Synthesis of Spiro[cycloalkane-1,3′-[3*H*]indoles] from Cycloalkanecarbaldehydes. Acid-Catalyzed Rearrangement to Cycloalkano[*b*]indoles

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Spiro[cycloalkane-1,3′-[3*H*]indoles] **2** can be obtained from the cycloalkanecarbaldehydes **1** by the Fischer reaction of their phenylhydrazones. These cyclizations are sensitive to the acid catalyst, solvent and temperature employed. Rearrangement of the **2** to the homologous cycloalkane derivatives **3** can occur by an acid catalyst or by thermal treatment of **2** in ethyleneglycol.

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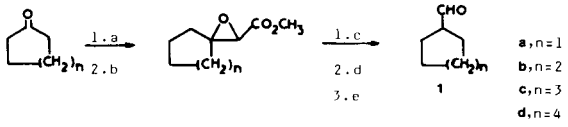
This paper describes the preparation of spiro[cycloalkane-1,3′-[3*H*]indoles] **2**. We are particularly interested in the structural behaviour of these tricyclic compounds because some derivatives have shown antidepressant action [1].

Cycloalkanones served as the starting products for the synthesis of **1**, employing a special treatment in the decarboxylation reaction of the glycidic acids, obtained by the Darzens reaction. Thus, the glycidic esters were obtained from the convenient cycloalkanone and methyl chloroacetate in presence of potassium *t*-butoxide. Hydrolysis of these esters with sodium methoxide in absolute methanol [2] provided the sodium salts of the cycloalkane glycidic acids, which enable decarboxylation by treatment of a suspension of these salts in aqueous sulfuric acid (10%) under a vigorous stream of steam that quickly removed the cycloalkanecarbaldehydes **1** purely, in quantitative yields (Scheme 1, See Experimental).

Scheme 1



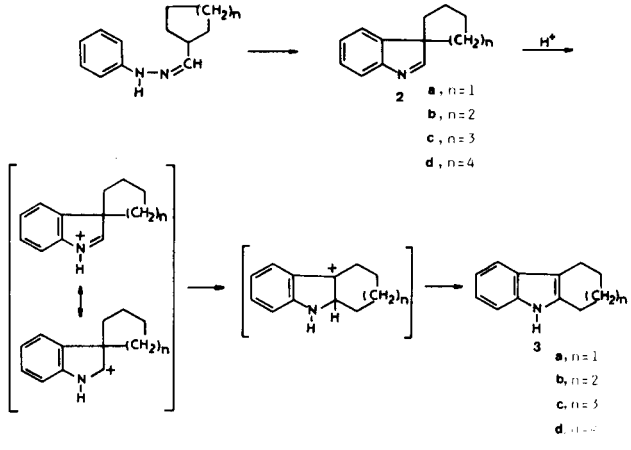
Reagents: [a] $ClCH_2CO_2CH_3$; [b] $(CH_3)_3COK$, $(CH_3)_3COH$; [c] CH_3ONa, CH_3OH; [d] H_2O; [e] H_2SO_4 (10%), Stream of steam.

Synthetic methods reported for the preparation of the aldehydes and ketones give poor yields [3].

The spiro[3*H*]indoles **2** were obtained from the phenylhydrazones of the aldehydes **1** by Fischer method. The acid catalyst used in this reaction has been carefully analyzed due to the easy acid-catalyzed rearrangement of **2** in respect to cycloalkano[*b*]indoles **3** (Scheme 2). In Table 1, are summarized the results of these analyses involving catalyst type, temperature and solvent.

All the [3*H*]indoles **2** gave the indoles **3** with sulfuric acid catalyst and so, the mechanism of this rearrangement is shown in Scheme 2.

Scheme 2



From Table 1 can be deduced, that the Fischer reaction of the phenylhydrazones of the **1** to form the [3*H*]indoles **2** and also the rearrangement product **3** is sensitive to the nature of the acid catalyst. A special behaviour of the phenylhydrazone **1a** was observed in the presence of the acid catalyst due to the instability of the **2a** product, since in all the cases the rearrangement product **3a** was recovered, and thus, **2a** has been prepared by other method [4]. However, in absence of the acid catalyst, thermal reaction of the phenylhydrazone of **1a**, in diethyleneglycol dimethyl ether does not transform into **2a** or **3a** products, while in ethyleneglycol only the rearrangement product **3a** was recovered.

