

Catalysts for Vapor-Phase Fischer Indole Synthesis<sup>1</sup>HIROMU HAYASHI, KIYOHIRO KUROKAWA, WATARU HOSOKAWA,  
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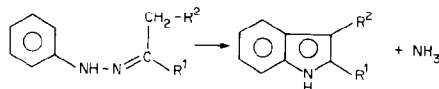
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A variety of oxide catalysts were found to give indole by the vapor-phase cyclization of acetaldehyde phenylhydrazone. The reaction was carried out by a conventional fixed-bed flow apparatus at 300°C with a space velocity of 1000 hr<sup>-1</sup>. Among single oxides,  $\eta$ -Al<sub>2</sub>O<sub>3</sub> showed an excellent stability to give 59% indole with 35% aniline, while  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> degenerated with time. MgO gave indole in a rather high yield. Although the activity degenerated with time, the observation that basic species catalyze the cyclization of phenylhydrazone seems to be less common in the literature. Among binary oxides, weakly acidic SiO<sub>2</sub>-MgO was an excellent catalyst comparable with  $\eta$ -Al<sub>2</sub>O<sub>3</sub>, while strongly acidic catalysts, such as Al<sub>2</sub>O<sub>3</sub>-B<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>-SiO<sub>2</sub>, and CaX zeolite, gave predominantly aniline with rapid deactivation. Skatole,  $\alpha$ -methylindole, and indole-3-acetonitrile were obtained from the corresponding phenylhydrazones over SiO<sub>2</sub>-MgO at 300°C in yields of 88, 76, and 20%, respectively. CaX zeolite also rapidly deactivated in the synthesis of  $\alpha$ -methylindole.

## INTRODUCTION

Hydrazine and its derivatives are the promising source in organic chemistry of nitrogen (1). The present work is an extension of a series of our publications on hydrazine synthesis (2-4).

The cyclization of arylhydrazone is the most versatile and widely applicable route to indole nucleus (5, 6). However, the attempted preparations of indole itself from acetaldehyde phenylhydrazone in liquid phase by the Fischer synthesis resulted in complete failure (7).



In 1970, Kanterov *et al.* (8) successfully tried to obtain indole ( $R^1 = R^2 = H$ ) in 60% yield with 22% aniline by the vapor-phase catalytic cyclization of acetaldehyde phenylhydrazone over  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> at 310°C. Thereafter, Nakazaki and Yamamoto (9) obtained 36% indole with 46% aniline over zinc chloride coated on porous glass beads at 290-300°C. The vapor-phase approach of

the Fischer synthesis was first described by Venuto and Landis (10) to yield 45%  $\alpha$ -methylindole ( $R^1 = CH_3$ ,  $R^2 = H$ ) from acetone phenylhydrazone over CaX zeolite at 150°C, although it could also be obtained in the liquid phase.

Numerous results of the Fischer synthesis suggest (7) that acidic catalysts might effect the cyclization of phenylhydrazones: catalysts mentioned above fall in this category. Metal oxides, especially binary oxides, are known to show acidic properties with a variety of strengths and amounts (11).

Attempted cyclization of acetaldehyde phenylhydrazone to indole was carried out in the present work over various oxides at 300°C with a space velocity of 1000 hr<sup>-1</sup>. All 18 catalysts examined gave indole without exception. Among single oxides,  $\eta$ -Al<sub>2</sub>O<sub>3</sub> was an excellent catalyst. MgO gave indole in a rather high yield, although the activity degenerated with time. Among binary oxides, weakly acidic SiO<sub>2</sub>-MgO was an excellent catalyst comparable with  $\eta$ -Al<sub>2</sub>O<sub>3</sub>, while strongly acidic catalysts, such as Al<sub>2</sub>O<sub>3</sub>-B<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>-SiO<sub>2</sub>, and CaX zeolite, gave predominantly aniline with rapid deac-

<sup>1</sup> Chemical Utilization of Hydrazine Derivatives, I.

tivation. Results for  $\alpha$ -methylindole ( $R^1 = \text{CH}_3$ ,  $R^2 = \text{H}$ ), skatole ( $R^1 = \text{H}$ ,  $R^2 = \text{CH}_3$ ), and indole-3-acetonitrile ( $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{CN}$ ) are also described.

