N-Carbobenzoxy-S-acetyl-L-cysteinylglycylglycine Ethyl Ester (VIII).—This compound was prepared from N-carbobenzoxy-L-β-chloroalanylglycylglycine ethyl ester (VI) (0.4 g, 1 mmole) in the same manner as described for the preparation of compound (II) (method A); yield 0.4 mg (91%); mp 128°; $[\alpha]^{25}D$ −42.4° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{19}H_{25}N_3O_7S$: C, 51.93; H, 5.73; N, 9.56; S, 7.28. Found: C, 52.23; H, 5.88; N, 9.25; S, 7.23.

A neutral equivalent of 435 was found by iodine titration after alcoholysis of the S-acetyl group.

N-Carbobenzoxyglycyl-S-acetyl-L-cysteinylglycine Ethyl Ester (XI).—To a solution of 0.4 ml of thioacetic acid in 5 ml of ethyl acetate, 0.7 ml of triethylamine and 0.4 g (1 mmole) of compound (IX) were added. The solution was allowed to stand for 3 hr at 50°, and was diluted with ethyl acetate. The triethylamine hydrochloride (131 mg, 96%) was filtered and the solution was washed with 0.5 *N* hydrochloric acid, water and 1 *N* sodium hydrogen carbonate, water, and dried over sodium sulfate. Removal of the solvent yielded a crystalline residue which was triturated with ether and recrystallized from ethyl acetate–petroleum ether; yield 0.35 g (80%); mp 94°; $[\alpha]^{25}D$ −29° (*c* 1.5, dimethylformamide) [lit.[2] mp 92–95°; $[\alpha]^{19}D$; −28.6° (*c* 1.5, dimethylformamide)].

Anal. Calcd for $C_{19}H_{25}N_3O_7S$: C, 51.93; H, 5.73; N, 9.56; S, 7.28. Found: C, 51.75; H, 5.51; N, 9.53; S, 7.39.[13]

N-Carbobenzoxyglycylglycyl-S-acetyl-L-cysteinylglycylglycine Ethyl Ester (XII).—This compound was prepared from N-carbobenzoxyglycylglycyl-L-β-chloroalanylglycylglycine ethyl ester (X, 0.25 g, 0.5 mmole) in the same manner as described for the preparation of compound XI (methods A, B). The product was recrystallized from ethyl acetate; yield 0.24 g (87%); mp 172°; $[\alpha]^{25}D$ −17.2° (*c* 1, dimethylformamide).

(13) A yield of 78% was found when the reaction was performed by method IIB.

Anal. Calcd for $C_{23}H_{31}N_5O_9S$: C, 49.90; H, 5.60; N, 12.66; S, 5.79. Found: C, 49.58; H, 5.90; N, 12.82; S, 5.99.

A neutralization equivalent of 568 was determined by iodine titration after alcoholysis of the S-acetyl group.

Nonaqueous Titration of Chloroalanyl Peptides.—The chloroalanyl peptide (0.1–0.2 mmole) is treated with a known volume of standardized 0.1 *M* sodium methoxide solution in methanol–benzene (1:3) in the presence of 1 drop of thymol blue (0.5% in dioxane). The mixture is stirred until all peptide dissolves. Sometimes light heating is recommended to facilitate the reaction. After 3 min the solution is titrated back to the red end point of the indicator with a standard solution of 0.1 *N* perchloric acid in dioxane. The molecular weight of the compound is calculated according to the formula: mol wt = mg × 10/ml; mg = weight of sample, ml = milliliters of 0.1 *N* sodium methoxide consumed. The accuracy of the method is 2–3%. The method is based on the formation of sodium chloride during the β-elimination reaction which chloroalanine peptides undergo when treated with sodium methoxide.

Argentometric Determination of Chloroalanyl Peptides.—The chloroalanyl peptide (0.02–0.1 mmole) is treated with 1 *N* NaOH (2 ml) with light heating. After 3 min, 2 ml of 6 *N* nitric acid and a known volume of standard 0.01 *N* silver nitrate are added. The mixture is shaken and warmed to coagulate and 0.05 ml of saturated ferric alum solution is added. The residual silver nitrate is titrated back with 0.01 *N* thiocyanate solution. The molecular weight calculation is performed as described above. The accuracy of the method is 2–4%.

Acknowledgment.—This investigation was supported by Grants No. AM-5098 and GM-11628 of the National Institute of Health, U. S. Public Health Service. The authors thank Professor Ephraim Katchalski for his interest in this work.

A New Synthesis of Unsaturated Acids. IV. Further Aspects of the Scope and Mechanism of the Conversion of Halopyrazolones to α,β-Acetylenic and Olefinic Acids[1]

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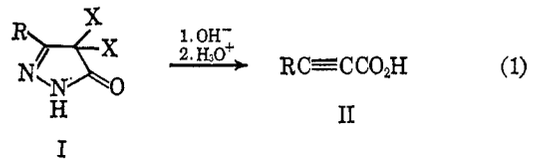
Additional examples are reported illustrating the generality of a new synthesis of α,β-acetylenic and α,β-olefinic acids which involves treatment of 3-substituted 4,4-dihalo- and 3,4-disubstituted 4-halopyrazolones with aqueous sodium hydroxide. By substituting triethylamine for sodium hydroxide it has been possible to demonstrate the transient formation of a diazacyclopentadienone intermediate which can be trapped in the presence of butadiene or cyclopentadiene as the appropriate Diels–Alder adducts. The structures of the adducts have been established by alternate syntheses.

Several years ago we reported a new method for the synthesis of α,β-acetylenic and α,β-olefinic acids which involved the alkaline degradation of 4,4-dihalo- and 4-substituted 4-halo-2-pyrazolin-5-ones, respectively (eq 1 and 2).[3] An interesting feature of this reaction in the case of its application to α,β-olefinic acids was the observation that in the three cases examined the labile isomer (*cis*-IVb) predominated in the mixture of *cis* and *trans* acids obtained. This was true for both α-phenyl- and α-methylcinnamic acid and for α-phenylcrotonic acid. In the present study we have further investigated the application of these



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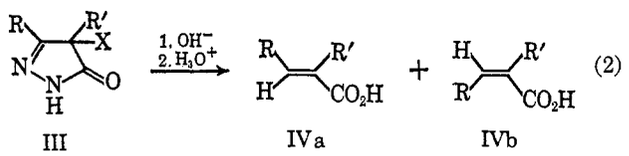


III IVa IVb (2)

reactions as a general synthetic route to α,β-acetylenic acids and particularly to the labile isomer of an α,β-olefinic pair. In addition it was hoped that at least the gross aspects of the mechanism of this novel reaction could be uncovered.

