NOTE

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Tubercidin: Its Conversion to 5′-Amino-5′-deoxytubercidin

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The conversion of tubercidin (I)[1~3] to N^6,N^6-dibenzoyl-2′,3′-O-isopropylidene-5′-O-mesyltubercidin (II) has already been reported.[4] Compound II served as an important intermediate for the synthesis of 5′-deoxytubercidin (III).[4] In this paper, the conversion of II to 5′-amino-5′-deoxytubercidin is reported.

Treatment of II with sodium azide in hexamethylphosphoric triamide afforded N^6-benzoyl-5′-azido-5′-deoxy-2′,3′-O-isopropylidenetubercidin (V) in 68% yield, and the cyclonucleoside VI was also obtained as a minor product (yield, 7%).[8] The formation of VI on treatment of II with sodium hydroxide has already been reported.[5] In this case the reaction may be initiated by nucleophilic attack of the azide ion on the benzoyl group, and benzazide thus formed may be converted further to various products through Curtius rearrangement (Chart 1). In fact, N,N′-diphenylurea and benzanilide were isolated from the reaction mixture.

Alkaline hydrolysis of V afforded 5′-azido-5′-deoxy-2′,3′-O-isopropylidenetubercidin (VII) as well as 2,3′-O-isopropylidenetubercidin (VIII)[7] as a minor product. On catalytic hydrogenation of VII, 5′-amino-5′-deoxy-2′,3′-O-isopropylidenetubercidin IX was obtained quantitatively. Surprisingly, IX was scarcely deacetonated in hot aqueous acetic acid. We supposed that protonated 5′-amino group hindered the approach of protons to the isopropylidene group, the hydrolysis of which was, thus, prevented.

Compound IX was deacetonated with hydrochloric acid in refluxing aqueous alcohol to give syrupy 5′-amino-5′-deoxytubercidin (IV). To confirm the identification, IV was converted to crystalline 5′-acetamido-5′-deoxytubercidin X.

5′-Deoxy-5′-methanesulfonylaminotubercidin (XI) was also prepared. Treatment of IX with an equimolar amount of mesyl chloride afforded 5′-deoxy-2′, 3′-O-isopropylidene-5′-methanesulfonylaminotubercidin (XII), which was deacetonated in aqueous acetic acid to yield XI. 5′-Deoxy-5′-methanesulfonylaminoadenosine, the adenosine analogue of XI, has already been synthesized, and the antiviral activity has also been reported.[6]

EXPERIMENTAL

N^6-Benzoyl-5′-azido-5′-deoxy-2′,3′-O-isopropylidenetubercidin (V)

A solution of II (592 mg) and sodium azide (200 mg) dissolved in hexamethylphosphoric triamide (20 ml) was heated at 80~100°C for 4 hr. Water was added to the solution, and the products were distributed between water and ether; yield 25 mg. On leaving the aqueous layer to stand at room temperature for several days, crystals of the cyclonucleoside VI[5] separated out.

The organic layer was washed repeatedly with water. The presence of three compounds was shown under ultraviolet light on TLC, and they were separated by silicic acid chromatography, developing with a mixture of benzene and ethyl acetate (4: 1). The compound which eluted first was identified as N,N′-diphenylurea by comparison with an authentic sample, and that eluted second was identified as benzanilide. Compound V was eluted with a mixture of benzene and ethyl acetate (2: 1), and was obtained as a syrup, yield 278 mg; $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 303 (5100), 240 (shoulder, 11500) and 225 (15000); $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2100 (N_3); Mass *m/e*: 435.1653 (M^+, $C_{21}H_{21}N_7O_4$ gives 435.1655), 407.1645 (M^+-N_2, $C_{21}H_{21}N_5O_4$ gives 407.1624).

Found: C, 58.37; H, 4.78; N, 22.02%. Cacld. for $C_{21}H_{21}N_7O_4$: C, 57.92; H, 4.86; N, 22.52%.

