2-(2-methylbenzoyl)benzoic acid[15] in 1700 ml of water and 0.2 g of NaOH was heated on a steam bath with stirring and then carefully treated with solid $KMnO_4$ in small portions over 0.5 hr, after which time the vigorous foaming had subsided. Over the following 8 hr a total of 230 g of $KMnO_4$ was added portionwise. After an additional 15 hr of heating the mixture was cooled, treated with excess $NaHSO_3$ and filtered through Celite. The $MnO_2$ was washed with two 1-l. portions of hot water and the combined decolorized filtrates were acidified with hydrochloric acid to give 80.3 g (77%) of the acid, mp 185°, resolidification and final mp 212–213.5° [lit.[16] mp 210° (final)].

**6-(*t*-Butyloxycarbonylamino)-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine.**—A solution of 26.3 g of 2,2′-bis(bromomethyl)diphenylmethane (obtained from benzophenone-2,2′-dicarboxylic acid by the method of Bergmann and Pelchowicz[16]) and 9.9 g of *t*-butyl carbazate in 150 ml of DMF was warmed to 50° and 15.2 g of triethylamine added dropwise with stirring at a rate to keep the temperature < 60°. After the mixture was allowed to stir overnight 400 ml of water was added and the gummy solid extracted with $CH_2Cl_2$. Evaporation of the solvent followed by recrystallization from cyclohexane gave 13 g (53%) of the azocine: mp 104–105°; nmr δ ($CCl_4$) 1.38 s (*t*-Bu, 9 H), 4.3 m ($CH_2$, 6 H), 7.1 m (phenyl, 8 H).

*Anal.* Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.99; H, 7.41; N, 8.50.

**6-Amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine.**—A solution of 1.3 g of the carbo-*t*-butoxy derivative above in 25 ml of methanol was added to 75 ml of methanol which had been saturated with hydrogen chloride in an ice bath. The solution was allowed to stir overnight and evaporated to dryness and the residue recrystallized from methanol–ether to give 0.6 g (58%) of the hydrochloride, mp 210–214° dec (softening at 209°).

*Anal.* Calcd for $C_{15}H_{17}N_2Cl$: C, 69.08; H, 6.57; N, 10.74; Cl, 13.59. Found: C, 69.01; H, 6.62; N, 10.56; Cl, 13.66.

Conversion to the **free base** was effected by shaking with $CH_2Cl_2$ and $NaHCO_3$ solution. Recrystallization of the crude product from petroleum ether gave 72% of the hydrazine, mp 114–116°.

*Anal.* Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.10; H, 7.34; N, 12.27.

The **benzal** derivative, recrystallized from ethanol, had mp 165–166.5°.

*Anal.* Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.57; H, 6.33; N, 9.01.

The ***p*-toluenesulfonyl** derivative, recrystallized from benzene–hexane had mp 146–148.5° dec.

*Anal.* Calcd for $C_{22}H_{22}N_2SO_2$: C, 69.82; H, 5.87; N, 7.40; S, 8.46. Found: C, 70.04; H, 6.01; N, 7.58; S, 8.42.

**10,11-Dihydro-5H-dibenzo[*a*,*d*]cycloheptene.**—A mixture of 20 ml of 20% NaOH and 2.5 g of the *p*-toluenesulfonyl derivative of VIII was heated for 10 min on a steam bath and cooled to room temperature and the oil extracted with $CH_2Cl_2$. Evaporation and recrystallization from methanol gave 1.1 g (85%) of the hydrocarbon, mp 74–76.5° (lit.[17] mp 78–79°), which was identified by comparison with an authentic sample.

**Registry No.**—II, 19406-76-9; 2-*p*-toluenesulfonylamino-1,2,3,4-tetrahydroisoquinoline, 19350-92-6; 6-(*t*-butyloxycarbonylamino)-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine, 19350-93-7; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine, 19350-94-8; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine hydrochloride, 19350-95-9; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine benzal derivative, 19350-96-0; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine *p*-toluenesulfonyl derivative, 19350-97-1.

