A Reagent, Ethyl 2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate (DMTE), for Facile Synthesis of 2,3-(Ring Fused)-5-(5-tetratzolyl)-4*H*-pyrimidin-4-one Derivatives

Hideyuki KANNO,* Hitoshi YAMAGUCHI, Yoshifumi ICHIKAWA, and Sumiro ISODA

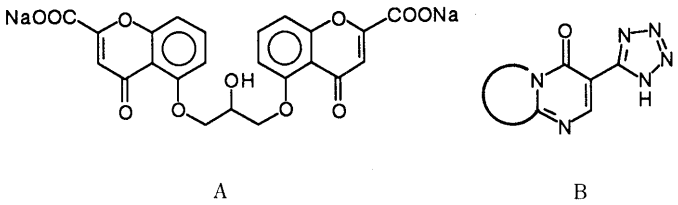
Research Institute, Daiichi Pharmaceutical Co., Ltd., 16–13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan. *Received August 10, 1990*

A method for synthesizing 2,3-(ring fused)-5-(5-tetrazolyl)-4*H*-pyrimidin-4-one derivatives from ethyl 2-(2-*tert*-butyl-2*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate (DMTE) (4a) and amino-heterocycles is described. The structure of DMTE, which was prepared from ethyl (2-*tert*-butyl-2*H*-tetrazol-5-yl)acetate (3a) with dimethylformamide diethylacetal, was determined by X-ray analysis to be *Z* form. The reaction of 2-amino-5-methyloxazole (6) with DMTE in acetic acid gave the oxazolo[3,2-*a*]pyrimidine derivative (8), heating of which in concentrated sulfuric acid afforded the desired tetrazole derivative (20). Pyrimido[2,1-*b*]benzothiazole (21), pyrazolo[1,5-*a*]pyrimidine (22 and 23) and [1,2,4]triazolo[1,5-*a*]pyrimidine (24) derivatives were prepared in a similar manner.

Keywords ethyl 2-(2-*tert*-butyl-2*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate; DMTE; fused pyrimidine; tetrazole derivative; cyclization; X-ray analysis

Disodium cromoglycate (DSCG),[1] which acts mainly as an inhibitor of chemical mediator release from sensitized mast cells, is used clinically for the prophylactic treatment of bronchial asthma. Many 5-(5-tetrazolyl)-4*H*-pyrimidin-4-ones fused at the 2,3 positions with a heterocycle have been reported to possess DSCG-like antiallergic activity.[2,3] During our search for new antiallergic drugs, we became interested in these tetrazolylpyrimidines, which, with respect to the carbonyl and acidic groups, have different chemical properties from those of DSCG.

Synthetic methods for the desired compounds has not been fully explored, affording only a limited number of analogues. The tetrazolyl derivatives were generally synthesized from the corresponding nitriles.[2] In the present cases, however, the synthesis of cyano derivatives sometimes presents difficult problems. For example, some ring systems (*e.g.*, pyrimido[2,1-*b*]benzoxazole) are so unstable under acidic or basic conditions, because of their facile ring-opening,[2] that the conversion from esters into nitriles *via* the amides is difficult. Also, the cyclization reaction of (3-pyrazolyl)aminomethylene cyanoacetate does not give 6-cyanopyrazolo[1,5-*a*]pyrimidin-5-one but instead yields 5-aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylate.[4,5] Wade *et al.*[2] and Yevich *et al.*[3] reported methods for the synthesis of some 5-(5-tetrazolyl)-4*H*-pyrimidin-4-ones, but there still seems to be much room for improvement, since the yields and ranges of applicability were unsatisfactory.



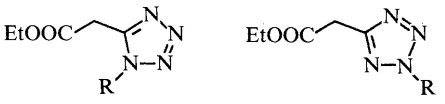
A B

Fig. 1. Chemical Structures of DSCG (A) and 2,3-(Ring Fused)-5-(5-tetrazolyl)-4*H*-pyrimidin-4-one (B)

In the present paper, we report a new reagent, ethyl (*Z*)-2-(2-*tert*-butyl)-2*H*-tetrazol-5-yl)-3-(dimethylamino)-acrylate (DMTE) (**4a**) for the efficient construction of ring systems which contain the 2,3-(ring fused)-5-(5-tetrazolyl)-4*H*-pyrimidin-4-one component.

Preparation and Structure of DMTE Derivatives Ethyl (1- or 2-substituted-1*H* or 2*H*-tetrazol-5-yl)acetates (**2b—e**

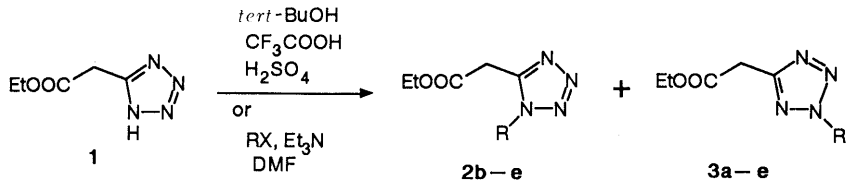
TABLE I. Ethyl (1- or 2-Substituted tetrazol-5-yl)acetates