Three additional examples of the use of the method in the case of aliphatic α,β-acetylenic acids involved

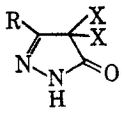
(1) Supported in part by grants from the U. S. Army Research Office (Durham). A portion of this work has appeared in preliminary form.[2] Taken in part from the Ph.D. thesis of P. H. T., University of Massachusetts, 1963.

(2) L. A. Carpino, P. H. Terry, and S. D. Thatte, *Tetrahedron Letters*, 3329 (1964).

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

TABLE I

CONVERSION OF 3-ALKYL-2-PYRAZOLIN-5-ONES TO 3-ALKYL-4,4-DIHALO-2-PYRAZOLIN-5-ONES



Run	R	X	Yield, %	Mp, °C	Recrystn solvent	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
1[a]	C_2H_5	Br	96	155–156 dec	Toluene	$C_5H_8Br_2N_2O$	22.25	22.33	2.24	2.22
2[b]	n-C_3H_7	Cl	100	53.5–54.5	Ligroin (bp 35–40°)	$C_6H_8Cl_2N_2O$	36.94	37.23	4.13	4.11
3[b]	n-C_3H_7	Br	77	83–84	Ligroin (bp 60–90°)[c]	$C_6H_8Br_2N_2O$	25.38	25.55	2.84	2.75
4[d]	t-C_4H_9	Br	94	152–154	Ligroin (bp 60–90°)	$C_7H_{10}Br_2N_2O$	28.21	28.41	3.38	3.30

[a] The precursor, mp 189–191°, was obtained in 83% yield by reaction of ethyl propionyl acetate with hydrazine hydrate in ethyl alcohol. *Anal.* Calcd for $C_5H_8N_2O$: C, 53.55; H, 7.19. Found: C, 53.32, H, 7.27. [b] The precursor, mp 203–205°, was obtained as in *a* in 95% yield. B. van der Ven, P. H. Begemann, and J. C. M. Schogt [*J. Lipid Res.*, **4**, 91 (1963)] report mp 195–199° for the precursor. [c] Because of the pronounced thermal instability of the dibromide, recrystallization was best effected by adding the pyrazolone to boiling ligroin (bp 60–90°), filtering at once, and cooling rapidly in an ice bath. [d] The precursor was obtained in 78% yield by the method of S. Veibel, K. Eggersen, and S. C. Linholt, *Acta Chem. Scand.*, **8**, 768 (1954).

TABLE II

FORMATION OF α,β-UNSATURATED ACIDS FROM 3,4-DISUBSTITUTED 4-HALO-2-PYRAZOLIN-5-ONES

Run	R_1	R_2	X	R_3	R_4	R_5	Yield,[k] %	Mp, °C	Recrystn solvent
1	CH_3	p-$CH_3OC_6H_4$	Br	CH_3	H	p-$CH_3OC_6H_4$	37 (46)	124–126[a]	Ligroin (bp 90–120°)
				H	CH_3	p-$CH_3OC_6H_4$	5 (7)	147–151[b]	Ligroin (bp 90–120°)
2	p-$NO_2C_6H_4$	CH_3	Cl	p-$NO_2C_6H_4$	H	CH_3	37 (50)	141–152.5[c]	Benzene–ligroin (bp 69–90°) (2:1)
				H	p-$NO_2C_6H_4$	CH_3	18.5	205.5–208[d]	Ethanol
3	C_6H_5	$C_6H_5CH_2$	Cl	C_6H_5	H	$C_6H_5CH_2$	14 (31)	103–105[e]	Ligroin (bp 90–120°)
				H	C_6H_5	$C_6H_5CH_2$	6 (13)	156–158[f]	Benzene–ligroin (bp 90–120°) (2:1)
4	p-$CH_3OC_6H_4$	CH_3	Br	p-$CH_3OC_6H_4$	H	CH_3	14 (30)	118–119[g]	Benzene–ligroin (bp 90–120°) (1:2)
				H	p-$CH_3OC_6H_4$	CH_3	9 (16)	154–156.5[h]	Benzene–ligroin (bp 90–120°) (1:1)
5	CH_3	p-$NO_2C_6H_4$	Cl	CH_3	H	p-$NO_2C_6H_4$	24 (31)	163.5–164.5[i]	Benzene–ligroin (bp 30–60°) (1:1)
				H	CH_3	p-$NO_2C_6H_4$	1.2 (4)	169–172[j]	Benzene–ligroin (bp 30–60°) (1:1)

[a] *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.92; H, 6.32. [b] *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.52; H, 6.19. [c] *Anal.* Calcd for $C_{10}H_9NO_4$: C, 57.96; H, 4.37. Found: C, 58.25; H, 4.53. [d] W. J. Gensler and E. Berman [*J. Am. Chem. Soc.*, **80**, 4949 (1958)] report mp 205–206.5°. Identified by comparison with an authentic sample. [e] F. Kögl and H. I. Becker [*Ann.*, **465**, 211 (1928)] report mp 100.5°. [f] Lit.[e] mp 157–158°. [g] R. M. da Costa [*Compt. Rend.*, **198**, 1996 (1934)] reports mp 113°. [h] Lit.[d] mp 154.5–155.5°. [i] *Anal.* Calcd for $C_{10}H_9NO_4$: C, 57.96; H, 4.37. Found: C, 58.13; H, 4.43. [j] Lit.[33] mp 174–175°. [k] Where different, the yield of crude product is given in parentheses.

the synthesis of ethyl- (72%), *n*-propyl- (71%), and *t*-butylpropiolic acid (57%). The precursor 4,4-dihalopyrazolones are described in Table I.

Since a mixture of geometric isomers is obtained from the 3,4-disubstituted 4-halopyrazolones, isolation of the desired *cis* acid in a state of purity often presents a serious problem. In the present work we have again made use of the fractional extraction procedure employed previously which is based on the significantly greater acidity of the labile *cis* isomer. The earlier generalization that the method provides the labile isomer in greater amount has been confirmed in all cases studied. Initially it was hoped that a study of the various alkyl- and aryl-substituted pyrazolones might yield some correlation between the nature of the substituents and the ratio in which the *cis* and *trans* acids were formed. However, no such correlation was discernable from the limited data obtained. The results of the present study are collected in Table II. The observed *cis/trans* ratios vary from about 8/1 to 2/1.

