Synthesis of Some 5,6,7,8-Tetrahydro-4-cinnolone Derivatives and 1-Methyl-3-arylacetyl-4,5,6,7-tetrahydroindazoles

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2-Arylidene-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2** react with hydrazine hydrate to afford 5,6,7,8-tetrahydro-4-cinnolones. By methylation, these compounds gave the corresponding N-1 and N-2 methyl derivatives. The mesoionic compounds are obtained, accompanied by 3-arylacetyl-4,5,6,7-tetrahydroindazoles upon reaction of **2** with methylhydrazine.

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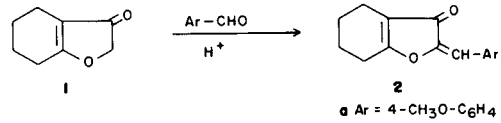
In connection with our continuing interest in 3(2*H*)-furanone chemistry (1,2), we wish to describe here the synthesis of 2-arylidene-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2** and their ability to form new heterocyclic compounds, either the 5,6,7,8-tetrahydro-4-cinnolone derivatives **3**, **5** and **6**, or the 3-arylacetyl-1-methyl-4,5,6,7-tetrahydroindazoles **4** by reaction upon hydrazine hydrate and methylhydrazine.

The acid-catalyzed condensation of 3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furan **1** (3) with several aromatic aldehydes afforded the 2-arylidene-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2**; benzaldehyde does not react. In all cases, a single stereoisomer was obtained, consequently its configuration could not be unequivocally assigned and is under investigation. It is known that benzo-3(2*H*)-furanone with aromatic aldehydes furnished only the *(Z)* isomers (4).

Scheme 1



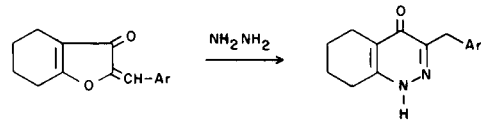
1

2

a Ar = 4-CH_3O-C_6H_4
b Ar = 4-Cl-C_6H_4
c Ar = 3,4(O-CH_2-O)C_6H_3
d Ar = 3,4$(CH_3O)_2C_6H_3$

Compounds **2** upon treatment with hydrazine hydrate afforded the new 5,6,7,8-tetrahydro-4-cinnolones **3** in good yields.

Scheme 2



2

3a-d

Table 1

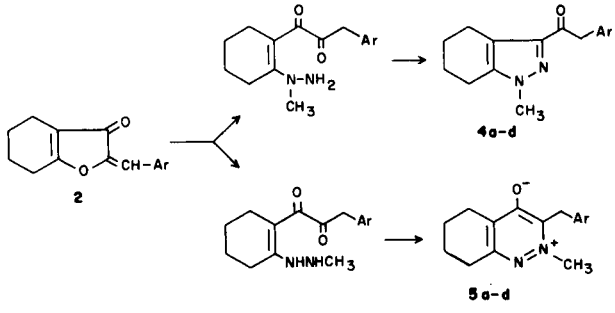
Physical Properties of 2-Arylidene-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2**

