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FORMYLATION OF DEOXYVASICINONE BY ALKYLFORMATES: SYNTHESIS AND REACTION OF α-HYDROXYMETHYLIDENEDEOXYVASICINONE WITH ISOMERIC AMINOPHENOLS AND AMINOBENZOIC ACIDS

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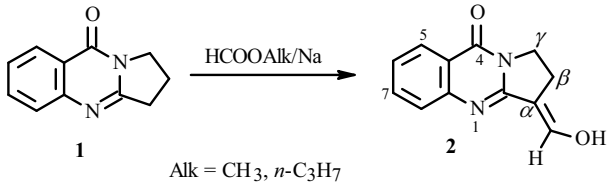
A new method for formylation of deoxyvasicinone (DOV) was developed. Nucleophilic substitution of α-hydroxy- and -dimethylaminomethylidene-DOV by isomeric aminophenols and benzoic acids to give α-arylaminomethylidene-DOV was studied.

Keywords: deoxyvasicinone, alkylformates, formylation, transamination, isomeric aminophenols and aminobenzoic acids.

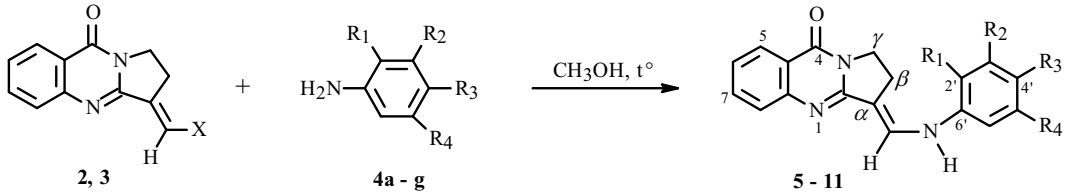
We demonstrated earlier that Vilsmeier–Haack (DMF–$POCl_3$) formylation of deoxyvasicinone (DOV, **1**) gave, depending on the work-up conditions, either α-hydroxymethylidene-DOV (**2**) or α-dimethylaminomethylidene-DOV (**3**) [1]. These compounds were isolated pure and their structures were convincingly proved [2]. However, **2** was to a certain extent difficult to purify because of the presence of small quantities of other products.

Herein we present results from the development of an alternate synthetic method for **2** that includes the reaction of DOV with ethyl- and *n*-propylformates in the presence of metallic sodium.



It was shown earlier that **2** reacts with aliphatic and aromatic amines to form α-aminomethylidene derivatives [3–6]. The hydroxyl of **2** undergoes nucleophilic substitution with *o*-, *m*-, and *p*-aminophenols (**4a–c**); *o*-, *m*-, and *p*-aminobenzoic acids (**4d–f**); and 5-bromo-2-aminobenzoic acid (**4g**). The reaction of **2** with **4a–c** was carried out by refluxing equimolar amounts of the reagents in MeOH for 3 h. This produced the corresponding α-(*o*-, *m*-, and *p*-hydroxyphenylamino)methylidene-DOV (**5–7**) in relatively high (77–80%) yields.

The reaction went more difficultly for the isomeric aminobenzoic acids. This produced the corresponding α-(*o*-, *m*-, and *p*-hydroxycarbonylphenylamino) and (5′-bromo-2′-hydroxycarbonylphenylamino)methylidene-DOV (**8–11**). If *o*-aminobenzoic acid was used as the nucleophilic reagent, the yield of **8** was 89%. In the other instances it did not exceed 38–65%. The difficulty in carrying out the reaction was probably related to the decreased nucleophilicity of the amine due to the influence of the electron-accepting carboxylic group:



