g of 10% Pd/C were hydrogenated at room temperature and pressure until 1 equiv of hydrogen had been taken up (ca. 1 h) after which the rate of uptake slowed essentially to zero. The filtered solution was then freeze–dried to obtain the sodium salts of the products. To obtain the products free of phosphate, the reaction mixture was stirred at 0 °C under a layer of diethyl ether and the pH of the aqueous layer reduced to 1 by the addition of 1 M hydrochloric acid. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. The resulting acid, an oil, could be used as such or converted into the sodium salt (add 1 equiv of aqueous sodium bicarbonate and freeze–dry) or the *N,N'*-dibenzylethylenediamine salt (oil dissolved in ether and 1 equiv of the amine added).

(b) In Dioxan. Samples of 6,6-dibromopenicillanic acid (0.5 g) dissolved in 50 mL of dioxane (freshly distilled from sodium) to which had been added 1.8 g of disodium hydrogen phosphate heptahydrate and 0.1 g of 10% Pd/C were hydrogenated at room temperature and pressure for 2 h. The filtered solution was evaporated to dryness under reduced pressure. The residue was extracted with ether and the solution dried and evaporated. The residual acidic oil could be converted to its sodium or *N,N'*-dibenzylethylenediamine salts as above.

Total isolated monobromopenicillanic acid yields were about 50% in each case.

The infrared spectra of the amine salt of **1a** and the amine salts from the hydrogenation mixtures were very similar. Their NMR spectra, which are discussed in detail above, indicate that the hydrogenation products were mixtures of **1a** and **1d** with the latter making up approximately 10% (aqueous hydrogenation) or 30% (dioxane hydrogenation) of the total. It is clear also from the NMR spectra that the amine salts from the hydrogenations contained small but variable quantities of excess amine and thus these salts were not suitable for chemical analysis. Consequently, sodium salts of pure **1a** and of the dioxan hydrogenation mixture were converted essentially quantitatively into *p*-bromophenacyl esters by the method of Bamberg and co-workers.[17] The **1a** ester (mp 93.5–94 °C) was purified by recrystallization from methanol and yielded the following spectral data: IR (KBr) 1775 (β-lactam C=O), 1740, 1700 cm^{-1}; NMR ($CDCl_3$) τ 8.32 (6 H, broad s, $(CH_3)_2$), 5.34 (1 H, s, 3-H), 5.19 (1 H, d, J = 1.5 Hz, 6-H), 4.63 (2 H, s, CH_2), 4.58 (1H, d, J = 1.5 Hz, 5-H), and 3.20, 2.09 (4 H, AB quartet, J = 8.5 Hz, Ar-H). Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: C, 40.28; H, 3.17; N, 2.94; Br, 33.49. Found: C, 40.35; H, 3.09; N, 3.28; Br, 33.20. The hydrogenation product esters, an oil, were purified as a mixture by elution from a silica column with benzene and yielded the following spectral data: IR (neat) 1775 (β-lactam C=O), 1750, 1700 cm^{-1}; NMR ($CDCl_3$), the peaks of the α-epimer as above and the following peaks integrating to ca. 30% of the total: τ 8.28 (6 H, s, $(CH_3)_2$), 5.37 (1 H, s, 3-H), and 4.71, 4.34 (2 H, AB quartet, J = 4.6 Hz, 5-H, 6-H). The remaining peaks of the β-epimer are superimposed on those of the α-epimer. Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: as above. Found: C, 40.25; H, 3.27; N, 3.11; Br, 33.60.

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Registry No.—**1a,** 24138-28-1; **1a** *p*-bromophenacyl ester, 66842-39-5; **1c,** 24158-88-1; **1d,** 26631-90-3; **1d** *p*-bromophenacyl ester, 66842-40-8.

