[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS]

A New Synthesis of Unsaturated Acids. I. α,β-Acetylenic Acids[1,2]

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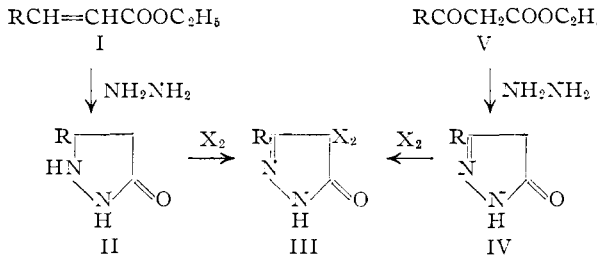
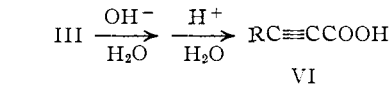
A new synthesis of α,β-acetylenic acids is described which involves conversion of a β-keto ester (or alternatively an α,β-olefinic acid) to the corresponding pyrazolone, then by halogenation and treatment of the resultant 4,4-dihalopyrazolone with dilute aqueous alkali. The reaction was examined initially as a possible route to cyclopropenones.

Because of the considerable theoretical interest in cyclopropenones[3], methods for the synthesis of these compounds have been examined in these laboratories. The first method studied involved treatment of halopyrazolones with alkali.[4] Because of its availability through reaction of chlorine[5] with the substance described by Muckermann[6] as cinnamic acid hydrazide,[7] 3-phenyl-4,4-dichloro-2-pyrazolin-5-one (III, R = C_6H_5, X = Cl), was first examined.



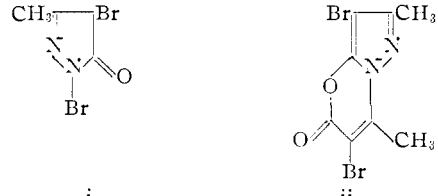
When III (R = C_6H_5, X = Cl) was treated with a five molar excess of 1 *N* sodium hydroxide at 0–5° for five hours gas evolution occurred and on acidification of the resulting solution phenylpropiolic acid was isolated in a yield of 89%. Acidification of the clear yellow solution after only five minutes at 0–5° gave the unchanged dichloropyrazolone. A cyclopropenone probably is not an intermediate in the formation of the acetylenic acid.[8,9]

It is of importance that the presently described reaction represents a very convenient method for the synthesis of α,β-acetylenic acids which can be considered to proceed from the corresponding β-keto ester, or, less generally, the corresponding α,β-olefinic acid.[10]



Arylpropiolic acids are ordinarily not difficult to obtain by the classical dehydrohalogenative routes, although convenient methods for the preparation of alkyl propiolic acids have not been available. Dehydrohalogenation of α,β-dihalo acids or their derivatives is not generally applicable[11] in the aliphatic series and the somewhat inconvenient acetylide-carbonation reaction is widely used.[12,13] Therefore it is of particular interest that the 3-methyl compound (III, R = CH_3, X = Br), easily obtainable from ethyl acetoacetate, is converted to tetrolic acid ($CH_3C{\equiv}CCOOH$) in a yield of 62–76%. The pyrazolones and halopyrazolones, required as intermediates in the present synthetic method, are generally easily handled, nicely crystalline substances. *m*-Nitrophenylpropiolic acid (75%) also has been prepared by the method described. From the results obtained to date it appears that the bromo and chloro derivatives may be used interchangeably. The iodo compounds have not yet been examined. A single attempt to carry out the reaction in one step by treatment of 3-phenyl-2-pyrazolin-5-one with two equivalents of sodium hypoiodite or hypobromite in the presence of an excess of sodium hydroxide gave a brown amorphous material in the first case and tarry brown substances in the latter. We did not examine these reactions in detail since the results were not promising.

NOTE ADDED IN PROOF (December 11, 1957).—After the present work was submitted, a paper by R. Huttel, E. Wagner and B. Sickenberger [*Ann.*, **607**, 109 (1957)] appeared in which is reported a study of the reaction of halopyrazolones and alkali. Huttel, *et al.*, state that the dibromination product of 3-methyl-2-pyrazolin-5-one, considered to be the 1,4-dibromo compound (i), yields upon treatment with 2 *N* sodium hydroxide the lactone (ii) of α-



bromo-β-[5-hydroxy-3-methyl-4-bromo-1-pyrazolyl]-crotonic acid (87%). The reason for the discrepancy between

(1) Presented in part at the 132nd National Meeting of the American Chemical Society, Sept. 13, 1957, New York, N. Y., Abstracts, p. 82-P.

