Table I—Mean Isoniazid Metabolic Clearance Values as a Function of Acetylator Status

Acetylator Status	Number of Subjects	Isoniazid Clearance ± *SD*, ml/min/kg
Slow	10	2.0 ± 0.8
Intermediate	5	5.1 ± 0.6
Rapid	3	7.9 ± 0.6

and Ac^S (slow acetylator), for one autosomal gene locus (8). Slow acetylators are designated Ac^S/Ac^S, while intermediate and rapid acetylators are designated Ac^R/Ac^S and Ac^R/Ac^R, respectively.

As reported in Table I, the arithmetic mean of the acetylation capacity of the genotype Ac^S/Ac^S is 2.0 ml/min/kg. The value of the allele Ac^S is thus 2.0/2 = 1.0. Genotype Ac^R/Ac^R has the mean value of 7.9 ml/min/kg; for the allele Ac^R, 7.9/2 = 3.95 or approximately 4.0. Since the quantitative effect (or gene product) of the alleles is considered additive, the mean acetylation capacity for the group Ac^R/Ac^S should follow the relationship:

$$\frac{Ac^S/Ac^S}{2} + \frac{Ac^R/Ac^R}{2} = Ac^R/Ac^S \qquad \text{(Eq. 2)}$$

Thus, based on the calculations from the mean slow and rapid acetylator modes, the expected mean acetylation capacity of the heterozygote would be 5.0 ml/min/kg [(2.0/2) + (7.95/2)]. The observed mean value for the intermediate acetylator was 5.10 ml/min/kg, a difference of less than 3% from the expected value of 5.0 ml/min/kg. Although these retrospective data apply only to uremic patients, they do support the concept that acetylation clearance determinations may represent a useful method for identifying slow, intermediate, and rapid acetylators.

Finally, significant amounts of acetylisoniazid appear in the urine of normal subjects following oral administration of isoniazid, approximately 49 and 32% of the dose in fast and slow acetylators, respectively (10). Obviously, kidney failure should reduce significantly the contribution of the renal excretory pathway for acetylisoniazid. Thus, uremic patients receiving isoniazid might accumulate substantial levels of acetylisoniazid and, subsequently, be exposed to excessive amounts of its metabolite, acetylhydrazine. Acetylhydrazine is subsequently oxidized to hepatotoxic substances (15).

None of the published reports of isoniazid kinetics in renal failure examined the possibility of metabolite accumulation (12, 16, 17). There is a great need to study the effects of renal insufficiency on the plasma and urinary excretion kinetics of acetylisoniazid and metabolites and the potential for removal by dialysis. It is also important to investigate the effects of uremia on acetylisoniazid hydrolysis, as well as the oxidative activation of acetylhydrazine to toxic substances.

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Ketonic Oxidation Products of Cyclobarbital

R. BOUCHE *x, M. DRAGUET-BRUGHMANS *, J. P. FLANDRE *, C. MOREAUX ‡, and M. VAN MEERSSCHE ‡

Received July 12, 1977, from the **Laboratoire d'Analyse des Médicaments, Institut de Pharmacie, U.C.L. 7340, 1200 Bruxelles, Belgium,* and the ‡*Unité de Chimie Physique et de Cristallographie, Bâtiment Lavoisier, 1348 Louvain-La-Neuve, Belgium.* Accepted for publication October 25, 1977.

Abstract □ Chemical or biochemical oxidation of cyclobarbital yielded 5-(3-oxo-1-cyclohexen-1-yl)-5-ethyl -2,4,6- (1*H*,3*H*,5*H*)-pyrimidinetrione, and photochemical oxidation gave 5-(6-oxo-1-cyclohexen-1-yl)-5-ethyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione. These compounds were isolated and purified by TLC, and their structures were determined by UV, IR, NMR, and mass spectral data; the crystalline structure was determined by X-ray diffraction.

Keyphrases □ Cyclobarbital—oxidation products isolated and identified □ Oxidation—cyclobarbital, products isolated and identified □ Depressants, central—cyclobarbital, oxidation products isolated and identified

The identification of ketonic oxidation products of cyclobarbital[1] [5-(1-cyclohexen-1-yl)-5-ethyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione] (I) has been reported by several investigators. Tsukamoto *et al.* (1) isolated a ketonic derivative from rabbit urine; it was identified by UV spectrometry and chemical means as 5-(3-oxo-1-cyclohexen-1-yl)-5-ethyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (II). Later, Goldschmidt and Koss (2) extracted this same product (II) from rat urine, while Willems *et al.* (3) iden-

[1] Phanodorm, British pat. 231,150 (1924) to Farbenfabriken Bayer and Co.