Compound No.	Yield %	Mp (°C)	Molecular Formula	Analyses Calcd./Found % C	H	N	IR (cm^{-1}) (a) ν C=O	UV (ethanol) λ nm ($\epsilon.10^{-3}$)	^{1}H NMR (δ) (Deuteriochloroform)
2a	16	140	$C_{16}H_{16}O_3$	74.98 74.82	6.29 6.28		1690	242 (10.9) 369 (20.2)	1.50-2.05 (m, 4H), 2.15-2.45 (m, 2H), 2.45-2.70 (m, 2H), 3.85 (s, 3H), 6.68 (s, 1H), 6.93 (d, 2H, J = 8.5 Hz), 7.76 (d, 2H, J = 8.5 Hz)
2b	21	151	$C_{15}H_{13}ClO_2$	69.10 69.06	5.03 4.97	13.60 13.72	1690	235 (10.8) 316 (21.0)	1.55-2.15 (m, 4H), 2.20-2.45 (m, 2H), 2.50-2.80 (m, 2H), 6.68 (s, 1H), 7.40 (d, 2H, J = 9 Hz), 7.78 (d, 2H, J = 9 Hz)
2c	67	197	$C_{16}H_{14}O_4$	71.10 71.04	5.22 5.33		1695	244 (8) 266 (9.5) 376 (18.1)	1.55-2.10 (m, 4H), 2.20-2.45 (m, 2H), 2.50-2.75 (m, 2H), 6.05 (s, 2H), 6.68 (s, 1H), 6.88 (d, 1H, J = 8 Hz), 7.28 (d, 1H, J = 8 Hz), 7.48 (s, 1H)
2d	63	180	$C_{17}H_{16}O_4$	71.31 71.09	6.34 6.43		1700	260 (8.7) 372 (21.7)	1.55-2.10 (m, 4H), 2.20-2.45 (m, 2H), 2.50-2.75 (m, 2H), 3.95 (s, 6H), 6.69 (s, 1H), 6.91 (d, 1H, J = 8.5 Hz), 7.25-7.50 (m, 2H)

(a) In chloroform.

Compounds **2** and methylhydrazine gave an approximately 1:1 ratio of chromatographically separable isomers, namely, the 1-methyl-3-arylacetyl-4,5,6,7-tetrahydroindazoles **4** and the anhydro-3-benzyl-4-hydroxy-2-methyl-5,6,7,8-tetrahydrocinnolinium hydroxides **5** (see experimental).

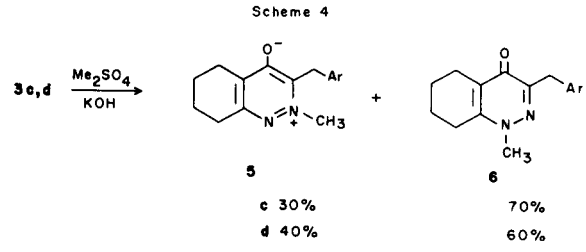
Scheme 3



The formation of products could be explained, as shown in 3(2*H*)-furanone systems (1,2) by assuming that the reaction occurs by a nucleophilic conjugate addition to the tetrahydrofuranone ring arising from one or the other nitrogen atom of methylhydrazine, with concomitant ring opening and recyclization either at the C-2 or at the C-3 carbon atom of the open intermediate (Scheme 3).

Proof of the structure for compounds **3** and **5** come from their spectral data and by the methylation reaction, under basic condition, of the tetrahydro-4-cinnolones **3c,d**. This reaction afforded the N-1 and N-2 methyl derivatives **6** and **5**, respectively. These results are in accord with those previously described concerning the methylation of the 4-cinnolones (5,6).

Scheme 4



Both compounds **5** and **6** were isolated by chromatography on silica gel. Compounds **5** were the more polar derivatives. Moreover, the determination of the position of the *N*-methyl group could be assigned upon chemical shift comparison of the *N*-methyl protons of each pair of isomers. The N-1 methyl protons in compounds **6** were observed at higher field (δ 3.80) than those of the corresponding anhydro base **5** (δ 4.01-4.09), as showed in the 4-cinnolone (6) or in the 1,4-dihydropyridazine-4-one (7) series.

The spectral data of compounds **4** readily established the 3-arylacetyltetrahydroindazole structure (Table 4) but cannot allow unequivocally the determination of the position of the *N*-methyl group. Our assignment was determined by ^{1}H-nmr comparison of the two isomeric 3-methoxycarbonyl derivatives obtained *via* oxidation of the known corresponding 3-(1-hydroxyethyl) derivatives (3), with the one prepared from **4a** under the same conditions. The melting points of the two isomeric acids, given in a patent (8) are very close to each other and does not allow an unambiguous structural assignment.