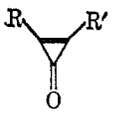
The β-keto esters utilized in this work were synthesized by well-known methods. These are recorded in the Experimental Section, comments being restricted to cases in which some difficulty was encountered. The method of Ireland and Marshall[4] which involves decarboxylative acylation of alkyl hydrogen malonates was found to be advantageous in the synthesis of ethyl α-methyl-*p*-nitrobenzoylacetate and the corresponding *p*-methoxybenzoylacetate. Since several attempts to obtain ethyl α-(*p*-nitrophenyl)-acetoacetate were unsuccessful, an alternate route to

(4) R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).

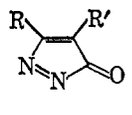
the corresponding halopyrazolone was devised which involved prior formation of the pyrazolidone by reaction of methyl α-*p*-nitrophenylcrotonate with hydrazine. A similar method had earlier been used in the preparation of 3,4-diphenyl-4-chloro-2-pyrazolin-5-one.[3b,5] The β-keto esters were converted to the pyrazolones in the usual manner by reaction with hydrazine hydrate in ethanol. Conversion of the pyrazolones to the 4-bromo and 4,4-dibromo derivatives was generally carried out by bromination in acetic acid, whereas chlorinations were commonly run in methylene dichloride or nitromethane solution. In the case of 3-methyl-4-*p*-methoxyphenyl-2-pyrazolin-5-one the bromination had to be carried out very rapidly in order to obtain satisfactory results. The difficulty may have been due to competing halogenation of the reactive methoxy-substituted aromatic ring.

Alkaline degradation of the halopyrazolones was carried out as described earlier.[3] The fractional extraction procedure for the isolation of the α,β-olefinic acids worked reasonably well in all cases except that involving 3-benzyl-4-phenyl-4-chloro-2-pyrazolin-5-one. For cases in which the break between the isomers could not be determined by the behavior on acidification of the bicarbonate extracts, the melting points and infrared spectra of each fraction were determined. Because of inevitable losses on recrystallization this separation technique, while indicative of the relative amounts of the two isomers which can be obtained preparatively, cannot be considered a highly accurate reflection of the ratio of isomers formed.

Turning to the nature of the reaction by which the 4-halopyrazolones are converted to unsaturated acids some gross features of the mechanism have been uncovered in the present study. Our initial interest in studying the alkaline degradation of halopyrazolones was prompted by the possibility that the sequence might provide a route to substituted cyclopropenones (V) since it was expected that the first step would involve dehydrohalogenation to give the diazacyclopentadienone (VI) which might undergo loss of nitrogen to



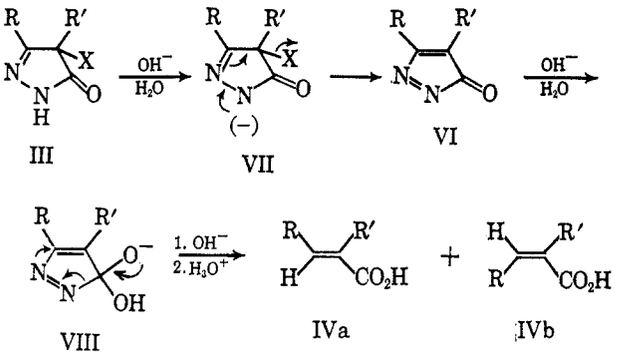
V



VI

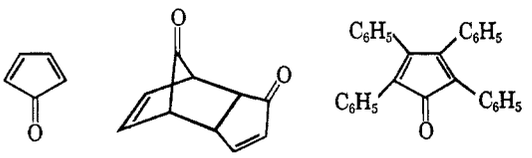
give V. However, no cyclopropenones could be isolated under the conditions of the reaction and, although authentic cyclopropenones were subsequently shown[9,10] to undergo ring opening with the formation of α,β-unsaturated acids, it was shown that such compounds could not be involved in the halopyrazolone reaction.[3b] A plausible scheme to account for the

CHART I



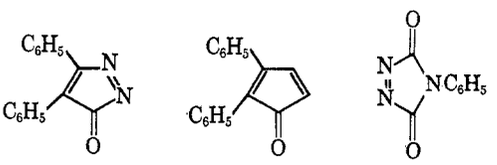
results is detailed in Chart I. Several of the halopyrazolones studied have been noted to dissolve in dilute aqueous sodium hydroxide solution at 0° with regeneration of the unchanged halopyrazolone provided the solution is acidified soon there after. On storage, even at 0°, nitrogen is evolved and conversion to the mixture of olefinic acids takes place. The first step in the reaction is believed to involve elimination of halide ion from anion VII to give a diazacyclopentadienone intermediate (VI). Ring opening of VI by hydroxide ion with concomitant loss of nitrogen followed by appropriate protonation steps would yield the acids IVa and b.

Although it has not been possible to isolate the diazacyclopentadienone (VI), indirect evidence for its involvement in this reaction has been obtained by trapping experiments. As an analog of cyclopentadienone (IX)[11,12] the diaza compound VI might be



IX X XI

expected to be inherently unstable. Although cyclopentadienone has never been isolated, it can be generated in solution and it can be trapped by means of the Diels–Alder reaction. In the absence of dienes cyclopentadienone yields the dimer X. On the other hand heavily arylated derivatives of cyclopentadienone such as tetracyclone (XI) are stable and have been known for many years.[12] To provide for added stability in our initial studies it was decided to examine the most highly phenylated diazacyclopentadienone possible, namely XII. It should be noted in this connection, however, that the analogous carbocyclic derivative XIII is apparently not stable as the monomer but has been obtained only in the



XII XIII XIV

(5) More recently this compound has been prepared from 3,4-diphenyl-2-pyrazolin-5-one[6] which can be obtained from the appropriate β-keto ester.[7,8]

(6) P. Gruenanger and P. Finzi, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.*, **31**, 128 (1961); *Chem. Abstr.*, **58**, 516e (1963).

(7) B. W. Howk and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 282 (1932).

(8) E. P. Kohler, *ibid.*, **46**, 1733 (1925).

