Notes

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Formic Acid Reduction. XI.[1] Reduction of Schiff Bases

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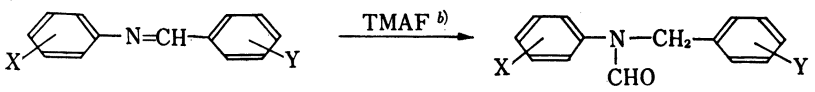
The reduction of Schiff base leading to secondary amine is a very valuable synthetic method. The formic acid reductions of Schiff bases have been indicated in scattered reports.[3,4] Normally, the reduction is carried out by heating with formic acid alone or in the presence of basic reagent such as sodium formate or triethylamine. However, because of high sensitivity of the Schiff base to hydrolysis even by trace of water, yield of secondary amine becomes poor, as reported in most of the published papers.

Table I. TMAF Reduction[a] of N-Benzylideneanilines



Substituents X	Substituents Y	Reaction time (hr)	Yield (%)
p-NO_2	H	2.5	98[c]
p-CO_2H	H	1.5	97
p-Cl	H	1.5	97
H	H	1.5	96
p-CH_3	H	1.25	98
p-OCH_3	H	1.0	97
p-OH	H	1.0	94
m-NO_2	H	3.0	80[d]
m-Cl	H	1.5	99
m-CH_3	H	1.0	99
H	*p*-NO_2	2.0	98
H	*p*-Cl	1.5	94
H	*p*-CH_3	1.0	99
H	*p*-OCH_3	0.75	98
H	*p*-OH	0.75	99
H	*m*-NO_2	2.5	100
H	*m*-Cl	1.5	99
H	*m*-OH	1.0	100

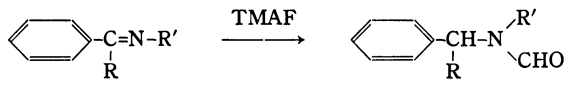
a) Substrate to TMAF (as HCO_2H) molar proportion is 1:30. reaction Temp., 100°
b) Yield based on the product isolated.
c) The whole product was obtained as the free amine not formylated.
d) Additionally N-benzyl-*m*-nitroanilline was obtained in 10% yield.

1) Part X: M. Sekiya and K. Suzuki *Chem. Pharm. Bull.* (Tokyo), **19**, 1540 (1971).
2) Location: *2-2-1 Oshika, Shizuoka.*
3) H.T. Clarke, H.B. Gillespie and S.Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1934); R. Baltzly and O. Kauder, *J. Org. Chem.*, **16**, 173 (1951); Z. Eckstein and A. Lukasiewicz, *Bull. Acad. Polon. Sci. Ser. Sci. Chim., Geol. et Geograph*, **7**, 789 (1959)[*C.A.*, **54**, 24679 (1960)]; *idem, ibid.*, **7**, 797 (1959)[*C.A.*, **54**, 24680 (1960)]; *idem, Prezemyst. Chem.*, **39**, 367 (1960)[C.A., **55**, 3501 (1961)].
4) E.R. Alexander and R.B. Wildman, *J. Am. Chem. Soc.*, **70**, 1187 (1948).

Alexander[4] reduced N-benzylideneaniline with the formate reagent, which was prepared by evaporation of aqueous formic acid solution neutralized with triethylamine, in fair yield of benzylaniline hydrochloride. From this laboratory the several salts, which may be represented by the general formula $5HCOOH \cdot 2NR_3$ and which are polar liquids of constant high boiling point, have been developed as reducing agents. Using $5HCOOH \cdot 2N(CH_3)_3$, refered to as TMAF, good adaptability of this reagent for the reductions of Schiff bases has now been found. A variety of Schiff bases derived from aromatic aldehydes and ketones can be conveniently reduced with this reagent to N-formylated secondary amines in excellent yields with selectivities. In general, the reactions are carried out by heating the substrate along with excess of TMAF, the process of which can be checked by noting carbon dioxide emission. Our results and the reaction condition are summarized in Table I and Table II.

All of the reaction products, the N-formylated secondary amines obtained in the present work, have not been previously described.