Table 2

Physical Properties of 3-Benzyl-5,6,7,8-tetrahydro-(1*H*)-4-cinnolones **3**

Compound No.	Yield %	Mp (°C)	Molecular Formula	Analyses Calcd./Found % C	H	N	Cl	UV (ethanol) λ nm (ε.10^{-3})	^{1}H NMR (δ) (DMSO-d$_6$)
3a	95	208 ethanol	$C_{16}H_{18}N_2O_2$	71.09 71.21	6.71 6.59	10.36 10.35		275 (10.8)	1.50-1.90 (m, 4H), 2.20-2.45 (m, 2H), 2.45-2.70 (m, 2H), 3.73 (s, 3H), 3.83 (s, 2H), 6.83 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.5 Hz), 12.7 (s, 1H, exchangeable)
3b	66	245 ethanol	$C_{15}H_{15}N_2ClO$	65.57 65.70	5.50 5.77	10.20 9.92	12.90 13.05	277 (10.5)	1.50-1.90 (m, 4H), 2.20-2.45 (m, 2H), 2.45-2.70 (m, 2H), 3.89 (s, 2H), 7.33 (s, 4H), 12.7 (s, 1H, exchangeable)
3c	77	217	$C_{16}H_{16}N_2O_3$	67.59 67.20	5.67 5.74	9.85 9.78		281 (13.7)	1.50-1.90 (m, 4H), 2.20-2.45 (m, 2H), 2.45-2.70 (m, 2H), 3.81 (s, 2H), 5.96 (s, 2H), 6.75-6.95 (m, 3H), 12.7 (s, 1H, exchangeable)
3d	87	213	$C_{17}H_{20}N_2O_3$	67.98 67.89	6.71 6.91	9.33 9.28		280 (14.7)	1.50-1.85 (m, 4H), 2.20-2.70 (m, 4H), 3.72 (s, 6H), 3.85 (s, 2H), 6.75-7.00 (m, 3H), 12.7 (s, 1H, exchangeable)

Ir (cm^{-1}) ν NH: 3500-3200, ν C=O 1585-1590 (chloroform).

Table 3

Physical Properties of Anhydro-3-benzyl-4-hydroxy-2-methyl-5,6,7,8-tetrahydrocinnolinium Hydroxides **5** and 3-Benzyl-1-methyl-(1*H*)-4-cinnolones **6**

Compound No.	Yield %	Mp (°C) (a)	Molecular Formula	Analyses Calcd./Found % C	H	N	Cl	UV (ethanol) λmax (ε.10⁻³)	¹H NMR (δ) (Deuteriochloroform)
5a	50	159	$C_{17}H_{20}N_2O_2$	71.80	7.09	9.85		268 (5.7)	1.65-2.00 (m, 4H), 2.50-2.90 (m, 4H),
		(E)		71.53	7.13	9.72		319 (8.8)	3.75 (s, 3H), 4.01 (s, 3H), 4.35 (s, 2H), 6.70-6.95 (d, 2H, J = 8 Hz), 7.10-7.25 (d, 2H, J = 8 Hz)
5b	35	163	$C_{16}H_{17}N_2ClO$	66.55	5.93	9.70	12.28	265 (3.4)	1.65-2.05 (m, 4H), 2.50-2.85 (m, 4H),
		(E)		66.99	5.93	9.63	12.53	320 (6.0)	4.01 (s, 3H), 4.39 (s, 2H), 7.21 (s, broad, 4H)
5c	37 (b)	142	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39		274 (4.2)	1.60-2.00 (m, 4H), 2.45-2.80 (m, 4H),
	15 (c)	(E)		68.14	6.37	9.31		290 (4.6)	4.03 (s, 3H), 4.34 (s, 2H), 5.95 (s, 2H),
								319 (5.1)	6.70-6.90 (m, 3H)
5d	35 (b)	141	$C_{18}H_{22}N_2O_3$	68.77	7.05	8.91		272 (5.6)	1.75-2.00 (m, 4H), 2.60-2.90 (m, 4H),
	16 (c)	(A)		68.55	7.10	8.74		320 (8.4)	3.88 (s, 6H), 4.09 (s, 3H), 4.41 (s, 2H), 6.85-7.10 (m, 3H)
6c	36 (c)	158	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39		285 (16.4)	1.50-2.00 (m, 4H), 2.50-2.75 (m, 4H),
		(A)		68.81	6.10	9.22			3.80 (s, 3H), 3.93 (s, 2H), 5.93 (s, 2H), 6.65-7.00 (m, 3H)
6d	31 (c)	68	$C_{18}H_{22}N_2O_3$	68.77	7.05	8.91		284 (15.5)	1.50-2.00 (m, 4H), 2.40-2.70 (m, 4H),
		(A)		68.56	7.25	8.52			3.80 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 6.75-7.10 (m, 3H)