The spiro[3*H*]indole **2b** shows greater chemical inertia to the rearrangement reaction than the remaining [3*H*]indoles and thus, the Fischer reaction to obtain **2b** has been made with various homogeneous and heterogeneous acid catalyst types, Table 1.

Thermal reaction of the phenylhydrazone of **1b** in ethyleneglycol affords a mixture of **2b** and **3b**. The rearrangement product **3b** seems to be formed from **2b**, since a pure sample of **2b**, provides **3b** under the same thermal conditions. No change was observed by the addition of a radical inhibitor, which could prevent a possible radical rear-

Table 1

Phenylhydrazone of **1**	Catalyst	r_m	Solvent	T (°C) [a]	t (h)	Products [b] **2a** (%)	**3a** (%)
1a	AcOH (99%)	—	AcOH (99%)	60	2	—	90
1a	AcOH (85%)	—	AcOH (85%)	60	2	—	90
1a	$BF_3 \cdot Et_2O$	½	Et_2O	30	17	—	30
1a	$BF_3 \cdot Et_2O$	10	Et_2O	50	5	—	20
1a	$BF_3 \cdot Et_2O$	½	THF	90	5	—	85
1a	—	—	DG	180	24	—	—
1a	—	—	EG	180	4	—	75

Phenylhydrazone of **1**	Catalyst	r_m	Solvent	T (°C) [a]	t (h)	Products [b] **2b** (%)	**3b** (%)
1b	H_2SO_4 (10%)	—	H_2O (99%)	90	1	—	89
1b	AcOH (99%)	—	AcOH (99%)	100	4	57	6
1b	AcOH (85%)	—	AcOH (85%)	90	4	92	—
1b	AcOH (50%)	—	AcOH (50%)	100	4	39	13
1b	$BF_3 \cdot Et_2O$	½	THF	80	6	50	—
1b	$B(OAc)_3$	1	Dioxane	90	20	—	—
1b	$ZnCl_2$	2	Benzene	100	30	40	—
1b	—	—	EG	180	4	7	50

Phenylhydrazone of **1**	Catalyst	r_m	Solvent	T (°C) [a]	t (h)	Products [b] **2c** (%)	**3c** (%)
1c	AcOH (99%)	—	AcOH (99%)	100	2	5	42
1c	AcOH (85%)	—	AcOH (85%)	100	2	4	35
1c	$BF_3 \cdot Et_2O$	½	THF	80	5	47	—

Phenylhydrazone of **1**	Catalyst	r_m	Solvent	T (°C) [a]	t (h)	Products [b] **2d** (%)	**3d** (%)
1d	AcOH (99%)	—	AcOH (99%)	100	2	4	45
1d	AcOH (85%)	—	AcOH (85%)	100	2	5	39
1d	$BF_3 \cdot Et_2O$	½	THF	80	5	46	—

r_m = Molar ratio of phenylhydrazone of **1** to catalyst. [a] T (°C) referred to the temperatures of an external bath. [b] Yields were obtained from ^{1}H-nmr spectrum. EG = Ethyleneglycol. DG = Dimethyl ether diethyleneglycol.

Table 2

Thermal Treatment of the [3*H*]Indole **2b** to Observe the Rearrangement to **3b**

Compound	Solvent	T (°C)	t (h)	**3b** (%)
2b	EG	180	4	73
2b	EG + HQ	180	4	73
2b	DG	180	24	—

EG = Ethyleneglycol. HQ = Hydroquinone. DG = Dimethyl ether diethyleneglycol.

rangement of **2b** to **3b** in the above thermal reaction. However, when the ethyleneglycol was changed for the aprotic diethyleneglycol dimethylether, the rearrangement of **2b** to **3b** was not observed (Table 2) and hence ethyleneglycol seems to behave as a mild protic acid catalyst in this reaction, and thus this rearrangement can be justified by a similar mechanism to that shown in Scheme 2.