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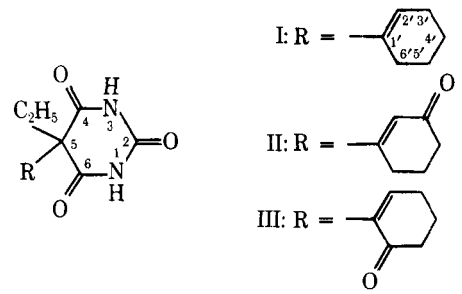

tified 5-(6-oxo-1-cyclohexen-1-yl)-5-ethyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (III) as a degradation product of I using IR, NMR, and mass spectral data.

The purposes of this study were to establish the definitive characteristics of both II and III by physicochemical methods and to prove exclusive production of II or III from I by photochemical, chemical, and human biochemical means.

EXPERIMENTAL

TLC System—Silica gel[2] glass plates (20 × 20 cm, thickness of 0.5 mm) were activated for 1 hr at 100° and used immediately after cooling. A portion (20 mg) of the product, dissolved in a minimum volume of acetone, was deposited in a band 2 cm from the bottom edge of the plate. Ascending development was achieved in a chromatographic tank saturated with chloroform–acetone–methanol [90:10:1 (v/v)].

GLC System[3]—A glass column (2.0 m long and 4.0 mm i.d.) was packed with 3% OV-17[4] on 100–120-mesh Gas Chrom Q[4] and then conditioned at 240° overnight. Chromatographic conditions were: column oven, 230°; injection port and flame-ionization detector, 250°; and nitrogen gas flow, 40 ml/min. A 2-μl aliquot of a 1-mg/ml methanol solution was injected.

UV Spectrophotometry[5]—UV spectra of the derivatives were recorded between 220 and 300 nm with a double-beam spectrophotometer in 1-cm quartz cells. The pH of the solutions was adjusted to 2.0, 10.0, and 13.0 by appropriate buffers. Concentrations were $\sim 10^{-4}$ *M*.

IR Spectrophotometry[6]—IR spectra were recorded in potassium bromide disks (0.5% w/w) and in saturated dichloromethane solutions (cell thickness of 1.0 mm).

Mass Spectrometry[7]—A portion (1.0 mg) of solid substance was injected into the spectrometer. The ionization potential was 70 ev.

Proton NMR Spectroscopy[8]—Spectra were recorded from a saturated solution of deuterated methanol.

X-Ray Diffraction[9]—The diffractometer was a four-circle, punchcard-operated unit. Signal intensities were measured by ω–2θ scanning to $2\theta_{max}$: 110°. Radiation was Cu–K with λ = 1.5418 Å. Structures were resolved by the MULTAN 74 computer program and refined by a full-matrix least-squares procedure[10,11].

Preparation of I—A commercial product[12] was extracted and purified by successive methanol extractions; it was then dried to a constant melting point (170°).

Preparation of II—A portion (500 mg) of I purified by TLC was administered orally to human subjects. Urine was monitored for 24 hr after administration and ether extracted in an acid medium [10% (w/w) sulfuric acid]. The ether fraction was evaporated to dryness and separated by TLC. Four spots appeared at R_f 0.05, 0.07, 0.25, and 0.48. The band corresponding to R_f 0.25 was methanol extracted. After the methanol was evaporated, the residue was purified by fractional sublimation at 200° under 10^{-1} torr.

