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A CONVENIENT SYNTHESIS AND STRUCTURAL ANALYSIS OF NOVEL 4,5,6,7-TETRAHYDRO-1H-INDAZOLES

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A new series of t-4-aryl-3,c-6-dihydroxy-6-methyl-4,5,6,7-tetrahydro-1H-indazole-r-5-carboxylic acid isopropyl esters has been synthesized by adopting a conventional method from cyclic β-keto esters. ^{1}H, ^{13}C NMR, and IR spectra for all the compounds were investigated. HMBC, HSQC, COSY, and NOESY spectra of the representative compounds were studied. The stereochemistry of a six-membered ring of the fused indazoles resembled that of keto esters. From the HMBC correlations the indazole structure was confirmed as 1H-indazole.

Keywords: cyclic β-keto esters, 1H-indazole, tetrahydroindazole, HMBC, NOESY spectra.

The universal requirements on heterocyclic compounds for their potential activities against microorganisms and significance in the pharmaceutical field prompted us to synthesize indazoles from cyclic keto esters. Several pathways have been described for the synthesis of indazoles [1–5].

Recently we reported the synthesis and structural studies of *r*-2,*c*-4-bis(alkoxycarbonyl)-*t*-3-aryl-*c*-5-hydroxy-*t*-5-methylcyclohexanone by the condensation of acetoacetic esters with different aromatic aldehydes in the presence of methylamine [6–8]. The conformation of the two isopropyl groups of compound **1** was also studied with the help of X-ray crystallography of *t*-2-aryl-*c*-4-hydroxy-4-methyl-6-oxocyclohexane-*r*-1,*c*-3-dicarboxylic acid diisopropyl ester [9]. The present paper describes the use of the above compounds [8] as synthons for the preparation of 4,5,6,7-tetrahydro-1H-indazole. The synthesis of 4,5-*trans*-2-alkyl-4-hetaryl-5-ethoxycarbonyl(acetyl)-6-hydroxy-6-methyl-4,5,6,7-tetrahydro-2H-indazole has been reported [10]. Nevertheless, the published NMR spectral data aplies more to 1H-indazole than to 2H-indazole. N(2)-Substituted tetrahydroindazoles have been reported in [11].

Synthesis of 4,5,6,7-1H-indazoles involves two steps. The first step, condensation of isopropyl acetoacetate with aromatic aldehydes in the presence of methylamine in ethanol, yielded cyclic β-keto esters **1**–**7**. They were treated with hydrazine hydrate in ethanol under reflux to give compounds **8**–**14** (Scheme). The mechanism of this second step was different from the expected one. Dehydration was faster than cyclization, and the cyclic intermediates formed in the reaction course were unstable and easily underwent amido-imidol tautomerism, yielding stable 1H-indazoles.

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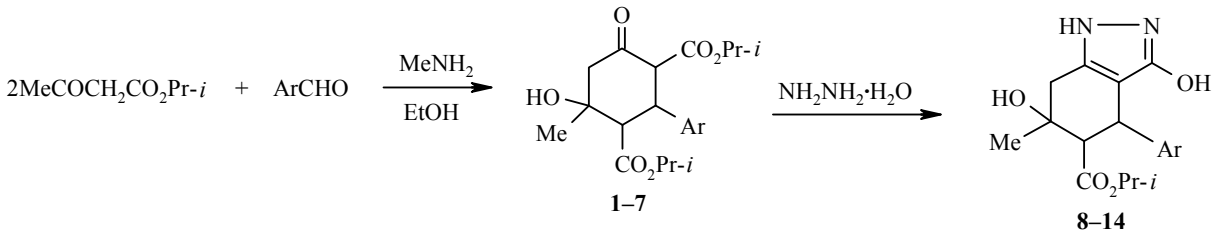
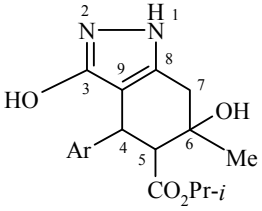
The structure of the compounds was elucidated by IR, mass, and one- and two-dimensional NMR spectra. Physical and analytical data of the synthesized compounds are given in Table 1.

