the anionic product corresponding to (E^-). However, one very promising substitute for cyanide ion is presently being investigated in these laboratories, namely, the nitrite ion. This reagent appears to possess the dimensions and geometry necessary for easy attack at the carbonyl as well as a strong inductive effect (as a group covalently bonded to carbon) capable of assisting bond breaking in the anionic intermediate analogous to (C^-).

Acknowledgment.—We are obliged to various friends who have read portions of the manuscript while in preparation, including H. K. Hall, Jr., N. N. Lichtin, W. F. Sager and M. Weiss as well as a referee for very helpful discussions. Support of our work by a grant from the Research Corporation of New York is also gratefully acknowledged.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Reaction of Diazo Compounds with Nitroölefins. V. The Orientation of Addition of Disubstituted Diazo Compounds to Nitroölefins[1]

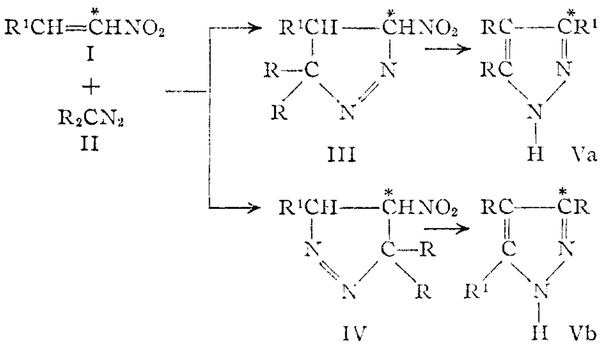
BY WILLIAM E. PARHAM, CARL SERRES, JR.,[2,3] AND PAUL R. O'CONNOR

RECEIVED OCTOBER 14, 1957

It has been shown, by radio tracer studies, that disubstituted diazomethane adds to nitroölefins of the type $RCH{=}CHNO_2$ to give pyrazolines in which the diazonitrogen atom becomes attached to the β-carbon atom of the nitroölefin. This is opposite to the orientation generally observed for additions involving diazomethane or monosubstituted diazomethane. The pyrazoles, obtained in quantitative yield from these pyrazolines, are thus formed by a single migration of substituent during loss of nitrous acid.

In the preceding articles of this series[4–6] the reaction of diazo compounds with nitroölefins was described, and mechanisms for the conversion of the resulting 3-nitropyrazolines into pyrazoles, by loss of the elements of nitrous acid, were discussed.

Reactions involving disubstituted diazo compounds were of particular interest to us, since loss of the elements of nitrous acid from the intermediate pyrazolines was accompanied by migration of groups to give pyrazoles of type V (Va = Vb unless pyrazole ring is tagged).



These pyrazoline intermediates could have either structure III or IV; consequently the derived pyrazole could result from either a single migration of R from IV, or a concerted twofold migration of groups from III.[4] No direct evidence bearing on these alternative routes has been offered; however, Parham and Hasek[4] have suggested the course I → III → V by virtue of the fact that diazomethane and diazoacetic ester generally add to nitroölefins and other activated olefins[5,6] to give products in which the diazo linkage becomes attached to the α-carbon of the olefin (products such as III). Two possible adducts were, however, reported from the reaction of diazoacetic ester and phenylpropiolic ester[7]; consequently, the possibility remains that disubstituted diazo compounds add to activated olefins to give products in which the diazo linkage becomes attached to the β-carbon atom of the olefin (products such as IV) and the above reaction sequence is I → IV → V. This paper describes studies relative to the orientation of addition of disubstituted diazo compounds to nitroölefins, and to the reaction sequence leading to V.

Tautomeric pyrazoles of type Va and Vb, in which the carbon atoms are not tagged, are known to be rapidly interconverted, and are generally represented by a single structure. Inspection of the above formula, however, reveals that a decision between the single or twofold migration (or between III or IV) can be made provided: (a) the α-carbon atom of the nitroölefin is tagged, and (b) the pyrazole V can be suitably degraded to determine the fate of the radioactive carbon.

The synthetic and degradative schemes used in this work, both for tagged and untagged experiments, are outlined in the series of equations.