[2] Silica gel GF_{254}, type 60, Stahl (Merck).
[3] HP 5750 gas chromatograph fitted with a flame-ionization detector.
[4] Applied Science Laboratories.
[5] Perkin-Elmer model 124 UV-visible double-beam spectrophotometer.
[6] Perkin-Elmer model 580 IR spectrophotometer.
[7] LKB model 9000 S mass spectrometer.
[8] Varian model XL 100 NMR spectrometer.
[9] Picker X-ray four-circle diffractometer.
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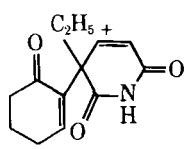
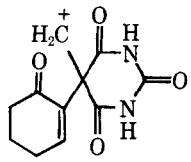

IV: *m/e* 233


V: *m/e* 235

Preparation of III—One gram of I (acid form) was exposed for 48 hr to 254-nm UV radiation, and the product was purified by TLC. Four spots appeared at R_f 0.13, 0.19, 0.28, and 0.52. The band corresponding to the third spot was methanol extracted. After methanol evaporation, the residue was purified by fractional sublimation at 250° under 10^{-1} torr.

RESULTS AND DISCUSSION

The melting temperature of II, 227°, was in good agreement with the oxidation product melting temperature (222°) reported previously (4), taking into account a possible sublimation of the product. On the other hand, no sudden melting point was observed for III, which decomposed at about 290°. The much lower melting temperature reported in the literature (3, 5) may have been due to impurities or, more probably, to sublimation of III at 255°.

In solution, II and III had the same IR absorption bands as I at 1762, 1740, and 1712 cm^{-1}; this finding supports the integrity of the 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione ring. In addition, these products showed the same spectral changes as I in the UV region, dependent on pH.

Nevertheless, II and III differed from I by an additional absorption band at 218 (II) and 213 (III) nm (pH 2.0), by a fourth band at 1677 (II) and 1670 (III) cm^{-1}, and by an ion molecular peak at *m/e* 250. The additional oxygen atom in the carbonyl group conjugated together with a double bond allows two structure possibilities: the 5-(3-oxo-1-cyclohexen-1-yl) or the 5-(6-oxo-1-cyclohexen-1-yl) substituent. The NMR spectra of I and III were identical with those published (3); the chemical shifts of the olefinic proton were 5.84 and 7.32 ppm, respectively. The olefinic proton chemical shift of II was 6.06 ppm.

The theoretical value of the olefinic proton chemical shift may be calculated for the two possible isomers using the additive increments of

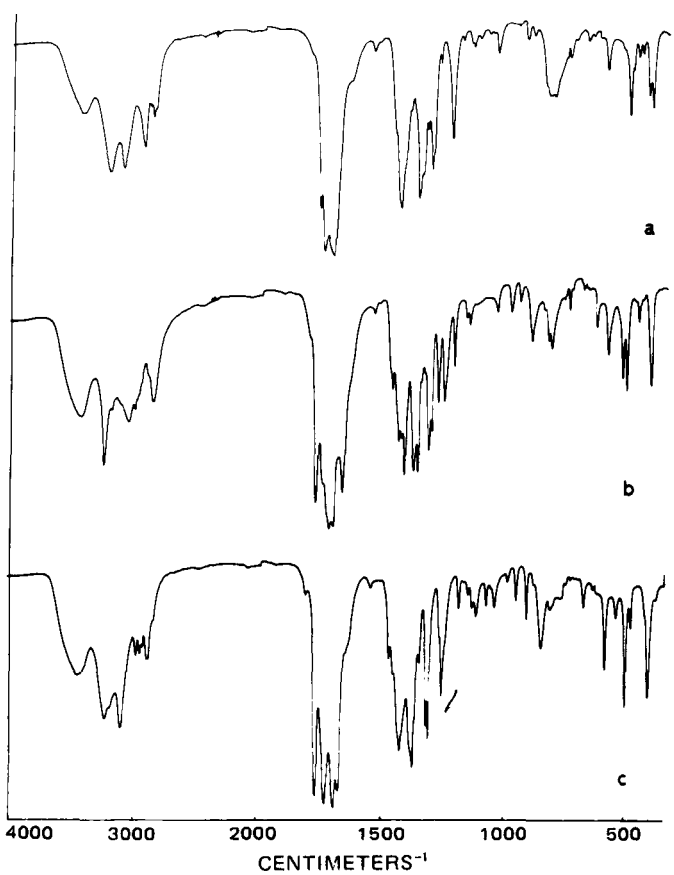


Figure 1—*IR spectra in potassium bromide disks of I (a), II (b), and III (c).*

Table I—Crystal Data of I–III

	I[a]	II	III
Molecular formula	$C_{12}H_6N_2O_3$	$C_{12}H_{14}N_2O_4$	$C_{12}H_{14}N_2O_4$
Molecular weight	236.26	250.25	250.25
System	Monoclinic	Monoclinic	Monoclinic
Space group	C2/c	$P2_1$	$P2_1/c$
Unit cell dimensions, Å or degrees			
a	22.415 (6)	8.822 (3)	9.719 (3)
b	10.770 (6)	10.072 (3)	17.081 (5)
c	10.350 (5)	6.848 (2)	12.273 (4)
β	92.29 (5)	104.07 (2)	143.11 (3)
Unit cell volume, Å^3	2496.6	590.2	1223.0
Number of formula units per cell = z	8	2	4
Density, D_X, g/cm^3	1.258	1.407	1.358