2b—e **3a—e**

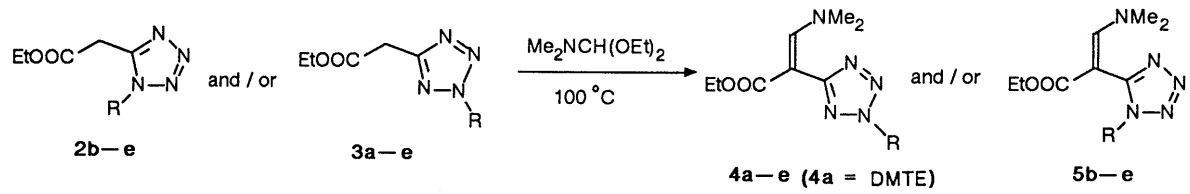
R	Reaction conditions	1-Substituted derivatives			2-Substituted derivatives		
		Compd.	Yield (%)	mp or bp (°C) (Reported)	Compd.	Yield (%)	mp or bp (°C) (Reported)
tert-Bu	*tert*-BuOH, CF_3COOH, conc. H_2SO_4, r.t., 17 h				**3a**	44	bp 113—120 (3 mmHg) (Oil)[7]
Me	MeI, Et_3N, DMF, r.t., 26 h	**2b**	16	mp 67—69[b] (mp 67—68)[8]	**3b**	24	bp 125—135 (3 mmHg) (bp 103—104 (0.8 mmHg))[8]
Et	EtI, Et_3N, DMF, r.t., 16 h	**2c**	13[a]	bp 160—180 (3 mmHg) (Oil)[7]	**3c**	41[a]	bp 117—120 (3 mmHg) (Oil)[7]
Benzyl	$C_6H_5CH_2Cl$, Et_3N, DMF, r.t., 16 h	**2d**	15[a]	Oil	**3d**	23[a]	Oil
p-Methoxy benzyl	*p*-(MeO)$C_6H_4CH_2Cl$, Et_3N, DMF, r.t., 93 h	**2e**	33[a]	Oil	**3e**	26[a]	Oil

a) Determined by comparison of integration ratios of ^{1}H-NMR signals. *b*) Recrystallized from benzene–*n*-hexane.



a : R=*tert*-Bu b : R=Me c : R=Et d : R=benzyl e : R=*p*-methoxybenzyl

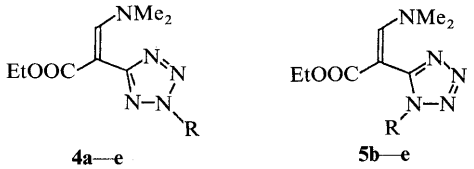
Chart 1



a : R=*tert*-Bu b : R=Me c : R=Et d : R=benzyl e : R=*p*-methoxybenzyl

Chart 2

TABLE II. Ethyl 3-(Dimethylamino)-2-(1- or 2-Substituted tetrazol-5-yl)acrylates



Compd.	R	Yield (%)	mp (°C)	$(CH_3)_2N$–	>NCH=C<	$-CH_2$-Tet[g]	^{1}H-NMR ($CDCl_3$): δ ppm		Miscellaneous
							CH_3CH_2O	CH_3CH_2O	
4a	*tert*-Bu	69	73—75[d]	2.74 (s)	7.78 (s)		1.15 (t, J=7.0)	4.13 (q, J=7.0)	1.73 (9H, s, $C(CH_3)_3$)
4b	Me	55	101—103[e]	2.76 (s)	7.84 (s)	4.40 (s)	1.20 (t, J=7.0)	4.16 (q, J=7.0)	
5b	Me	56	94—95[f]	2.25—3.25 (br s)	7.93 (s)	3.98 (s)	1.21 (t, J=7.0)	4.18 (q, J=7.0)	
4c	Et	84	Oil	2.77 (s)	7.82 (s)	4.70 (q, J=7.0)	1.19 (t, J=7.0)	4.15 (q, J=7.0)	1.66 (3H, t, J=7.0, CH_3CH_2-Tet)
5c	Et	40[a]	Oil	2.1— 3.5 (br s)	7.91 (s)	4.29 (q, J=7.0)	1.20 (t, J=7.0)	4.16 (q, J=7.0)	1.56 (3H, t, J=7.0, CH_3CH_2-Tet)
4d	Benzyl	46[b]	Oil	2.65 (s)	7.76 (s)	5.79 (s)	1.13 (t, J=7.0)	4.11 (q, J=7.0)	7.37 (5H, s, Ar-H)
5d	Benzyl	34[b]	Oil	1.5— 3.4 (br s)	7.79 (s)	5.46 (s)	1.16 (t, J=7.0)	4.14 (q, J=7.0)	7.37 (5H, s, Ar-H)
4e	*p*-Methoxy benzyl	43[c]	Oil	2.65 (s)	7.77 (s)	5.73 (s)	1.13 (t, J=7.0)	4.12 (q, J=7.0)	3.81 (3H, s, CH_3O) 6.89 (2H, d, J=9.0, Ar-H) 7.34 (2H, d, J=9.0, Ar-H)
5e	*p*-Methoxy benzyl	49[c]	100—103[f]	1.7— 3.4 (br s)	7.80 (s)	5.39 (s)	1.17 (t, J=7.0)	4.15 (q, J=7.0)	3.82 (3H, s, CH_3O) 6.83 (2H, d, J=8.0, Ar-H) 7.29 (2H, d, J=8.0, Ar-H)

a) Prepared from a mixture of **2c** and **3c** (**2c**/**3c**=5/3). *b*) Prepared from a mixture of **2d** and **3d** (**2d**/**3d**=2/3). *c*) Prepared from a mixture of **2e** and **3e** (**2e**/**3e**=5/4). *d*) Recrystallized from ether–petroleum ether. *e*) Recrystallized from benzene–*n*-hexane. *f*) Recrystallized from benzene–petroleum ether. *g*) Tet=tetrazole.

and **3a—e**), listed in Table I, were prepared from ethyl (5-tetrazolyl) acetate (**1**)[6] according to the known method. Alkylation[7] of **1** yielded a mixture of 1- and 2-substituted derivatives (**2b—e** and **3b—e**), except that *tert*-butylation[8] of **1** yielded only the 2-substituted product (**3a**). The structures of the products were assigned on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra. It is known that the signals of *N*-methyl or *N*-methylene protons of 2-substituted tetrazole derivatives appear at lower field than those of 1-substituted ones,[9-12] and hence the substituted position in the products could be unambiguously determined.