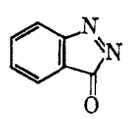
(9) D. N. Kursanov, M. E. Volpin, and Y. D. Koreshkov, *J. Gen. Chem. USSR*, **30**, 2855 (1960). It is interesting to note that alkaline hydrolysis of diphenylcyclopropenone yields the stable *trans*-α-phenylcinnamic acid, whereas with the corresponding pyrazolone a mixture is obtained in which the *cis* isomer predominates.

(10) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965).

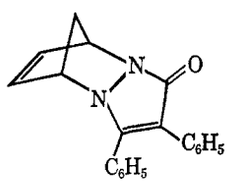
(11) C. H. DePuy, M. Isaks, K. L. Eilers, and C. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).

(12) For a recent review, see M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).

form of various derivatives of its dimer.[13] As a *cis*-linked acylazo compound, XII would be expected to be a potent dienophile. For example related cyclic azo compounds such as XIV[14] and various diazaquinones[15,16] are far more reactive than ethyl azodiformate in the Diels–Alder reaction. The same increased reactivity has also been demonstrated for acyclic *cis*-azo compounds[17] and in fact for the only known analog of XII, namely the benzo derivative



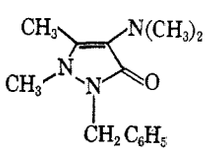
XV



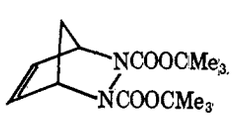
XVI

XV which has been implicated in the von Richter reaction[18,19] and has also been obtained in solution at low temperatures by oxidation of indazolone.[20]

When an ether solution of 3,4-diphenyl-4-chloro-2-pyrazolin-5-one was treated with triethylamine in the presence of cyclopentadiene, an excellent yield was obtained of a compound (A), $C_{20}H_{16}N_2O$, which has been shown to be the Diels–Alder adduct XVI derived from cyclopentadiene and XII. The unlikely possibility that A could have the alternate structure in which XII acts as diene rather than dienophile can be eliminated on the basis of the appearance of normal hydrazide carbonyl absorption ($\lambda_{max}^{CHCl_3}$ 6.07 μ).[21] For comparison the analogous antipyrine derivative[22] XVII shows a



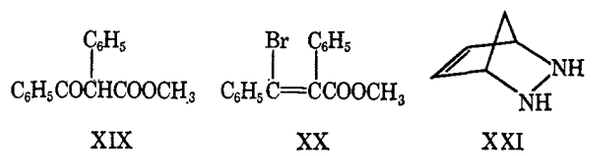
XVII



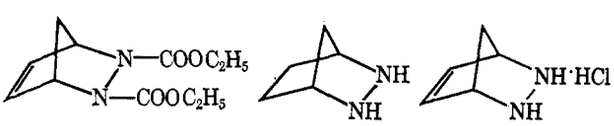
XVIII

carbonyl band at 6.12 μ. The nmr spectrum of A exhibits six sets of complex multiplets centered at δ 2.15 (2 H, quartet, CH_2), 4.63 (1 H, bridgehead$_1$), 5.27 (1 H, bridgehead$_2$), 5.68 (1 H, doublet, vinyl$_1$), 6.44 (1 H, doublet, vinyl$_2$), and 7.30 (10 H, aromatic). A model for the bicyclic portion of the adduct, the 2,3-diazabicyclo[2.2.1]heptane diester (XVIII),[23] showed absorption at δ 1.5 (18 H, singlet, *t*-butyl), 1.70 (2 H, triplet, CH_2), 5.20 (2 H, multiplet, bridgehead), and 6.60 (2 H, triplet, vinyl).

Attempts to establish the structure of A by a direct unequivocal synthesis were not successful. Two approaches were examined based on earlier described[24] routes to compounds of the antipyrine type. These involved attempted reaction of the β-keto ester XIX or the β-bromocinnamate XX with the bicyclic hydrazo compound XXI. Unfortunately the unsaturated hydrazo compound XXI proved not to be sufficiently stable to be used in such reactions. Cohen and coworkers[25] previously attempted to prepare XXI by hydrolysis of the dicarbethoxy derivative XXII. However only the saturated 2,3-diazanorbornane

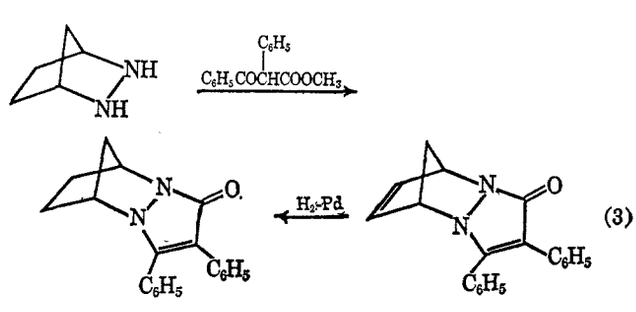


XIX XX XXI



XXII XXIII XXIV

(XXIII) could be obtained in this reaction and it was postulated that the intermediate XXI underwent a retrograde Diels–Alder reaction to give cyclopentadiene and diimide followed by reduction of XXI by the latter to give XXIII. It seemed reasonable to expect that cleavage of the dicarbo-*t*-butoxy derivative XVIII by hydrogen chloride in an inert solvent at a low temperature might yield the hydrochloride XXIV which would be expected to be more stable than the corresponding free base. Although it was possible to cleave XVIII in carbon tetrachloride–nitromethane (10:1) by means of hydrogen chloride at a temperature of 0° with the formation of a granular solid, preliminary attempts to purify this material or to establish its structure were unsuccessful as were attempts to use the crude hydrochloride in reaction with the β-keto ester XIX or the bromocinnamate XX. We therefore turned our attention to an indirect method of establishing the structure of adduct A. Since the saturated 2,3-diazabicyclo[2.2.1 heptane (XXIII) is easily obtainable,[26] its reaction with the β-keto ester XIX was investigated. Condensation occurred readily to give a material (XXV) which proved to be identical with the dihydro derivative of adduct A obtained by low-pressure hydrogenation over a palladium–carbon cata-



XXV (3)