Table II. TMAF Reduction[a] of N-α-Alkylbenzylideneamines



Substrate R	Substrate R'	Reaction Temp., °C	Reaction time, hr	Yield[b] (%)
C_2H_5	$C_6H_5CH_2$	95—100[c] 120—125	0.5 2	88
C_2H_5	$C_6H_5CH_2$	95—100	0.5	57[d]
$C_6H_5CH_2$	$C_6H_5CH_2$	95—100[c] 120—125	0.5 2	86
$C_6H_5CH_2$	$C_6H_5CH_2$	95—100	0.5	49[e]
$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	95—100[c] 120—125	0.5 2	87
$C_6H_5CH_2$	$CH_3CH_2CH_2CH_2$	95—100[c] 120—125	0.5 2	86
CH_3	$C_6H_5CH_2CH_2$	95—100[c] 120—125	0.5 2	87

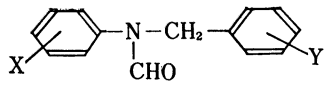
a) Substrate to TMAF (as HCO_2H) molar proportion is 1:20.
b) Yield based on the product isolated.
c) heating at 95—100° for 0.5 hr and succeedingly at 120—125° for 2 hr
d) Additionally the free amine not formylated was obtained in 29% yeild.
e) Additionally the free amine not formylated was obtained in 32% yield.

Experimental

Preparation of N-Benzylideneanilines——Equimolar amounts of aromatic aldehyde and amine were allowed to react in benzene solution at room temperature. K_2CO_3 was added so as to remove the water formed by the reaction. Evaporation of the dry benzene solution followed by recrystallization or distillation gave the following materials, which were used for the TMAF reduction: N-benzylidene-*p*-nitroaniline,[5] mp 114—117°; *p*-benzylideneaminobenzoic acid, mp 191—193°; N-benzylidene-*p*-chloroaniline,[5] mp 61—63°; N-benzylideneaniline,[5] mp 48—49°; N-benzylidene-*p*-toluidine,[5] mp 34—36°; N-benzylidene-*p*-anisidine,[5] mp 71—72.5°; N-benzylidene-*p*-hydroxyaniline,[6] mp 184—185°; N-benzylidene-*m*-nitroaniline,[7] mp 69—72°; N-benzylidene-*m*-chloroaniline,[8] bp 142—144° (3 mmHg); N-benzylidene-*m*-toluidine,[5] bp 153—156° (4 mmHg); N-*p*-nitrobenzylideneaniline,[9] mp 86—90°; N-*p*-chlorobenzylideneaniline,[5] mp 62—

5) A.Roe and J.A. Montgomery, *J. Am. Chem. Soc.*, **75**, 910 (1953).
6) H.H. Keasling and F.W. Schueler, *J. Am. Pharm. Assoc.*, **39**, 87 (1950).
7) G.Smets and A.Delvaux *Bull. Soc. Chim. Belges.*, **56**, 106 (1947).
8) Luciano do Amaral, W.A. Sandsrom and E.H. Cordes, *J. Am. Chem. Soc.*, **88**, 2225 (1966).
9) W. Paterson and G.R. Proctor, *J. Chem. Soc.*, **1965**, 485.

