shift was estimated by ^{13}C–NMR spectrum of N-methylbenzylamine hydrochloride as follows: C_1' +3.3; C_o' +2.0; C_m' +2.5; C_p' +2.4. The signals of C_o and C_m were not certainly assigned, but the small difference between the two shifts did not give a large influence on the calculated values. The ^{1}H–NMR spectrum of the model compound showed the singlets at 6.62 and 6.72 ppm, supporting the proposed structure. Thus the site of attachment on catechol will be different from that suggested on phenols in their conjugates.

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Synthesis of Xanthines by Dehydrogenative Cyclization of 6-Amino-5-benzylideneaminouracils with Diethyl Azodicarboxylate

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The treatment of 6-amino-5-benzylideneaminouracil derivatives with diethyl azodicarboxylate gave the corresponding xanthines in high yields.

Keywords——xanthine derivatives; 6-amino-5-benzylideneaminouracils; diethyl azodicarboxylate; dehydrogenative cyclization; oxidation

It is well known that diethyl azodicarboxylate (DAD) is a strong hydrogen acceptor.[2] For instance, DAD is capable of dehydrogenating alcohols,[2] mercaptans,[2,3] hydrazobenzene,[2] hydroxylamines,[4,5] phenols,[6] secondary formamides,[7] and tertiary amines[8,9] and converting them into carbonyl compounds, disulfides, azobenzenes, nitroso compounds, biphenyls, isocyanates, and enamines. In this process DAD undergoes hydrogenation to diethyl hydrazodicarboxylate. DAD is also an effective reagent for the oxidation of several sulfur-containing amino acids[10] to sulfoxides, and for the dehydrogenation of imines of amino acid esters[11] to imines of the corresponding dehydroamino acid esters.

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1) Location: *a) 5-1, Oe-honmachi, Kumamoto, 862, Japan; b) 35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.*
2) *a*) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Am. Chem. Soc.*, **88**, 2328 (1966); *b*) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Org. Chem.*, 32, 727 (1967).
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The usefulness of this reagent as an oxidant has been extended to the syntheses of a variety of heterocycles. Namely, the dehydrogenation of 1,2-dihydropyrimido[5,4-*e*]-*as*-triazines,[12,13] 1,2,3,4-tetrahydroquinoxalines,[14] cyclic hydrazine derivatives,[15,16] 1,2-dihydropyrimido[4,5-*c*]pyridazines,[17] 1,3-diphenylimidazolidine,[18] and the alkaloids mesembrine and mesembrene[19] were successfully accomplished with DAD to yield pyrimido[5,4-*e*]-*as*-triazines, 1,2-dihydroquinoxalines, cyclic azo derivatives, pyrimido[4,5-*c*]pyridazines, 1,3-diphenylimidazolium salts, and the corresponding β-enaminoketones, respectively.

Furthermore, new syntheses of alloxazines,[20] purines,[21] flavins,[22,23] pyrimido[5,4-*e*]-*as*-triazine 4-oxides,[24] dithia[3.3]metacyclophanes[25] and 5-amino-3,4-diphenylisoxazole,[26] in which DAD as an oxidant played an important role, have been reported successively. Recently a transformation of 1-anilino-1-hydroxybenzylcyclopropane into 2-benzoylquinoline was reported where several oxidation steps with DAD are involved.[27] Oxidative ring enlargement of a penicilline S-oxide into a cephem with DAD was also reported.[28] In the present paper we describe the dehydrogenative cyclization of 6-amino-5-benzylideneaminouracils to the corresponding xanthines with DAD.[29]