#### EXPERIMENTAL

**Apparatus and procedure.** The reaction was carried out by a conventional fixed-bed flow apparatus at 300°C. Catalyst (10–14 mesh) was packed in a 8-mm-i.d. glass tubing inserted in an electrically heated furnace. Acetaldehyde phenylhydrazone was supplied as a 25 wt% benzene solution through a Teflon capillary. The liquid feed was evaporated at the preheater (200°C) and diluted with nitrogen. Flow rate of the total gas, partial pressure of hydrazone, and space velocity were 3.6 liters/hr (NTP), 0.05 atm, and 1000 hr<sup>-1</sup>, respectively. The effluent gas was scrubbed by an ice-cooled toluene trap for 15 min intermittently to analyze for hydrazone, indole, and aniline by gas chromatography. A stainless-steel column of 3mm  $\times$  2 m packed with 15% Apiezon Grease L on Uniport B (Gaschro Kogyo Co., Tokyo) was used at 140°C with a helium flow rate of 40 ml/min. The reactions of phenylhydrazones of acetone, propionaldehyde, and  $\beta$ -cyanopropionaldehyde were also carried out at 300°C in a similar fashion.

**Materials.** Phenylhydrazones were prepared by dehydrative condensation of phenylhydrazine with carbonyl compounds.  $\beta$ -Cyanopropionaldehyde was prepared by hydrolysis of the dimethylacetal, which was provided by Ajinomoto Company, Osaka.

Single oxides, TiO<sub>2</sub>, ZrO<sub>2</sub>, and MgO, were obtained from Wako Pure Chemicals Company, Tokyo.  $\gamma$ - and  $\eta$ -Al<sub>2</sub>O<sub>3</sub> were provided by Central Research Laboratory, Sumitomo Chemical Company, Osaka. These oxides and their binary oxides were kneaded for 2 hr with a proper amount of water. The paste was dried overnight at room temperature, then overnight at 70°C, and calcined at 500°C in air for 5 hr.  $\eta$ -Al<sub>2</sub>O<sub>3</sub> was used for alumina-based binary oxides. SiO<sub>2</sub> and silica-based binary oxides were prepared from Snowtex 20 (silica sol containing 20% SiO<sub>2</sub>, pH 9.6; Nissan Chemical Co., Tokyo). Calculated amounts of another oxide powder or salts were added into the silica sol. The coagulated hydrogel was kneaded for 2 hr, and then dried and calcined similarly as above. Zinc chloride on silica was prepared from the chloride and silica sol. Calcination at 300°C under nitrogen for 3 hr resulted in a chlorine loss of about 15–20%. Thus, the white mass dried at 70°C was used. CaX zeolite was

