Synthesis of 3-(1-Hydroxyalkyl)-4,5,6,7-tetrahydroindazole Derivatives. Structure Determination of *N*-Alkyl Isomers

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A novel series of 3-(1-hydroxyalkyl)-4,5,6,7-tetrahydroindazoles and their 1 and 2-alkyl-3-(1-hydroxyalkyl)- or-3-(1-acetoxyalkyl) derivatives were synthesized *via* condensation between 3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans or 2-(2-acetoxyacyl)cyclohexanones and hydrazines. Structure assignment are based on ^1H and ^{13}C nmr spectra.

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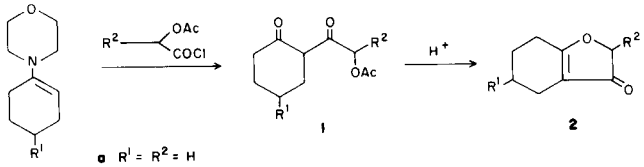
The reaction of hydrazines with 3-2*H*-furanone derivatives was investigated in this laboratory some years ago (1-5). Application of this reaction to 3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furans **2** provides a convenient route for the preparation of 3-(1-hydroxyalkyl)-4,5,6,7-tetrahydroindazole derivatives hitherto unknown. Compounds **2** have been synthetized earlier, according to Scheme 1 (6-8).

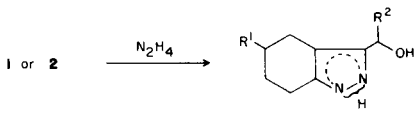
Scheme 1



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = CH_3$
c $R^1 = t\text{-}Bu$, $R^2 = H$

Reaction between the compounds **1** or **2** and hydrazine hydrate afforded the 3-(1-hydroxyalkyl)-4,5,6,7-tetrahydroindazoles **3** in good yields (Scheme 2).

Scheme 2

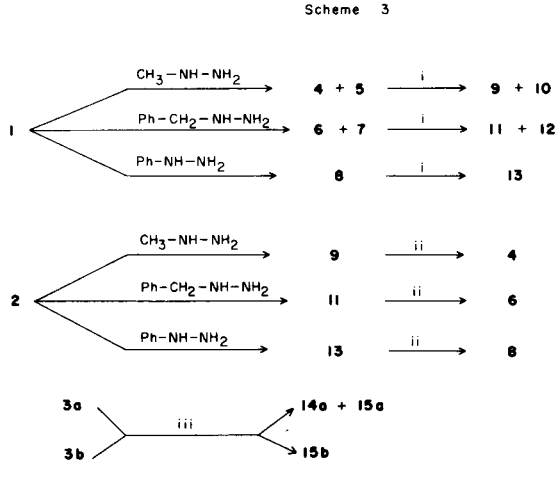


3 a-c

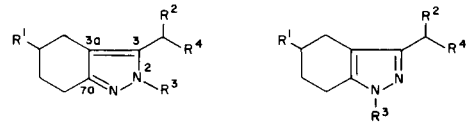
When compounds **2** were treated with monosubstituted hydrazines (methylhydrazine, benzylhydrazine and phenylhydrazine), only one *N*-alkyltetrahydroindazole derivative was obtained. As no way for an unambiguous structural assignment of a single isomer was evident, we have prepared the isomeric 1 and 2-alkyl derivatives (Scheme 3). Thus, by comparison of the ^{13}C and ^1H nmr spectra of the isomeric pairs, the formation of 2-alkyl-3-(1-hydroxyalkyl)-4,5,6,7-tetrahydro-2*H*-indazoles **9**, **11** and **13** by treating the compounds **2** with alkylhydrazines was unequivocally established. This regioselectivity was consistent with a ring-opening ring-closure sequence performed by the selective nucleophilic attack by the primary amino group of hydrazines at the C-7a position of the 3-oxohexahydrobenzofuran ring.