We attempted to introduce a formyl or its equivalent group at the methylene moiety of **3a**. Neither ethoxymethylation of **3a** using triethyl orthoformate in acetic anhydride nor formylation using sodium methoxide in ethyl formate succeeded. The synthesis of DMTE from **3a** was accomplished in satisfactory yield by reacting **3a** with excess *N*,*N*-dimethylformamide (DMF) diethylacetal at 100 °C. The other derivatives (**4b—e** and **5b—e**) listed in Table II were prepared in a similar manner.

The structure of DMTE was estimated by examination of the ^{13}C-NMR spectrum. Measurement of the vicinal ^{13}C, H coupling constant ^3J(CO, H) is a useful tool for the configurational assignment of C=C double bonds. Braun[13] reported that the *trans* ^3J(CO, H) value (12 Hz) is characteristically greater than the *cis* ^3J(CO, H) one (7 Hz). The ^3J (CO, H) value (6.9 Hz) of DMTE indicates that the ester moiety and the olefin proton have a *cis* configuration. Finally, to elucidate the stereostructure of DMTE, an X-ray crystallographic analysis was carried out. DMTE was found to be present in the *Z* form, and a computer-generated drawing of the structure is shown in Fig. 2. Selected X-ray data are listed in Table III. On the basis of the above results,

TABLE III. Bond Distances and Bond Angles for **4a**[a] with Their Estimated Standard Deviations in Parentheses

Bond distances (Å)[b]

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C4	1.209 (5)	N5	C7	1.441 (6)	C2	C4	1.447 (6)
O2	C4	1.358 (5)	N5	C8	1.457 (6)	C5	C6	1.430 (8)
O2	C5	1.468 (6)	N6	N7	1.318 (5)	C9	C10	1.474 (9)
O3	C15	1.207 (5)	N6	C13	1.327 (5)	C9	C11	1.477 (9)
O4	C15	1.346 (6)	N7	N8	1.315 (5)	C9	C12	1.445 (8)
O4	C19	1.461 (8)	N7	C21	1.493 (5)	C13	C14	1.460 (6)
N1	N2	1.330 (5)	N8	N9	1.315 (5)	C14	C15	1.447 (6)
N1	C1	1.319 (5)	N9	C13	1.350 (6)	C14	C16	1.362 (7)
N2	N3	1.316 (5)	N10	C16	1.321 (6)	C19	C20	1.42 (1)
N2	C9	1.475 (5)	N10	C17	1.461 (7)	C21	C22	1.501 (8)
N3	N4	1.318 (5)	N10	C18	1.449 (7)	C21	C23	1.475 (8)
N4	C1	1.348 (5)	C1	C2	1.461 (6)	C21	C24	1.496 (8)
N5	C3	1.326 (6)	C2	C3	1.370 (6)			

Bond angles (°)[b]

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C4	O2	C5	116.9 (4)	C16	N10	C18	120.6 (5)	C11	C9	C12	111.1 (6)
C15	O4	C19	118.1 (5)	C17	N10	C18	116.0 (5)	N6	C13	N9	111.4 (4)
N2	N1	C1	103.0 (3)	N1	C1	N4	111.6 (4)	N6	C13	C14	124.0 (4)
N1	N2	N3	112.5 (3)	N1	C1	C2	124.6 (4)	N9	C13	C14	124.6 (4)
N1	N2	C9	123.3 (4)	N4	C1	C2	123.8 (4)	C13	C14	C15	120.0 (5)
N3	N2	C9	123.9 (4)	C1	C2	C3	125.3 (4)	C13	C14	C16	125.5 (5)
N2	N3	N4	106.8 (4)	C1	C2	C4	120.2 (4)	C15	C14	C16	114.5 (5)
N3	N4	C1	106.1 (3)	C3	C2	C4	114.6 (4)	O3	C15	O4	121.8 (5)
C3	N5	C7	121.3 (4)	N5	C3	C2	132.2 (4)	O3	C15	C14	126.3 (5)
C3	N5	C8	124.4 (4)	O1	C4	O2	121.4 (4)	O4	C15	C14	111.9 (4)
C7	N5	C8	114.3 (4)	O1	C4	C2	126.8 (4)	N10	C16	C14	133.6 (6)
N7	N6	C13	102.4 (4)	O2	C4	C2	111.8 (4)	O4	C19	C20	108.3 (7)
N6	N7	N8	113.6 (4)	O2	C5	C6	108.4 (6)	N7	C21	C22	109.2 (4)
N6	N7	C21	122.0 (4)	N2	C9	C10	108.4 (5)	N7	C21	C23	107.9 (5)
N8	N7	C21	124.1 (4)	N2	C9	C11	106.8 (4)	N7	C21	C24	106.3 (4)
N7	N8	N9	106.2 (4)	N2	C9	C12	111.0 (4)	C22	C21	C23	111.3 (6)
N8	N9	C13	106.3 (4)	C10	C9	C11	109.4 (6)	C22	C21	C24	110.4 (6)
C16	N10	C17	123.4 (5)	C10	C9	C12	110.0 (7)	C23	C21	C24	111.4 (7)

a) Crystal data: Single-crystal diffractometry, graphite-monochromated CuK_α, $\lambda = 1.54178$ Å. Monoclinic cell parameters and calculated volume: $a = 15.606\,(5)$, $b = 11.701\,(3)$, $c = 18.224\,(7)$ Å, $\beta = 115.01\,(4)°$, $V = 3016\,(3)$ Å^3. For $z = 8$ and $M_r = 267.33$, the calculated density is 1.178 g/cm^3. Space group $P2_1/n$ (#14). *b*) Between the nonhydrogen atoms.

