Reactions of Phosphorus Compounds. 31.[1] Reactions of Substituted α-Imino Ketones with Vinyltriphenylphosphonium Bromide

EDWARD E. SCHWEIZER* AND CHARLES M. KOPAY

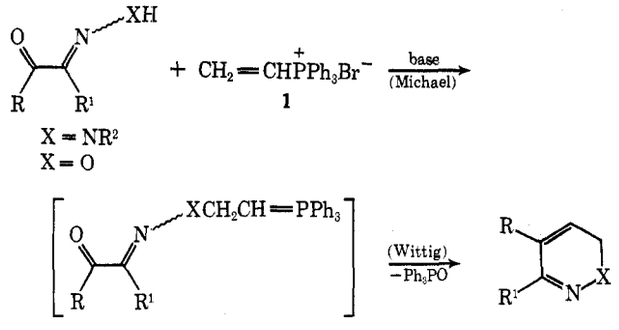
Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received October 8, 1971

Treatment of substituted α-imino ketones with vinyltriphenylphosphonium bromide (1) gave moderate yields of 1-hydroxypyrroles, 1-aminopyrroles, or 2,3-dihydropyridazines. A mechanism for the formation of the five- and six-membered rings is provided and appears to be dependent upon the geometry of the α-imino ketone.

Continuing our interest in the use of vinyltriphenylphosphonium bromide (**1**) for the syntheses of heterocyclic compounds,[2] we undertook a study of the reactions of some substituted α-imino ketones (oximes and hydrazones) with **1** in the hopes of forming substituted 6*H*-oxazines and 2,3-dihydropyridazines (Scheme I).[3]

SCHEME I
PROPOSED REACTIONS OF
1 WITH SUBSTITUTED α-IMINO KETONES

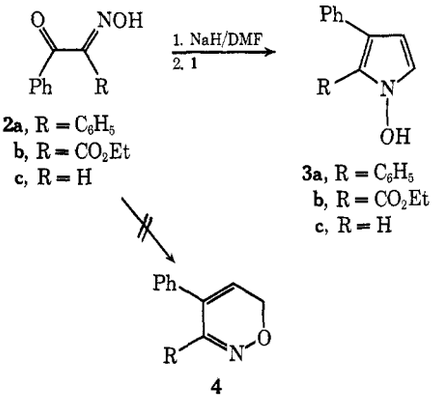


Oximes.—Treatment of (*E*)-benzil monoxime (**2a**) with 1 equiv of NaH in DMF followed by 1 equiv of **1** gave the unexpected 1-hydroxy-2,3-diphenylpyrrole (**3a**)[4] in 26% yield. An nmr spectrum of the crude reaction mixture gave no indication of the presence of 6*H*-oxazine (**4**). The structure of **3a** was based on the following spectral data. The infrared spectrum (Nujol) of **3a** exhibited a broad OH stretching frequency at 3320 cm^{-1}; nmr ($CDCl_3$) δ 6.23 (1, d, J = 3.0 Hz), 6.86 (1, d, J = 3.0 Hz), and 7.0–7.5 (10, m). The proton resonances at δ 6.23 and 6.86 were assigned to the AB pattern of the pyrrole ring positions 4 and 5, respectively. The OH resonance was not detected in **3a**, a phenomenon that had previously been noted in the case of 1-hydroxyindoles.[5]

The mass spectrum showed the molecular ion m/e 235) as the base peak. Fragmentation took place by the loss of HO· from the molecular ion $(M - HO\cdot)^+$, this pattern of fragmentation being in accord with the fragmentation occurring in substituted 1-hydroxyindoles.[5]

Likewise monoximes **2b** and **2c** gave the 1-hydroxypyrroles **3b** and **3c** in yields of 44 and 29%, respectively (Scheme II, Tables I and II).

SCHEME II
FORMATION OF 1-HYDROXYPYRROLES



A mechanism for the formation of the 1-hydroxypyrroles can be rationalized as occurring through the attack of nitrogen on **1** to generate the ylide **5** (pathway 1, Scheme III). Attack of ylide **5** on the benzoyl carbonyl in a normal Wittig reaction would lead to the amine oxide **6b**, which is a tautomeric form of **3** (Scheme III).

