The Synthesis of 3-Isopropylidene-2, 5-dioxopiperazines

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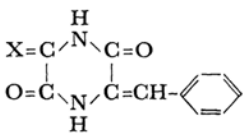
Albonoursin, isolated from the culture filtrates of Streptomyces noursei and Streptmyces albus var. fungatus, has been concluded to be 3-benzylidene-6-isobutylidene-2, 5-dioxopiperazine (I) by Khokhlov et al.,[1] Vondráček et al.,[2] and Brown et al.[3]



X: $(CH_3)_2CHCH=$ (I)

$(CH_3)_2C=$ (II)

Dioxopiperazine has been known to condense with aromatic aldehyde in the presence of acetic anhydride and sodium acetate, yielding mono- or di-benzylidene derivatives.[4,5] However, the synthesis of 3-alkylidene or 3, 6-dialkylidene derivatives of dioxopiperazine has never been reported.

In connection with a program directed toward a total synthesis of albonoursin, we have sought a method of synthesizing of 3-alkylidene dioxopiperazine. We wish to report in the present paper a synthesis of 3-isopropylidene dioxopiperazine and a homolog of albonoursin, 3-benzylidene-6-isopropylidene-2, 5-dioxopiperazine (II) by a new method.

Methyl α-amino-β, β-dimethylacrylate (III), obtained by the reduction of the corresponding nitro compound, was treated in an aqueous solution of sodium bicarbonate with phthaloylglycyl chloride; it thus gave methyl α-phthaloylglycylamino-β, β-dimethyl acrylate (IV) as colorless needles with a m. p. of 234—235°C in a quantitative yield (Found: C, 60.50; H, 5.38; N, 8.95. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86%). The hydrolysis of IV with 1 N sodium hydroxide afforded α-phthaloylglycylamino-β, β-dimethyl acrylic acid (V) in a 31.8% yield, colorless fibrous needles from methanol, m. p. 258—259°C (decomp.) (Found: C, 59.21; H, 4.82; N, 9.44. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27%). By treatment with hydrazine hydrate, V was converted into α-glycylamino-β, β-dimethylacrylic acid (VI) in an almost quantitative yield, colorless prisms with a m. p. of 232—234°C (decomp.) from a 50% aqueous ethanol (Found: C, 49.05 H, 7.09; N, 16.31. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27%), which was then esterified with methanol - hydrogen chloride to give the corresponding methyl ester hydrochloride (VII) as colorless prisms with a m. p. of 178—180°C (Found: N, 12.58. Calcd. for $C_8H_{14}N_2O_3 \cdot HCl$: N, 12.58%).

When VII was heated with an aqueous solution of an equivalent mole of sodium bicarbonate on a boiling water bath for 30 min., a cyclization reaction occured and 3-isopropylidene-2, 5-dioxopiperazine (VIII) was obtained in a 70% yield. Recrystallization form boiling water afforded colorless prismatic needles with a m. p. of 260—261°C (decomp.) (Found: C, 54.52; H, 6.83; N, 18.16. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17%), λ_{max}^{EtOH} 230 mμ (ε= 22800), 240 mμ (ε=23000), ν_{max}^{KBr} 3200, 3050, 1680, 1665 and 1625 cm^{-1}. VIII was also obtained in a 54% yield by heating IV with hydrazine hydrate in a small amount of methanol.

The condensation reaction of VIII with benzaldehyde was carried out by heating it in acetic anhydride in the presence of sodium acetate at 120—130°C for 8 hr.; II was thus obtained in a 77% yield. Recrystallization from boiling acetic acid afforded colorless needles with a m. p. of 283—284°C (decomp.) (Found: C, 69.45; H, 5.72; N, 11.81. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56%), λ_{max}^{DMF} 321 mμ (ε= 21600), ν_{max}^{KBr} 3250, 3050, 1680 and 1635 cm^{-1}. These data of the ultraviolet and infrared absorption spectra are very similar to those of albonoursin.

III was heated in a sealed tube at 180—190°C for 48 hr.[6] to yield 3, 6-diisopropylidene-2, 5-dioxopiperazine in a 27% yield, colorless needles with a m. p. of 264—265°C (decomp.) (Found: N, 14.43. Calcd. for $C_{10}H_{14}N_2O_2$: N, 14.42%).

The details of the present communication and the methods of preparing the starting meterials will be described shortly in a further publication.

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3) R. Brown, C. Kelley and S. E. Wiberley, *J. Org. Chem.*, **30**, 277 (1965).
4) T. Sasaki, *Ber.*, **54**, 163 (1921).
5) T. Sasaki and T. Hashimoto, ibid., **54**, 168 (1921).
6) E. Fischer, ibid., **34**, 433 (1901).