The yield of VI, from *p*-benzyloxybenzaldehyde and nitromethane, was 20–25%, 55–65% and 80–83%, respectively, when methyl, ethyl and isopropyl alcohol were employed as solvents. When a benzene solution of VI and diphenyldiazomethane was allowed to stand for five weeks, a crystalline nitropyrazoline was obtained in 40% yield. This product (VIIa or VIIb) melted at 130.5–131.5°, and there was no evidence for the formation of an isomeric pyrazoline.

---

(1) Supported in part by the Smith, Kline and French Research Foundation and by the Greater University Fund of the University of Minnesota.

(2) From the Ph.D. Thesis of Carl Serres, Jr., University of Minnesota, 1956.

(3) Monsanto Chemical Fellow, 1955–1956; Procter and Gamble Summer Fellow 1955; E. I. du Pont de Nemours Summer Fellow 1956.

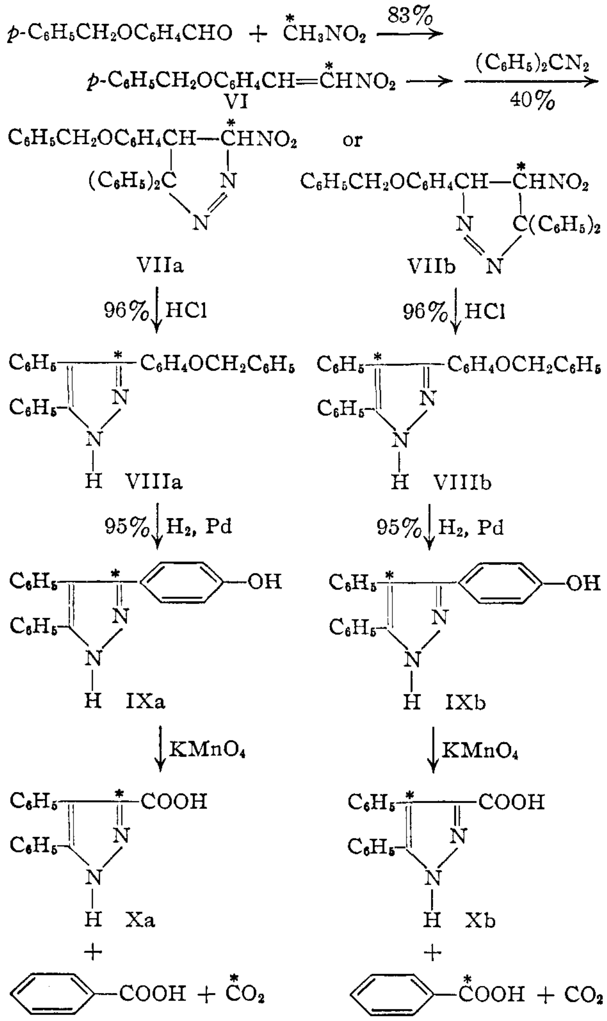
(4) W. E. Parham and W. R. Hasek, THIS JOURNAL, **76**, 799 (1954).

(5) W. E. Parham and J. L. Bleasdale, *ibid.*, **73**, 4664 (1951).

(6) W. E. Parham and J. L. Bleasdale, *ibid.*, **72**, 3843 (1950).

(7) K. von Auwers and O. Ungemach, *Ber.*, **66B**, 1205 (1933).

The reaction of the pyrazoline VIIa or VIIb with hydrochloric acid in ethanol resulted in the elimination of oxides of nitrogen, and the formation of 3-(*p*-benzyloxyphenyl)-4,5-diphenylpyrazole (VIII) in 96% yield. Low pressure hydrogenation of VIII, using a palladium-on-charcoal catalyst, cleaved this ether to give 3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (IX) in 90–95% yields.



Unequivocal proof of structure of the phenol IX was afforded by its oxidation with permanganate in water to the known 4,5-diphenylpyrazole-3-carboxylic acid (X). Finally, exhaustive oxidation of 3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (IX) with hot alkaline permanganate in *t*-butyl alcohol and water gave carbon dioxide and benzoic acid (50–65% calculated for two moles). This oxidation was found suitable as a degradative scheme for determining the fate of the radioactive tagged carbon.