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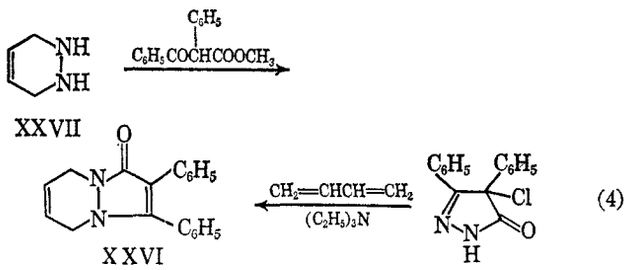
lyst. The nmr spectrum of XXV is consistent with this formulation, the absorption in the vinyl region of XVI having been replaced by a complex set of multiplets at δ 1.2–2.5. This sequence of reactions provides indirect evidence that the transient intermediate in the original reaction of the halopyrazolone with triethylamine is indeed the diazacyclopentadienone XII. That the original difficulty in the direct alternate synthesis of adduct XVI was in fact due to the indicated instability of 2,3-diazabicyclo[2.2.1]hept-5-ene (XXI) is made apparent by studies on the analogous adduct derived from diazacyclopentadienone



(4)

(XII) and 1,3-butadiene. 1,2,3,6-Tetrahydropyridazine (XXVII), lacking the strain characteristic of the bicyclic analog XXI, shows no tendency to undergo the reverse Diels–Alder reaction and can be isolated and manipulated without difficulty.[27] Reaction of XXVII with methyl α-phenylbenzoylacetate gave the same pyrazolone XXVI which was obtained by trapping XII in the presence of 1,3-butadiene. In view of the ready availability of halopyrazolones this new route to compounds of the antipyrine type may have considerable practical value. Currently attempts are underway to isolate XII and its congeners and/or determine its fate in the absence of trapping agents.

Having established the transient existence of diazacyclopentadienones in the reaction of III (R = R′ = C_6H_5; X = Cl) with triethylamine it is reasonable to assume that the same intermediate might also be formed by the action of sodium hydroxide on the halopyrazolone in aqueous solution (Chart I). It appears reasonable to postulate subsequent opening of the hetero ring of VI by reaction with excess alkali with concerted loss of nitrogen to give, eventually, the α,β-unsaturated acids (IVa and b). In the case of 4,4-dihalopyrazolones loss of the second halide ion might be concerted with ring opening leading directly to the α,β-acetylenic acid. It remains to account for the preponderant formation of the labile isomer (*cis*, IVb) in the set of *cis*- and *trans*-α,β-olefinic acids obtained in the case of 3,4-disubstituted 4-halopyrazolones. It might at first have been thought that the *trans* isomer (IVa) would predominate in view of its greater stability and direct geometric relationship to the cyclic azo compound (VI) presumed to be an intermediate in the reaction. As yet we are not able to suggest a satisfactory explanation for the predominance of the *cis* isomer in this reaction.

Experimental Section[28]

Ethyl α-(*p*-methoxyphenyl)acetoacetate was prepared from the corresponding nitrile by the method described for ethyl α-phenylacetoacetate.[29] The solid imino ester proved to be less soluble in ether than the unsubstituted analog but otherwise the reaction proceeded as described. The β-keto ester, mp 65–67°, was obtained in 80% yield. The analytical sample, from a 2:1 mixture of ligroin (bp 40–60°) and hexane, was obtained in the form of tiny needles, mp 65–66°. *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.90; H, 6.84.

Ethyl hydrogen methylmalonate proved useful in the synthesis of several β-keto esters and since poor results were obtained by the procedure of Roland and McElvain[30] and since the procedure of Corey[31] for the corresponding phenyl derivative did not work well when applied to the methyl derivative, the following modification of the published procedure is given. To a mechanically stirred solution of 87.1 g of diethyl methylmalonate in 250 ml of absolute ethyl alcohol was added dropwise over 5 hr a filtered solution of 28 g of potassium hydroxide in 450 ml of absolute ethyl alcohol. The mixture was stirred for an additional 2 hr, let stand for 2 days, and then heated to the boiling point and filtered hot in order to remove a small amount of the dipotassium salt. Removal of the alcohol from a water bath at 40° with a rotary evaporator gave 83 g of white solid which was dissolved in 200 ml of water. Unreacted ester was removed by extraction with ether and the aqueous layer was cooled in an ice bath and acidified with concentrated hydrochloric acid with stirring. Extraction with ether followed by removal of solvent from the dried solution and distillation through a 15-cm Vigreux column gave 41.4 g (68%, based on 14.4 g of recovered starting material) of the half-acid, bp 86–88° (0.40 mm), lit.[30] bp 100–102° (2 mm).

Ethyl α-Methyl-*p*-nitrobenzoylacetate.—The general method of Ireland and Marshall[4] was used. To a hot stirred solution of 0.2 mole of isopropylmagnesium bromide in 100 ml of tetrahydrofuran was added slowly over about 75 min a solution of 14.6 g of ethyl hydrogen methylmalonate in 50 ml of tetrahydrofuran. When the vigorous reaction subsided the mixture was refluxed for 6 hr, cooled in an ice bath and addition of 18.56 g of *p*-nitrobenzoyl chloride in 50 ml of tetrahydrofuran was begun. Since no carbon dioxide was evolved the mixture was heated and after about half of the acid chloride had been added evolution of carbon dioxide began. After the addition was complete (1 hr), the mixture was refluxed overnight and the solvent was removed by distillation. The yellow gummy residue was hydrolyzed by means of 600 ml of half-saturated ammonium chloride solution by stirring for several hours. Extraction with ether, drying, and removal of solvent followed by distillation gave 19.06 g (76%) of the pure ester, bp 150–152° (0.9 mm). *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.29; H, 5.22; N, 5.62.

Ethyl α-methyl-*p*-methoxybenzoylacetate was obtained by the method described above for the corresponding *p*-nitro ester. On the scale indicated there was obtained 18.59 g (79%) of the pure ester, bp 128–130° (0.60 mm).[32] *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.02; H, 6.98.

Methyl *trans*-α-*p*-Nitrophenylcrotonate.—*trans*-α-*p*-Nitrophenylcrotonic acid was obtained by the method of Häffcke and Becker.[33] A suspension of 72.7 g of the acid in 350 ml of methanol was treated with a slow stream of gaseous hydrogen chloride for 3 hr and the mixture was let stand overnight in an open vessel. Seeding the clear solution caused crystallization. Filtration and addition of water to the filtrate gave 74.2 g (96%) of the ester, mp 58.5–61°. The analytical sample was obtained by recrystallization from a 5:1 mixture of ligroin (bp 40–60°) and hexane as a pale cream-colored powder, mp 59–60°. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.89; H, 5.13; N, 6.45.

(27) P. Baranger, J. Levisalles, and M. Vuidart, *Compt. Rend.*, **236**, 1365 (1953).

