# A New Synthesis of Unsaturated Acids. V. Application to Cycloalkene-1-carboxylic and β,γ-Unsaturated Acids[1]

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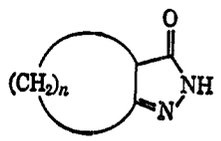
The method of converting 4-halo-4-substituted 2-pyrazolin-5-ones into α,β-unsaturated acids by treatment with aqueous alkali has been extended to the 3,4-polymethylene derivatives (II, X = Cl or Br; $n$ = 4–6) although the reaction was unsuccessful in the case of the trimethylene derivative (II, X = Cl or Br; $n$ = 3). It has also been possible to extend the reaction to the synthesis of β,γ-unsaturated acids. Treatment of 3-(bromomethyl)-4,4-dimethyl-2-pyrazolin-5-one (X) with sodium hydroxide gave 2,2-dimethyl-3-butenoic acid. The precursor (X) was obtained by treatment of ethyl γ-bromo-α,α-dimethylacetoacetate with hydrazine or NBS bromination of 1-acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (XIII).

Previous studies[2,3] have demonstrated the generality of the conversion of 4,4-dihalo- and 4-substituted 4-halo-2-pyrazolin-5-ones to α,β-unsaturated acids upon treatment with aqueous alkali. In the present paper we describe extensions of this reaction to two special cases, cycloalkene-1-carboxylic acids for which previously described synthetic methods[4–7] are not completely satisfactory, and β,γ-unsaturated acids. In view of the



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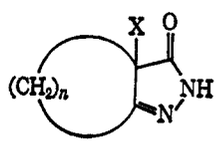
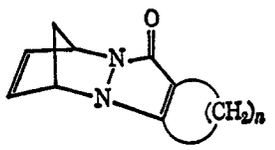


II

earlier demonstration[2b,3] that it is the labile isomer which predominates in the case of acyclic α,β-olefinic acids, it seemed possible that its application in the cyclic series might allow eventual development of a synthetic route to the unique, unknown *trans* isomers of the higher ring acids.[8] A series of 3,4-polymethylene-4-halo-2-pyrazolin-5-ones (II, X = Cl or Br, $n$ = 3–6) has been prepared and studied. The precursor β-keto esters were obtained from the corresponding cycloalkanones by methods cited in Table I. Halogenation of the pyrazolones was carried out by treatment with chlorine in methylene chloride, bromine in acetic acid, or, most conveniently, by the use of N-bromosuccinimide in carbon tetrachloride. Both the 4-chloro- and 4-bromo-3,4-trimethylene-2-pyrazolones (II, X = Cl or Br, $n$ = 3) were too unstable to be purified for elemental analysis. In the cases of the chloro and bromo derivatives of the 3,4-tetra-, -penta-, and -hexamethylene-2-pyrazolin-5-ones (II, X = Cl or Br, $n$ = 4–6) alkaline degradation gave the corresponding cycloalkene-1-carboxylic acids in moderate-to-fair yields, consistently better in the bromo series (30–70% in comparison with yields of 19–50% for the analogous chloro derivatives). In the case of the hexamethylene derivative (II, X = Cl or Br, $n$ = 6) only the known[9] *cis* acid was obtained. Thus the driving force[2b,3] favoring the labile isomer of a geometric pair of α,β-olefinic acids is not sufficient to overcome the natural reluctance of a 1-substituted cyclooctene to support the strained *trans* structure.[9,10] Whether the present method will be applicable to the synthesis of the larger ring *trans*-cycloalkene-1-carboxylic acids remains to be determined.

As in the previous work[3] it has been possible in two cases (II, X = Cl or Br, $n$ = 5,6) to demonstrate the labile intermediacy in these reactions of fused diazacyclopentadienones by trapping reactions with cyclopentadiene.[11] Curiously the 3,4-trimethylene derivative (II, X = Cl or Br, $n$ = 3) gave no cyclopentene-1-carboxylic acid. In this case treatment with aqueous alkali gave only a charcoal-like cindery material which could not be identified. In an effort to determine whether this effect was general for other pyrazolones bridged by three methylene units, attempts were made to obtain pyrazolones from 2-carbethoxy-1-indanone,[12] 1-carbethoxy-2-indanone[13] and 3-carbethoxycamphor[14] but in no case could the appropriate compounds be made by reaction of the β-keto esters with hydrazine. In addition trapping experiments with II (X = Cl or Br, $n$ = 3) in the presence of triethylamine and cyclopentadiene at −80° gave the same cindery material obtained at higher temperatures in the presence of aqueous alkali. However, in one case a trace of a crystalline white substance was isolated which on the basis of spectral data is believed to be the adduct (III, $n$ = 3) derived from the appropriate diazacyclopentadienone and cyclopentadiene. In the cases of the



III

(1) Abstracted from a portion of the Ph.D. thesis of E. G. S. Rundberg, Jr., 1967.