The objective of the carbon-14 study is readily apparent from the above equations. The nitropyrazoline resulting from the reaction of β-C^{14}-p-benzyloxy-β-nitrostyrene (VI) and diphenyldiazomethane must have either structure VIIa or VIIb. If the nitropyrazoline has structure VIIa, 3-C^{14}-3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (IXa) derived from it would yield, upon oxidation, non-radioactive benzoic acid and radioactive carbon dioxide. If the nitropyrazoline has structure VIIb, then oxidation of the derived pyrazole IXb would give radioactive benzoic acid and non-active carbon dioxide.

The radioactivity of samples studied, expressed in counts per minute per sample (c./m.), were obtained by counting "infinitely" thick samples of barium carbonate and thus may be compared directly. Activities from the thick sample measurements are directly proportional to the specific activities of the compounds assayed. Details of the tracer studies are found in the Experimental section and are summarized in Table I.

TABLE I

RADIOACTIVITY MEASUREMENTS OF OXIDATION PRODUCTS OF IXb

	Calcd.	Observed
Benzoic acid	1504 ± 9	1515 ± 13
Carbon dioxide	0	268 ± 6

It can be seen that the counting rate for the benzoic acid derived from the X-C^{14}-pyrazole should be 1504 c./m. if the pyrazole has structure IXb, and 0 c./m. if the pyrazole has structure IXa.

The near identity in activity of the pyrazole and the derived benzoic acid clearly establishes structures IXb and VIIIb for the pyrazoles and structure VIIb for the intermediate pyrazoline. Thus, it is clear that the orientation of addition of diphenyldiazomethane to the nitroölefin is opposite to the orientation observed for addition of diazomethane and diazoacetic ester; furthermore, the derived pyrazole is formed by a single migration of a group in the pyrazoline during elimination of nitrous acid (IV → Vb). Essentially quantitative yields of pyrazoles have been obtained from a variety of pyrazolines[4] in which R and R^1 (I, II, IV) are both aromatic and aliphatic; consequently, the available data clearly suggest that disubstituted diazo compounds generally add to nitroölefins of type I to give pyrazolines in which the diazonitrogen atom is attached to the β-carbon atom of the nitroölefin. It is anticipated that this orientation may be general for additions involving disubstituted diazo compounds and other activated olefins.

In view of the excellent agreement in radioactivities of IXb and benzoic acid, an activity of zero would be expected for the carbon dioxide fraction. The carbon dioxide, however, had an activity of 268 c./m. The source of this activity was shown to be due to oxidation and/or decarboxylation of radioactive benzoic acid. A sample of carboxyl-C^{14}-benzoic acid (radioactivity 1515 c./m.) was subjected to the same oxidizing procedure as for IXb and a carbon dioxide fraction having an activity of 243 c./m. was obtained.

In our initial studies on this problem, *p*-methoxyphenyl-β-nitrostyrene and diphenyldiazomethane were used as the starting materials. A quantitative yield of 3-(*p*-methoxyphenyl)-4,5-diphenylpyrazole (V) was obtained from the single pyrazoline IV which was obtained in 30% yield. Attempts to cleave the methyl ether group in this pyrazole to IX by action of concentrated hydrobromic acid or hydroiodic acid in acetic acid were unsuccessful. Low yields (6–15%) of IX were obtained by cleavage with hot sodium hydroxide in diethylene glycol. The resistance to cleavage of the ether group in the pyrazole to give IX can be explained by the amphoteric character of the pyrazole ring.

Experimental

p-Benzyloxy-β-nitrostyrene (VI).—Potassium hydroxide (1.2 g. in 40 ml. of absolute ethanol) was added to a cold solution (2°) containing nitromethane (1.0 g., 0.0163 mole), *p*-benzyloxybenzaldehyde[8] (3.45 g., 0.0163 mole) and isopropyl alcohol (175 ml.). Ice-water (500 ml.) was added after the reaction mixture had stood at 0° for 1.5 hours, and the resulting solution was poured into a mixture of ice and water containing hydrochloric acid (12 ml.). The crude solid that separated was collected and recrystallized from ethanol which afforded 3.3 g. (80% yield) of VI melting at 115–120°. Pure VI (m.p. 121–122°) was obtained, with little loss, by further crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.60; H, 5.33; N, 5.56.

