New Dehydration in the Pyrrolo[1,2-b]isoquinoline Series. Preparation and Structural Identification of 3,5-Dihydrobenz[f]indolizin-3-one

Benoît Rigo [a] and Etienne Tullier

Laboratoire de Synthèses Organiques,
Ecole des Hautes Etudes Industrielles, 13, rue de Toul,
59046 Lille Cedex, France

Didier Barbry* and Daniel Couturier

Laboratoire de Synthèse Organique,
Université des Sciences et Techniques de Lille Flandres-Artois,
59655 Villeneuve d'Ascq Cedex, France

Vincent Warin, Jocelyne Lamiot and François Baert

Laboratoire de Dynamique des Cristaux Moléculaires, UA 801 CNRS,
Université des Sciences et Techniques de Lille Flandres-Artois,
59655 Villeneuve d'Ascq Cedex, France
Received January 11, 1990

3,5-Dihydrobenz[f]indolizin-3-one was prepared by a novel dehydration reaction involving the heating of 1,2,3,5,10,10a-hexahydro[f]indolizine-3,10-dione with polyphosphoric acid. The structure of this new compound was established by X-ray crystallography, by nmr spectroscopy and by reduction to the known products 1,2,3,5-tetrahydrobenz[f]indolizin-3-one and 1,2,3,5,10,10a-hexahydrobenz[f]indolizin-3-one.

Introduction.

We recently described the synthesis of 1,2,3,5,10,10a-hexahydrobenz[f]indolizine-3,10-dione **1** [1], and another group [2,3] found that the treatment of the oxime of this ketone under Beckman conditions (PPA, 100°), gave 1,4-dihydrobenzo[c]-1,5-naphtthyridin-2(3H)-one **2**. In an attempt to obtain the oxygenated analog **3** of the lactam **2**, the ketone **1** was subjected to the same reaction. However, a new dehydration reaction was observed and the lactam **4** was obtained with a 70% yield as the sole isolated product [4].

Results and Discussion.

Polyphosphoric acid at 140° was the most efficient reagent to promote the dehydration of ketone **1**, but good results were also obtained with either methanesulfonic acid or the mixture phosphorus pentoxide/methanesulfonic acid [5], nothing being isolated from 95% sulfuric acid. This reaction was rationalized as involving the protonated ketone **1** which rearranges itself to the more stable iminium salt **5**; the formation of the ethylenic compound **6**, as described for other iminium salts [6,7], was then followed by the dehydration of the alcohol [8].
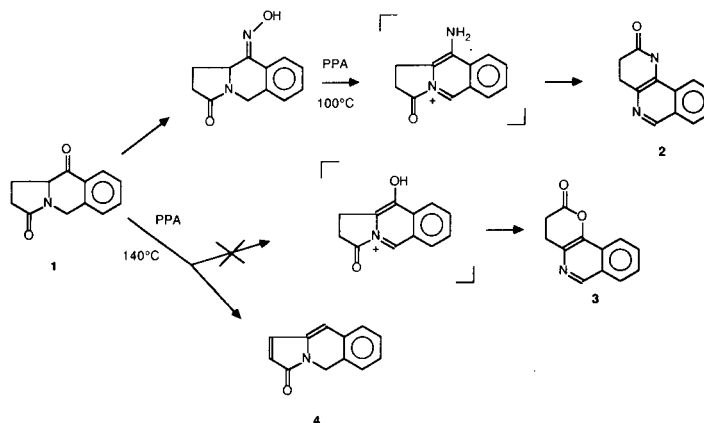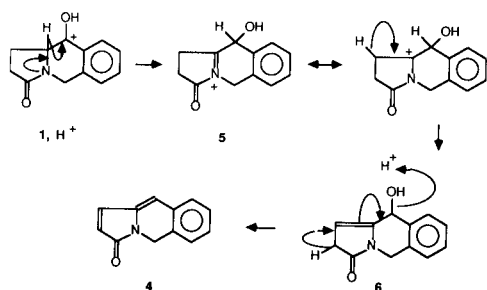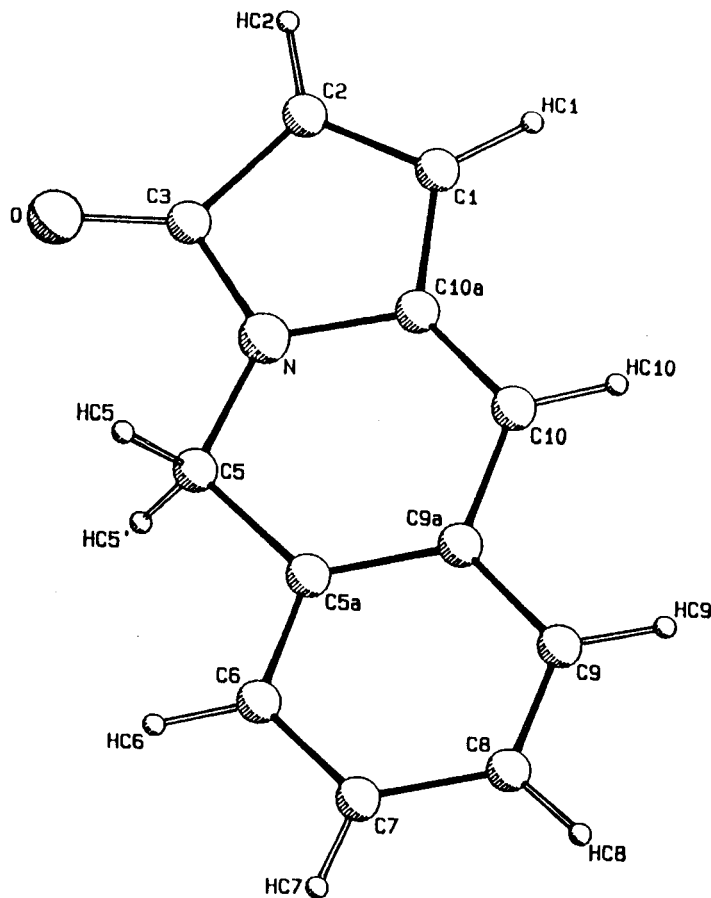