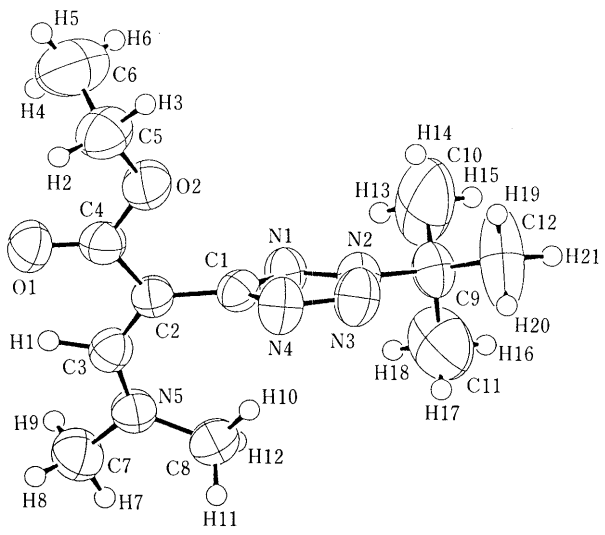


Fig. 2. Stereostructure of **4a**

we concluded from the ^{1}H-NMR spectra that the other derivatives (**4b**—**e**) also have the *Z* configuration. In the case of 1-substituted derivatives (**5b**—**e**), we considered that they also have the *Z* configuration, because **5b** exhibited a ^3J (CO, H) value of 3.0 Hz in its ^{13}C-NMR spectrum and **5b**—**e** showed similar patterns in their ^{1}H-NMR spectra.

Reactions of DMTE with Amino-heterocycles We next examined the reaction of DMTE with amino-heterocycles, which contained a cyclic amidine component, to obtain the fused pyrimidine derivatives. Heating a mixture of DMTE and 2-amino-5-methyloxazole (**6**)[14] in acetic acid at reflux temperature gave a mixture of regioisomers (**7**) whose ^{1}H-NMR spectrum showed signals due to the olefin and NH protons with a coupling constant of 15 Hz. The subsequent heating of **7** in acetic acid caused cyclization to the oxazolo[3,2-*a*]pyrimidine derivative (**8**) (procedure A). The structure of **8** was assigned on the basis of the ^{1}H-NMR spectra: the proton on the oxazole ring was shifted further downfield in comparison with that of **7** (7.64 ppm for **8**, 6.60 ppm for **7**) because of the additional deshielding effect of the carbonyl group. The direct conversion of **6** into **8** was accomplished by reacting DMTE with **6** in refluxing acetic acid for a longer time (procedure B).

The conversions of 2-aminobenzothiazole (**9**), 3-aminopyrazole (**10**),[15] ethyl 3-aminopyrazole-4-carboxylate (**11**)[15] and 3-amino-1,2,4-triazole (**12**) into pyrimido[2,1-

b]benzothiazole derivative (**16**), pyrazolo[1,5-*a*]pyrimidine derivatives (**17**, **18**) and [1,2,4]triazolo[1,5-*a*]pyrimidine derivative (**19**), respectively, were carried out in a similar manner to the above, with the results shown in Tables IV and V. The one-pot reactions (procedure B) were always superior to the method *via* intermediates (**7** and **13**—**15**) in terms of total yield.

In the cyclization reaction of **12** with DMTE, the direction of cyclization was examined on the basis of the ^{1}H-NMR spectra. In the ^{1}H-NMR spectrum of **19**, the signal of the proton on the triazole ring appeared at 8.27 ppm, which was about the same value as that for **15** (8.05 ppm), and did not suffer the deshielding effect of the carbonyl group. This clearly showed that the cyclization of **15** occurred at the 2-position of the triazole ring as shown in Chart 4.

Removal of the *tert*-butyl moiety of **8** and **16**—**19** by heating at 100—140 °C in concentrated sulfuric acid gave the desired tetrazoles (**20**—**24**) in satisfactory yields, and the results are shown in Table VI. In the case of the pyrazolo[1,5-*a*]pyrimidine derivative (**18**) with an ethoxycarbonyl group, not only removal of the *tert*-butyl moiety but also hydrolysis of the ester group occurred at the same time to give **23** under these conditions. Later, the removal of the *tert*-butyl group was achieved by several methods, such as the use of *p*-toluenesulfonic acid in sulfolane, trifluoroacetic acid or boron trifluoride. Infrared (IR) spectra of the tetrazoles (**17**—**19** and **22**—**24**) showed that they contained a carbonyl group. As we did not identify the position of NH hydrogen of the compounds (**17**—**24**), they are tentatively depicted as 1*H*-pyrimidin-4-one (**17**—**19** and **22**—**24**) or 1*H*-tertazole (**20**—**24**) derivatives.

The reactions of DMTE and cyclic amidine type amino-heterocycles thus provide a general method for synthesizing a variety of fused pyrimidine derivatives containing the tetrazole moiety. This method not only provides a very simple, two-step conversion from amino-heterocycles to 2,3-(ring fused)-5-(5-tetrazolyl)-4*H*-pyrimidin-4-ones under mild conditions, but should also be applicable to the conversion of many heterocycles, of which only a few could be directly converted to the tetrazoles by other methods.

When the tetrazoles (**20**—**24**) were tested in the rat passive cutaneous anaphylaxis (PCA) assay, **21** showed activity when given by oral administration and **23** showed activity by intravenous administration. Details of syntheses of other ring systems and their biological activities will be reported elsewhere.