TABLE III. N-Benzylformanilides



Substituent X	Substituent Y	Appearance (recryst. solv.)	mp °C	bp °C/mmHg	IR ν_{max}^{KBr} cm^{-1} (>NCHO)	Formula	Elemental analysis Calcd. C	H	N	Cl	Found C	H	N	Cl
p-CO_2H	H	white powder (EtOH)	191—193		1675	$C_{15}H_{13}O_3N$	70.85	5.13	5.49		70.41	5.17	5.44	
p-Cl	H	colorless prisms (iso-PrOH)	66—67	170—175/0.03	1670	$C_{14}H_{12}ONCl$	68.44	4.92	5.70	14.43	68.33	4.92	5.94	14.38
H	H	colorless needles (iso-PrOH)	47—48	139—142/0.1	1660	$C_{14}H_{13}ON$	79.59	6.20	6.63		79.77	6.10	6.91	
p-CH_3	H	colorless needles (iso-PrOH)	62—63	148—151/0.01	1670	$C_{15}H_{15}ON$	79.97	6.71	6.22		80.23	6.68	6.26	
p-OCH_3	H	colorless prisms (iso-PrOH)	41.5—42	173—176/0.07	1670	$C_{15}H_{15}O_2N$	74.66	6.27	5.81		74.48	6.31	5.93	
p-OH	H	colorless prisms (benzene)	127—128		1665	$C_{14}H_{13}O_2N$	73.99	5.77	6.16		74.17	5.72	6.04	
m-NO_2	H	reddish oil		230—236/4	1670[a]	$C_{14}H_{12}O_3N_2$	65.63	4.72	10.93		65.27	4.84	11.38	
m-Cl	H	colorless needles (iso-PrOH)	36—38	179—185/3	1670	$C_{14}H_{12}ONCl$	68.44	4.92	5.70	14.43	68.17	4.91	5.89	14.89
m-CH_3	H	colorless prisms (iso-PrOH)	58—59	151—156/4	1670	$C_{15}H_{15}ON$	79.97	6.71	6.22		80.09	6.68	6.11	
H	*p*-NO_2	colorless prisms (ligroin–benzene)	97—99		1665	$C_{14}H_{12}O_3N_2$	65.63	4.72	10.93		65.63	4.75	11.07	
H	*p*-Cl	colorless needles (iso-PrOH)	68.5—69.5		1660	$C_{14}H_{12}ONCl$	68.44	4.92	5.70	14.43	68.24	4.98	5.65	14.55
H	*p*-CH_3	colorless needles (iso-PrOH)	40—41	159—167/3	1670	$C_{15}H_{15}ON$	79.97	6.71	6.22		80.03	6.79	6.08	
H	*p*-OCH_3	colorless prisms (iso-PrOH)	88—89		1670	$C_{15}H_{15}O_2N$	74.66	6.27	5.81		74.41	6.14	5.76	
H	*p*-OH	colorless needles (iso-PrOH)	140—141		1650	$C_{14}H_{13}O_2N$	73.99	5.77	6.16		73.90	5.81	6.08	
H	*m*-NO_2	yellow needles (iso-PrOH)	95—97		1670	$C_{14}H_{12}O_3N_2$	65.63	4.72	10.93		65.88	4.78	10.87	
H	*m*-Cl	colorless needles (iso-PrOH)	41—43	168—175/3	1670	$C_{14}H_{12}ONCl$	68.44	4.92	5.70	14.43	68.38	4.98	5.66	14.77
H	*m*-OH	colorless needles (iso-PrOH)	103—104		1660	$C_{14}H_{13}O_2N$	73.99	5.77	6.16		73.89	5.68	6.32	

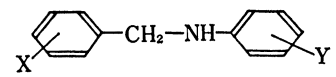
a) This was measured as liquid film.

64°; N-*p*-methylbenzylideneaniline,[6] mp 42—43°; N-*p*-methoxybenzylideneaniline,[5] mp 63—64°; N-*p*-hydroxybenzylideneaniline,[6] mp 190—192°; N-*m*-nitrobenzylideneaniline, mp 65—66°; N-*m*-chlorobenzylideneaniline,[5] bp 184—192° (15 mmHg); N-*m*-hydroxybenzylideneaniline,[10] mp 89—90°.

TMAF Reduction of N-Benzylideneanilines——General Procedure: A mixture of N-benzylideneaniline (0.08 mole) and TMAF in 1:30 (the latter is based on HCO_2H) molar proportion was heated with constant stirring at 95—100° on a boiling water bath. By means of passing a stream of air free from CO_2, emission of CO_2 was checked by Ba $(OH)_2$ solution. After subsidence of the CO_2 emission, the reaction solution was evaporated under reduced pressure. The resulting residue was washed with 5% aqueous ammonia and recrystallized from requisite solvent, or, when was a liquid, extracted with benzene and, after drying and removal of benzene, the residual liquid was distilled under reduced pressure. In most cases the product was obtained as the corresponding N-benzylformanilides. In the run with N-benzylidene-*p*-nitroaniline the product was obtained as not formylated N-benzyl-*p*-nitroaniline and, in the run with N-benzylidene-*m*-nitroaniline, both N-(*m*-nitrobenzyl)-formanilide and N-benzyl-*m*-nitroaniline were obtained. In all runs the yields of the reduction products were almost theoretical as seen in Table I. Physical and analytical data of the N-benzylformanilides and N-benzylanilines obtained by hydrolysis are recorded in Table III and IV.