[a] Values from Ref. 12.

Matter *et al.* (6): $\delta = 5.25 + Z_{cis} + Z_{gem} + Z_{trans}$. The Z_{cis} shielding increment corresponding to 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione-5-ethyl radical was estimated at 0.14 when using the olefinic proton chemical shift of I. This procedure provided chemical shifts of 6.21 (II) and 6.95 (III) ppm. Moreover, the NMR spectrum of the olefinic proton of II exhibited a nonresolved multiplet, corresponding to only lone-range coupling. For III, a triplet corresponding to a J_3 coupling constant due to the neighboring methylene was observed. This observation removed any ambiguity about formulas of II and III.

The main difference between the mass spectra of II and III was the presence of two very strong peaks at M − 15 and M − 17 for III (3, 7), which may be explained by formation of radicals IV and V. They arise from a stronger interaction of the cyclohexenyl ring and the ethyl substituent of the 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione ring.

In the solid phase, the IR absorption of these chemically related products showed appreciable differences of the crystalline lattice. In solution, IR spectra of I, II, and III showed the same absorption bands with the same relative intensities at 1760, 1737, and 1712 cm^{-1} and additional bands at 1677 and 1670 cm^{-1} for II and III, respectively. However, the print of these three compounds differed in this latter region when spectra were recorded in potassium bromide disks (Fig. 1).

The very strong intensity of the 1760-cm^{-1} band of II and III suggests a decoupling of the 4,6-carbonyl vibrators (8) arising either from a change in the geometry and rigidity of the 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione ring or from an intermolecular hydrogen bond asymmetry. Moreover, the shift of the absorption band corresponding to the ethylenic carbonyl group, 27 (II) and 7 (III) cm^{-1}, indicates the existence of a hydrogen bond, including an oxygen atom, in II. In a diluted solution, the 3380-cm^{-1} band arose for the three compounds from the free NH valence vibration. As a potassium bromide disk, I gave two broad bands at 3210 and 3090 cm^{-1}, which Bellamy (9) associated with cyclic dimer formation. In the spectrum of III, the same two bands appeared; however, the first was accompanied by a distinct shoulder at 3170 cm^{-1}. This fact may suggest the existence of two different intermolecular hydrogen bonds.

Compound II showed a very strong absorption band at 3230 cm^{-1} with two relatively weak bands at 3170 and 3030 cm^{-1}. Miyazawa (10, 11) studied and solved the problems of the secondary associated amide absorption and, more specifically, of the *cis*-cyclic lactams. He identified the in-plane deformation band as dropping near 1440 cm^{-1}. Therefore, it is possible to consider the absorption band in the 3100-cm^{-1} region as a combination band of the NH in-plane mode and the carbonyl absorption. The existence of two separate bands in this region suggests the existence of two intermolecular bond types, which differ one from another in length and/or NH···O bond angle. This fact must be considered together with the shift of the cyclohexenyl carbonyl vibration frequency. This assignment was confirmed by the partially deuterated product

Table II—Interatomic Lengths[a] of the Carbonyl Groups in II and III[b]

Carbonyl Group Position	II	III
2	1.205	1.203
4	1.201	1.223
6	1.220	1.225
3′[c]	1.229	—
6′[c]	—	1.214

[a] Lengths in angstroms. [b] Results obtained by X-ray diffraction. [c] The 3′- and 6′-carbonyls are the 3-oxo-1-cyclohexen-1-yl and 6-oxo-1-cyclohexen-1-yl carbonyl groups, respectively.