4a, 5: R_1 = OH, R_2 = R_3 = R_4 = H; **4b, 6:** R_2 = OH, R_1 = R_3 = R_4 = H; **4c, 7:** R_3 = OH, R_1 = R_2 = R_4 = H; **4d, 8:** R_1 = COOH, R_2 = R_3 = R_4 = H
4e, 9: R_2 = COOH, R_1 = R_3 = R_4 = H; **4f, 10:** R_3 = COOH, R_1 = R_2 = R_4 = H; **4g, 11:** R_1 = COOH, R_2 = R_3 = H, R_4 = Br

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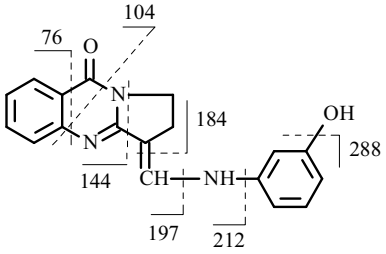
We developed another method for preparing **5**–**11**, i.e., transamination of α-dimethylaminomethylidene-DOV (**3**) with the isomeric aminophenols (**4a**–**c**) and aminobenzoic acids (**4d**–**g**). The substitution reaction went slower and required longer heating (5 h) if **3** was used rather than **2**. The transamination products were formed in relatively low (34–40% for aminophenols and 12–37% for aminobenzoic acids) yields. Thus, a new alternate method was developed for preparing α-hydroxymethylidene-DOV (**2**).

The structures of the synthesized compounds were proved by spectral methods.

Stretching vibrations ν_{OH} for **5**–**7** appeared in the IR spectrum at 3136–3342 cm^{-1}; ν_{OH} of carboxylic group (**8**–**11**), at 3292-3593; ν_{N-H}, at 3088–3256; $\nu_{C=O}$, at 1621–1666; $\nu_{C=O}$ (carboxyl) (**8**–**11**), at 1686–1715; $\nu_{C=N}$, at 1547–1577; and ν_{C-N}, at 1466–1480.

A study of mass spectra of the synthesized compounds suggested the following fragmentation pattern (using **6** as an example, $[M]^+ = 305$):



6

The γ-CH_2 methylene protons of **5**–**7** appeared in the PMR spectrum at 4.09–4.11 ppm as 2H triplets with chemical shifts (CS) of β-CH_2 groups at 2.75–2.80 ppm (2H, triplet). Resonances of the hydroxyl protons of **5** and **6** were found at weak field (10.97 and 10.89 ppm) as 1H singlets. Resonances of =CH–N<u>H</u>- protons had CS in the range 8.02–8.18 ppm as 1H doublets with SSCC J = 14.0–14.2 Hz. Their CS differed slightly depending on the position of the hydroxyl. For example, if the OH group was located in the *ortho*-position of the benzene ring (**5**), then its CS was 8.18 ppm; in the *meta*-position, 8.12; and in the *para*-position, 8.02. Olefinic protons (CHNH) of **5–7** also appeared as 1H doublets in the range 7.77–8.02 ppm (1H, d) with SSCC J = 14.0–14.2. The CS was located at relatively power (7.77 ppm) field for an *o*-OH group (**5**). This was related to the electron-donating effect of the OH as compared with a =CH–NH- group. Moreover, resonances of the corresponding protons in the aromatic part of the spectra could be observed in the range 6.44–7.85 ppm.

Resonances of olefinic protons (=CHNH) were shifted to weaker field (8.35 and 8.41 ppm) in spectra of **8–11** with an electron-accepting substituent (COOH) or a substituent with a –I-inductive effect (Br) in the *ortho*-position of the benzene ring (**8** and **11**) than in those of compounds with *m*- and *p*-isomeric aminobenzoic acids (8.13, 1H doublets). Furthermore, the resonance of NH protons was observed only for **9** and **10** with SSCC 13.7–13.9 Hz also as 1H doublets. The γ-methylene protons of **8**–**11** were also found, like for **5**–**7**, as 2H triplets but at relatively weaker (4.13–4.20 ppm) field than the γ-CH_2 protons of **5**–**7** (4.09–4.11). Such a phenomenon was also observed for the β-CH_2 groups of **8**–**11** (2.80–2.85 ppm, 2H, triplet).

