propylanisole and 3-benzyl-2,6-dipropylanisole as a colorless oil.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the BRSG program of the National Institutes of Health for grants in support of this work.

Registry No. 1, 41772-31-0; 2, 31040-78-5; 2-4-*d*, 80227-74-3; 3, 80227-75-4; 4, 80227-76-5; 5, 61259-78-7; 6, 69804-73-5; 6-4-*d*, 6-4-*d*; 9, 80227-78-7; 10, 80227-79-8; 12, 80227-80-1; 13, 80227-81-2; 14, 80227-82-3; 16, 80227-83-4; benzyl chloride, 100-44-7; 2,6-dimethylcyclohex-2-en-1-one, 40790-56-5; 3-benzyl-2,6-dimethylcyclohexanone, 80227-84-5; 3-benzyl-2,6-dichloro-2,6-dimethylcyclohexanone, 80227-85-6; 3-benzyl-4-bromo-2,6-dimethylanisole, 80227-86-7; 2,6-dimethylphenol, 25134-01-4; benzyl alcohol, 100-51-6; 2,6-dimethylphenol-4-*d*, 22100-63-6; 2,6-dimethylanisole, 1004-66-6; 2,6-dimethyl-4-bromoanisole, 14804-38-7; 2,6-dimethylanisole-4-*d*, 80227-87-8; 2,6-dimethylphenyl propyl ether, 61144-80-7; 2,6-dimethylphenyl hexyl ether, 80227-88-9; 2,6-dimethyl-4-benzylphenyl propyl ether, 80242-66-6; 2,6-dimethyl-3-benzylphenyl propyl ether, 80242-67-7; 3-benzyl-2,6-dimethylphenyl hexyl ether, 80227-89-0; 4-benzyl-2,6-dimethylphenyl hexyl ether, 80227-90-3; 3-benzyl-4-bromo-2,6-dimethylphenyl hexyl ether, 80227-91-4; 2,6-dimethylphenyl benzyl ether, 19578-74-6; 2,6-dimethylphenyl isopropyl ether, 54350-31-1; 2-benzylphenyl isopropyl ether, 80227-92-5; 2-benzylphenol, 534-83-8; 4-benzylphenyl isopropyl ether, 35672-53-8; 4-benzylphenol, 101-53-1; 3-benzyl-2,6-dimethylphenyl isopropyl ether, 69804-74-6; 4-benzyl-2,6-dimethylphenyl isopropyl ether, 80227-93-6; 2,6-diallylphenol, 3382-99-8; allyl 4-benzylphenyl ether, 22857-99-4; 2-allyl-4-benzylphenol, 80227-94-7; 2,6-diallyl-4-benzylphenol, 80227-95-8; 4-benzyl-2,6-diallylanisole, 80227-96-9; 3-benzyl-2,6-diallylanisole, 80227-97-0; 3-benzylphenol, 22272-48-6; 2,6-diallylanisole, 55980-23-9; anisole, 100-66-3; 2-benzylanisole, 883-90-9; 4-benzylanisole, 834-14-0; isopropyl phenyl ether, 2741-16-4; phenol, 108-95-2.

(*E*)-5-Hydroxypyrrolizidin-3-one: Versatile Synthon for the Synthesis of 5-Substituted 2-Pyrrolidones and (*Z*)-3-Alkylpyrrolizidines

Peter Buchs and Arnold Brossi*

Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

Judith L. Flippen-Anderson

Laboratory of the Structure of Matter, Navy Research Laboratories, Washington, DC 20201

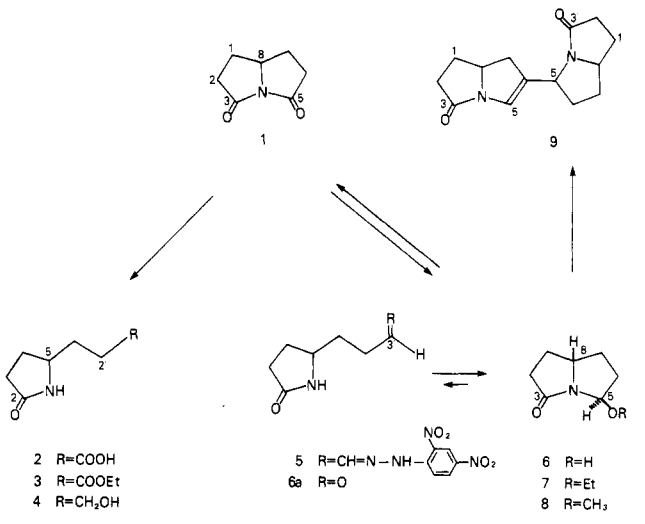
Received September 21, 1981

Carbinol lactam **6** of secured stereochemistry served as a synthon to prepare 5-substituted 2-pyrrolidones and pyrrolizidin-3-ones. The relative stereochemistry of **6** and the dithioketal **13**, prepared from the keto lactam **11**, was established by single-crystal X-ray analysis. Desulfurization of the dithioketals **13** and **14** afforded the 5-*n*-propylpyrrolizidin-3-ones **15** and **16**. Reduction of lactam **15** with $LiAlH_4$ gave the racemic (*Z*)-3-*n*-propylpyrrolizidine (**17**), an analogue of a substance recently detected in ant species.

