BENZINDAZOLES FROM TRIKETONES OF THE INDAN SERIES

II. 5-Hydroxy-4-phenyl-1H-benz[g]indazoles*

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In the reaction of 2-acetonyl- and 2-phenacyl-2-phenylindan-1, 3-diones with hydrazine hydrate, the five-membered ring of the indandione system isomerizes into a six-membered ring forming derivatives of 5-hydroxy-1H-benz[g]indazole. Derivatives of 3, 4-(CO)-benzoylenepyridazine have been isolated as intermediates. The benzindazoles mentioned have been obtained by independent synthesis from the corresponding 2-acyl-1, 4-dihydroxynaphthalenes.

We have established previously that with phenylhydrazine in acetic acid, 2-acetonyl- and 2-phenacyl-2-phenylindan-1, 3-diones (**Ia** and **Ib**, respectively) form phenylhydrazones. On prolonged heating, a reaction takes place with the expansion of the five-membered ring into a six-membered ring and the formation of the corresponding 5-hydroxy-1-phenylbenz[g]indazoles [1].

In order to study the formation of benzindazole derivatives from triketones of the indan series more deeply, in the present work we have investigated the raction of the triketones **Ia**, **b** with hydrazine hydrate.

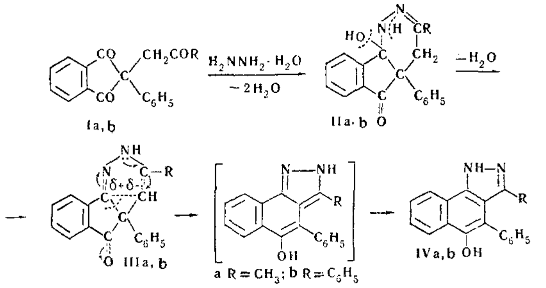
When the triketones **Ia**, **b** were heated in ethanol with hydrazine hydrate, colorless substances were isolated as the primary reaction products to which, on the basis of elementary analysis, chemical properties, and IR spectra, we were forced to ascribe the structure of 3, 4-CO-benzoylene-3-hydroxytetrahydropyridazines, **IIa**, **b**. The fact that the reaction is not limited to the formation of a monohydrazone is shown clearly by the presence in the IR spectra of the compounds obtained of only one band of the vibrations of a C=O bond, while in the case of the phenylhydrazones of the corresponding triketones the doublet carbonyl absorption that is characteristic for the indandione system is retained [1]. Evidently, the free amino group of the hydrazones first formed readily reacts with the carbonyl group of the indandione ring with the formation of the tricyclic pyridazine derivatives **II**. The addition products, containing an angular hydroxy group, are fairly stable and can be isolated. It has been stated repeatedly in the literature that 1, 4-diketones readily react with hydrazine hydrate in ethanolic solution with the formation of pyridazine derivatives [2, 3]. A similar cyclization is known in the 2-(β-aminoethyl)indandione series: when 2-phenyl-2-(β-phthalimidoethyl)indan-1, 3-dione is treated in alcoholic solution with hydrazine hydrate, 2,3-CO-benzoylene-2-hydroxy-3-phenylpyrrolidine is formed instead of 2-(β-aminoethyl)-2-phenylindan-1, 3-dione [4].

On being heated in acetic acid (or on prolonged heating in ethanol), **IIa** and **IIb** each lose a molecule of water and are converted into yellow substances for which, on the basis of their IR spectra, we propose the structure of 3, 4-(CO)-benzoylene-1, 4-dihydropyridazine derivatives (**IIIa**, **b**).

