New phenylglyoxal aldoximes were prepared following procedures for the known compounds in this series.[9,10] The properties of the new phenylglyoxal aldoximes are described in Table I.

We have observed that in all cases different amounts of corresponding substituted benzoic acids appeared as by-products. The crude compounds were washed with an excess of 5% cold solution of sodium bicarbonate, which dissolved all free acid present. Analytical samples were prepared by recrystallization in diluted ethyl alcohol.

Substituted Glyoxal Aldoxime Semicarbazones.—Pyruvaldehyde aldoxime semicarbazone[11] and phenylglyoxal aldoxime semicarbazone[12] are known compounds. New phenylglyoxal aldoxime semicarbazones were prepared according to the Dey procedure[12] by interaction of corresponding phenylglyoxal aldoximes with equimolecular quantities of semicarbazide hydrochloride and sodium acetate dissolved in a minimum quantity of 50% ethyl alcohol at 50°. The solvent of recrystallization was also 50% ethyl alcohol. The physical data of semicarbazones obtained are summarized in Table II.

***as*-Triazine-3,5(2H,4H)-dione (Azauracil).**—3-Amino-5-hydroxy-*as*-triazine,[7] 2.25 g (0.02 mol) in 10 ml of concentrated hydrochloric acid and 10 ml of water, was treated with a concentrated solution of 1.5 g (0.022 mol) of sodium nitrite, below 5°. The solution was shaken occasionally during 3 hr standing at room temperature, after which pure azauracil crystallized out. A further quantity can be obtained by concentration of the mother liquor. The yield was 70%, mp 283° (water) (lit.[8] mp 272°). Mixture melting point with a specimen of the same compound prepared with a 15% yield by cyclization of glyoxylic acid semicarbazone[5] was not depressed.

6-Methyl-*as*-triazine-3,5(2H,4H)-dione (Azathymine).—A suspension of pyruvaldehyde aldoxime semicarbazone, 7.20 g (0.05 mol) in 40 ml of water, was refluxed for 20 hr with 7 g (0.05 mol) of anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the refrigerator was removed each 3 hr by circulating water through it. Finally, the solution was charcoaled, acidified with hydrochloric acid, and evaporated until dry on a steam bath. The dry residue was extracted in a Soxhlet apparatus with ethyl acetate. The solvent was distilled off, and the residue was recrystallized in water to give 2.1 g (36%), mp 216° (lit.[13] mp 212°). The infrared spectrum of the compound obtained was identical with the spectrum of a specimen prepared by another method.[13]

6-Phenyl-*as*-triazine-3,5(2H,4H)-dione.—Phenylglyoxal aldoxime semicarbazone,[12] 2 g (0.01 mol) in 25 ml of water, was refluxed for 8 hr with 2.76 g (0.02 mol) of the anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the course of reaction in the condenser was removed occasionally by washing the condenser. The solution was charcoaled and acidified with concentrated hydrochloric acid to give a white crystalline powder. The yield was 1.2 g (64%), mp 262° (from diluted alcohol) (lit.[5] mp 262°).

When the same reaction was conducted with sodium bicarbonate instead of potassium carbonate a 25% yield was obtained.

Substituted 6-phenyl-*as*-triazine-3,5(2H,4H)-diones were prepared by cyclization of the corresponding phenylglyoxal aldoxime semicarbazones according to the above method. The properties of the compounds obtained are summarized in Table III.

Registry No.—Table I—1, 17628-74-9; 2, 1823-76-3; 3, 17628-76-1; Table II—1, 17628-77-2; 2, 17628-78-3; 3, 17628-79-4; 4, 17628-80-7; 5, 17628-81-8; 6, 17628-82-9; 7, 17628-83-0; Table III—1, 17629-10-6; 2, 17629-11-7; 3, 17629-12-8; 4, 17629-16-2; 5, 17629-17-3; 6, 17629-18-4; 7, 17629-19-5.

Acknowledgment.—The author wishes to thank Professor N. Sharghi for his constant encouragement and the Central Treaty Organization for provision of essential materials.

(9) L. Claisen, *Ber.*, **20**, 655 (1887).
(10) W. Borsche, *ibid.*, **62**, 1360 (1929).
(11) H. Rupe and S. Kessler, *ibid.*, **42**, 4715 (1909).
(12) B. B. Dey, *J. Chem. Soc.*, **105**, 1039 (1914).
(13) K. Chang Pauline, *J. Org. Chem.*, **23**, 1951 (1958).