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Reaction of α-Aryl-*N*-alkyl- and α,*N*-Diarylnitrones with Aroyl Chlorides. A New Synthesis of *N*-Alkyl-*O*-aroylhydroxylamines

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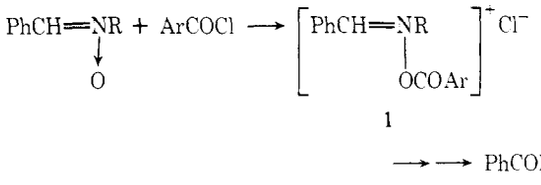
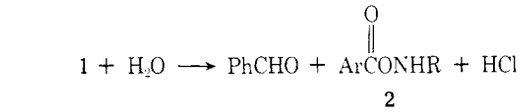
In 1890 Beckmann observed that acetyl chloride, benzoyl chloride, and acetic anhydride catalyzed the isomerization of α-phenyl-*N*-benzylnitrone to *N*-benzylbenzamide.[1] Since then many examples of the isomerization of nitrones into amides by acylating reagents have been reported.[2] Discussion continues on the mechanism of the rearrangement,[2-5] but all investigators agree that the first step of the reaction is a nucleophilic displacement by the nitrone oxygen on the electrophilic carbon of the acylating reagent. Thus, in the case of the isomerization of an α-phenyl-*N*-alkylnitrone by an aroyl chloride it is presumed that the aroyloxy(benzylidene)ammonium chloride **1** is formed initially (eq 1). With the exception of a few compounds obtained from the interaction of heterocyclic *N*-oxides with very electrophilic acyl halides,[6-8] compounds such as **1** have not been isolated.



We have augmented the evidence for the existence of **1** by treating α-phenyl-*N*-alkylnitrones and aroyl chlorides at ambient temperature in moist solvents (acetone, ether, and acetonitrile). The products, which apparently arise by the hydrolysis of **1**, are *N*-alkyl-*O*-aroylhydroxylamines (**2**) and aldehydes (eq 2).



The crude hydrochlorides **2**·HCl separated from the reaction mixture and were hydrolyzed to give the bases **2** (Table I). In those cases where **2** were oils ($PhCO_2NHMe$, $PhCO_2NH$-*t*-Bu, and 3,4-$Cl_2C_6H_3CO_2NH$-*t*-Bu) the corresponding hydrochlorides (**2**·HCl) were isolated and purified (Table I). *N*-Methyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochloride was also prepared in 58% yield when α-(*p*-nitrophenyl)-*N*-methylnitrone was substituted for α-phenyl-*N*-methylnitrone in the reaction with *p*-nitrobenzoyl chloride.

The proof of structure for **2** consists of NMR, IR, and mass spectroscopy. Unequivocal characterization was provided by utilizing a synthesis developed by Zinner[9] to prepare *N*-methyl- and *N*-*tert*-butyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochlorides and *N*-methyl- and *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochlorides. The spectral and physical properties of the *N*-alkyl-*O*-aroylhydroxylamine hydrochlorides made by our method and that of Zinner's were identical. The yields were comparable by the two methods in those in-

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Table I. The Reaction of α-Aryl-*N*-alkylnitrones with Aroyl Chlorides

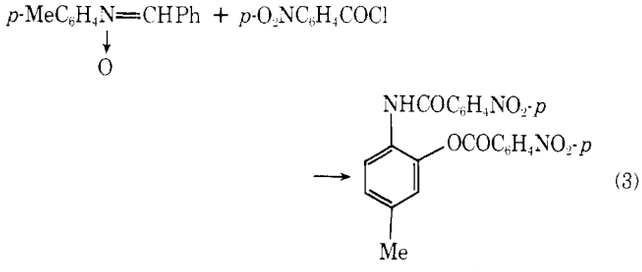
$$ArCH{=}N(O)R + Ar'COCl \xrightarrow{(Me)_2CO-H_2O} \underset{\mathbf{2}}{Ar'CO_2NHR} + HCl + ArCHO$$

			2			2·HCl		
Ar	R	Ar'[f]	% yield	mp, °C	registry no.	% yield	mp, °C	registry no.
Ph	Me[d]	Ph		oil	66809-88-9	67	131–134[a,b]	27130-46-7
Ph	Me	p-$O_2NC_6H_4$	63	107–110[a]	66809-82-3			
Ph	Me	m-$O_2NC_6H_4$	68	75–76[a]	66809-83-4			
Ph	Me	3,4-$Cl_2C_6H_3$	32	75–77[a]	66809-84-5			
Ph	t-Bu[e]	Ph		oil	51339-03-8	69	173–179[c]	66809-86-7
Ph	t-Bu	p-$O_2NC_6H_4$	60	69–71[a]	1746-98-1			
Ph	t-Bu	m-$O_2NC_6H_4$	44	57–60[a]	66809-85-6			
Ph	t-Bu	3,4-$Cl_2C_6H_3$		oil	66809-89-0	49	145–148[a]	66809-87-8