(2) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **80**, 599 (1958); (b) *ibid.*, **80**, 601 (1958); (c) *ibid.*, **80**, 5796 (1958).

(3) L. A. Carpino, P. H. Terry, and S. D. Thatte, *J. Org. Chem.*, **31**, 2867 (1966).

(4) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950).

(5) E. A. Braude, W. F. Forbes, and E. A. Evans, *ibid.*, 2202 (1953).

(6) A. C. Cope, M. Burg, and S. W. Fenton, *J. Amer. Chem. Soc.*, **74**, 173 (1954).

(7) O. H. Wheeler and I. Lerner, *ibid.*, **78**, 63 (1956).

(8) The patent literature contains an unconfirmed report of the isolation of a pair of cycloundecene-1-carboxylic acids; see Pierre Lafont and Y. Bonnett, German Patent 1,145,169 (March 14, 1963); *Chem. Abstr.*, **59**, 7392*h* (1963).

(9) E. A. Braude, W. F. Forbes, B. F. Gofton, R. P. Houghton, and E. S. Waight, *J. Chem. Soc.*, 4711 (1957).

(10) *Cf.* A. C. Cope, E. Ciganek, C. F. Howell, and E. E. Schweizer, *J. Amer. Chem. Soc.*, **82**, 4663 (1960).

(11) Since our earlier studies B. T. Gillis and R. Weinkham [*J. Org. Chem.*, **32**, 3321 (1967)] have generated and trapped similar intermediates by the oxidation of pyrazolones with lead tetraacetate in the presence of cyclopentadiene.

(12) W. H. Perkin and A. F. Titley, *J. Chem. Soc.*, **121**, 1562 (1922).

(13) A. F. Titley, *ibid.*, 2571 (1928).

(14) T. F. Dankova, L. G. Evdokimova, I. I. Stepanov, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **18**, 1724 (1948); *Chem. Abstr.*, **43**, 2606 (1946).

TABLE I

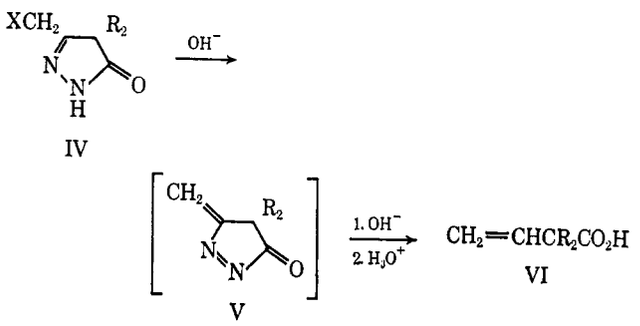
3,4-POLYMETHYLENE-2-PYRAZOLIN-5-ONES (II)[a-d]

| X | n | Yield, % | Mp, °C | Formula | Calcd, % | | | | Found, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Br (Cl) | C | H | N | Br (Cl) |
| Cl[e] | 3 | 79 | 117–118 dec | $C_6H_7ClN_2O$ | | | | | | | | |
| Br[e] | 3 | 53 | 102–103 dec | $C_6H_7BrN_2O$ | | | | | | | | |
| Cl | 4 | 58 | 112.5–113 | $C_7H_9ClNO_2$ | 48.71 | 5.25 | 16.23 | (20.54) | 48.59 | 5.25 | 16.02 | (20.41) |
| H | 5 | 96 | 211–212 dec | $C_8H_{12}N_2O$ | 63.14 | 7.94 | 18.46 | | 63.28 | 8.03 | 18.42 | |
| Cl | 5 | 40 | 54–55.5 | $C_8H_{11}ClN_2O$ | 51.48 | 5.94 | 15.00 | (18.99) | 51.36 | 6.02 | 14.80 | (18.79) |
| Br | 5 | 61 | 80–80.5 | $C_8H_{11}BrN_2O$ | 41.58 | 4.80 | 12.12 | 34.58 | 41.70 | 4.81 | 11.98 | 34.44 |
| H | 6 | 88 | 230–232 dec | $C_9H_{14}N_2O$ | 65.03 | 8.48 | 16.86 | | 65.03 | 8.36 | 16.93 | |
| Cl | 6 | 69 | 73–75 | $C_9H_{13}ClN_2O$ | 53.88 | 6.53 | 13.96 | (17.67) | 53.97 | 6.73 | 13.83 | (17.53) |
| Br | 6 | 79 | 85.5–86.3 | $C_9H_{13}BrN_2O$ | 44.10 | 5.34 | 11.43 | 32.60 | 44.23 | 5.51 | 11.37 | 32.53 |