**Acknowledgment.**—This work was supported by a grant (NSF GP-4283) from the National Science Foundation. We are indebted to Mr. Robert Kirkley for checking the oxidation of VII.

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## Reaction of 6-Hydroxy-2-pyridone with Diazomethane. Isolation of a Novel Product

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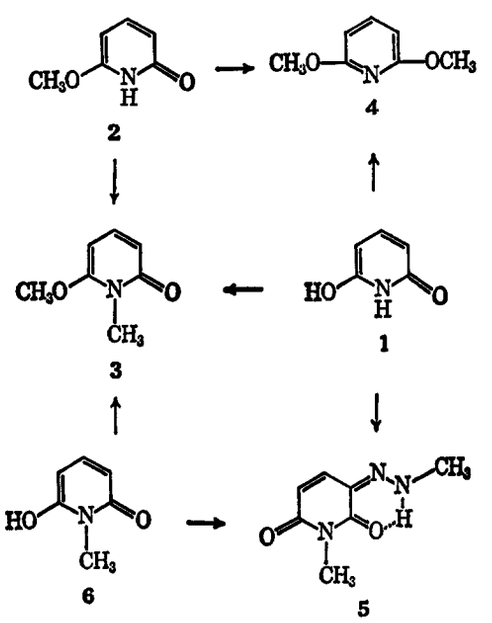
*Received October 17, 1968*

Alkylation reactions of nitrogenous heterocycles have been investigated extensively because of the biological importance of such reactions.[3] In the course of a study of the tautomerism and reactivity of 2,6-disubstituted pyridines, we investigated the reaction of 6-hydroxy-2-pyridone (**1**) (glutaconimide) with diazomethane. In addition to the expected N- and O-methylated products [6-methoxy-2-pyridone (**2**), 6-methoxy-1-methyl-2-pyridone (**3**), and 2,6-dimethoxypyridine (**4**)], an additional substance was observed upon thin layer chromatography. When a large ratio of diazomethane to 6-hydroxy-2-pyridone (**1**) was used (100:1), this product was the one isolated in largest yield. It has been assigned the structure of 1-methyl-1,2,3,6-tetrahydropyridine-2,3,6-trione 3-methylhydrazone (**5**) on the basis of the evidence discussed below. To our knowledge, the isolation of **5** represents the first reported example of substitution of a methylazo group on an aromatic or heterocyclic ring with diazomethane. We feel that this report is not a unique example of this type of substitution but that it may have occurred in methylations of phenols[4] and pyridones[5] with diazomethane and that the corresponding products have been overlooked as minor impurities.

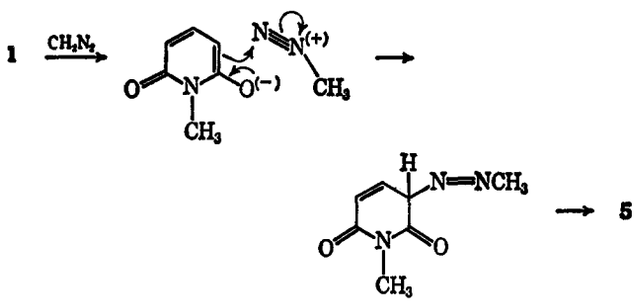
Products **2**, **3**, and **4** were identified by comparison of their ir spectra and/or melting points with those of authentic samples.[6]



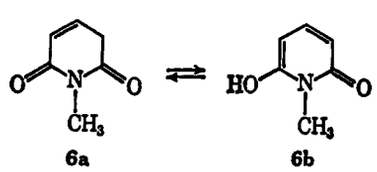

(1) New York University special Predoctoral Fellow, 1966–1967.
(2) Inquiries should be addressed to this author.
(3) A. Loveless, "Genetic and Allied Effects of Alkylating Agents," The Pennsylvania State University Press, University Park, Pa., 1966.
(4) H. von Pechmann, *Chem. Ber.*, **28**, 857 (1895).
(5) N. Kornblum and G. P. Coffey, *J. Org. Chem.*, **31**, 3447 (1966).
(6) A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc., B*, 562 (1966).