5′-Azido-5′-deoxy-2′,3′-O-isopropylidenetubercidin (VII)

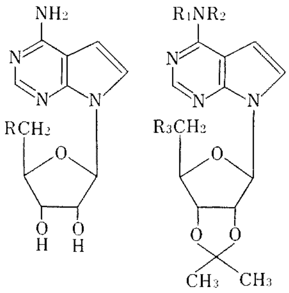
A solution of V (1.13 g) dissolved in a mixture of 1 N NaOH (5 ml) and ethanol (15 ml) was refluxed for 1 hr. After evaporation of the ethanol, the products were extracted with chloroform. TLC showed the presence of two compounds, which were separated by silicic acid chromatography, developing with a mixture of ethyl acetate and methanol (95: 5) and gradually increasing the methanol content. The compound, which was eluted later, was identified as 2′,3′-O-isopropylidenetubercidin (VIII)[7] by comparison with an authentic sample, yield 72 mg.

The less polar compound was obtained as a syrup, and was identified as VII, yield 602 mg; $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 270 (11200); ν^{KBr}: 2100 cm^{-1} (N_3).

Found: C, 50.90; H, 5.30; N, 17.85%. Calcd. for $C_{14}H_{17}N_7O_3$: C, 50.74; H, 5.17; N, 18.29%.

5′-Amino-5′-deoxy-2′,3′-O-isopropylidenetubercidin (IX)

Compound VII (500 mg) was catalytically hydrogenated over 10% palladium on charcoal (100 mg) using ethanol as the solvent at a hydrogen pressure of 3 kg/cm^2 for 2 hr. Evaporation of the ethanol to dryness afforded 485 mg of a syrup which showed positive ninhydrin reaction. This material was frac-



I	R=OH
III	R=H
IV	R=NH_2
X	R=CH_3CONH
XI	R=CH_3SO_2NH

II	R_1, R_2=C_6H_5CO R_3=CH_3SO_3
V	R_1=H, R_2=C_6H_5CO, R_3=N_3
VII	R_1, R_2=H R_3=N_3
VIII	R_1, R_2=H R_3=OH
IX	R_1, R_2=H R_3=NH_2
XII	R_1, R_2=H R_3=CH_3SO_2NH

tionally precipitated from ethanol and benzene; $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 270 (8700); Mass *m/e*: 305.1498 (M^+, $C_{14}H_{19}N_5O_3$ gives 305.1488).

Found: C, 55.24; H, 6.62; N, 22.45%. Calcd. for $C_{14}H_{19}N_5O_3$: C, 55.07; H, 6.27; N, 22.94%.

5′-Amino-5′-deoxytubercidin (IV)

A solution of IX (400 mg) dissolved in a mixture of ethanol (8 ml) and 1 N HCl (2 ml) was refluxed for 5 hr, and was concentrated to dryness. The residue, after drying over sodium hydroxide *in vacuo*, was dissolved in water, excluding insoluble impurities. To convert the hydrochloride to the free base, the product was adsorbed on a column of IR 120 (H-cycle) and was eluted with 0.5 N NH_4OH. The ninhydrin-positive fractions were combined and concentrated to dryness, affording 150 mg of a syrup. Though TLC on cellulose (butanol, acetic acid, water (4: 1: 2) or *n*-propanol, pyridine, acetic acid, water (15: 10: 3: 5)) showed that the syrup was practically homogeneous, it was further purified for analysis by repeated precipitation from ethanol and benzene, $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 270 (9300); NMR (100 MHz, D_2O) δ: 2.92 (broad s, 2H, H-5′), 4.0~4.5 (complex, H-2′, H-3′ and H-4′, partially overlapped with the signal of HDO), 6.10 (d, 1H, H-1′, $J_{1',2'}=5$ Hz), 6.52, 7.21 (a pair of doublets, 2H, -CH=CH-N< $J=3$ Hz), 8.00 (s, 1H, -N=CH-N=).

Found: C, 49.64; H, 5.21; N, 25.97%. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40%.

5′-Acetamido-5′-deoxytubercidin (X)

To a solution of IV (410 mg) dissolved in methanol (10 ml), acetic anhydride (1 ml) was added with stirring and the solution was allowed to stand overnight at room temperature. The solvent was evaporated to dryness and the residue was crystallized from dimethylformamide and ethanol. To exclude the acetic acid, the sample was dried at 100°C for 4 hr, yield 283 mg; mp 148~150°C; $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 270 (11200); NMR (60 MHz, DMSO-d_6) δ: 1.86 (s, 3H, CH_3CONH), 5.96 (d, 1H, H-1′, $J_{1',2'}=5$ Hz), 6.54, 7.26 (a pair of doublet, 2H, -CH=CH-N< $J=3$ Hz), 8.08 (s, 1H, -N=CH-N=).

