ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 11, pp. 1590–1593. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © V.A. Osyanin, D.D. Borisov, D.V. Osipov, Yu.N. Klimochkin, 2014, published in Zhurnal Organicheskoi Khimii, 2014, Vol. 50, No. 11, pp. 1604–1607.

Synthesis of Uvarindole A

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Received July 29, 2014

Abstract—Procedure was developed for the synthesis of an alkaloid of indole series uvarindole A. The key step of the synthesis is a successive indole alkylation with salicylic alcohol catalyzed with $ZnCl_2$. The presumed intermediates are *o*-hydroxybenzyl carbocation and *o*-quinone methide.

DOI: 10.1134/S1070428014110098

One of the methods of introducing *o*-hydroxy-benzyl group into the unsubstituted pyrrole ring of an indole may be a direct alkylation of indoles with *o*-quinone methides [1]. The structural fragment of 2-hydroxybenzylindole is present in the structure of certain alkaloids, e.g., of nudicaulines **I** found in the flowers of Iceland poppy *Papaver nudicaule* [2] and of uvarindoles **II**–**V** isolated from plants of the genus *Uvaria* [3]. Uvarindoles reduce the heartbeat frequen-cy [4], and the synthetically prepared 3-(2-hydroxy-benzyl)indoles (**VI**) show a high anticancer action [5] (Scheme 1).

We recently developed two noncatalytic procedures for indoles hydroxybenzylation [6]. However it was not possible in the absence of catalyst to introduce several hydroxybenzyl groups even applying a large excess of salicylic alcohol, although this reaction is practically important in particular for the synthesis of uvarindole A (**II**).

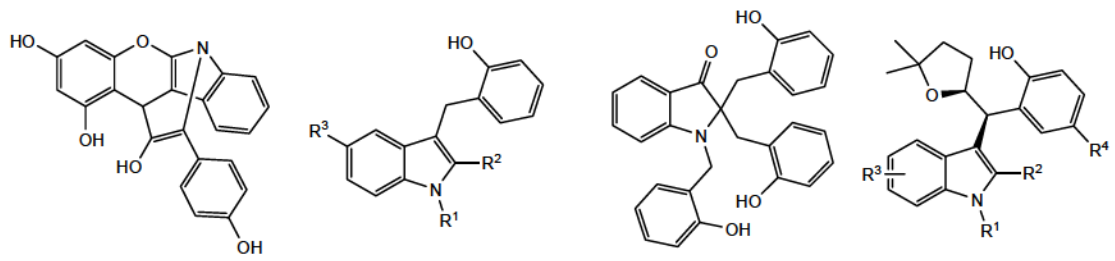
Using 3 equiv. of anhydrous $ZnCl_2$, 3 equiv. of salicylic alcohol, and 1 equiv. of indole in boiling dioxane a product of indole bishydroxybenzylation **VII** was obtained in 35% yield (Scheme 2).

Decreasing the amounts of salicylic alcohol and $ZnCl_2$ to 2.2 equiv. reduced the yield to 20%. At the same time the formation of uvarindole A (**II**) containing three hydroxybenzyl groups was not observed. In the presence of 3 equiv. of salicylic alcohol and 3 equiv. of $AlCl_3$ or TsOH the tarring of the reaction mixture occurred. Therefore the synthesis of uvarindole A (**II**) was carried out in three steps: First a 2-methoxybenzyl group was introduced to the nitrogen atom, then the double *C*-alkylation was performed and finally the ether was subjected to acidolysis at treatment with BBr_3 (Scheme 3).

The spectral characteristics of obtained uvarindole A (**II**) are well consistent with the published data for the natural alkaloid [7].

The assumed mechanism of the acid-catalyzed indole hydroxybenzylation includes the formation of the resonance-stabilized *o*-hydroxybenzyl carbocation **A** existing in a protolithic equilibrium with the corresponding *o*-quinone methide **B** [8], which alkylates indole in the position *3*. The reaction with the

Scheme 1.