(2) Supported by the Office of Ordance Research, U. S. Army.

(3) *Cf.* J. D. Roberts, A. Streitwieser and C. Regan [THIS JOURNAL, **74**, 4581 (1952)] on the expected stability of $C_3H_1^+$.

(4) *Cf.* N. Kishner, *J. Russ. Phys.-Chem. Soc.*, **61**, 781 (1929), and earlier papers on the synthesis of cyclopropanes from pyrazolines.

(5) *Cf.* L. A. Carpino, THIS JOURNAL, **79**, 96 (1957).

(6) E. Muckermann, *Ber.*, **42**, 3449 (1909).

(7) W. O. Godtfredsen and S. Vangedal [*Acta Chem. Scand.*, **9**, 1498 (1955)] and J. B. Jensen [*ibid.*, **10**, 667 (1956)] recently have shown that Muckermann's "cinnamic acid hydrazide" is actually the pyrazolidone II (R = C_6H_5).

(8) In the second paper of this series it is shown that cyclopropenones are not intermediates in the conversion of 3,4-disubstituted pyrazolones to α,β-olefinic acids.

(9) It is possible to rationalize the reaction on the basis of synchronous ring opening and loss of chloride ion from a possible dehydrohalogenation product of III. No experimental evidence is available on this point.

(10) Reaction between an α,β-unsaturated ester and hydrazine often, but not always, yields the corresponding pyrazolidone (for a discussion see the paper by Godtfredsen and Vangedal[7]). In the following paper it is shown that methyl α-methylcinnamate, on refluxing with hydrazine hydrate in ethanol, yields the hydrazide rather than the pyrazolidone.

(11) See *e.g.*, E. Schjanberg, *Ber.*, **71**, 569 (1938).

(12) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(13) A. O. Zoss and G. F. Hennion, THIS JOURNAL, **63**, 1151 (1941).

this result and our formation of tetrolic acid from the same compound [formulated in the present paper as III (R = CH_3, X = Br)] is not at present known although the results obtained with the 3-phenyl-4,4-dichloro compound (see Experimental section) suggest that the amount and concentration of alkali may have a pronounced effect on the course of the reaction.

In the present work we have assumed, following Muckermann,[6] that the halogenation of 4-unsubstituted and 4-monosubstituted pyrazolones occurs at the available 4-position(s) whereas Huttel, *et al.*, have suggested, on the basis of infrared data, that the products are 1,4-dihalo and 1-halo compounds, respectively. In view of this suggestion we have examined the chemical and spectral properties of certain of the halopyrazolones studied in the course of this work. It was found, *e.g.*, that N-acetylation of IV (R = C_6H_5) followed by dichlorination yields the same substance that is obtained by acetylation of the direct dichlorination product of IV. Details of this and related chemical and spectral evidence in favor of 4-halo as opposed to 1-halo structures will be presented in a forthcoming paper.

Experimental[14-16]

Preparation of 3-Phenyl-4,4-dichloro-2-pyrazolin-5-one.—A solution of 10 g. of 5-phenyl-3-pyrazolidone[17] (m.p. 100–102°) in 125 ml. of nitromethane was saturated with dry hydrogen chloride[18] and chlorine was passed through the mixture until a definite excess was present (about 30 min.). The first-precipitated hydrochloride dissolved and was replaced by a greenish-yellow crystalline solid. The mixture was filtered after cooling in an ice-bath for 30 min. and gave 12 g. (85.1%) of the pyrazolone, m.p. 173–175° (softening at 170°). Recrystallization from nitromethane gave 11 g. (78%) of large block-like crystals, m.p. 173–175° (very slight gas evolution). The combined filtrates gave an additional 1 g. of the pure compound, m.p. 173–175°. The analytical sample (once from ethanol, twice from nitromethane) had the same m.p. and was almost white but had a faint color as above, $\lambda_{C=O}^{Nujol}$ 5.72 μ (1748 cm.$^{-1}$).

Anal. Calcd. for $C_9H_6N_2OCl_2$: C, 47.19; H, 2.64. Found: C, 47.10; H, 2.69.