An alternative mechanism (pathway 2, Scheme III), assuming $E \rightarrow Z$ conversion, would occur through the attack of the oxygen anion with the formation of ylide **7**, which would then undergo a Wittig reaction with the benzoyl carbonyl to form the 6*H*-oxazine (**8**). The oxazine (**8**) could in turn undergo an electrocyclic ring opening to the nitrosobutadiene **9**; ensuing reattack by the nitroso nitrogen would lead to the amine oxide **6**. The alternative mechanism (pathway 2) was dismissed on the basis of the following reactions. When (*Z*)-benzil monoxime was employed as the starting material, no 1-hydroxypyrrole (**3a**) was obtained and only polymeric material isolated. Under the reaction conditions the *E* and *Z* oximes were not isomerized. Therefore it appears necessary to have the *E* isomer in order to synthesize the 1-hydroxypyrroles.

Nmr studies of the 1-hydroxypyrroles **3a–c** in various solvents, both protic and aprotic, did not indicate the presence of substantial quantities of the tautomeric forms **6a** and/or **6b**.[6] However, the addition of D_2O to a $CHCl_3$ solution of **3a** showed, after 2 hr, a com-

(1) Previous paper in this series: E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, **36**, 4041 (1971).

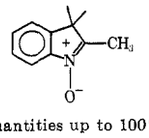
(2) E. E. Schweizer, J. Liehr, and D. T. Monaco, *J. Org. Chem.*, **33**, 2416 (1968); E. E. Schweizer, *J. Amer. Chem. Soc.*, **86**, 2744 (1964).

(3) Part of this work was presented at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971, p 83.

(4) This product was first prepared by J. G. Thompson and isolated and characterized by G. Hollander in these laboratories.

(5) R. M. Acheson, R. G. Bolton, and I. Hunter, *J. Chem. Soc. C*, 1067 (1970).

(6) Studies of the 1-hydroxy-2-methylindole[5] showed that in phenol and other acidic solvents



could be shown to exist in quantities up to 100%.

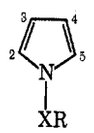
TABLE I

PREPARATION OF N-SUBSTITUTED PYRROLES AND PYRIDAZINES

Starting material	Reaction time, hr (temp, °C)	Product (% yield, solvent)		Analysis, % C	H	N
2a	4 (25)	**3a** (26, hexane)	Calcd	81.68	5.57	5.93
			Found	82.07	5.55	5.98
2b	3 (25)	**3b** (44, hexane)	Calcd	67.52	5.67	6.06
			Found	67.82	5.65	6.13
2c	2.5 (25)	**3c** (29, hexane)	Calcd	75.45	5.70	8.80
			Found	75.19	5.85	8.89
11a	2 (25)	**12a** (67, EtOH)	Calcd	85.13	5.85	9.03
			Found	85.17	5.87	8.72
11b	2 (25)	**12b** (27, sublimed)	Calcd	82.33	6.50	11.28
			Found	82.45	6.39	11.21
11c	1 (25)	**12c** (74, hexane)	Calcd	74.49	5.92	9.15
			Found	74.39	5.97	9.11
11d	40 (50)	**13** (31, EtOAc–hexane)	Calcd	81.63	5.36	8.28
			Found	81.56	5.23	8.21