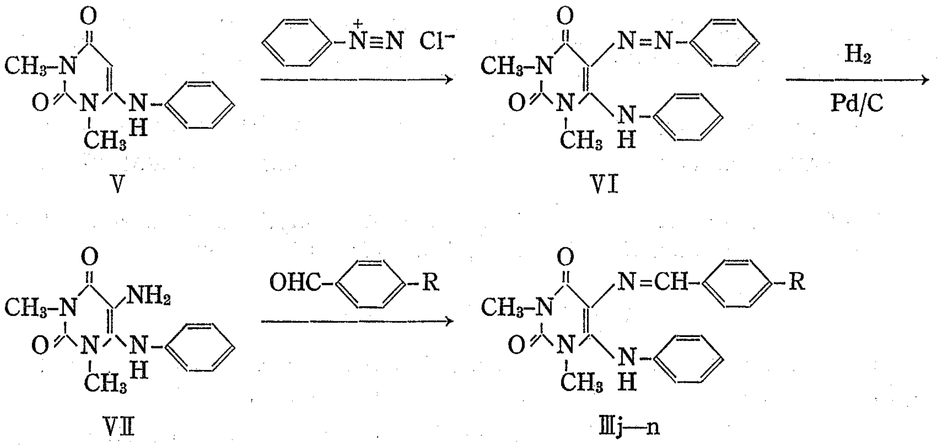

Chart 1

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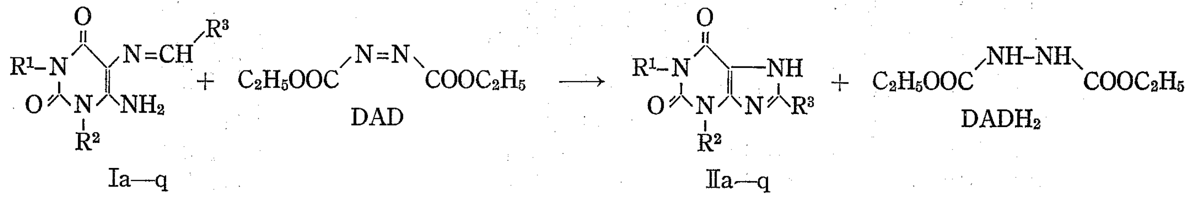
Synthesis of 6-Amino-5-benzylideneaminouracil Precursors

The 6-amino-5-benzylideneaminouracils (Ia—q) were prepared by condensation of 5,6-diaminouracils and aryl aldehydes according to the reported procedure.[30] 6-Alkylamino-5-benzylideneaminouracils (IIIa—i and o—q) were prepared by condensation of 6-alkylamino-5-aminouracils and arylaldehydes, the former of which was generated *in situ* by treatment of the corresponding 5-nitrosouracils[31,32] with sodium dithionite. 6-Anilino-5-benzylideneamino-1,3-dimethyluracils (IIIj—n) were synthesized as follows. 6-Anilino-1,3-dimethyluracil (V)[31] was converted into the corresponding 5-phenylazouracil (VI) by the conventional coupling reaction with phenyldiazonium chloride. Catalytic hydrogenation of the latter over palladium-charcoal gave the 5-aminouracil (VII), which was treated with aryl aldehydes to give the respective 6-anilino-5-benzylideneamino-1,3-dimethyluracils (IIIj—n).

Dehydrogenative Cyclization of 6-Amino-5-benzylideneaminouracils to Xanthines with DAD

Heating of a suspension of 6-amino-5-benzylideneamino-1,3-dimethyluracil (Ia) in an excess of DAD for 5 minutes, followed by dilution with ethanol, caused the separation of 8-phenyltheophylline (IIa) in a high state of purity. Concentration of the filtrate gave diethyl hydrazodicarboxylate. Similarly, other anils (Ib—q) gave the corresponding 8-aryl xanthines (IIb—q)[33,34] under the conditions indicated in Chart 2.