In dichloroethane, in the 3 μ region the 3, 4-(CO)-benzoylene-3-hydroxytetrahydropyridazines (**IIa**, **b**) exhibit two bands at 3340 and 3545 cm^{-1} due to the stretching vibrations of the NH and OH bonds, respectively. In Nujol, only one broad band with a frequency of 3250 cm^{-1} is seen. Consequently, in the solid state the molecules of **IIa** and **IIb** are highly associated. The 3, 4-(CO)-benzoylene-1, 4-dihydropyridazines **IIIa** and **IIIb** exhibit only one absorption band in the 3415–3430 cm^{-1} region in dichloroethane and the 3340–3390 cm^{-1} region in Nujol, which shows the presence of a N—H bond and the absence of a hydroxy group. Furthermore, with nitrous acid, compound **IIIb** forms a N-nitroso derivative having no absorption in the region of the spectrum under consideration.

In dichloroethane solution, the 3, 4-(CO)-benzoylene-3-hydroxytetrahydropyridazines **IIa** and **IIb** have carbonyl absorption at about 1720 cm^{-1}, while in the dihydropyridazines **IIIa** and **IIIb** it appears at 1725 cm^{-1}. According to the literature, 2-aryl- and 2-aralkyl-3-hydroxyindan-1-ones are characterized by carbonyl absorption in the 1680–1705 cm^{-1} region [5, 6]; 2-benzylindan-1-one absorbs at 1717 cm^{-1} [7], and indandione itself in the solid state has a carbonyl band at 1721 cm^{-1} [8].

A more detailed study of the chemical properties of the 3, 4-(CO)-benzoylene-1, 4-dihydropyridazines **IIIa** and **IIIb** showed that they are only intermediates in the formation of benzindazoles. On being heated in glacial acetic acid, on acetylation, or at the melting point they isomerize into 5-hydroxy-4-phenyl-1H-benz[g]indazoles (**IVa**, **b**). We assume that the process of rearrangement is effected by a redistribution of the electron density within the five- and six-membered condensed systems of **III**, as a result of which the partially hydrogenated polycyclic system forms the aromatic system of benzindazole.



The 5-hydroxy-4-phenyl-1H-benz[g]indazoles **IVa** and **IVb** have also been obtained directly by heating 2-

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*For part I, see [1].

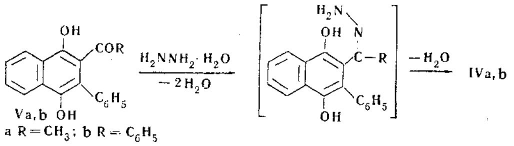
Table 1

IR Spectra* of the Products of the Transformation of 2-Acetonyl- and 2-Phenacyl-2-phenylindandiones

Compound	Medium	ν in the 1500-1604 cm-1 region	$\nu_{C=O}$, cm-1	ν_{NH}, ν_{OH} cm-1
IIa	Dichloroethane	1504, 1604	1720	3335, 3545
IIb	Dichloroethane	1500, 1603	1720	3340, 3545
	Nujol	1500, 1600	1719	3250 (lat.)
IIIa	Dichloroethane	1599	1728	3415
	Nujol	1595	1702	3340
IIIb	Dichloroethane	1600	1723	3430
	Nujol	1594	1706	3390
IVa	Dichloroethane	1593, 1604		3450, 3550
	Nujol	1547, 1595		3150 (lat.), 3528
IVb	Dichloroethane	1608		3450, 3600
	Nujol	1560, 1600		3371
VIa	Nujol	1593	1724, 1753	
VIb	Nujol	1593	1727, 1746	

*Spectra recorded on a UR-10 instrument.

acetyl- and 2-benzoyl-2-phenyl-1, 4-dihydroxynapthalenes (Va and Vb) with hydrazine hydrate in ethanol. The reaction takes place in a few minutes, i.e., far more readily than with phenylhydrazine [1]. This independent synthesis definitively showed the isomerization of the five-membered ring of the triketone into a six-membered ring in the reaction with hydrazine hydrate.



Va,b

a R=CH$_3$; b R=C$_6$H$_5$

The 5-hydroxy-1H-benz[g]indazoles IVa and IVb are colorless high-melting substances. It is stated in the literature that the 5-hydroxyindazoles have higher melting points than the isomeric hydroxy compounds [9]. On acetylation they form the 5-acetoxy-N-acetyl derivatives VIa, b.