[a] Satisfactory analytical data for C, H, and N were reported. [b] Zinner[10] reported a melting point of 123–124 °C. [c] Zinner[9] reported a melting point of 178–180 °C. [d] Registry no.: 3376-23-6. [e] Registry no.: 3376-24-7. [f] Registry no.: PhCOCl, 98-88-4; p-$O_2NC_6H_4COCl$, 122-04-3; m-$O_2NC_6H_4COCl$, 121-90-4; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4.

stances when the *N*-alkyl group was *tert*-butyl, but were dramatically lower by Zinner's method (e.g., 7–14%) when the *N*-alkyl group was methyl. The molecular ions for *N*-methyl-*O*-(*p*-nitrobenzoyl)- and *N*-methyl-*O*-(3,4-dichlorobenzoyl)hydroxylamines were determined and corresponded to the theoretical values. The NMR spectra taken in Me_2SO-d_6 for all the *N*-methyl-*O*-aroylated hydroxylamines and hydroxylamine hydrochlorides showed a single sharp absorption peak for the methyl group at δ 2.95–3.10, while the methyl groups of the *N*-*tert*-butyl-*O*-aroylated hydroxylamine hydrochlorides all absorbed at δ 1.30–1.40.

The reaction of α,*N*-diarylnitrones and aroyl chlorides in ether followed by the addition of water afforded *O*,*N*-diaroyl-*o*-aminophenols. For example, reaction of *p*-nitrobenzoyl chloride and α-phenyl-*N*-*p*-tolylnitrone gave a 74% yield of *N*-(*p*-nitrobenzoyl)-2-(*p*-nitrobenzoyloxy)-4-methylaniline (**3**) (eq 3). Similarly, reaction of α-phenyl-*N*-*p*-tolylnitrone



(3)

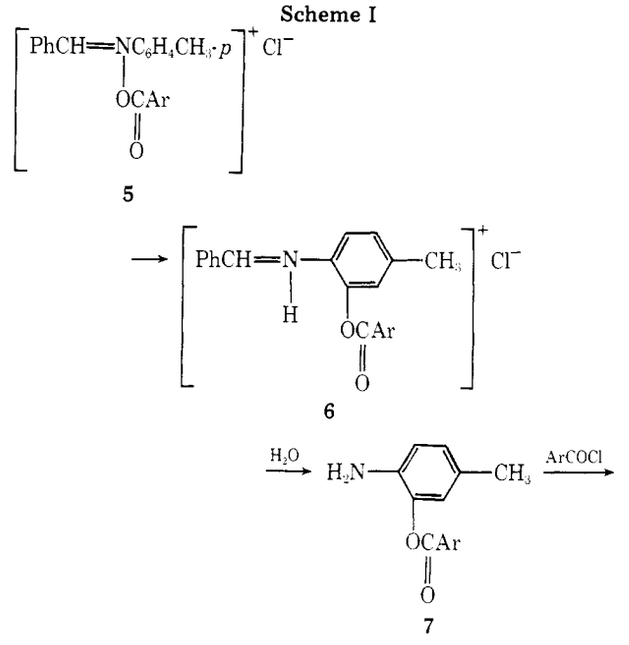
3

with *p*-chlorobenzoyl chloride formed *N*-(*p*-chlorobenzoyl)-2-(*p*-chlorobenzoyloxy)-4-methylaniline (**4**) in 53% yield. The identities of **3** and **4** were substantiated by alternate syntheses involving the reaction of 2-amino-5-methylphenol with *p*-nitrobenzoyl chloride and *p*-chlorobenzoyl chloride, respectively.

A reasonable mechanism to account for **3** and **4** is the formation and rearrangement of an aroyloxy(benzylidene)-ammonium chloride (**5**) into **6**, subsequent hydrolysis of **6** to **7**, and further aroylation of **7** (Scheme I). The rearrangement of **5** to **6** is quite similar to the reaction of *N*-arylnitrones with oxalyl chloride, in which a chloroglyoxalate group is introduced into the ortho position of the *N*-aryl ring.[11]