		reaction condition (°C, min)	yield (%)
a :	$R^1=R^2=CH_3$, $R^3=C_6H_5$	(90, 5)	96
b :	$R^1=R^2=CH_3$, $R^3=4\text{-}Cl\text{-}C_6H_4$	(90, 5)	100
c :	$R^1=R^2=CH_3$, $R^3=3,4\text{-}Cl_2\text{-}C_6H_3$	(90, 5)	99
d :	$R^1=R^2=CH_3$, $R^3=4\text{-}CH_3\text{-}C_6H_4$	(90, 5)	100
e :	$R^1=R^2=CH_3$, $R^3=4\text{-}CH_3O\text{-}C_6H_4$	(90, 5)	98
f :	$R^1=R^2=CH_3$, $R^3=3,4\text{-}CH_2O_2\text{-}C_6H_3$	(90, 5)	95
g :	$R^1=R^2=CH_3$, $R^3=4\text{-}(CH_3)_2N\text{-}C_6H_4$	(90, 5)	90
h :	$R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$	(90, 30)	92
i :	$R^1=H$, $R^2=CH_3$, $R^3=4\text{-}Cl\text{-}C_6H_4$	(90, 30)	98
j :	$R^1=H$, $R^2=CH_3$, $R^3=3,4\text{-}Cl_2\text{-}C_6H_3$	(90, 30)	96
k :	$R^1=H$, $R^2=CH_3$, $R^3=4\text{-}CH_3O\text{-}C_6H_4$	(90, 30)	96
l :	$R^1=H$, $R^2=CH_3$, $R^3=3,4\text{-}CH_2O_2\text{-}C_6H_3$	(90, 30)	100
m:	$R^1=R^2=H$, $R^3=C_6H_5$	(120, 100)	91
n :	$R^1=R^2=H$, $R^3=4\text{-}Cl\text{-}C_6H_4$	(120, 100)	95
o :	$R^1=R^2=H$, $R^3=3,4\text{-}Cl_2\text{-}C_6H_3$	(120, 100)	93
p :	$R^1=R^2=H$, $R^3=4\text{-}CH_3O\text{-}C_6H_4$	(120, 100)	92
q :	$R^1=R^2=H$, $R^3=3,4\text{-}CH_2O_2\text{-}C_6H_3$	(120, 100)	93

Chart 2

This dehydrogenative cyclization was successfully applied for the preparation of several 9-substituted xanthines. In complete analogy with the above result, 9-alkyl- and 9-phenyltheophyllines (IVa—n) and 9-alkyl-1-methylxanthines (IVo—q) were prepared by the

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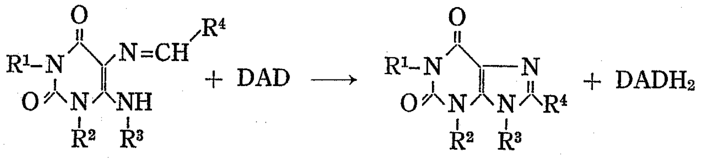
treatment of the respective anils (IIIa—q) with DAD. It is noted that the synthesis of the 9-substituted theophyllines has not been widely investigated[35] and that the alkylation of 9-alkyl-1-methylxanthines in the presence of alkali not give the corresponding 3,9-dialkyl-1-methylxanthines but 3,7-dialkyl-1-methylxanthines by simultaneous elimination of the 9-alkyl group.[32]