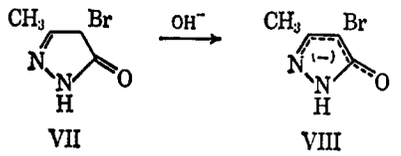
[a] The 4-unsubstituted 3,4-polymethylene-2-pyrazolin-5-ones were obtained by modifications of standard techniques; see W. Dieckmann, *Ann.*, **317**, 60 (1901). [b] Chlorination was carried out using molecular chlorine in methylene chloride; bromination by means of molecular bromine in acetic acid or N-bromosuccinimide in carbon tetrachloride. The yields given in the table are those obtained by the latter method. An example is given in the Experimental Section. [c] The precursor 2-carbethoxycycloalkanones were obtained by three general methods: (1) the Stork enamine technique [$n$ = 4; G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963)]; (2) carbethoxylation by diethyl carbonate–sodium hydride [$n$ = 4, 5, 6; S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963)]; and (3) carbethoxylation by triethyl phosphonoformate-sodium hydride [$n$ = 4; I. Shahak, *Israel J. Chem.*, **3** (No. 4a), 45 (1966); *Tetrahedron Lett.*, 2201 (1966)]. [d] The halopyrazolones were recrystallized from benzene–ligroin. [e] This compound was too unstable to be purified for elemental analysis. Spectral data (infrared and nmr) confirmed the structure.

penta- and hexamethylene pyrazolones no difficulty was experienced in obtaining the corresponding adducts (III, $n$ = 5 or 6).

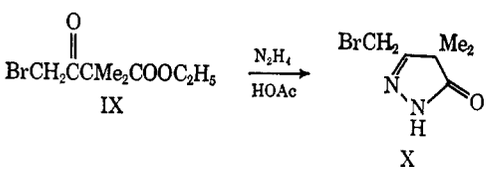
The second extension of the halopyrazolone reaction examined in the present work involved its possible use in the synthesis of acids having unsaturation at the $\beta,\gamma$ position. By assuming a mechanism analogous to that which has been demonstrated to be likely in the case of 4-substituted 4-halopyrazolones it would be expected that a 3-(halomethyl) derivative such as IV would yield the corresponding $\beta,\gamma$-olefinic acid VI




through the intermediacy of the methylene diazacyclopentenone V. As a model a 4,4-disubstituted pyrazolone was chosen in order to avoid possible complication due to the formation of a stable anion from a 4-substituted pyrazolone. Thus, in contrast to the cases of 3,4-dimethyl-4-bromo- and 3-methyl 4,4-dibromo-2-pyrazolin-5-ones, 3-methyl-4-bromo-2-pyrazolin-5-one[15] (VII) does not undergo the alkaline degradation reaction presumably because of the stability of anion VIII, from which loss of bromide ion is precluded.




An appropriate substrate, 3-(bromomethyl)-4,4-dimethyl-2-pyrazolin-5-one (IV, X = Br; R = $CH_3$), was obtained by two procedures, one of which promises to be of general utility. The first approach involved the carefully controlled reaction of ethyl $\gamma$-bromo-$\alpha,\alpha$-dimethylacetoacetate (IX) with hydrazine in ethanol in the presence of acetic acid.[16] Since the method was