The elemental analysis of **5** indicated that it had been produced by monomethylation and addition of $CH_2N_2$ to **1**. The presence of a $CH_3N_2$ group conjugated with the heterocyclic ring was suggested by the yellow color of **5** ($\lambda_{max}$ 270 and 374 m$\mu$) and supported by a positive test for an N–N linkage (Zn–HCl, then *p*-dimethylaminobenzaldehyde).[7] The nmr spectrum revealed the presence of two *ortho* protons ($\tau$ 2.79 and 3.88, $J$ = 10.0 Hz), a strongly hydrogen-bonded exchangeable proton ($\tau$ − 4.50) and two N-methyl groups ($\tau$ 6.52 and 6.70). The N-methyl absorbance at $\tau$ 6.52 appeared as a doublet ($J$ = 4.2 Hz) in $CDCl_3$. On addition of $D_2O$, this collapsed to a singlet over 1 hr, as the hydrogen-bonded proton exchanged. This indicated that **5** existed as the hydrozone tautomer rather than in an isomeric methylazo form. A similar effect has been observed in the 1-arylazo-2-naphthol series.[8,9] The major mass spectral fragmentation patterns of **5**—P − 15 ($CH_3$), P − 28 (C=O),[10] and P − 42 ($CH_2CO$ or $CH_2N_2$)—were consistent with the proposed structure. Additional evidence supporting the assigned structure of **5** came from the following experiments: reaction of 6-methoxy-2-pyridone (**2**) with diazomethane, and reaction of 6-hydroxy-1-methyl-2-pyridone (**6**) with diazomethane. The products of the first reaction were **3** and **4**. The products of the second reaction were **3** and **5**.

A mechanism which accounts for the formation of **5** is illustrated below. In the reaction of **1** with diazomethane, it was also possible that ring methylation occurred after substitution by $CH_2N_2$.




The existence of **5** as the diketohydrazone tautomer in $CDCl_3$ has caused us to reinvestigate the tautomerism of the related compound **6** by nmr. Katritzky, *et al.*, studied the tautomerism of this compound by p$K_a$ determinations and ultraviolet spectroscopy, and found that **6** existed to an equal extent in both tautomers, **6a** and **6b**, in aqueous solution. We now wish to report that in $CDCl_3$, only the diketo tautomer, **6a**, was observed.




**6a** **6b**

## Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 or Beckman DU spectrophotometer, infrared spectra with a Perkin-Elmer Model 137 spectrophotometer, and nuclear magnetic resonance spectra with a Varian A-60 spectrometer using tetramethylsilane as internal reference ($\tau$ 10.0). Analyses were performed by Mr George Robertson, Jr., Florham Park, N. J. Mass spectra were determined with a Varian M-66 double-focusing cycloidal mass spectrometer at 70 eV. Thin layer chromatography was performed on plates prepared with Merck silica gel (Brinkmann Instruments, Westbury, N. Y.) to which approximately 5% Radelin phosphor GS-115 had been incorporated. The plates were visualized with an ultraviolet lamp equipped with a short-wave filter.

**Reaction of 6-Hydroxy-2-pyridone with Diazomethane.**—To a stirred mixture of 1.0 g (9 mmol) of 6-hydroxy-2-pyridone (**1**)[11] and 60 ml of ethyl ether, under a nitrogen atmosphere, was added 900 mmol of ethereal diazomethane. The reaction was allowed to proceed, with stirring, for 30 min at 0° (ice bath) and then for 14 hr at room temperature. Nitrogen was then bubbled into the reaction mixture to remove the unreacted diazomethane. The yellow solution was filtered and the filtrate evaporated to a thick brown oil. This oil was subjected to thin layer chromatography on twenty-five 1.00-mm silica plates employing a solvent system of chloroform–methanol, 95/5 (v/v). The plates exhibited four major bands, $R_f$ 0.15, 0.30, 0.85 and 0.99, which were cut out separately and extracted with dichloromethane–methanol. The fractions produced by this were worked up in the manner indicated below.

