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

# A New Synthesis of Unsaturated Acids. III. Structures of the Halogenation Products of 4-Unsubstituted and 4-Monosubstituted-2-pyrazolin-5-ones[1]

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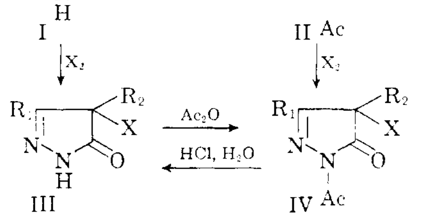
Chemical and spectral evidence is presented to show that the mono- and dihalogenation products of 4-mono- and 4-unsubstituted pyrazolones, respectively, are the 4-halo- and 4,4-dihalopyrazolones rather than 1-halo derivatives.

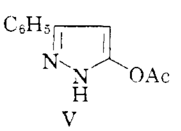
Recently[2,3] it was shown that halogenated pyrazolones upon treatment with an excess of dilute sodium hydroxide underwent ring opening with the formation of $\alpha,\beta$-acetylenic or olefinic acids. Following Muckermann[4] it had been assumed in the earlier work that pyrazolones of the type involved were chlorinated or brominated at the available 4-positions. After the completion of this work Huttel, Wagner and Sickenberger[5] published infrared data on analogous compounds and suggested that the substances were 1-halo derivatives.

Since the halopyrazolones as prepared by us did not appear to have the chemical properties generally associated with N-halo compounds we examined in greater detail several of the derivatives used in the previous work. The dichloro-2-pyrazolin-5-one (A) obtained by chlorination of 3-phenyl-2-pyrazolin-5-one (I, $R_1 = C_6H_5$, $R_2 = H$) or the corresponding pyrazolidone, upon treatment with acetic anhydride yielded a monoacetyl derivative (IV) which proved to be identical with the dichlorination product of 1-acetyl-3-phenyl-2-pyrazolin-5-one (II, $R_1 = C_6H_5$, $R_2 = H$) which was prepared by the method of Weissberger and Porter.[6] This indicates that A is the 4,4-dichloro derivative (III, $R_1 = C_6H_5$, $R_2 = X = Cl$) as previously considered. Brief treatment of IV ($R_1 = C_6H_5$, $R_2 = X = Cl$) with hydrochloric acid regenerated III ($R_1 = C_6H_5$, $R_2 = X = Cl$). The structure of the 1-acetyl derivative (II, $R_1 = C_6H_5$, $R_2 = H$) was established by Weissberger and Porter.[6] Two other acetyl derivatives of 3-phenyl-2-pyrazolin-5-one are known, the acetoxypyrazole V[6] and the 4-acetyl derivative VI.[7] Chlorination of the acetoxypyrazole (V) in acetic acid solution yielded the trichloropyrazolone VII (R = Cl). This is to be expected[8] since V was shown previously to be hydrolyzed readily to I ($R_1 = C_6H_5$, $R_2 = H$). Compound VII (R = Cl) shows the typical properties of an N-haloamide. Upon attempted recrystallization from ethanol a vigorous reaction with the solvent occurs yielding the dichloro derivative III ($R_1 = C_6H_5$, $R_2 = X = Cl$) accompanied by the evolution of acetaldehyde. Both VII (R = Cl) and 1,4-dichloro-3,4-diphenyl-2-pyrazolin-5-one (VII, $R = C_6H_5$), prepared similarly, gave positive tests with starch–iodide paper without prior acidification, whereas the corresponding di- and monochloro compounds III ($R_1 = C_6H_5$, $R_2 = X = Cl$ and $R_1 = R_2 = C_6H_5$, $X = Cl$) do not. Caution must be exercised in applying such tests since 1-phenyl-3-methyl-4,4-dibromo-2-pyrazolin-5-one also gives a positive test with starch–iodide paper under the same conditions.[9]



The monochlorination product III ($R_1 = C_6H_5$, $R_2 = CH_3$, $X = Cl$) of 3-phenyl-4-methyl-2-pyrazolin-5-one was monoacetylated to the same product as was obtained by chlorination of the 1-acetyl derivative II ($R_1 = C_6H_5$, $R_2 = CH_3$). A similar sequence of reactions was carried out on the 3,4-dimethylpyrazolone (I, $R_1 = R_2 = CH_3$) with analogous results (see Experimental section). These results, coupled with the infrared and n.m.r. data discussed below suggest that the other pyrazolones previously discussed are also 4-halo derivatives.