Preparation of N-α-Alkylbenzylideneamines——On referring to the previous report,[11] equimolar amount of aromatic ketone and amine were allowed to react in benzene solution in the presence of *p*-toluenesulfonic

TABLE IV. N-Benzylanilines



Substituents X	Substituents Y	Appearance (recryst. solv.)	mp (lit.) °C	bp (lit.) °C/mmHg
p-NO_2	H	yellow plates (ligroin)	70—71 (70—71)[a]	
p-Cl	H	pale yellow oil		198—200/12[b]
p-CH_3	H	colorless plates (ligroin)	44—45 (42—45)[c]	
p-OCH_3	H	colorless plates (ligroin)	63—64 (63.5—64)[d]	
m-NO_2	H	orange prisms (iso-PrOH)	83.5—84.5 (84—84.5)[e]	
m-Cl	H	colorless oil		198—201/14 (144—145/2)[5]
m-OH	H	colorless plates (ligroin)	103—104 (101—103)[5]	
H	H	pale yellow plates (iso-PrOH)	37—38 (37—38)[a]	172—174/14
H	*p*-NO_2	yellow plates (benzene)	103—104.5 (103.5—104)[e]	
H	*p*-Cl	colorless prisms (ligroin)	47—48 (48.5—49)[d]	
H	*p*-CH_3	colorless oil		174—178/12 (180/10)[f]
H	*p*-OCH_3	colorless leaflets (ligroin)	50—51 (47.3—48)[d]	
H	*p*-OH	colorless leaflets (ligroin)	88—89 (88—89)[d]	
H	*m*-NO_2	yellow plates (EtOH)	106—109 (106—106.5)[e]	
H	*m*-Cl	colorless oil		198—200/12 (172—173/3)[g]
H	*m*-CH_3	colorless oil		178—181/12 (164—165/4)[g]

a) S. Ikegami and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1389 (1966).
b) *Anal.* Calcd. for $C_{13}H_{12}NCl$: C, 71.72; H, 5.55; N, 6.43; Cl, 16.28. Found: C, 71.79; H, 5.66; N, 6.14; Cl, 15.95
IR $\nu_{max}^{liq.}$ cm^{-1}: 3410 (NH)
c) J.O. Jilek, J. Pomykecek and M. Protiva, *Chem. Listy*, **48**, 232 (1954) [*C.A.*, **49**, 2425 (1955)]
d) J.H. Billman and J.W. McDowell, *J. Org. Chem.*, **26**, 143 (1961)
e) J.H. Billman and A.C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957)
f) S. Murahashi, S. Horiie and T. Jo, *Nippon Kagaku Zasshi*, **79**, 68 (1958)
g) V.I. Stavrovskaya, *Zhur. Obsh. Khim.*, **24**, 1038 (1954) [*C.A.*, **49**, 8839 (1955)]

10) E. Bambergar and J. Muller, Ann., **313**, 112 (1900).
11) C.G. Overberger, N.P. Marullo and R.G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1376 (1961).

acid at the refluxing temperature for about 30 hr. The following known and unknown materials were prepared by this method and used for TMAF reduction.

N-α-Ethylbenzylidenebenzylamine: Liquid, bp 137—139° (0.4 mmHg), [lit.,[12] bp 127° (0.1 mmHg)]. n_D^{15} 1.5860. IR $\nu_{max}^{liq.}$ cm^{-1}: 1627 (C=N). *Anal.* Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.80; H, 7.55; N, 6.47.

N-α-Benzylbenzylidenebenzylamine: Liquid, bp 169—171° (0.08 mmHg). n_D^{15} 1.6288. IR $\nu_{max}^{liq.}$ cm^{-1}: 1626 (C=N). *Anal.* Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.02; H, 6.65; N, 6.46.