The dioxopyrrolizidine **1**, prepared by Šorm et al.[1] and Micheel et al.[2,3] from γ-oxopimelic acid, is an attractive substance for preparing 5-substituted 2-pyrrolidones and 3- and 3,5-substituted pyrrolizidines. Representatives of the latter group of compounds have been described by several investigators[4] and recently have been found to occur in nature.[5] We now report a successful conversion of **1** into 5-(3-hydroxypropyl)-2-pyrrolidone (**4**) and an almost stereocontrolled synthesis of (±)-(*Z*)-3-*n*-propylpyrrolizidine (**17**), a close analogue of a natural ant toxin.[5]

The strained dilactam **1** reacted smoothly with ethanol in the presence of catalytic amounts of acid or base to give the ester **3** in 96% yield (Scheme I). Reduction of **1** with LAH in THF at room temperature gave the crystalline carbinol lactam **6** in 30% yield. Oxidation of **6** with Jones reagent regenerated the dilactam **1**. The structure of **6** was also in agreement with its spectral data, showing multiplets for C_8 H at δ 4.14. The relative stereochemistry present in **6** (C_5 H to C_8 H) could, however, not be solved unambiguously, and this point was determined by a single-crystal X-ray analysis. These data showed that the carbinol lactam **6** had the *E* configuration (C_5 H trans to C_8 H) and are summarized below (Figure 1).

Scheme I



Carbinol lactam **6** in solution is in equilibrium with the tautomeric aldehyde **6a** and the reaction products obtained can be correlated with this tautomerism.[6] The formation of a crystalline dinitrophenylhydrazone, **5**, and the re-

(1) R. Lukes and F. Šorm, *Collect. Czech. Chem. Commun.*, **12**, 278 (1947).
(2) F. Micheel and W. Flitsch, *Chem. Ber.*, **88**, 509 (1955).
(3) F. Micheel and W. Flitsch, *Chem. Ber.*, **89**, 129 (1956).
(4) R. Seiwerth and S. Djokic, *Croat. Chem. Acta*, **29**, 403 (1957); O. Cervinka, K. Pelz, and I. Jrkovsky, *Collect. Czech. Chem. Commun.*, **26**, 3116 (1961); F. Micheel and W. Flitsch, *Chem. Ber.*, **94**, 1749 (1961); W. Flitsch and B. Mueter, *ibid.*, **104**, 2852 (1971); Y. A. Pentin, I. M. Skvortsov, and I. V. Antipova, *Dokl. Akad. Nauk. SSSR*, **230**, 617 (1976).
(5) T. H. Jones, M. S. Blum, H. M. Fales, and C. R. Thompson, *J. Org. Chem.*, **45**, 4778 (1980).
(6) J. J. deBoer and W. N. Speckamp, *Tetrahedron Lett.*, 4039 (1975).

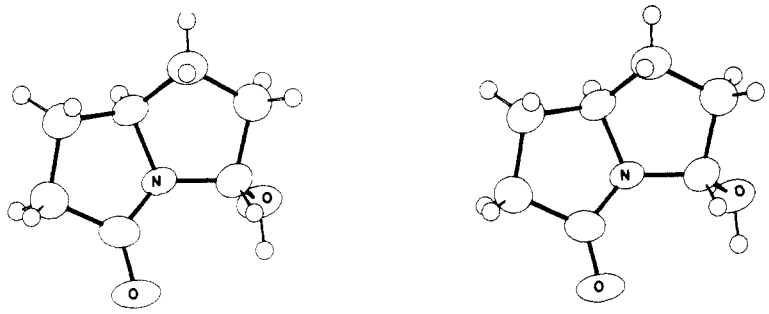


Figure 1. X-ray structure of carbinollactam **6**. The figure is drawn by using experimentally determined coordinates.

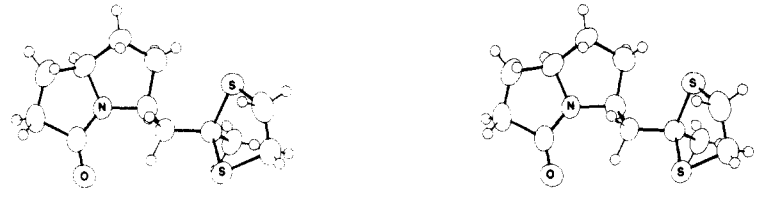


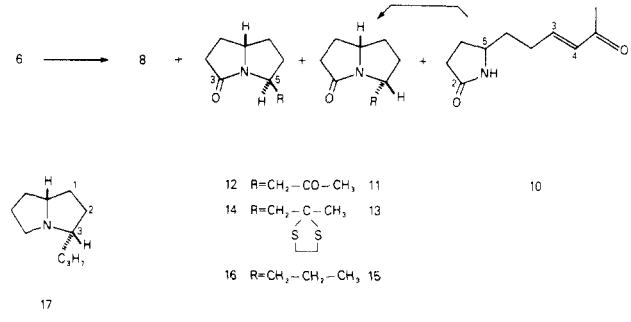
Figure 2. X-ray structure of dithioketal **13**. The figure is drawn by using experimentally determined data.

duction of **6** in ethanol with $NaBH_4$, affording the crystalline alcohol **4**, could best be explained with the open structure **6a**. Alcohol **4** could also be obtained from the acid **2** with BH_3 in THF or from the reduction of **1** with $Zn(BH_4)_2$ in THF or $NaBH_4$ in aqueous alcohol.