Fischer Indole Synthesis. Direction of Cyclization of Isopropylmethyl Ketone Phenylhydrazone

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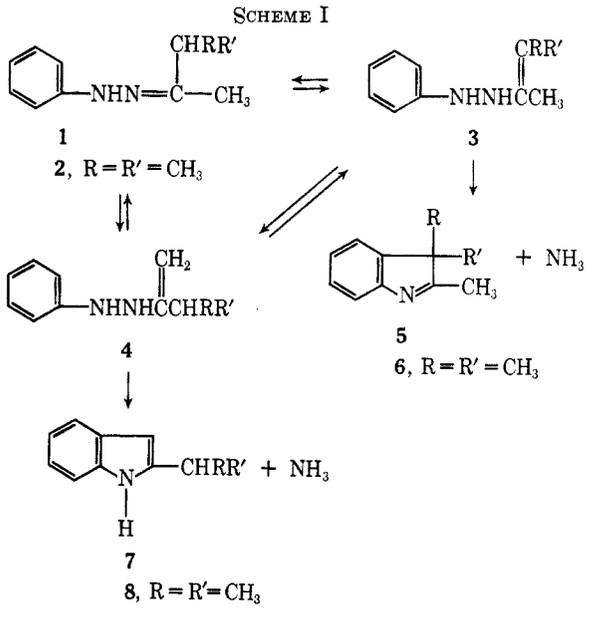
Plancher obtained 2,3,3-trimethylindolenine (2,3,3-trimethylpseudoindole) (**6**) by treating isopropylmethyl ketone phenylhydrazone (**2**) with zinc chloride in alcohol.[1] After observing the reactions of other phenylhydrazones (**1**), he established the rule that ketone arylhydrazones containing the group —NHN=C(CH_3)CH< cyclize exclusively at the tertiary carbon atom to give 2-methylindolenines (**5**).[2] More recent reports have shown that the direction of ring closure of unsymmetrical methyl ketone phenylhydrazones is dependent on the nature of the acid catalysts.[3-5] This dependence has been attributed to shifts in the equilibrium (**3** ⇌ **4**)[4] and, more specifically, to steric interactions in the transition state which are affected by the size of the acid.[5] See Scheme I.

SCHEME I



We wish to report another interesting exception to Plancher's rule. The phenylhydrazone **2** cyclizes to give both the indolenine **6** and 2-isopropylindole **8**, with the product ratio depending on the strength and amount of acid catalyst. Thus, the product ratio (**6**:**8**) decreases from 95:1 with dilute H_2SO_4 to 0.15:1 with 6 mol of 78% H_2SO_4. This is the first recorded case in which both directions of cyclization have been obtained by varying the concentration and amount of one catalyst. Weak acids give **6** exclusively. The results are given in Tables I and II. Samples of 2,3,3-tri-

(1) G. Plancher, *Ber.*, **31**, 1496 (1898).
(2) G. Plancher and A. Bonavia, *Gazz. Chim. Ital.*, **32**, 418 (1902).
(3) For a thorough review of the Fischer indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 387 (1963).
(4) N. P. Buu-Hoi, P. Jacquignon, and D. Perin-Roussel, *Bull. Soc. Chim. Fr.*, 2849 (1965).
(5) R. E. Lyle and L. Skarlos, *Chem. Commun.*, **18**, 644 (1966).