**Fraction I** ($R_f$ **0.15**).—The crude material obtained from the extraction was recrystallized from hexane–benzene to yield 25.0 mg (2%), large colorless plates, mp 103–104.5° (lit.[6] mp 102–104°) of 6-methoxy-2-pyridone (**2**), mmp 103–105° with an authentic sample of **2**. This material had an infrared spectrum identical with that of an authentic sample of **2**:[6] nmr ($CDCl_3$) $\tau$ − 4.51 (broad s, 1, NH), 2.57 (d of d, 1, $J_{34}$ = 8.8 Hz, $J_{45}$ = 7.7 Hz, H-4), 3.75 (d of d, 1, $J_{34}$ = 8.8 Hz, $J_{35}$ = 0.8 Hz, H-5), 6.16 (s, 3, $CH_3O$).

**Fraction II** ($R_f$ **0.30**).—The crude material from the extraction was recrystallized from hexane–benzene with Norit A. This yielded 49.0 mg (4%), colorless plates, mp 59–72°, of hydrated 6-methoxy-1-methyl-2-pyridone (**3**). This material was dissolved in dry chloroform and dried over Linde Molecular Sieve 4X to give a colorless crystalline solid, mp 78–79.5° (lit.[6] mp 52–54°). An elemental analysis showed that the material was still hydrated. Both the nmr and ir of this material agreed with those of an authentic sample of **3**:[6] nmr ($CDCl_3$) $\tau$ 2.68 (d of d, 1, $J_{34}$ = 9.1 Hz, $J_{45}$ = 7.7 Hz, H-4), 3.79 (d of d, 1, $J_{34}$ = 9.1 Hz, $J_{35}$ = 1.1 Hz, H-3), 4.45 (d of d, 1, $J_{45}$ = 7.7 Hz, $J_{35}$ = 1.1 Hz, H-5), 6.10 (s, 3, $CH_3O$), 6.53 (s, 3, $CH_3N$).

**Fraction III** ($R_f$ **0.85**).—The crude extracts were recrystallized from hexane to yield 204.1 mg (14%), yellow plates, mp 163° (sealed tube), of 1-methyl-1,2,3,6-tetrahydropyridine-2,3,6-trione-3-methylhydrazone (**5**): $\lambda_{max}^{MeOH}$ 270 m$\mu$ ($\epsilon$ 8980), 374 (20,700); ir (KBr) 1678, 1621, 1493, 1393, 1307, 1277, 1247, 1101, 1047, 990, 840, 794 cm$^{-1}$; nmr ($CDCl_3$) $\tau$ − 4.50 (m, 1, NH), 2.79 (d, 1, $J_{45}$ = 10.0 Hz, H-4), 3.88 (d, 1, $J_{45}$ = 10.0 Hz, H-5) 6.52 (d, 3, $J$ = 4.2 Hz, $CH_3NH$), 6.70 (s, 3, $CH_3N$); mass spectrum *m/e* (relative intensity) 168 (10), 167 (89), 152 (42), 139 (98), 125 (34), 124 (24), 97 (19), 96 (100), 95 (14). Only absorbances above *m/e* 94 have been reported.

*Anal.* Calcd for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14; mol wt, 167.069. Found: C, 50.70; H, 5.65; N, 25.41; mol ion, 167.067.

**Fraction IV** ($R_f$ **0.99**).—The crude extracts were rechromatographed on silica using a solvent system of pure chloroform. The band corresponding to the product ($R_f$ 0.81) was extracted with chloroform and the chloroform evaporated to yield 100.2 mg (8%), colorless oil of 2,6-dimethoxypyridine (**4**). The infrared spectrum of this material was identical with that of an authentic sample (Baker Chemical) of **4**.

