Synthesis and Conformational Analysis of 7,8-Diphenyl-1,3,4,6,9,9a-hexahydro-2*H*-quinolizines

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New analogues of julandine with different aromatic methoxy- and chloro-substituents have been synthesized. Some features of the nmr spectra of the final products and lactams are discussed. The conformational structure of the final products was determined.

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The alkaloid julandine has been isolated in 1968 from *Boehmeria platyphylla (Urticaceae)* (1) and is considered to be the 7-(*p*-methoxyphenyl)-8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine. This structure was confirmed by synthesis by Paton, *et al.*, (2). There is a biosynthetic relationship between this alkaloid and the more complex phenanthro[9,10-*b*]quinolizidine alkaloid cryptopleurine (Fig. 1), a substance of known vesicant (3) and anticancer (4) action.

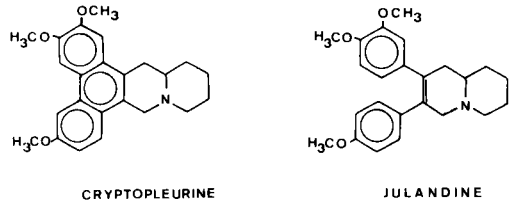
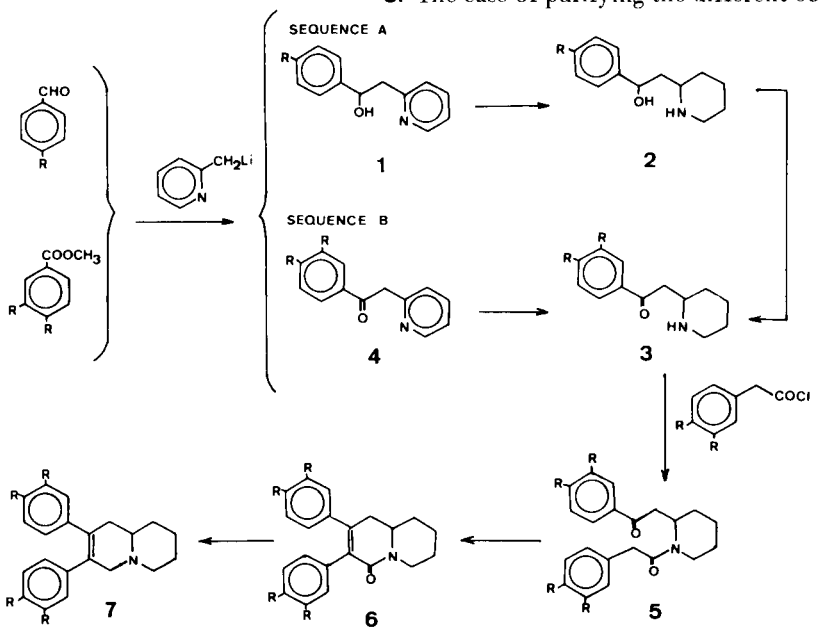


FIGURE 1

Performing an extensive study about the structure-activity relationships of cryptopleurine as an inhibitor of the protein synthesis on ribosomes, we proceeded to synthesize some new derivatives **7a-f** of its biological precursor julandine and also some different lactams **6a-k.**

The synthesis of the alkaloid julandine has been hitherto performed by two routes (2,5), both of them based on biogenetic considerations. We followed principally the synthetic scheme of Paton, *et al.*, (2) for the synthesis of the 7,8-diphenyl-1,3,4,6,9,9a-hexahydro-2*H*-quinolizines, introducing in this scheme some small modifications (Scheme 1).

The condensation between the suitably substituted benzaldehyde and α-picolyllithium under nitrogen, gives the corresponding 1-phenyl-2-(2-pyridyl)ethanol (**1**). The hydrochloride of **1** was hydrogenated over platinum in ethanol. Oxidation of the alcohol group of **2** with chromium trioxide in acetic acid led to the aminoketone **3**. The ease of purifying the different compounds induced



SCHEME 1

0022-152X/79/081625-06$02.25

us to choose the before-mentioned reaction sequence. However, the poor yields of the 3,4-dimethoxyphenacylpiperidine, compelled us to follow sequence B (Scheme 1) for this product. Condensation of **3** with the corresponding acyl chloride led to the ketoamide **5**. The condensation of **5** with alcoholic potassium hydroxide (5%), as described by Kotani, *et al.*, (6) proceeded in better yields to the lactam, than the condensation of **5** with potassium *t*-butoxide. Finally, lithium aluminium hydride reduction afforded the quinolizidine derivatives **7**. The products are listed in Tables I and II.