TABLE I  
Composition, Surface Area, and Bulk Density of Catalysts<sup>a</sup>

Catalysts	Surface area (m <sup>2</sup> /g)	Bulk density (g/cm <sup>3</sup> )	Catalysts	Surface area (m <sup>2</sup> /g)	Bulk density (g/cm <sup>3</sup> )
CaX zeolite	466	0.65	Al <sub>2</sub> O <sub>3</sub> -20% B <sub>2</sub> O <sub>3</sub>	127	0.57 <sub>8</sub>
16% ZnCl <sub>2</sub> -SiO <sub>2</sub> <sup>b</sup>	—	0.68	-10% ZnO	191	0.54 <sub>6</sub>
$\gamma$ -Al <sub>2</sub> O <sub>3</sub>	62	0.56 <sub>6</sub>	-15% MgO	223	0.49 <sub>5</sub>
$\eta$ -Al <sub>2</sub> O <sub>3</sub>	196	0.73 <sub>9</sub>	SiO <sub>2</sub> -13% Al <sub>2</sub> O <sub>3</sub>	160	0.50
TiO <sub>2</sub>	11	0.74 <sub>7</sub>	-53% TiO <sub>2</sub>	86	0.56 <sub>1</sub>
ZrO <sub>2</sub>	21	1.03	-30% ZnO	69	0.18 <sub>6</sub>
SiO <sub>2</sub>	133	0.52	-20% ThO <sub>2</sub>	119	0.39 <sub>7</sub>
MgO	59	0.33	-25% MgO	254	0.47 <sub>2</sub>
			TiO <sub>2</sub> -60% ZrO <sub>2</sub>	17	1.02
			-20% MgO	20	0.64

<sup>a</sup> Calcined at 500°C in air for 5 hr. Composition is given in wt%.

<sup>b</sup> Dried at 70°C, not calcined.

Linde molecular sieve 10X, calcined at 500°C.

*Properties of catalysts.* Surface area was measured by nitrogen adsorption. An apparatus of Shibata P-700 was used. Acidity distribution for SiO<sub>2</sub>-MgO was measured by *n*-butylamine titration in benzene (17), using Hammett indicators (p*K<sub>a</sub>*): methyl red (4.8), *p*-dimethylaminoazobenzene (3.3), benzeneazodiphenylamine (1.5), and benzalacetophenone (-5.6). Reproducible acidity was obtained by calcination of the powdered sample at 300°C under dry air for 1 hr immediately before titration.

## RESULTS AND DISCUSSION

### Indole Synthesis over Various Oxides

Catalysts prepared and their surface areas with bulk density are summarized in Table 1. In reference to the liquid-phase Fischer synthesis, it seemed likely that acidic catalysts might be favorable also in the vapor-phase cyclization to indole. However, strongly acidic CaX zeolite, previously claimed to give  $\alpha$ -methylindole by Venuto and Landis (10), was disappointing as shown in Fig. 1(a). The cleavage of the N-N bond in acetaldehyde phenylhydrazone was predominant to yield aniline with rapid deactivation and a trace of indole. Zinc chloride is also an acidic material and the well-known Arbusov catalyst (12) in the liquid-phase Fischer synthesis. Zinc chloride on silica gave a constant yield of 37% indole with 27% aniline during 2 hr on stream at 300°C as shown in Fig. 1(b), in good agreement with the results of Naka-

zaki and Yamamoto (9). However, this catalyst seems to be unfavorable for the vapor-phase reaction at high temperature. Formation of indole accompanies the elimination of 2-nitrogen in phenylhydrazone as ammonia (7), which causes the loss of chlorine in the catalyst. Plugging of the outlet of the reactor by white ammonium chloride powder made it difficult to continue steady operation.

*Single oxides.* Results for vapor-phase indole synthesis over various oxides are compared in Fig. 2. In the case of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> (a), the initial yield of indole was comparable with that of Kanterov *et al.* (8), but this catalyst degenerated with time, whereas  $\eta$ -Al<sub>2</sub>O<sub>3</sub> (b) showed an excellent stability to give 59% indole with 35% aniline. Although a high conversion of hydrazone was observed to continue for 3 hr on stream over TiO<sub>2</sub> (c) and ZrO<sub>2</sub> (d), the detected products,<sup>2</sup> indole and aniline, could not account for the balance. During the time of operation for TiO<sub>2</sub> and ZrO<sub>2</sub>, a white mist passed through the ice-cooled toluene trap. SiO<sub>2</sub> (e) decomposed hydrazone to aniline with deactivation and gave only 5% indole.