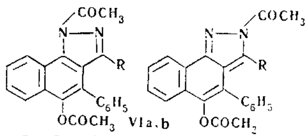
In dichloroethane solution, in the 3 μ region the benzindazoles IVa and IVb are characterized by two bands assigned to the stretching vibrations of the NH and OH bonds—at 3450 cm^{-1} and in the range from 3550 to 3600 cm^{-1}. On acetylation, these bands disappear and carbonyl absorption bands appear close to 1725 cm^{-1} for the N-acetyl group and in the 1746–1753 cm^{-1} region for the acetoxy group. While esters are generally characterized by carbonyl absorption in the 1740–1760 cm^{-1} region, in N-acetyl derivatives it appears over a very wide range (1640–1800 cm^{-1}) according to the structure of the amide [10]. In the indazoles, it is observed in the 1725–1755 cm^{-1} region; for example, 1-acetylbenz[g]indazole absorbs at 1730 cm^{-1} [11].

In all the compounds obtained, the IR spectra exhibit absorption in the 1500–1604 cm^{-1} region, which is ascribed to the stretching vibrations of conjugated double bonds and also to the deformation vibrations of the NH bond.

Details of the UV spectra of the 5-hydroxy-4-phenyl-1H-benz[g]indazoles IVa and IVb and of their 5-acetoxy-N-acetyl derivatives VIa and VIb are given in Table 2.

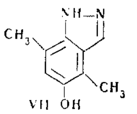
In a comparison of the spectra of 5-hydroxy-4, 7-dimethyl-1H-indazole (VII) and of 5-acetoxy-1-acetyl-4, 7-dimethylindazole (VIII), which have been described in the literature [12], with the spectra of the compounds that we have obtained, some similarity is found.

The benz[g]indazoles can exist in two tautomeric forms: in benzoid and quinoid forms. On the basis of literature data [9, 12] it may be concluded that the 5-hydroxybenz[g]indazoles IVa and IVb have the benzoid structure, but the question of the structure of their diacetyl derivatives VIa and VIb has not yet been solved.

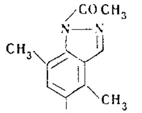


VIa,b

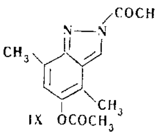
a R = CH$_3$; b R = C$_6$H$_5$



VII



VIII



IX

5-Hydroxy-4, 7-dimethyl-1H-indazole (VII) has given two isomeric 5-acetoxy-N-acetyl derivatives. To one of them the benzoid structure VIII (5-acetoxy-1-acetylindazole) has been ascribed, and to the other the quinoid structure IX (5-acetoxy-2-acetylindazole) [9]. The choice between the two structures was made on the basis of the UV spectra, since the 2-acetyl derivatives IX, in contrast to the 1-acetyl derivatives VIII, exhibit another new absorption band in the long-wave region, at 340 nm [12]. Since an absorption band also appears in compounds VIa and VIb at 345 nm, it may be assumed that they possess the quinoid structure. However, there is information in the literature that N-acetylindazole, with the benzoid structure, has carbonyl absorption at 1726 cm^{-1}, and the quinoid isomer absorbs at 1754 cm^{-1} [10]. As already mentioned, the 5-acetoxy-N-acetyl derivatives VIa and VIb that we have obtained are characterized by two bands at about

Table 2

UV Spectra of Some Indazole Derivatives in Ethanol

Compound	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	ν_{max}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
IVa	224 (35.04)	256 (31.40) 270 Shoulder	315 (8.22)	
IVb	223 (42.80)	256 (36.50) 278 Shoulder	318 (11.76)	
VIa		240 (25.00) 261 (35.20)	329 (3.98)	344 (4.34)
VIb	225 (47.40)	243 (38.40) 262 (5.23)	332 (6.50)	348 (7.10)
VII	215 (19.95)	255 (6.76)	314 (5.50)	
VIII	232 (24.50)	255 Shoulder	308 (8.10)	
IX	230 (22.91)		293 (9.55)	336 (4.07)