TABLE II

SPECTRA OF SUBSTITUTED PYRROLES

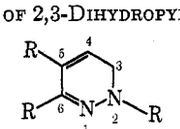


Compd	Ir,[a] cm^{-1}	Nmr,[b] δ 2	3	4	5	Other protons
3a	3320 (w), 1595 (w), 1075 (m)		6.23 (d, 1, J = 3.0 Hz)		6.86 (d, 1, J = 3.0 Hz)	C_6H_5 (m, 10) 7.0–7.5 OH not detectable
3b	3370 (w), 1660 (s), 1575 (s)		5.97 (d, 1, J = 2.8 Hz)		6.93 (d, 1, J = 2.8 Hz)	C_6H_5 (m, 5) 7.1–7.6 $-OCH_2$ (q, 2, J = 7.0 Hz) 4.12 $-CH_3$ (t, 3, J = 7.0 Hz) 1.07 –OH (s, 1) 10.2[c]
3c	3325 (w), 1595 (w), 1080 (m)	6.86 (m, 1)	6.19 (m, 1)		6.61 (m, 1)	C_6H_5 (m, 5) 7.0–7.5 –OH (s, 1) 10.1[c]
13	3250 (w), 1660 (s), 1075 (w)		6.38 (d, 1, J = 3.0 Hz)		6.65 (d, 1, J = 3.0 Hz)	C_6H_5 (m, 15) 6.9–7.7 NH (s, 1) 9.31[c]

[a] All ir spectra were run as a Nujol mull. [b] $CDCl_3$ solvent; all chemical shifts reported in parts per million followed by the splitting patterns, the number of protons, and the coupling constants. [c] Proton exchangeable with D_2O.

TABLE III

SPECTRA OF 2,3-DIHYDROPYRIDAZINES



Compd	Ir,[a] cm^{-1}	Nmr,[b] δ 3	4	Other protons
12a	1590 (m), 1190 (s), 955 (s)	4.25 (d, 2, J = 5.0 Hz)	5.99 (t, 1, J = 5.0 Hz)	C_6H_5 (m, 15) 6.9–7.6
12b	1595 (w), 1160 (m), 1120 (m)	3.42 (d, 2, J = 5.3 Hz)	6.10 (t, 1, J = 5.3 Hz)	NCH_3 (s, 3) 3.05 C_6H_5 (m, 10) 6.9–7.6
12c	1710 (s), 1180 (s), 1125 (m)	4.43 (d, 2, J = 5.0 Hz)	6.22 (t, 1, J = 5.0 Hz)	OCH_2CH_3 (t, 3, J = 7.0 Hz) 1.37 OCH_2CH_3 (q, 2, J = 7.0 Hz) 4.35 C_6H_5 (m, 10) 6.9–7.6

[a] All ir spectra were run as a Nujol mull. [b] $CDCl_3$ solvent; all chemical shifts reported in parts per million followed by the splitting patterns, the number of protons, and the coupling constants.

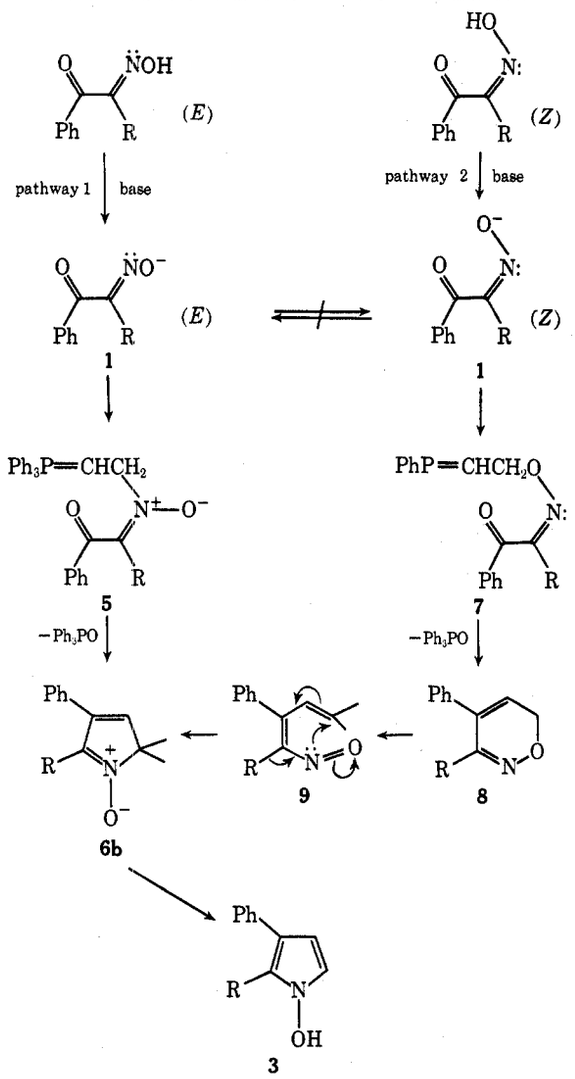
plete deuterium exchange in the 4 and 5 positions of the pyrrole ring, exchange taking place five times faster in the 5 position. The deuterium exchange experiment thus indicates the contribution of tautomeric forms **6a** and **6b** to the hydroxypyrrole **3** (Scheme IV).