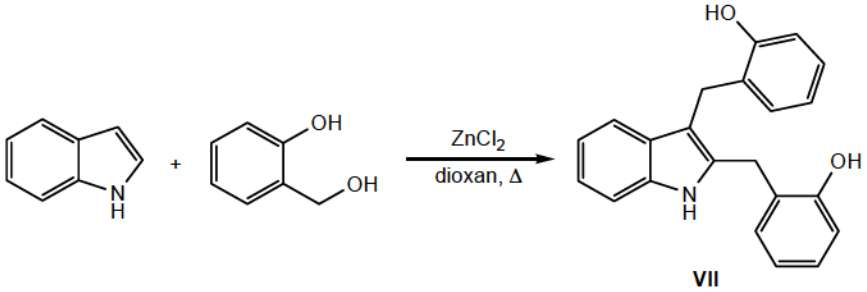
I Aglicon nudicauline

II-IV $R^3 = H$, $R^1 = R^2 = 2$-hydroxybenzyl (Uvarindole A, **II**)
$R^1 = R^2 = R^3 = 2$-hydroxybenzyl (Uvarindole B, **III**)
$R^1 = R^3 = H$, $R^2 = 2$-hydroxybenzyl (Uvarindole C, **IV**)

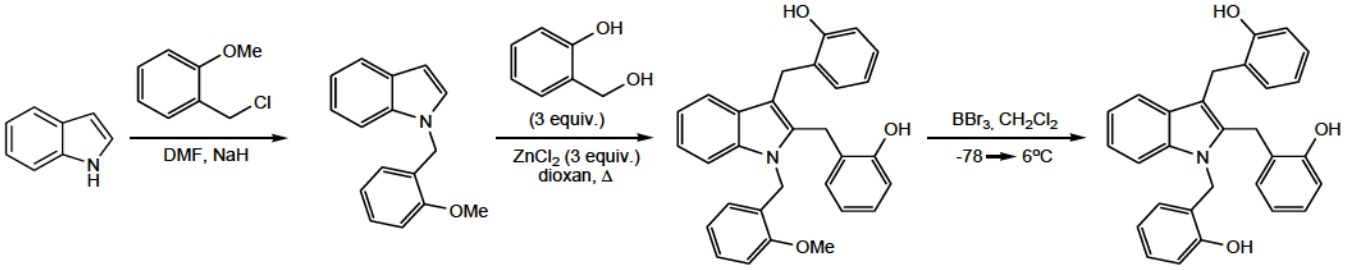
V Uvarindole D

VI

Scheme 2.



Scheme 3.



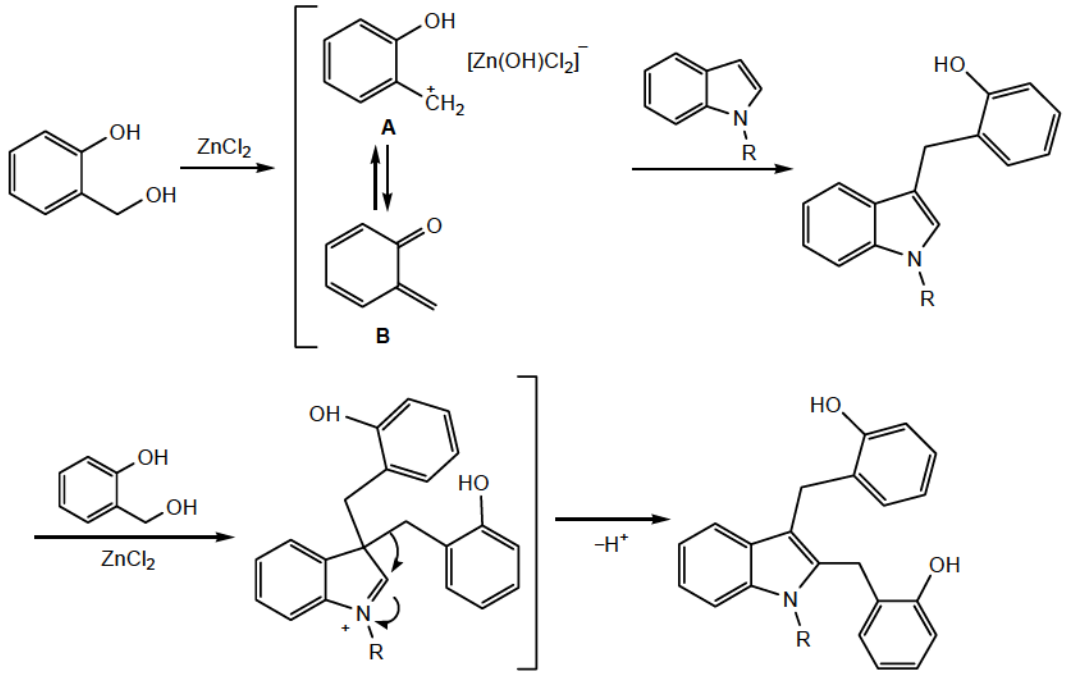
second equiv. of salicylic alcohol occurs presumably also at the atom C^3 followed by the migration of the hydroxybenzyl group to the contiguous position (Planchet rearrangement) [9] (Scheme 4).