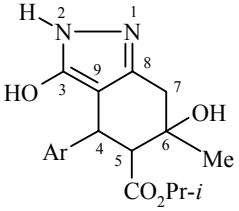


1, 8 Ar = Ph; **2, 9** Ar = *p*-FC_6H_4; **3, 10** Ar = *p*-$MeOC_6H_4$; **4, 11** Ar = *p*-$Me_2NC_6H_4$; **5, 12** Ar = *p*-ClC_6H_4; **6, 13** Ar = *m*-$O_2NC_6H_4$; **7, 14** Ar = *m*-$PhOC_6H_4$

The structure of the indazoles prepared could be *t*-4-aryl-3,*c*-6-dihydroxy-6-methyl-4,5,6,7-tetrahydro-1H-indazole-*r*-5-carboxylic acid isopropyl ester or the respective 2H-indazole derivative.



1H-indazole



2H-indazole

In the HMBC spectrum the cross peak (38.7/7.07–7.02 ppm) reveals that the aromatic protons show multiple bond correlations with the cyclohexanone ring carbon at 38.7 ppm. Hence, the ^{13}C resonance at 38.7 ppm has been assigned to C-4. In the HSQC spectrum the one-bond correlation (38.7/4.06 ppm) between C-4 and H-4*a* confirms that the doublet at 4.06 ppm is due to H-4*a*. Hence, another doublet with a diaxial coupling constant around 10 Hz to 2.57 ppm is conveniently assigned to H-5*a*. Once H-5*a* is assigned, from the HSQC spectrum (59.9/2.57 ppm) the ^{13}C resonance at 59.9 ppm is confirmed to be due to C-5. Among the two doublets

TABLE 1. Physical and Analytical Characteristics of Compounds **8-14**

Compound	Empirical formula	Found, % / Calculated, %			*m/z* [M+H$^+$]	mp, °C	Yield, %
		C	H	N			
8	$C_{18}H_{22}N_2O_4$	65.60 / 65.45	7.20 / 6.71	8.67 / 8.48	331	218	82
9	$C_{18}H_{21}FN_2O_4$	62.27 / 62.06	6.12 / 6.08	8.21 / 8.04	349	238	78
10	$C_{19}H_{24}N_2O_5$	63.51 / 63.32	6.79 / 6.71	7.94 / 7.77	361	218	75
11	$C_{20}H_{27}N_3O_4$	64.59 / 64.32	7.35 / 7.29	11.52 / 11.25	374	125	70
12	$C_{18}H_{21}ClN_2O_4$	59.42 / 59.26	5.84 / 5.80	7.91 / 7.68	365	243	80
13	$C_{18}H_{21}N_3O_6$	57.74 / 57.59	5.07 / 5.64	11.39 / 11.19	376	250	75
14	$C_{24}H_{26}N_2O_5$	68.44 / 68.23	6.22 / 6.20	6.81 / 6.63	423	215	70

due to H-7*a* and H-7*e* the doublet at 2.52 ppm has NOE with H-4*a* and H-5*a* in the NOESY spectrum. Therefore the doublet at 2.52 ppm is assigned to H-7*a*, while the chemical shift of H-7*e* is 2.77 ppm. Based on the one-bond correlation between H-7*a* and H-7*e* with C-7 in HSQC, the C-7 resonance is fixed as 36.5 ppm. In the HSQC the ^{13}C resonance at 69.9 ppm has no correlations with protons and hence it is due to quaternary carbon C-6.

Among the quaternary carbon resonances 99.2, 138.8, 143.8, and 159.9, the ^{13}C resonance at 143.0 ppm has a multiple-bond correlation (143.0/7.07-7.29 ppm) with aromatic protons in the HMBC and hence that resonance is assigned to C-1' (*ipso* carbon of the Ar ring). The ^{13}C resonance at 99.2 ppm shows cross peaks (99.2/4.06 and 99.2/2.57 ppm) with H-5*a* and hence that resonance has been assigned to C-9.