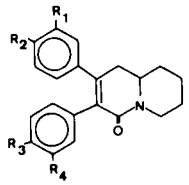
The synthetic julandine has the same nmr, mass spectra and analytical data as those described for an authentic sample of julandine (1). Most of the intermediates and final compounds have been characterized by ir, nmr spectra and microanalyses, as well as mass spectra in some cases. Details are reported in the corresponding tables and experimental section, but there are several features of interest.

In the nmr spectra of the lactams (Table III), the methylene protons at C-6 are assigned to a pair of doublets ($J_{6,6}$ = 14 Hz) at 4.58 and 2.61 ppm and the proton at C-9a appears at 3.61 ppm. This chemical shift can be ascribed to the deshielding effect by the lactam group on the protons of the vicinal methylene groups. The difference in chemical shift, between the two methylene C-6 protons, of 1.97 ppm can be explained by the differential deshielding of the equatorial and axial protons caused by the electron attracting lactam group. Comparison of the spectra of 17-oxosparteine and D-lupanine (7) shows a similar difference in chemical shift between axial and equatorial protons at this positions. The signal for the C-6 proton at 4.58 ppm shows a large geminal coupling of 14 Hz, together with smaller vicinal couplings, whereas the signal at 2.61 ppm shows two large couplings, presumably geminal and axial-axial, as well as smaller couplings, so there can be suggested that the lower field signal is due to the equatorial proton and the higher field to the axial one.

The methylene protons C-6 of 7,8-diphenyl-1,3,4,6,9,9a-hexahydro-2*H*-quinolizines (Table IV) are assigned to a pair of doublets ($J_{6,6}$ = 16 Hz) at 3.67 and 3.06 ppm.

Table I

Physical Data for Compounds **6a-k**



Compound	R_1	R_2	R_3	R_4	Yield %	M.p. °C acetone/water	Molecular formula	Analyses Calcd. Found C	H	N	Ir (cm^{-1}) Potassium bromide
6a	H	H	H	H	34.1	174-175	$C_{21}H_{21}NO$	83.16 83.47	6.93 6.83	4.67 5.02	1645
6b	H	H	Cl	H	30.2	154-157	$C_{21}H_{20}ClNO$	74.67 74.39	5.93 5.93	4.15 4.49	1653
6c	H	H	OMe	H	85.7	147-148.5	$C_{22}H_{22}NO_2$	79.52 79.35	6.63 6.70	4.22 4.61	1645
6d	OMe	OMe	H	H	62.6	108-109	$C_{23}H_{25}NO_3$	76.03 75.96	6.88 7.09	3.85 3.86	1647
6e	H	OMe	OMe	H	49.7	147.5-149	$C_{23}H_{25}NO_3$	76.03 76.32	6.88 6.70	3.85 3.85	1642
6f	H	H	OMe	OMe	78.9	159-159.5	$C_{23}H_{25}NO_3$	76.03 76.16	6.88 6.93	3.85 3.81	1650
6g	OMe	OMe	OMe	H	54.2	139-140	$C_{24}H_{27}NO_4$	73.24 73.22	6.86 7.03	3.56 3.49	1643
6h	OMe	OMe	Cl	H	67.9	114-116	$C_{23}H_{24}ClNO_3$	69.43 69.76	6.04 6.38	3.52 3.47	1645
6j	H	OMe	OMe	OMe	44.4	161-162.5	$C_{24}H_{27}NO_4$	73.24 73.45	6.86 6.85	3.56 3.48	1648
6k	OMe	OMe	OMe	OMe	26.1	142-143	$C_{25}H_{29}NO_5$	70.89 70.97	6.85 6.89	3.30 3.34	1647

