

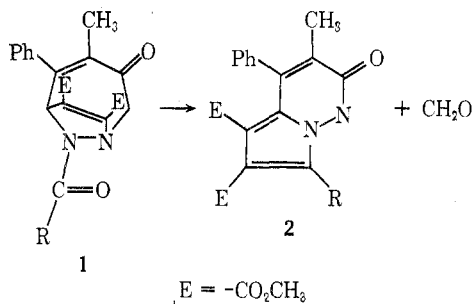
Heterocyclic Studies. 43. The Crystal Structure of 2,3,4,7-Tetrahydro-3a,4-bis(methoxycarbonyl)-2,6-dimethyl-5-phenylindazol-7-one

Richard C. Gearhart, Robert H. Wood, Patricia C. Thorstenson, and James A. Moore*

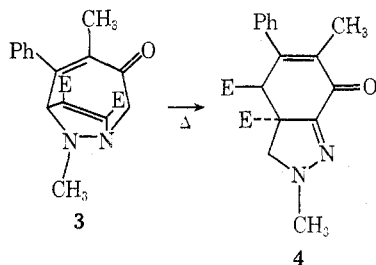
Department of Chemistry, University of Delaware, Newark, Delaware 19711

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We recently described the thermal reaction of the 9-acyldiazabicyclic ketone **1** to give pyrrolopyridazine **2** and formaldehyde;¹ the same reaction occurs also on treat-



ment of **1** with acid or base. The reactions of the 9-methyl ketone **3**² present a marked contrast. Different product mixtures are obtained with base, with acid, and with heat. Two rearrangement products have been isolated and characterized from thermolysis of **3**. This note describes the structure determination of one of these products, the tetrahydroindazolone **4**.

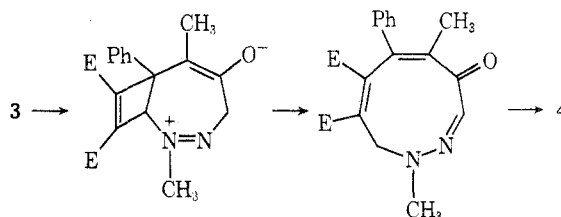


Compound **4** and an isomer were produced in approximately equal amounts (ca. 10–15% yields of crystalline compounds) on heating **3** for 90 min in a melt at 170°. (The same products were obtained very slowly on heating **3** in a sealed tube in benzene solution at 150°.) The products were separated by chromatography; **4** was the more polar substance. Compound **4** crystallized in pale yellow

prisms; the nmr spectrum contained the expected methyl and phenyl peaks, an AB pattern at δ 3.34 (1 H) and 4.06 (1 H, $J = 12$ Hz) and a doublet (1 H, $J = 0.8$ Hz) at 4.32 ppm.

Structure **4** was established by single-crystal X-ray analysis. Table I⁴ gives the fractional atomic coordinates and thermal parameters (with their respective estimated standard deviations) for the atoms comprising **4**; Figure 1 is a stereodrawing of the molecule. All bond lengths and bond angles for the structure are within the expected ranges tabulated in the literature.^{3,4}

Structure **4** represents the original diazepine framework with the two carbon bridge shifted to a new location. One of several possible rationalizations of the reaction is the formation and cyclization of a diazonine intermediate. Discussion of the mechanism will be deferred until information is available on other products.



Experimental Section

Thermolysis of 3. A 0.3-g sample of the *N*-methylbicyclic ketone **3** (mp 103°) in a small test tube was heated in an oil bath at 170° for 90 min. Tlc (ether–pentane) showed the appearance of two products: A, colorless (visualized with I₂), slightly slower moving than unreacted **3**, and B, yellow, moving about one-fifth as fast as **3**.

The dark oil was chromatographed in CHCl₃ on 10 g of SiO₂. Two fractions were obtained; the first contained product A and unreacted **3**. Crystallization of this fraction gave 30 mg of compound A: mp 160–163°; ν (KBr) 1730, 1700, 1610 (s), 1550 cm⁻¹; δ (CDCl₃) 1.88 (d, 3, $J = 1$ Hz), 2.67 (s, 3), 3.88 (s, 3), 3.92 (s, 3), 4.49 (br s, 1), 4.74 (d, 1, $J = 1.8$ Hz), 4.94 (d, 1, $J = 1.8$ Hz) (the 4.74 and 4.94 signals are not a symmetrical AB pattern), 7.39 (m, 5). Recrystallization from ether gave colorless crystals, mp 165–167°.

Anal. Calcd for C₁₉H₂₀N₂O₅: C, 64.03; H, 5.66; N, 7.86. Found: C, 63.26; H, 5.51; N, 7.60.

The second fraction from the column contained product B, identified as indazolone **4**. Preparative tlc gave a bright yellow band from which 40 mg of yellow crystals of **4** were obtained: mp 117–119°; ν (KBr) 1720, 1650, 1620 (w), 1550; nmr, see text.

Anal. Calcd for C₁₉H₂₀N₂O₅: C, 64.03; H, 5.66; N, 7.86. Found: C, 64.00; H, 5.60; N, 7.86.