Products which could better be explained with the bicyclic carbinol lactam structure **6**, or its equivalents such as its carbonium ion species or its ene lactam, were evident in the formation of ether **7** of unproven stereochemistry obtained from **6** and ethanol in the presence of HCl. The formation of the dimer **9** of undefined stereochemistry, obtained by heating **6** in toluene in the presence of TsOH, can also be explained with a sequence involving bicyclic intermediates and is in accord with findings reported recently[7] but already made earlier by Leonard and his colleagues.[8] Especially interesting and relevant to the suggested tautomerism between **6** and **6a** were the products obtained in the reaction of **6** with acetoacetic acid (Scheme II). Chromatography of the reaction mixture obtained after treating **6** with acetoacetic acid in aqueous methanol at pH 3 gave a mixture of the keto lactams **11** and **12** as a major component (44%). The unsaturated trans ketone **10** (14%), with a UV absorption at 228 nm (ϵ 13.600) and vinylic protons in the ^1H NMR at δ 6.08 and 6.76, and the methyl ether **8** of unproven stereochemistry (15%) were minor contaminants. The keto lactam mixture (**11** + **12**) behaved on TLC and during chromatography as a single entity, but its ^1H NMR spectrum showed a doublet of doublets for the C1′ H at δ 3.02 and 3.70, suggesting a mixture of the (*Z*)-pyrrolizidine **11** and its *E* epimer **12** in a proportion of 5:2. The NMR spectrum displayed single-proton multiplets at δ 3.70–4.30 for the C8 H, characteristic for cis-fused pyrrolizidines.[5]

Acid-catalyzed cyclization of the unsaturated ketone **10** afforded almost exclusively lactam **11**. This conversion is possibly the result of a Michael reaction favored in the cyclization of the *Z* isomer through intramolecular hydrogen bonding. Since both lactams are cis-fused pyrrolizidines, **13** and **15** also belong to the *Z* series, whereas

Scheme II



12, **14**, and **16** belong to the epimeric *E* series. It seemed reasonable to speculate that **11** originated from **6a** by condensation with acetoacetic acid, followed by decarboxylation to **10** and acid-catalyzed cyclization. For the formation of **12** it was assumed that the initial reaction was a condensation of acetoacetic acid with a bicyclic species such as the lactam carbonium ion. The lactams **11** and **12** could not be epimerized with base. Epimerization of **11** could readily be accomplished with HCl in refluxing methanol, affording the more stabile epimer **12**.

Separation of **11** and **12** could be accomplished after thioketalization and careful chromatography of the dithioketals **13** and **14**, prepared from the mixture of **11** and **12** by standard procedures. The slower running material **13** was the major component and afforded, after crystallization, crystals with a melting point of 60–61 °C which were found suitable for a single-crystal X-ray analysis. The data discussed below (Figure 2) confirmed that **13** had the structure shown in its formula and belonged to the *Z* series.

The removal of the dithioketal group in **13** and **14** was achieved with Raney nickel and afforded the 5-*n*-propylpyrrolizidin-3-ones **15** and **16**. Reduction of lactam **15** with LAH in THF finally afforded the oily (±)-(*Z*)-3-*n*-propylpyrrolizidine (**17**), a simpler analogue of a compound recently detected in thief ants. Since the *Z* isomer has been obtained under the reported reaction conditions, including the material obtained from **10**, in more than 80% yield, this synthesis is highly stereocontrolled.

X-ray Structure Determination of Compounds 6 and 13

The stereochemistry of molecules **6** and **13** was unambiguously determined by single-crystal X-ray analysis using

(7) (a) K. Sumoto, S. Fuji, O. Yamashita, T. Somehara, and S. Miyano, *J. Heterocycl. Chem.*, **18**, 413 (1981); (b) J. C. Hubert, J. B. P. A. Wijnberg, and W. N. Speckamp, *Tetrahedron*, **31**, 1437 (1975).

(8) N. J. Leonard and E. P. Houck, *J. Am. Chem. Soc.*, **79**, 5279 (1957); N. J. Leonard and A. G. Cook, *ibid.*, **81**, 5627 (1959).

(9) L. Marion in "The Alkaloids", Vol. I, R. H. F. Manske, Ed., Academic Press, New York, 1950, pp 91–106.

direct methods[10] and the MULTAN 78 system of computer programs.[11] The X-ray results are displayed as stereodiagrams[12] and shown in Figures 1 and 2. In **6** the salient feature is that the hydrogen on C8 is cis with respect to the hydroxyl group on C3, while in **13** the hydrogen on C8 is trans with respect to the CH_2R moiety on C3. Details of this analysis, including bond length and angles for the two molecules and complete tables of atomic coordinates, will be reported in a technical paper.[13]

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes on a Thomas-Hoover apparatus. Kugelrohr distillation of the products occurred in a Büchi GKR 50 apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. UV spectra were recorded on a Hewlett-Packard UV8450 spectrometer. IR spectra were recorded on a Beckman IR 4230 instrument. NMR spectra were determined by using a JEOL FX-100 spectrometer if not specified otherwise. Chemical-ionization (CI) mass spectra were obtained by using a Finnigan 1015D spectrometer with a Model 6000 data collection system, and electron ionization (EI) mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Short-range Hydrion paper was used for pH determinations. Merck silica gel 60 F_{254} analytical thin-layer chromatography (TLC) plates and Merck silica gel 60 (70–230 mesh) used throughout this work were purchased from EM Laboratories.