The signal at 3.67 ppm is some what broadened, probably due to a small homoallylic coupling between the C-6 axial proton and the C-9 proton. The non equivalence of these protons is in agreement with previous observations made by Fitzgerald, *et al.*, (7) and Hamlow *et al.*, (8). The latter authors ascribe this non equivalence between the axial and equatorial protons in quinolizidines to the differential location of the protons to the lone pair of the nitrogen, that is, the bond between C-6 and the nitrogen atom in quinolizidines has some partial double bond character, and so the electron density at the C-6 axial proton is increased. Such a difference in chemical shift has also been noted by Johns, *et al.*, (9), who found the coupling constants of the C-9 protons in cryptopleurine to be 16 Hz.

This non equivalence of C-6 protons relative to the lone pair of the nitrogen atom allows us to assign the conformation of the quinolizidine system in the molecule. Among the three possible conformations for a quinolizidine system A, B and C (Figure 2), the latter one is the less probable, because there are strong interactions among the protons of C-1, C-3 and C-6, which are within the van der Waals radius. In relation to the other two possible conformations, there is only a non equivalence between the C-6 protons and the lone pair of nitrogen in structure A. This fact allows us to assign a conformation of *trans*-quinolizidine for this structure as it is showed in structure A. This conclusion is in agreement with the study carried out by Földeak, *et al.*, (10) for phenanthro-[9,10-*b*]quinolizidines. The Bohlmann bands (11) in the ir spectra also confirm a *trans*-quinolizidine conformation.

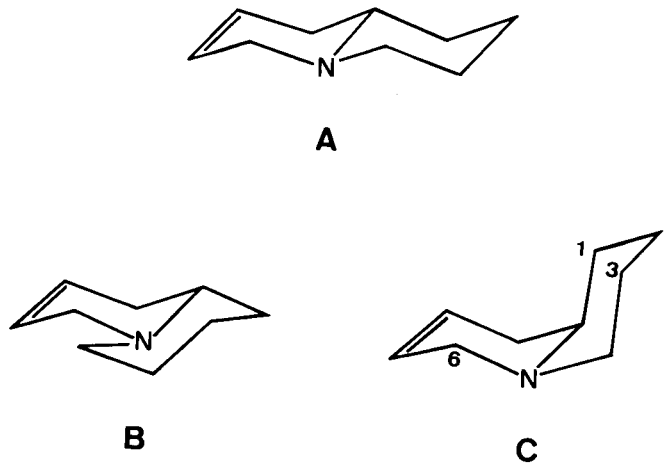


FIGURE 2

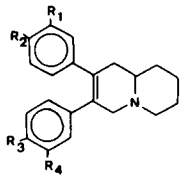
The retro-Diels-Alder fragmentation with the expulsion of a C_5H_9N fragment from the parent ion, observed for compounds **6a, 6g, 7a** and **7f** confirms their structure by mass spectra as previously described (1,2).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer 577 spectrometer. The nmr spectra were measured using tetramethylsilane as the internal standard, with a Perkin-Elmer model R-24A (60 MHz) and a Variant XL

Table II

Physical Data for Compounds **7a-f**



Compound	R_1	R_2	R_3	R_4	Yield %	M.p. °C acetone/water	Molecular formula	Analyses Calcd. Found C	H	N	Ir (cm^{-1}) Potassium bromide
7a	H	H	H	H	88.2	131-133	$C_{21}H_{23}N$	87.20	7.94	4.84	2810, 2770
								86.96	8.21	4.64	2748, 2680
7b	H	H	Cl	H	81.4	98-100	$C_{21}H_{20}ClN$	74.67	5.93	4.15	2800, 2760
								74.39	5.93	4.47	2740, 2665
7c	H	H	OMe	H	82.4	102-103	$C_{22}H_{24}NO$	83.02	7.55	4.40	2800, 2780
								82.83	7.71	4.37	2740, 2675
7d	H	OMe	OMe	H	81.2	104-105.5	$C_{23}H_{27}NO_2$	79.08	7.74	4.01	2800, 2770
								79.36	7.87	4.26	2730, 2670
7e	H	H	OMe	OMe	84.7	130-131	$C_{23}H_{27}NO_2$	79.08	7.74	4.01	2800, 2770
								79.00	7.66	4.10	2740, 2670
7f	OMe	OMe	OMe	H	93.7	134-136	$C_{24}H_{29}NO_3$	75.99	7.65	3.69	2800, 2775
								75.83	7.87	3.95	2740, 2675

100 spectrometer. Microanalyses were done with a Carlo Erba 1104 analyser. The mass spectra were obtained with a Hitachi Perkin Elmer, RMU-6M spectrometer.