Treatment of **3a** with either benzoyl chloride or acetic anhydride in pyridine gave the expected O-acylated products **10a** and **10b** in yields of 78 and 80%, respectively.

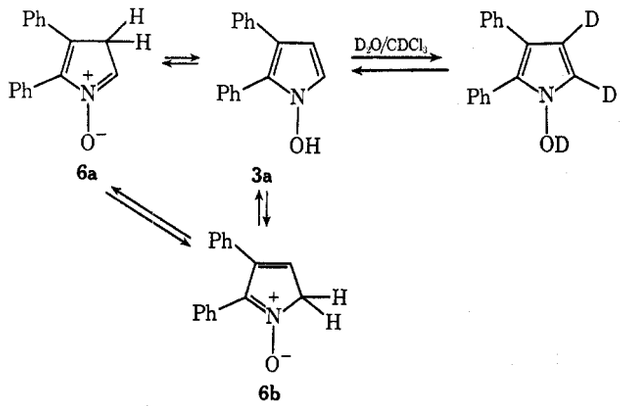
Monohydrazones.—Treatment of monohydrazones **11a–c** with **1** gave exclusively the substituted 2,3-dihydropyridazines **12a–c** in good yields (Scheme V, Table III), without any indication as to the presence of any 1-aminopyrrole **13**. Although the geometric configurations of the hydrazones **11a** and **11b** are not known, it must be assumed that they exist as the *Z* isomer[7] in order to yield pyridazines. It is known

(7) If they do not exist as the *Z* isomer, the energy of isomerization to the *Z* isomer from the *E* must lie sufficiently low for this to occur under reaction conditions.

SCHEME III
MECHANISMS OF 1-HYDROXYPYRROLE FORMATION



SCHEME IV
TAUTOMERIC 1-HYDROXYPYRROLES

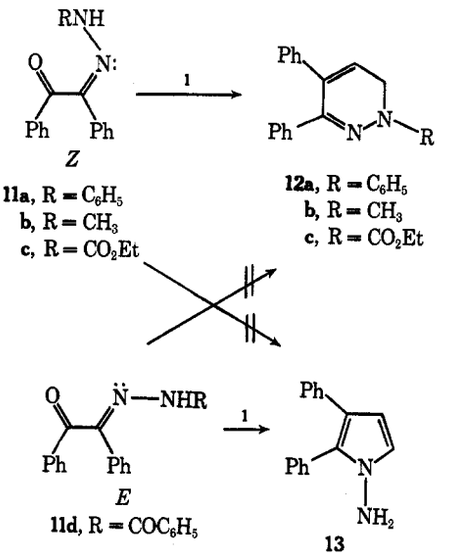


that the *N*-carboethoxybenzil monohydrazone (**11c**) used in our work exists as the *Z* isomer;[8] sufficient quantities of the *E* isomer could not be obtained in order to test its reactivity with **1**.

Benzoylation of benzil monohydrazone with benzoyl chloride in pyridine gave a 42% yield of (*E*)-*N*-benzoyl-

(8) M. Rosenblum, V. Nayak, S. K. Das Gupta, and A. Longroy, *J. Amer. Chem. Soc.*, **85**, 3874 (1963).