5-[2-(Carboethoxy)ethyl]pyrrolidin-2-one (3). (a) With $NaBH_4$ in Ethanol. To a stirred solution of 20 mg (0.14 mmol) of **1** in 2 mL of EtOH was added 20 mg (0.26 mmol) of $NaBH_4$. After being stirred for 75 min at room temperature, the mixture was poured into 20 mL of H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on 8 g silica gel by using CH_2Cl_2/MeOH (20:1) to afford 22 mg (83%) of waxlike **3**: mp 58.5–60.5 °C (after recrystallization from CCl_4/petroleum ether); IR (CCl_4) 3450 (w), 3200 (w), 3105 (w), 1738 (s), 1700 (s), 1465 (w), 1447 (w), 1426 (w), 1391 (w), 1375 (w), 1350 (w), 1300 (w), 1250 (m), 1182 (m), 1151 (w), 1097 (w), 1037 (w); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.45–2.60 (m, 8 H), 3.68 (m, 1 H, H5), 4.12 (q, 2 H, J = 7 Hz, CH_3CH_2O), 6.48 (br s, 1 H, HN); CI mass spectrum, m/e 186 ($M^+ + 1$).

(b) Base Catalyzed. A solution of 98 mg (0.70 mmol) of **1** in 3 mL EtOH and 10 mg (0.14 mmol) of NaOEt were stirred during 16 h at room temperature. The slightly milky solution was evaporated and the residue purified chromatographically on 20 g silica gel with CH_2Cl_2/MeOH (2:1) to yield 128 mg (98%) of **3**.

(c) Acid Catalyzed. A solution of 99 mg (0.71 mmol) of **1** in 3 mL EtOH was mixed with 1 mL of 0.1 N ethanolic HCl and stirred for 13 h at room temperature. The reaction mixture was worked up and the residue purified as described in part b. The yield of **3** was 127 mg (96%).

5-(3-Hydroxy-*n*-propyl)pyrrolidin-2-one (4). (a) By "Acid" $NaBH_4$ Reduction[7b,14] of 1. To a cooled (−5 °C) solution of 1.018 g (7.32 mmol) of **1** in 100 mL of EtOH/H_2O (9:1) was added 1.03 g (27.23 mmol) of solid $NaBH_4$. Every 10 min during the following 5 h 2 drops of 2 N aqueous HCl were added while the temperature was exactly kept at −5 °C. The solution was acidified to pH 3 by slow addition of 2 N aqueous HCl during 45 min at −5 °C, stirred an additional 75 min at −5 to +3 °C, concentrated to a volume of 40 mL by evaporation, diluted with 80 mL of H_2O, and extracted with CH_2Cl_2 (3 × 100 mL). The organic phases furnished 511 mg (38%) of **3**.[15] The aqueous phase was saturated with 45 g of solid K_2CO_3 and extracted with $CHCl_3$ (4 × 100 mL). In this case the organic phases yielded 504 mg (48%) of **4**: mp 55–57 °C (after recrystallization from EtOAc); IR ($CHCl_3$) 3630 (w), 3440 (m), 3350 (w), 3240 (w), 1689 (s), 1460 (w), 1383 (w), 1312 (w), 1050 (m), 995 (w), 900 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–1.9 (m, 5 H), 2.0–2.5 (m, 3 H), 2.97 (br s, 1 H, HO), 3.4–3.9 (m, 3 H, H5 and CH_2O), 7.24 (br s, 1 H, HN); CI mass spectrum, m/e 144 ($M^+ + 1$).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.44; H, 9.12; N, 9.66.

(b) By Reduction of 1 with $Zn(BH_4)_2$. To a solution of 100 mg (0.72 mmol) of **1** in 100 mL of THF (freshly distilled over $LiAlH_4$) was added 5 mL (~4.5 mmol) of an etherial $Zn(BH_4)_2$ solution.[16] After the mixture was stirred for 90 min under argon at room temperature, about 0.5 mL of H_2O was added dropwise during 20 min (H_2 evolution), and stirring was continued for a total of 5 h. At that point a white precipitate and a slightly turbid supernatant solution were observed. The latter was dried with $MgSO_4$, filtered through Celite, and evaporated. The residue (113 mg) was purified by chromatography on 8 g of silica gel by using CH_2Cl_2/MeOH (10:1) to afford 79 mg (77%) of **4**.

(c) By Reduction of 2 with BH_3–THF. A solution of 471 mg (3 mmol) of **2** in 85 mL of THF was cooled to −15 °C in an ice–NaCl mixture. Then 5 mL of a 1 M BH_3–THF solution was added dropwise during 20 min while the temperature was kept below −14 °C all the time. The milky mixture was allowed to warm to 0 °C during 3 h and from 0 °C to room temperature during 12 h. Then the mixture was cooled again to 0 °C and hydrolyzed by dropwise addition of 15 mL of H_2O. After warming to room temperature, the clear solution was stirred for 10 h and subsequently saturated with 9 g of solid K_2CO_3. The THF phase was separated and the aqueous phase extracted with $CHCl_3$ (3 × 15 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated to an oil (276 mg) which gave 172 mg (40%) of **4** after chromatography on 20 g of silica gel with CH_2Cl_2/CH_3OH (10:1).

(d) By Reduction of 6 with $NaBH_4$. To a stirred solution of 22 mg (0.15 mmol) of **6** in 2 mL of absolute EtOH was added 12 mg (0.32 mmol) of solid $NaBH_4$. After 5 min all starting material had disappeared on TLC (CH_2Cl_2/MeOH, 10:1), and the solution was acidified with 1 N aqueous HCl to pH 3 and evaporated. The residue was dissolved in 5 mL of H_2O with $CHCl_3$ (3 × 10 mL). The combined organic layers were treated as above to afford 22 mg (98%) of **4**.