Preparation of Compounds **1**.

To a well stirred 60 ml. ethereal solution of 0.1 mole phenyllithium was added under nitrogen 0.1 mole of freshly distilled α-picolin during 15 minutes, then the mixture was stirred one hour. To the red solution of α-picolillithium obtained, was added dropwise a solution of the suitable substituted benzaldehyde (0.1 mole) in 80 ml. of ether. The mixture was heated under reflux for two hours, then treated with water (100 ml.) and with three portions of 18% hydrochloric acid. The acidic aqueous layers were neutralized with 40 g. of sodium carbonate to *p*H 8 and the free base was extracted with chloroform and concentrated.

1-Phenyl-2α-pyridylethanol.

This compound was obtained in a yield of 62.8%, m.p. 108-109° (from water) (12); ir (potassium bromide): 3420, 3270; nmr (deuterochloroform): δ 3.13 (2H, d, J = 6 Hz), 5.16 (1H, t, J = 6 Hz), 5.31 (1H, s), 7.34 (5H, m), 7.1 (2H, m), 7.5 (1H, t), 8.5 (1H, m, J = 5.5 Hz).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 77.96; H, 6.58; N, 6.95.

1-(4-Methoxyphenyl)-2α-pyridylethanol.

This compound was obtained in a yield of 30.1%, m.p. 102-103° (from water), lit. 108° (13); nmr (deuterochloroform): δ 3.09 (2H, d, J = 6 Hz), 3.73 (3H, s), 5.09 (1H, t, J = 6 Hz), 5.21 (1H, s), 6.84 (2H, d, J = 8.8 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.15 (2H, m), 7.6 (1H, t, J = 7.5 Hz), 8.5 (1H, d, J = 7.5 Hz); ir (potassium bromide): 3200.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.32; H, 6.59; N, 6.08.

Preparation of Compounds **2**

The hydrochloride (0.2 mole) of **1** was dissolved in 150 ml. of ethanol and 0.5 ml. of concentrated hydrochloric acid and hydrogenated over 130 mg. of platinum oxide with stirring. The evaporation in vacuum of the filtered solution gave the hydrochloride in quantitative yield. The base was obtained by dissolving the hydrochloride in water, making basic with sodium carbonate and extracting with chloroform.

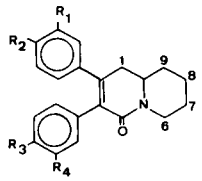
2-(β-Phenyl-β-hydroxyethyl)piperidine.

This compound was obtained in a yield of 98.1%, m.p. 83.5-85° (from benzene/light petroleum), lit. 85° (12); nmr (deuterochloroform): δ 1.5 (6H, m), 1.65 (2H, t), 2.95 (3H, m), 4.45 (1H, t), 4.9 (1H, t), 7.3 (5H, m).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.09; H, 9.27; N, 6.83. Found: C, 75.77; H, 9.32; N, 6.71.

Table III

Proton Magnetic Resonance Parameters of Lactams **6a-k**. Spectra were run at 100 Mc/s in deuterochloroform solution and chemical shifts are relative to tetramethylsilane (δ, 0.00).



