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Synthesis of New Water-soluble Dihydropyridine Vasodilators

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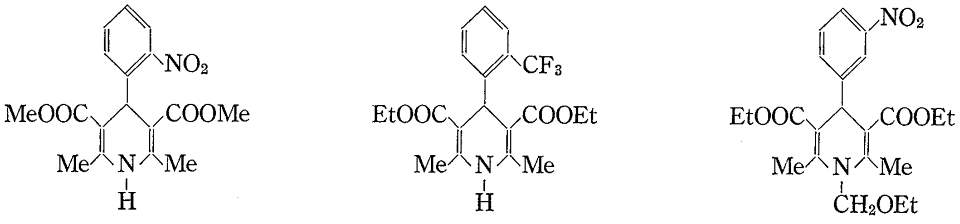
Several kinds of water-soluble dihydropyridine vasodilators were prepared and their vasodilating activities were evaluated. Among them, 2-(N-benzyl-N-methylamino)-ethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (YC-93) was found to have outstanding activity and bioavailability. Various synthetic routes for this compound were examined.

Keywords——dihydropyridine; vasodilating activity; Hantzch reaction; asymmetric; Nifedipine; ester; vasodilators

Since the discovery of a simple procedure for the synthesis of 1,4-dihydropyridine by Hantzch2) in 1882, a number of dihydropyridines have been synthesized. In recent years, dimethyl 2,6-dimethyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate3) (Bayer 1040; Nifedipine) and diethyl 2,6-dimethyl-4-(*o*-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate4) (SKF 24260) have been studied and developed as clinically useful vasodilators. These compounds, however, are only slightly soluble in water. Thus, it has been reported4) that SKF 24260 is poorly absorbed when it is administered to dogs as a crystalline powder in gelatine capsules, although solubilization with polyethylene glycol 200 results in a 5-fold increase in absorption.



Bayer-1040 SKF-24260 **1**

Chart 1

Our recent study demonstrated that diethyl 2,6-dimethyl-1-ethoxymethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**1**) has a vasodilating activity of long duration (about 10 times that of papaverine). However, **1** was more insoluble in water than Bayer 1040 or SKF 24260. Accordingly, our efforts were directed to finding more water-soluble dihydropyridines in order to improve the bioavailability. First, we considered the introduction of water-soluble substituents into the N-alkyl side chain of **1**. Dihydropyridine contains a weakly acidic proton at the 1 position, which is abstracted by sodium hydride in absolute

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1) Location: *Azusawa 1-1-8, Itabashi Ku, Tokyo 174, Japan.*

2) A. Hantzch, *Ann. Chim.*, **215**, 1 (1882).

3) F. Bossert and W. Yater, *Naturwissenschaften*, **58**, 578 (1971).

4) *a*) S.S. Walkenstein, A.P. Inotoccia, T.L. Flanagan, B. Hawang, D. Flint, J. Villani, D. Blackburn, J. Weinstock, and H. Green, *J. Pharm. Sci.*, **62**, 580 (1973); *b*) B. Loev, M.M. Goodman, K.M. Snader, R. Tedeschi, and E. Marco. *J. Med. Chem.*, **17**, 956 (1974).

tetrahydrofuran to yield an anion.[5] The anion thus formed reacts with several electrophilic reagents[6-9] to yield N-alkyl-dihydropyridine derivatives. N-Substituted derivatives of **1** with various polar functions (**2**—**6**) were prepared by analogous N-substitution or by the Hantzch reaction followed by alkaline hydrolysis (Chart 2 and Table I).

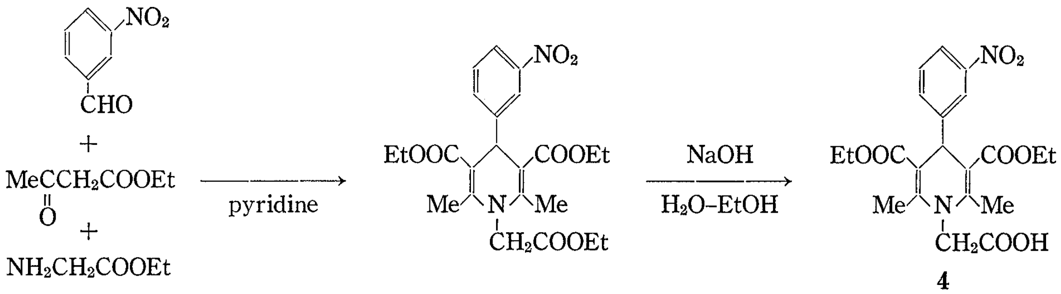

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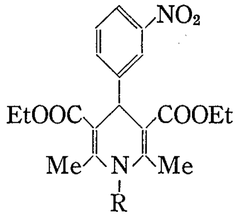
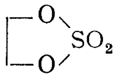
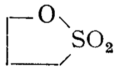
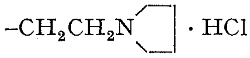
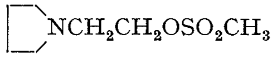
Chart 2