2,4-Dinitrophenylhydrazone 5. A solution of 37 mg (0.26 mmol) of **6** in 1 mL of EtOH was added to 2.6 mL of a 0.1 M (2,4-dinitrophenyl)hydrazine solution in 85% H_3PO_4/95% EtOH (1:1). After the solution was allowed to stand at room temperature for 50 h, the precipitate was filtered, washed three times with 0.5 mL of cold EtOH/H_2O (1:1), and dried under vacuum to afford 35 mg (42%) of the dark yellow hydrazone **5**, mp 163–164 °C (after recrystallization from EtOH). The mother liquor was diluted with 40 mL of H_2O, extracted with CH_2Cl_2 (3 × 40 mL), and dried over Na_2SO_4. The residue obtained was purified by chromatography on 15 g silica gel by using CH_2Cl_2/Et_2O/MeOH (10:10:1), yielding another 24 mg (28%) of **5**. The total yield of **5** was 70%: IR (KBr) 3330 (w), 1685 (m), 1613 (s), 1585 (m), 1511 (m), 1416 (w), 1323 (s), 1307 (m), 1265 (m), 1215 (m), 1127 (m), 1070 (m), 1070 (w), 913 (w), 822 (w), 735 (m), 712 (w) cm^{-1}; ^1H NMR (acetone-d_6) δ 1.5–2.8 (m, 8 H), 3.75 (m, 1 H, H5), 7.12 (br s, 1 H HN), 7.99 (t, 1 H, J = 5 Hz, CH=N), 8.00 (d, 1 H, J = 10 Hz, Ar H), 8.36 (dd, 1 H, J = 10, 2 Hz, ArH), 8.96 (d, 1 H, J = 2 Hz, Ar H), 11.20 (m, ArNHN=C); CI mass spectrum, m/e 322 ($M^+ + 1$).

Anal. Calcd for $C_{13}H_{15}N_5O_5$: C, 48.60; H, 4.70; N, 21.79. Found: C, 48.29; H, 4.39; N, 22.15.

(*E*)-5-Hydroxypyrrolizidin-3-one (6). To a solution of 2.00 g (14.39 mmol) of **1** in 190 mL of THF (freshly distilled from $LiAlH_4$) was added 200 mg (5.27 mmol) of $LiAlH_4$ at once. After being stirred for 10 min at room temperature under argon, the mixture was treated rapidly with 2.8 mL of saturated $(NH_4)_2SO_4$ solution, stirred 10 min, treated with 3 g of anhydrous $MgSO_4$,

(10) J. Karle and I. L. Karle, *Acta Crystallogr.*, 21, 849 (1966).
(11) P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. DeClercq, and M. M. Woolfson, "MULTAN78", University of York, England, and University of Louvain, Belgium, 1978.
(12) C. K. Johnson, Report ORNL 3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
(13) J. L. Flippen-Anderson, P. D'Antonio, and J. H. Konnert, to be submitted for publication in *J. Cryst. Spectrosc. Res.* A list of structure factors will be deposited with the editor of the journal.
(14) (a) J. C. Hubert, W. Steege, W. N. Speckamp, and H. O. Huisman, *Synth. Commun.*, 1, 103 (1971); (b) G. A. Kraus and K. Neuenschwander, *Tetrahedron Lett.*, 3841 (1980).
(15) Containing an impurity corresponding to **4**.
(16) W. J. Gensler, F. Johnson, and A. D. B. Sloan, *J. Am. Chem. Soc.*, 82, 6074 (1960).

and stirred another 15 min. The mixture was filtered through Celite, the filter cake was washed with $CHCl_3$ (2 × 40 mL), and the filtrate and washings were evaporated to an oil (2.11 g) which was purified chromatographically on 120 g silica gel by using CH_2Cl_2/MeOH (20:1) to yield 627 mg (30.5%) of **6**. A sample (520 mg) was dissolved in 0.8 mL hot EtOAc and cooled for 45 min in ice. The precipitate was filtered and washed with cold EtOAc (3 × 0.8 mL) to give 250 mg of **6**: mp 91–94 °C (mp 93–95 °C after an additional recrystallization); IR ($CHCl_3$) 3660 (w), 3585 (w), 3360 (m), 1670 (s), 1457 (m), 1403 (m), 1360 (w), 1347 (m), 1296 (m), 1127 (w), 1065 (m), 972 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–3.0 (m, 8 H), 3.70 (br s, 1 H, OH), 4.14 (quintet, 1 H, J = 7 Hz, H8), 5.52 (dd, 1 H, J = 5, 6 Hz, H5); EI mass spectrum, m/e (relative intensity) 141 (M^+, 8), 123 (22), 97 (27), 84 (100), 68 (68).

5-Ethoxypyrrolizidin-3-one (7). A solution of 54 mg (0.38 mmol) of **6** in 0.5 mL of absolute EtOH was cooled to 0 °C, diluted with 2.5 mL of a 0.04 N ethanolic HCl solution, and stirred at 0–5 °C. After 3 h the reaction mixture was evaporated to an oil which was chromatographically purified and subsequently distilled [50 °C (0.45 torr)] to afford 54 mg (83%) of **7** as a colorless oil: IR (CCl_4) 1705 (s), 1456 (m), 1440 (w), 1387 (s), 1340 (m), 1326 (m), 1293 (m), 1265 (m), 1170 (m), 1146 (m), 1088 (s), 1120 (w), 910 (w), 876 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.0–3.0 (m, 8 H), 3.62 (m, 2 H, CH_3CH_2O), 4.08 (quintet, 1 H, J = 7 Hz, H8), 5.18 (dd, 1 H, J = 7, 3 Hz, H5); CI mass spectrum, m/e 170 ($M^+ + 1$).