In Table I are listed the infrared absorption bands of the 4,4-disubstituted pyrazolones examined in the course of this work. In all cases the dihalo compounds have carbonyl absorption bands which are similar to those of the known model compound 3,4,4,-trimethyl-2-pyrazolin-5-one. On the other hand, none of the 4-unsubstituted or 4-monosubstituted pyrazolones (Table II) shows any



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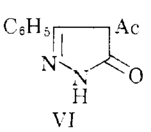

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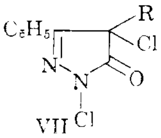

VII

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[1] Supported by the Office of Ordnance Research, U. S. Army.

[2] L. A. Carpino, THIS JOURNAL, **80**, 599 (1958).

[3] L. A. Carpino, *ibid.*, **80**, 601 (1958).

[4] E. Muckermann, *Ber.*, **42**, 3449 (1909).

[5] R. Huttel, E. Wagner and B. Sickenberger, *Ann.*, **607**, 109 (1957).

[6] A. Weissberger and H. D. Porter, THIS JOURNAL, **65**, 1495 (1943).

[7] M. Ridi, *Gazz. chim. ital.*, **82**, 746 (1952).

[8] As indicated previously[3] chlorination of I ($R_1 = C_6H_5$, $R_2 = H$) in nitromethane stops with the introduction of two chlorine atoms whereas it is now shown (Experimental section) that chlorination in acetic acid yields VII (R = Cl).

[9] Other workers [L. Smith, I. Merits and B. Norlov, *Kgl. Fysiograf. Sallskap. Lund Forh.*, **23**, 51 (1953)] have used "positive halogen" character such as the formation of bromoacetone from acetone as evidence for N-halo rather than C-halo structures in the pyrazolone series. G. Westöö [*Acta Chem. Scand.*, **6**, 1499 (1952)] has shown, however, that 4-halopyrazolones often give positive tests under comparable conditions.

absorption in the region 5.6–6.1 μ.[10] This is further evidence for the postulation that the dihalopyrazolones in question are 4,4-rather than 1,4-dihalo derivatives.

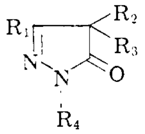
Finally, the n.m.r. spectrum of the dibromination product of 3-methyl-2-pyrazolin-5-one is in agreement with the suggested structure (III, $R_1 = CH_3$, $R_2 = X = Br$) and definitely excludes the 1,4-dibromo structure.[11]

## Experimental[12–14]

**1-Acetyl-3-phenyl-4,4-dichloro-2-pyrazolin-5-one.** (A).—A suspension of 1 g. of 1-acetyl-3-phenyl-2-pyrazolin-5-one[6] in 10 ml. of acetic acid was treated with a stream of chlorine until the first-precipitated solid dissolved and a definite excess of chlorine was present. Dilution with water to 25 ml., filtration and washing with water gave 1 g. (74.6%) of the dichloro compound, m.p. 145–147°. Recrystallization from ethanol gave long white needles, m.p. 146–148°.