Table III—Intermolecular Hydrogen Bond Characteristics of I–III

	Contact	Length, Å, N···O	Length, Å, NH	Angle, NH···O
I[a]				
$N_1I^b \rightarrow O_2III$	+ + 1 0 1	2.89		
$N_3I \rightarrow O_4III$	+ 1 0 0	2.85		
$N_2II \rightarrow O_2IV$	− − 1 0 2	2.89		
$N_3II \rightarrow O_4IV$	− − 1 0 1	2.85		
$N_1V \rightarrow O_2VII$	+ + 1 0 1	2.89		
$N_3V \rightarrow O_4VII$	+ 1 0 0	2.85		
$N_1VI \rightarrow O_2VIII$	− − 1 0 2	2.89		
$N_3VI \rightarrow O_4VII$	− − 1 0 1	2.85		
II				
$N_1I \rightarrow O_{3'}{}^bII$	+ − + 2 1 2	2.82	1.03	170.5°
$O_6I \rightarrow N_3I$	+ 0 0 1	2.88	0.90	164.5°
$N_3I \rightarrow O_6I$	− 0 0 1	2.88	0.90	164.5°
$O_{3'}{}^bI \rightarrow N_1II$	+ + 2 0 2	2.82	1.03	170.5°
III				
$N_1I \rightarrow O_4IV$	− − 1 0 1	2.99	0.94	167.3°
$O_6I \rightarrow N_3IV$	− − 1 0 1	2.85	0.95	174.5°
$N_3I \rightarrow O_6IV$	+ 1 0 0	2.85	0.95	174.5°
$O_4I \rightarrow N_1IV$	+ 1 0 0	2.99	0.94	167.3°
$N_1II \rightarrow O_4III$	+ − 1 1 0	2.99	0.94	167.3°
$O_6II \rightarrow N_3III$	+ − 1 1 0	2.85	0.95	174.5°
$N_3II \rightarrow O_6III$	− − − 1 1 1	2.85	0.95	174.5°
$O_4II \rightarrow N_1III$	− − − 1 1 1	2.99	0.94	167.3°

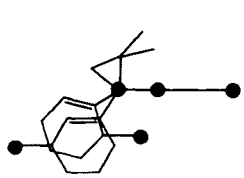
[a] Values from Ref. 12. The hydrogen atoms are not positioned. [b] N_1I represents the N_1 atom in the pyrimidinetrione ring, included in the molecule I of the (000) projection of the unit cell.

spectrum; it showed three absorption bands at 2395 (strong), 2340 (weak), and 2235 (medium) cm^{-1}.

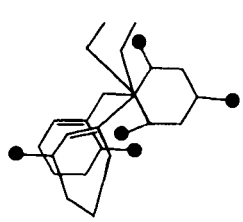
The crystalline structure, the spectrometric data confirmation, and the explanation of the thermal behavior differences between II and III are given by X-ray diffraction results (Table I).

The geometry of the two molecules was practically identical. The interatomic length mean value of the CN bond, 1.368 (II) and 1.367 (III) Å, exhibited a certain double bond character according to the observed lengths, 1.47 Å for a single CN bond and 1.352 Å for pyrimidinic CN bonds. On the other hand, the CO bond lengths showed significant differences, taking into account the environment and the existence of the intermolecular hydrogen bonds (Table II).

In II and III, the planes were nearly perpendicular; they formed 78° (II) and 99° (III) dihedral angles. The ethylenic bond occupied a transoide space orientation with regard to the 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione ring, but the angle formed with the plane of this latter ring was 30° larger in III (Structure B) than in II (Structure A) because of electrostatic interaction between the 6-pyrimidinetrione oxygen atom and the 6-oxocyclohexenyl carbonyl group.



A



B

With regard to the intermolecular bond, however, the three compounds differed entirely. In I and II, the hydrogen bonds were arranged alternately; they included the 2- and 4-pyrimidinetrione carbonyl groups (I) and the 4-pyrimidinetrione and 3-oxocyclohexenyl carbonyl groups (II). In III, hydrogen bonds generated cyclic structures, analogous to the adenine–thymine configuration in the Watson–Crick model of DNA, which included the 4- and 6-pyrimidinetrione carbonyl groups (Table III), and the molecules formed two linear interlacing chains. The structure's tenseness explains the high melting temperature (>290°) of III.