Dimerization of 6. A solution of 19 mg (0.14 mmol) of **6** in 5 mL of toluene was refluxed in the presence of 2 mg of p-TsOH and 2 g of 4A molecular sieves for 40 min.[17] After that time essentially one new spot was observed on TLC (CH_2Cl_2/MeOH, 10:1). The mixture was cooled to room temperature, saturated with gaseous NH_3, mixed with 5 mL of concentrated NH_4OH solution, and diluted with 15 mL of $CHCl_3$. After being shaken, the two layers were separated, and the aqueous phase was extracted three times more with 15 mL of $CHCl_3$. The residue from the combined organic phases was purified on 7 g of silica gel by using CH_2Cl_2/MeOH (20:1) to yield 5 mg (30%) of **9** [mp 55–60 °C (very unstable; corresponding to main spot on TLC)] besides **2** and other components not further characterized: IR (CCl_4) 3105 (w), 1710 (s), 1600 (w), 1453 (w), 1447 (w), 1395 (s), 1337 (m), 1332 (m), 1297 (m), 1277 (m), 1220 (w), 1193 (w), 1117 (w), 1037 (w), 930 (w), 647 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.6–3.0 (m, 14 H), 3.4–4.6 (m, 2 H, H8, and H8′), 5.32 (m, 1 H, H5′), 6.55 (m, 1 H, H5); CI mass spectrum, m/e 247 ($M^+ + 1$).

Treatment of 6 with Acetoacetic Acid. A mixture of 1.42 mL (1.45 g, 11.0 mmol) of ethyl acetoacetate and 0.44 g of NaOH in 11 mL of H_2O was stirred 15 h at room temperature. After addition of 0.8 mL of concentrated HCl, a solution of 1.41 g (10.0 mmol) of **6** in 4.2 mL of MeOH and 3.8 mL of H_2O was added. After being stirred for 24 h at room temperature, the solution was diluted with 21 mL of 2 N Na_2CO_3 and extracted with $CHCl_3$ (3 × 50 mL). From chromatography of the residue from concentration of the combined organic phases on 135 g of silica gel with CH_2Cl_2/Et_2O/MeOH (20:20:1) three fractions were collected. The first fraction was distilled at 100 °C (0.9 torr) to yield 250 mg (16%) of methyl ether **8**. The main fraction was distilled at 110 °C (0.5 torr) and gave 799 mg (44%) of a mixture of **11** and **12** (ratio **11**/**12** of 5:2 according to a 220-MHz ^1H NMR spectrum). Finally, the third fraction was rechromatographed on 20 g of silica gel with the same solvent system as above to afford 250 mg (16%) of **10** after drying under vacuum. The following spectral data were obtained.

5-Methoxypyrrolizidin-3-one (8): IR (CCl_4) 2830 (w), 1706 (s), 1458 (m), 1442 (w), 1392 (m), 1343 (m), 1331 (m), 1293 (m), 1267 (w), 1180 (m), 1126 (w), 1084 (s), 960 (w), 942, 890 (m) cm^{-1}; H NMR ($CDCl_3$) δ 1.05–2.95 (m, 8 H) 3.36 (s, 3 H, CH_3O), 4.06 (quintet, 1 H, J = 6 Hz, H8), 5.08 (dd, 1 H, J = 6, 3 Hz, H5); EI mass spectrum, m/e (relative intensity) 155 (M^3, 15), 140 (9), 124 (82), 28 (100).

Mixture of (*Z*)-5-(acetylmethyl)pyrrolizidin-3-one (11) and (*E*)-5-(acetylmethyl)pyrrolizidin-3-one (12): IR (CCl_4) 1719 (s), 1688 (s), 1454 (m), 1444 (w), 1430 (sh, m), 1408 (s), 1370 (m), 1352 (m), 1322 (m), 1300 (m), 1292 (m), 1273 (w), 1158 (m), 1128 (w), 652 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.85 (m, 9 H), 2.15 (s, 3 H, CH_3CO), 3.02 (dd, 0.3 H, J = 17, 4 Hz), 3.70 (dd, 0.7 H, J = 17, 4 Hz), 3.70–4.30 (m, 2 H, H5 and H8); CI mass spectrum, m/e 182 ($M^+ + 1$).

Lactam 10: UV (EtOH) 228 nm (ϵ 13 600); IR (CCl_4) 3200 (m), 3100 (m), 1692 (s), 1680 (sh, s), 1643 (sh, w), 1630 (m), 1461 (w), 1443 (w), 1425 (m), 1385 (m), 1358 (m), 1311 (m), 1292 (sh, m), 1278 (m), 1263 (m), 1250 (m), 1194 (w), 1173 (w), 975 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–3.0 (m, 11 H), 3.66 (m, 1 H, H_5), 6.08 (d, 1 H, J = 16 Hz, H4′), 6.76 (dt, 1 H, J = 16, 6 Hz, H3′), 6.95 (br s, HN); CI mass spectrum, m/e 182 ($M^+ + 1$).

The ratio of **11**/**12** was not affected when a methanolic solution of 18 mg of **11** and **12** was stirred either in the presence of 12 mg of NaOMe at room temperature for 19 h or together with 9 mg of NaOMe under reflux for 3 h.

Acid Catalyzed Cyclization of Enone 10. A solution of 7 mg (0.04 mmol) of **10** in 0.2 mL of MeOH and 0.7 mL of H_2O was treated with 10 μL of concentrated HCl and stirred during 100 min at room temperature. The solution was diluted with 5 mL of 2 N Na_2CO_3 solution and extracted with $CHCl_3$ (3 × 10 mL). Chromatography of the residue on 7 g silica gel with CH_2Cl_2/MeOH (10:1) gave after distillation [110 °C (0.6 torr)] 5 mg (71%) of **11** containing only traces of **12** according to the ^1H NMR spectrum.