The same substance, m.p. and mixed m.p. 173–175°, was obtained by chlorination of 1-nitroso-5-phenyl-3-pyrazolidone[6] and 3-phenyl-2-pyrazolin-5-one.[19]

Phenylpropiolic Acid from 3-Phenyl-4,4-dichloro-2-pyrazolin-5-one.—A solution of 2 g. (0.05 mole) of sodium hydroxide in 50 ml. of water was cooled in an ice-bath (internal temperature about 5°) and 2.29 g. (0.01 mole) of the finely powdered pyrazolone was added during 2–3 min. with mechanical stirring. The mixture was allowed to stir for four hours. During the fourth hour much of the ice had melted and the temperature rose to 10°. The cold solution was acidified with dilute hydrochloric acid (congo red) and the cream-white solid filtered and washed with water; amount 1.3 g. (89%), m.p. 135–137.5°. Recrystallization from chloroform gave 1 g. (68.5%) of snow-white needles, m.p. 137–139°; $\lambda_{C\equiv C}^{Nujol}$ 4.46, 4.53 μ (2242, 2208 cm.$^{-1}$). Evaporation of the filtrate gave an additional 0.1 g. of pure acid, m.p. 137–139°, so that the total yield was 1.1 g. (75.3%). The mixed m.p. with an authentic sample of phenylpropiolic acid[20] showed no depression and the infrared spectra were superimposable. Treatment of the pyrazolone with sodium hydroxide at room temperature was accompanied by spontaneous warming and the propiolic acid was contaminated by an orange-colored impurity, although it was obtained in about the same yield.

When the powdered pyrazolone (4.58 g., 0.02 mole) was stirred for four hours at 0–5° with a solution of 0.8 g. (0.02 mole) of sodium hydroxide in 100 ml. of water, a yellow powder was slowly precipitated from the frothy solution. Filtration and recrystallization from nitromethane gave 0.5 g. of bright yellow needles, m.p. 317–320°. The analytical sample had m.p. 319–320°. This substance is recorded here simply as a characteristic derivative of the dihalopyrazolone. Its structure is under examination.

Anal. Calcd. for $C_{18}H_{10}N_2Cl_2O_2$: C, 60.52; H, 2.82; N, 7.85; Cl, 19.85; mol. wt., 357. Found: C, 60.60; H, 2.92; N, 7.76; Cl, 20.25; mol. wt. (Rast), 334.

Evaporation of the nitromethane filtrate gave 0.8 g. of the original pyrazolone, m.p. 173–175°. Acidification of the original aqueous filtrate gave only a trace of tacky brown material indicating that little, if any, phenylpropiolic acid is formed under these conditions.

3-*m*-Nitrophenyl-4,4-dichloro-2-pyrazolin-5-one.—5-*m*-Nitrophenyl-3-pyrazolidone (m.p. 140–142°) was prepared in 57% yield by the method of Curtius and Bleicher[21] (lit.[21] m.p. 139°; yield of pure compound not reported). Chlorination of 3 g. of the pyrazolidone in 25 ml. of hot nitromethane was carried out by the method indicated for the phenyl derivative except that passage of hydrogen chloride was dispensed with and the solution was kept near the boiling point by occasional heating on a hot-plate while the chlorine was passed through the solution. On cooling there was obtained 3.1 g. (77.5%) of the pyrazolone, m.p. 199–203° dec. An additional 0.2 g., m.p. 199–205° dec., was obtained from the filtrate (total yield 3.3 g., 82.5%). Two recrystallizations from nitromethane gave small white needles, m.p. 204–205° dec., $\lambda_{C=O}^{Nujol}$ 5.63 μ (1776 cm.$^{-1}$).

Anal. Calcd. for $C_9H_5N_3O_3Cl_2$; C, 39.44; H, 1.84. Found: C, 39.10; H, 1.94.

The dichloropyrazolone was converted to *m*-nitrophenylpropiolic acid by a method similar to that described for the phenyl derivative. The yield was 75%, m.p. 143.6–144.8°, $\lambda_{C\equiv C}^{Nujol}$ 4.50 μ (2222 cm.$^{-1}$); lit.[22] m.p. 143.7–144.4°.

3-Methyl-4,4-dichloro-2-pyrazolin-5-one.—A solution of 65 g. of ethyl acetoacetate in 110 ml. of ethanol was treated slowly with a solution of 25 g. of 64% hydrazine in 40 ml. of ethanol. Cooling in an ice-chest gave 42 g. (85.6%) of 3-methyl-2-pyrazolin-5-one, m.p. 221.5-224.5°, pure enough for further use.[23] A mixture of 5 g. of the pyrazolone and 50 ml. of nitromethane was chlorinated by heating to the boiling point, removing from the source of heat and passing a stream of chlorine through the mixture until the solid dissolved (10–15 min.). On cooling only 3 g., m.p. 111–115°, of crystalline white solid separated. Evaporation of the filtrate by means of a water aspirator and a water-bath at 60–75° gave an additional 3.5 g., m.p. 108–111°. The combined solid (6.5 g., 76.5%) was recrystallized from nitromethane which gave 6 g. (70.5%) of long snow-white needles, m.p. 113–115°. The analytical sample melted at 112–114°, $\lambda_{C=O}^{Nujol}$ 5.73 μ (1745 cm.$^{-1}$).