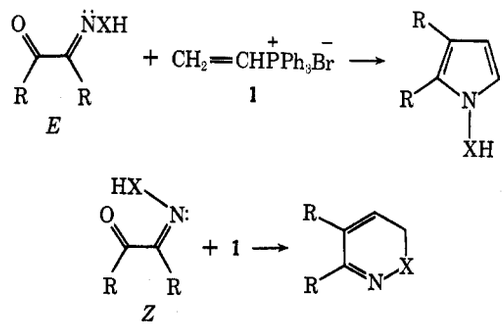
SCHEME V
REACTION OF BENZIL MONOHYDRAZONES WITH 1



benzil monohydrazone (**11d**), mp 139–140°. Refluxing the *E* isomer in dry toluene for 43 hr gave a 52% yield (based on nmr integration of the NH resonances) of the *Z* isomer **14**. The *E* and *Z* isomers were differentiated on the basis of their nmr NH resonances. The *Z* isomer, capable of intramolecular hydrogen bonding, exhibited a broad singlet (exchangeable with D_2O) at δ 10.17; the *E* isomer, not capable of intramolecular hydrogen bonding, at δ 9.37. This same trend had appeared in the (*E*)- and (*Z*)-*N*-carboethoxybenzil monohydrazones. However, only small amounts of *Z* isomer could be obtained pure by fractional crystallization from ether. Isolation and identification of the *Z* and *E* isomers of the *N*-benzoylhydrazone, and the reaction of **11d** (the *Z* isomer) to give only the 1-aminopyrrole **13** (Scheme V) was totally predictable, and paralleled the reactions of the oximes **2a–c** with vinyl salt **1**.

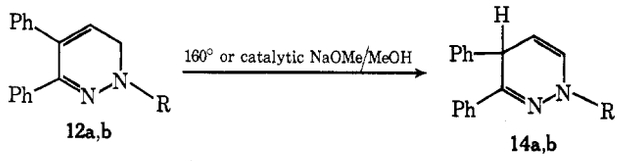
A more general scheme for the reactions of α-imino ketones with vinyl salt **1** can be written, the *E* isomer leading to the 1-substituted pyrroles and the *Z* isomer giving the pyridazine (Scheme VI).

SCHEME VI



The thermal rearrangement of pyridazines **12a** and **12b** at 160° in a sealed tube gave 1 4-dihydropyridazines **14a** and **14b** in 52 and 44% yields (by nmr integration). This apparent [1,3] sigmatropic rearrangement cannot be considered as such, since the heating of **12a** and **12b** as a dilute solution in refluxing mesitylene gave no 1,4-dihydropyridazine and starting material

SCHEME VII
THERMAL AND BASE-CATALYZED REARRANGEMENT OF 12a AND 12b



12a,b 14a,b

was recovered. Treatment of **12a** and **12b** with a catalytic amount of NaOMe in refluxing MeOH gave the 1,4-dihydropyridazine in quantitative yield (Scheme VII).

Thus the use of vinyltriphenylphosphonium bromide as a versatile reagent for the synthesis of heterocyclic species has been expanded to include N-substituted pyrroles and pyridazines.

Experimental Section

General Procedure for the Preparation of 1-Hydroxypyrroles (3a–c), N-Substituted 2,3-Dihydropyridazines (12a–c), and *N*-Benzamidopyrrole.—To a slurry of 480 mg of NaH dispersion (57% in mineral oil) in 10 ml of dry DMF was added dropwise 10 mmol of the appropriate monoxime (**2a–c**) or monohydrazone (**11a–d**) in 30 ml of DMF. The deeply colored reaction mixture was stirred at room temperature until all hydrogen evolution had ceased, and vinyltriphenylphosphonium bromide (**1**) (3.69 g, 10 mmol) was introduced all at once; the reaction mixture became almost colorless. After stirring for the appropriate time (Table I) the reaction mixture was poured into 800 ml of H_2O and extracted with two 200-ml portions of ether. The ether extracts were combined, backwashed with 600 ml of H_2O, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to an oil. The oil was chromatographed on silica gel powder, eluting with benzene. The chromatographic fractions were monitored by tlc to ensure the separation from triphenylphosphine oxide. The pure fractions were combined, concentrated *in vacuo* to a solid material, and recrystallized from the appropriate solvent (Table I).