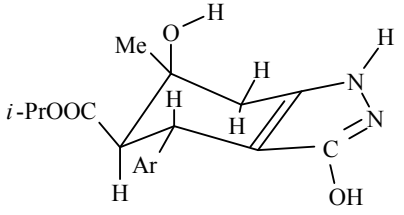
The assignment of ^{13}C resonances C-3 and C-8 determines whether the compound is 1H-indazole or 2H-indazole. If the indazole is 2H-indazole, then C-8 is C=N and the ^{13}C resonance must be 157.9 ppm. This ^{13}C resonance should exhibit multiple-bond correlations with H-7*a*, H-7*e*, and methyl protons at C-6 in HMBC.

If the indazole is 1H-indazole, then C-3 is C=N and the ^{13}C resonance 157.9 ppm assigned to C-3 and C-8 must be 138.8 ppm. Further, the ^{13}C resonance 138.8 ppm (C-8) must exhibit a multiple-bond correlation with H-7a, H-7e, and methyl protons at C-6 in HMBC.

The HMBC spectrum of indazole proves that there are multiple-bond correlations between ^{13}C resonance 138.8 ppm and H-7*a*, H-7*e*, and methyl protons at C-6. Therefore, the ^{13}C resonance 138.8 ppm is assigned to C-8 and the compound is 1H-indazole. This has been proved beyond doubt by X-ray structure study [12]. The spectral and crystal study of indazole proves that it is *t*-4-aryl-3,*c*-6-dihydroxy-6-methyl-4,5,6,7-tetrahydro-1H-indazole-*r*-5-carboxylic acid isopropyl ester.

Re-examination of NMR spectral data of 4,5-*trans*-2-alkyl-5-ethoxycarbonyl(acetyl)-4-hetaryl-6-methyl-4,5,6,7-tetrahydro-2H-indazole suggests that based on the assignment of C-13 chemical shifts of C-3 and C-8 (mentioned as C-7 in [10]) the indazoles reported then must be 1H-indazoles and not 2H-indazoles.

Based on the observed chemical shifts and coupling constants, the indazoles obtained adopt a normal *chair* conformation with axial orientation of OH group at C-6 and equatorial orientation of other substituents like in cyclic β-keto esters.



Conformation of *t*-4-aryl-3,*c*-6-dihydroxy-6-methyl-4,5,6,7-tetrahydro-1H-indazole-*r*-5-carboxylic acid isopropyl ester

EXPERIMENTAL

The progress of the reaction and compound purity were checked by TLC. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively). HMBC, HSQC, and NOESY spectra were recorded on a Bruker DRX 500 NMR spectrometer. DMSO-d_6 was used as a solvent. Mass spectra were recorded on a JEOL DX 303 and HP-5889A mass engine. Elemental analyses were performed on Perkin–Elmer CHNS/O analyzer.

Compounds **1-7** were prepared by adopting the literature procedure [8].

Synthesis of *t*-4-Aryl-3,*c*-6-dihydroxy-6-methyl-4,5,6,7-tetrahydro-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (General Method). *t*-3-Aryl-*r*-2,*c*-4-bis(isopropoxycarbonyl)-*c*-5-hydroxy-*t*-5-methyl-

cyclohexanone (100 mmol) was dissolved in hot ethanol (25 ml) and after addition of hydrazine hydrate (150 mmol) the reaction mixture was heated under reflux for 2 h. Then the reaction mixture was cooled and poured onto crushed ice, and the precipitate was filtered off, dried, and recrystallized from ethanol.

3,*c*-6-Dihydroxy-6-methyl-*t*-4-phenyl-4,5,6,7-tetrahydro-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (8). IR spectrum, ν cm^{-1}: 3494, 3327 (OH and NH), 1700 (CO), 1618 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.77 (3H, d, *J* = 6.2, C$\underline{H}_3$CH); 1.05 (3H, d, *J* = 6.2, CHC$\underline{H}_2$); 1.21 (3H, s, 6-CH_3); 2.50 (2H, m, H-5*a* and H-7*a*); 2.74 (1H, d, *J* = 16.0, H-7*e*); 4.00 (1H, d, *J* = 10.4, H-4*a*); 4.34 (1H, s, 6-OH); 4.73 (1H, m, C$\underline{H}$$CH_3$); 7.13 (5H, m, Ar); 9.05 (1H, br. s, H-1); 10.95 (1H, br. s, 3-OH).