It is well known that condensation of β-diketones with alkylhydrazines affords a mixture of both *N*-alkylpyrazoles (9). Thus, treatment of compounds **1** with methylhydrazine or benzylhydrazine led to a mixture of 1 and 2-alkyl-3-(1-acetoxyalkyl)-4,5,6,7-tetrahydro-1*H*-and-2*H*-indazoles **4-7**. The composition of the isomeric mixture, as evidenced by ^1H nmr, is outlined in the Table 1. Only one

Scheme 3



i, 10% NaOH ; ii, acetyl chloride, pyridine; iii, acetic anhydride, pyridine



R^3	R^4	N-2	N-1
CH_3	$OCOCH_3$	**4 a,b**	**5 a,b**
CH_2-Ph	$OCOCH_3$	**6 a,b**	**7 a,b**
Ph	$OCOCH_3$	**8 a,b**	
CH_3	OH	**9 a,b,c**	**10 a,b**
CH_2-Ph	OH	**11 a,b**	**12 a,b**
Ph	OH	**13 a,b,c**	
CO-CH_3	$OCOCH_3$	**14 a**	**15 a,b**

a $R^1 = R^2 = H$, **b** $R^1 = H$, $R^2 = CH_3$, **c** $R^1 = t\text{-}Bu$, $R^2 = H$

Table 1

3-(1-Acetoxyalkyl)-tetrahydro-1*H*-and-2*H*-indazole Derivatives (**4-8**, **14**, **15**).

Compound	%	%	Yield	Bp/Torr		Molecular	Analyses					
N-2 N-1	N-1	N-2	%	or mp	n_D^{20}	Formula	Calcd. %			Found %		
			(a) (b)	°C			C	H	N	C	H	N
4a + **5a**	50	50	83	95-100$_{0.05}$		$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45	63.37	7.85	13.38
4a		100	88		1.5095							
4b + **5b**	54	46	80	90-100$_{0.05}$		$C_{12}H_{18}N_2O_2$	64.84	8.16	12.60	64.72	8.39	12.57
4b		100	88		1.5025							
6a + **7a**	40	60	84	145-155$_{0.05}$		$C_{17}H_{20}N_2O_2$	71.80	7.09	9.85	71.47	7.03	9.80
6a		100	93		1.5585							
7a	100		23 (c)		1.5560							
6b + **7b**	20	80	90	145-150$_{0.05}$								
						$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39	72.58	7.72	9.35
6b		100	80		1.5530							
8a	0	100	75	77		$C_{16}H_{18}N_2O_2$	71.09	6.71	10.36	71.06	6.81	10.34
8b	0	100	87	(cyclohexane)	1.5610	$C_{17}H_{20}N_2O_2$	71.80	7.09	9.85	72.03	7.26	9.86
14a+**15a**	70	30	64 (d)			$C_{12}H_{16}N_2O_3$	61.00	6.83	11.86	61.16	6.72	11.87
15a	100		50 (e)	57								
15b	100		68 (d)	(ethyl acetate)	1.5185	$C_{13}H_{18}N_2O_3$	62.38	7.25	11.19	62.67	7.29	11.19

(a) From compound **1**. (b) From compound **2**. (c) Isolated by column chromatography from **6a**/**7a**. (d) From compound **3**. (e) Isolated by column chromatography from **14a**/**15a**.

Table 2

Selected ^{13}C NMR Spectral Data (δ ppm) (a) for Compounds **3-15**

Compounds	C-3	C-7a	C-3a	N-CH_3	N-CH_2	CH_2 (C-3)	CH (C-3)
3a (NH)	145.9 (b)	143.9 (b)	113.8			56.7	
4a (N-2)	133.1	147.3	116.6	36.1		54.4	
5a (N-1) (c)	142.5	139.4	115.3	35.4		58.8	
4b (N-2)	137.1	147.4	114.4	36.8			63.8
5b (N-1) (b)	146.7	139.6	113.8	35.3			66.4
6a (N-2)	132.4	148.2	117.1		53.2 (b)	54.5 (b)	
7a (N-1)	143.1	138.9	115.5		52.6	59	
9a (N-2)	139.1	147.3	115.0	37.3		53.6	
10a (N-1) (e)	148.8	139.9	114.9	36.3		57.6	
11a (N-2)	139.4	148.0	115.0		53.5	53.5	
12a (N-1) (e)	149.4	139.6	115.2		52.9	57.7	
13a (N-2)	141.1	149.9	117.9			53.5	
14a (N-2) (f)	135.1	153.1	121.7			56.9	
15a (N-1)	148.6	142.7	119.7			58.8	
15b (N-1)	152.6	142.6	118.7				66.5

(a) R^4 = OAc in deuteriochloroform. R^4 = OH in DMSO-d_6. (b) Assignment may be interchanged recorded from a mixture: (c) **4a**/**5a**. (d) **4b**/**5b**. (e) **9a**/**10a**. (f)**14a**/**15a**.

species, with the 2-phenyl structure was isolated from the reaction with phenylhydrazine, according to the observed orientation upon the reaction of 2-acetylcyclohexanone and 2,4-dinitrophenylhydrazine (10).