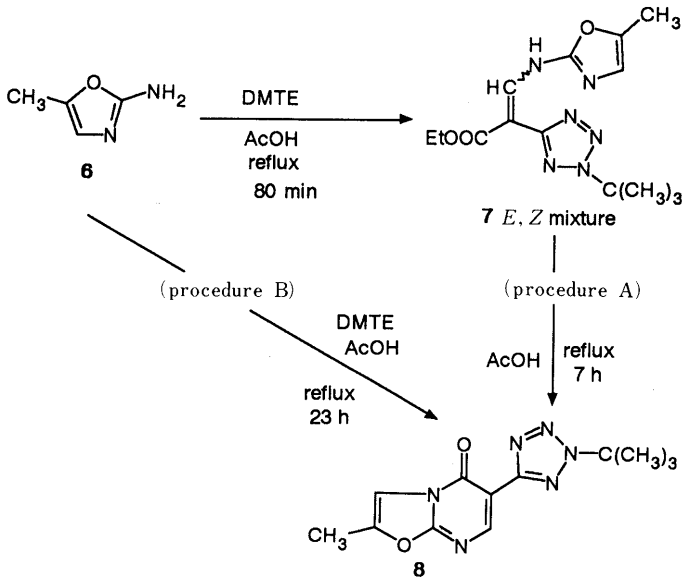


Chart 3

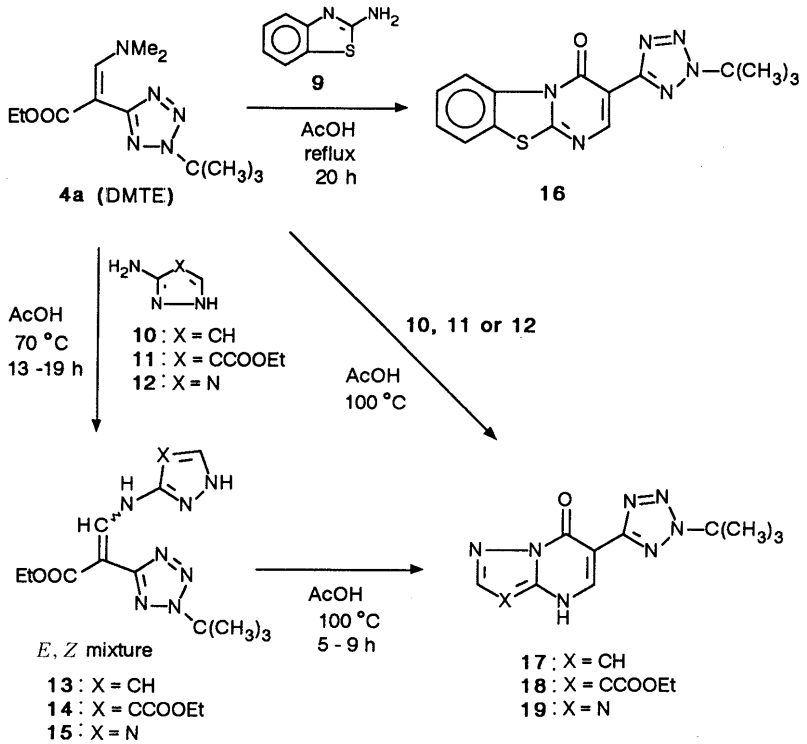
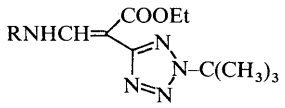
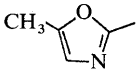
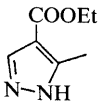


Chart 4

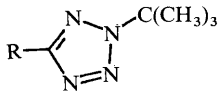
TABLE IV. Ethyl 2-(*tert*-Butyl-2*H*-tetrazol-5-yl)-3-(substituted amino)acrylates (A mixture of *E* and *Z* isomers)

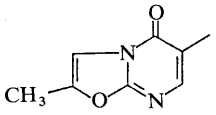
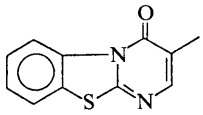
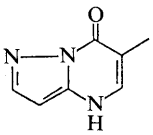
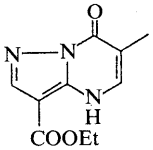
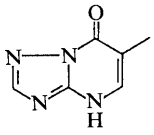


Compd.	R	Reaction conditions	Yield (%)	^{1}H-NMR ($CDCl_3$): δ ppm
7		Reflux 80 min	56	1.33, 1.37 (total 3H, each t, J=7.0 Hz), 1.77, 1.82 (total 9H, each s), 2.28, 2.30 (total 3H, each d, J=2.0 Hz), 4.35, 4.38 (total 2H, each q, J=7.0 Hz), 6.60 (1H, m), 8.20, 8.57 (total 1H, each d, J=13 Hz)
13		70 °C 12.5 h	73	1.32, 1.35 (total 3H, each t, J=7.0 Hz), 1.76, 1.80 (total 9H, each s), 4.34, 4.36 (total 2H, each q, J=7.0 Hz), 6.05, 6.12 (total 1H, each d, J=2.0 Hz), 7.57, 7.21 (total 1H, each d, J=2.0 Hz), 8.26, 8.60 (total 1H, each d, J=13 Hz), 10.24, 10.32 (total 1H, each d, J=13 Hz)
14		70 °C 18.5 h	53 (20)[a]	1.37 (3H, t, J=7.0 Hz), 1.43 (3H, t, J=7.0 Hz), 1.77, 1.85 (total 9H, each s), 4.38 (2H, q, J=7.0 Hz), 4.43 (2H, q, J=7.0 Hz), 8.05, 8.08 (total 1H, each s), 8.57, 8.90 (total 1H, each d, J=13 Hz), 11.24, 11.49 (total 1H, each d, J=13 Hz)
15		70 °C 16.5 h	36[b]	1.37 (3H, t, J=7.0 Hz), 1.81 (9H, s), 4.36 (2H, q, J=7.0 Hz), 8.05 (1H, s), 8.83 (1H, d, J=13 Hz), 10.55 (1H, d, J=13 Hz)

a) The cyclized product (**18**) was obtained in 20% yield. *b*) Isolated as a single isomer. mp 208—211 °C ($CHCl_3$). *Anal.* Calcd for $C_{12}H_{18}N_8O_2$: C, 47.05; H, 5.92; N, 36.58. Found: C, 46.80; H, 5.97; N, 36.31.