Anal. Calcd. for $C_4H_4N_2OCl_2$; C, 28.77; H, 2.41. Found: C, 29.20; H, 2.64.

Preparation of Tetrolic Acid.—3-Methyl-2-pyrazolin-5-one (prepared as given above) was converted to the corresponding 4,4-dibromo derivative of the method of Muckermann[6] in a yield of 54%, m.p. 130–132° (lit.[6] m.p. 132°, no yield given). A solution of 10 g. of sodium hydroxide in 300 ml. of water was cooled in an ice-bath and treated as in the previous cases with 12.8 g. of the powdered dibromopyrazolone and the mixture stirred two hours at 0–5° and one hour at room temperature. The solution was cooled, acidified with concentrated hydrochloric acid and extracted with 10–15 ml. portions of ether until addition of 2 ml. of the extract to acetone–potassium permanganate gave no brown precipitate. A total of about 16 extractions was required. After spontaneous evaporation of the ether the liquid residue was placed in a vacuum desiccator over sul-

(14) Melting points are uncorrected.

(15) Analyses are by Drs. Weiler and Strauss, Oxford, England.

(16) Infrared spectra were taken as Nujol mulls and recorded linearly in wave length on a Perkin-Elmer model 21 spectrophotometer, sodium chloride optics. We are indebted to the National Science Foundation and the Research Corporation for funds with which to purchase the spectrophotometer (NSF G-2368).

(17) Prepared by the method of Muckermann[6] who reports a yield of 52–54%, m.p. 101°. By using 175 g. of ethyl cinnamate, 105 g. of ethanol and 55 g. of 64% hydrazine and refluxing for 40 hours the yield was increased to 80–90%.

(18) Hydrogen chloride was used in this case under the impression that we were dealing with an acid hydrazide, since this reaction was carried out prior to the availability of ref. 7. See ref. 5. It could probably be omitted and in other analogous cases carried out later, we have not used this gas.

(19) T. Curtius, *J. prakt. Chem.*, [2] **50**, 508 (1895).

(20) M. Reimer, THIS JOURNAL, **64**, 2510 (1942).

(21) T. Curtius and F. A. Bleicher, *J. prakt. Chem.*, [2] **107**, 86 (1924).

(22) M. S. Newman and S. H. Merrill, THIS JOURNAL, **77**, 5549 (1955).

(23) T. Curtius and R. Jay, *J. prakt. Chem.*, [2] **39**, 27 (1889), report m.p. 215°.

furic acid and silica gel. An orange crystalline solid formed (3.2 g., 76.3%, m.p. 70–75°). Recrystallization from a mixture of 30–60° and 60–90° ligroin (1:1) gave 2.6 g. (62%) of nearly white needles, m.p. 74–76° (lit.[12] m.p. 76°), $\lambda_{C\equiv C}^{Nujol}$ 4.46 μ (2242 cm.$^{-1}$).

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A New Synthesis of Unsaturated Acids. II. α,β-Olefinic Acids[1,2]

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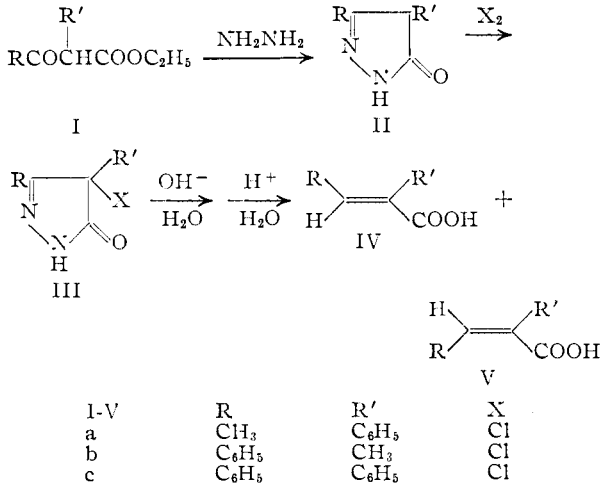
A new synthesis of α,β-olefinic acids is described which involves treatment of a 4-substituted-4-halo-2-pyrazolin-5-one with aqueous sodium hydroxide. While the yield of mixed acids is not exceedingly high (40–65%) the reaction promises to be useful since the labile isomer of the *cis,trans* pair predominates in the mixture. A simple method of separating the isomeric acids, fractional extraction with sodium bicarbonate solution, is described.