Of course, the hydroxyalkyl or acetoxyalkyl moiety can be respectively acetoxylated or hydrolyzed by the conventional routes (Scheme 3).

All attempts to induce alkylation of the tetrahydroindazoles **3** resulted in tar formation. In contrast, reaction of **3** with acetic anhydride in pyridine generated the *N*-acetyl derivatives. Orientation of the acylation is strikingly R^2 substituent dependent. Treatment of **3a** (R^2 = H) yielded a 7:3 mixture of **15a**/**14a**, whereas **3b** (R^2 = CH_3) gave only the 1-acetyl derivative **15b** (Scheme 3).

Structure Determination of *N*-1 and *N*-2 Alkylated or Acetylated Derivatives.

The structural assignments for these compounds rest on their ^{13}C and ^1H nmr spectra. The carbon shifts are listed in Table 2, they were assigned on the basis of chemical shift data in the pyrazole literature, off-resonance decoupling and observation of the coupled spectra. The basic

Table 3

Selected ^{1}H NMR Data of Isomeric *N*-Alkyltetrahydroindazoles (δ ppm)

(a)

Compounds						N-CH_3 or
R^1	R^2	R^3	R^4	N-2	N-1	N-CH_2-Ph
H	H	CH_3	OAc	**4a**		3.90
					5a	3.77
H	CH_3	CH_3	OAc	**4b**		3.82
					5b	3.67
H	H	CH_2Ph	OAc	**6a**		5.35
				7a		5.23
H	CH_3	CH_2Ph	OAc	**6b**		5.42
				7b		5.22
H	H	CH_3	OH	**9a**		3.73
				10a		3.61
H	CH_3	CH_3	OH	**9b**		3.70
				10b		3.56
tBu	H	CH_3	OH	**9c**		3.77
H	H	CH_2Ph	OH	**11a**		5.40
				12a		5.25
H	CH_3	CH_2Ph	OH	**11b**		5.31
				12b		5.14

(a) R^4 = OAc in carbon tetrachloride; R^4 = OH in DMSO-d_6.

principle guiding interpretation of the ^{13}C nmr spectra of isomeric *N*-alkylpyrazoles is that the carbon resonance for a pyridine-like environment (N=C) occurs at lower field than for a pyrrole-like environment (N-C=) (11-14). Furthermore, a methyl or methylene carbon of a side chain which is bonded to a carbon adjacent to an alkylated nitrogen resonates at higher field that the same carbon in the other isomer (4,5). Comparison of the spectra of the isomeric pairs **4a/5a**, **4b/5b**, **9a/10a**, **11a/12a**, revealed that it was easy to assign their structures by the shift of the methylene or methine carbon of the acetoxyalkyl or hydroxyalkyl residue. The *N*-2 alkylated derivatives showed an upfield shift. The *N*-1 structure is further substantiated by the coupled spectra of **5a** and **7a**. The resonance lines at respectively δ 142.5 (t, ^2J = 5 Hz) and 143.1 (t, ^2J = 3 Hz) were assigned, therefore, to C-3, while those at δ 139.4 and 138.9 were attributed to C-7a. These signals are significantly broadened by the ^2J and ^3J long-range proton-carbon couplings with the methylene protons of the cyclohexene ring and with the *N*-alkyl protons. Similarly, the structure of the 1-acetyl derivatives **15a** and **15b** was deduced by establishing the shift of the deshielded pyridine-like carbon at δ 148.6 (t, ^2J = 5 Hz) and 152.6 (d, ^2J = 4 Hz) to C-3.

Additional support for the correctness of the structures was furnished by the ^{1}H nmr chemical shift of the *N*-methyl protons. The isomers with a methyl group on nitrogen which is bonded to the carbocyclic ring exhibit methyl signals at higher field that their *N*-2 isomers, according to the tetrahydroindazole data (15). The same variations are observed in the *N*-benzyl series. (Table 3).