Slow crystallization from ether gave well-formed crystals, mp 120°, used for X-ray analysis.

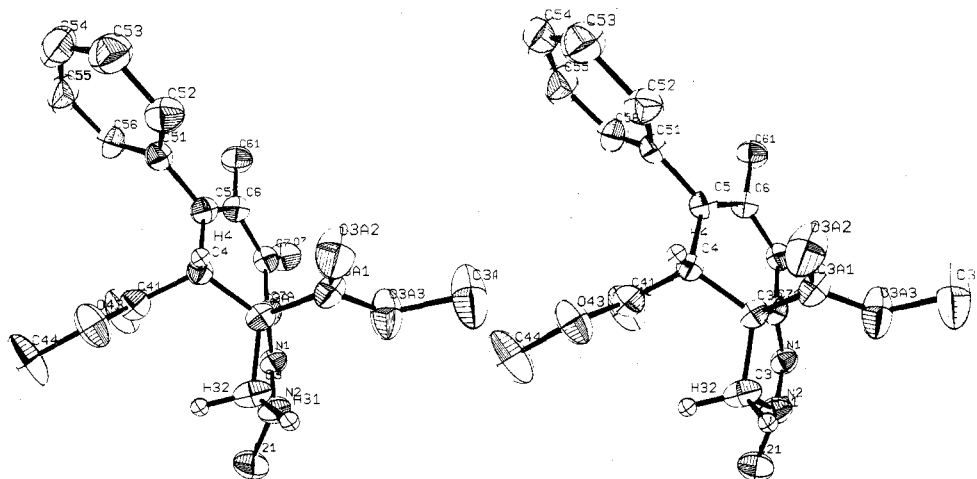


Figure 1. ORTEP stereodrawing of 2,3,4,7-tetrahydro-3a,4-bis(methoxycarbonyl)-2,6-dimethyl-5-phenylindazol-7-one showing 50% probability ellipsoids. For clarity, ring and methyl hydrogens are excluded.

X-Ray Crystallography. Crystals were received as prismatic needles; a sample showing good crystal quality under microscopic examination, with and without polarized light, was chosen from the batch. The sample was approximately $0.3 \times 0.2 \times 0.5$ mm and was mounted with the largest dimension as the goniometer rotation axis.

Preliminary precession camera investigation showed the unit cell to be monoclinic with a choice of either $P2_1/c$ or $P2_1/n$ as the space group; because of the near-cubic geometry of the resulting unit cell, $P2_1/n$ was chosen for indexing [general positions $\pm(x, y, z; x + \frac{1}{2}, y - \frac{1}{2}, z + \frac{1}{2})$].

Precision lattice constants were obtained by least-squares refinement⁵ of 2θ diffractometer angular settings on 18 independent reflections within the range $23 < 2\theta < 43^\circ$ (λ 0.7107 Å, Mo $K\alpha$ radiation). This calculation gave $a = 14.148$ (4), $b = 11.432$ (1), $c = 11.318$ (4) Å, $\beta = 97.50$ (4) $^\circ$. Assuming four formula units per cell, the calculated density, ρ_{calcd} , was found to be 1.304 (6) g/cm³, which agrees favorably with the experimental density (determined by immersion in a mixed solvent of equal density) of 1.32 g/cm³ at room temperature.

The linear absorption coefficient, μ , for the compound is 1.04 cm⁻¹ for Mo $K\alpha$ radiation. An absorption correction for data collected using Mo $K\alpha$ radiation was, therefore, deemed unnecessary.

Approximately 2400 independent reflections in the range $0.05 < \sin \theta/\lambda < 0.75$ were measured by the θ - 2θ scanning technique using a card-controlled Picker diffractometer. With 235 parameters to be set in the final anisotropic model (excluding hydrogens), this gives approximately ten reflections per parameter to be set.

Diffracted intensities were measured at a take-off angle of about 2° ; the range of each scan, at a rate of $2^\circ/\text{min}$, consisted of a reflection base width of 2° and an increment, $\Delta(2\theta) = (0.285 \tan \theta)^\circ$, to allow for spectral dispersion. Background counts, for 30-sec duration, were taken at the limits of the scan. The intensities of three standard reflections were monitored at intervals of 50 data points as alignment checks while these three plus three others were used at roughly 12-hr intervals as decomposition checks. Through the data collection period, these monitored reflections showed no noticeable trend. The criteria for distinguishing observed from unobserved reflections was set such that, to be "observed," $F_{\text{obsd}} > 3.0\sigma_F$, where σ_F is the standard deviation on F_{rel} as computed from scan and background counts corrected for instrumental instability (estimated as 0.5%).

The structure was resolved using direct method techniques: Karle-Hauptmann statistics⁶ and symbolic addition.⁷ This led to determination of 288 phases with high probability of being correctly determined (approximately 11 reflections per nonhydrogen atom; 26 nonhydrogen atoms in the molecule). An E map using these phased reflections was then searched for the 26 largest peaks; 25 were easily chosen, the 26th had several possibilities and so was ignored in this first screening. The program OR-TEP-II⁸ was used to "search" for a "molecule" among these 25 peak positions, working out from the highest one and using criteria of reasonable ranges for bond lengths;³ each peak position was tested in each of the four possible positions allowed by the general positions of the space group. The resulting "molecule" was then drawn in stereo on a graphics display terminal⁹ and studied for chemical sense.