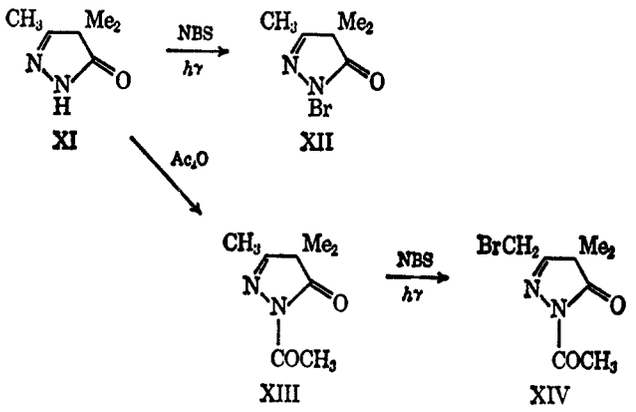



tedious and the yield poor, other approaches were sought. Although direct NBS bromination of 3,4,4-trimethyl-2-pyrazolin-5-one (XI) gave the N-bromo derivative (XII)[17] as expected, use of the N-acetyl derivative (XIII) allowed bromination at the 3-methyl group. Unexpectedly the 3-bromomethylpyrazolone (X) was obtained directly, the first-formed N-acetyl derivative XIV being presumably hydrolyzed during the reaction or the subsequent work-up. Treatment

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

(16) This method was first applied by Paul H. Terry (Ph.D. Thesis, University of Massachusetts, 1963).

(17) R. Hüttel, E. Wagner, and B. Sickenberger, *Ann.*, **607** 109 (1957).




of X with aqueous sodium hydroxide at 0° was accompanied by vigorous gas evolution and gave 2,2-dimethyl-3-butenoic acid in 37% yield. No direct evidence has yet been obtained relative to the postulated occurrence of V as a labile intermediate in this reaction.

## Experimental Section[18]

**4-Bromo-3,4-tetramethylene-2-pyrazolin-5-one (II, X = Br, $n$ = 4).**—A suspension of 1.38 g of 3,4-tetramethylene-2-pyrazolin-5-one[19] and 1.78 g of N-bromosuccinimide in 80 ml of $CCl_4$ was stirred for 2 hr while irradiating with a 275-W sun lamp (Westinghouse). The reaction mixture was cooled, filtered and the filtrate evaporated from a water bath with the aid of a water aspirator to give an orange solid. The solid was treated successively with eight 50-ml portions of hot ligroin (bp 60–70°), the ligroin evaporated and the resulting solid recrystallized from benzene–ligroin (bp 60–70°) (1:9) to give 1.43 g (66.9%) of the pyrazolone as pale yellow platelets: mp 126.5–128°; ir ($CHCl_3$) 3475, 1725, 1610 $cm^{-1}$; nmr ($CDCl_3$) δ 1.10–2.85 (complex multiplet, 8 H), 9.95 (broad singlet, 1 H). Related compounds were made similarly. Chlorination was carried out as previously described.[2] In most cases bromination could be carried out with free bromine in acetic acid but the products were less easily purified than those obtained by the NBS procedure given here. The results are collected in Table I.

*Anal.* Calcd for $C_7H_9BrN_2O$: C, 38.73; H, 4.18; Br, 36.81; N, 12.90. Found: C, 38.86; H, 4.33; Br, 36.65; N, 12.75.

**7,8-Pentamethylene-1,4-methano-1,4-dihydropyrazolo[1,2-a]-pyridazin-6-one (III, $n$ = 5).**—To a stirred, ice-cold solution of 2.31 g of 4-bromo-3,4-pentamethylene-2-pyrazolin-5-one and 3.3 g of freshly cracked cyclopentadiene in 100 ml of anhydrous ether there was added 1.21 g of triethylamine. After 2 hr in the ice bath, the mixture was filtered and the filtrate evaporated to give a solid which was dissolved in the minimum amount of ether and the solution cooled in a Dry Ice–acetone bath. Rapid filtration gave 1.04 g (48%) of the adduct as pale yellow flakes: mp 117.5–118.3° dec; ir ($CHCl_3$) 1645, 1605, 2990, 2930, 2860 $cm^{-1}$; nmr ($CDCl_3$) δ 1.0–2.73 (complex multiplet, 12 H), 4.73 (broad singlet, 1 H), 5.08 (broad singlet, 1 H), 5.80–5.95 (multiplet, 1 H), 6.00–6.20 (multiplet, 1 H).

*Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.40; H, 7.59; N, 13.11.