(a) Recrystallization solvent: E = ethanol, A = ethyl acetate. (b) From compounds **2**. (c) From compounds **3**.

Table 4

Physical Properties of 3-Arylacetyl-1-methyl-4,5,6,7-tetrahydroindazoles **4**

Compound No.	Yield %	Mp (°C) (a)	Molecular Formula	Analyses Calcd./Found % C	H	N	Cl	UV (ethanol) λ max (ε.10⁻³)	¹H NMR (δ) (Deuteriochloroform)
4a	30	55	$C_{17}H_{20}N_2O_2$	71.80	7.09	9.85		224 (10.4)	1.50-2.00 (m, 4H), 2.45-2.95 (m, 4H),
		(A)		71.54	7.09	9.82		246 (11.2)	3.75 (s, 3H), 3.78 (s, 3H), 4.20 (s, 2H), 6.75-6.90 (d, 2H, J = 8 Hz), 7.15-7.30 (d, 2H, J = 8 Hz)
4b	52	112	$C_{16}H_{17}N_2ClO$	66.55	5.93	9.70	12.28	217 (11.3)	1.60-2.00 (m, 4H), 2.45-2.85 (m, 4H),
		(B)		66.76	6.09	9.74	12.06	246 (14.0)	3.79 (s, 3H), 4.23 (s, 2H), 7.24 (s, 4H)
4c	40	108	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39		243 (11.6)	1.55-2.00 (m, 4H), 2.45-2.90 (m, 4H),
		(B)		68.29	6.09	9.03		283 (6.0)	3.80 (s, 3H), 4.18 (s, 2H), 5.90 (s, 2H), 6.75-6.95 (m, 3H)
4d	54	105	$C_{18}H_{22}N_2O_3$	68.77	7.05	8.91		234 (13.2)	1.55-2.00 (m, 4H), 2.45-2.95 (m, 4H),
		(B)		68.66	7.10	8.77		277 (6.9)	3.80 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.21 (s, 2H), 6.75-7.00 (m, 3H)

(a) Recrystallization solvent, A, hexane-ethyl acetate 1:1, B, ethyl acetate. Ir: ν C=O 1690-1670 cm^{-1} (chloroform).

EXPERIMENTAL

Melting points were determined on a Kofler hot plate. Infrared and ultraviolet spectra were obtained with a Beckmann Model Acculab 2 and DB spectrometers. ¹H nmr spectra were taken on a Brucker WP 80 spectrometer. The chemical shifts reported are in parts per million from TMS as an internal standard. Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

2-Arylidene-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2**.

General Procedure.

To a solution of **1** (2.76 g, 0.02 mole) and an aromatic aldehyde (anisaldehyde, 4-chlorobenzaldehyde, piperonal or veratraldehyde) (0.02 mole) in anhydrous ether (100 ml) was added 5 drops of concentrated hydrochloric acid, with stirring. After 12 hours, the solution was concentrated under reduced pressure to 50 ml. The precipitated solid was removed by filtration and crystallized from ethanol (Table 1).

3-Benzyl-5,6,7,8-tetrahydro-4(1*H*)-cinnolones **3**.

General Procedure.

To a solution of **2** (0.02 mole), in ethanol (20 ml) was added hydrazine hydrate (1.25 g, 0.025 mole). The mixture was allowed to stand at room temperature for a night and then the solvent was removed under reduced pressure. Trituration of the residue with ether (50 ml) produced a precipitate which was collected and crystallized from ethanol (Table 2).