1725 and 1750 cm^{-1}. By ascribing the band at 1725 cm^{-1} to the vibrations of the N-acetyl group, we thereby assume the benzoid structure for the acetyl derivatives, which apparently contradicts the information from the UV spectra. Thus, in spite of some differences in the process of the formation of 5-hydroxybenz[g]indazole derivatives from the triketones **Ia** and **Ib** with phenylhydrazine and with hydrazine hydrate, the isolation and study of the intermediate products obtained from the reaction of the triketones with hydrazine hydrate fully confirms the reaction mechanism of the triketones with phenylhydrazine put forward in the preceding paper [1].

EXPERIMENTAL

3,4-(CO)-Benzoylene-3-hydroxy-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridazine (IIa). A mixture of 5.56 g (0.02 mole) of 2-acetonyl-2-phenylindan-1,3-dione (Ia), 2 ml (0.04 mole) of hydrazine hydrate, and 35 ml of ethanol was heated in the water bath for 5–10 min. On cooling, 4.7 g (76%) of **IIa** deposited. Colorless crystals with mp 167–168° C (from ethanol). On being heated in acetic acid, the substance changed into yellow crystals of **IIIa**. Found, %: C 69.46; H 6.00; N 9.39, 8.97. Calculated for $C_{18}H_{16}N_2O_2 \cdot H_2O$, %: C 69.66; H 5.84; N 9.03.

3,4-(CO)-Benzoylene-3-hydroxy-4,6-diphenyl-2,3,4,5-tetrahydropyridazine (IIb). A mixture of 10.2 g (0.03 mole) of 2-phenacyl-2-phenylindan-1,3-dione (Ib), 3 ml (0.06 mole) of hydrazine hydrate, and 70 ml of ethanol was heated in the water bath for 15 min. On cooling, 8.3 g (78%) of **IIb** deposited. Colorless crystals with mp 175–176° C (from ethanol). When melted, the **IIb** became yellow and then solidified to a colorless crystalline mass which melted again at 278–280° C. On being heated in ethanol or acetic acid, **IIb** was converted into the yellow substance **IIIb**. Found, %: C 77.81; H 5.11; N 7.69. Calculated for $C_{23}H_{18}N_2O_2$, %: C 77.93; H 5.12; N 7.91.

3,4-(CO)-Benzoylene-6-methyl-4-phenyl-1,4-dihydropyridazine (IIIa). A mixture of 6.2 g (0.02 mole) of **IIa**, 7.5 ml of ethanol, and 2.5 ml of acetic acid was heated for 5 min. On cooling, 4.4 g (80%) of **IIIa** deposited in the form of yellow crystals, mp 160° C (from ethanol). On being heated in acetic acid or on fusion, the substance changed into the colorless **IVa**. Found, %: C 78.52; H 5.05; N 10.41. Calculated for $C_{18}H_{14}N_2O$, %: C 78.81; H 5.14; N 10.21.

3,4-(CO)-Benzoylene-4,6-diphenyl-1,4-dihydropyridazine (IIIb). With heating, 3.54 g (0.01 mole) of **IIb** was dissolved in 10 ml of glacial acetic acid. On cooling, 2.8 g (83%) of **IIIb** deposited in the form of yellow crystals. After recrystallization from ethanol, mp 199–200° C (if the substance is placed in the melting-point apparatus just below the melting point). On prolonged heating, **IIIb** is converted into a colorless substance **IVb** melting at 278–280° C. Found, %: C 82.13; H 4.81; N 8.67. Calculated for $C_{23}H_{16}N_2O$, %: C 82.12; H 4.80; N 8.33. **Nitroso derivative.** A few grams of sodium nitrite was added gradually to a suspension of 2 g of **IIIb** in 150 ml of glacial acetic acid. The **IIIb** dissolved and the nitroso derivative soon precipitated. The precipitate was filtered off, washed with water, and recrystallized from ethanol, giving a yellow crystalline substance with mp 229–230° C. Found, %: C 75.70; H 4.18; N 11.60. Calculated for $C_{23}H_{15}N_3O_2$, %: C 75.61; H 4.14; N 11.49.