Thus, the appearance of two 2H triplets for the β- and γ-methylene groups in the aliphatic part of the spectrum and the CS of the NH-groups as 1H doublets with SSCC 13.7–14.2 Hz (relative to olefinic protons =CHNH) confirmed the structures of the nucleophilic substitution products **5**–**11**.

EXPERIMENTAL

Mass spectra were recorded on an MS-30 (Kratos) instrument; IR spectra, in KBr pellets on a System 2000 IR-Fourier spectrometer; PMR spectra, in CD_3COOD (**9**) and TFA + CD_3COOD (**5**–**8**, **10**, **11**) on a Unity 400+ instrument (operating frequency 400 MHz, HMDS internal standard, δ scale). The purity of products and course of reactions were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:MeOH (5:1, system A; 10:1, system B).

Deoxyvasicinone (1) was prepared by the literature method [1].

α-Hydroxymethylidenedeoxyvasicinone (2) (from ethylformate). A mixture of **1** (1.0 g, 5 mmol) in ethylformate (5 mL) was cooled to 0°C, stirred, and treated in portions with metallic sodium (0.23 g, 10 mmol) over 30 min. A thick dark-yellow mass formed. The mixture was left at room temperature overnight, decomposed using ground ice, and extracted with

$CHCl_3$ (2 × 30 mL). The extract was dried over anhydrous Na_2SO_4. The solvent was distilled off. The solid was recrystallized from acetone to afford **2** (0.8 g, 70%), mp 206–208°C, in agreement with the literature (206–208°C [7]), R_f 0.48 (system B).

From *n*-propylformate: In analogy with the method given above, **1** (1 g, 5 mmol), *n*-propylformate (5 mL), and metallic sodium (0.23 g, 10 mmol) afforded **2** (0.86 g, 75%), mp 206–208°C, R_f 0.48 (system B).

A mixed melting point sample of **2** obtained using ethyl- and *n*-propylformates did not show depression.

α-Dimethylaminomethylidenedeoxyvasicinone (3) was prepared by the literature method [1].

α-(*o*-Hydroxyphenylamino)methylidenedeoxyvasicinone (5). Method A (from 2): Starting **2** (0.21 g, 1 mmol) in MeOH (50 mL) was treated with *o*-aminophenol (0.11 g, 1 mmol), refluxed for 3 h, and cooled when the reaction was finished. The resulting precipitate was filtered off, washed with MeOH, and dried. Recrystallization from aqueous DMF afforded **5** (0.25 g, 80%), $C_{18}H_{15}N_3O_2$, mp 279–281°C, R_f 0.73 (system B).

Method B (from 3): α-Dimethylaminomethylidenedeoxyvasicinone (**3**) (0.12 g, 0.5 mmol) was dissolved in MeOH (10 mL), treated with *o*-aminophenol (0.05 g, 0.5 mmol), refluxed for 5 h, and cooled. The resulting precipitate was filtered off, washed with MeOH, and dried. The product was recrystallized from aqueous DMF to afford **5** (0.06 g, 40%).

IR spectrum (ν, cm^{-1}): 3136 (OH), 3092 (NH), 1666 (C=O), 1577 (C=N), 1466 (C–N).

PMR spectrum (δ, ppm, J/Hz): 10.97 (1H, s, OH), 8.18 (1H, d, J = 14.2, NH), 7.85 (1H, d, J = 7.8, H-5), 7.77 (1H, d, J = 14.2, CHNH), 7.47 (1H, t, J = 8.1, H-7), 7.16 (1H, t, J = 7.8, H-4′), 7.08 (1H, d, J = 8.1, H-8), 6.80 (1H, d, J = 7.8, H-3′), 6.71 (1H, t, J = 7.8, H-6), 6.60 (1H, t, J = 7.8, H-5′), 6.58 (1H, d, J = 7.8, H-6′), 4.11 (2H, t, J = 7.8, γ-CH_2), 2.80 (2H, t, J = 7.8, β-CH_2).