**7,8-Pentamethylene-1,4-methano-1,2,3,4-tetrahydropyrazolo-[1,2-a]pyridazin-6-one.**—Hydrogenation of the above adduct in THF over 10% Pd–C on a Parr apparatus at 46 psi gave the dihydro derivative: mp 116–117° (methylene chloride–petroleum ether, bp 30–59°); ir ($CHCl_3$) 1615, 2980, 2940, 2870 $cm^{-1}$; nmr ($CDCl_3$) δ 1.0–2.85 (complex multiplet, 16 H), 4.48 (broad singlet, 1 H), 4.77 (broad singlet, 1 H). The same compound, identified by infrared spectral comparison, was obtained by reaction of 2-carbethoxycycloheptanone,[20,21] with 2,3-diazabicyclo[2.2.1]heptane hydrochloride.[3,22]

*Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.36; H, 8.25; N, 13.01.

**7,8-Hexamethylene-1,4-methano-1,4-dihydropyrazolo[1,2-a]-pyridazin-6-one (III, $n$ = 6)** was obtained as described for the corresponding pentamethylene analog, mp 98–98.5°.

*Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.93; H, 8.03; N, 12.06.

***cis*-Cyclooctene-1-carboxylic Acid.**—Treatment of 4-bromo-3,4-hexamethylene-2-pyrazolin-5-one (II, X = Br; $n$ = 6) with ice-cold aqueous NaOH as described earlier[2] gave *cis*-cyclooctene-1-carboxylic acid in 65.7% yield, mp 100.5–102° (lit.[6] mp 101.8–102.6°). From the corresponding chloro derivative the yield was 46.7%. The related cyclohexene- and cycloheptene-1-carboxylic acids were obtained similarly in 29.8 and 70% yields from the bromopyrazolones and 19 and 50% yields from the chloropyrazolones, respectively.

**1-Acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (XIII).**—A solution of 12.6 g of 3,4,4-trimethyl-2-pyrazolin-5-one[23] in 50 ml of acetic anhydride was refluxed for 6 hr, the mixture cooled, excess anhydride removed by evaporation from a water bath with the aid of a water aspirator and the residue recrystallized from ligroin (bp 60–70°) to give 14.6 g (86.9%) of the 1-acetyl derivative[24] as yellow needles: mp 112–113°; ir ($CHCl_3$) 1785, 1755, 1720 $cm^{-1}$; nmr ($CDCl_3$) δ 1.35 (singlet, 6 H), 2.15 (singlet, 3 H), 2.57 (singlet, 3 H).

*Anal.* Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 57.29; H, 7.33; N, 16.46.

**3-Bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (X). A.—From 1-Acetyl-3,4,4-trimethyl-2-pyrazolin-5-one.**—A stirred solution of 8.40 g of the 1-acetylpyrazolone and 9.79 g of N-bromosuccinimide in 200 ml of $CCl_4$ was irradiated with a 275-W sun lamp (General Electric) for 10.5 hr. The mixture was cooled, succinimide removed by filtration and the residue obtained on evaporation of the filtrate by means of a current of air was recrystallized from benzene–ligroin (bp 60–70°) to give 4.67 g (53%) of the pyrazolone as pale yellow needles, mp 135.5–137°.

**B.[16] From Ethyl γ-Bromo-α,α-dimethylacetoacetate.**—To a stirred solution of 47.4 g of the β-keto ester[25] and 12.5 g of acetic acid in 180 ml of 60% aqueous ethanol there was added dropwise over 30 min a solution of 10 g of hydrazine hydrate (100%) in 60 ml of ethanol. The solution was stored in a refrigerator at 5° for 17 days, treated with 175 ml of water and extracted with 800 ml of ether in a liquid–liquid extractor for 3 days. Recrystallization of the residue obtained after evaporation of the ether extracts gave 16.4 g (40%) of the bromomethylpyrazolone, mp 135–136.5°, identified by comparison with a sample prepared as described in A: ir ($CHCl_3$) 3400, 1735 $cm^{-1}$; nmr ($CDCl_3$) δ 1.40 (singlet, 6 H), 4.21 (singlet, 2 H) and 10.06 (broad singlet, 1 H).

*Anal.* Calcd for $C_6H_9BrN_2O$: C, 35.14; H, 4.92; Br, 38.97; N, 13.66. Found: C, 35.33; H, 4.58; Br, 38.96; N, 13.57.