Another mechanistic possibility is the formation of *O*-(*p*-nitrobenzoyl)-*N*-*p*-tolylhydroxylamine (similar to the formation of **2**) which ionizes to the nitrenium ion *p*-$CH_3C_6H_4NH^+$ and a *p*-nitrobenzoate ion. Recombination of these ions gives **7** and further aroylation of **7** yields **3**. A precedent for this view is the ionization of *N*-alkyl-*N*-chloroanilines to *N*-alkyl-*N*-phenylnitrenium ions and a chloride ion, which then forms *o*-chloro- and *p*-chloro-*N*-alkylanilines.[12]

Scheme I



Experimental Section

Synthesis of 2 and 2·HCl. The aroyl chloride (2 mmol) is added all at once to a well-stirred solution of the nitrone (2 mmol) in 6 mL of commercial acetone. Within several minutes the *N*-alkyl-*O*-aroylhydroxylamine hydrochloride (**2**·HCl) precipitates and is filtered, followed by washing with ether, whereupon more of the hydrochloride is collected from the filtrate. The **2**·HCl's were slurried with water for a few minutes and the crude **2** was filtered. *N*-Methyl-*O*-(*m*-nitrobenzoyl)- and *N*-*tert*-butyl-*O*-(*p*-nitrobenzoyl)hydroxylamines were recrystallized from cyclohexane, *N*-methyl-*O*-(*p*-nitrobenzoyl)-hydroxylamine was recrystallized from 95% ethanol, *N*-methyl-*O*-(3,4-dichlorobenzoyl)hydroxylamine was recrystallized from hexane, and *N*-*tert*-butyl-*O*-(*m*-nitrobenzoyl)hydroxylamine was recrystallized from petroleum ether (bp 63–65 °C).

Synthesis of 3. *p*-Nitrobenzoyl chloride (0.371 g, 2 mmol) was added to a solution of 0.211 g (1 mmol) of α-phenyl-*N*-*p*-tolylnitrone in 10 mL of dry ether. After 5 min some nitrone hydrochloride precipitated and was filtered. The filtrate was allowed to stand overnight and then treated with a few drops of water. The solvent was evaporated, the residue was slurried with a small quantity of cold methanol, and the crude **3** (0.30 g, 74%) was filtered. After recrystallization from ethanol **3** melted at 240–242 °C. Anal. Calcd for $C_{21}H_{15}N_3O_7$: C, 59.86; H, 3.59; N, 9.97. Found: C, 59.85; H, 3.73; N, 9.60.

Synthesis of 4. Compound **4** was prepared in a similar manner as **3** in 53% yield. It melted at 202–203 °C after recrystallization from

toluene. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3$: C, 63.02; H, 3.78; N, 3.50. Found: C, 62.88; H, 4.20; N, 3.96.

Alternate Synthesis of 3. To a rapidly stirred mixture of 1.23 g (10 mmol) of 2-amino-5-methylphenol, 100 mL of benzene, and 21 mL of 1 N NaOH was added in portions 3.71 g (20 mmol) of *p*-nitrobenzoyl chloride. After 1.5 h the crude **3** was filtered, washed with water, and weighed (3.64 g, 87%). Recrystallization of **3** from ethanol gave crystals melting at 240–242 °C.

Alternate Synthesis of 4. By employing the same procedure described above for the synthesis of **3**, compound **4** was prepared in 95% yield by admixing 0.620 g (5 mmol) of 2-amino-5-methylphenol, 25 mL of benzene, 10 mL of 1 N NaOH, and 1.75 g (10 mmol) of *p*-chlorobenzoyl chloride. Recrystallization of **4** from toluene gave crystals that melted at 203–204 °C.

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Registry No.—**3**, 66809-90-3; **4**, 66809-91-4; α-phenyl-*N*-*p*-tolylnitrone, 19064-77-8; *p*-chlorobenzoyl chloride, 122-01-0; 2-amino-5-methylphenol, 2835-98-5.

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4,5-Dihydropyridazines: X-ray Structure of a Dimer