Mass spectrum (*m*/*z*, %): 305 (90) $[M]^+$, 288 (28) $[M - OH]^+$, 212 (7.6) $[M - C_6H_4OH]^+$, 197 (33) $[M - NH - C_6H_4OH]^+$, 186 (100), 185 (98), 159 (8), 145 (3.5), 144 (10), 130 (7).

Mixed melting point samples of **5**–**7** prepared by methods A and B did not show depression.

α-(*m*-Hydroxyphenylamino)methylidenedeoxyvasicinone (6). In analogy with method A given above **2** (0.21 g, 1 mmol) and *m*-aminophenol (0.11 g, 1 mmol) afforded **6** (0.23 g, 77%), $C_{18}H_{15}N_3O_2$, mp 274–276°C (MeOH), R_f 0.64 (system B).

In analogy with method B, **3** (0.24 g, 1 mmol) and *m*-aminophenol (0.11 g, 1 mmol) afforded **6** (0.1 g, 34%).

IR spectrum (ν, cm^{-1}): 3342 (OH), 3100 (NH), 1656 (C=O), 1547 (C=N), 1470 (C–N).

PMR spectrum (δ, ppm, J/Hz): 10.89 (1H, s, OH), 8.12 (1H, d, J = 14.0, NH), 8.00 (1H, d, J = 14.0, CHNH), 7.86 (1H, d, J = 7.8, H-5), 7.49 (1H, t, J = 8.4, H-7), 7.18 (1H, t, J = 8.1, H-6), 7.08 (1H, d, J = 8.4, H-8), 6.90 (1H, d, J = 8.1, H-5′), 6.51 (1H, d, J = 2.0, H-2′), 6.44 (2H, d, J = 8.1, H-4′, 6′), 4.10 (2H, t, J = 8.1, γ-CH_2), 2.77 (2H, t, J = 8.1, β-CH_2).

Mass spectrum (*m*/*z*, %): 305 (100) $[M]^+$, 304 (90) $[M - 1]^+$, 288 (1.5) $[M - OH]^+$, 212 (17) $[M - C_6H_4OH]^+$, 197 (10) $[M - NH - C_6H_4OH]^+$, 186 (13), 184 (6), 171 (6.3), 144 (6), 130 (19).

α-(*p*-Hydroxyphenylamino)methylidenedeoxyvasicinone (7). According to method A as described above, **2** (0.21 g, 1 mmol) and *p*-aminophenol (0.11 g, 1 mmol) afforded **7** (0.24 g, 79%), $C_{18}H_{15}N_3O_2$, mp 290–292°C (MeOH), R_f 0.53 (system B).

In analogy with method B, **3** (0.24 g, 1 mmol) and *p*-aminophenol (0.11 g, 1 mmol) afforded **7** (0.11 g, 35%).

IR spectrum (ν, cm^{-1}): 3333 (OH), 3256 (NH), 1650 (C=O), 1574 (C=N), 1466 (C–N).

PMR spectrum (δ, ppm, J/Hz): 8.07 (1H, d, J = 14.1, NH), 8.02 (1H, d, J = 14.1, CHNH), 7.84 (1H, d, J = 7.7, H-5), 7.46 (1H, t, J = 8.4, H-7), 7.15 (1H, t, J = 7.7, H-6), 7.06 (1H, d, J = 8.4, H-8), 6.7 (2H, d, J = 9.0, H-2′, 6′), 6.61 (2H, d, J = 9.0, H-3′, 5′), 4.09 (2H, t, J = 8.2, γ-CH_2), 2.75 (2H, t, J = 8.2, β-CH_2).