SCHEME 1

SCHEME 2

Elemental analysis and mass spectrum of the lactam **4** are in good agreement with the structure. This is verified by 1D and 2D correlated nmr spectra; in the ¹H spectrum, singlets at 4.89 ppm (2H) and 6.18 (1H) are assigned respectively to H-5 and H-10 whereas the doublets (J = 5.7 Hz) at 6.28 (1H) and 7.12 (1H) are the H-2 and H-1 signals; the aromatic protons resonate between 7.15 and 7.25 ppm. The only one ¹³C aliphatic signal (47.5 ppm) is assigned to C-5; ¹H-¹³C correlated spectrum allow the assignment of the C-10 (110.4 ppm), C-2 (124.3 ppm) and C-1 (133.2 ppm) signals. The carbonyl of the amide group resonates at 169.2 ppm. Structure of **4** is also established by reduction to a mixture of known compounds **7** and **8** (60:40) and comparison of spectral data with those of the literature [1].
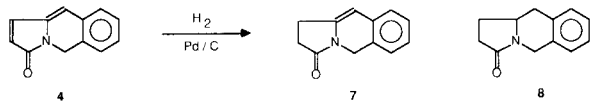
SCHEME 3

The crystal conformation is depicted in Scheme 4 as a PLUTO drawing and a packing diagram is given as Scheme 5. Molecular dimensions are given in Table 1 and a short table of C, O and N parameters as Table 2. Bond lengths and angles are in good agreement with the generally reported values; C-H bond lengths are included between 0.87 and 1.07 Å; planarity of the molecule is shown by the packing diagram.

The antitumor effects of **4** was tested *in vivo* against P-388 leukemia in mice, according to a typical NCI protocol [9]. This product has not activity under the testing conditions.

EXPERIMENTAL

Synthesis.

Melting points are uncorrected. Elemental analysis were performed by the Central Microanalytical Department of CNRS (Vernaison, France). The ir spectra were recorded on a Perkin Elmer 700 spectrometer. The nmr spectra were recorded on a Bruker AM 400 instrument in 5 mm tubes using standard pulses sequences, deuteriochloroform as the solvent and TMS as the internal reference.
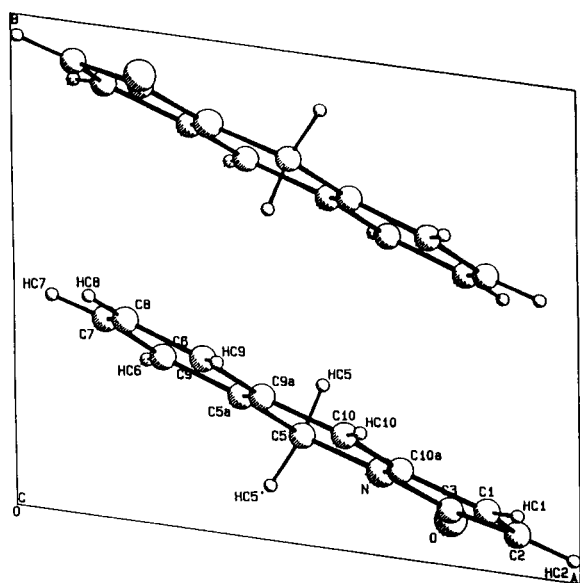

SCHEME 4

3,5-Dihydrobenz[*f*]indolizin-3-one **4**.

