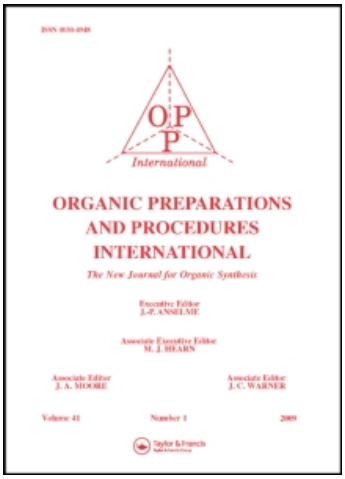

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Wawzonek, S. and Chen, M. C.(1985) 'PREPARATION OF 6-SUBSTITUTED-6H-7-AZA-INDENO[1,2-c] ISOQUINOLINE-5, 11-DIONES', Organic Preparations and Procedures International, 17: 2, 115 — 120
To link to this Article: DOI: 10.1080/00304948509355483
URL: http://dx.doi.org/10.1080/00304948509355483

ORGANIC PREPARATIONS AND PROCEDURES. INT. 17(2), 115-120 (1985)

PREPARATION OF 6-SUBSTITUTED-6H-7-AZA-INDENO[1,2-c] ISOQUINOLINE-5,11-DIONES

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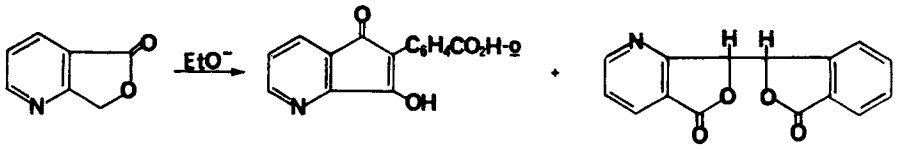
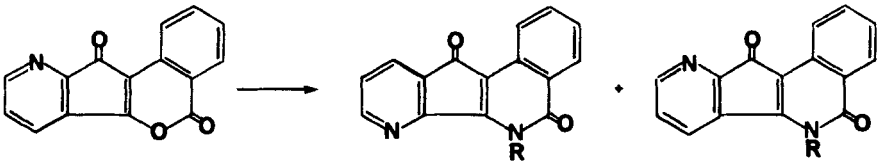
The reported anti-tumor activity in the National Cancer Institute 3PS31 test for 6-methyl-6H-indeno[1,2-c]isoquinoline-5,11-dione[1] suggested the synthesis of the pyridine analog (Vb) to determine whether the anti-tumor activity could be enhanced. Compound Vb has structural features which are present in the antibiotic streptonigrin[2,3] that has shown activity against leukemia; Vb is now being tested by the National Cancer Institute. 11-Keto-7-azaindeno[1,2-c]isocoumarin (IV) which is an intermediate in the synthesis of the isoquinolines was prepared from one of the products of the base-catalyzed condensation of 4-azaphthalide (I)[4] with phthaldehydic acid. Upon heating, the dark reddish purple β-diketone (II), assigned an enol structure [hydrogen bonded to the nitrogen] on the



I II III

basis of the absence of absorption in the 3μ region of the IR spectrum, yielded the isocoumarin IV quantitatively. Unfortunately, the major product, 3-(3'-phthalidyl)-4-azaphthalide (III) could not be rearranged successfully to the diketone (II); treatment of III with sodium ethoxide gave mixtures which were not investigated further.

Treatment of the isocoumarin (IV) with amines such as methylamine and aniline gave a mixture of V and VI which could be separated by chromatography on silica. The formation of isomeric compounds V and VI results



IV V VI

a) R = Ph b) R = CH_3

from the opening of the isocoumarin (IV) ring to an amide of a β-diketone which can cyclize in two ways. The structure assignments for V and VI were based on their nmr spectra. The isoquinoline VIa showed a doublet at δ 5.72 ppm for the 7-H. This low value is the result of shielding by the 6-phenyl group in a fashion similar to that observed for the analogous compound prepared earlier;[1] this type of shielding is absent in Va because of the 7-nitrogen and subsequently all chemical shifts of the aromatic protons are normal. Reversed shieldings are observed with the methyl derivatives (Vb, VIb); the chemical shift for the methyl group in VIb occurs at δ 4.05 and that for Vb at δ 4.25 in agreement with the greater shielding by the 7-hydrogen in VIb than that by the nitrogen in Vb. Further support for these formulations was provided by the chemical shifts of the 8-Hs in Va and Vb and of the 9-Hs in VIa and VIb; the former were further upfield than the latter. All of these protons were easily identified in the nmr spectra by their coupling constant of approximately 5 Hz.