Acylation of 3a with Benzoyl Chloride and Acetic Anhydride.—To a solution of 1.0 mmol of **3a** in 5 ml of dry pyridine was added 1.1 mmol of benzoyl chloride or acetic anhydride. The reaction mixture was allowed to stand for 3 days at −10°. The reaction mixture, with small amounts of pyridine hydrochloride present, was poured onto 40 g of crushed ice. Stirring and scratching afforded a white solid, which was filtered and washed with 20 ml of ice water. The product was air dried and recrystallized from small amounts of petroleum ether (bp 30–60°) to give an analytically pure sample.

Compound **10a** (*O*-benzoyl) was obtained in 78% yield: mp 80–83°; ν (Nujol) 1760 (s), 1575 cm^{-1} (m); nmr ($CDCl_3$) δ 6.43 (d, 1, J = 3.3 Hz, 4 proton), 6.82 (d, 1, J = 3.3 Hz, 5 proton), 7.0–8.1 (m, 15, C_6H_5).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.10; H, 5.20; N, 4.08.

Compound **10b** (*O*-acetyl) was obtained in 80% yield: mp 104–107°; ν (Nujol) 1700 (s), 1595 cm^{-1} (m); nmr ($CDCl_3$) δ 2.20 (s, 3, $CDCH_3$), 6.37 (d, 1, J = 3.3 Hz, 4 proton), 6.78 (d, 1, J = 3.3 Hz, 5 proton), 6.9–7.4 (m, 10, C_6H_5).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.00. Found: C, 77.64; H, 5.55; N, 5.01.

(*E*)-*N*-Benzoylbenzil Monohydrazone (11d).—To a solution of 21.0 g (0.1 mol) of benzil monohydrazone in 200 ml of dry pyridine was added 14.0 g (0.1 mol) of benzoyl chloride over a period of 10 min. The solution was stirred for 14 hr at room temperature. The reaction mixture was poured onto 600 g of cracked ice and stirred until all of the ice had melted. The water was decanted and the remaining gummy yellow residue was dissolved in CH_2Cl_2 and washed with three 100-ml portions of water. The CH_2Cl_2 was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to a volume of 50 ml, and 100 ml of ether was added. Scratching and chilling furnished 13.2 g (42%) of **11d**. Recrystallization from EtOH–Et_2O furnished an analytical sample: mp 139.5–140°; ν (Nujol) 3320 (w), 1690 (s), 1640 cm^{-1} (m); nmr ($CDCl_3$) δ 7.1–8.3 (m, 15, C_6H_5), 9.37 (s, 1, NH).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.56; H, 4.95; N, 8.88.

(*Z*)-*N*-Benzoylbenzil Monohydrazone.—A solution of 2 g of **11d** in 20 ml of dry toluene was refluxed for a period of 24 hr. The isomerization was monitored by nmr following the NH resonances, until the per cent of *Z* isomer reached a maximum. After 24 hr the percentages of *Z* and *E* isomers were 52 and 48%, respectively. The toluene was removed *in vacuo* and the solid residue was fractionally crystallized from ether–hexane to yield 230 mg of pure **14**: mp 123–125°; ν (Nujol) 3310 (w), 1690 (s), 1630 cm^{-1} (m); nmr ($CDCl_3$) δ 7.1–8.2 (m, 15, C_6H_5), 10.17 (s, 1, NH).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.76; H, 5.01; N, 8.85.