In the preceding paper it was shown that the readily available 4,4-dihalo-2-pyrazolin-5-ones were converted by an excess of aqueous alkali at 0–5° to α,β-acetylenic acids in fair to good yields (75–90%). This reaction has now been extended to the corresponding 4-substituted-4-halo compounds since it was expected that the process might lead to a convenient synthesis of α,β-olefinic acids and examination of a pair of isomeric 3,4-disubstituted-4-halo derivatives would yield evidence as to the possibility of cyclopropenone intermediates which was previously considered.

In order to determine whether cyclopropenones intervened in the reaction, 3-methyl-4-phenyl-4-chloro- and 3-phenyl-4-methyl-4-chloro-2-pyrazolin-5-ones (IIIa and IIIb, respectively) were treated with an excess of sodium hydroxide. If cyclopropenones were involved, both IIIa and IIIb should yield the same unsaturated acid. The isolation of IV-Va and IV-Vb, respectively, from these reactions disposes of the possibility of cyclopropenone intermediates.[3] As has been determined by previous workers[4] the acid having the β-substituent and the carboxyl group *trans* to one another is the more stable isomer (IV) of a *cis,trans* pair. Such acids are easily obtainable by the Perkin and Reformatsky reactions. On the other hand, it was found in the present case that a mixture of the *cis,trans* pair was formed in which the labile isomer predominated (see Table I).



I-V	R	R′	X
a	CH_3	C_6H_5	Cl
b	C_6H_5	CH_3	Cl
c	C_6H_5	C_6H_5	Cl

TABLE I

YIELDS OF LABILE AND STABLE ACIDS FROM HALOPYRAZOLONES (%)[a]

Acid	Labile	Stable
α-Phenylcinnamic	35.7 (44.6)	14.7 (17.4)
α-Phenylcrotonic	44.5 (55.5)	8.0 (10.5)
α-Methylcinnamic	21.6 (28)	8.6 (11)

[a] The yield of crude material is given in parentheses.

In view of the ready availability[5] of β-keto esters of all types it would seem that the present reaction represents a useful synthetic route to acids difficult to obtain by other methods.[6] Furthermore by isomerization of the reaction mixture prior to isolation it should be possible to obtain solely the stable isomer although the Perkin and Reformatsky reactions would usually be more suitable providing the requisite aldehydes are available. The 4-halo-2-pyrazolin-5-one precursors are available from the corresponding pyrazolidones[8] as well as from the pyrazolones so that the reaction also can be used as a method of converting the stable isomer IV to

(1) Presented in part at the 132nd National Meeting of the American Chemical Society, September 13, 1957, New York, N. Y.

(2) Supported by the Office of Ordnance Research, U. S. Army.

(3) Several self-evident rationalizations of this reaction are conceivable. Discussion is omitted at the suggestion of the referee since no experimental evidence is available to decide among various possibilities.

(4) See L. Crombie, *Quart. Revs.*, **6**, 101 (1952), for a discussion and review.

(5) Recently several new convenient procedures for the synthesis of β-keto esters have become available: (a) Ester acylations by means of sodium hydride, sodium amide and particularly diisopropylaminomagnesium bromide: E. E. Royals and D. G. Turpin, THIS JOURNAL, **76**, 5452 (1954); F. Y. Swamer and C. R. Hauser, *ibid.*, **72**, 1352 (1950); F. C. Frostick and C. R. Hauser, *ibid.*, **71**, 1350 (1949); J. C. Shivers, M. L. Dillon and C. R. Hauser, *ibid.*, **69**, 119 (1947). (b) Condensation of an α-bromoester with an ordinary ester by means of magnesium: M. Montague, *Bull. soc. chim. France*, 63 (1946) (c) The method of Blaise as modified by Cason, Rinehart and Thornton (ref. 20). (d) Acylation of ketone enamines: G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).

(6) Previously two methods have been available for the synthesis of labile acids of type V. Isomerization of the stable acid (IV) by ultraviolet irradiation has been used, although the conversions generally are not high. For example, H. Burton and C. W. Shoppee [*J. Chem. Soc.*, 1156 (1935)] obtained a conversion of 8% by a 70-hour irradiation of *trans*-α-methylcinnamic acid.[7] Recently, a stereospecific method has become available [see *e.g.* (a) A. S. Dreiding and R. J. Pratt, THIS JOURNAL, **76**, 1902 (1954), and (b) D. Y. Curtin and E. E. Harris, *ibid.*, **73**, 2716, 4519 (1951)].

(7) In this paper *cis* and *trans* refer to the configurations of the parent α,β-unsaturated acids (*e.g.*, V and IV, respectively).

(8) Pyrazolidinone in *Chem. Abstr.* terminology.