The yield of VI was 20–25 and 55–65%, respectively, when methyl alcohol and ethyl alcohol were used as solvent.

Nitromethane[9] (1.0 g.) containing approximately one-third millicurie of C^{14} was employed for the preparation of tagged VI.

3-(p-Benzyloxyphenyl)-4-nitro-5,5-diphenylpyrazoline (VIIb).—A solution of VI (3.30 g., 0.0129 mole) and diphenyldiazomethane[10] (2.60 g., 0.0134 mole) in thiophene-free benzene (30 ml.) was allowed to stand at room temperature until the deep red color of the diazo compound disappeared (one to three weeks). An additional 1.0 g. of diazo compound was added and the mixture was allowed to stand an additional week. The solid that precipitated was washed successively with cold petroleum ether, benzene and ethanol. There was obtained 2.45 g. (41.5% yield) of white product, the melting point of which (130.5–131.5°) was not changed upon recrystallization from benzene.

Anal. Calcd. for $C_{28}H_{23}O_3N_3$: C, 74.81; H, 5.16; N, 9.35. Found: C, 74.95; H, 5.42; N, 9.29.

3-(p-Benzyloxyphenyl)-4-nitro-5,5-diphenylpyrazole (VIIIb).—A solution containing VIIb (2.35 g., 0.005 mole), absolute ethanol (300 ml.) and concentrated hydrochloric acid (23 ml.) was heated at the reflux temperature until tests with starch–iodide paper indicated that the evolution of oxides of nitrogen was complete (about three hours). The solution was added to one liter of water and the resulting mixture was neutralized with 10% sodium hydroxide. The solid product (2.0 g., 96% yield, m.p. 213–215°) was collected and recrystallized from ethanol. Pure VIIIb melted at 214.5–215.5°.

Anal. Calcd. for $C_{28}H_{22}ON_2$: C, 83.55; H, 5.51; N, 6.96. Found: C, 83.62; H, 5.42; N, 7.19.

3-(p-Hydroxyphenyl)-4,5-diphenylpyrazole (IXb).—A mixture of 3-(*p*-benzyloxyphenyl)-4,5-diphenylpyrazole (VIIIb, 2.0 g., 0.005 mole), absolute ethanol (200 ml.), palladium-on-charcoal (10%, 0.5 g.) and hydrogen (35 p.s.i.) was shaken at 52°. The pyrazole, initially in suspension, had disappeared after four hours. The catalyst was then removed (filtration through Hi-flo), and the resulting solution was poured into one liter of cold water. The white flocculent precipitate (1.40 g., 90% yield, m.p. 248–249°) was recrystallized from ethanol to give white needles melting at 248–249°.

Anal. Calcd. for $C_{21}H_{16}ON_2$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.47; H, 5.27; N, 8.83; radioactive assay, 2867 ± 17 c./m.

A sample of radioactive IXb (0.350 g.) was diluted with non-radioactive IXb (0.650 g.) to give a sample of calculated activity 1003 ± 6 c./m. This material was used for subsequent oxidation to benzoic acid and carbon dioxide.

Oxidation of 3-(p-Hydroxyphenyl)-4,5-diphenylpyrazole to 4,5-Diphenylpyrazole-3-carboxylic Acid (X).—A mixture of 3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (0.25 g., 0.0008 mole), saturated sodium hydroxide solution (5 drops), potassium permanganate (0.5 g.) and water was heated on a steam-bath. Two additional 0.5-g. samples of potassium permanganate were added over a 2-hour period and the resulting mixture was heated for five hours. Excess permanganate was then decomposed with methanol and the hot mixture was filtered. The filtrate was acidified and the white mixture (0.2 g.) of X and benzoic acid was filtered. The mixture was extracted with hot water to remove benzoic acid and was found to contain approximately equal quantities of benzoic acid and 4,5-diphenylpyrazole-3-carboxylic acid[4,11] (XI, m.p. and mixed m.p. 266–267°).