**Reaction of 6-Methoxy-2-pyridone (2) with Diazomethane.**—Pyridone **2**, 10 mg (0.08 mmol), was treated with diazomethane (8 mmol) in the manner described above. Thin layer chromatography with the above-mentioned systems indicated that three products were present: unreacted **2**, **3**, and **4**.

**Reaction of 6-Hydroxy-1-methyl-2-pyridone (6) with Diazo-**

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(9) A. Burawoy, H. G. Salem, and A. R. Thompson, *ibid.*, 4793 (1952).

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(11) This material was prepared by the sublimation–decomposition of 2,6-dihydroxypyridine hydrochloride (Koch-Light Ltd., Colnbrook, England).

methane.—Pyridone **6**, 10 mg (0.08 mmol), was treated with diazomethane (8 mmol) in the manner described above. Thin layer chromatography with the above-mentioned systems indicated that two products were present: **3** and **5**.

The nmr spectrum of 6-hydroxy-1-methyl-2-pyridone (**6**) in deuteriochloroform is as follows: $\tau$ 3.26 (d of t, 1, $J_{34}$ = 10.0 Hz, $J_{45}$ = 3.5 Hz, H-4), 3.76 (d of t, 1, $J_{34}$ = 10.0 Hz, $J_{35}$ = 2.0 Hz, H-3), 6.55 (d of d, 2, $J_{45}$ = 3.5 Hz, $J_{35}$ = 2.0 Hz, H-5), 6.70 (s, 3, $CH_3$–N).

**Registry No.**—**1**, 14346-45-3; **5**, 19350-90-4; **6**, 6231-17-0; diazomethane, 334-88-3.

## 3-Benzylidene-2,5-diketopiperazine

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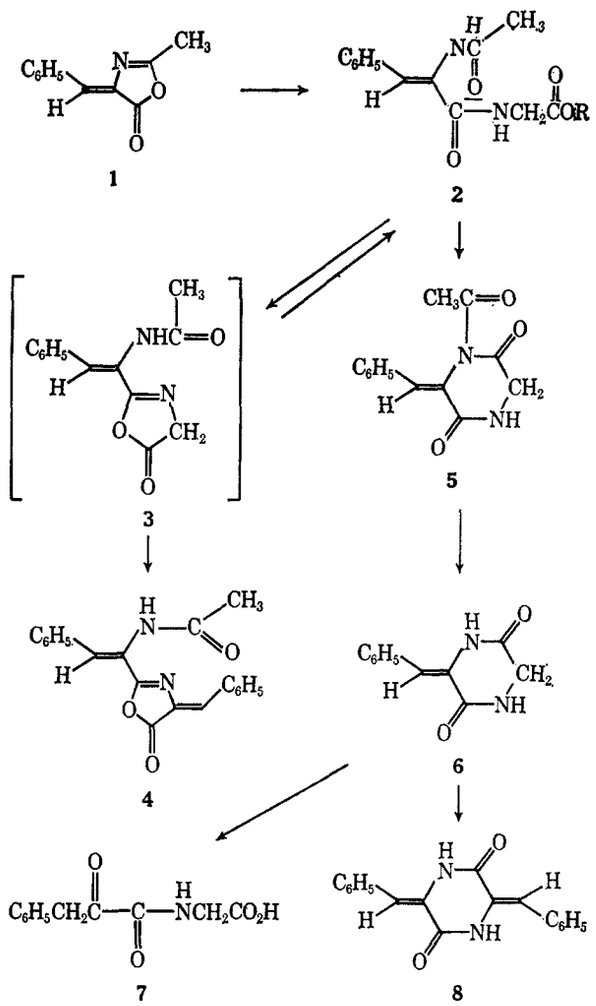
*Received December 3, 1968*

Although 3,6-dibenzylidene-2,5-diketopiperazine (**8**) has been known since 1921,[1] 44 years prior to its isolation as a natural product,[2] the monobenzylidene derivative **6** has not previously been described. As both this compound and the process by which it is produced have a variety of potential synthetic uses,[3] we wish to report our observation of its synthesis.