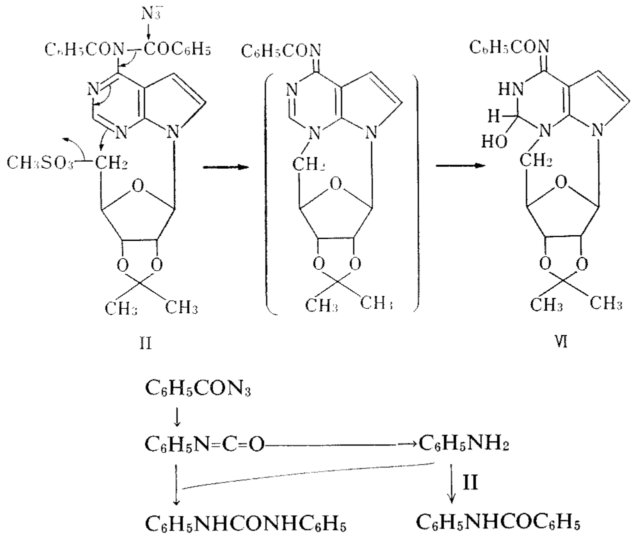


CHART 1.

Found: C, 50.00; H, 5.53; N, 22.29%. Calcd. for $C_{13}H_{17}N_5O_4 \cdot 1/2H_2O$ C, 49.36; H, 5.72; N, 22.14%.

5′-Deoxy-2′,3′-O-isopropylidene-5′-methanesulfonylaminotubercidin (XII)

To a solution of IX (351 mg, 1.15 mM) dissolved in pyridine (20 ml), mesyl chloride (160 mg, 1.4 mM) was added at 0°C with stirring. The solution was left in a refrigerator overnight, and was poured into an ice-cooled solution of sodium bicarbonate. The product was extracted with chloroform. Silicic acid chromatography, developing with a mixture of ethyl acetate and methanol (9: 1), afforded 274 mg of a solid, which was crystallized from ethyl acetate and benzene, mp 136~140°C; $\lambda_{\max}^{\text{MeOH}}$ mμ (ε): 268 (11600); Mass *m/e*: 382 (M^+), 304 (M^+-CH_3SO_2+H); NMR (60 MHz, $CDCl_3$) δ: 1.32, 1.58 (two singlets, 6H, two isopropylidene methyls), 2.90 (s, 3H, CH_3SO_2NH).

Found: C, 47.74; H, 5.46; N, 18.22; S, 8.16%. Calcd. for $C_{15}H_{20}N_5O_5S$; C, 47.11; H, 5.27; N, 18.32; S, 8.39%.

5′-Deoxy-5′-methanesulfonylaminotubercidin (XI)

A solution of XII (200 mg) dissolved in 70% acetic acid (10 ml) was heated at 100°C for 5 hr. The residue was dried over sodium hydroxide *in vacuo*, and was fractionally precipitated from methanol and ethyl acetate to obtain 150 mg of a syrup. The material was identified as XI, having one mole of acetic acid, $\lambda_{\max}^{\text{MeOH}}$ mμ (ε): 269 (12000); NMR (100 MHz, $CDCl_3$) δ: 1.94 (s, 3H, CH_3COOH), 2.92 (s, 3H, CH_3SO_2NH).

Found: C, 42.24; H, 5.42; N, 16.96; S, 7.76%. Calcd. for $C_{14}H_{21}N_5O_7S$: C, 41.78; H, 5.25; N, 17.36; S, 7.95%.

On heating at 100°C for 4 hr *in vacuo* the acetic acid was lost.

Found: C, 42.02; H, 5.18; N, 19.97; S, 9.08%. Calcd. for $C_{21}H_{17}N_5O_5S$; C, 41.68; H, 4.99; N, 20.40; S, 9.34%.

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