Compound	C_7-C_9	C_1	C_{9a}	C_{6ax}	C_{6eq}	$J_{6,6}$ Hz	OCH_3	Aromatic
6a	1.70	2.82	3.61	2.61	4.58	14	—	7.13 (10H, m)
6b	1.66	2.80	3.56	2.57	4.49	14	—	6.88 (2H, d, J = 8 Hz); 7.05 (2H, d, J = 8 Hz); 7.04 (5H, m).
6c	1.75	2.90	3.60	2.70	4.65	14	3.78	6.8 (2H, d, J = 9 Hz); 7.05 (2H, d, J = 9 Hz); 7.2 (5H, m).
6d	1.68	2.78	3.58	2.58	4.52	14	3.38 3.78	6.34 (1H, d, J = 1.8 Hz); 6.7 (2H, d, J = 1.8 Hz); 7.02 (5H, m).
6e	1.70	2.77	3.60	2.62	4.56	14	3.82 3.84	6.64; 6.7; 6.96; 6.98 (8H, 4d, J = 9 Hz).
6f	1.65	2.75	3.55	2.58	4.53	14	3.61 3.78	6.49 (1H, s); 6.59 (2H, s); 7.06 (5H, m).
6g	1.68	2.78	3.60	2.64	4.52	13.5	3.47, 3.8 3.71	6.72 (2H, d); 6.4 (1H, s); 6.7; 6.95 (4H, 2d, J = 9 Hz)
6h	1.66	2.76	3.50	2.54	4.52	14	3.47 3.8	6.31 (1H, s); 6.66 (2H, d); 6.95; 7.1 (4H, 2d, J = 9 Hz).
6j	1.62	2.68	3.64	2.73	4.56	13.5	3.7 3.82	6.68 (3H, m); 6.66; 6.96 (4H, 2d, J = 9 Hz).
6k	1.70	2.70	3.60	2.60	4.52	14	3.50 3.70 3.80	6.4-6.62 (6H, m)

2-(β-4-Methoxyphenyl-β-hydroxyethyl)piperidine.

This compound was obtained in a yield of 97.8%, m.p. 181-183° (hydrochloride, from benzene); nmr (deuterochloroform): δ 1.8 (8H, m), 3.15 (3H, m), 3.81 (3H, s), 4.67 (1H, s), 5.15 (1H, t), 6.95 (2H, d, J = 7 Hz), 7.4 (2H, d, J = 7 Hz).

Anal. Calcd. for $C_{14}H_{21}NO_2HCl$: C, 61.78; H, 8.10; N, 5.15. Found: C, 61.77; H, 8.05; N, 4.87.

Preparation of Compounds **3**.

Compound **2** (0.022 mole) was added to a solution of 3.5 g. of chromium trioxide in 50 ml. of acetic acid and 0.5 ml. of water and the mixture was refluxed during 40 minutes. The cold solution was then poured into 200 ml. of water and made basic with a solution of concentrated sodium hydroxide to *p*H 10. Extraction with chloroform and concentration of the organic layer gave the product.

2-Phenacylpiperidine.

This compound distills at 118-120° (0.02 mm, Kugelrohr), yield, 89.4%; m.p. (hydrochloride): 167-169° (14); ir (liquid film): 1687; nmr (deuterochloroform): δ 1.6 (6H, m), 2.45 (2H, m), 3.1 (3H, m), 7.5 (3H, m), 8.1 (2H, m).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.90. Found: C, 77.04; H, 8.40; N, 6.61.

2-(4-Methoxyphenacyl)piperidine.

This compound distills at 132° (0.25 mm, Kugelrohr), yield, 88.5%; picrate m.p. 162°; ir (liquid film): 1670; nmr (deuterochloroform): δ 1.6 (6H, m); 2.55 (2H, m), 3.05 (3H, m), 3.9 (3H, s), 7 (2H, d, J = 8.6 Hz), 8.05 (2H, d, J = 8.6 Hz).

Anal. Calcd. for $C_{20}H_{22}N_4O_9$: C, 51.95; H, 4.76; N, 12.12. Found: C, 51.69; H, 4.71; N, 11.8.

Preparation of Compounds **5** and **6a-k**.

To a solution of 0.005 mole of **3**, 0.005 mole of pyridine and 20 ml. of dry benzene were added 0.005 mole of the suitable phenylacetyl chloride. The mixture was set aside 20 hours at room temperature, the pyridine hydrochloride was filtered off, and the liquids were washed with diluted hydrochloric acid and water. Evaporation of the dried benzene layer left the product **5** as a gum, which was dissolved in 90 ml. of 5% ethanolic sodium hydroxide and refluxed on a water bath two hours. The cold solution was concentrated under vacuum, taken up with chloroform and then washed with hydrochloric acid (10%). The organic layer was concentrated giving a gum which solidifies by adding ether and scratching. The products were purified by recristallization. (See Table I).