Table I. N-Alkyl Dihydropyridines



	R	Alkylating reagent	mp (°C)	Potency[a]
2	$-CH_2CH_2OSO_3Na$			1
3	$-CH_2CH_2CH_2SO_3Na$			1/3
4	$-CH_2COOH$		125—127	1/3
5	$-CH_2CH_2N\langle^{Me}_{Me}\cdot HCl$	$^{Me}_{Me}\rangle NCH_2CH_2Br$	190—191	1/3
		$^{Me}_{Me}\rangle NCH_2CH_2OSO_3Me$	190—191	1/3
6			187—189	1/3

[a] The potency is expressed as the ratio of cerebral vasodilating activity to that of papaverine taken as 1 (blood flow of a dog).

The structure of these compounds (**2**—**6**) were confirmed by their spectral data. While compounds **2**—**4** had increased water-solubility, their potency was reduced to 1/10 to 1/30 of that of **1**. Compounds **5**—**6** were slightly soluble in water.

When we tried to react **1** with dimethylaminoethanol in benzene in the presence of sodium in order to prepare an N-substituted compound, ester exchange occurred rather than

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5) R. Gompper and H.U. Wagner, *Angew. Chem. Int. Ed. Engl.* **15**, 321 (1976).

6) J. Blunken and G. Glocken, Ger. Patent 15024 (1960).

7) D.A. Tomalia and J.C. Falk, *J. Heterocycl. Chem.*, **9**, 891 (1972).

8) "Organic Synthesis," Coll. Vol. II, ed. by A.H. Blatt, John Willey and Sons, Inc., New York, 1963, p. 91.

9) A.C. Cope, *J. Am. Chem. Soc.*, **74**, 611 (1952).

substitution of the N-alkyl side chain, and the reaction gave a mixture of asymmetric and symmetric esters, followed by acid-catalyzed removal of the ethoxymethyl group from the intermediates[10] (Chart 3).

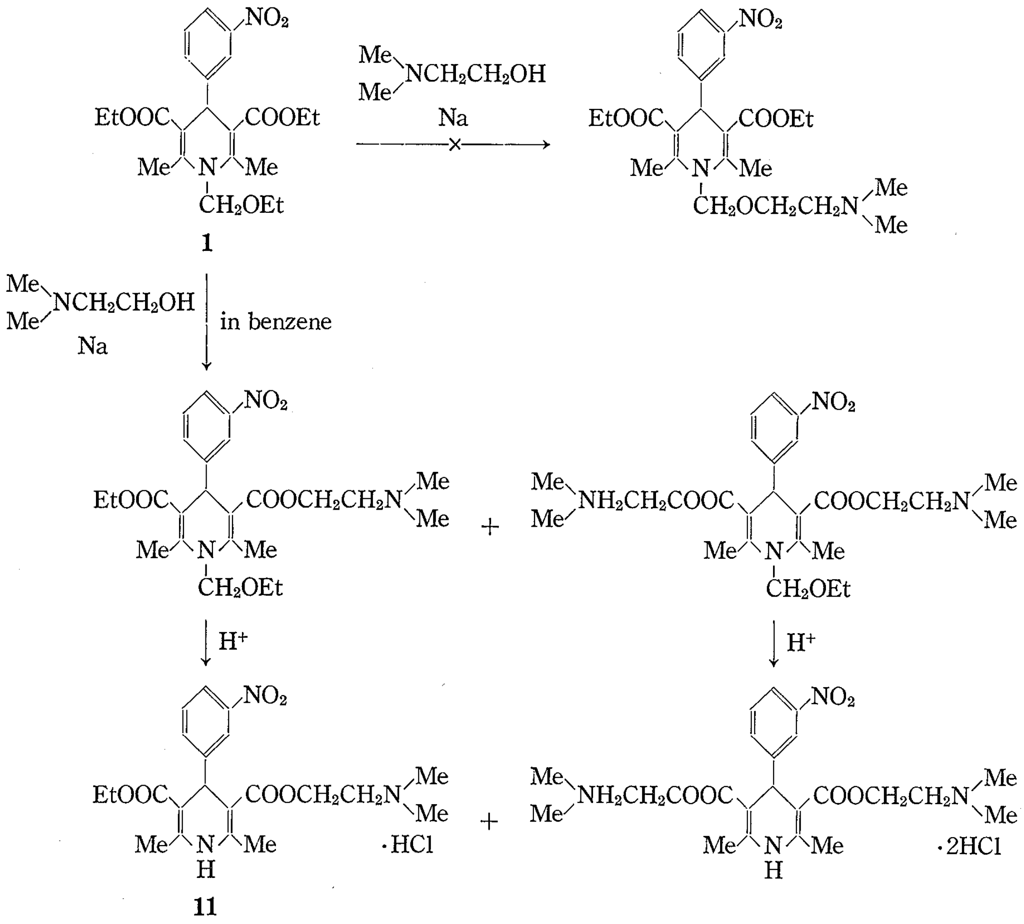

Chart 3

The asymmetric esters of dihydropyridine (**11**) thus obtained had both water solubility and vasodilating activity which was 10 times that of papaverine. Accordingly, analogous ester exchange reactions were investigated to find more active compounds. Thus, compounds **7** to **19** were prepared.