IIIa—q IVa—q

		reaction condition (°C, min)
a :	$R^1=R^2=R^3=CH_3$, $R^4=C_6H_5$	(90, 15)
b :	$R^1=R^2=R^3=CH_3$, $R^4=4\text{-}Cl\text{-}C_6H_4$	(90, 15)
c :	$R^1=R^2=R^3=CH_3$, $R^4=3,4\text{-}Cl_2\text{-}C_6H_3$	(90, 15)
d :	$R^1=R^2=R^3=CH_3$, $R^4=4\text{-}Br\text{-}C_6H_4$	(90, 15)
e :	$R^1=R^2=R^3=CH_3$, $R^4=4\text{-}CH_3\text{-}C_6H_4$	(90, 15)
f :	$R^1=R^2=R^3=CH_3$, $R^4=4\text{-}CH_3O\text{-}C_6H_4$	(90, 15)
g :	$R^1=R^2=CH_3$,$R^3=C_2H_5$, $R^4=C_6H_5$	(90, 15)
h :	$R^1=R^2=CH_3$, $R^3=C_2H_5$, $R^4=4\text{-}Br\text{-}C_6H_4$	(90, 15)
i :	$R^1=R^2=CH_3$, $R^3=C_2H_5$, $R^4=4\text{-}CH_3O\text{-}C_6H_4$	(90, 15)
j :	$R^1=R^2=CH_3$, $R^3=R^4=C_6H_5$	(90, 30)
k :	$R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=4\text{-}Cl\text{-}C_6H_4$	(90, 30)
l :	$R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=4\text{-}Br\text{-}C_6H_4$	(90, 30)
m:	$R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=4\text{-}CH_3\text{-}C_6H_4$	(90, 30)
n :	$R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=4\text{-}CH_3O\text{-}C_6H_4$	(90, 30)
o :	$R^1=CH_3$, $R^2=H$, $R^3=CH_3$, $R^4=C_6H_5$	(100, 90)
p :	$R^1=CH_3$, $R^2=H$, $R^3=n\text{-}C_3H_7$, $R^4=C_6H_5$	(100, 90)
q :	$R^1=CH_3$, $R^2=H$, $R^3=n\text{-}C_4H_9$, $R^4=C_6H_5$	(100, 90)

Chart 3

Wc consider this xanthine synthesis as possessing considerable synthetic utility because of the high yields and purity of products, the simplicity of procedure, and the mild and neutral conditions employed.

Experimental[36]

6-Alkylamino-5-benzylideneamino-1,3-dimethyluracils (IIIa—i). General Procedure——A mixture of a 6-alkylamino-1,3-dimethyl-5-nitrosouracil (0.001 mol) and sodium dithionite (0.522 g, 0.006 mol) in water (10 ml) was stirred at room temperature for 10 min. To this reaction mixture, a solution of the respective aryl aldehyde (0.0015 mol) in ethanol (10 ml) was added and the mixture was further stirred for 1 hr. After evaporation, the residue was diluted with water and the undissolved material was filtered off. The filtrate was extracted with chloroform, the chloroform extracts were dried over Na_2SO_4 and the solvent was evaporated to give the corresponding 6-benzylideneaminouracils (Table I).

6-Alkylamino-6-benzylideneamino-3-methyluracils (IIIo—q). General Procedure——A mixture of a 6-alkylamino-3-methyl-5-nitrosouracil (0.001 mol) and sodium dithionite (0.522 g, 0.006 mol) in 10% aqueous ammonia (10 ml) was stirred at 60° for 1 hr. The reaction mixture was evaporated and the residue was washed with water to give the crude 5-aminouracil, which was used for next step without purification.

A mixture of the crude 5-aminouracil (0.001 mol) and benzaldehyde (0.159 g, 0.0015 mol) in dimethylformamide (DMF) (10 ml) was refluxed for 30 min in the dark. The reaction mixture was evaporated *in vacuo* and the residue was washed with water and recrystallized from DMF to give the corresponding 5-benzylideneaminouracil (Table I).

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36) All melting points were uncorrected. Nuclear magnetic resonance (NMR) spectra were determined with a JEOL-PMX 60 spectrometer (tetramethylsilane as internal standard). Identity of compounds was confirmed by comparison of infrared (IR) spectra (Nujol mulls) with JASCO IR-IA spectrophotometer.