TABLE V. 5-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)pyrimidin-4-one Derivatives

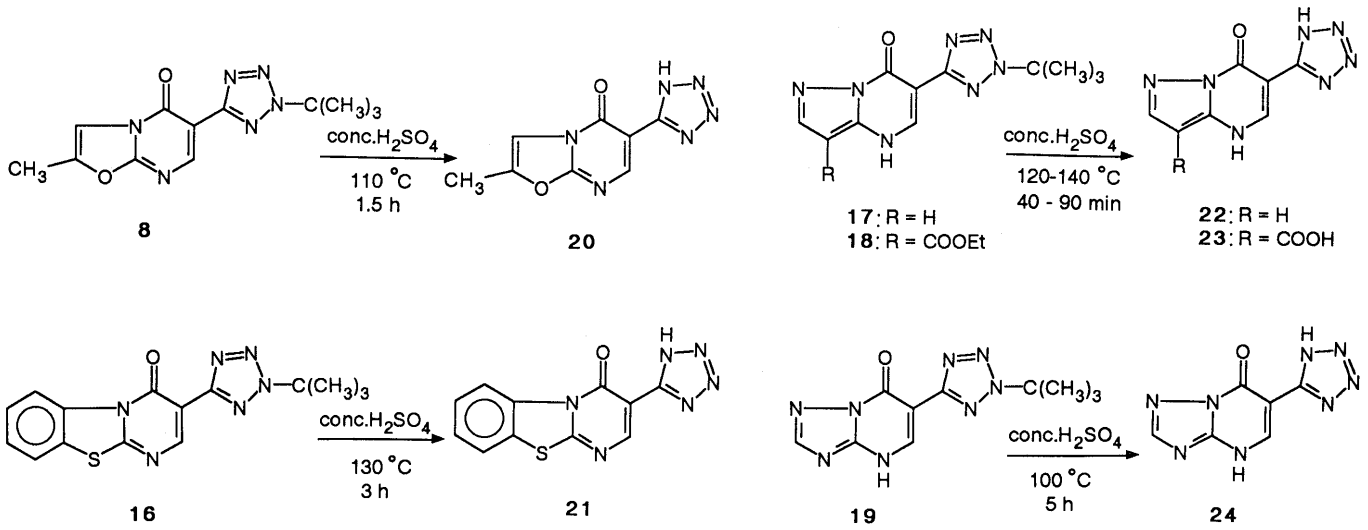


Compd.	R	Procedure[a]	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
8		A B	26 39	202—203.5 (MeOH)	$C_{12}H_{14}N_6O_2$	52.55 (52.51	5.15 5.32	30.64 30.50)
16		B	61	226—227 (EtOH)	$C_{15}H_{14}N_6OS$	55.20 (55.30	4.32 4.35	25.75 25.75)
17		A B	63 76	Over 300 (DMF–MeOH)	$C_{11}H_{13}N_7O$	50.96 (50.75	5.05 5.26	37.82 37.57)
18		A B	61 81	264—267 ($CHCl_3$–MeOH)	$C_{14}H_{17}N_7O_3$	50.75 (50.55	5.17 5.27	29.59 29.40)
19		A B	41 65	195—198 (AcOEt–MeOH)	$C_{10}H_{12}N_8O$	46.15 (45.71	4.65 5.14	43.05 42.60)

a) See text.

Experimental

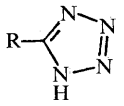
All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. ^{1}H-NMR spectra were obtained at 60 MHz with a Varian EM-360 spectrometer, and ^{13}C-NMR spectra, at 500 MHz with a JEOL GSX 500 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as the internal standard. The abbreviations used are follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Hitachi 260-30 spectrometer

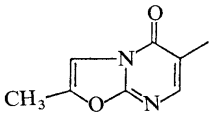
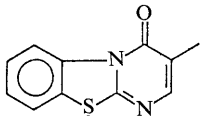
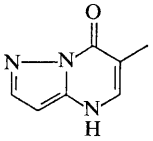
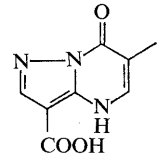
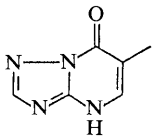


8 20 17: R = H 18: R = COOEt 22: R = H 23: R = COOH 16 21 19 24

Chart 5

TABLE VI. 5-(Tetrazol-5-yl)-4*H*-pyrimidin-4-one Derivatives



Compd.	R	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
20		72	Over 300 (DMF)	$C_8H_6N_6O_2$	44.04 (44.41	2.77 2.95	38.52 38.21)
21[2,3]		64	Over 300 (DMF–EtOH)	$C_{11}H_6N_6OS$	48.98 (48.99	2.24 2.49	31.10 30.90)
22		99	Over 300 (DMF)	$C_7H_5N_7O$	41.38 (41.58	2.48 2.79	48.26 47.98)
23		83	Over 300 (DMF)	$C_8H_5N_7O_3$ DMF	41.25 (41.29	3.78 3.78	34.99 35.26)
24		75	Over 300 (DMF)	$C_6H_4N_8O$	35.30 (35.66	1.98 2.34	54.89 54.58)

using KBr disks. Silica gel 60 (E. Merck, 0.063—0.200 mm) was used for column chromatography, unless otherwise noted. Organic extracts were dried over anhydrous Na_2SO_4.

Ethyl (Substituted tetrazol-5-yl)acetates (Table I). Ethyl (1-Benzyl-1*H*-tetrazol-5-yl)acetate (2d) and Ethyl (2-Benzyl-2*H*-tetrazol-5-yl)acetate (3d) Benzyl chloride (3.17 g, 25 mmol) was added to a mixture of ethyl (5-tetrazolyl)acetate (**1**) (3.12 g, 20 mmol) and Et_3N (9.10 g, 90 mmol). The mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The residue was taken up in 50 ml of water, and the aqueous mixture was extracted with EtOAc. The extract was washed successively with 14% NH_4OH and brine, then the organic layer was dried. Removal of the solvent gave a mixture of **2d** and **3d** (1.87 g, total 37%, **2d**/**3d** = 2/3) as an oil. The product was used in the next step without further purification. The following ^{1}H-NMR data are based on the spectrum of the mixture **2d**: ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2O$), 3.83 (2H, s, $C\underline{H}_2COO$), 4.14 (2H, q, J = 7.0 Hz, $CH_3C\underline{H}_2O$), 5.63 (2H, s, $PhC\underline{H}_2$),

7.38 (5H, s, Ar-H). **3d**: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz, CH_3CH_2O), 3.94 (2H, s, CH_2COO), 4.19 (2H, q, J=7.0 Hz, CH_3CH_2O), 5,76 (2H, s, $PhCH_2$), 7.38 (5H, s, Ar-H).