When we used 1-dimethylamino-2-propanol containing about 2% water, the monocarboxylic acid of dihydropyridine was obtained in fairly good yield as a result of ester hydrolysis rather than ester exchange (Chart 4).

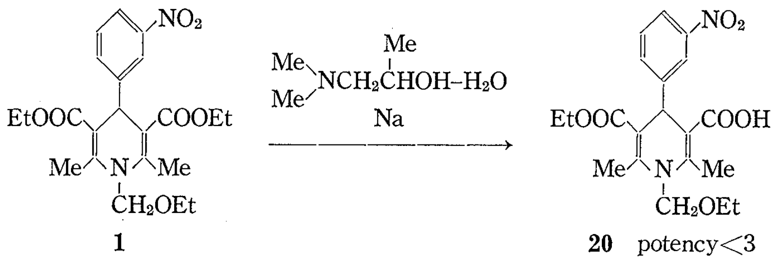

Chart 4

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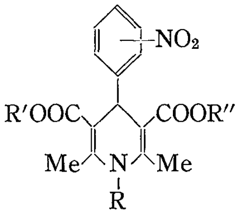
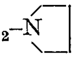
[10] F. Bossert, H. Meyer, and W. Vater, Ger. Patent 218664 (1974).

It has been reported that the formation of monocarboxylic acid of dihydropyridine is very difficult, especially if there is no substituent in 1-position.[11] This reaction, however, seems to be useful for preparing such dihydropyridines, because the ethoxymethyl group of the compound (**20**) can easily be removed by mild acid hydrolysis as we noted previously.

Table II. Dihydropyridines prepared by Ester Exchange



	Position of NO_2	R	R'	R"	mp (°C)	Potency
7	*m*	CH_2OEt	Et	$-CH_2CH_2N<^{Me}_{Me}$	90—92	1/3
8	*m*	CH_2OEt	$-CH_2CH_2N<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$	95—97	<1/3
9	*m*	H	Me	$-CH_2CH_2N<^{Me}_{Me}$	110—114(HCl)	10
10	*o*	H	Me	$-CH_2CH_2N<^{Me}_{Me}$	211—213(HCl)	10
11	*m*	H	Et	$-CH_2CH_2N<^{Me}_{Me}$	126—128(HCl)	10
12	*m*	H	Me	$-CH_2CH_2-$ 	194—197(HCl)	10
13	*m*	H	Me	$-CH(Me)CH_2N<^{Me}_{Me}$	225—228(HCl)	10
14	*o*	H	Me	$-CH(Me)CH_2N<^{Me}_{Me}$	268—270(HCl)	10
15	*m*	H	Me	$-CH_2CH_2CH_2N<^{Me}_{Me}$	228—231(HCl)	10
16	*m*	H	$-CH_2CH_2N<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$	95— 97(HCl)	1
17	*m*	Me	Et	$-CH_2CH_2N<^{Me}_{Me}$	158—160(HCl)	1/3
18	*o*	Me	Et	$-CH_2CH_2N<^{Me}_{Me}$		1/3
19	*m*	Me	$-CH_2CH_2N<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$	198—200(HCl)	<1/3

As shown in Table II, it is clear that a substituent on the ring-nitrogen decreases the potency, and that the potency of asymmetric esters of dihydropyridines is better than that of symmetric ones. Thus our attention was focused on modification of the ester group of asymmetric dihydropyridines. These asymmetric esters can be prepared in good yield by a modification of the Hantzch reaction, rather than by ester exchange.

The Hantzch reaction involves the simultaneous reaction of an aldehyde, acetoacetic acid ester, and ammonium hydroxide. It is not necessary to isolate the intermediates, and the procedure is simple. A variation of the modified procedure involves preformation of the presumed intermediate, aminocrotonic acid ester, and reaction of this with the aldehyde and the substituted acetoacetic acid ester. This method is most useful for the synthesis of asymmetric esters of dihydropyridines.