This trial molecule was found to be entirely satisfactory in all chemical respects; the position of the 26th atom previously ignored was determined visually and found to agree with the position of a peak on the E map. Chemical considerations also readily led to the definition of atom types (C, N, or O) in all positions but the two positions occupied by C3 and N1 (refer to Figure 1) where the question of which position should be carbon and which nitrogen depended entirely on nmr data. The initial model defined the atoms in these two positions as they are shown in Figure 1.

A test of the model was made by performing two cycles of full-matrix least-squares on the nonhydrogen atoms of this model; unit weights and individual isotropic thermal parameters were used. The two cycles caused "R" to fall from an initial value of 0.24 for the raw model to 0.13; at the end of the two cycles, the model appeared quite reasonable with respect to individual atomic thermal parameters, bond lengths, and angles, and the appearance of a difference Fourier synthesis.

At this time, weights and anisotropic thermal parameters were introduced for all nonhydrogen atoms; hydrogen positions were introduced by calculation;¹⁰ and cycles of full-matrix least-squares were continued. Hydrogen positions were recalculated at the close

of each cycle according to shifts in the nonhydrogen atoms. The weighting function used was $w = 1/|\Delta F|^2$, where $|\Delta F| = A + B|F_{\text{obsd}}|$, and A and B are obtained from a plot of $|\Delta F|$ vs. F_{obsd} for 20 groups of reflections, each group containing about the same number of reflections. The plot was linear and gave values of 2.80 and 0.0492 for A and B, respectively. The final cycle gave a conventional R value of 0.064 and weighted R of 0.072.

A final structure factor calculation was made using σ values from counting statistics as weights. The weighted R value for this calculation did not differ significantly from the above weighted R value.

As a test of the possibility that C3 and N1 should be interchanged, two additional cycles of full-matrix least squares were made for the entire molecule with these two atoms interchanged as to atomic type. The resultant R value, changes in atomic parameters, and the appearance of a subsequent difference Fourier map were used as criteria of the correctness of this alternative structure. It was found that the R value increased to 0.076, thermal parameters for C3 (now defined as a nitrogen) became smaller while those for N1 (now defined as a carbon) became larger (atomic coordinate values for all nonhydrogen atoms did not change appreciably; thermal parameters for all nonhydrogen atoms but C3 and N1 did not change appreciably), and, on the difference Fourier, a hole was noted at the position of C3 while a peak was noted at the position N1 (all other atom positions showed neither appreciable peaks nor holes). This evidence led to the conclusion that C3 and N1 were correctly defined from the start.

A final difference Fourier synthesis, on the correct model, having a maximum electron density of $1 \text{ e}/\text{Å}^3$ was judged to be free of significant features. Because the goal of this structure determination was to find the molecular architecture of this compound rather than details of accurate bond lengths and thermal parameters, additional refinement cycles were deemed unnecessary. As a final observation, only five of the original 288 reflections phased by direct method techniques were found to be incorrect.

Supplementary Material Available. Tables of bond distances and bond angles (with their estimated standard deviations), and atomic coordinates, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105×148 mm, $24\times$ reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JOC-74-1007.

Registry No.—3, 35324-31-3; 4, 50378-65-9.

References and Notes

- (1) J. A. Moore, R. C. Gearhart, O. S. Rothenberger, P. C. Thorstenson, and R. H. Wood, *J. Org. Chem.*, **37**, 3774 (1972).
- (2) O. S. Rothenberger, R. T. Taylor, D. L. Dalrymple, and J. A. Moore, *J. Org. Chem.*, **37**, 2640 (1972).
- (3) "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.
- (4) See paragraph at end of paper regarding supplementary material.
- (5) All structure refinements were done using "X-ray '70" programs from Dr. James Stewart, University of Maryland.
- (6) J. Karle and H. Hauptmann, *Acta Cryst.*, **3**, 181 (1950).
- (7) I. L. Karle, K. Britts, and P. Gum, *Acta Cryst.*, **17**, 496 (1964).
- (8) "Oak Ridge Thermal-Ellipsoid Program," Dr. Carroll K. Johnson, Oak Ridge National Laboratory, ORNL-3794, 1971.
- (9) The Burroughs B-6700 at the University of Delaware Computing Center was employed for all programs used for this structure.
- (10) Hydrogen positional parameters were calculated with ATMICAL, adapted from a general hydrogen position calculating program supplied by Dr. Lloyd D. Guggenberger, Du Pont, Wilmington, Del.

A Novel Synthesis of 4-Hydroxycoumarin-3-carboxamides

Stanley A. Lang, Jr.,* and Elliott Cohen

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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The formation of amides of 4-hydroxycoumarin-3-carboxylic acid has been well documented.¹⁻⁵ These methods