(28) Melting and boiling points are uncorrected. Elemental analyses were by Dr. A. Bernhardt, Mülheim (Germany), and Galbraith Laboratories, Knoxville, Tenn. Unless otherwise noted nmr spectra were taken in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Infrared spectra were recorded on Perkin-Elmer 21 and Beckman IR-5 instruments.

(29) R. H. Kimball, G. D. Jefferson, and A. B. Pike, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. 1943, p 284.

(30) J. R. Roland and S. M. McElvain, *J. Am. Chem. Soc.*, **59**, 132 (1937).

(31) E. J. Corey, *ibid.*, **74**, 5897 (1952).

(32) This ester (bp 148–152° at 7 mm) has been reported recently although the authors were unable to obtain it in a pure state: see S. E. Mhasalker and C. V. Deliwala, *Indian J. Chem.*, **3**, 139 (1965).

(33) W. Häffcke and E. Becker, *J. Org. Chem.*, **16**, 863 (1951).

3-Benzyl-4-phenyl-2-pyrazolin-5-one.—Since the methods previously described[34,35] for the preparation of this compound led to extremely poor yields, the following method was developed. A solution of 18.7 g of ethyl α,γ-diphenylacetoacetate in 150 ml of 95% ethyl alcohol and 3.3 g of 64% hydrazine was refluxed for 24 hr and then poured into a large evaporating dish from which the solvent was removed by spontaneous evaporation or on a steam bath. The residue was transferred to a large open test tube and heated in an oil bath for 8 hr at 155–165° without condensation of volatile material. Recrystallization was effected by solution in 200 ml of boiling ethanol, decolorizing, and addition of 200 ml of water. Refrigeration gave 12.7 g (76.8%) of the pyrazolone, mp 166–170°, pure enough for further use. Recrystallization from ethanol–water (3:1) gave the pyrazolone as a white powder, mp 170–172° (lit.[34] mp 172°).

3-Benzyl-4-chloro-4-phenyl-2-pyrazolin-5-one.—A suspension of 2.0 g of the 3-benzyl-4-phenyl-2-pyrazolin-5-one in 50 ml of methylene dichloride was treated with a rapid stream of chlorine gas for 10 min. After standing for 1 hr the solution was poured into an evaporating dish, and the solvent was removed on a steam bath by gentle heating. The residual solid was dissolved in 15 ml of hot benzene and filtered, and 50 ml of petroleum ether (bp 30–60°) was added to the filtrate. Refrigeration gave 1.8 g (78.9%) of the chloro compound as light tan plates, mp 109–111°. The analytical sample had mp 107–108° (ligroin, bp 90–120°). *Anal.* Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60. Found: C, 67.58; H, 4.85.

3-Phenyl-4-bromo-4-benzyl-2-pyrazolin-5-one.—A solution of 2.5 g of the pyrazolone (prepared in 96% yield by the method of Gagnon, Boivin, and Paquin[36]) in 20 ml of acetic acid was treated with a solution of 1.6 g of bromine in 10 ml of acetic acid over 3–5 min. After the mixture had stood for 25 min a small amount of solid was removed by filtration and the filtrate on dilution with water gave a gummy substance. This was dissolved in 10 ml of hot benzene, and the solution was treated with charcoal, cooled, and filtered to give 1.1 g (33.4%) of a yellow hygroscopic solid, mp 133–134.5°. The analytical sample, recrystallized several times from the same solvent, was obtained as nonhygroscopic yellow platelets, mp 134–134.5°. *Anal.* Calcd for $C_{16}H_{13}BrN_2O$: C, 58.37; H, 3.98. Found: C, 58.42; H, 4.14.

3-Phenyl-4-chloro-4-benzyl-2-pyrazolin-5-one.—The pyrazolone[35] was chlorinated in methylene dichloride solution in a manner similar to that described for the isomeric 3-benzyl-4-phenyl derivative. The crude product was obtained in 56% yield as light yellow needles, mp 134–136°. The analytical sample, recrystallized from benzene and benzene–petroleum ether, was obtained in the form of white needles, mp 145–146°. *Anal.* Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60. Found: C, 67.53; H, 4.42.

3-Methyl-4-*p*-methoxyphenyl-2-pyrazolin-5-one.—Treatment of a 50% solution of ethyl α-(*p*-methoxyphenyl)acetoacetate in warm ethanol with a 50% solution of hydrazine hydrate in the same solvent was accompanied by spontaneous warming and precipitation of a quantitative yield of the crude pyrazolone. Recrystallization from nitromethane–dimethylformamide (3:1) gave the pure pyrazolone in 89.6% yield as a coarse powder, mp 213–214.5°. *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.86; H, 6.12.

3-Methyl-4-bromo-4-*p*-methoxyphenyl-2-pyrazolin-5-one.—In this case the results were unsatisfactory unless the bromination was carried out rapidly. A solution of 2.04 g of 3-methyl-4-*p*-methoxyphenyl-2-pyrazolin-5-one in 20 ml of glacial acetic acid was cooled to 16° and a solution of 1.6 g of bromine in 5 ml of glacial acetic acid was added over a period of 1–2 min. As soon as the bromine addition was completed water was added to the red-orange solution until a white solid precipitated. After standing for 1 hr in an ice bath the solid was filtered to give 2.6 g (91.9%) of the pyrazolone as a fluffy white powder, mp 129–131°. The analytical sample, mp 131–132°,[37] was obtained by recrystallization from benzene and benzene–ligroin (bp 60–90°). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92. Found: C, 46.40; H, 3.94.

3-*p*-Methoxyphenyl-4-methyl-2-pyrazolin-5-one.—A mixture of 16.2 g of ethyl α-methyl-*p*-methoxybenzoylacetate, 3.43 g of 64% hydrazine, and 17 ml of ethanol was heated on a steam bath for 5 min and then stored for 24 hr in a refrigerator. The solvent was removed by heating on a steam bath. The residual solid amounted to 11 g (78.6%), mp 193–197°. The analytical sample was recrystallized from 2-nitropropane to give white, plate-like needles, mp 198–200°. *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.85; H, 6.25.