It must be noticed that MgO (f) gave indole in a rather high yield. Although the activity degenerated with time, the fact that basic species catalyze the cyclization of phenylhydrazone seems to be less common in the literature. To our knowledge, the formation of 2,3-dimethylindole (R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub>) in 68% yield from methyl ethyl ketone phenylhydrazone in refluxing ethylene glycol in the presence of 2% sodium hydroxide described by Fitzpatrick and Hiser (13) is the only case. However, they obtained a better yield (70%) for the same reaction in ethylene glycol without alkali, suggesting the thermal indolization in a high boiling solvent (14).

To check for thermal effects in the vapor-

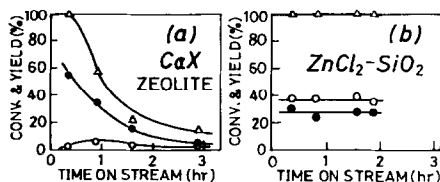


Fig. 1. Vapor-phase catalytic indole synthesis over CaX zeolite and zinc chloride on silica. Temperature, 300°C; feed pressure of acetaldehyde phenylhydrazone, 0.05 atm; flow rate, 3.6 liters/hr; space velocity, 1000 hr<sup>-1</sup>. ( $\Delta$ ) Hydrazone conversion; ( $\circ$ ) indole yield; ( $\bullet$ ) aniline yield.

<sup>2</sup> Retention times of aniline, indole, and acetaldehyde phenylhydrazone were 2.6, 12.5, and 15.8 min, respectively. Two peaks appeared at 4.3 and 5.2 min as strangers, but the amounts were too small to account for the balance.

phase approach, the reactions over glass flakes (10–14 mesh) at the same conditions were carried out at 200–300°C. About 6% of hydrazone was converted at 300°C to yield 3–4% aniline; no indole was detected.

**Binary oxides.** It is well known that binary oxides generally show surface properties quite different from the composing oxides (15).  $\text{SiO}_2\text{-Al}_2\text{O}_3$  exhibits strong acidity while  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  are neutral and slightly acidic, respectively.  $\text{MgO}$  is a typical basic oxide, but  $\text{SiO}_2\text{-MgO}$  has many more acidic sites, though weak in strength, than  $\text{SiO}_2\text{-Al}_2\text{O}_3$ . Literature values (16–19) of the acidity distribution of various binary oxides are shown in Fig. 3.

Among alumina-based oxide catalysts,  $\eta\text{-Al}_2\text{O}_3$  itself was most favorable. Contamination of another oxide decreased the yield of indole as shown in Fig. 4. The effect seems rather slight in the case of weakly acidic  $\text{ZnO-Al}_2\text{O}_3$  (a) and  $\text{Al}_2\text{O}_3\text{-MgO}$  (b). Drastic decreases in indole yield with rapid deactivation are shown for strongly acidic  $\text{Al}_2\text{O}_3\text{-B}_2\text{O}_3$  (c) and  $\text{SiO}_2\text{-Al}_2\text{O}_3$  (d). Similar results were observed for silica-based binary oxides as shown in Fig. 5.  $\text{SiO}_2\text{-MgO}$

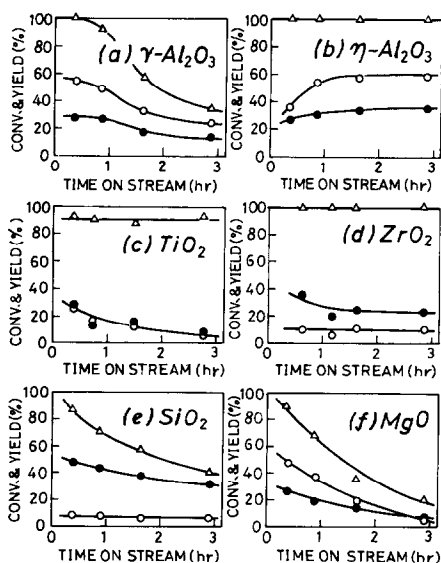


FIG. 2. Vapor-phase catalytic indole synthesis over single oxides. Conditions and symbols are the same as in Fig. 1.