The presence of labile protons, OH proton at C-3, NH proton, and OH proton at C-6 was confirmed by recording the ^{1}H NMR spectrum after adding D_2O.

^{13}C NMR spectrum, δ, ppm: 20.6 (CH_3 *i*-Pr); 20.8 (CH_3 *i*-Pr); 27.6 (6-CH_3); 35.8 (C-7); 39.6 (C-4); 58.9 (C-5); 65.9 (CH *i*-Pr); 69.3 (C-6); 98.7 (C-9); 125.2–127.5 (Ar); 138.2 (C-8); 142.5 (*ipso*-C); 157.3 (C-3); 171.31 (C=O).

***t*-4-*p*-Fluorophenyl-3,*c*-6-dihydroxy-6-methyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (9).** IR spectrum, ν cm^{-1}: 3437, 3267 (OH and NH); 1721 (CO group); 1619 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.09 (3H, d, *J* = 6.2, C$\underline{H}_3$CH); 1.21 (3H, s, 6-CH_3); 2.52 (2H, m, H-5*a* and H-7*a*); 2.76 (1H, d, *J* = 16.1, H-7*e*); 4.03 (1H, d, *J* = 10.6, H-4*a*); 4.42 (1H, s, 6-OH); 4.76 (1H, m, C$\underline{H}$$CH_3$); 7.1̃17.04 (4H, m, Ar); 8.92 (1H, br. s, NH); 11.10 (1H, br. s, 3-OH). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_3 *i*-Pr); 21.3 (CH_3 *i*-Pr); 28.1 (6-CH_3); 36.4 (C-7); 40.1 (C-4); 59.4 (C-5); 66.5 (CH *i*-Pr); 69.8 (C-6); 99.2 (C-9); 113.9–129.8 (Ar); 138.7 (C-8); 157.7 (C-3); 159.4, 161.8 (*ipso*-C-1); 171.6 (C=O).

3,*c*-6-Dihydroxy-*t*-4-*p*-methoxyphenyl-6-methyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (10). IR spectrum, ν cm^{-1}: 3446, 3316 (OH and NH); 1700 (C=O); 1608 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, d, *J* = 6.2, C$\underline{H}_3$CH); 1.15 (3H, d, *J* = 6.2, C$\underline{H}_3$CH); 1.22 (3H, s, 6-CH_3); 2.49 (2H, m, H-5*a* and H-7*a*); 2.74 (H, d, *J* = 16.0, H-7*e*); 3.70 (3H, s, OCH_3); 3.97 (1H, d, *J* = 10.3, H-4*a*); 4.43 (1H, s, 6-OH), 4.76 (1H, m, C$\underline{H}$$CH_3$), 6.77-6.99 (4H, m, Ar); 8.80 (1H, br. s, NH); 11.05 (1H, br. s, 3-OH). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3 *i*-Pr); 21.4 (CH_3 *i*-Pr); 28.1 (6-CH_3); 36.3 (C-7); 39.9 (C-4); 54.8 (OCH_3); 59.6 (C-5); 66.4 (CH *i*-Pr); 69.8 (C-6); 112.9–128.9 (Ar); 134.5, 157.4 (C-*ipso*); 138.6 (C-8); 157.8 (C-3); 171.9 (C=O).

***t*-4-*p*-(N,N-Dimethylamino)phenyl-3,*c*-6-dihydroxy-6-methyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (11).** IR spectrum, ν cm^{-1}: 3447, 3286 (OH and NH); 1723 (CO); 1613 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, d, *J* = 6.1, C$\underline{H}_3$CH *i*-Pr); 1.11 (3H, d, *J* = 6.2, C$\underline{H}_3$CH); 1.21 (3H, s, 6-CH_3); 2.45 (1H, d, *J* = 10.9, H-5*a*); 2.50 (1H, d, *J* = 15.9, H-7*a*); 3.72 (1H, d, *J* = 15.9, H-7*e*); 3.92 (1H, d, *J* = 10.9, H-4*a*); 4.28 (1H, s, 6-OH); 4.77 (1H, m, C$\underline{H}$$CH_3$); 2.74 (6H, s, $N(CH_3)_2$); 6.58–6.89 (4H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3 *i*-Pr); 21.5 (CH_3 *i*-Pr); 28.3 (6-CH_3); 36.4 (C-7); 40.2 (N–CH_3); 40.3 (C-4); 59.9 (C-5); 66.5 (CH *i*-Pr); 70.0 (C-6); 99.8 (C-9); 112.1–130.5 (Ar); 138.7 (C-8); 149.0 (C-*ipso*); 158.0 (C-3); 172.2 (C=O).