Concerning the preparation of II and III, the chemical oxidation of I, using *tert*-butyl chromate and the *in vivo* biochemical oxidation by six human subjects, gave exclusively the ketonic derivative II. On the other hand, UV irradiation of I gave III and not II. The results were unambiguous; the compounds were purified by fractional sublimation at 220° and then at 280°. Thus, detection of 0.5% of III in II and vice versa was very easy. Conflicting results (4) were probably due to the use of poorly purified materials.

A yield of oxidation products with different structures as a result of the different experimental conditions may be explained by the reaction mechanisms: a radical reaction for III and a chemical or biochemical mechanism, which implies steric hindrance with regard to enzyme or reactant, for II.

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Synthesis and Hypotensive Activity of a Series of 2-Substituted 5,6-Dimethoxyindazoles

THOMAS J. SCHWAN ˣ, LeROY J. HONKOMP, CHARLES S. DAVIS, and GUY S. LOUGHEED

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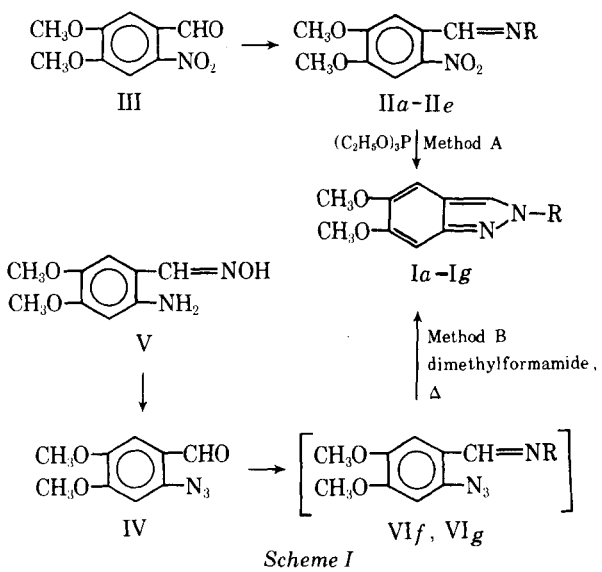
Abstract □ The synthesis and hypotensive activity in the dog of a series of 2-substituted 5,6-dimethoxyindazoles are reported. Structure–activity relationships for this class of compounds are discussed. Indazoles containing the diethylaminoethyl, 3-pyridyl, and hydroxyethyl functions in the 2-position were the most effective in lowering blood pressure for the longest times (>270 min).

Keyphrases □ Indazoles, substituted—synthesized, evaluated for hypotensive activity □ Hypotensive activity—various substituted indazoles evaluated □ Structure–activity relationships—various substituted indazoles evaluated for hypotensive activity

A limited number of 2-substituted indazoles have been subjected to extensive pharmacological screening (1–4). For example, 2-(2-aminoethyl)indazole showed only weak serotonin-like activity and exhibited no appreciable pharmacological responses in smooth muscle tests (5). This report describes the synthesis and results of a pharmacological evaluation of a series of 2-substituted 5,6-dimethoxyindazoles.

EXPERIMENTAL[1]

Chemistry—The majority of the 2-substituted 5,6-dimethoxyindazoles (Ia–Ie, Table I) were synthesized from *N*-substituted 6-nitroveratrylideneamines (IIa–IIe) in refluxing triethyl phosphite (6). These intermediate Schiff bases were conveniently prepared by the acid-catalyzed condensation of 6-nitroveratraldehyde (III) with primary amines

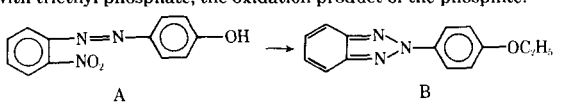


Scheme I

(Scheme I). However, since Schiff bases containing labile hydrogens are susceptible to alkylation by triethyl phosphite or the triethyl phosphate formed during indazole synthesis[2], an alternative route using nonal-

[1] Melting points were determined on a Mel-Temp apparatus, and those below 230° are corrected. IR spectra were determined as Nujol mulls on a Perkin-Elmer 137-B spectrophotometer and were consistent with the assigned structures.

[2] Cadogan *et al.* (6) showed that 2-nitro-4'-hydroxyazobenzene (A) in refluxing triethyl phosphite gave the ethoxy compound (B), presumably by alkylation of the phenol with triethyl phosphate, the oxidation product of the phosphite.



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