Thioketalization of the Mixture of 11 and 12. A solution of 640 mg (3.53 mmol) of **11** and **12** in 35 mL of AcOH was treated with 2.3 mL of 1,2-ethanedithiol and 2.3 mL of BF_3-Et_2O and stored for 28 h at room temperature. The mixture was concentrated to a syrup, diluted with 10 mL of H_2O, and extracted with Et_2O (4 × 20 mL). Chromatography of the residue (950 mg) on 120 g of silica gel with Et_2O yielded 223 mg (25%) of the oily **14** and 608 mg (67%) of solid waxlike **13**.

Thioketal 13: mp 60–61 °C (after recrystallization from petroleum ether/acetone); IR (CCl_4) 1694 (s), 1449 (m), 1434 (m), 1412 (s), 1383 (w), 1357 (m), 1305 (m), 1294 (m), 1275 (w), 1234 (w), 1203 (w), 1186 (w), 1168 (w), 1141 (w), 1104 (w), 1032 (w), 947 (w), 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–2.95 (m, 13 H), 3.18 (d, 1 H, J = 14 Hz), 3.33 (s, 3 H, CH_3C), 3.50–4.10 (m, 2 H, H5 and H8); EI mass spectrum, m/e 257 (M^+).

Anal. Calcd for $C_{12}H_{19}NOS_2$: C, 55.99; H, 7.44; N, 5.45. Found: C, 55.95; H, 7.40; N, 5.62.

Thioketal 14: IR (CCl_4) 1697 (s), 1458 (nw), 1445 (w), 1397 (m), 1346 (w), 1275 (m), 1162 (w), 1138 nw) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.90 (m, 14 H), 3.29 ns, 3 H, CH_3C), 3.70–4.30 (m, 2 H, H5 and H8); EI mass spectrum, m/e 257 (M^+).

(*Z*)-5-*n*-Propylpyrrolizidin-3-one (15). A solution of 400 mg (1.55 mmol) of **13** in 25 mL of absolute ethanol was refluxed together with a 45-fold excess of wet Raney nickel over absolute EtOH during 2.5 h. The catalyst was removed by filtration through Celite and the filtrate evaporated to an oil which was purified chromatographically on 120 g of silica gel in Et_2O/CH_2Cl (1:1) to afford 159 mg (61%) of **15** after distillation at 60 °C (0.8 torr); IR (CCl_4) 1697 (s), 1462 (m), 1437 (w), 1416 (s), 1387 (w), 1372 (w), 1361 (w), 1343 (w), 1328 (w), 1315 (w), 1297 (m), 1283 (m), 1236 (w), 1186 (w), 1172 (w), 1110 (w), 1042 (w), 1027 (w), 947 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 6 Hz, CH_3C), 1.00–2.95 (m, 12 H) 3.55 (m, 1 H, H5), 3.88 (m, 1 H, H8); CI mass spectrum, m/e 168 ($M^+ + 1$).

(*E*)-5-*n*-Propylpyrrolizidin-3-one (16). Similarly to the desulfurization of **13**, a solution of 23 mg (0.09 mmol) of **14** in 3 mL of absolute EtOH was reduced with Raney nickel. After purification by chromatography on 20 g of silica gel with Et_2O/CH_2Cl_2 (1:1) and distillation [60 °C (0.88 torr)], 8 mg (54%) of **16** was obtained: IR (CCl_4) 1698 (s), 1462 (w), 1448 (w), 1404 (m), 1348 (w), 1293 (w), 1277 (w), 1175 (w), 1122 (w), 1100 (w), 1043 (w), 958 (w), 914 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 6 Hz, CH_3C), 1.00, 3.00 (m, 12 H), 3.55–4.10 (m, 2 H, H5 and H8); CI mass spectrum, m/e 168 ($M^+ + 1$).

(*Z*)-3-*n*-Propylpyrrolizidine (17). A solution of 114 mg (0.68 mmol) of **15** in 6 mL of freshly distilled THF was refluxed in the presence of 100 mg (2.64 mmol) of $LiAlH_4$ for 80 min, then hydrolyzed with 4 drops of saturated $(NH_4)_2SO_4$ solution after being cooled to room temperature and filtered through Celite. After careful evaporation of the solvent the oily residue was dissolved in 7 mL of 0.2 N HCl, and the solution was extracted with ether

(17) A similar experiment was carried out in the presence of 2 molar equiv of ethylene glycol without having an effect on the product formation.

(2 × 10 mL). The acidic phase was rendered basic with 2 N NaOH and extracted with Et_2O (4 × 12 mL). After drying over Na_2SO_4, the Et_2O was carefully removed, and the residue was distilled)65 °C (24 torr)] to yield 68 mg (65%) of 17: IR (CCl_4) 2870 (m), 2830 (w), 1471 (m), 1462 (m), 1451 (w), 1382 (w), 1344 (w), 1292 (w), 1187 (w), 1161 (sh, w), 1142 (w), 1111 (w), 1078 (nw), 902 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 0.92 (t, 3 H, J = 6.5 Hz CH_3C), 1.15–1.90 (m, 10 H), 2.08 (m, 1 H), 2.20–2.55 (m, 2 H), 2.65 (m, 1 H), 2.87 (m, 1 H), 3.38 (m, 1 H, H_8); CI mass spectrum, 154 (M^+ + 1).

Acknowledgment. We thank Dr. P. Wehrli, Chemical Research Department, Hoffmann-La Roche Inc., for having supported this project with the preparation of substantial amounts of intermediates.