3-*p*-Methoxyphenyl-4-bromo-4-methyl-2-pyrazolin-5-one.—Bromination of the pyrazolone was carried out as described for the isomer except that in this case it was not critical to add the bromine solution rapidly. A crystalline yellow solid separated during the addition of bromine. Upon dilution with water this solid dissolved completely and a new solid precipitated upon continued addition of water. The yield of the crude pyrazolone which was obtained as a golden yellow powder, mp 165–167°, was 95.4%. The analytical sample was obtained in the form of orange crystals, mp 164–166°, by recrystallization from benzene and benzene–ligroin (bp 60–90°). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92. Found: C, 46.68; H, 3.92.

3-*p*-Nitrophenyl-4-methyl-2-pyrazolin-5-one.—The method described for 3-methyl-4-*p*-methoxyphenyl-2-pyrazolin-5-one was used except that the mixture was allowed to stand for 24 hr prior to filtration. The yield of pyrazolone, mp 249–252.5°, was 81–85%. The analytical sample was obtained from nitromethane–dimethylformamide as lemon yellow needles, mp 255–257° dec. *Anal.* Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14. Found: C, 54.51; H, 4.11.

3-*p*-Nitrophenyl-4-chloro-4-methyl-2-pyrazolin-5-one.—Chlorine was passed through a suspension of 8.48 g of the corresponding unhalogenated pyrazolone in 150 ml of methylene dichloride for 5 min following the time required for complete solution (15 min). After 1–2 hr the solvent was allowed to evaporate from a flat dish and the crystalline residue was dissolved in 150 ml of hot benzene. The mixture was filtered and the filtrate was treated with 40 ml of petroleum ether (bp 30–60°) in order to precipitate 8.66 g (88.5%) of the halopyrazolone as long yellow needles, mp 156–157.5° dec. The analytical sample, from benzene–ligroin (bp 60–90°) had mp 157–158.5° dec. *Anal.* Calcd for $C_{10}H_8ClN_3O_3$: C, 47.35; H, 3.18. Found: C, 47.07; H, 3.33.

5-Methyl-4-*p*-nitrophenyl-3-pyrazolidone.—A solution of 8.84 g of methyl *trans*-α-*p*-nitrophenylcrotonate and 2.0 g of 64% hydrazine in 40 ml of methyl alcohol was refluxed for 12 hr. There was added to the hot solution 150 ml of water (nearly to the cloud point) and the solution was allowed to cool slowly to room temperature and then refrigerated. There was obtained 7.81 g (88.2%) of light powder, mp 87–140°. The crude material was recrystallized from 400 ml of benzene containing 10 ml of nitromethane which gave 4.54 g (51.3%) of a white or light tan fluffy powder, mp 152–154°. The analytical sample was obtained from benzene–nitromethane (30:1) and benzene alone as a fluffy yellow-tan powder, mp 151–153°. *Anal.* Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01. Found: C, 54.18; H, 5.13.

3-Methyl-4-chloro-4-*p*-nitrophenyl-2-pyrazolin-5-one.—Chlorine was passed through a suspension of 7.4 g of 5-methyl-4-*p*-nitrophenyl-3-pyrazolidone in 400 ml of methylene dichloride. At first a gummy material separated which subsequently solidified and eventually dissolved as the gas was introduced (45 min). The gas stream was continued for 15 min longer and the solvent was then allowed to evaporate from a flat dish. The yellow crystalline residue was dissolved in 100 ml of hot benzene, the solution was filtered, and 40 ml of petroleum ether (bp 30–60°) was added to the filtrate. There was obtained after refrigeration 7.4 g (87.4%) of the halopyrazolone as cream-colored platelike needles, mp 150–153° dec. The analytical sample was obtained from benzene as pale yellow needles, mp 151–152° dec.

Anal. Calcd for $C_{10}H_8ClN_3O_3$: C, 47.35; H, 3.18. Found: C, 47.21; H, 3.13.

3,4-Diphenyl-4-chloro-2-pyrazolin-5-one.—Since some investigators have obtained poor results in carrying out the preparation of this key compound as described earlier,[3b] a more detailed procedure is given here. Chlorine was passed through a suspension of 5 g of 4,5-diphenyl-3-pyrazolidone in 30 ml of nitromethane. The pyrazolidone dissolved in about 0.5 min and a new white solid precipitated as the solution became very hot. Within 5 min this solid had redissolved and in another 1–2 min another solid began to precipitate. At this point the chlorination was stopped and after another 20–25 min the mixture was transferred to an evaporating dish and the solvent was allowed to evaporate spontaneously. Recrystallization of the residue

(34) J. Volhard, *Ann.*, **296**, 10 (1897).

(35) M. Rodionov and N. M. Suvorov, *Zh. Obshch. Khim.*, **20**, 1273 (1950).

(36) P. E. Gagnon, J. L. Boivin, and R. J. Paquin, *Can. J. Chem.*, **31**, 1025 (1953).

(37) Unless the bath temperature was raised at the rate of 0.5–1°/min, lower and inconsistent melting points were observed.

from 15 ml of 2-nitropropane gave 4.22 g (74.2%) of the halopyrazolone, mp 166–170° dec (sintering slightly at 163°), lit.[3b] mp 171.8–173.8°. This material was pure enough for subsequent use.

Diels–Alder Adduct of 4,5-Diphenyl-2,3-diazacyclopentadienone and Cyclopentadiene.—A solution of 2.71 g of 3,4-diphenyl-4-chloro-2-pyrazolin-5-one in 150 ml of anhydrous ether was cooled to −5° in an ice–salt bath and dry nitrogen was passed through the solution for 2 hr. There was then added 20 ml of freshly distilled cyclopentadiene[38] followed by 1.01 g of triethylamine. The flask was tightly corked, the cork was wired on, and the mixture was stirred magnetically at room temperature for 36 hr. The mixture was filtered and the solid was washed well with 250 ml of cold water. There was obtained 2.13 g (71%) of the adduct, mp 149.5–152° dec. The analytical sample was purified by recrystallization from benzene, mp 149–151° dec (prior darkening).

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.38; N, 9.33; mol wt, 300.3. Found: C, 79.92; H, 5.45; N, 9.39; mol wt, 310.

Hydrogenation of the Diels–Alder Adduct of 4,5-Diphenyl-2,3-diazacyclopentadienone and Cyclopentadiene.—A suspension of 7.5 g of XVI in 350 ml of commercial absolute ethanol was hydrogenated in the presence of 0.5 g of palladium–carbon catalyst (10%) in a Parr apparatus at 43 psi. After 0.5 hr evaporation of solvent gave 7.5 g. (99.4%) of the crude dihydro derivative, mp 208–220°. Recrystallization from nitromethane and benzene–nitromethane (1:1) gave 4.5 g (59.6%) of the pure pyrazolone, mp 229.5–232°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.45; H, 6.03; N, 8.93.