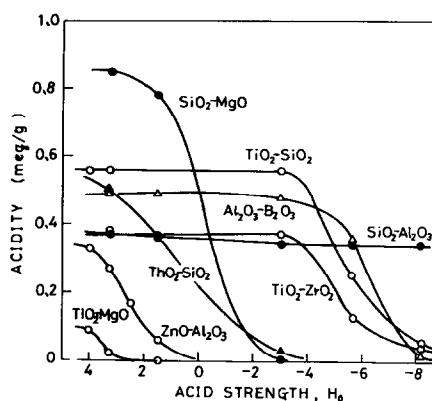


FIG. 3. Literature values of acidity distribution of binary oxides. (O) Shibata *et al.* (16); (●) Benesi (17); (Δ) Takamiya *et al.* (18); (▲) Walvekar and Halgeri (19).

(b) was found to be an excellent catalyst comparable with  $\eta\text{-Al}_2\text{O}_3$ . Although  $\text{SiO}_2$  itself gave only 5% indole in contrast to  $\text{Al}_2\text{O}_3$ , combination with another oxide favored indole for weakly acidic  $\text{ThO}_2\text{-SiO}_2$  (a) and  $\text{SiO}_2\text{-MgO}$  (b), while it was unfavorable for strongly acidic  $\text{TiO}_2\text{-SiO}_2$  (c). Among titania-based binary oxides,  $\text{TiO}_2\text{-ZrO}_2$  and  $\text{TiO}_2\text{-MgO}$  caused no improvements as shown in Figs. 6(a) and (b).

Acid strength seems to be a rough measure for screening of catalysts favorable for indole in the vapor-phase Fischer synthesis. Initial yield of indole for weakly acidic catalysts, such as  $\gamma\text{-Al}_2\text{O}_3$  and  $\eta\text{-Al}_2\text{O}_3$ ,  $\text{SiO}_2\text{-MgO}$ ,  $\text{ThO}_2\text{-SiO}_2$ ,  $\text{ZnO-SiO}_2$ ,  $\text{Al}_2\text{O}_3\text{-}$

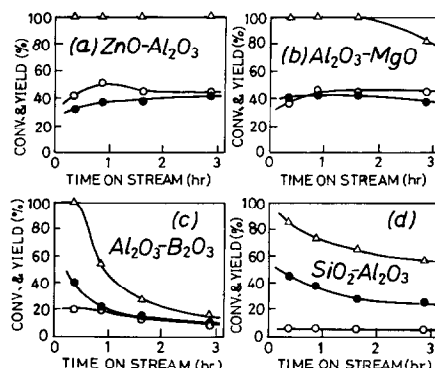


FIG. 4. Vapor-phase catalytic indole synthesis over alumina-based binary oxides. Conditions and symbols are the same as in Fig. 1.

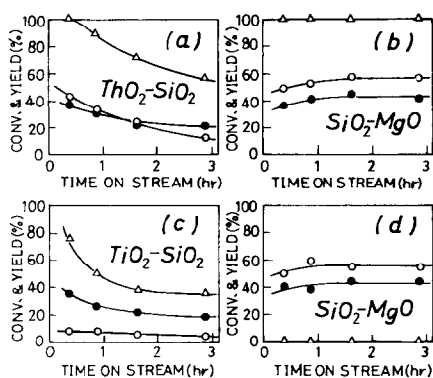


FIG. 5. Vapor-phase catalytic indole synthesis over silica-based binary oxides. Conditions and symbols are the same as in Fig. 1.

$MgO$ , and  $TiO_2-MgO$ , lies in the range of 40–60%. Strongly acidic catalysts, such as  $CaX$  zeolite,  $Al_2O_3-B_2O_3$ ,  $SiO_2-Al_2O_3$ ,  $TiO_2-SiO_2$ , and  $TiO_2-ZrO_2$ , predominantly gave aniline with rapid deactivation, the indole yield being in the range of 5–20%.