Treatment of the phenylhydrazone of each **1c** and **1d** in tetrahydrofuran with boron trifluoride dimethyl etherate as the catalyst, effected cyclization only to **2c** (47%) and **2d** (46%) respectively, but the rearrangement products **3c** and **3d** were not detected, while the unreacted phenylhydrazones **1c** and **1d** were recovered.

EXPERIMENTAL

Melting points were determined by using a Reichert stage microscope and are uncorrected. Infrared spectra were recorded using an SP 1100 Phillips Pye Unicam Spectrophotometer. Nuclear magnetic resonance spectra were recorded at 60 MHz using a R-24A Hitachi Perkin-Elmer spectrometer. Chemical shifts are given relative to internal tetramethylsilane. Elemental analysis were performed with a Model 240 Perkin-Elmer analyzer.

Cycloalkanecarbaldehydes **1**.

a. Preparation of the Cycloalkane Glycidic Esters.

To a mixture of cycloalkanone (0.14 mole) and methyl chloroacetate (0.14 mole) in inert nitrogen atmosphere, was added dropwise a solution

of potassium *t*-butoxide (0.15 g-atom of potassium in 125 ml of dry *t*-butyl alcohol) at 10-15° during 90 minutes. After the mixture was stirred for 12 hours the *t*-butyl alcohol was removed by distillation. The brown residual oil was extracted with diethyl ether, washed with water and dried over magnesium sulfate. Diethyl ether was evaporated and the residual orange oil was distilled under vacuum to give a colourless liquid with the following yields and spectral data:

2-Carbomethoxy-1-oxaspiro[2,4]heptane.

This compound had bp 68°/1 mm, 79% yield; nmr (deuteriochloroform): δ 3.9 (s, 3H, CH_3), 3.4 (s, 1H, CH), 1.7 (m, 10H $(CH_2)_n$); ir (film): 1755 and 1730 (st C=O), 1300 and 840 (st oxirane ring).

2-Carbomethoxy-1-oxaspiro[2,6]nonane.

This compound had bp 85°/1 mm, 86% yield; nmr (deuteriochloroform): δ 3.9 (s, 3H, CH_3), 3.4 (s, 1H, CH), 1.7 (m, 12H $(CH_2)_n$); ir (film): 1755 and 1730 (st C=O), 1300 and 840 (st oxirane ring).

2-Carbomethoxy-1-oxaspiro[2,7]decane.

This compound had bp 104°/1 mm, 63% yield; nmr (deuteriochloroform): δ 3.9 (s, 3H, CH_3), 3.4 (s, 1H, CH), 1.7 (m, 14H $(CH_2)_n$); ir (film): 1755 and 1730 (st C=O), 1300 and 840 (st oxirane ring).

b. Hydrolysis of the Cycloalkane Glycidic Esters [2].

To a solution of sodium methoxide, resulting from the treatment of (2.32 g, 0.01 g-atom) of sodium with 45 ml of dry methanol, was added dropwise 0.09 mole of the glycidic ester. The mixture was cooled and then 2 ml of water was added and allowed to stand overnight. The solid was filtered off and washed with methanol and diethyl ether. Pure sodium salt of the glycidic ester was isolated as a colourless solid with 82, 94, 98 and 93% for cyclopentane, cyclohexane, cycloheptane and cyclooctane oxaspiro derivatives respectively.

c. Decarboxylation of the Glycidic Acids.

A suspension of the salts of the glycidic acids (0.07 mole) in 400 ml of aqueous sulfuric acid (10%) was treated with a vigorous stream of steam under a carbon dioxide atmosphere. The vapour mixture was quickly cooled at room temperature and carried to a collector-flask through a diffusor plate submerged in methylene chloride at 0°. The distillation was finished when the salt suspension became transparent or when 4 litres of distillate were collected. The organic layer was removed and the water layer extracted with methylene chloride. The combined methylene chloride extracts were dried over magnesium sulfate, filtered off and concentrated under vacuum in an atmosphere of carbon dioxide to provide the cycloalkanecarbaldehydes **1** as pure colourless liquids, in quantitative yields. 2,4-Dinitrophenylhydrazones of the aldehydes **1** are orange crystals of mp: **1a**, 160-162°; **1b**, 174-175°; **1c**, 132-133° and **1d**, 125-126°.