2,3-Diphenyl-1,6,7,8,9,9a-hexahydro-4*H*-quinolizin-4-one (**6a**).

The mass spectrum had the molecular ion peak at m/e 303 and abundant fragment peaks at m/e 302, 220 (100%, retro-Diels Alder fragmentation), 192, 191, 178, 165, 115, 84 and 55.

2-(3,4-Dimethoxyphenyl)-1,6,7,8,9,9a-hexahydro-3-(4-methoxyphenyl)-4*H*-quinolizin-4-one (**6f**).

The mass spectrum had the molecular ion peak at m/e 393 and abundant fragment peaks at m/e 378, 310 (100%, retro-Diels Alder fragmentation), 295, 279, 267, 251, 165, 145, 115 and 84.

Preparation of Compounds **7a-f**.

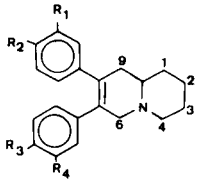
Lactam **6** (0.0017 mole) dissolved in 50 ml. of ether/benzene (1:1) was added dropwise to a stirred suspension of 0.3 g. of lithium alumunium hydride in 50 ml. of ether. The mixture was heated under reflux for four hours and then left 8 hours at room temperature. The excess of lithium aluminium hydride was destroyed with moist ether and crushed ice. The ethereal layer was separated, dried over sodium sulfate and evaporated. (See Table II).

7,8-Diphenyl-1,3,4,6,9,9a-hexahydro-2*H*-quinolizidine (**7a**).

The mass spectrum had the molecular ion peak at m/e 289 and abundant fragment peaks at m/e 288, 232, 213, 212, 206, 205,

Table IV

Proton Magnetic Resonance Parameters of Compounds **7a-f**. Spectra were run at 100 Mc/s in deuterochloroform solution and chemical shifts are relative to tetrametilsilane (δ, 0.00).



Compound	C_2	C_1,C_3	C_9,C_{9a}	C_{4ax}	C_{4eq}	$J_{4,4}$ Hz	C_{6ax}	C_{6eq}	$J_{6,6}$ Hz	OCH_3	Aromatic
7a	1.35	1.78	2.38	2.07	3.03	11	3.06	3.67	16	—	7.03 (10H, m)
7b	1.34	1.74	2.42	2.12	3.06	11	3.08	3.58	16.5	—	6.94; 7.11 (4H, 2d, J = 9 Hz); 7.1 (5H, m).
7c	1.35	1.78	2.42	2.10	3.14	10	3.17	3.62	15.5	3.72	6.68; 6.99 (4H, 2d, J = 9.5 Hz); 7.09 (5H, m).
7d	1.32	1.72	2.39	2.08	3.06	10.5	3.02	3.61	16	3.71	6.64; 6.74; 6.8; 6.9 (8H, 4d, J = 9 Hz)
7e	1.35	1.80	2.42	2.03	3.08	10	3.06	3.68	16.5	3.56 3.80	6.48 (1H, s); 6.69 (2H, m); 7.10 (5H, m).
7f	1.30	1.70	2.43	2.06	3.06	11	3.02	3.60	16	3.55 3.71 3.80	6.48 (1H, s); 6.58 (2H, s); 6.7; 7.0 (4H, 2d, J = 9 Hz).

191, 178, 165, 128, 115, 91, 84 and 77.

7-(*p*-Methoxyphenyl-8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (**7f**).

The mass spectrum had the molecular ion peak at m/e 378 and abundant fragment peaks at m/e 364, 296, 281, 272, 265 (100%), 242, 234, 98, 95 and 83.

2-(3,4-Dimethoxyphenacyl)pyridine (**4**).

This compound was prepared as previously described (2).

2-(3,4-Dimethoxyphenacyl)piperidine.

This compound was prepared as described for compounds **3**, interrupting the uptake of hydrogen by 3 moles.

Acknowledgement.

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