***t*-4-*p*-Chlorophenyl-3,*c*-6-dihydroxy-6-methyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (12).** IR spectrum, ν, cm^{-1}: 3415, 3274 (OH and NH); 1607 (C=O); 1614 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.84 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.10 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.24 (3H, s, 6-CH_3); 2.52 (2H, m, H-5*a* and H-7*a*); 2.77 (1H, d, *J* = 15.9, H-7*e*); 4.03 (1H, d, *J* = 10.5, H-4*a*), 4.48 (1H, s, 6-OH); 4.77 (1H, m, C$\underline{H}$$CH_3$); 7.11-7.27 (4H, m, Ar); 9.05 (1H, br. s, NH); 11.10 (1H, br. s, 3-OH). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3 *i*-Pr); 21.5 (CH_3 *i*-Pr); 28.3 (6-CH_3); 36.5 (C-7); 41.1 (C-4); 59.3 (C-5); 66.7 (CH *i*-Pr); 99.1 (C-9); 127.59–130.10 (Ar); 138.9 (C-8); 141.9, 149.9 (C-*ipso*); 157.8 (C-3); 171.6 (C=O).

3,*c*-6-Dihydroxy-6-methyl-*t*-4-*m*-nitrophenyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (13). IR spectrum, ν cm^{-1}: 3492, 3273 (OH and NH); 1705 (C=O); 1613 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (3H, d, *J* = 6.0, C$\underline{H}_3$CH); 1.09 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.27 (3H, s, 6-CH_3); 2.54 (1H, d, *J* = 15.9, H-7*a*); 2.62 (1H, d, *J* = 10.6, H-5*a*); 2.84 (1H, d, *J* = 15.9, H-7*e*); 4.21 (1H, d, *J* = 10.3, H-4*a*); 4.55 (1H, s, 6-OH); 4.77 (1H, m, C$\underline{H}$$CH_3$); 7.54–8.07 (4H, m, Ar); 9.12 (1H, br. s, NH); 11.20 (1H, br. s, 3-OH). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3 *i*-Pr); 21.4 (CH_3 *i*-Pr); 28.1 (6-CH_3); 36.5 (C-7); 40.2 (C-4); 59.0 (C-5); 66.9 (CH *i*-Pr); 98.5 (C-9); 121.2-135.4 (Ar); 145.5, 147.5 (C-*ipso*); 157.8 (C-3); 139.2 (C-8); 171.1 (C=O).

3,*c*-6-Dihydroxy-6-methyl-*t*-4-*m*-phenoxyphenyl-1H-indazole-*r*-5-carboxylic Acid Isopropyl Ester (14). IR spectrum, ν cm^{-1}: 3498, 3324 (OH and NH); 1698 (C=O); 1617 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.10 (3H, d, *J* = 6.1, C$\underline{H}_3$CH); 1.23 (3H, s, 6-CH_3); 2.50 (1H, d, *J* = 15.9, H-7*a*); 2.52 (1H, d, *J* = 10.3, H-5*a*); 2.76 (1H, d, *J* = 15.9, H-7*e*); 4.03 (1H, d, *J* = 10.3, H-4*a*); 4.40 (1H, s, 6-OH); 4.78 (1H, m, C$\underline{H}$$CH_3$); 6.7–7.3 (Ar); 9.25 (1H, br. s, NH); 11.02 (1H, br. s, 3-OH). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3 *i*-Pr); 21.5 (CH_3 *i*-Pr); 28.2 (6-CH_3); 36.4 (C-7); 40.0 (C-4); 59.4 (C-5); 66.7 (CH *i*-Pr); 69.9 (C-6); 116.9-129.8 (Ar); 145.2, 157.2 (C-*ipso*); 138.8 (C-8); 157.9 (C-3); 171.7 (C=O).

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