Finely powdered **1** (1 g, 4.97 mmoles) [1] was quickly added to hot (140°), stirred polyphosphoric acid (20 g). The mixture was vigorously stirred for one hour. The hot mixture was decanted over crushed ice (150 ml). The aqueous solution was extracted with dichloromethane. The organic phase was washed with water, dried (potassium carbonate), filtered and concentrated to give 70% of a red powder which was treated at room temperature overnight in dichloromethane with activated carbon, filtered and concentrated in part; yellow crystals of pure **4**, turning red in the air, were obtained by slow evaporation of solvent from this solution, mp 164°; ir (nujol): ν max 1660 and 1645 cm⁻¹; ¹H nmr: δ 4.89 (2H, s, H-5), 6.18 (1H, s, H-10), 6.28 (1H, d, J = 5.7 Hz, H-2), 7.12 (1H, d, J = 5.7 Hz, H-1), 7.15-7.25 (4H, m, H-6, H-7, H-8, H-9); ¹³C nmr: δ 47.5 (C-5), 110.4 (C-10), 124.3 (C-2), 126.8 and 127.8 (C-7 and C-9), 129.8 and 130.6 (C-5a and C-9a), 133.2 (C-1), 137.5 (C-10a), 169.2 (C-3); ms: m/z (relative intensity) 182 (100, M⁺-1), 183 (70, M⁺).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.23; H, 5.32; N, 7.43.

Mixture of 1,2,3,5-Tetrahydrobenz[*f*]indolizin-3-one **7** and 1,2,3,-5,10,10a-Hexahydrobenz[*f*]indolizin-3-one **8**.

Lactam **4** (0.4 g, 2.2 mmoles) in ethanol (20 ml) was hydrogenated over 0.1 g of 5% palladium on charcoal at room temperature

SCHEME 5

under 100 atmospheres (1 atmosphere = 101.3 kPa) during 5 hours. After filtration and concentration of the solution, a mixture of **7** and **8** (60:40, 0.31 g) was obtained, mp 126-136°; ¹H nmr: δ 1.74-1.83 (1H, m, H-1 of **8**), 2.33-2.43 (1H, m, H-1 of **8**),

2.45-2.50 (2H, m, H-10 of **8**), 2.50-2.55 (2H, m, H-1 of **7**), 2.65-2.70 (1H, m, H-2 of **8**), 2.70-2.80 (2H, m, H-2 of **7**), 2.90-2.95 (1H, m, H-2 of **8**), 3.70-3.80 (1H, m, H-10a of **8**), 4.25 (1H, d, ²J = −17.2 Hz, H-5 of **8**), 4.85 (2H, s, H-5 of **7**), 4.91 (1H, d, H-5 of **8**), 5.45 (1H, t, I⁴J = 1.5 Hz I, H-10 of **7**), 6.90-7.20 (m, H-6, H-7, H-8, H-9 of **7** and **8**); ¹³C nmr: δ 22.9 (C-2 of **7**), 25.2 (C-1 of **8**), 28.7 (C-1 of **7**), 30.1 (C-10 of **8**), 36.8 (C-2 of **8**), 42.5 (C-5 of **8**), 43.6 (C-5 of **7**), 53.9 (C-10a of **8**), 99.5 (C-10 of **7**), 124.6, 126.0, 126.1, 126.5, 126.6, 126.7, 127.7, 129.0, 131.5 and 140.5 (C-5a, C-6, C-7, C-8, C-9, C-9a of **7** and **8**, C-10a of **7**), 174.2 (C-3 of **8**), 174.8 (C-3 of **7**).