Table 4

3-(1-Hydroxyalkyl)-tetrahydro-1*H*-and-2*H*-indazole Derivatives (**3,9,11,13**)

Compound	Yield (a)	Mp (°C) Solvent	Molecular Formula	Analyses Calcd. % Found C	H	N	Uv in Ethanol λ max (nm) ε
3a	76 (72)	129	$C_8H_{12}N_2O$	63.13	7.95	18.41	288 (4290)
		ethanol		63.01	7.95	18.51	
3b	79 (61)	109	$C_9H_{14}N_2O$	65.03	8.49	16.85	227 (4176)
		cyclohexane		65.23	8.63	16.65	
3c	71	211	$C_{12}H_{20}N_2O$	69.19	9.68	13.45	230 (3719)
		ethyl acetate		69.05	9.46	13.45	
9a	91	91	$C_9H_{14}N_2O$	65.03	8.49	16.85	236 (5590)
		cyclohexane		64.88	8.45	17.02	
9b	68	81	$C_{10}H_{16}N_2O$	66.63	8.95	15.54	234 (5203)
		cyclohexane		66.51	9.08	15.26	
9c	80	150	$C_{13}H_{22}N_2O$	70.23	9.91	12.60	236 (5240)
		ethyl acetate		70.02	9.57	12.52	
11a	64	113	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	239 (6428)
		ethyl acetate		74.16	7.68	11.80	
11b	54	81	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	234 (7513)
		ethyl acetate		75.25	7.86	10.98	
13a	40	170	$C_{14}H_{16}N_2O$	73.15	7.06	12.27	258 (12682)
		ethanol		73.40	6.98	12.27	
13b	66 (b)	135	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	252 (10300)
		ethyl acetate		74.26	7.68	11.80	
13c	44	193	$C_{18}H_{24}NO_2$	76.02	8.51	9.85	259 (13357)
		ethyl acetate		75.73	8.59	9.68	

(a) Yields between parentheses are referred to procedure A. (b) By hydrolysis of the corresponding acetoxyalkyl derivative.

Table 5

Proton Magnetic Resonance Parameters of Compounds (**3,9,11,13**) in DMSO-d_6 δ (ppm)

Compound	
3a	1.5-1.85 (m, 4H), 2.30-2.70 (m, 4H), 4.37 (s, 2H), 4.75 (s, 1H, exchangeable with deuterium oxide), 12.10 (broad, 1H, exchangeable).
3b	1.37 (d, 3H, J = 7 Hz), 1.55-1.90 (m, 4H), 2.30-2.70 (m, 4H), 4.78 (q, 1H, J = 7 Hz), 4.85 (broad, 1H, exchangeable), 12.0 (broad, 1H, exchangeable).
3c	0.92 (s, 9H), 1.10-2.70 (m, 7H), 4.50 (2H, d, J = 5 Hz), 4.90 (t, 1H, J = 5 Hz exchangeable), 12.10 (broad 1H).
9a	1.50-1.80 (m, 4H), 2.30-2.60 (m, 4H), 3.73 (s, 3H), 4.38 (d, 2H, J = 5 Hz), 5.0 (t, 1H, J = 5 Hz, exchangeable).
9b	1.38 (d, 3H, J = 7 Hz), 1.50-1.80 (m, 4H), 2.30-2.70 (m, 4H), 3.70 (s, 3H); 4.77 (broad, 1H, exchangeable), 4.88 (q, 1H, J = 7 Hz).
9c	0.90 (s, 9H), 1.00-2.70 (m, 7H), 3.77 (s, 3H), 4.48 (d, 2H, J = 5 Hz), 5.08 (t, 1H, J = 5 Hz, exchangeable).
11a	1.50-1.90 (m, 4H), 2.30-2.70 (m, 4H), 4.50 (d, 2H, J = 5,5 Hz), 5.25 (t, 1H, J = 5,5 Hz, exchangeable), 5.40 (s, 2H), 7.30-7.60 (m, 5H).
11b	1.26 (d, 3H, J = 7 Hz), 1.50-1.90 (m, 4H), 2.30-2.65 (m, 4H), 4.85 (m, 1H), 5.23 (d, 1H, J = 4,5 Hz, exchangeable), 5.31 (s, 2H), 7.0-7.40 (m, 5H).
13a	1.60-2.00 (m, 4H), 2.40-2.90 (m, 4H), 4.52 (d, 2H, J = 5.5 Hz), 5.42 (t, 1H, J = 5.5 Hz, exchangeable), 7.50-8.0 (m, 5H).
13b	1.41 (d, 3H, J = 7 Hz), 1.60-1.90 (m, 4H), 2.55-2.90 (m, 4H), 4.88 (m, 1H), 5.40 (d, 1H, J = 4.5 Hz, exchangeable), 7.55-7.70 (m, 5H).
13c	0.93 (s, 9H), 1.20-3.00 (m, 7H), 4.50 (d, 2H, J = 5 Hz), 5.37 (broad, 1H, exchangeable), 7.50-8.0 (m, 5H).