Registry No. 1, 18356-28-0; 2, 80262-59-5; 3, 80243-72-7; 4, 80243-73-8; 5, 80243-74-9; 6, 80243-75-0; 7, 80243-76-1; 8, 80243-77-2; 9, 80243-78-3; 10, 80243-79-4; 11, 80243-80-7; 12, 80243-81-8; 13, 80243-82-9; 14, 80243-83-0; 15, 80243-84-1; 16, 80243-85-2; 17, 80243-86-3.

Novel Synthesis of the Mesoionic System 1,3-Oxazolium-4-olate

Makhluf J. Haddadin,† Asma M. Kattan,† and Jeremiah P. Freeman*‡

Departments of Chemistry, American University of Beirut, Beirut, Lebanon, and University of Notre Dame, Notre Dame, Indiana 46556

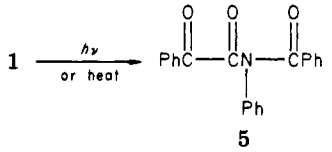
Received August 10, 1981

Thermolysis or photolysis of *N*-phenyldibenzoylnitrone (1) produces *N*-benzoylphenylglyoxanilide (5) and not the previously reported oxaziridine 2. Treatment of imide 5 with triethyl phosphite produced 2,3,5-triphenyl-1,3-oxazolium-4-olate (8), a new member of this little-known mesoionic system. Hydrolysis of 8 produced *O*-benzoylmandelanilide (9) and reaction of 8 with *N*-phenylmaleimide yielded a mixture of exo and endo cycloaddition products, **10a** and **10b**.

During the process of writing a review on oxaziridines,[1] we observed a report of a remarkable exception to the general photolytic rearrangement of *N*-arylnitrones and aromatic *N*-oxides to amides and lactams, respectively. It was claimed that *N*-phenyldibenzoylnitrone (1) rearranged photochemically to give "*N*-phenyldibenzoyloxazirine" (2) in essentially quantitative yield.[2] Later, others reported[3] the same compound was obtained thermally from 1 at the reflux temperature of *p*-xylene.

Moreover, it was claimed that oxaziridine 2 "can be recovered unchanged after heating to 250 °C in an inert atmosphere". Further chemical transformations were carried out and the products were assigned the structures shown in Scheme I.

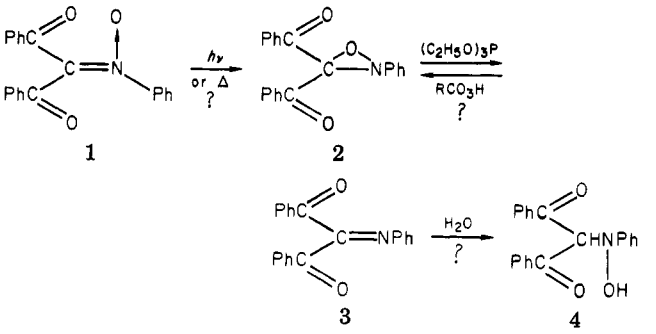
We have found that both the photolysis and thermolysis of nitrone 1 lead to *N*-benzoylphenylglyoxanilide (5), not



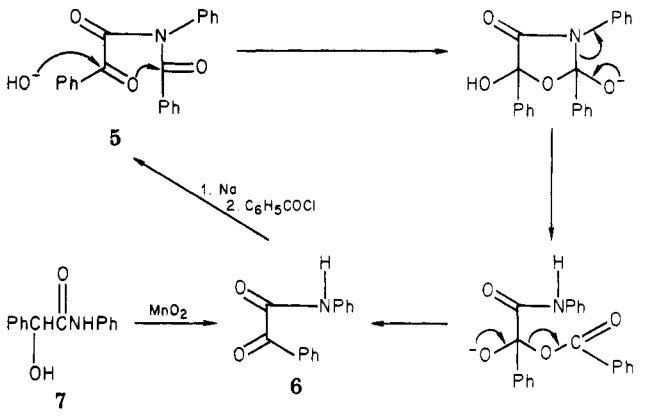
oxaziridine 2. The ^{13}C NMR spectrum of 5 showed, in addition to the aromatic carbons, three peaks at δ 170.08, 171.74, and 187.11, indicating the presence of three carbonyl groups.

Imide 5 did not oxidize potassium iodide as would be expected of an oxaziridine. On the other hand, basic hydrolysis of 5 under rather mild conditions gave phenylglyoxanilide 6 (Scheme II). The unexpectedly fast rate of hydrolysis of imide 5 and the selective removal of the benzoyl rather than the more electrophilic phenylglyoxalyl group is most likely due to neighboring participation as shown below. The identity of 6 was confirmed by manganese dioxide oxidation of mandelanilide 7 into 6. Finally, treatment of the sodium salt of 6 with benzoyl chloride gave a compound identical with imide 5 (mixture melting

Scheme I



Scheme II



point, IR, and chemical transformations).

Heating imide 5 with triethyl phosphite gave an orange-red solid[2] to which we assign the mesoionic structure 8 rather than that of anil 3 proposed earlier.[2] The reaction

† American University of Beirut.
‡ University of Notre Dame.

(1) Haddadin, M. J.; Freeman, J. P. In "The Chemistry of Heterocyclic Compounds"; Hassner, A., Ed.; Wiley: New York, in press.
(2) Scheinbaum, M. L. *Tetrahedron Lett.* **1969**, 4221–4223.
(3) Larson, H. O.; Ing, K. Y. W.; Adams, D. L. *J. Heterocycl. Chem.* **1970**, *7*, 1227.

0022-3263/82/1947-0723$01.25/0