TABLE I

CARBONYL INFRARED ABSORPTIONS OF SUBSTITUTED PYRAZOLONES

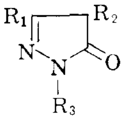


| Cpd. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Position, μ |
|---|---|---|---|---|---|
| 1[2] | $CH_3$ | Cl | Cl | H | 5.73s |
| 2[4] | $CH_3$ | Br | Br | H | 5.75s |
| 3[2] | $C_6H_5$ | Cl | Cl | H | 5.72s |
| 4[4] | $C_6H_5$ | Br | Br | H | 5.71s |
| 5 | $C_6H_5$ | $CH_3$ | Br | H | 5.74s |
| 6[2] | $p$-$O_2NC_6H_4$ | Cl | Cl | H | 5.63s |
| 7 | $CH_3$ | $CH_3$ | Cl | H | 5.83s |
| 8[a] | $CH_3$ | $CH_3$ | $CH_3$ | H | 5.84s, 5.95s |
| 9[b] | $C_6H_5$ | $C_6H_5$ | Br | H | 5.80s |
| 10[3] | $C_6H_5$ | $CH_3$ | Cl | H | 5.74s |
| 11[3] | $C_6H_5$ | $C_6H_5$ | Cl | H | 5.75s |
| 12[c] | $CH_3$ | Br | Br | $C_6H_5$ | 5.83s |
| 13 | $C_6H_5$ | Cl | Cl | Cl | 5.70s |
| 14[d] | $CH_3$ | Cl | Cl | $C_6H_5$ | 5.81s |
| 15 | $C_6H_5$ | $C_6H_5$ | Cl | Cl | 5.66s |

[a] H. J. Backer and W. Meyer, *Rec. trav. chim*, **45**, 82 (1926). [b] Prepared from the corresponding pyrazolidone by bromination in acetic acid, precipitation with water and recrystallization from nitromethane, m.p. 181–184° dec. *Anal.* Calcd. for $C_{15}H_{11}N_2OBr$: C, 57.16; H, 3.52. Found: C, 57.18; H, 3.76. [c] L. Smith, *Kgl. Fysiograf. Sallskap Lund Forh.*, **18**, No. 1, 3 (1948). [d] G. Westöö, *Acta Chem. Scand.*, 6, 1499 (1952).

TABLE II

SUBSTITUTED PYRAZOLONES EXHIBITING NO INFRARED ABSORPTION IN THE REGION 5.5–6.1 μ



| Cpd. | $R_1$ | $R_2$ | $R_3$ | Position(μ) of first absorption beyond 6μ. |
|---|---|---|---|---|
| 1[a] | $CH_3$ | $CH_3$ | H | 6.16s |
| 2[b] | $C_6H_5$ | $CH_3$ | H | 6.21m |
| 3[c] | $CH_3$ | H | H | 6.14s |
| 4[d] | $C_6H_5$ | H | H | 6.12s |
| 5[4] | $CH_3$ | Br | H | 6.16s |
| 6[e] | $CH_3$ | $CH_3$ | $C_6H_5$ | 6.25s |
| 7[f] | $CH_3$ | $CH_3$ | $CH_3$ | 6.23s |
| 8 | $C_6H_5$ | H | $CH_3$ | 6.38s |
| 9 | $CH_3$ | $C_6H_5$ | $CH_3$ | 6.27s |
| 10[g] | $CH_3$ | H | $C_6H_5$ | 6.21s |
| 11[h] | $CH_3$ | Br | $C_6H_5$ | 6.14s |
| 12[i] | $CH_3$ | Cl | $C_6H_5$ | 6.15s |

[a] P. E. Verkade and J. Dhont, *Rec. trav. chim.*, 64, 165 (1945). [b] K. V. Auwers and H. Mauss, *J. prakt. Chem.*, [2] 110, 221 (1925). [c] T. Curtius and R. Jay, *ibid.*, [2] **39**, 27 (1889). [d] T. Curtius, *ibid.*, [2] **50**, 508 (1895). [e] D. Biquard and P. Grammaticakis, *Bull. soc. chim. France*, **8**, 246 (1941). [f] K. V. Auwers and K. Bahr, *J. prakt. Chem.*, [2] 116, 65 (1927). [g] A. Michael, *Am. Chem. J.*, 14, 481 (1892). [h] Ref. *c* of Table I. [i] Ref. *d* of Table I.

*Anal.* Calcd. for $C_{11}H_8N_2O_2Cl_2$: C, 48.73; H, 2.98. Found: C, 49.04; H, 2.86.