Compound **1a** had nmr (deuteriochloroform): δ 9.6 (d, 1H, J = 2 Hz, H-aldehyde), 2.6 (m, 1H), 1.7 (m, 8H, $(CH_2)_n$); ir (film): 1750 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.03; N, 20.14. Found: C, 51.68; H, 5.01; N, 20.06.

Compound **1b** had nmr (deuteriochloroform): δ 9.7 (d, 1H, J = 1 Hz, H-aldehyde), 2.2 (m, 1H), 1.6 (m, 10H, $(CH_2)_n$); ir (film): 1730 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.47; N, 19.17. Found: C, 53.31; H, 5.45; N, 18.98.

Compound **1c** had nmr (deuteriochloroform): δ 9.7 (d, 1H, J = 1 Hz, H-aldehyde), 2.2 (m, 1H), 1.6 (m, 12H, $(CH_2)_n$); ir (film): 1730 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.90; H, 5.88; N, 18.30. Found: C, 54.47; H, 5.93; N, 18.29.

Compound **1d** had nmr (deuteriochloroform): δ 9.7 (d, 1H, J = 1 Hz, H-aldehyde), 2.2 (m, 1H), 1.6 (m, 14H, $(CH_2)_n$); ir (film): 1730 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.25; H, 6.25; N, 17.50. Found: C, 56.35; H, 6.17; N, 17.20.

Spiro[cycloalkane-1,3'-[3*H*]indoles] (**2**).

Results of the Fischer reaction of the phenylhydrazones of the cycloalkanecarbaldehydes **1** are summarized in Table 1. In this experimental section, only optimal or representative results are considered.

Spiro[cyclopentane-1,3'-[3*H*]indole (**2a**).

All the attempts to transform the phenylhydrazone of **1a** to **2a** were unsuccessful (see Table 1). However, the rearrangement product **3a** was always present. Compound **3a** was characterized by spectral and analytical data and by comparison with a pure sample obtained by an independent route.

Compound **3a** had mp 114-115°; ir (nujol): 3420 (st NH), 740 (aromatic); nmr (deuteriochloroform): δ 7.3-7.0 (m, 5H, aromatic, and NH), 2.6 (m, 4H, CH_2 benzylic type), 1.8 (m, 4H, (CH_2) remaining cyclohexane ring).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{12}H_{13}N$: C, 84.16; H, 7.65; N, 8.18. Found: C, 84.11; H, 7.73; N, 7.83.

Spiro[cyclohexane-1,3'-[3*H*]indole] (**2b**).

a. The phenylhydrazone of the cyclohexanecarbaldehyde **1b** was obtained by azeotropic benzene-water distillation. Compound **1b** (7.0 g, 0.035 mole) and 160 ml of acetic acid (85%) were stirred at 90°, under a nitrogen atmosphere during 4 hours, cooled to ice bath temperature, made basic with aqueous sodium hydroxide (10%) and extracted with chloroform. The chloroform solution was dried over magnesium sulfate and concentrated to give an oil, which was chromatographed on a silica gel column, eluting with toluene-ethyl acetate (1:1) to provide 5.9 g (92%) of the **2b** as a colourless solid, mp 121-122°; ir (potassium bromide): 1610 (st C=N), 740 (aromatic); nmr (deuteriochloroform): δ 8.4 (s, 1H, HC=N), 7.5 (m, 4H, aromatic), 1.7 (m, $(CH_2)_n$).

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.27; H, 8.17; N, 7.56. Found: C, 84.20; H, 8.03; N, 7.30.

b. The phenylhydrazone of **1b** (3.40 g, 0.01 mole) in 50 ml of ethyleneglycol, under a nitrogen atmosphere was warmed at 180° during 4 hours. The mixture was added in to 150 ml of ice-water and extracted with chloroform. The chloroform solution was distilled and the residual brown oil was chromatographed on a silica gel column, eluting with toluene-ethyl acetate (1:1) to provide **2b** (7%) and **3b** (50%). Compound **3b** was characterized by spectral and analytical data and also by comparison with a pure sample obtained by an independent route.

