Notes

[Chem. Pharm. Bull.
29(3) 861-862 (1981)]Formation of Isopavine by the Cyclization of N-[α -(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal with Chlorosulfonic Acid¹⁾

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Treatment of N-[α -(3,4-dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (**1**) or its oxalate with chlorosulfonic acid at low temperature gave isopavine (**3**) in extremely good yield.

Keywords—isopavine synthesis; N-[α -(3,4-dimethoxybenzyl)-3,4-dimethoxybenzyl]-aminoacetal; chlorosulfonic acid; acid-catalyzed cyclization; spectra (UV, IR, and MS)

In a previous paper^{1b)} we reported that the treatment of N-(benzyl)-aminoacetals ($R^1 = R^2 = H$; $R^1 = OCH_3$, $R^2 = H$; $R^1 = R^2 = OCH_3$, and $R^3 = H$, CH_3 , CH_2CH_3 , or $CH_2CH_2CH_3$) with chlorosulfonic acid ($ClSO_3H$) directly afforded fully aromatized isoquinolines ($R^1 = R^2 = H$; $R^1 = OCH_3$, $R^2 = H$; $R^1 = R^2 = OCH_3$, and $R^3 = H$, CH_3 , CH_2CH_3 , or $CH_2CH_2CH_3$) with yields in the range of 15–75% (Chart 1).

Chart 1

This experimental result prompted us to attempt the cyclodehydrogenation of N-[α -(3,4-dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (**1**) with $ClSO_3H$, to obtain papaverine (**2**). N-[α -(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (**1**), or preferably, its oxalate²⁾ (1 eq) was added in small portions to $ClSO_3H$ (10 eq) at -60 — -50° with vigorous stirring, and the mixture was held at the same temperature for 30 min, then allowed to stand at -15° for 3 hr.

By the subsequent procedures described in the experimental section, a basic substance was isolated as colorless crystals, mp 153.5 — 155° . Its infrared (IR) spectrum ($\nu_{max}^{CHCl_3}$ 3325 cm^{-1}) indicates the presence of an $>NH$ group. The ultraviolet (UV) absorption spectrum showed maxima at 207 nm ($\log \epsilon$ 5.06) and 284 (4.25), suggestive of the isopavine chromophore.³⁾ The molecular formula of this base was assigned as $C_{20}H_{23}NO_4$ on the basis of elemental analysis and its mass spectrum (MS) (M^+ , m/e 341).

Chart 2

The base obtained by the treatment of **1** with $ClSO_3H$ was identical with an authentic sample of isopavine (**3**) prepared by the intramolecular condensation of **1** with H_2SO_4 .^{2,4)} Thus, although we failed to obtain papaverine (**2**), the present synthesis of isopavine (**3**) is

characterized by very high yield (97%) in comparison with the conventional method using $\text{H}_2\text{SO}_4^{2,4)}$ or a mixture of H_2SO_4 and $\text{CH}_3\text{CO}_2\text{H}^{2)}$

Experimental

Melting points were determined on Yanaco melting point apparatus and are uncorrected. UV, IR and MS spectra were taken on Shimadzu UV-200, Jasco IRA-1 and JEOL JMS-D 100 machines, respectively. All solutions were dried over anhyd. MgSO_4 .

Treatment of N-[α -(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (1) Oxalate with ClSO_3H —1 oxalate (2.48 g, 4.7 mmol) prepared according to the method in the lit.²⁾ was added little by little to ClSO_3H (3.1 ml) and the reaction mixture was held at -60 — -50° for 30 min with vigorous stirring, then allowed to stand at -15° for 3 hr in the absence of moisture. The reaction mixture was poured into 100 ml of ice-water and extracted with Et_2O to remove non-basic substances. The aq. layer was made alkaline with 10% aq. NaOH , then shaken with hot C_6H_6 . The benzene solution was dried, and the solvent was distilled off. A basic substance was deposited which melted at 153.5 — 155° . This base was shown to be identical with an authentic sample of isopavine (3). Yield 1.57 g (97%). *Anal.* Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.94; H, 6.84; N, 4.10. MS: *m/e* (%), 156 (10.7), 190 (72), 191 (10.5), 269 (17.9), 281 (10.7), 312 (100), 313 (24.7), 314 (35.9), 341, M^+ (43.6).

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References and Notes

- 1) a) This paper forms Part IV of "Halosulfonic Acid as a Cyclizing Agent for Isoquinoline Synthesis"; b) Part III: K. Kido and Y. Watanabe, *Heterocycles*, **14**, 1151 (1980).
- 2) E. Waldmann and C. Chwala, *Ann. Chem.*, **609**, 125 (1957).
- 3) M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, 1972, pp. 112—113.
- 4) D.A. Guthrie, A.W. Frank, and C.B. Purves, *Can. J. Chem.*, **33**, 729 (1955); A.R. Battersby and D.A. Yeowell, *J. Chem. Soc.*, **1958**, 1988.

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Studies on Ketene and Its Derivatives. CII.¹⁾ Reaction of Diketene with Cyanamide Derivatives

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The reaction of diketene with cyanamide gave 2-amino-6-methyl-4*H*-1,3-oxazin-4-one, which was transformed to 6-methyluracil by refluxing it in acetic acid. Diketene also reacted with monosubstituted cyanamides to give 1,3-oxazin-4-one derivatives, which could be similarly converted into 1-substituted 6-methyluracils. The reaction of diketene with dicyanodiamide afforded 2-guanidino-6-methyl-4*H*-1,3-oxazin-4-one, which, on treatment with ammonia, afforded 2-guanidino-4-hydroxy-6-methylpyrimidine.

Keywords—diketene; cyanamide; monosubstituted cyanamides; 6-methyluracils; dicyanodiamide; 4*H*-1,3-oxazin-4-ones; ring transformation

It has been reported that diketene reacts with compounds having a $\text{C}=\text{N}$ double bond, such as S-alkylthiourea,²⁾ diphenylguanidine,³⁾ N-trimethylsilylketimine,⁴⁾ and some Schiff bases⁵⁾ to give 6-methyl-4*H*-1,3-oxazin-4-one derivatives. Similarly, Gompper *et al.*⁶⁾ reported the reaction of diketene with disubstituted cyanamides, such as dimethyl-, diethyl-, and