(B).—By warming on a hot-plate 2.5 g. of 3-phenyl-4,4-dichloro-2-pyrazolin-5-one[2] was dissolved in 8 ml. of acetic anhydride. After standing for two hours at room temperature, 4 ml. of acetic acid was added followed by the gradual addition of 25 ml. of water. The crude pyrazolone [2.5 g. (84.5%), m.p. 119–135°] was recrystallized from ethanol, m.p. 146–148°. The melting point was not depressed on admixture with the pyrazolone obtained by procedure A.

**1-Acetyl-3-phenyl-4,4-dibromo-2-pyrazolin-5-one.**—Bromination of 1-acetyl-3-phenyl-2-pyrazolin-5-one[6] and acetylation of the dibromination product[4] of 3-phenyl-2-pyrazolin-5-one as described for the corresponding chloro derivative gave the same substance, m.p. and mixed m.p. 187–189° (from acetic acid).

*Anal.* Calcd. for $C_{11}H_8N_2O_2Br_2$: C, 36.69; H, 2.24. Found: C, 37.10; H, 2.16.

**1,4,4-Trichloro-3-phenyl-2-pyrazolin-5-one.**—A suspension of 1.8 g. of 3-phenyl-4,4-dichloro-2-pyrazolin-5-one[2] in 20 ml. of acetic acid was treated with a stream of dry chlorine until the solid dissolved and a definite excess of chlorine was present. Dropwise addition of water caused the precipitation of 1.5 g. (72.5%) of lemon-yellow crystals, m.p. 85–90°. The pyrazolone was recrystallized by solution at room temperature or very slightly above in 5–7 ml. of chlorine-saturated acetic acid followed by immediate precipitation by dropwise addition of one volume of water which gave 1.3 g. (62.8%) of the trichloro compound, m.p. 89–91°. The analytical sample from acetic acid–water (10:1) had m.p. 90–92°.

*Anal.* Calcd. for $C_9H_5N_2OCl_3$: C, 41.02; H, 1.91. Found: C, 40.80; H, 2.20.

The trichloropyrazolone was readily soluble in warm ligroin (b.p. 60–90°), although some decomposition apparently occurred as the lemon-yellow crystals which separated had an erratic melting point behavior (m.p. 85–92°). Attempted recrystallization from ethanol was accompanied by vigorous spontaneous boiling, evolution of acetaldehyde

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(10) 1,3-Diphenyl-2-pyrazolin-5-one and various of its 4-substitution products are apparently exceptions since they exhibit strong absorptions near 5.85 μ [P. E. Gagnon, J. L. Boivin and R. J. Paquin, *Can. J. Chem.*, **31**, 1025 (1953)].

(11) We are indebted to Dr. L. F. Johnson of Varian Associates for aid in the determination and interpretation of the n. m. r. spectrum. The spectrum was determined in deuteriochloroform. A large sharp peak at 244 cycles (relative to an external benzene sample) is assigned to the protons of the methyl group. The structure proposed by Huttel, *et al.*, is ruled out by absence of a peak corresponding to a CHBr proton. A broad peak at −190 cycles is assigned to an N–H proton broadened by the quadrupole moment of the $N^{14}$ nucleus. A considerable sharpening of this signal was noted when the double-resonance technique was used to eliminate quadrupole broadening. Complete elimination of the broadening was not observed. It is not possible to say at present whether this is due to insufficient power in the double resonance apparatus to completely cancel the effects of the $N^{14}$ nucleus or to the effect of keto–enol exchange.

(12) Melting points are uncorrected.

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

(14) 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.

(odor) and the separation on cooling of the corresponding dichloropyrazolone, m.p. and mixed m.p. 173–175° dec.