A mixture of **2e** and **3e** (**2e**/**3e**=5/4) was prepared in a similar manner. **2e**: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz, CH_3CH_2O), 3.80 (3H, s, OCH_3), 3.83 (2H, s, CH_2COO), 4.15 (2H, q, J=7.0 Hz, CH_3CH_2O), 5.55 (2H, s, $PhCH_2$), 6.88 (2H, d, J=8.8 Hz, Ar-H), 7.18 (2H, d, J=8.8 Hz, Ar-H). **3e**: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz, CH_3CH_2O), 3.80 (3H, s, OCH_3), 3.93 (2H, s, CH_2COO), 4.19 (2H, q, J=7.0 Hz, CH_3CH_2O), 5.68 (2H, s, $PhCH_2$), 6.88 (2H, d, J=9 Hz, Ar-H), 7.33 (2H, d, J=9 Hz, Ar-H).

Ethyl 3-(Dimethylamino)-2-(substituted tetrazol-5-yl)acrylates (Table II). Ethyl 2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate (4a) A mixture of **3a** (58.7 g, 0.28 mol) and DMF diethylacetal (75% purity, 59.7 g, 0.31 mol) was heated at 100 °C for 8 h, then concentrated *in vacuo*. The residue was dissolved in ether, and petroleum ether was added and then left standing. The precipitated prisms were collected by filtration to give 31.1 g (42%) of **4a**. The mother liquor was concentrated and then diluted with benzene, washed with water, dried and concentrated *in vacuo*. The resultant crystals were recrystallized from ether–petroleum ether to give a further 19.6 g (27%) of **4a**, which was identical with the first crop IR: 1695 cm^{-1} (C=O). ^{13}C-NMR ($CDCl_3$)δ: 14.4 (CH_2CH_3), 29.3 ($C(CH_3)_3$), 35—50 (br, N (CH_3)$_2$), 59.7 (OCH_2CH_3), 63.4 ($C(CH_3)_3$), 85.1 (=CCOOEt), 152.4 ($CHNMe_2$), 161.3 (NC=N), 168.6 (COOEt). *Anal.* Calcd for $C_{12}H_{21}N_5O_2$: C, 53.92; H, 7.92; N, 26.20. Found: C, 53.83; H, 7.85; N, 26.55.

Compounds **4b**, **4c** and **5b** were prepared in a similar manner. **4b**: IR 1685 cm^{-1} (C=O). ^{13}C-NMR ($CDCl_3$) δ: 14.5 (CH_2CH_3), 39.5 (NCH_3), 35—50 (broad, N (CH_3)$_2$), 59.9 (OCH_2CH_3), 85.2 (=CCOOEt), 152.7 ($CHNMe_2$), 162.1 (NC=N), 168.5 (COOEt). *Anal.* Calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 47.94; H, 6.59; N, 31.87. **5b**: ^{13}C-NMR ($CDCl_3$) δ: 14.6 (CH_2CH_3), 34.1 (NCH_3), 35—50 (br, N (CH_3)$_2$), 60.2 (OCH_2CH_3), 78.9 (=CCOOEt), 151.7 (NC=N), 154.3 ($CHNMe_2$), 166.9 (COOEt). *Anal.* Calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.06; H, 6.67; N, 30.99. **4c**: This compound was purified by column chromatography with benzene–acetone (20:1). IR: 1690 cm^{-1} (C=O).

Ethyl 2-(2-Benzyl-2*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate (4d) and Ethyl 2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(dimethylamino)acrylate (5d) DMF diethylacetal (94% purity, 1.43 g, 9.1 mmol) was added to a mixture of **2d** and **3d** (**2d**/**3d**=2/3, 1.87 g, 7.6 mmol). The mixture was heated at 100 °C for 20 h and concentrated *in vacuo*. The residue was chromatographed with benzene–acetone (20:1) to give 1.04 g (46%) of **4d** as an oily product from the first eluate. IR: 1695 cm^{-1}(C=O). The second eluate gave 0.78 g (34%) of **5d** as an oily product. IR: 1690 cm^{-1} (C=O).

Compound **5c**, **4e** and **5e** were prepared in a similar manner. **5c**: IR; 1690 cm^{-1} (C=O). **4e**: IR: 1690 cm^{-1} (C=O). **5e**: IR 1690 cm^{-1} (C=O). *Anal.* Calcd for $C_{16}H_{21}N_5O_3$: C, 57.99; H, 6.39; N, 21.14. Found: C, 58.11; H, 6.45; N, 21.00.

Ethyl 2-(*tert*-Butyl-2*H*-tetrazol-5-yl)-3-(substituted amino)acrylates (Table IV). Ethyl 2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)-3-[(5-methyloxazol-2-yl)-amino]acrylate (7) A mixture of 2-amino-5-methyloxazole (**6**) (100 mg, 1.0 mmol) and DMTE (267 mg, 1.0 mmol) in AcOH (5 ml) was refluxed for 80 min. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$ and water. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried and then concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (E. Merck, Silica gel 60 F_{254}) to give 180 mg (56%) of **7** as a colorless oil.

Compound **13**—**15** were prepared in a similar manner. **15**: mp 208—211 °C (recrystallized from benzene). IR: 1710 cm^{-1} (C=O).

2,3-(Ring Fused)-5-(2-*tert*-butyl-2*H*-tertazol-5-yl)-4*H*-pyrimidin-4-one Derivatives (Table V) Procedure A, 6-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one (**17**): A solution of **13** (1.79 g, 5.9 mmol) in AcOH (20 ml) was refluxed for 7 h. The reaction mixture was concentrated *in vacuo*, and MeOH was added to the residue to give 440 mg (63%) of **17** as colorless crystals. mp over 300 °C.