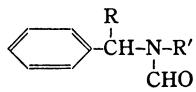
N-α-Benzylbenzylidene-β-phenethylamine: Liquid, bp 172—174° (0.02 mmHg). n_D^{28} 1.5749. IR $\nu_{max}^{liq.}$ cm^{-1}: 1626 (C=N). *Anal.* Calcd. for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 87.60; H, 6.98; N, 4.88.

N-α-Benzylbenzylidenebutylamine: Liquid, bp 132—134° (0.3 mmHg). n_D^{18} 1.5806. IR $\nu_{max}^{liq.}$ cm^{-1}: 1628 (C=N). *Anal.* Calcd. for $C_{18}N_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.43; H, 8.17; N, 4.92.

N-α-Methylbenzylidene-β-phenethylamine: Liquid, bp 134—136° (0.5 mmHg). n_D^{13} 1.5869. IR $\nu_{max}^{liq.}$ cm^{-1}: 1630 (C=N). *Anal.* Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.75; H, 7.60; N, 6.40.

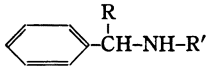
TMAF Reduction of N-α-Alkylbenzylideneamines——General Procedure: A mixture of N-α-alkylbenzylideneamine and TMAF in 1:20 (the latter is based on HCO_2H) molar proportion was heated with constant stirring at 95—100° on a boiling water bath, while considerable emission of CO_2 was checked by test with

Table V. N-Alkyl-N-(α-alkylbenzyl)formamides



R	R′	bp °C/mmHg	n_D (°C)	IR $\nu_{max}^{liq.}$ cm^{-1} (C=O)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
C_2H_5	$C_6H_5CH_2$	196—201/2	1.5675 (19)	1668	$C_{17}H_{19}ON$	80.57	7.56	5.53	80.46	7.50	5.67
$C_6H_5CH_2$	$C_6H_5CH_2$	192—194/0.02	1.6051 (19)	1668	$C_{22}H_{21}ON$	83.77	6.71	4.44	84.27	6.71	4.46
$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	205—210/0.02	1.5879 (30)	1667	$C_{23}H_{23}ON$	83.85	7.04	4.25	83.54	7.04	4.11
$C_6H_5CH_2$	$CH_3(CH_2)_2CH_2$	160—163/0.5	1.5680 (14)	1666	$C_{19}H_{23}ON$	80.25	8.61	5.20	80.20	8.56	5.31
CH_3	$C_6H_5CH_2CH_2$	190—193/0.4	1.5984 (19)	1668	$C_{17}H_{19}ON$	80.57	7.56	6.32	81.00	7.50	6.20

Table VI. N-Alkyl-α-alkylbenzylamines



R	R′	Appearance (recryst. solv.)	mp °C	bp °C/mmHg	n_D^{19}	IR ν_{max} cm^{-1} (>NH)	Formula		Analysis (%) C	H	N
C_2H_5	$C_6H_5CH_2$			129—132/2[a]	1.5591	3284 (liq.)	$C_{16}H_{19}N$	Calcd.	85.28	8.50	6.22
								Found	84.88	8.37	6.60
$C_6H_5CH_2$	$C_6H_5CH_2$	colorless granulas (petr. ether)	51—53	165—167/0.5		3253 (KBr)	$C_{21}H_{21}N$	Calcd.	87.76	7.35	4.87
								Found	87.27	7.31	5.16
$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	colorless granulas (petr. ether)	30	170—174/0.35		3396 (KBr)	$C_{22}H_{23}N$	Calcd.	87.66	7.69	4.65
								Found	87.78	7.69	4.82
$C_6H_5CH_2$	$CH_3(CH_2)_2CH_2$			127—128/0.5	1.5515	3290 (liq.)	$C_{18}H_{23}N$	Calcd.	85.32	9.15	5.26
								Found	85.23	8.50	5.26
CH_3	$C_6H_5CH_2CH_2$			179—182/2	1.5561	3272 (liq.)	$C_{16}H_{19}N$	Calcd.	85.28	8.50	6.22
								Found	85.00	8.65	6.20

a) P. Grammaticakis, *Compt. Rend.*, **207**, 1224 (1938) [*C.A.*, **33**, 2494 (1939)], bp 135° (1 mmHg)

12) R.P. Ossorio, F.G. Herrera and A. Hidalgo, *Anales Real Soc. Españ. Fis. y Quim.* (Madrid), **52B**, 123 (1956) [*C.A.*, **51**, 1056 (1957)].