Reaction of **2** With Methylhydrazine.

A solution of **2** (0.01 mole) in ethanol was heated at 30°, then methylhydrazine (0.55 g, 0.012 mole) was added with stirring. The reaction mixture was then allowed to stand overnight. Evaporation of the solvent gave an oil which was analyzed by ^{1}H nmr.

The composition of the isomeric mixture is given below:

	% **4**	% **5**
a	40	60
b	55	45
c	45	55
d	55	45

Chromatography of silica gel using ethyl acetate as eluent afforded first the 3-arylacetyl-4,5,6,7-tetrahydroindazoles (**4**). The more polar anhydro-3-benzyl-4-hydroxy-2-methyl-5,6,7,8-tetrahydrocinnolinium hydroxide (**7**) was then eluted with ethyl acetate/methanol 4:1. The yields and the physical properties are summarized in Table 2.

Methylation of **3**.

A solution of **3c,d** (0.02 mole) in 4*N* potassium hydroxide (70 ml) was stirred at 40° while dimethyl sulfate (3.4 g, 0.027 mole) was added. The mixture was heated at 40° for 30 minutes and allowed to stand at room temperature for 3 hours and then was extracted with chloroform. After evaporation of the solvent, the residue was shown to be a mixture of **5c** + **6c** 7:3 (63% yield); **5d** + **6d** = 3:1 (55% yield). Pure compounds were obtained by column chromatography on silica gel. Elution with ethyl acetate gave the less polar compounds **6c,d**. The more polar compounds **5c,d** were then eluted with ethyl acetate/methanol 4:1. Yields and physical properties are given in Table 3.

Oxidation of the 3-(1-Hydroxyethyl)-1 or 2-methyl-4,5,6,7-tetrahydroindazole.

A solution of alcohol (0.005 mole) in acetone (15 ml) was treated dropwise with 0.007 mole of chromic oxide as Jones reagent (9) with stirring. The mixture was refluxed for 20 minutes. Acetone was evaporated under reduced pressure and the cooled solution was extracted repeatedly with chloroform. The chloroform layers were then washed with 10% aqueous sodium hydroxide (4 × 10 ml). The aqueous layers were acidified with 2*N* hydrochloric acid and extracted with chloroform. After drying, the solvent was evaporated under reduced pressure. Treatment of the residue with ethereal diazomethane afforded the corresponding 3-methoxycarbonyl derivatives in a yield of 30% (N-1) and 50% (N-2). Their ^{1}H nmr data given above, clearly showed significant differences in the chemical shifts of their methyl protons.

1-Methyl-3-methoxycarbonyl-4,5,6,7-tetrahydroindazole.

This compound had ^{1}H nmr (deuteriochloroform): δ 3.81 (s, 3H, N-CH_3), 3.91 (s, 3H, OCH_3).

2-Methyl-3-methoxycarbonyl-4,5,6,7-tetrahydroindazole.

This compound had ^{1}H nmr (deuteriochloroform): δ 3.89 (s, 3H, N-CH_3), 4.13 (s, 3H, OCH_3).

Oxidation of Compound **4d**.

A solution of **4d** (1.57 g, 0.005 mole) in acetone (15 ml) was treated with 0.01 mole of chromic acid as Jones reagent (9). The reaction was then carried out in the same procedure as described above. Treatment of the residue with ethereal diazomethane gave a mixture of 3-methoxycarbonyl-1-methyl-4,5,6,7-tetrahydroindazole and methyl veratrate which were separated by column chromatography over silica gel, using ethyl acetate as eluent. The first compounds was obtained in a yield of 30%. Its ^{1}H nmr spectrum showed a striking correspondence to the spectrum of the authentic N-1 methylated isomer prepared from the known 1-methyl-3-(1-hydroxyethyl)-4,5,6,7-tetrahydroindazole (3).

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