SCHEME II

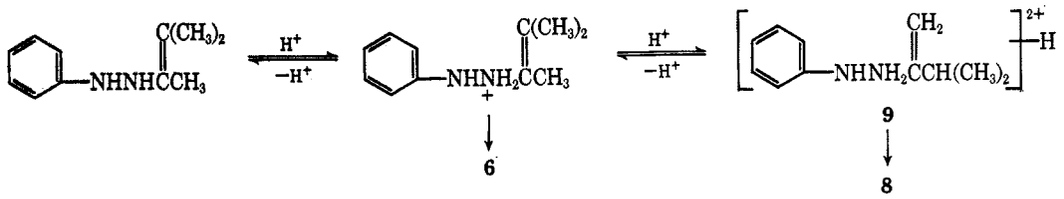


TABLE I
EFFECT OF CONCENTRATION AND AMOUNT OF H_2SO_4 ON YIELD IN THE CYCLIZATION OF 2 AT 90°

% H_2SO_4	$-H_0$[a]	Mole ratio of H_2SO_4: hydrazone	% 2,3,3-trimethylindolenine[b]	% 2-isopropylindole[b]
10	0.31	1:1	94.8	1.1
		5:1	88.5	2.1
20	1.01	1:1	93.9	1.4
		5:1	93.0	1.8
30	1.72	1:1	97.7	<1.0
		5:1	91.4	<1.0
40	2.41	1:1	96.4	1.0
		5:1	91.2	<1.0
50	3.38	1:1	97.8	<1.0
		5:1	85.3	4.4
60	4.46	1:1	98.1	<1.0
		5:1	56.1	30.3
70	5.65	1:1	96.5	<1.0
		5:1	27.1	67.1
78	6.71[c]	1:1	91.5	2.1
		5:1	20.2	79.0
		6:1	12.9	84.0

[a] All H_0 values are taken from M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] Analysis by gas chromatography. [c] Determined graphically from values in footnote *a*.

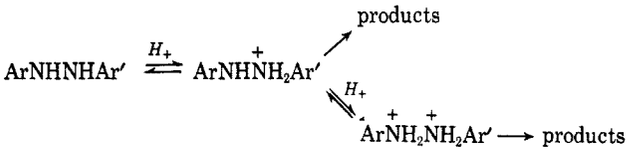
TABLE II
EFFECT OF CATALYST ON YIELD IN THE CYCLIZATION OF 2 AT 90°

Catalyst	$-H_0$[a]	Mole ratio of catalyst: hydrazone	% 2,3,3-trimethylindolenine[b]	% 2-isopropylindole[b]
$ZnCl_2$[c]		1:1	87.3	
		5:1	90.4	
100% HOAc		6:1	90.3	
50% $KHSO_4$	−0.4[d]	5:1	98.0	
75% $KHSO_4$	−0.4[d]	5:1	95.2	
85% H_3PO_4	3.7[d]	5:1	97.2	
PPA[e]	4.80[f]	1:1	73.5	14.3
PPA[e]	4.80[f]	5:1	8.4	72.2
10% HCl	1.00	1:1	59.0[g]	
		5:1	91.5	2.1
37% HCl	4.41	1:1	81.2[g]	
		2:1	95.4	
		5:1	81.7	10.1
		17:1	69.9	23.8

[a] See Table I, footnote *a*. [b] Analysis by gas chromatography. [c] Toluene was the solvent. [d] Determined graphically from values given in footnote *a*. [e] PPA = polyphosphoric acid. Toluene was the solvent. [f] Value for 100% H_3PO_4. [g] The reaction was incomplete.

methylindolenine (**6**) which were treated with an excess of 78% sulfuric acid gave no indication of isomerization to **8**.

These data indicate that the direction of cyclization of **2** is affected by the acidity of the reaction medium. For instance, only the strong acids (H_2SO_4, HCl, and H_3PO_4) give **8** and, even then, only when sufficiently concentrated. In fact, H_3PO_4 gives **8** only when anhydrous. This necessity of a minimum acidity for the formation of **8** can be explained if we compare the mechanisms of the Fischer indole synthesis and the benzidine rearrangement.[3,6] The benzidine rearrangement can be either first or second order with respect to hydrogen ion concentration, depending on the nature of the hydrazo compound and the acidity of the reaction medium. In fact, some such rearrangements are first order at low acidity values and become second order as the acidity is increased.[6] The accepted mechanism of the Fischer



indole synthesis involves a single protonation step, although the possibility of a second protonation has been considered.[3-6]

Our results indicate that double protonation may occur, initiating a new mechanism which leads to the formation of compound **8**. See Scheme II above. This hypothesis receives additional support from the observation that **8** forms only if more than 2 mol of HCl or H_2SO_4 is used. Thus, 1 mol is needed for the first protonation, another mole for the second protonation, and an additional amount is required to bind with the NH_3, which is a by-product. Protons from the second ionization of H_2SO_4 lack the activity to effect the second protonation; this is demonstrated by the failure of $KHSO_4$ to form any **8**. Unfortunately, the data do not indicate the point of attachment of the second proton, although strict comparison with the benzidine rearrangement would place the second proton on the other nitrogen of the enehydrazine (**9**). The acidity dependence could also mean that the two-proton mechanism is really one with one less base molecule in the activated complex. In this case the second proton would be removing an electron donor, such as a nitrogen-containing species, instead of adding to the enehydrazine as in **9**.[7] Kinetic studies are being conducted to determine the specific role of the second proton in the mechanism.