**Chlorination of 3-Phenyl-5-acetoxypyrazole.**—A solution of 0.6 g. of the pyrazole[6] in 5 ml. of acetic acid was treated with a stream of chlorine until a definite excess was present. The solution was allowed to stand for 10 min. and barely brought to the cloud point by the dropwise addition of water which precipitated 0.5 g. (64%) of yellow crystals, m.p. 84–86° (cloudy melt). Recrystallization from acetic acid and water as described directly above gave small lemon-yellow needles, m.p. and mixed m.p. with 1,4,4-trichloro-3-phenyl-2-pyrazolin-5-one, 88–91°.

**3,4-Dimethyl-4-chloro-2-pyrazolin-5-one.**—A suspension of 20 g. of 3,4-dimethyl-2-pyrazolin-5-one (ref. *a* of Table II) in 40 ml. of nitromethane was treated with a stream of chlorine until the solid dissolved and a yellow-green color remained (15–20 min.). The solution, after standing for two hours, was evaporated from a steam-bath with the aid of a water aspirator. The residual oil crystallized on standing in a refrigerator overnight. By solution in warm benzene and precipitation with petroleum ether (b.p. 30–60°), 19.5 g. (74.5%) of white powder was obtained, m.p. 50–54°. Recrystallization from the same solvent pair gave 16.5 g. (63%) of white crystals, m.p. 57–59°.

*Anal.* Calcd. for $C_5H_7N_2OCl$: C, 40.96; H, 4.81. Found: C, 40.70; H, 4.62.

The same substance, m.p. and mixed m.p. 57–59°, was obtained when the chlorination was carried out in boiling chloroform following the directions of Huttel, *et al.*,[5] who report a hygroscopic monochloro derivative of m.p. 104° (no elemental analysis is given).

**1-Acetyl-3,4-dimethyl-4-chloro-2-pyrazolin-5-one.** (A).—A solution of 2 g. of 1-acetyl-3,4-dimethyl-2-pyrazolin-5-one[15] (ref. *a* of Table II) in 6 ml. of acetic acid was treated with a stream of chlorine until an excess was present. After evaporation of the solution by means of a water aspirator and a steam-bath the residual oil was allowed to stand in an ice-chest overnight whereupon 1.4 g. (57.2%) of white solid formed, m.p. 46–48°. Recrystallization from petroleum ether (b.p. 30–60°) gave tiny white needles, m.p. 51–53°.

(B).—A solution of 1.5 g. of 3,4-dimethyl-4-chloro-2-pyrazolin-5-one in 5 ml. of acetic anhydride was heated in a water-bath (90–95°) for 12 hours. The excess anhydride was removed from a steam-bath with the aid of a water aspirator. The oil which solidified on cooling was recrystallized from benzene–petroleum ether (30–60°) which gave 0.6 g. (31.1%) of tiny white needles, m.p. 51–53°. No depression was observed on admixture with the substance formed in A.

*Anal.* Calcd. for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81. Found: C, 44.82; H, 4.81.

**1-Acetyl-3-phenyl-4-methyl-2-pyrazolin-5-one.**—A mixture of 5 g. of 3-phenyl-4-methyl-2-pyrazolin-5-one (ref. *b* of Table II) and 10 ml. of acetic anhydride was warmed on a steam-bath for 5 min. and allowed to stand overnight, diluted with 80 ml. of water and stirred well. After standing for one hour the solid which had formed was filtered and recrystallized at once from ethanol which gave 5 g. (80.6%) of small white crystals, m.p. 65–68°. Recrystallization from ligroin (60–90°) gave 4.6 g. (74.2%) of the acetyl derivative, m.p. 77–79.5°. The analytical sample melted at 78–80° (ligroin).

*Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.60. Found: C, 66.40; H, 5.50.

**1-Acetyl-3-phenyl-4-methyl-4-chloro-2-pyrazolin-5-one.** (A).—Chlorination of 2.5 g. of 1-acetyl-3-phenyl-4-methyl-2-pyrazolin-5-one in 8 ml. of acetic acid by the method described above gave 2.3 g. (79.3%) of small white crystals, m.p. 108–112° (softening at 104°). Recrystallization from ligroine (b.p. 60–90°)–benzene (1:1) gave block-like crystals, m.p. 115–117°.