The isocoumarin IV has been formulated as a 10-aza derivative on the basis of the chemical shift for the 9-H at δ 8.62, and of the stability of the parent ion in the mass spectrum. The 9-hydrogens of IV, VIb (δ 8.60) appeared as doublets with a coupling constant of 5 Hz. In the mass spectra the parent ions of IV, V, and VIb at 249(100), 324(100), 262(100) respectively, are stable in contrast to the parent ion of Va at 324(92.9).

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were determined on a Perkin-Elmer Model 137B spectrophotometer. NMR spectra were obtained with JEOL FX90q and 360 Hz Bruker spectrometers. Mass spectra were measured using a Hewlett-Packard Model 5985 AGC-M5 system.

4-Azaphthalide was prepared from 2,3-pyridinedicarboxylic acid.[4]

NMR($CDCl_3$): δ 5.36 (s, 2H, CH_2), 7.53 (q, 1H, 6-H), 8.24 (d, 1H, 7-H, J = 7.8 Hz), 8.90 (d, 1H, 5-H, J = 4.4 Hz).

Condensation of 4-Azaphthalide with Phthaldehydic Acid.- To a solution of sodium ethoxide (prepared from 4.68 g, (0.2 g atom) of sodium) in ethanol (250 ml) was added with stirring a hot ethanol (100 ml) solution of phthaldehydic acid (15 g, 0.1 mole) and 4-azaphthalide (13.5 g, 0.1 mole). The initially clear solution gave within a minute an orange red precipitate which upon stirring and heating for 20 hrs turned dark red. The resulting dark red mixture was cooled and acidified with the theoretical amount of 6N hydrochloric acid. Removal of the solvent gave a solid which upon extraction with hot ethanol gave an insoluble solid (16.2 g, 60% yield). Recrystallization of this solid in 2 g portions from methanol (350 ml) gave a solution which upon concentration to 250 ml and cooling gave a mixture (0.99 g) of the biphthalide III and the isocoumarin IV. Fractional crystallization from petroleum ether (bp 60-68°) followed by recrystallization from ethanol gave the isocoumarin IV (0.17 g, 5.5% yield), mp. 257-262°. Further crystallization from ethyl acetate gave a

sample melting at 258-261°.

IR(Nujol): 5.70(OCO), 5.80(CO) μ; NMR($CDCl_3$) δ 7.22-7.92 (m, 4H, aromatic Hs), 8.22-8.40 (m, 2H, 1-and 4-Hs), 8.62 (d, 1H, 9-H, J = 5 Hz); MS, m/e(%): 250(16.8, M^++1), 249(100, M^+), 248(3.3, M^+-1), 221(36, M^+-CO).

Anal. Calcd for $C_{15}H_7O_3N$: C, 72.29; H, 2.81; N, 5.62

Found: C, 71.94; H, 2.68; N, 5.50

The more soluble white colored biphthalide (III) (0.82 g, 25% yield) from the fractional crystallization after two crystallizations from methanol melted at 241-243°. An additional 0.45 g could be obtained from the original methanol solution by concentration to 100 ml.

IR(Nujol): 5.7(CO) μ. NMR($CDCl_3$): δ 5.92 (s, 1H, 3 or 3'H), 6.17 (s, 1H, 3 or 3'H), 7.28-7.63 (m, 4H, aromatic Hs), 7.92 (d, 1H, 7'-H, J = 7.8 Hz), 8.20 (d, 1H, 7-H, J = 8 Hz), 8.91 (d, 1H, 5-H, J = 5 Hz). MS m/e (%): 268(3.3, M^++1), 267(15.8, M^+), 134(14.2, $C_7H_4O_2N$), 133(100, $C_7H_3O_2N$).

Anal. Calcd for $C_{15}H_9O_4N$: C, 67.41; H, 3.37; N, 5.24

Found: C, 67.16; H, 3.18; N, 5.12

On rare occasions the crystallization from methanol (350 ml) gave dark red crystals of the β-diketone (II), mp. 208-210° (color changed to orange) followed by melting at 259-260°; IR(Nujol): 3.3-4.3(COOH), 5.8(COOH) μ. Insolubility of this solid in $CDCl_3$ and CD_3SOCD_3 precluded further spectral studies of this solid.

Anal. Calcd for $C_{15}H_{10}O_4N$: C, 67.16; H, 3.73; N, 5.22

Found: C, 67.44; H, 3.87; N, 4.86

The β-diketone II (0.27 g) upon heating at 210-220° until it turned orange gave 0.23 g of the isocoumarin IV, mp. 259-260.5°, after crystallization from ethyl acetate.