α-(*o*-Hydroxycarbonylphenylamino)methylidenedeoxyvasicinone (8). The reaction was performed analogously to method A using **2** (0.67 g, 3.1 mmol) and *o*-aminobenzoic acid (0.42 g, 3.1 mmol) to afford **8** (0.91 g, 89%), $C_{19}H_{15}N_3O_3$, mp 266°C (dec.) (aq. DMF), R_f 0.34 (system A).

In analogy with method B (from **3**), **3** (0.12 g, 0.5 mmol) and *o*-aminobenzoic acid (0.07 g, 0.5 mmol) synthesized **8** (0.05 g, 27%).

IR spectrum (ν, cm^{-1}): 3467 (OH), 3137 (NH), 1697, 1621 (C=O), 1567 (C=N), 1478 (C–N).

PMR spectrum (δ, ppm, J/Hz): 8.41 (1H, s, CHNH), 7.91 (2H, d, J = 8.2, H-5), 7.90 (1H, d, J = 8.5, H-3′), 7.54 (1H, t, J = 8.5, H-4′), 7.36 (1H, t, J = 8.5, H-5′), 7.24 (1H, t, J = 8.2, H-7), 7.18 (1H, d, J = 8.5, H-6′), 7.09 (1H, d, J = 8.2, H-8), 6.94 (1H, t, J = 8.2, H-6), 4.2 (2H, t, J = 8.4, γ-CH_2), 2.85 (2H, t, J = 8.4, β-CH_2).

Mass spectrum (*m*/*z*, %): 333 (65) $[M]^+$, 288 (100) $[M - COOH]^+$, 212 (14) $[M - C_6H_4COOH]^+$, 199 (44), 197 (15) $[M - NH - C_6H_4COOH]^+$, 186 (68), 185 (50), 184 (32) $[M - CH - NH - C_6H_4COOH]^+$, 169 (29), 130 (25).

α-(*m*-Hydroxycarbonylphenylamino)methylidenedeoxyvasicinone (9). In analogy with method A as described above, **2** (0.43 g, 2 mmol) and *m*-aminobenzoic acid (0.27 g, 2 mmol) afforded **9** (0.39 g, 64%), $C_{19}H_{15}N_3O_3$, mp 288°C (dec.) (DMF), R_f 0.29 (system A).

In analogy with method B, **3** (0.12 g, 0.5 mmol) and *m*-aminobenzoic acid (0.07 g, 0.5 mmol) afforded **9** (0.06 g, 36%).

IR spectrum (ν, cm^{-1}): 3406 (ν_{OH}), 3244 (ν_{NH}), 1697, 1677 ($\nu_{C=O}$), 1555 ($\nu_{C=N}$), 1480 (ν_{C-N}).

PMR spectrum (δ, ppm, J/Hz): 8.29 (1H, br.d, J = 13.9, NH), 8.13 (1H, br.d, J = 13.9, CHNH), 7.88 (1H, d, J = 8.0, H-5), 7.62 (2H, br.d, J = 8.3, H-4′, 6′), 7.51 (1H, d, J = 8.0, H-7), 7.21 (1H, d, J = 8.0, H-2′), 7.17 (1H, t, J = 8.0, H-5′), 7.09 (2H, br.d, J = 8.0, H-6, 8), 4.13 (2H, t, J = 7.6, γ-CH_2), 2.80 (2H, t, J = 7.6, β-CH_2).

Mass spectrum (*m*/*z*, %): 333 (100) $[M]^+$, 332 (49) $[M - 1]^+$, 288 (3.5) $[M - COOH]^+$, 286 (10.5), 212 (25) $[M - C_6H_4COOH]^+$, 197 (8) $[M - NH - C_6H_4COOH]^+$, 186 (9), 185 (31), 184 (5) $[M - CH - NH - C_6H_4COOH]^+$, 172 (4.2), 158 (4), 146 (7), 130 (4).