Thus we developed for the first time an efficient method of uvarindole A synthesis and a fundamental possibility was demonstrated of introducing two hydroxybenzyl groups in 2,3-unsubstituted indoles.

EXPERIMENTAL

IR spectra were registered on an IR Fourier-spectrometer Shimadzu IRAffinity-1 in KBr tablets.

Scheme 4.



^{1}H, ^{13}C, and DEPT NMR spectra were registered on a spectrometer JEOL JNM-ECX400 [399.78 (^{1}H) and 100.53 (^{13}C) MHz], solvent $CDCl_3$, internal reference TMS. Elemental analysis was carried out on an automatic CHNS-analyzer Euro Vector EA-3000. Melting points were measured by capillary method on a PTP-M device. TLC was carried out on Silufol UV-254 plates, development under UV irradiation and in iodine vapor.

2,3-Bis(2-hydroxybenzyl)-1*H*-indole (VII). A mixture of 1 g (8.5 mmol) of indole, 3.4 g (27 mmol) of salicylic alcohol, and 3.7 g (27 mmol) of anhydrous $ZnCl_2$ in 30 mL of dioxane was refluxed for 15 h, the obtained solution was cooled, poured in 100 mL of water, the reaction product was extracted with ethyl acetate (3 × 30 mL). The extract was washed with water, dried over Na_2SO_4, evaporated in a vacuum, the residue was chromatographed on silica gel, eluent $CHCl_3$. The obtained light yellow oily substance was dissolved in 5 mL of CCl_4, precipitated from the solution by adding 10 mL of hexane. After recrystallization from CCl_4 yield 0.99 g (35%), colorless crystals, mp 134–135°C. IR spectrum, cm^{-1}: 3501, 3404 (NH, OH), 3032, 2932, 1589, 1499, 1454, 1431, 1329, 1300, 1275, 1258, 1209, 1190, 1165, 1126, 1105, 1084, 1040, 843, 756. ^{1}H NMR spectrum, δ, ppm: 4.11 s (2H, CH_2), 4.21 s (2H, CH_2), 5.47 br.s (2H, 2OH), 6.66 d (1H$_{Ar}$, ^3J 7.8 Hz), 6.72 d (1H$_{Ar}$, ^3J 8.2 Hz), 6.87 t (1H$_{Ar}$, ^3J 7.3 Hz), 6.90 t (1H$_{Ar}$, ^3J 7.3 Hz), 6.99 t (1H$_{Ar}$, ^3J 7.8 Hz), 7.07–7.13 m (4H$_{Ar}$), 7.19 d (1H$_{Ar}$, ^3J 8.3 Hz), 7.29 d.d (1H$_{Ar}$, ^3J 7.4, ^4J 1.4 Hz), 7.45 d (1H$_{Ar}$, ^3J 7.8 Hz), 8.09 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 26.3 (CH_2), 27.6 (CH_2), 108.2 (C), 110.7 (CH), 115.8 (CH), 116.0 (CH), 118.9 (CH), 119.6 (CH), 121.0 (CH), 121.4 (CH), 121.8 (CH), 124.8 (C), 126.9 (C), 127.8 (CH), 128.4 (C), 128.6 (CH), 130.7 (CH), 131.0 (CH), 134.3 (C), 135.7 (C), 153.6 (C), 154.3 (C). Found, %: C 80.20; H 5.77; N 4.18. $C_{22}H_{19}NO_2$. Calculated, %: C 80.22; H 5.81; N 4.25.