***N*-Methylbenzil Monohydrazone (11b).**—To a solution of 21.0 g (0.10 mol) of benzil dissolved in a minimum amount of dry CH_3CN (200 ml) was added 4.2 g (0.10 mol) of methyl hydrazine. The reaction became extremely exothermic and the acetonitrile began to reflux. After the exotherm had subsided the mixture was allowed to remain at room temperature for 10 hr. Evaporation *in vacuo* to a yellow oil gave upon addition of 100 ml of ether a white solid, mp 136–137°. Recrystallization from CH_2Cl_2–Et_2O afforded 16.2 g (65%) of **11b**: mp 138–140°; ν (Nujol) 3260 (w), 1650 (s), 1590 cm^{-1} (m); nmr ($CDCl_3$) δ 2.95 (s, 3, $-NCH_3$), 4.36 (s, 1, NH), 7.0–8.2 (m, 10, C_6H_5).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.91; H, 5.87; N, 12.02.

(*Z*)-*N*-Carboethoxybenzil Monohydrazone (11c).—To a slurry of 22.4 g (0.10 mol) of benzil monohydrazone in 120 ml of dry pyridine cooled to 0° was added dropwise 0.11 mol of ethyl chloroformate. Immediately a red solution formed and a crystallization of pyridine hydrochloride occurred. The slurry was stirred for 4 hr at 0° and then 4 days at room temperature. The reaction mixture was then poured into 600 ml of water and extracted with ether. The ether layer was washed five times with water, dried (Na_2SO_4), and evaporated *in vacuo* to a pale pink solid. Recrystallization from CH_2Cl_2–hexane afforded 11.2 g (37%) of **11c**, mp 123.5–124° (lit.[8] mp 124–125°).

Base-Catalyzed Isomerization of 2,3-Dihydropyridazines (12a,b) to 1,4-Dihydropyridazines (14a,b).—To a solution of 12 mg of sodium in 40 ml of dry EtOH was added 2 mmol of the 2,3-dihydropyridazine (**12a,b**). The yellow solution was refluxed for 7 days, tlc indicating the complete disappearance of starting material. The solution was concentrated *in vacuo* to a yellow oil, and water and ether were added. The ether extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to a yellow solid, which upon recrystallization from EtOH–hexane afforded the 1,4-dihydropyridazines in quantitative yield.

1,3,4-Triphenyl-1,4-dihydropyridazine (14a) had mp 131–133°; ν (Nujol) 1590 (m), 1310 (s), 1250 cm^{-1} (m); nmr ($CDCl_3$) δ 4.85 (d, 1, J = 6.0 Hz, 4 proton), 5.31 (dd, 1, J = 7.5, 6.0 Hz, 5 proton), 6.93 (d, 1, J = 7.5 Hz, 6 proton), 7.0–8.1 (m, 15, C_6H_5).

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.84; H, 5.78; N, 8.92.

1-Methyl-3,4-diphenyl-1,4-dihydropyridazine (11b) had mp 69–70°; ν (Nujol) 1595 (m), 1315 (s), 1250 cm^{-1} (m); nmr ($CDCl_3$) δ 3.28 (s, 3, NCH_3), 2.60 (d, 1, J = 5.5 Hz, 4 proton), 4.91 (dd, 1, J = 7.3, 5.5 Hz, 5 proton), 6.13 (d, 1, J = 7.5 Hz, 6 proton).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.62; H, 6.35; N, 10.99.

Heating **12a** and **12b** at 160° neat for 1.5 hr gave approximately 60% of **14a** and **14b**, respectively, before extensive decomposition occurred. Yields were determined by nmr integration with an internal standard and identification of **14a** and **14b** was accomplished by peak enhancement with authentic samples.

Registry No.—**1**, 5044-52-0; **3a**, 34288-44-3; **3b**, 34288-45-4; **3c**, 34288-46-5; **10a**, 34288-47-6; **10b**, 34288-48-7; **11b**, 34289-86-6; **11d**, 34289-87-7; **11d** *Z* isomer, 34289-88-8; **12a**, 34288-49-8; **12b**, 34288-50-1; **12c**, 34288-51-2; **13**, 34288-52-3; **14a**, 34288-53-4; **14b**, 34288-54-5.

Acknowledgment.—This work was supported by a U. S. Public Health Service Grant (CA 11000) for which we are most grateful.