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PARTIAL DEHYDROGENATION OF SATURATED 4-PHENYL-1(2*H*)-PHTHALAZINONE DERIVATIVES BY THIONYL CHLORIDE

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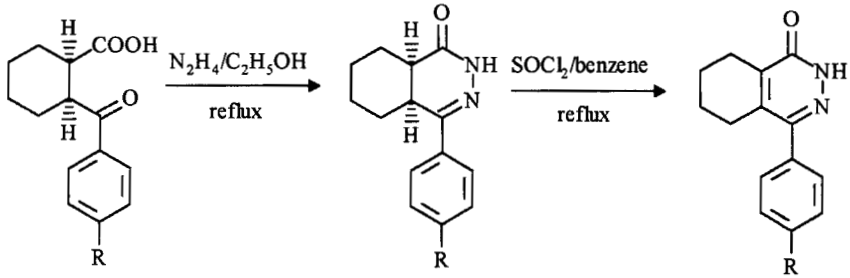
Abstract: *cis*-4a,5,6,7,8,8a-Hexahydro-4-phenyl-1(2*H*)-phthalazinones (**2**) react with thionyl chloride in benzene to give tetrahydro derivatives (**3**); the corresponding reaction of methylene bridged derivatives (**5**) is also described.

Recently, several methods were described for the dehydrogenation of the 4,5-dihydro-3(2*H*)-pyridazinones. These compounds were easily converted to the 3(2*H*)-pyridazinones either by Br_2/acetic acid[1] or by NBS in DMSO-water[2] and two convenient synthetic routes were elaborated, *i. e.* treatment of dihydro derivatives with SeO_2 in ethanol[3] or with MnO_2 in hot *N,N*-dimethylformamide[4]. Furthermore, a milder method for the preparation of 3(2*H*)-pyridazinones has been worked out by the treatment of dihydro derivatives with *m*-nitrobenzenesulfonic acid in aqueous solution at 100°C[5]. Mueller carried out this reaction by refluxing over



1 2 3

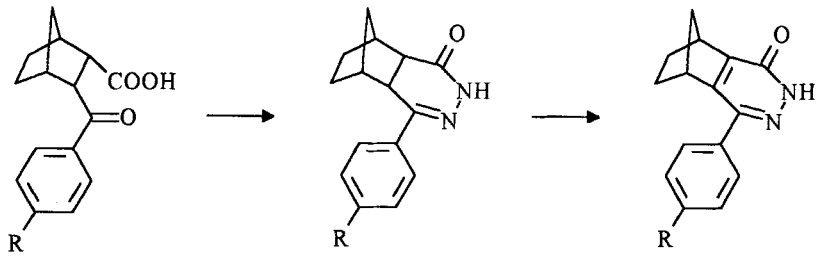
a; R = H **b**; R = CH_3 **c**; R = F **d**; R = Cl **e**; R = Br

Scheme 1

Pd/Al_2O_3 in dry methylbutyldiglycol[6] and finally, Nakao *et al.* published the acid catalysed dehydrogenation of a tricyclic pyridazinone derivative[7].

In this paper we report a simple and convenient method for the partial dehydrogenation of cyclohexane and norbornane condensed dihydropyridazinones by thionyl chloride in benzene. Relatively few publication is available concerning thionyl chloride as dehydrogenating agent.[8-10] We have found that, treatment of **2** with excess of thionyl chloride in benzene under reflux for several hours resulted in the formation of tetrahydro derivatives **3** (Scheme 1).

This dehydrogenation process takes place selectively at the annelation. The chlorination followed by elimination of hydrogen chloride mechanism might be responsible for this transformation. Similarly, the reaction of **5** with thionyl chloride (Scheme 2) afforded the corresponding norbornane condensed pyridazinones **6**. Starting keto acids (**1** and **4**) were prepared according to the procedure of Fieser and Novello[11], and these



4 5 6

a; R = H b; R = CH_3 c; R = F

Scheme 2

were condensed with hydrazine under reflux in ethanol affording **2** and **5** respectively in excellent yields.

On the basis of our experimental results we concluded that the yields of the dehydrogenation reactions were dependent on the substituent of the aromatic ring. The yield was moderate and the dehydrogenation process was slower in presence of electron-withdrawing substituents.

The structure of the compounds prepared were determined by microanalysis and by IR and ^{1}H-NMR spectroscopy, and relevant data are summarized in Tables 1 and 2. We observed strong IR absorption at 3211-3233 cm^{-1} (N-H band) and 1663-1670 cm^{-1} (C=O band) for the hexahydrophthalazinone derivatives **2** and **5**, whereas the intensity of the absorption of the N-H band was decreased for the partially dehydrogenated derivatives (**3** and **6**), and that was found between 3188-3197 cm^{-1}. Similarly, the ^{1}H-NMR spectra of saturated and partially dehydrogenated derivatives show significant differences for the NH protons. The character-

istic singlets of the NH protons appeared at 8.60-8.70 ppm for the compounds **2** and **5**, whereas the same signals were detected at lower field (11.00-12.50 ppm) in the case of the tetrahydro derivatives (**3** and **6**).