***N*-(2-Methoxybenzyl)indole (VIII)**. To a slurry of 0.86 g (0.018 mol) of sodium hydride (as a 50% dispersion in paraffin) in 30 mL of DMF was added 2 g (0.017 mol) of indole, and the mixture was stirred for 10 min till the end of hydrogen liberation. To the solution obtained was added within 30 min a solution of 2.68 g (0.017 mol) of 2-methoxybenzyl chloride in 10 mL of DMF, the mixture was stirred for 3 h and poured into 200 mL of cold water. The precipitate was filtered off, washed with water, dried, and recrystallized from methanol. Yield 2.5 g (62%), mp 75–76°C (75–77°C [10]). IR spectrum, cm^{-1}: 2924, 2855, 1597, 1493, 1462, 1439, 1300, 1250, 1115, 1026, 760, 745, 721. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H, CH_3O), 5.33 s (2H, CH_2), 6.54 d.d (1H, H^3 of indole, ^3J 3.2, ^5J 0.5 Hz), 6.71 d.d (1H$_{Ar}$, ^3J 7.6, ^4J 1.4 Hz), 6.80 t.d (1H$_{Ar}$, ^3J 7.6, ^4J 0.7 Hz), 6.90 d (1H, H^6 of indole, ^3J 8.2 Hz), 7.10 t.d (1H$_{Ar}$, ^3J 7.1, ^4J 0.9 Hz), 7.15–7.26 m (3H$_{Ar}$), 7.33 d (1H, H^7 of indole, ^3J 8.2 Hz), 7.65 d (1H, H^4 of indole, ^3J 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 45.2 (CH_2), 55.4 (CH_3), 101.4 (CH), 109.9 (CH), 110.2 (CH), 119.4 (CH), 120.7 (CH), 120.9 (CH), 121.6 (CH), 126.0 (C), 128.0 (CH), 128.6 (C), 128.7 (CH), 128.8 (CH), 136.5 (C), 156.8 (C). Found, %: C 81.07; H 6.31; N 5.82. $C_{16}H_{15}NO$. Calculated, %: C 80.98; H 6.37; N 5.90.

2,3-Bis(2-hydroxybenzyl)-1-(2-methoxybenzyl)-1*H*-indole (VIII). A mixture of 2.25 g (9.5 mmol) of 1-(2-methoxybenzyl)indole, 3.53 g (28.5 mmol) of salicylic alcohol, and 3.88 g (28.5 mmol) of anhydrous $ZnCl_2$ in 50 mL of dioxane was boiled for 30 h. The obtained solution was poured in 200 mL of cold water, the reaction product was extracted with ethyl acetate (4 × 50 mL). The extract was washed with water, dried over Na_2SO_4, evaporated in a vacuum, the residue was chromatographed on silica gel, eluent CH_2Cl_2. The obtained light yellow oily substance was dissolved in 5 mL of CCl_4, precipitated from the solution by adding 10 mL of hexane. After recrystallization from CCl_4 yield 2.43 g (57%), colorless crystals, mp 114–116°C. IR spectrum, cm^{-1}: 3431, 3298 (NH, OH), 3046, 2997, 2945, 2911, 2839, 1585, 1491, 1464, 1437, 1408, 1362, 1339, 1285, 1240, 1207, 1167, 1155, 1105, 1046, 1026, 787, 754, 735. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, CH_3O), 4.10 s (2H, CH_2), 4.20 s (2H, CH_2), 4.95 br.s (2H, 2OH), 5.21 s (2H, CH_2N), 6.26 d.d (1H$_{Ar}$, ^3J 7.6, ^4J 1.4 Hz), 6.62 d.d (1H$_{Ar}$, ^3J 8.0, ^4J 0.9 Hz), 6.66–6.78 m (4H$_{Ar}$), 6.81–6.85 m (2H$_{Ar}$), 6.98–7.20 m (7H$_{Ar}$), 7.44 d (1H$_{Ar}$, ^3J 7.6 Hz). ^{13}C NMR spectrum, δ, ppm: 25.3 (CH_2), 26.1 (CH_2), 42.2 (CH_2N), 55.3 (CH_3O), 109.7 (C), 109.8 (CH), 109.9 (CH), 115.4 (CH), 115.7 (CH), 119.0 (CH), 119.6 (CH), 120.76 (CH), 120.79 (CH), 121.0 (CH), 121.8 (CH), 124.5 (C), 125.9 (C), 126.5 (CH), 126.8 (C), 127.6 (CH), 127.8 (CH), 127.9 (C), 128.1 (CH), 129.7 (CH), 130.3 (CH), 135.3 (C), 137.4 (C), 153.4 (C), 154.3 (C), 156.3 (C). Found, %: C 80.20; H 5.98; N 3.06. $C_{30}H_{27}NO_3$. Calculated, %: C 80.15; H 6.05; N 3.12.