TABLE 2 - PARAMETERS FOR C, O AND N ATOMS *

	X	Y	Z	U
C1	8350 (3)	1192 (4)	-213 (4)	45 (2)
C2	8883 (3)	809 (4)	-2242 (5)	53 (3)
C3	7697 (3)	1119 (4)	-3283 (4)	44 (4)
N	6499 (2)	1698 (3)	-1732 (3)	38 (4)
C5	5095 (3)	2214 (4)	-2032 (4)	37 (3)
C5a	4018 (3)	2846 (4)	-7 (4)	35 (2)
C6	2641 (3)	3415 (4)	-36 (4)	50 (3)
C7	1629 (4)	4028 (5)	1779 (5)	59 (2)
C8	1982 (4)	4058 (5)	3645 (5)	62 (2)
C9	3347 (4)	3490 (4)	3703 (4)	52 (2)
C9a	4392 (4)	2888 (4)	1886 (4)	35 (3)
C10	5846 (3)	2329 (3)	1941 (3)	40 (3)
C10a	6833 (3)	1784 (4)	192 (4)	36 (3)
O	7711 (3)	924 (4)	-5117 (3)	66 (3)

*Positional parameters are multiplied by 10 000 and équivalent U values by 1000

$$U_{eq} = 1/3 \Sigma_i \, \Sigma_j \, U_{ij} \, a_i^* \, a_j^* \, a_i \, a_j$$

Crystallography.

$C_{12}H_9NO$ M = 183.21 Triclinic, P1; a = 8.837(6), b = 7.910(6), c = 6.903(5), α = 108.2°(1), β = 77.7°(1), γ = 101.4°(1), V = 443.36 Å³, Z = 2, D_x = 1.372 g cm⁻³, λ (M_oK_α) = 0.7109 Å, μ = 0.5 mm⁻¹, F(000) = 192, T = 293°K, final R = 0.054 for 1626 observed reflections {with I > 3σ(I)}. Diffractometer and data collection method: Philips PW 1100, graphite monochromator, M_oK_α (λ = 0.7109 Å), θ/2θ scan; maximum θ = 33°; Variation of intensity standards 2% measured every 2 hours, structure solving using SHELXS-86 [10]. Function minimized: $\Sigma \, \omega \, (\, | \, F_o \, | - | \, F_c \, | \,)^2$; weights (ω) = 1/σ² (F), (Δ / σ < 0.14). Refinement: full matrix least squares with SHELX76 [11] with anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal for H atoms. Crystal size: 0.3 x 0.4 x 0.5 mm, counter aperture 3.4 mm, scan width (θ): 1.4. Reflections used for lattice parameters: 25; maximum (sin θ/λ): 0.7 Å⁻¹; range of h, k, l: −14: +14, −13: 13, 0:11; reflections measured: 2625; intensity standards: 1 −1 3, −2 1 −2, 2 0 0; extrema of density, at C, O positions in final difference synthesis: 0.25, −0.35 eÅ⁻³.

TABLE 1 - MOLECULAR DIMENSIONS IN Å OR DEGREES AS APPROPRIATE

Atoms	Length (Å)	Atoms	Length (Å)
C1-C2	1.336 (4)	C5a-C6	1.384 (4)
C1-C10a	1.450 (4)	C5a-C9a	1.404 (4)
C2-C3	1.486 (4)	C6-C7	1.386 (4)
C3-N	1.371 (3)	C7-C⁴	1.381 (5)
C3-O	1.225 (3)	C8-C9	1.381 (5)
N-C5	1.453 (3)	C9-C9a	1.400 (4)
N-C10a	1.399 (3)	C9a-C10	1.450 (4)
C5-C5a	1.516 (4)	C10-C10a	1.324 (3)

Atoms	Angle (deg)
C2-C1-C10a	109.0 (3)
C1-C2-C3	108.6 (3)
C2-C3-N	105.5 (2)
C2-C3-O	130.0 (3)
N-C3-O	124.6 (3)
C3-N-C5	124.7 (2)
C3-N-C10a	110.9 (2)
C5-N-C10a	124.4 (2)
N-C5-C5a	111.9 (2)
C5-C5a-C6	118.8 (3)
C5-C5a-C9a	121.7 (3)
C6-C5a-C9a	119.6 (3)
C5a-C6-C7	120.9 (3)
C6-C7-C8	119.9 (3)
C7-C8-C9	120.0 (3)
C8-C9-C9a	120.8 (3)
C5a-C9a-C9	118.9 (3)
C5a-C9a-C10	120.1 (3)
C9-C9a-C10	121.0 (3)
C9a-C10-C10a	120.0 (2)
C1-C10a-N	106.1 (2)
C1-C10a-C10	132.0 (3)
C1-C10a-C10	132.0 (3)
N-C10a-C10	121.9 (2)

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[a] To whom correspondence should be addressed.

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