A convenient measure for the acidity of this system is the Hammett acidity function. Actually, H_0 should be used for the first protonation and H_+ for the second; however, Bonner and Lockhart[8] have shown that, in aqueous H_2SO_4, H_0 and H_+ either differ by a small constant or are identical. The data in Table I show that H_2SO_4 solutions must have a $-H_0$ value of at least 3.38 in order to produce significant amounts of **8**. A comparison with Table II indicates that H_2SO_4 of a given $-H_0$ value gives more **8** than does H_3PO_4 or HCl having

(6) The similarity between these mechanisms has been discussed by H. J. Shine, "Aromatic Rearrangements," Elsevier Publishing Co., New York, N. Y., 1967, p 190.

(7) We wish to thank Dr. Edward S. Lewis for this and other valuable suggestions.

(8) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 364 (1957).

the same value. Weak acids do not effect the second protonation because their acidity does not increase sufficiently with concentration.[9]

Experimental Section

All melting and boiling points are uncorrected. Infrared absorption spectra were determined on a Perkin-Elmer Model 421. Gas chromatography was conducted on an F & M Model 500 (thermal conductivity detector) using a 15 ft × 0.25 in. column containing 15% methyl silicone stationary phase on a support of 60–80 mesh diatomaceous earth. Elemental analyses were determined by Galbraith Laboratories and by our analytical department on a Perkin-Elmer Model 210 elemental analyzer.

Isopropylmethyl Ketone Phenylhydrazone (2).—Phenylhydrazine (324 g, 3 mol) and isopropylmethyl ketone (258 g, 3 mol) were heated together at 70° for 4 hr. Distillation under vacuum gave 477 g (90% theory) of **2**, bp 85–87° (11 mm).

Cyclization of 2. A. with $ZnCl_2$.—Isopropylmethyl ketone phenylhydrazone (**2**) (17.6 g, 0.1 mol) was dissolved in 30 ml dry toluene, and anhydrous zinc chloride (13.6 g, 0.1 mol) was added. The mixture was heated at 90° for 3 hr and drowned into 200 ml of water. The toluene layer was collected, and the solvent was evaporated under vacuum.

B. With Protonic Acids.—Isopropylmethyl ketone phenylhydrazone (**2**, 1.67 g, 0.1 mol) was added to the acid at 25°, heated at 90° for 3 hr, cooled to 25°, and neutralized with sodium carbonate. The organic layer was extracted with ether and dried over magnesium sulfate, and the solvent was evaporated.

Analysis of Products.—The mixture of reaction products was analyzed by gas chromatography. The peaks for **6** and **8** were compared with those for known samples. For identification purposes, **6** was separated by distillation, an ether solution was treated with hydrogen chloride gas, and the white hydrochloride was recrystallized from ethyl acetate: mp 188–189°.

Anal. Calcd for $C_{11}H_{14}ClN$: C, 67.5; H, 7.21; N, 7.16. Found: C, 67.4; H, 7.3; N, 7.1.

2-Isopropylindole (**8**) was recrystallized from methanol and water. Ir spectra and mixture melting point (73–74°) showed the reaction product to be identical with the known sample.

Anal. Calcd for $C_{11}H_{13}N$: C, 83.0; H, 8.17; N, 8.80. Found: C, 82.96; H, 8.37; N, 8.52.

2-Isopropylindole (**8**).—Isobutyryl chloride (52.2 g, 0.5 mol) was added dropwise to *o*-toluidine (107 g, 1.0 mol) in 100 ml of ether. The mixture was heated at reflux (35°) for 1 hr; 200 ml H_2O was added; and the ether was evaporated on a steam bath. Ethanol was added at 65° until the white solid dissolved and the solution was allowed to cool. The N-isobutyryl-*o*-toluidine (**10**) was collected by filtration to yield 81 g (0.45 mol), mp 115–116°.