1,2,3-Tris(2-hydroxybenzyl)-1*H*-indole (uvarindole A) (II). In 5 mL of anhydrous dichloromethane was dissolved 0.2 g (0.44 mmol) of compound **VIII**,

the mixture was cooled to –78°C, and thereto was added dropwise at stirring 0.21 mL (0.56 g, 2.2 mmol) of BBr_3 in 2 mL of dichloromethane. After completing the addition the reaction mixture was kept at –78°C for 1 h and afterwards for 48 h at 6°C. The solution was poured on ice, the reaction product was extracted with chloroform (3 × 10 mL). The extract was washed with water, dried over Na_2SO_4, evaporated in a vacuum, the residue was dissolved in 2 mL of CCl_4, and poured into 10 mL of cold hexane at vigorous stirring. The separated colorless precipitate was filtered off. Yield 0.15 g (79%), mp 69–70°C (66–68°C [7]). IR spectrum, cm^{-1}: 3500–3100 (OH), 3034, 2922, 1608, 1593, 1501, 1489, 1454, 1364, 1341, 1327, 1254, 1215, 1169, 1092, 1042, 843, 750. ^{1}H NMR spectrum, δ, ppm: 4.13 s (2H, CH_2), 4.20 s (2H, CH_2), 5.24 s (2H, CH_2N), 5.56 br.s (3H, 3OH), 6.32 d (1H_{Ar}, ^3J 7.6 Hz), 6.62 t (1H_{Ar}, ^3J 7.7 Hz), 6.67 d (1H_{Ar}, ^3J 7.4 Hz), 6.68 d (1H_{Ar}, ^3J 8.0 Hz), 6.72–6.76 m (3H_{Ar}), 6.80 d.d (1H_{Ar}, ^3J 8.2, ^4J 0.9 Hz), 6.94–7.11 m (5H_{Ar}), 7.14 d (1H_{Ar}, ^3J 8.2 Hz), 7.20 d (1H_{Ar}, ^3J 8.0 Hz), 7.43 d (1H_{Ar}, ^3J 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 24.8 (CH_2), 25.9 (CH_2), 42.2 (CH_2N), 109.8 (CH), 109.9 (C^3 of indole), 115.3 (CH), 115.6 (CH), 115.7 (CH), 119.0 (CH), 119.5 (CH), 120.6 (CH), 120.7 (2CH), 121.6 (CH), 124.6 (C), 124.9 (C), 127.0 (C), 127.2 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.1 (C), 129.6 (CH), 130.3 (CH), 135.9 (C^2 of indole), 137.3 (C), 153.1 (C), 153.7 (C), 154.4 (C). Found, %: C 80.07; H 5.74; N 3.14. $C_{29}H_{25}NO_3$. Calculated, %: C 79.98; H 5.79; N 3.22.

The research was carried out with the financial support of the Russian Ministry of Science and Education as a project part of the State contract on R&D studies (project no. 4.1597.2014/K) using the equipment of the Center of Joint Usage of Samara State Technical University "Investigation of physicochemical properties of matters and materials."

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