Compounds **8**, **18** and **19** were prepared in a similar manner. The IR and ^{1}H-NMR spectra of these products coincided with those of the products obtained in procedure B.

Procedure B, 6-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)-2-methyl-5*H*-oxazolo-[3,2-*a*]pyrimidin-5-one (**8**): A mixture of **6** (1.47 g, 15 mmol) and DMTE (4.01 g, 15 mmol) in AcOH (30 ml) was refluxed for 30 h. The reaction mixture was concentrated *in vacuo*, and MeOH (3 ml) was added to the residue to give 1.60 g (39%) of **8** as pale yellow crystals. A part of the crystals was recrystallized from MeOH to give colorless needles, mp 202—203.5 °C. IR: 1700 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.83 (9H, s, C (CH_3)$_3$), 2.50 (3H, d, J=2.0 Hz, CH_3), 7.64 (1H, d, J=2.0 Hz, C_3-H), 8.86 (1H, s, C_7-H).

Compounds **16**—**19** were prepared in a similar manner. **16**: IR: 1705 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.82 (9H, s, C(CH_3)$_3$), 7.40—7.85 (3H, m, C_7-H, C_8-H and C_9-H), 8.85 (1H, s, C_2-H), 9.15—9.40 (1H, m, C_6-H). **17**: IR: 1690 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3COOH) δ: 1.92 (9H, s, C (CH_3)$_3$), 7.04 (1H, d, J=3.0 Hz, C_3-H), 8.52 (1H, d, J=3.0 Hz, C_2-H), 9.23 (1H, s, C_5-H). **18**: IR: 1700 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3COOH) δ: 1.44 (3H, t, J=7.0 Hz, CH_3CH_2O), 1.93 (9H, s, C (CH_3)$_3$), 4.58 (2H, q, J=7.0 Hz, CH_3CH_2O), 8.64 (1H, s, C_2-H), 9.07 (1H, s, C_5-H). **19**: IR: 1710 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.83 (9H, s, C(CH_3)$_3$), 8.27 (1H, s, C_2-H), 8.88 (1H, s, C_5-H).

2,3-(Ring Fused)-5-(5-tetrazolyl)-4*H*-pyrimidin-4-one Derivatives (Table VI). 2-Methyl-6-(5-tetrazolyl)-5*H*-oxazolo[3,2-*a*]pyrimidin-5-one (20) A mixture of **8** (1.60 g, 5.8 mmol) and concentrated H_2SO_4 (4.5 ml) was heated at 110 °C and stirred for 90 min. The reaction mixture was cooled, and then poured into ice water to yield a solid. The resulting solid was collected by filtration, washed thoroughly with water, and recrystallized from DMF to give 0.91 g (72%) of **20** as colorless prisms, mp over 300 °C. IR: 1690 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3COOH) δ: 2.63 (3H, d, J=2.0 Hz, CH_3), 7.93 (1H, d, J=2.0 Hz, C_3-H), 9.32 (1H, s, C_7-H).

Compounds **21**—**24** were prepared in a similar manner. **21**: IR: 1670 cm^{-1} (C=O). ^{1}H-NMR (CF_3COOH) δ: 7.90—8.30 (3H, m, C_7-H, C_8-H and C_9-H), 9.63 (1H, m, C_2-H), 9.30—9.70 (1H, m, C_6-H). **22**: IR: 1660 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3COOH) δ: 6.99 (1H, d, J=3.0 Hz, C_3-H), 8.63 (1H, d, J=3.0 Hz, C_2-H), 9.56 (1H, s, C_5-H). **23**: ^{1}H-NMR (CF_3COOH) δ: 8.80 (1H, s, C_2-H), 9.61 (1H, s, C_5-H). **24**: IR: 1665 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3COOH) δ: 8.70 (1H, s, C_2-H), 9.52 (1H, s, C_5-H).

References

1) J. C. G. Cox, J. E. Beach, A. M. J. N. Blair, A. J. Clarke, J. King, T. B. Lee, D. E. E. Loveday, G. F. Moss, T. S. C. Orr, J. T. Ritchie, and P. Shear, *Advan. Drug Res.*, **5**, 115 (1970).
2) J. J. Wade, C. B. Toso, C. J. Matson, J. Charles, and V. L. Stelzer, *J. Med. Chem.*, **26**, 608 (1983).
3) J. P. Yevich, D. L. Temple, Jr., R. R. Convington, D. A. Owens, R. J. Seidehamel, and K. W. Dungan, *J. Med. Chem.*, **25**, 864 (1982).
4) K. Saito, I. Hori, M. Igarashi, and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **47**, 476 (1974).
5) S. V. Sunthankar and S. D. Vaidya, *Indian J. Chem. Sect. B*, **15B**, 349 (1977).
6) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
7) J. Cohen, W. G. Finnegan, and R. A. Henry, U. S. Patent 3073731 (1963) [*Chem. Abstr.*, **58**, 11164*c* (1964)]
8) A. Nohara, T. Kato, T. Kawazaki, and Y. Sawa, Japan. Patent Kokai, 52-116469 (1977) [*Chem. Abstr.*, **88**, 22927*b* (1977)]
9) R. Raap and J. Howard, *Can J. Chem.*, **47**, 813 (1969).
10) J. H. Markbraf, W. T. Bachmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965).
11) L. Huff and R. A. Henry *J. Med. Chem.*, **13**, 777 (1970).
12) R. N. Butler, *Can. J. Chem.*, **51**, 2315 (1973).
13) S. Braun, *Org. Magn. Reson.*, **11**, 197 (1978).
14) C. Tanaka and H. Shibakawa, *Yakugaku Zasshi*, **91**, 425 (1971).
15) P. Shmidt and J. Druey, *Helv. Chim. Acta.*, **39**, 986 (1956).