Diels–Alder Adduct of 4,5-Diphenyl-2,3-diazacyclopentadienone and 1,3-Butadiene. A.—A stream of nitrogen was passed for 1 hr at 0° through a solution of 4 g. of 3,4-diphenyl-4-chloro-2-pyrazolin-5-one in 150 ml of dry ether. There was added 1.8 g of triethylamine, the solution was stirred mechanically, and a stream of butadiene was passed in gently for 3 hr. The mixture was stored at room temperature for 24 hr, the solvent was evaporated, and the resulting solid was washed well with water. Recrystallization of the crude yellow solid from benzene–ligroin (bp 60–70°) (1:1) gave 2.4 g (54.5%) of white needles, mp 187–189° dec.

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.71. Found: C, 79.04; H, 5.68; N, 9.61.

B.—A mixture of 1 g of 1,2,3,6-tetrahydropyridazine[39] and 2.54 g of ethyl α-phenylbenzoylacetate[7] in a 50-ml round-bottomed flask was placed in an oil bath at 85° and the temperature was allowed to rise slowly over a period of 1 hr to 145° where it was held for 1 hr. The mixture was poured into 50–75 ml of water which caused separation of an oil which soon solidified. After washing with water and ethanol there was obtained 1.9 g (66%) of pink solid, mp 174–183°. Recrystallization from benzene–ligroin (bp 60–70°) gave 1.2 g (41.6%) of light yellow crystals, mp 187–189°. The infrared spectrum was identical with that of the sample prepared by A and the mixture melting point showed no depression.

2,3-Dicarbo-*t*-butoxy-2,3-diazabicyclo[2.2.1]heptane.—A solution of 29.6 g. of 2,3-dicarbo-*t*-butoxy-2,3-diazabicyclo[2.2.1]-hept-5-ene[23] in 200 ml of ethanol was hydrogenated over 0.25 g of palladium–carbon catalyst (10%) in a Parr apparatus at 42 psi for 1 hr. Removal of solvent and recrystallization from benzene–ligroin (bp 60–70°) gave 22 g (73.8%) of the hydrazo compound, mp 97–99°.

Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.40; H, 8.72; N, 9.39. Found: C, 60.56; H, 8.72; N, 9.43.

Condensation of Methyl α-Phenylbenzoylacetate and 2,3-Diazabicyclo[2.2.1]heptane. Alternate Synthesis of XXV.—Gaseous hydrogen chloride was passed through a solution of 10 g of 2,3-dicarbo-*t*-butoxy-2,3-diazabicyclo[2.2.1]heptane in 125 ml. of 2-nitropropane for 25–30 min. The mixture, from which a white powder slowly separated, was allowed to stand for 6 hr at room temperature. The solid was filtered and washed several times with absolute ether and dried *in vacuo* to give 5.9 g of the crude hydrochloride. This crude material which may have been a mixture of the mono- and dihydrochlorides was not purified but used as such in the next step. For purposes of identification a portion of the hydrochloride was dissolved in absolute ethanol and the solution was shaken with a crystal of stannic chloride pentahydrate. The resulting solid was recrystallized from ethanol to give well-formed crystals, mp 226.5–229° dec, lit.[36] 224–229° dec. A mixture of 0.68 g of the above crude hydrochloride and 0.64 g of methyl α-phenylbenzoylacetate[8] was melted by heating gently over a low flame. Frothing occurred and when this subsided (less than 1 min) the mixture was cooled and diluted with 5 ml of water. The mixture was made basic by the addition of solid potassium hydroxide and heated to the boiling point. Seeding gave 0.2 g (26%) of the adduct, mp 229–230.5°, after recrystallization from ethanol and benzene–nitromethane. The infrared spectrum was identical with that of a sample prepared by catalytic reduction of XVI and a mixture melting point showed no depression.

1,2-Dicarbo-*t*-butoxy-1,2,3,6-tetrahydropyridazine.—Butadiene was slowly passed into a solution of 4 g of *t*-butyl azodiformate[40] dissolved in 15 ml of benzene while irradiating with a sunlamp for 4 hr. Evaporation of solvent gave 4.28 g (95%)[41] of the hydrazo compound, mp 73–74.5°, on recrystallization from ligroin (bp 60–70°).

Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.15; H, 8.45; N, 9.85. Found: C, 59.25; H, 8.55; N, 9.90.

Conversion of 3,4-Disubstituted 4-Halopyrazolones to α,β-Unsaturated Acids.—Since the methods used in each case were similar to those previously described, only an outline of the procedure used will be presented. For specific details in each case the Ph.D. thesis of P. H. Terry should be consulted.

A solution of 4 g of sodium hydroxide in 100 ml. of distilled water was cooled in an ice bath with agitation by means of a magnetic stirrer. There was then added the halopyrazolone (0.02 mole) over 1–3 min. Stirring in the ice bath was continued for 1 hr and at room temperature for about 4 hr. The mixture was filtered if necessary, often with decolorizing carbon, cooled, and acidified with concentrated hydrochloric acid (congo red). The crude acidic material was extracted into one 100-ml and five 25-ml portions of ether and the combined ether extracts were then fractionally extracted with sodium bicarbonate solution as previously described.[3b] Upon acidification of the bicarbonate extracts the nature of the precipitation behavior often suggested the point of separation between the *cis* and *trans* acids. If not, appropriate fractions were filtered and the melting points or infrared spectra were determined in order to locate the separation point. The results are collected in Table II. The stereochemical assignments made in this table on the basis of the greater acidity of the *cis* isomer were confirmed in all cases by spectral examination (infrared, ultraviolet, and particularly nmr data.[42]

(38) R. Riemschneider, *Z. Naturforsch.*, **18b**, 641 (1963).

(39) Obtained both by the method of Baranger, Levisalles, and Vuidart[27] and by hydrogen chloride cleavage of the corresponding carbo-*t*-butoxy derivative.

(40) L. A. Carpino and P. J. Crowley, *Org. Syn.*, **44**, 18 (1964).

(41) Occasionally yields as low as 20–30% were obtained in this reaction. The reason for the variable results could not be determined although it may have been associated with the age of the particular sunlamp used.

(42) *cf.* K. Nilsson and S. Sternhell, *Acta Chem. Scand.*, **19**, 2441 (1945).