$Ba(OH)_2$ solution. Although the emission of CO_2 subsided within 30 min in most cases, N-formylation of the reduction product was inperfect under this condition (see Table II). Succeedingly the mixture was heated for additional two hour at 120—125°. After this, the reaction solution was evaporated under reduced pressure to remove TMAF. The residual liquid was distilled under high reduced pressure to give the product, N-alkyl-N-(α-alkylbenzyl)formamide. In all the runs yields of the product are about 90% as shown in Table II. Physical and analytical data of the products and the corresponding free N-alkyl-α-alkylbenzylamines are recorded in Table V and VI.

Acknowledgement We are grateful to the members of Analytical Center of this college for the elemental analyses.

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C-2 Hydroxylation of 2-Deuterioestrogen in the Rat. Lack of "NIH Shift"[1]

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(Received February 1, 1971)

In a previous paper the occurrence of "NIH shift" during aromatic ring hydroxylation with 3-deoxyestrone has been reported.[3] Further interest in hydroxylation mechanism prompted us to examine whether or not *in vivo* formation of the catechol estrogen would similarly be accompanied by a migration of the heavy isotope labeled at C-2.

For this purpose an initial project was focused to the preparation of 2-deuterioestrogen as a substrate. First, 2-hydroxyestrone 3-benzyl ether (I) derivable from estrone in several steps[4] was taken as a starting compound. Condensation with 1-phenyl-5-chlorotetrazole in the presence of potassium carbonate[5] provided phenyltetrazolyl ether (II) in satisfactory yield. Hydrogenolysis over palladium-on-barium carbonate with use of deuterium gas proceeded readily to give 2-deuterioestrone (IIIa).

This synthetic route, however, appeared to be of disadvantage in the availability of the starting material. Accordingly, an attempt was then made on the utilization of 2-haloestrogen for the preparation of the specifically deuterated substrate. Treatment of estradiol with bromine in acetic acid resulted in formation of a mixture of 2- and 4-bromo derivatives in a ratio of *ca.* 1 to 1.[6] The isolation of the desired 2-bromo isomer (IV) could be attained by preparative thin-layer chromatography (TLC) upon multiple development. However, separation of these two positional isomers was a tedious work because of close similarity in their chromatographic behaviors. Therefore, the more suitable method for preparation of 2-halo derivative was explored. When estrone was treated with iodine in the presence of mercuric acetate as catalyst,[7] halogenation occurred selectively at C-2 yielding

1) This paper constitutes Part XLVII of the series entitled, "Analytical Chemical Studies on Steroids"; Part XLVI: T. Nambara and M. Numazawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 990 (1971). When this work was almost completed we learned a paper dealing with the preparation of C-2 isotope labeled estradiol from 2-bromo derivative and the loss of tritium during *in vivo* hydroxylation at C-2 in man (J. Fishman, H. Guzik, and L. Hellman, *Biochemistry*, **9**, 1593 (1970)).
2) Location: *Aobayama, Sendai.*
3) T. Nambara, M. Numazawa, and S. Akiyama, *Chem. Pharm. Bull.* (Tokyo), **19**, 153 (1971).
4) T. Nambara, S. Honma, and S. Akiyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 474 (1970).
5) W.J. Musliner and J.W. Gates, Jr., *J. Am. Chem. Soc.*, **88**, 4271 (1966).
6) T. Utne, R.B. Jobson, and F.W. Landgraf, *J. Org. Chem.*, **33**, 1654 (1968).
7) A. Hillmann-Elies, G. Hillmann, and U. Schiedt, *Z. Naturforschung* (*B*), **8**, 436 (1953).