EXPERIMENTAL

Melting points were determined using an Electrothermal block and are uncorrected. IR spectra were measured for KBr discs with a Perkin -Elmer 177 instrument. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer at 200 MHz in $CDCl_3$ (internal standard Me_4Si, δ = 0.00 ppm) at room temperature. Ascending thin layer chromatography was performed on precoated plates of silica gel 60F 254 (Merck) and spots were visualised by using UV lamp or iodine vapor. Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70 eV.

General Procedure for the Synthesis of Compounds 2 and 5.

The mixture of 20 mmol keto acid (**1** and **4**) and 1.02 g (20 mmol) hydrazine monohydrate (98%) was refluxed in ethanol (25 ml) for 2 h, cooled to room temperature and the precipitate was filtered off, washed with water and crystallized from benzene to afford **2** and **5**. Physical and spectral data of these compounds are given in Tables 1 and 2.

General Procedure for the Preparation of Compounds 3 and 6.

Compound **2** or **5** (10 mmol) and thionyl chloride (5 ml) in dry benzene (25 ml) were refluxed for 5-15 h. The solvent was evaporated *in vacuo* and the residue crystallized from benzene or purified by column chromatography (silica gel packing, $CHCl_3$-EtOAc (2:1 v/v) eluent).

Table 1 Physical and analytical data for compounds **2-3** and **5-6**.

	M. p. (°C)	Yield (%)	Formula	Microanalysis (%) Calcd. (Found)		
				C	H	N
2a	173-174[a]	90	$C_{14}H_{16}N_2O$	73.65(73.34)	7.06(7.23)	12.27(12.45)
2b	169-170[a]	88	$C_{15}H_{18}N_2O$	74.35(74.10)	7.48(7.25)	11.56(11.72)
2c	159-160[a]	75	$C_{14}H_{15}FN_2O$	68.27(68.53)	6.14(6.22)	11.37(11.55)
2d	183-185[a]	83	$C_{14}H_{15}ClN_2O$	63.99(64.20)	5.75(5.58)	10.66(10.49)
2e	192-194[a]	80	$C_{14}H_{15}BrN_2O$	54.73(54.97)	4.92(5.15)	9.12(9.34)
3a	219-221[b]	79	$C_{14}H_{14}N_2O$	74.31(74.65)	6.23(6.40)	12.38(12.52)
3b	209-211[a]	85	$C_{15}H_{16}N_2O$	74.97(75.28)	6.71(6.80)	11.66(11.75)
3c	236-238[a]	58	$C_{14}H_{13}FN_2O$	68.83(69.15)	5.36(5.50)	11.47(11.61)
3d	241-243[c]	49	$C_{14}H_{13}ClN_2O$	64.49(64.72)	5.02(5.18)	10.74(10.90)
3e	256-258[c]	35	$C_{14}H_{13}BrN_2O$	55.09(55.40)	4.29(4.41)	9.18(9.34)
5a	232-233[a]	81	$C_{15}H_{16}N_2O$	74.97(74.87)	6.71(6.80)	11.66(11.75)
5b	246-248[a]	76	$C_{16}H_{18}N_2O$	75.56(75.41)	7.13(7.20)	11.01(11.12)
5c	215-217[a]	77	$C_{15}H_{15}FN_2O$	69.74(69.90)	5.85(5.77)	10.85(10.73)
6a	193-195[c]	60	$C_{15}H_{14}N_2O$	75.60(75.84)	5.92(6.10)	11.76(11.81)
6b	220-222[c]	65	$C_{16}H_{16}N_2O$	76.16(76.40)	6.39(6.47)	11.10(11.22)
6c	201-203[c]	55	$C_{15}H_{13}FN_2O$	70.29(70.50)	5.11(5.26)	10.93(11.18)

[a] From benzene; [b] From $CHCl_3$; [c] By column chromatography.

Table 2 Spectral data of compounds **2-3** and **5-6**.