Oxidation of 3-(p-Hydroxyphenyl)-4,5-diphenylpyrazole to Benzoic Acid.—A solution of 3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (0.770 g., 0.0024 mole), sodium hydroxide (0.3 g.), potassium permanganate (9.0 g.), water (40 ml.) and *t*-butyl alcohol (40 ml.) was heated at the reflux temperature for 48 hours. The excess permanganate was removed with methanol and most of the *t*-butyl alcohol by distillation. The resulting hot mixture was filtered and the filtrate was made strongly acid by addition of hydrochloric acid. The acid solution was extracted eight times with 30-ml. portions of ether and the combined ether extract was dried ($MgSO_4$) and concentrated. The slightly impure benzoic acid thus obtained was recrystallized from hot water to give 370 mg. (61.5%) of benzoic acid melting at 120–121°. An additional 20 mg. (4%) of benzoic acid was recovered from the mother liquor of crystallization. The yields of benzoic acid from other runs ranged from 50–65%, calculated for two moles of benzoic acid. The results of the radiotracer studies are summarized in Table I.

3-(p-Methoxyphenyl)-4-nitro-5,5-diphenylpyrazoline.—A mixture of diphenyldiazomethane (4.0 g., 0.0206 mole) and *p*-methoxynitrostyrene[12,13] (3.69 g., 0.0206 mole) was allowed to stand at room temperature for 90 hours. The resulting yellow solid was recrystallized three times from ethanol to give 1.5 g. (19.7% yield) of white needles of 3-(*p*-methoxyphenyl)-4-nitro-5,5-diphenylpyrazoline (m.p. 136–137° dec.). Yields in other runs varied between 20 and 37%.

Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.51; H, 5.13; H, 10.92.

3-(p-Methoxyphenyl)-4,5-diphenylpyrazole was prepared from the corresponding pyrazoline described above by a procedure essentially identical to that described for the conversion of VIIb to VIIIb. The crude product was recrystallized from ethanol to give a quantitative yield of white needles melting at 213–214°.

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56; N, 8.58. Found: C, 81.01; H, 5.56; N, 8.47.

Conversion of 3-(p-Methoxyphenyl)-4,5-diphenylpyrazole to 3-(p-Hydroxyphenyl)-4,5-diphenylpyrazole.—A mixture containing 3-(*p*-methoxyphenyl)-4,5-diphenylpyrazole (6.7 g., 0.024 mole), sodium hydroxide (5.0 g., 0.13 mole) and diethylene glycol was heated at the reflux temperature for 22 hours. The brown solution was then diluted with water (600 ml.) and the resulting solution was acidified with hydrochloric acid. The precipitate (3.5 g., m.p. *ca.* 100°) was recrystallized from acetonitrite–water to give white crystals of impure 3-(*p*-hydroxyphenyl)-4,5-diphenylpyrazole (1.0 g., 13%, m.p. 235–240°). Additional recrystallization of this product from the same solvent pair afforded pure IX (m.p. and mixed m.p. 248–249°).

C-14-Assay Procedures.—The samples to be assayed were totally combusted using the Van Slyke–Folch wet oxidation method.[14] The counting rates were determined for "infinitely" thick uniform layers of barium carbonate.[15] The counting error is the standard deviation error for sample and background counting rates. The counting was done with a Nuclear Instrument and Chemical Corporation Scaling Unit, model 163, using a thin-window Geiger tube.

MINNEAPOLIS 14, MINN.

---

[8] E. G. Bergmann and M. Sulzbacher, *J. Org. Chem.*, **16**, 84 (1951).

[9] Radioactive nitromethane was obtained from Tracerlab, Inc., Boston, Mass., with authorization from the Isotope Division, Atomic Energy Commission.

[10] L. I. Smith and K. L. Howard, *Org. Syntheses*, **24**, 53 (1944).

[11] W. Borsche and H. Hahn, *Ann.*, **537**, 236 (1939).

[12] T. Kondo and Y. Shinozaki, *J. Pharm. Soc. Japan*, **49**, 267 (1929); *C. A.*, **24**, 5294 (1930).

[13] K. W. Rosenmund, *Ber.*, **42**, 4778 (1909).

[14] D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **163**, 509 (1940).

[15] The glass filter assembly used is described in M. Calvin, C. Heidelberger, J. C. Reid, B. M. Talbert and P. F. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949.