On the contrary, Suvorov *et al.* (20) described the activity of  $\gamma-Al_2O_3$  of increased acidity: the reaction temperature for maximum indole yield was 250°C for strongly acidic catalyst containing 4.8% fluoride and 310°C for unfluorinated  $Al_2O_3$ . However, strong adsorption of nitrogen bases (hydrazone, aniline, and ammonia) possibly retards the site regeneration. It seems rather reasonable that conversion of hydrazone decreased abruptly at about 1 hr on stream for strongly acidic  $CaX$  zeolite or  $Al_2O_3-B_2O_3$ . Adsorption of pyridine over  $SiO_2-MgO$  was reversible at 300°C, while it was irreversible for  $Al_2O_3-B_2O_3$  (21). Catalysts used were brown to black in color. Degeneration of activity while on stream

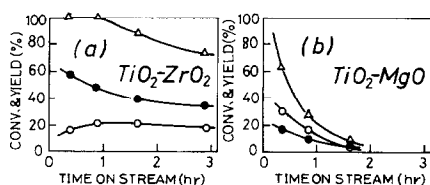


FIG. 6. Vapor-phase catalytic indole synthesis over titania-based binary oxides. Conditions and symbols are the same as in Fig. 1.

might be attributed in part to polymeric deposit.

Acidic properties of oxide catalysts include various factors, such as strength, amount, and their type (Brønsted or Lewis), and are dependent on calcination temperature, composition, etc. Acidity of the present  $SiO_2-MgO$  showed a maximum at 25%  $MgO$  (21). Effect of calcination temperature of  $SiO_2-25\% MgO$  on the acidity distribution and the results for indole synthesis are given in Fig. 7. The amounts of acidic sites showed a maximum at 400°C for  $H_0 \cong 3.3$  and at 550°C for  $H_0 \cong 1.5$ , and decreased above 650°C probably due to decrease in surface area; values of 725 and 800°C were 101 and 36  $m^2/g$ , respectively. Calcination of  $SiO_2-MgO$  above 600°C resulted in a drastic decrease in indole yield, while a slight effect was observed for aniline up to about 725°C. Effect of reaction temperature for  $SiO_2-MgO$  calcined at 500°C is shown in Fig. 8, where the maximum yield of indole was obtained at 275°C.

#### Indole from Paraldehyde and Phenylhydrazine

Phenylhydrazones are readily subject to oxidation to form Busch peroxide (22). The solution will change in color from yellow to

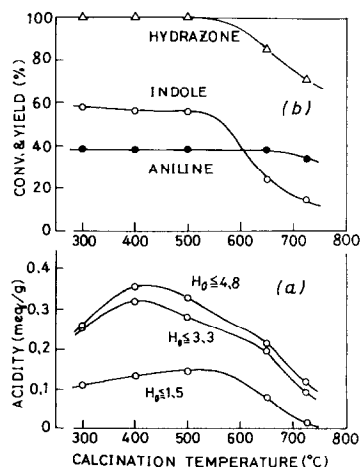


FIG. 7. Effect of calcination temperature on the acidity distribution of  $SiO_2-MgO$  (a) and the results for vapor-phase indole synthesis (b). Reaction temperature, 280°C; flow conditions, same as Fig. 1.

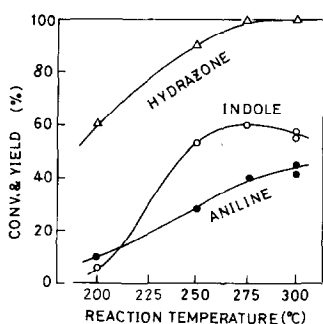
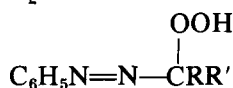
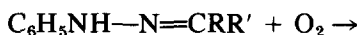


FIG. 8. Effect of reaction temperature on the vapor-phase indole synthesis over  $\text{SiO}_2\text{-MgO}$ . Flow conditions, same as Fig. 1.

red, if not carefully handled to avoid contact with air.



