Notes

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Formation of Isopavine by the Cyclization of N-[α-(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal with Chlorosulfonic Acid[1)]

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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).

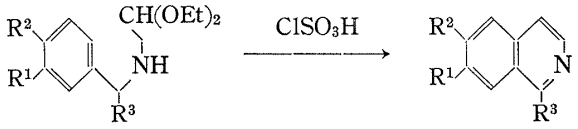

Chart 1

This experimental result prompted us to attempt the cyclodehydrogenation of N-[α-(3,4-dimethoxybenzyl)3,4-dimethoxybenzyl]aminoacetal (**1**) with $ClSO_3H$, to obtaine papaverine (**2**). N-[α-(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (**1**), or preferably, its oxalate[2)] (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 ε 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).

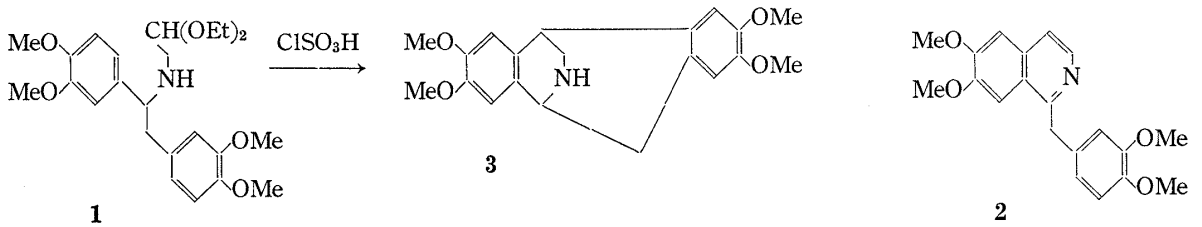

Chart 2

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

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characterized by very high yield (97%) in comparison with the conventional method using H_2SO_4[2,4] or a mixture of H_2SO_4 and CH_3CO_2H.[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 $C_{20}H_{23}NO_4$: 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).
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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 C=N double bond, such as S-alkylthiourea,[2] diphenylguanidine,[3] N-trimethylsilylketimine,[4] and some Schiff bases[5] 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

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