Table 6

Proton Magnetic Parameters of Compounds (**4-8**) (**14-15**) δ (Carbon Tetrachloride)

Compound	
4a	1.65-2.00 (m, 4H), 2.07 (s, 3H), 2.40-2.80 (m, 4H), 3.90 (s, 3H), 5.12 (s, 2H)
5a (a)	1.65-2.00 (m, 4H), 2.07 (s, 3H), 2.40-2.80 (m, 4H), 3.77 (s, 3H), 5.12 (s, 2H)
4b	1.50 (d, 3H, J = 7 Hz), 1.60-1.90 (m, 4H), 2.02 (s, 3H), 2.40-2.80 (m, 4H), 3.82 (s, 3H), 5.93 (q, 1H, J = 7 Hz)
5b (b)	1.54 (d, 3H, J = 7 Hz), 1.60-1.90 (m, 4H), 2.02 (s, 3H), 2.40-2.80 (m, 4H), 3.67 (s, 3H), 6.07 (q, 1H, J = 7 Hz)
6a	1.80 (s, 3H), 1.70-1.90 (m, 4H), 2.40-2.80 (m, 4H), 4.98 (s, 2H), 5.35 (s, 2H), 7.20-7.50 (m, 5H)
7a	2.02 (s, 3H), 1.60-1.90 (m, 4H), 2.35-2.70 (m, 4H), 5.09 (s, 2H), 5.23 (s, 2H), 7.20-7.50 (m, 5H)
6b	1.32 (d, 3H, J = 7 Hz), 1.78 (s, 3H), 1.60-1.90 (m, 4H), 2.40-2.80 (m, 4H), 5.42 (s, 2H), 5.98 (q, 1H, J = 7 Hz), 7.20-7.50 (m, 5H)
7b (c)	1.57 (d, 3H, J = 7 Hz), 2.02 (s, 3H), 1.60-1.90 (m, 4H), 2.40-2.80 (m, 4H), 5.22 (s, 2H), 6.05 (q, 1H, J = 7 Hz), 7.20-7.50 (m, 5H)
8a	2.05 (s, 3H), 1.70-2.10 (m, 4H), 2.50-2.90 (m, 4H), 5.10 (s, 2H), 7.35-7.75 (s, 5H)
8b	1.43 (d, 3H, J = 7 Hz), 1.98 (s, 3H), 1.60-2.00 (m, 4H), 2.50-2.90 (m, 4H), 6.03 (q, 1H, J = 7 Hz), 7.50-7.65 (s, 5H)
14a (d,e)	1.60-1.90 (m, 4H), 2.09 (s, 3H), 2.30-2.60 (m, 2H), 2.66 (s, 3H), 2.80-3.10 (m, 2H), 5.39 (s, 2H)
15a (e)	1.60-1.90 (m, 4H), 2.13 (s, 3H), 2.30-2.60 (m, 2H), 2.66 (s, 3H), 2.80-3.10 (m, 2H), 5.09 (s, 2H)
15b (e)	1.60 (t, 3H, J = 7 Hz), 1.60-1.90 (m, 4H), 2.10 (s, 3H), 2.35-2.60 (m, 2H), 2.65 (s, 3H), 2.85-3.10 (m, 2H), 5.95 (q, 1H, J = 7 Hz)

Recorded on a mixture (a) **4a/5a**, (b) **4b/5b**, (c) **6b/7b**, (d) **14a/15a**, (e) in deuteriochloroform.

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. The ^{1}H nmr spectra were taken on a Brucker WP 80 spectrometer and ^{13}C nmr spectra were obtained with a Varian XL 100 12 FT. The chemical shifts reported are in parts per million from internal TMS as an internal standard. Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

General Procedure for the Preparation of Compounds **1**.