Supplying a benzene solution of paraldehyde and phenylhydrazine in a molar ratio of 1 : 3 over  $\text{SiO}_2\text{-MgO}$  at  $300^\circ\text{C}$ , essentially the same results compared with previously prepared hydrazone were obtained as shown in Figs. 5(b) and (d). Paraldehyde, a ring trimer of acetaldehyde, has no carbonyl character and does not react with phenylhydrazine at room temperature. This makes it easy to handle. The results given in Fig. 5(d) show that the decomposition to monomeric aldehyde with succeeding for-

mation of hydrazone is sufficiently rapid at the high-temperature catalyst surface.

#### $\alpha$ -Methylindole and Skatole

$\alpha$ -Methylindole and skatole formation from the corresponding phenylhydrazones are the early examples of the Fischer synthesis. A mixture of acetone phenylhydrazone with a fivefold excess of  $\text{ZnCl}_2$  heated to  $180^\circ\text{C}$ , until the vigorous reaction ceased, gave  $\alpha$ -methylindole in 60% yield (23). Similarly, skatole was obtained in 38% yield (23).

Vapor-phase approach gave the indole derivatives in high yield. The results are shown in Fig. 9.  $\text{ThO}_2\text{-SiO}_2$  (a) gave a constant yield of  $\alpha$ -methylindole of 66% with 15% aniline, while it degenerated with time in the indole synthesis.  $\text{SiO}_2\text{-MgO}$ , an excellent catalyst for indole, gave 76%  $\alpha$ -methylindole with 8% aniline (b), and 88% skatole with 11% aniline (c). The rapid deactivation of  $\text{CaX}$  zeolite in the attempted cyclization of acetone phenylhydrazone was observed similarly as in acetaldehyde.

#### Indole-3-acetonitrile

Indole-3-acetonitrile is an important precursor for tryptamine (24) and indole-3-acetic acid (25). Tanaka (26) obtained indole-3-acetic acid in 12% yield by the liquid-phase cyclization of  $\beta$ -cyanopropionaldehyde phenylhydrazone to indole-3-acetonitrile at  $150^\circ\text{C}$  in the presence of zinc chloride and subsequent alkaline hydrolysis.

Higher yield of indoles in the vapor-phase approach of Fischer synthesis moved us to apply  $\text{SiO}_2\text{-MgO}$  as a catalyst for the synthesis of indole-3-acetonitrile. The carbonyl moiety is now available as the acetal in industrial scale (27). However, the results were not satisfactory as shown in Fig. 9(d). Degeneration by the deposition of tarry products seems to be unavoidable. The composition of thermoplastic tar agreed well with the starting phenylhydrazone, suggesting the polymerization of the isomer with acrylonitrile structure.

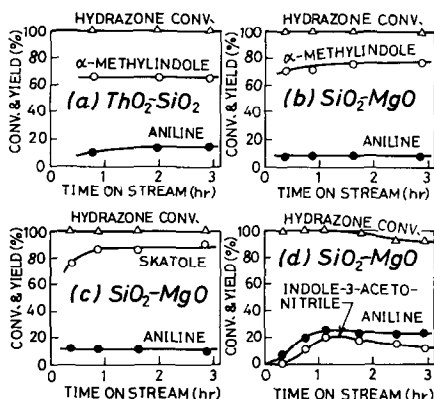


FIG. 9. Vapor-phase catalytic synthesis of indole derivatives. Temperature,  $300^\circ\text{C}$ ; feed pressure of hydrazone (atm) and space velocity ( $\text{hr}^{-1}$ ): (a) 0.08 and 500; (b, c) 0.05 and 1000; (d) 0.01 and 5000.

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