Reaction of Isocoumarin IV with Aniline.- A solution of isocoumarin IV (0.25) in absolute ethanol (100 ml) was refluxed with aniline sulfate

(0.17 g) and sodium bicarbonate (0.10 g) for 18 hrs. Removal of a portion of the ethanol followed by cooling gave a red solid (0.25 g), mp. 267-270°. Chromatography of a sample (0.12 g) on silica using chloroform for elution gave two bands. The first band gave upon extraction with chloroform Va (0.05 g), mp. at 275-279°.

IR(Nujol): 5.9(CO,CON) μ; NMR($CDCl_3$) δ 6.97-7.77 (m, 9H, aromatic Hs), 8.09 (d, 1H, 8-H, J = 4.9 Hz), 8.39 (d, 1H, 1-H, J = 9.8 Hz), 8.71 (d, 1H, 4-H, J = 8.7 Hz), MS, m/e (%): 325(19.4, M^++1), 324(92.9 M^+), 323(100 M^+-1).

Anal. Calcd for $C_{21}H_{12}O_2N_2$: C, 77.77; H, 3.70; N, 8.64

Found: C, 77.34; H, 3.79; N, 8.20

The second band upon extraction with chloroform gave VIa which after crystallization from ethyl acetate melted at 326-333° (dec.).

IR(Nujol): 5.87(CO), 5.97(CON) μ. NMR($CDCl_3$): 5.72 (d, 1H, 7-H, J = 7.7 Hz), 6.84 (q, 1H, aromatic H), 7.44-7.87 (m, 6-H, aromatic Hs), 8.39 (q, 2H, 9-H + unknown H, J = 7.7 Hz), 8.75 (d, 1H, 4-H, J = 8.1 Hz). MS m/e (%): 325(21.9, M^++1), 324(100, M^+), 323(45.8, M^+-1).

Anal. Calcd for $C_{21}H_{12}O_2N_2$: C, 77.77; H, 3.70; N, 8.60

Found: C, 77.88; H, 3.63; N, 8.46

Reaction of Isocoumarin IV with Methylamine.- A solution of isocoumarin IV (0.49 g) and methylamine (0.18 g) in 90% ethanol (5 ml) was refluxed for 16.5 hrs and upon cooling gave a mixture of isoquinolines (Vb and VIb) (0.43 g) melting at 222-223°. Chromatography of a sample (0.2 g) using silica and chloroform gave two bands. The first band upon extraction with chloroform gave 6-methyl-6H-7-azaindeno[1,2-c]isoquinoline-5,11-dione (Vb) (0.14 g), mp. 225-227°.

IR(Nujol): 5.92(CO), 6.03(CON) μ; NMR($CDCl_3$): δ 4.25 (s, 3H, CH_3), 7.19 (q, 1H, 9-H, Js = 5.2, 7.3 Hz); 7.46 (t, 1H, 2-H, J = 7.7 Hz);

7.68 (t, 1H, 3-H, J = 8.1 Hz); 7.72 (d, 1H, 10-H), J = 7.3 Hz); 8.31 (d, 1H, 1-H, J = 7.9 Hz); 8.47 (d, 1H, 8-H, J = 5.1 Hz); 8.55 (d, 1H, J = 8.1 Hz). MS m/e (%): 263(17.4, M^++1), 262(100, M^+), 261(2.5, M^+-1), 235(16.2, M^++1-CO), 234(92.9, M^+-CO), 233(59.1, M^+-1-CO).

Anal. Calcd for $C_{16}H_{10}O_2N_2$: C, 73.28; H, 3.82; N, 10.69

Found: C, 73.58; H, 3.68; N, 10.55

The second band upon elution with chloroform gave the isomeric isoquinoline (VIb), mp. 300-303°.

IR(Nujol): 5.88(CO), 6.04(CON) μ. NMR($CDCl_3$): δ 4.06 (s, 3H, CH_3), 7.27 (q, 1H, 9-H), 7.51 (t, 1H, 2-H, J = 7.6 Hz), 7.73 (t, 1H, 3-H, J = 7.9 Hz), 7.94 (d, 1H, 7-H, J = 7.9 Hz), 8.36 (d, 1H, 1-H, J = 7.8 Hz, 8.60 (d, 1H, 9-H, J = 5.0 Hz), 8.72 (d, 1H, 4-H, J = 8.2). MS m/e (%): 263(18.3, M^++1), 262(100, M^+), 261(34.6, M^+-1).

Anal. Calcd for $C_{16}H_{10}O_2N_2$: C, 73.28; H, 3.82; N, 10.69

Found: C, 73.14; H, 3.81; N, 10.68

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(Received March 26, 1984; in revised form October 15, 1984)