Table I. 6-Alkylamino- and 6-Anilino-5-benzylideneaminouracils

Compd. No.	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
IIIa	159—161	EtOH	68	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58	61.84	5.94	20.88
IIIb	178—180	EtOH	82	$C_{14}H_{15}ClN_4O_2$	54.79	4.93	18.28	54.89	5.15	18.58
IIIc	180—182	EtOH	90	$C_{14}H_{14}Cl_2N_4O_2$	49.26	4.14	16.43	49.33	4.14	16.67
IIId	167—168	EtOH	85	$C_{14}H_{15}BrN_4O_2$	47.86	4.31	15.96	47.63	4.27	16.11
IIIe	153—154	EtOH	81	$C_{15}H_{18}N_4O_2$	62.92	6.34	19.57	62.63	6.25	19.62
IIIf	174—175	EtOH	81	$C_{15}H_{18}N_4O_3$	59.59	6.00	18.53	59.49	5.93	18.86
IIIg	114—115	*n*-Hexane	82	$C_{15}H_{18}N_4O_2$	62.92	6.34	19.57	63.13	6.54	19.55
IIIh	148—150	EtOH	88	$C_{15}H_{17}BrN_9O_2$	49.30	4.70	15.35	49.21	4.65	15.60
IIIi	125—126	EtOH	78	$C_{16}H_{20}N_4O_3$	60.74	6.37	17.71	60.69	6.33	17.79
IIIj	183—185	EtOH	60	$C_{19}H_{18}N_4O_2$	68.24	5.42	16.76	68.44	5.48	16.92
IIIk	197—198	EtOH	67	$C_{19}H_{17}ClN_4O_2$	61.85	4.65	15.21	61.59	4.50	15.18
IIIl	218—219	EtOH	78	$C_{19}H_{17}BrN_4O_2$	55.20	4.12	13.56	55.17	4.07	13.62
IIIm	190—191	EtOH	74	$C_{20}H_{20}N_4O_2$	68.95	5.79	16.08	68.90	5.77	16.15
IIIn	217—218	EtOH	75	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.38	66.20	5.62	15.39
IIIo	284—286	DMF	70	$C_{13}H_{14}N_4O_2$	60.45	5.46	21.70	60.33	5.48	21.42
IIIp	248—250	DMF	77	$C_{15}H_{18}N_4O_2$	62.92	6.34	19.57	62.86	6.20	19.22
IIIq	225—227	DMF	81	$C_{16}H_{20}N_4O_2$	63.98	6.71	18.65	63.77	6.89	18.49

6-Anilino-1,3-dimethyl-5-phenylazouracil (VI)——Aniline (3.13 g, 0.034 mol) was dissolved in 10% HCl (60 ml) and $NaNO_2$ (3.31 g, 0.048 mol) in H_2O (10 ml) was added gradually under cooling with ice water. On the other hand, 6-anilino-1,3-dimethyluracil (2.77 g, 0.012 mol) was dissolved in 10% KOH solution (60 ml), to this solution the prepared diazonium chloride solution was added dropwise under stirring and the reaction mixture was heated at 90° for 1 hr and maintained at room temperature for 6 hr. The precipitated crystals were collected by filtration, washed with H_2O repeatedly and dried to give crude 6-anilino-1,3-dimethyl-5-phenylazouracil. Recrystallization from DMF gave yellow crystals, mp 212—214°. *Anal.* Calcd. for $C_{18}H_{17}N_5O_2$: C, 64.46; H, 5.11; N, 20.89. Found: C, 64.52; H, 5.02; N, 20.87.

5-Anilino-6-benzylideneamino-1,3-dimethyluracils (IIIj—n). General Procedure——A solution of VI (0.473 g, 0.014 mol) in EtOH (400 ml) containing 5% palladium-charcoal (0.2 g) was hydrogenated at room temperature and atmospheric pressure. After consumption of hydrogen (100—180 ml) had stopped, the solution was filtered. To the filtrate, the respective aryl aldehyde (0.016 mol) was added and the mixture

Table II. 9-Substituted Xanthine Derivatives[a]