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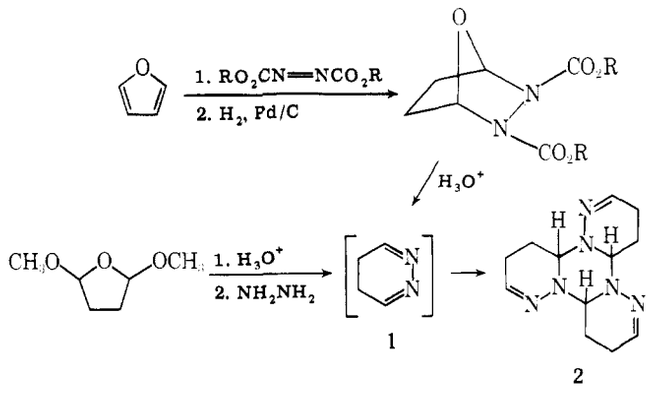
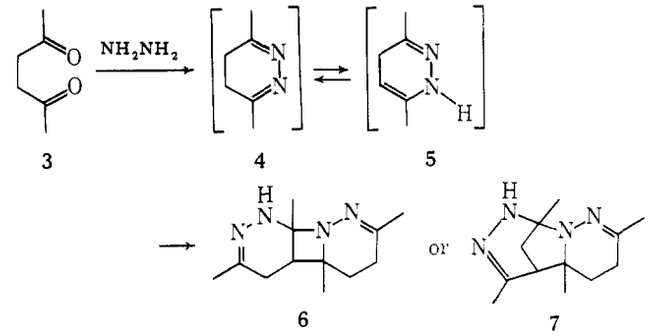
Our interest in 4,5-dihydropyridazines (**1**) as pseudodienes in Diels–Alder reactions prompted us to investigate the tautomerizations and self-condensations of this class of compounds.

Earlier[1] we reported the preparation and X-ray structure of a trimer (**2**) of 4,5-dihydropyridazine (**1**) obtained in ~5% overall yield from dialkyl azodicarboxylate and furan. We find that this trimer is more easily prepared by the aqueous hydrolysis of 2,5-dimethoxytetrahydrofuran, followed by addition of hydrazine to the hydrolysis mixture. Yields are 35–40% based on dimethoxytetrahydrofuran. Since the isolation of succinaldehyde from this hydrolysis is reported in 30% yield,[2] the conversion of aldehyde to trimer is reasonably good.



1 2

It is known that the condensation of hexane-2,5-dione (acetonylacetone (**3**)) with hydrazine affords a dimer of 3,6-dimethyl-4,5-dihydropyridazine[3,4] rather than the monomer or trimer. More recently, De Mayo, Stothers, and Usselman[4] reduced the possible structures of the dimer to **6** and **7**, giving



3 4 5 6 7

preference to **7** on the basis of ^{13}C NMR data. Initial attempts to take X-ray structural data of the dimer itself were unsuccessful due to the instability of the dimer. However, the N-acetylated derivative of the dimer, originally reported by De Mayo, Stothers, and Usselman[4] as being more stable, was successfully used in the structure determination. We have found, in support of the ^{13}C NMR work, that **7** is the correct structure.

Crystal Data. $C_{14}H_{22}N_4O$: monoclinic, $P2_1/c$, a = 12.145 (1) Å, b = 8.132 (1) Å, c = 15.536 (2) β = 110.44 (1)°, Z = 4, D_c = 1.21 g/cm^3, Cu = Kα, λ 1.54178 Å. Of the 1050 data collected with a G.E. XRD-490 computer controlled system by the stationary counter, stationary-crystal method 971 were considered statistically significant. Balanced Ross filters with Cu Kα radiation were used to measure all reflections to a 2θ maximum of 90°. The structure was solved by a multisolution $\Sigma 2$ sign expansion and ultimately refined (nonhydrogens) anisotropic, hydrogens with fixed isotropic temperature factor) to R_w = 0.038. The surprising feature is that all 22 hydrogen atoms are prominently displayed on the difference map. The hydrogens of the five methyl groups are rigidly constrained by the proximity of the other molecules and by steric requirements of the molecule itself and hence are readily apparent in the maps generated.

It is interesting to note the different reaction paths taken by 4,5-dihydropyridazine (**1**) and 3,6-dimethyl-4,5-dihydropyridazine (**4**) in their self-condensation reactions. While the steric requirements of the axial groups in the central ring are important in blocking trimerization of **4**, the basic difference is that trimerization occurs from a 4,5-dihydrotautomer (**1**)[5] and dimerization appears to occur through a key 1,4-dihydro tautomer (**5**).[4]

To test how monosubstitution at position 3 might affect these reactions we synthesized 3-*tert*-butyl-4,5-dihydropyridazine (**9**) by condensation of 4-oxo-5,5-dimethylhexanal (**8**) with hydrazine. If the reaction is worked up without allowing the temperature to rise above room temperature, the product obtained is a viscous oil having a complex NMR similar to that

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