation of isomer 2 is contingent on the use of

(1) Synthetic Quinine Analogs II, supported by the U. S. Army Medical Research and Development Command, Contract DADA-17-68-C-80-45. Part I: D. R. Bender and D. L. Coffen, *J. Org. Chem.*, **33**, 2504 (1968).

(2) M. C. Browning, R. F. B. Davies, D. J. Morgan, L. E. Sutton, and L. M. Venanzi, *J. Chem. Soc.*, 4816 (1961); R. H. Holm and K. Swaminathan, *Inorg. Chem.*, **2**, 181 (1963); A. Chakrovorty and R. H. Holm, *ibid.*, **3**, 1010 (1964); D. R. Eaton, W. D. Phillips, and D. J. Caldwell, *J. Amer. Chem. Soc.*, **85**, 397 (1963); L. Sacconi, M. Ciampolini, and N. Nardi, *ibid.*, **86**, 819 (1964).

(3) M. C. Browning, J. R. Mellor, D. J. Morgan, S. A. J. Pratt, L. E. Sutton, and L. M. Venanzi, *J. Chem. Soc.*, 693 (1962); R. E. Hayter and F. S. Humiec, *Inorg. Chem.*, **4**, 1701 (1965).

(4) W. Mathes and W. Sauermilch, *Chem. Ber.*, **90**, 758 (1957).

(5) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1966, pp 865, 899.