Acetoxyalkyl chloride (0.21 mole) in dry benzene (100 ml) was added slowly to a boiling solution of 1-*N*-morpholinocyclohexene (36.8 g, 0.2 mole) and dry triethylamine (30.6 ml, 0.22 mole) in benzene (280 ml). The mixture was heated under reflux for 4 hours and then hydrolyzed by refluxing for 4 hours with 2-*N*-hydrochloric acid (130 ml). The benzene layer was washed with water and dried and then evaporated. The resulting crude diketone was purified by recrystallization or distillation.

2-Acetoxyacetylcyclohexanone (**1a**).

This compound was obtained in a yield of 69%, mp 100°, lit (7) mp 99°.

2-(2-Acetoxypropionyl)cyclohexanone (**1b**).

This compound was obtained in a yield of 60%, bp 140° (1 mm); n_D^{20} 1.5025; uv (ethanol): λ nm (ϵ) 292 (7180); ir (carbon tetrachloride): 1755, 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.40 (t, 3H, J = 7 Hz), 1.60-1.85 (m, 4H), 2.13 (s, 3H), 2.25-2.60 (m, 4H), 5.38 (q, 1H, J = 7 Hz), 15.50 (s, 1H).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.12; H, 7.63.

General Procedure for the Preparation of Compounds **2**.

The diketone **1** (0.1 mole) was dissolved in cold (-15°) concentrated sulfuric acid (200 ml) with stirring, taking care to maintain the temperature between -5° to 0°. The solution was poured into ice water (200 ml) either immediately after complete dissolution in the case of **1a**, or after allowing for further 1 hour at room temperature for **1b**.

3-Oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furan (**2a**).

This compound was obtained in a yield of 68%, mp 39° lit (7) mp 39°.

2-Methyl-3-oxo-2,3,4,5,6,7-hexahydrobenzo[*b*]furan (**2b**).

This compound was obtained in a yield of 73%, bp 105° (2 mm); uv (ethanol): λ nm (ϵ) 270 (10,000); ir (carbon tetrachloride): 1635, 1705 cm^{-1}; ^{1}H nmr (carbon tetrachloride): 1.36 (d, 3H, J = 7 Hz), 1.50-1.90 (m, 4H), 2.0-2.50 (m, 4H), 4.30 (q, 1H, J = 7 Hz).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H. 7.95. Found: C, 70.95; H, 7.90.

3-Oxo-5-*t*-butyl-2,3,4,5,6,7-hexahydrobenzo[*b*]furan (**2c**).

The crude diketones **1c** prepared under similar conditions as for the preparation of **1a,b**, from 4-*t*-butyl-1-morpholinocyclohexene and acetoxyacetyl chloride was run in sulfuric acid as described for **1a**. Final purification by fractional distillation at reduced pressure gave compound **2c** (32% overall yield from enamine). This Compound had Eb_4 = 150°, n_D^{25} = 1.5098 uv (ethanol): λ nm (ϵ) 270 (10,000); ir (carbon tetrachloride): 1640, 1705 cm^{-1}; ^{1}H nmr (carbon tetrachloride): 0.93 (s, 9H), 1.20-2.60 (m, 7H), 4.38 (s, 2H).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.47.

3-(1-Hydroxyalkyl)-4,5,6,7-tetrahydroindazoles (**3a-c**).

To a solution of diketone **1** (0.01 mole) in ethanol (40 ml) (procedure A), or of 3-oxohexahydrobenzofuran (**2**) (0.01 mole) in ethanol (20 ml) (procedure B), was added hydrazine hydrate (1.25 g, 0.025 mole, procedure A) or (0.75 g, 0.015 mole, procedure B) The mixture was allowed to stand at room temperature for a night. Upon concentration *in vacuo*, the residual material recrystallized to give the title compounds **3**. The compounds prepared and their physical properties are listed in Tables 4 and 5.

2-Alkyl-3-(1-hydroxyalkyl)-4,5,6,7-tetrahydro-2*H*-indazoles (**9a-c**, **11a,b**, **13a,c**).

To a stirred solution of tetrahydrofuranone **2** (0.01 mole) in ethanol (20 ml) was added the alkylhydrazine (0.015 mole). The reaction mixture was then worked as described above for compounds **3** (Tables 4 and 5).

1-and (or) 2-Alkyl-3-(1-acetoxyalkyl)-4,5,6,7-tetrahydro-1*H*-and (or) 2*H*-indazoles (**4-8**).