5-Hydroxy-3-methyl-4-phenyl-1H-benz[g]indazole (IVa). a) A mixture of 6.2 g (0.02 mole) of **IIa**, 7.5 ml of ethanol, and 25 ml of acetic acid was heated for 2 hr. On cooling, 3.6 g (66%) of **IVa** precipitated in the form of colorless crystals with mp 224–225° C (from benzene). It dissolves in alcoholic alkali with a yellow coloration.

b) A mixture of 1.4 g (0.005 mole) of 3-acetyl-1,4-dihydroxy-2-phenylnaphthalene (**Va**), 0.4 ml (0.008 mole) of hydrazine hydrate, and 15 ml of ethanol was heated in the water bath for 5–10 min, giving a precipitate of 0.8 g (58%) of **IVa** in the form of colorless crystals with mp 225° C (from benzene). Found, %: C 78.98; H 5.12; N 10.21. Calculated for $C_{18}H_{14}N_2O$, %: C 78.81; H 5.14; N 10.21.

5-Hydroxy-3,4-diphenyl-1H-benz[g]indazole (IVb). a) A mixture of 10.2 g (0.03 mole) of **Ib**, 3 ml (0.06 mole) of hydrazine hydrate, and 70 ml of ethanol was heated in the water bath for 15 min. The solution was poured into water, and the precipitate was filtered off, dried, and heated for 10–15 min in glacial acetic acid. On cooling, 7.0 g (65%) of **IVb** deposited in the form of colorless crystals with mp 278–280° C (from a mixture of acetic acid and ethanol). The substance is very sparingly soluble in ethanol and dissolves in ethanolic alkali with a yellow coloration.

b) A mixture of 1.7 g (0.005 mole) of 3-benzoyl-1,4-dihydro-2-phenylnaphthalene (**Vb**) and 0.35 ml (0.07 mole) of hydrazine hydrate was heated in 15 ml of ethanol in the water bath for 1 hr. On cooling, 1.45 g (86%) of **IVb** deposited. Colorless crystals with mp 278–280° C (from a mixture of acetic acid and ethanol). Found, %: C 82.00; H 4.80; N 8.46. Calculated for $C_{23}H_{16}N_2O$, %: C 82.12; H 4.80; N 8.33.

5-Acetoxy-1-acetyl-3-methyl-4-phenylbenz[g]indazole (VIa). a) A mixture of 0.5 g of **IIIa**, 3 ml of acetic anhydride, and 1 ml of acetyl chloride was heated for 30 min and was then poured into water. Two recrystallizations of the precipitate from ethanol yielded **VIa** in the form of colorless crystals with mp 188–190° C.

b) Compound **VIa** with mp 188–190° C was obtained from **IVa** similarly. Found, %: C 73.33; H 5.27; N 7.62. Calculated for $C_{22}H_{18}N_2O_3$, %: C 73.69; H 5.06; N 7.82.

5-Acetoxy-1-acetyl-3,4-diphenylbenz[g]indazole (VIb). a) A mixture of 1 g of **IIIb**, 7 ml of acetic anhydride, and 3 ml of acetyl chloride was heated in the water bath for 30 min and then poured into water. Colorless crystals with mp 177–178° C (from ethanol).

b) Compound **VIb** with mp 177–178° C was obtained similarly from **IVb**. Found, %: C 77.29; H 4.76; N 6.80. Calculated for $C_{27}H_{20}N_2O_3$, %: C 77.13; H 4.80; N 6.67.

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