Compound **3b** had mp 132-133°; ir (nujol): 3420 (st NH), 740 (aromatic); nmr (deuteriochloroform): δ 7.4 (m, 5H, aromatic, and NH), 2.8 (m, 4H, CH_2 benzylic type), 1.8 (m, 6H, CH_2 remaining cycloheptane ring).

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.27; H, 8.17; N, 7.56. Found: C, 83.98; H, 8.23; N, 7.23.

b.1. A pure sample of **2b**, (0.10 g, 49 mmoles) in 25 ml of ethyleneglycol was warmed at 180° during 4 hours in similar conditions as referred to in b. Rearrangement product **3b** was recovered in 73% yield. The change in the yield of the product **3b** was not significant for the reaction in presence of hydroquinone.

b.2. A pure sample of **2b** (0.10 g, 49 mmoles) in 25 ml of diethyleneglycol dimethylether was warmed at 180° under a nitrogen atmosphere during 24 hours and finally only the starting product **3b** was recovered.

Spiro[cycloheptane-1,3'-[3*H*]indole] (**2c**) and Spiro[cyclooctane-1,3'-[3*H*]-indole (**2d**).

a. Phenylhydrazones of **1c** and **1d** were obtained removing water azeotropically. A mixture of 0.03 mole of the phenylhydrazone of **1c** (or **1d**) and boron trifluoride etherate (8.5 ml, 0.06 mole), in 200 ml of dry tetrahydrofuran were stirred at 80° during 5 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, hydrolyzed with aqueous sodium acetate and extracted with chloroform. Solvent was removed to give a red oil which was chromatographed on a silica gel column, eluting with diethyl ether to provide the [3*H*]indoles **2c** or **2d** as colourless crystals, mp 139-140° (or 114-115°) for **2c** and **2d** respectively; ir (potassium bromide): 1610 (st C=N), 740 (aromatic) for both **2c** and **2d**; nmr (deuteriochloroform): δ 8.4 (s, CH=N), 1.7 (m, $(CH_2)_n$) for both **2c** and **2d**.

Anal. Calcd. (**2c**) for $C_{14}H_{17}N$: C, 84.36; H, 8.60; N, 7.03. Found: C, 84.31; H, 8.20; N, 7.01.

Anal. Calcd. (**2d**) for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57. Found:

C, 84.35; H, 8.73; N, 6.19.

b. Phenylhydrazones of **1c** and **1d** (0.02 moles) in 85 ml of acetic acid, under a nitrogen atmosphere were stirred at 100° during 2 hours, cooled to ice bath temperature, made basic with aqueous sodium hydroxide (10%) and extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and concentrated to give an oil, which was chromatographed on a silica gel column, eluting with toluene-ethyl acetate (1:1), to provide 42% of **3c** (or 45% of **3d**) and 5% of **2c** (or 4% of **2d**) respectively. Rearrangement products **3c** and **3d** were characterized by spectral and analytical data and also by comparison with a pure sample obtained by an independent route.

Compound **3c** had mp 72-73°; ir (nujol): 3420 (st, NH), 740 (aromatic); nmr (deuteriochloroform): δ 7.4-7.1 (m, 5H, aromatic and NH), 2.8 (m, 2H, CH_2 benzylic type), 2.7 (m, 2H, CH_2 benzylic type), 1.6 (m, 8H, $(CH_2)_n$ remaining cyclooctane ring).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.59; N, 7.02. Found: C, 84.72; H, 8.81; N, 7.00.

Compound **3d** had mp 62°; ir (nujol): 3420 (st NH), 740 (aromatic); nmr (deuteriochloroform): δ 7.4-7.1 (m, 5H, aromatic and NH), 2.8 (m, 2H, CH_2 benzylic type), 2.7 (m, 2H, CH_2 benzylic type), 1.6 (m, 10H, $(CH_2)_n$ remaining cyclononane ring).

REFERENCES AND NOTES

[1] J. G. Rodríguez, Y. Benito and F. Temprano, to be published.

[2] L. Claisen, *Ber.*, **38**, 693 (1905).

[3] W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).

[4] A. H. Jacson and B. Naidoo, *Tetrahedron*, **25**, 4843 (1969).