**2,2-Dimethyl-3-butenoic Acid.**—To an ice cold, stirred solution of 50 ml of 2 *N* NaOH there was added 4.1 g of 3-bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (X). The reaction mixture was stirred for 1 hr at ice bath temperatures and for 2 hr at room temperature. Acidification by means of concentrated HCl (Congo red), saturation with NaCl and extraction with eight 25-ml portions of ether gave 0.84 g (36.8%) of the acid after distillation, bp 184–187° (lit.[26] bp 185°). The *dibromo derivative* had mp 90–91.5° (lit.[27] mp 89–91°).

**Registry No.**—II, X = Cl, $n$ = 3, 19462-57-8; II, X = Br, $n$ = 3, 19462-58-9; II, X = Cl, $n$ = 4, 19462-59-0; II, X = Br, $n$ = 4, 19462-60-3; II, X = H, $n$ = 5, 19462-61-4; II, X = Cl, $n$ = 5, 19462-62-5; II, X = Br, $n$ = 5, 19462-63-6; II, X = H, $n$ = 6, 19462-64-7; II, X = Cl, $n$ = 6,

(18) Elemental analyses are by A. Bernhardt, Mülheim (Ruhr), Germany. All melting and boiling points are uncorrected. Infrared spectra were recorded on Beckman IR-5 and IR-10 spectrophotometers. Nmr data were obtained on a Varian A-60 instrument in deuteriochloroform using TMS as internal standard.

(19) W. Dieckmann, *Ann.*, **317**, 60 (1901).

(20) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

(21) C. E. Sullivan, M. S. Thesis, Florida State University, 1962.

(22) O. Diels, J. H. Blom, and W. Koll, *Ann.*, **443**, 242 (1925).

(23) P. E. Verkade and J. Dhont, *Rec. Trav. Chim. Pays-Bas*, **64**, 165 (1945).

(24) A compound presumed to have structure XIII was first described by von Rothenberg [*J. Prakt. Chem.*, [2] **50**, 227 (1894)] but his formulation has now been shown to be incorrect. von Rothenberg claimed to have obtained XIII from the precursor XI which he described as having mp 268°. Subsequently Verkade and Dhont[23] showed that authentic XI had mp 108.5–109.5°.

(25) M. Conrad and R. Gast, *Ber.* **31**, 2726 (1898).

(26) A. Courtot, *Bull. Soc. Chim. Fr.*, [3] **35**, 111 (1906).

(27) H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, **76**, 5403 (1954).

19462-65-8; II, X = Br, $n$ = 6, 19462-66-9; III, $n$ = 5, 19462-67-0; 7,8′-pentamethylene-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-$a$]pyridozin-6-one, 19462-68-1; III, $n$ = 6, 19462-69-2; X, 19462-70-5; XIII, 19462-71-6.

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# The Lithium Aluminum Hydride Reduction Products from Heterocycles Containing an Isoindolone Nucleus

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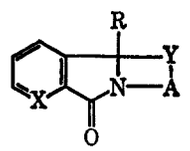
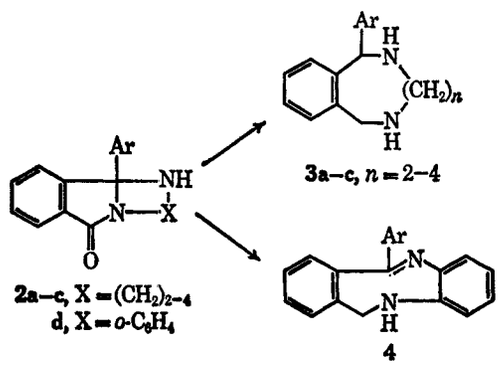
The lithium aluminum hydride reduction of a number of fused isoindolones (**1**) has been carried out in refluxing diethyl ether or tetrahydrofuran. Product composition was dependent on the type of heteroatom Y and the size of the fused ring A. All compounds where Y = O (**5a–c, 8, 11**) gave isoindolines as the major product while those with Y = NR (**13b** and **c, 26**) gave isoindoles. When Y = NH the products were either medium-sized heterocycles (**14** and **23**) or isoindoles (**15c** and **d, 19, 22a–c**). A mechanism is proposed to account for the variation in product composition.

Recent studies have demonstrated that the reaction of 2-alkanoyl or 2-aroylbenzoic acids with amino alcohols,[1a,b] diamines,[1b–g] mercaptoamines,[1b,h] anthranilic acid,[1i] anthranilamides,[1i] and salicylamides[1i] is a convenient method for preparing heterocycles containing an isoindolone nucleus. The types of ring systems that have been obtained by this procedure are exemplified by **1**.