A) Reaction of Diketones **1** with Alklhydrazines (path a).

To a solution of diketone **1** (0.01 mole) in ethanol (40 ml) was added methylhydrazine, benzylhydrazine or phenylhydrazine (0.015 mole). After concentration *in vacuo*, the residue was dissolved in chloroform (75 ml) and washed with 5% aqueous hydrochloric acid, then 5% sodium carbonate solution and then water. Evaporation of the chloroform gave a residue which was analyzed by ^{1}H nmr and distillated under reduced pressure. The product distribution and analyses are given in Table 1. Pure compound **7a** was isolated by chromatography on silica gel, using ethyl acetate/hexane 1:4 as eluent. The N-2 isomer **6a** was first eluted and then the N-1 isomer **7a**. In the other cases, we did not succeed in the separation of isomer pairs.

B) Acetoxylation of 2-Alkyl-3-(1-hydroxyalkyl)tetrahydro-2*H*-indazoles (path b).

To a solution of alcohols **9a,b**, **11a,b** (0.01 mole), in anhydrous pyridine (10 ml), was added acetic anhydride (2.55 g, 0.025 mole). After being boiled for 15 minutes, the reaction mixture was poured into ice water (150 g), acidified with concentrated hydrochloric acid and extracted with ether. The organic solution was dried and evaporated. The residue was distillated to afford the 2-alkyl-3-(1-acetoxyalkyl) derivatives **4a,b** and **6a,b** (Tables 1 and 6).

Hydroysis of 3-(1-Acetoxyalkyl)tetrahydroindazoles.

To a solution of 1-and (or) 2-alkyl derivatives prepared as described above **4a**/**5a**, **4b**/**5b**, **7a**, **8a** and **8b** (0.01 mole) in tetrahydrofuran (50 ml), was added 10% aqueous sodium hydroxide (30 ml). The resulting mixture was heated under reflux for 4 hours and then extracted with ether. The combined ether extracts were dried and evaporated to left the crude mixture of 1-and (or) 2-alkyl-3-(1-hydroxyalkyl)-tetrahydroindazoles respectively **9a**/**10a**, **9b**/**10b**, **12a**, **13a** and **13b**. Pure compound **10a** was isolated by column chromatography from the **9a**/**10a** mixture. Compound **9a** was first eluted and then **10a**. Compounds **9b** and **10b** could not be separated.

1-Methyl-3-hydroxymethyl-4,5,6,7-tetrahydro-1*H*-indazole (**10a**).

This compound was obtained in a yield of 12% (overall yield from **4a** + **5a**), mp 97-98°; uv (ethanol): λ nm (ε) 230 (4650); ir (chloroform): 3620, 3500-3200 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.50-1.80 (m, 4H), 2.30-2.60 (m, 4H), 3.61 (s, 3H), 4.28 (d, 2H, J = 5 Hz), 4.63 (t, 1H, J = 5 Hz, exchangeable).

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.91; H, 8.50; N, 16.72.

1-Benzyl-3-hydroxymethyl-4,5,6,7-tetrahydro-1*H*-indazole (**12a**).

This compound was obtained in a yield of 66% from **7a** (overall yield from **6a** + **7a** 15%); mp 78° (cyclohexane); uv (ethanol): λ nm (ε) 228 (6500); ir (chloroform): 3610, 3500-3200 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 1.55-1.80 (m, 4H), 2.30-2.65 (m, 4H); 4.38 (d, 2H, J = 5 Hz); 5.10 (t, 1H, J = 5 Hz, exchangeable), 5.25 (s, 2H), 7.15-7.40 (s, 5H).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.24; H, 7.33; N, 11.47.

1-Acetyl-3-(1-acetoxyalkyl)-4,5,6,7-tetrahydro-1*H*-indazoles (**15a,b**).

To a mixture of compounds **3** (0.01 mole) in anhydrous pyridine (10 ml), was added acetic anhydride (2.55 g, 0.025 mole). After being boiled for 15 minutes, the reaction mixture was poured into ice-water (150 g), acidified with concentrated hydrochloric acid and extracted with ether. The organic solution was dried and evaporated. The residue was analyzed by ^{1}H nmr spectroscopy and chromatographed on silica gel using ethyl acetate/hexane 1:4 as eluent to afford the pure 1-acetyl derivative **15a** or **15b**. Compound **14a** could not be isolated in a pure state. (Tables 1 and 6).

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