Compd. No.	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
IVa	221—222	EtOH	90	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73	62.44	5.20	20.37
IVb	227—228	EtOH	63	$C_{14}H_{13}ClN_4O_2$	55.16	4.30	18.40	55.34	4.30	18.62
IVc	242—244	EtOH	76	$C_{14}H_{12}Cl_2N_4O_2$	49.55	3.57	16.53	49.75	3.49	16.69
IVd	266—268	EtOH	63	$C_{14}H_{13}BrN_4O_2$	48.13	3.75	16.05	48.10	3.62	16.10
IVe	255—257	EtOH	62	$C_{15}H_{16}N_4O_2$	63.36	5.67	19.71	63.60	5.67	19.90
IVf	242—243	EtOH	73	$C_{15}H_{16}N_4O_3$	59.99	5.37	18.66	60.12	5.31	18.89
IVg	213—215	EtOH	55	$C_{15}H_{16}N_4O_2$	63.36	5.67	19.71	63.38	5.71	20.01
IVh	270—272	EtOH	78	$C_{15}H_{15}BrN_4O_2$	49.58	4.16	15.43	49.39	4.11	15.49
IVi	231—233	EtOH	88	$C_{16}H_{18}N_4O_3$	61.13	5.77	17.83	60.84	5.63	17.96
IVj	275—276	EtOH	45	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86	68.72	4.90	16.75
IVk	289—291	EtOH	71	$C_{19}H_{15}ClN_4O_2$	62.19	4.12	15.28	62.43	4.00	15.32
IVl	300—302	EtOH	55	$C_{19}H_{15}BrN_4O_2$	55.47	3.68	13.63	55.52	3.63	13.68
IVm	>300	EtOH	54	$C_{20}H_{18}N_4O_2$	69.35	5.24	16.18	69.28	5.15	16.08
IVn	258—259	EtOH	62	$C_{20}H_{18}N_4O_3$	66.28	5.01	15.46	66.52	5.01	15.52

a) Satisfactory spectral data (IR, NMR, MS) were obtained for all products.

was stirred at room temperature for 1 hr, and then evaporated *in vacuo* to dryness. The residue was washed with ethanol and recrystallized (Table I).

Dehydrogenative Cyclization of 6-Amino-5-benzylideneaminouracils (I and III) to Xanthines (II and IV). General Procedure——Heating of a suspension of a 5-benzylideneaminouracil (0.001 mol) in an excess of DAD (0.002—0.003 mol) under the conditions indicated in Charts 2 and 3, followed by dilution with EtOH, caused the separation of crude products.

Compounds IIa—q were recrystallized from DMF and did not melt below 350°. The structures of these compounds were established by satisfactory analytical and spectral data and by comparison with authentic samples[33,34] prepared by alternative routes.

Compounds IVo—q were also recrystallized from DMF and identical in all respects with authentic samples.[32]

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Screening of East African Plants for Antimicrobial Activity. I

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Screening of East African plants for antimicrobial activity was carried out. The plant materials were collected mainly on the basis of information gathered from "Bwana Mganga" (Swahili) meaning "medicine man" on "dawa ya miti" (Swahili) meaning "medicinal plants". Of 79 extracts from 72 species of plants belonging to 35 families, we found that 40 extracts gave initial positive results indicative of antimicrobial activity against one or more microorganisms. Interestingly, none of the extracts showed activity against *Escherichia coli*, a gram-negative bacterium.

Keywords——screening; antimicrobial activity; medicinal properties; East African plants; tropical flora; plant collection; medicine man; medicinal plants; *Escherichia coli*

There is little doubt that tropical flora, which are constantly exposed to attack by various parasites such as viruses, bacteria, protozoans, fungi and insects, are confronted with much harsher conditions for survival than their temperate counterparts. This necessarily leads to efficient built-in defense mechanisms and it is presumably for this reason that tropical flora offer a rich and intriguing source for isolating natural products possessing medicinal or pesticidal[2] properties.

The collection of plants in East Africa was carried out on the basis of information gathered from native people, especially "Bwana Mganga" (Swahili) or similar words meaning "medicine man".[3] It is difficult to make contact with a "Bwana Mganga" since it is no longer a legal occupation. Although people have developed a wealth of empirical knowledge on local plants, much valuable information can be lost or distorted whenever a "Bwana Mganga" dies without revealing his knowledge to his offspring. Traditionally, he only passes on his knowledge to his first-born son, but occasionally he might give some information to a trustworthy person.

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2) I. Kubo and K. Nakanishi, " ACS Symposium Series 62, Host Plant Resistance to Pests," ed. by P.A. Hedin, American Chemical Society, Washington D.C., 1977, pp. 165—178.

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