	IR ν (cm^{-1})	^{1}H-NMR δ (ppm), J (Hz)	ms m/z (%)
2a	3212, 1670	1.25-1.90 (m, 7H), 2.50-2.62 (m, 1H), 2.72-2.81 (m,1H), 3.08-3.22 (m, 1H), 7.40 (m, 3H), 7.75 (m, 2H), 8.92 (s, 1H).	228 (M^+, 71), 199 (12), 173 (100).
2b	3211, 1666	1.25-1.88 (m, 7H), 2.38 (s, 3H), 2.55 (m, 1H), 2.75 (m, 1H), 3.06-3.20 (m, 1H), 7.20 (d, J=8.7, 2H), 7.65 (d, J=8.7, 2H), 8.77 (s, 1H).	242 (M^+, 90), 213 (12), 187 (100).
2c	3217, 1668	1.25-1.90 (m, 7H), 2.50-2.62 (m, 1H), 2.72-2.83 (m, 1H), 3.03-3.18 (m, 1H), 7.02-7.16 (m, 2H), 7.68-7.82 (m, 2H), 8.70 (s, 1H).	246 (M^+, 67), 217 (12), 191 (100).
2d	3219, 1669	1.25-1.90 (m, 1H), 2.50-2.62 (m, 1H), 2.78 (m, 1H), 3.03-3.18 (m, 1H), 7.38 (m, 2H), 7.70 (m, 2H), 8.75 (s, 1H).	262 (M^+, 69), 233 (10), 207 (100).
2e	3218, 1668	1.25-1.90 (m, 7H), 2.50-262 (m, 1H), 2.77 (m, 1H), 3.03-3.17 (m, 1H), 7.50-7.67 (m, 4H), 8.74 (s, 1H).	308 (M^++ 1, 73), 307 (M^+, 20), 306 (75), 251 (100).
3a	3192, 1641	1.60-1.87 (m, 4H), 2.40 (t, J=6.2, 2H), 2.67 (t, J= 6.2, 2H), 7.40 (m, 5H), 11.78 (s, 1H).	226 (M^+, 92), 225 (100), 211 (20).
3b	3189, 1639	1.60-1.87 (m, 4H), 2.40 (m, 5H), 2.65 (t, J= 6.0, 2H), 7.25 (m, 4H), 11.22 (s, 1H).	240 (M^+, 94), 239 (100), 225 (25).
3c	3196, 1649	1.57-1.83 (m, 4H), 2.47 (m, 2H), 3.38 (s, 2H), 7.23-7.40 (m, 2H), 7.50 (m, 2H), 12.90 (s, 1H).	244 (M^+, 100) 229 (23), 133 (26).
3d	3196, 1653	1.50-1.80 (m, 4H), 2.48 (m, 2H), 3.32 (s, 2H), 7.50 (m, 4H), 12.92 (s, 1H).	260 (M^+, 97), 259 (100), 245 (24).

3e	3194, 1645	12.62-1.88 (m, 4H), 2.40 (t, J= 6.1, 2H), 2.68 (t, J= 6.1, 2H), 7.27 (d, J= 7.6, 2H), 7.57 (d, J= 7.6, 2H), 11.60 (s, 1H).	306 (M^++1, 96), 305 (M^+, 92), 304 (100).
5a	3213, 1664	1.20-1.67 (m, 6H), 2.64 (s, 1H), 2.88-3.08 (m, 2H), 3.50 (q, J= 4.4, 1H), 7.38 (m, 3H), 7.68 (m, 2H), 8.59 (s, 1H).	240 (M^+, 42), 173 (58), 149 (100).
5b	3188, 1663	1.23-1.70 (m, 6H), 2.38 (s, 3H), 2.65 (s, 1H),2.87-3.07 (m, 2H), 3.48 (q, J= 3.7, 1H), 7.22 (t, J= 7.9, 2H), 7.69 (d, J= 9.3, 2H), 8.60 (s, 1H).	254 (M^+, 85), 187 (100), 171 (6).
5c	3233, 1663	1.15-1.68 (m, 6H), 2.62 (s, 1H), 2.88-3.07 (m, 2H), 3.45 (q, J= 4.3, 2H), 7.07 (t, J= 8.5, 2H), 7.68 (m, 2H), 8.54 (s, 1H).	258 (M^+, 76), 191 (100), 162 (9).
6a	3193, 1657	1.20-1.55 (m, 3H), 1.68-1.85 (m, 1H), 2.08 (m, 2H), 3.58 (s, 1H), 3.73 (s, 1H), 7.38-7.68 (m, 5H), 11.60 (s, 1H).	238 (M^+, 51), 223 (4), 210 (100).
6b	3197, 1653	1.20-1.83 (m, 4H), 2.07 (m, 2H), 2.44 (s, 3H), 3.57 (s, 1H), 3.72 (s, 1H), 7.28 (d, J= 8.8, 2H), 7.50 (d, J= 8.8, 2H), 11.00 (s, 1H).	252 (M^+, 55), 224 (100), 187 (18).
6c	3219, 1657	1.20-2.18 (m, 6H), 3.53 (s, 1H), 3.72 (s, 1H), 7.19 (q, J= 8.0, 2H), 7.60 (m, 2H), 11.43 (s, br, 1H).	256 (M^+, 50), 228 (100), 212 (8).

Melting points, yields, analytical and spectral data of compounds **3** and **6** are also given in Tables 1 and 2.

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