Fruton and Bergman,[4] in their extensive investigations of dehydropeptides, reported that the azlactone, 2-methyl-4-benzal-5-oxazalone (**1**), condensed with glycine to afford acetyldehydrophenylalanylglycine (**2**, R = H) which upon treatment with benzaldehyde, acetic ahydride, and sodium acetate produced the unsaturated azlactone peptide derivative **4**. In an attempt to obtain the assumed intermediate saturated peptide azlactone (**3**) of the above reaction, we carried out the process with the omission of benzaldehyde. The expected intermediate **3** was not produced; instead N-acetylmonobenzylidinediketopiperazene (**5**) was formed in high yield. In the acetic anhydride–sodium acetate medium, the mixed anhydride–azlactone equilibrium (**2** → **3**, R = Ac) appears rapid and reversible. In the presence of benzaldehyde, the azlactone condensation proceeds to give **4** irreversibly, while in the absence of benzaldehyde a slower intramolecular acylation of the amide nitrogen occurs to give **5**. Trace amounts of **5** can be found in the preparation of **4**. Treatment of acetyldiketopiperazine **5** with a variety of nucleophiles affords monobenzylidene diketopiperazine **6** in high yield. The structure was confirmed by hydrolysis to phenylpyruvoylglycine **7** and condensation with benzaldehyde to afford the dibenzylidene derivative **8** (Scheme I).[1]

SCHEME I



### Experimental Section

**Acetyldehydrophenylalanylglycine (2, R = H).**—Dipeptide **2** was prepared according to the procedure of Fruton and Bergman.[4] From 6.0 g (0.032 mol) of 2-methyl-4-benzal-5-oxazolone (**1**),[5] 7.0 g (83%) of acetyldehydrophenylalanylglycine (**2**, R = H) was obtained which melted at 189–192° (lit.[4] mp 194–195°): $\nu_{max}^{CHCl_3/N(Et)_3}$ (cm$^{-1}$) 1670 (strong), 1630 (strong); $\tau^{CF_3CO_2H}$ (ppm) 2.51 (6 H, multiplet), 5.58 (2 H, multiplet), 7.62 (2.5 H, singlet), 7.88 (0.5 H, singlet).

The two N-methyl peaks may be due to either *cis–trans* isomerization about the double bond or restricted rotation about one of the amide bonds.

**N-Acetyl-6-benzylidene-2,5-diketopiperazine (5).**—A solution of 6.0 g (0.023 mol) of acetyldehydrophenylalanylglycine in 15 ml of acetic anhydride was warmed on a steam bath for 9 hr. The acetic anhydride was then removed by distillation leaving a brown solid which melted at 160–170°. After washing well with benzene, 3.82 g (68%) of a pale yellow solid was obtained which melted at 194–198°. Finally recrystallization from chloroform gave a colorless solid which melted at 200–202°: $\nu_{max}^{CHCl_3}$ (cm$^{-1}$) 3380 (weak), 3020 (weak), 1700 (strong), 1630 (weak), 1420 (medium), 1360 (strong), 1225 (broad, medium); $\tau^{CF_3COH_2}$ (ppm) 2.51 (1 H, singlet), 2.57 (6 H, broad singlet), 5.25 (2 H, singlet), 7.25 (3 H, s). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.4. Found: C, 63.93; H, 4.92; N, 11.42.

**3-Benzylidene-2,5-diketopiperazine (6).**—A solution of 0.10 g (0.00041 mol) of N-acetyl-6-benzylidene-2,5-diketopiperazine (**5**) and 1.0 g (0.01 mol) of aniline in 1 ml of chloroform was allowed to remain overnight at room temperature. The next day the slurry was filtered to give 0.82 g (99%) of crude product which melted at 274–278°. Recrystallization from acetic acid and

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