A mixture of 35.4 g (0.2 mol) of **10** and 19 g (0.49 mol) of $NaNH_2$ was heated to 250° for 10 min and then cooled. Ethanol (10 ml) and then 50 ml of H_2O were added dropwise. 2-Isopropylindole (**8**) was removed by steam distillation and recrystallized from water and methanol to yield 16.4 g (0.103 mol), mp 73–74°.

Anal. Calcd for $C_{11}H_{13}N$: C, 83.0; H, 8.17; N, 8.80. Found: C, 83.0; H, 8.5; N, 9.0.

Registry No.—**2**, 6243-71-6; **6** HCl, 17790-92-0; **8**, 17790-93-1.

(9) See Table I, footnote *a*.

Kinetics of the Thermal Rearrangement of Ascaridole

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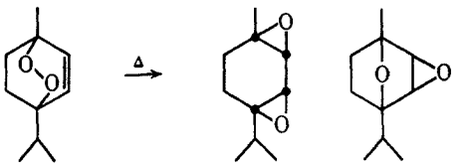
Ascaridole (I), the main constituent of chenopodium oil and one of the best known anthelmintics, is converted into an isomeric material when heated in an inert solvent.[1] The isomeric product can be isolated in pure form in yields up to 80% from the thermal rearrangement.[2] As a result of several investigations[1,3-6] two structures had been suggested for the rearrangement product: namely, 1,2:3,4-diepoxy-*p*-menthane (II) and 1,4:2,3-diepoxy-*p*-menthane (III). In 1956 a report[2] on the steriochemistry of products resulting from the acid hydrolysis of the isomeric material firmly established the 1,2:3,4-diepoxy structure (II).



I II III

Although the thermal rearrangement of ascaridole has been known since 1911,[1] no kinetic study of the reaction has been reported. The present work was undertaken to obtain rate data with a view toward evaluating the kinetic parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$. Specific rate constants for the isomerization of ascaridole have been obtained at a series of temperatures in the range 100 to 150°. Changes in concentration of the peroxide were followed by measurement of the ascaridole C-2 and C-3 proton area in the nmr spectra. An internal standard of toluene was utilized. Spectra of samples heated for varying lengths of time showed only peaks which could be attributed to toluene, ascaridole, or the diepoxide (II). The results of our measurements appear in Table I. Specific rate constants at each temperature were obtained using the *method of least squares*. The energy of activation (E_a) and the frequency factor (A) were evaluated from the Arrhenius equation, $\ln k_1 = -E_a/RT + \ln A$, and the kinetic parameters ($\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$) were calculated from the equations

$$\Delta H^{\ddagger} = E_a - RT;\ k_1 = \frac{h}{kT} e^{-\Delta G^{\ddagger}/RT};\ \Delta S^{\ddagger} = \frac{\Delta G^{\ddagger} - \Delta H^{\ddagger}}{T}$$

Figure 1 shows a typical plot of the rate equation, whereas Figure 2 gives the Arrhenius plot from which E_a and A were evaluated.

TABLE I

SUMMARY OF KINETIC DATA FOR THE THERMAL REARRANGEMENT OF ASCARIDOLE[a]

Temp, °C	$k_1 \times 10^5$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
98.5	2.14 ± 0.02	30.7	31.4	1.88
111.0	6.67 ± 0.01	30.6	31.6	2.60
132.0	74.1 ± 0.3	30.6	31.5	2.20
151.0	417. ± 3	30.6	31.6	2.36

[a] $E_a = 31.4 \pm 0.1$ kcal; $A = 6.6 \times 10^{12}$ sec^{-1}.

The simplest mechanism consistent with the values obtained, involves a homolytic cleavage of –O–O– bond

(1) (a) E. K. Nelson, *J. Amer. Chem. Soc.*, **33**, 1404 (1911); (b) E. K. Nelson, *ibid.*, **35**, 84 (1913).

(2) O. A. Runquist, Ph.D. Thesis, University of Minnesota, July 1956, p 20–46; *Dissertation Abstr.*, **16**, 2313 (1956).

(3) H. Thoms and W. Dobke, *Arch. Pharm.* (Weinheim), **268**, 128 (1930).

(4) F. Richter and W. Presting, *Ber.*, **64**, 878 (1931).

(5) T. A. Henry and H. Paget, *J. Chem. Soc.*, **119**, 1722 (1921).

(6) (a) M. Matic and D. A. Sutton, *ibid.*, 349 (1953); (b) M. Matic and D. A. Sutton, *ibid.*, 2679 (1952).