**1**, A = $(CH_2)_{2-4}$, $o$-$C_6H_4$, $o$-$COC_6H_4$; R = alkyl, aryl; X = CH or N; Y = NH, NR, O, S

The lithium aluminum hydride ($LiAlH_4$) reduction of some ring systems of type **1** has recently been reported. Compounds **2a–c** are reported[1c,e,f,2] to give the medium-sized heterocycles **3a–c** while **2d**[3] is reported to give dibenzo[$b$,$f$][1,4]diazocines[1c] **4**.




(1) (a) T. S. Sulkowski, U. S. Patent 3,336,306 (Aug 15, 1967); (b) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 165 (1969); (c) American Home Products Corp., Netherlands Patent Appl. 6,403,794 (1964); *Chem. Abstr.*, **63**, 9972 (1965); (d) J. R. Geigy, A.-G., Belgian Patent 659,530 (Aug 10, 1965); *Chem. Abstr.*, **64**, 664 (1966); (e) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebolt, *J. Org. Chem.*, **32**, 2180 (1967); (f) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967); (g) W. J. Houlihan, U. S. Patents 3,329,684 (July 4, 1967) and 3,334,113 (Aug 1, 1967); (h) J. R. Geigy, A.-G. Belgian Patent 659,528 (Aug 10, 1965); *Chem. Abstr.*, **64**, 3545 (1966); (i) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 2402 (1968).

(2) Sandoz, Ltd., Netherlands Patent Appl. 6,614,399 (April 19, 1967); *Chem. Abstr.*, **68**, 3861 (1968).

(3) These compounds are incorrectly reported as 11-aryldibenzo[$b$,$f$][1,4]-diazocin-6(5H)-ones in ref 1c. Evidence for structure **2d** is given in ref 1b.

In this work we present our findings on the products obtained when various **1** are treated with excess lithium aluminum hydride in refluxing diethyl ether or tetrahydrofuran.

Reduction of oxazolo[2,3-$a$]isoindol-5(9bH)-one **5a** with excess $LiAlH_4$ in refluxing diethyl ether gave the known[3] **6a**. Treatment of oxazino[2,3-$a$]isoindol-6-one **5b** and oxazepino[2,3-$a$]isoindol-6-one **5c** in a similar manner gave hydroxyalkyl isoindolines **6b** and **6c**. In addition phthalimidine **7** was isolated from the reduction of **5c**. As with **6a** the three benzylic protons in **6b** and **6c** produced an $H_AH_BCNCH_C$ nmr pattern that exhibited long-range spin–spin interactions[4] between $H_C$ and $H_AH_B$.

Reduction of isoindolo[1,2-$b$][1,3]benzoxazine-10,12-dione **8a** in refluxing tetrahydrofuran gave, after chromatography on silica gel, two products. The minor product was the known 3-methylphthalimidine **9a** and the major product has been assigned structure **10** based on nmr data. Reduction of the 9a-phenyl analog (**8b**) of **8a** gave as the only isolable product the known 3-phenylphthalimidine **9b**.

When **11** was reduced with LAH in refluxing tetrahydrofuran there were obtained after chromatography on silica gel two novel compounds in approximately equal quantities. The more polar substance was a blue oil that decomposed before identification could be completed. The nmr spectrum of the less polar compound gave the long-range coupled $CH_CNCH_AH_B$ system and other nmr data in agreement with isoindoline structure **12** (Chart I).

Treatment of imidazo[2,1-$a$]isoindol-5-one **13a** with $LiAlH_4$ in diethyl ether gave the previously reported[1e,2,5] 2,5-benzodiazocine **14a**. When the 1-methyl-9b-phenyl and 1-ethyl-9b-phenyl analogs (**13b–c**) of **13a** were reduced under similar conditions none of the eight-membered analogs of **14a** were obtained. Instead, the unstable 1-phenyl-2-N-alkylaminoethylisoindoles **15a**

(4) Long-range proton spin–spin interactions in the isoindoline system have been reported.[1b,e,f] A recent communication indicates the $J$ values for this type of interaction is influenced by the group attached to the isoindoline nitrogen atom; J. T. Gerig, *Tetrahedron Lett.*, 4625 (1967).

(5) An independent synthesis of this compound has been given by D. H. Kim, A. A. Santilli, T. S. Sulkowski, and S. J. Childress, *J. Org. Chem.*, **32**, 3720 (1967).