*Anal.*: Calcd. for $C_{12}H_{11}O_2N_2Cl$: C, 57.49; H, 4.42. Found: C, 57.82; H, 4.53.

(B).—A solution of 0.75 g. of 3-phenyl-4-methyl-4-chloro-2-pyrazolin-5-one[3] in 5 ml. of acetic anhydride was heated on a steam-bath for 12 hours, diluted with 80 ml. of water and the crystalline white solid (0.5 g., 55.5%) recrystallized from nitromethane, m.p. 115–117°. No depression of the melting point was observed on admixture with the compound formed by method A above.

**1,4-Dichloro-3,4-diphenyl-2-pyrazolin-5-one.**—A solution of 4 g. of 4,5-diphenyl-3-pyrazolidone[3] in 30 ml. of acetic acid was treated with a stream of chlorine until an excess was present (10–15 min.). After standing at room temperature for 15 min. the solution was diluted to 100 ml. with water which caused separation of an oil which rapidly solidified. Recrystallization from nitromethane gave 2.6 g. (57%) of greenish-yellow crystals, m.p. 127–128° dec. The analytical sample was crystallized from ligroin (60–90°)–benzene (1:1), m.p. 129.5–131.5° dec.

*Anal.* Calcd. for $C_{15}H_{10}N_2OCl_2$: N, 9.18; Cl, 23.24. Found: N, 9.11; Cl, 22.89.

**1-Methyl-3-phenyl-2-pyrazolin-5-one.**—A mixture of 3.84 g. of ethyl benzoylacetate and 0.92 g. of methylhydrazine was warmed slightly in a water-bath. A vigorous reaction set in and continued for 1–2 min. whereupon a solid mass suddenly separated. The solid was triturated with ethanol which gave 2.3 g. (68.6%) of tiny white crystals, m.p. 214–217°. The pyrazolone was recrystallized from nitromethane–dimethylformamide which gave shimmering white crystals, m.p. 214–216°.

*Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79. Found: C, 69.00; H, 5.79.

**1,3-Dimethyl-4-phenyl-2-pyrazolin-5-one.**—A mixture of 4.4 g. of isopropyl $\alpha$-phenylacetoacetate and 0.92 g. of methylhydrazine was shaken briefly. Spontaneous warming occurred accompanied by separation of 3 g. of white solid, m.p. 80–88°. Attempted crystallization from ethanol gave white flakes with an erratic melting behavior (m.p. 85–93°). This substance, which was not purified, may have been the corresponding hydrazone. Several crystallizations from (1) benzene–ethanol, (2) benzene–ethanol–ligroin (60–90°) and (3) methanol gave the pyrazolone as block-like crystals, m.p. 183–184.5°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.52; H, 6.21.

**3-Phenyl-4-methyl-4-bromo-2-pyrazolin-5-one.**—A suspension of 5 g. of 3-phenyl-4-methyl-2-pyrazolin-5-one in 50 ml. of methylene dichloride was treated during 5 min. with 4.59 g. of bromine. After standing for 20 min. the solution was allowed to evaporate in an open dish and the solid triturated with water. The air-dried solid (6 g.) was recrystallized from 40–50 ml. of nitromethane which deposited 4.8 g. (66%) of yellow needles, m.p. 168–175°. The analytical sample melted at 171–176° (nitromethane).

*Anal.* Calcd. for $C_{10}H_9N_2OBr$: C, 47.45; H, 3.58. Found: C, 47.36; H, 3.75.

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[15] When the acetyl derivative was prepared by the method of Verkade and Dhont it was obtained with m.p. 127–128.5° (lit. m.p. 126–127°, solidifying and remelting at 159–159.5°). Preparation of the acetyl derivative by solution of the pyrazolone in 2 parts by weight of acetic anhydride followed by cooling and recrystallization from benzene–60–90° ligroin or nitromethane gave small white crystals, m.p. 149–151.5°. The infrared spectrum (Nujol) of this material and that prepared by the method of Verkade and Dhont did not differ significantly.