α-(*p*-Hydroxycarbonylphenylamino)methylidenedeoxyvasicinone (10). In analogy with method A, **2** (0.43 g, 2 mmol) and *p*-aminobenzoic acid (0.27 g, 2 mmol) afforded **10** (0.43 g, 65%), $C_{19}H_{15}N_3O_3$, mp 334–336°C (1,4-dioxane), R_f 0.47 (system A).

In analogy with method B, **3** (0.12 g, 0.5 mmol) and *p*-aminobenzoic acid (0.07 g, 0.5 mmol) afforded **10** (0.06 g, 37%).

IR spectrum (ν, cm^{-1}): 3292 (ν_{OH}), 3165 (ν_{NH}), 1715, 1672 ($\nu_{C=O}$), 1570 ($\nu_{C=N}$), 1474 (ν_{C-N}).

PMR spectrum (δ, ppm, J/Hz): 8.26 (1H, br.d, J = 13.7, NH), 8.13 (1H, br.d, J = 13.7, CHNH), 7.89 (1H, dd, J = 8.1, 1.1, H-5), 7.78 (2H, br.d, J = 8.7, H-3′, 5′), 7.52 (1H, t, J = 8.1, H-6), 7.22 (1H, dd, J = 8.1, 1.1, H-7), 7.15 (1H, d, J = 8.1, H-8), 6.91 (2H, br.d, J = 8.7, H-2′, 6′), 4.14 (2H, t, J = 7.9, γ-CH_2), 2.81 (2H, t, J = 7.9, β-CH_2).

Mass spectrum (*m*/*z*, %): 333 (100) $[M]^+$, 332 (49) $[M - 1]^+$, 288 (17) $[M - COOH]^+$, 212 (15) $[M - C_6H_4COOH]^+$, 197 (12) $[M - NH - C_6H_4COOH]^+$, 185 (22.4), 184 (21) $[M - CH - NH - C_6H_4COOH]^+$, 169 (12.6), 144 (3), 131 (6.0).

α-(5′-Bromo-2′-hydroxycarbonylphenylamino)methylidenedeoxyvasicinone (11). In analogy with method A as described above, **2** (0.43 g, 2 mmol) and 5-bromo-2-aminobenzoic acid (0.43 g, 2 mmol) afforded **11** (0.31 g, 38%), $C_{19}H_{14}N_3O_3Br$, mp 320°C (dec.) (DMF), R_f 0.25 (system A).

Compound **3** (0.12 g, 0.5 mmol) and 5-bromo-2-aminobenzoic acid (0.11 g, 0.5 mmol) afforded **11** (0.025 g, 12%).

IR spectrum (ν, cm^{-1}): 3593 (ν_{OH}), 3088 (ν_{NH}), 1686 ($\nu_{C=O}$), 1570 ($\nu_{C=N}$), 1507 (ν_{C-N}).

PMR spectrum (δ, ppm, J/Hz): 11.49 (1H, s, OH), 8.35 (1H, br.d, J = 13.6, CHNH), 7.97 (1H, d, J = 2.3, H-6′), 7.90 (1H, d, J = 7.8, H-5), 7.53 (1H, t, J = 7.8, H-6), 7.42 (1H, dd, J = 9.1, 2.3, H-4′), 7.23 (1H, t, J = 7.8, H-7), 7.18 (1H, d, J = 7.8, H-8), 6.96 (1H, d, J = 9.1, H-3′), 4.17 (2H, t, J = 7.8, γ-CH_2), 2.80 (2H, t, J = 7.8, β-CH_2).

Mass spectrum (*m*/*z*, %): 411/413 (50) $[M]^+$, 367/369 (52) $[M - CO_2]^+$, 286 (21), 212 (17), 198 (20), 186 (75), 185 (100), 184 (37), 142 (13), 119 (15), 101 (17.5), 76 (36).

Mixed melting point samples of **8**–**11** prepared by methods A and B did not show depression.

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