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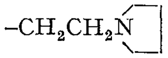
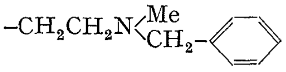
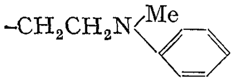
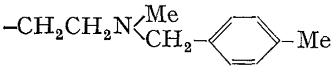
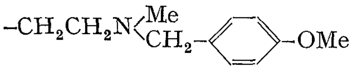
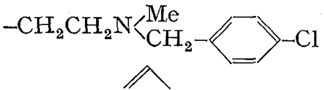
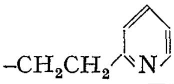
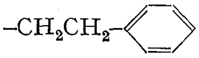
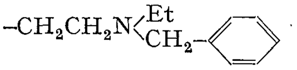
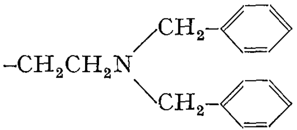
[11] A. Sausins, V. Lusis, B. Cekavicious, and G. Duburs, *Khim. Geterotsikl. Soedin.*, **2**, 272 (1978).

Table III. Substituted Acetoacetate (A)

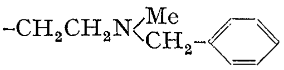
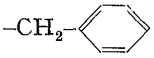
CH_3COCH_2COOR

R	bp (°C/Torr)	Method
$-CH_2CH_2N{<}^{Me}_{Me}$	103/2	A, B
	90/4	B
$-CH_2(Me)CH_2N{<}^{Me}_{Me}$	82—85/4	A
	140/0.25	A, B
$-CH_2CH_2CH_2N{<}^{Me}_{Me}$	160—163/0.25	A, B
$-CH_2CH_2N{<}^{Me}_{Et}$	115—117/5	B
	140—146/0.4	B
	140—147/1	A, B
	170/0.5—0.6	A
	140/0.5—0.6	A
		B
	118—120/0.4	A
	140/0.4	A
	190—192/1	A
$-CH_2CH_2Cl$	100—102/10	A
$-CH(CH_3)COOEt$	103/0.5	A
$-CH_2CH_2OCH_2CH_2CH_3$	130—137/20—21	A

Method A···diketene method. Method B···ester exchange reaction.

Table IV. Substituted Aminocrotonate (B)

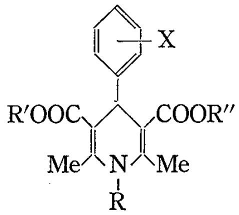
$$CH_3\underset{NH_2}{C}=CH-COOR$$

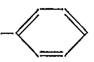
R	bp (°C/Torr) or mp (°C)	
Me	mp	83—84
Et	bp	80/1
$-CH{<}^{Me}_{Me}$	bp	80/1
$-C\begin{smallmatrix}Me\\Me\\Me\end{smallmatrix}$	bp	98—100/13
$-CH_2CH{<}^{Me}_{Me}$	bp	95—100/5—6
$-CH_2CH_2N{<}^{Me}_{Me}$	mp	55—57
	mp	59—61
$-CH_2CH_2OCH_2CH_2CH_3$	bp	120/0.7
	bp	140—150/3—4

Substituted acetoacetic acid esters and aminocrotonic acid esters used in the above reaction are listed in Table III and IV. These compounds have been prepared by the reaction of a diketene with corresponding disubstituted aminoalcohols, or by ester exchange between acetoacetic acid ester and corresponding disubstituted aminoalcohols in the presence of a base.

Dihydropyridines thus prepared by means of the modified Hantzch reaction are summarized in Table V.[12,13]

Table V. Dihydropyridines prepared by Means of the Modified Hantzch Reaction



	X	R	R′	R″	mp (°C)	Potency
18	*o*-NO_2	Me	Et	$-CH_2CH_2N<^{Me}_{Me}$		1/3
21	*o*-NO_2	Me	$-CH<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$		1
10	*o*-NO_2	H	Me	$-CH_2CH_2N<^{Me}_{Me}$	211—213(HCl)	10
9	*m*-NO_2	H	Me	$-CH_2CH_2N<^{Me}_{Me}$	110—114(HCl)	10
22	*p*-NO_2	H	Me	$-CH_2CH_2N<^{Me}_{Me}$		1/3
11	*m*-NO_2	H	Et	$-CH_2CH_2N<^{Me}_{Me}$		10
23	*m*-NO_2	H	$-CH<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$		10
24	*m*-NO_2	H	$-C\begin{smallmatrix}\diagup Me\\ -Me\\ \diagdown Me\end{smallmatrix}$	$-CH_2CH_2N<^{Me}_{Me}$	120(HCl)	10
25	*m*-NO_2	H	$-CH_2CH<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$	104—105(HCl)	10
26	*m*-NO_2	H	$-CH<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Me}$	138—140(HCl)	20
27	*m*-NO_2	H	$-C\begin{smallmatrix}\diagup Me\\ -Me\\ \diagdown Me\end{smallmatrix}$	$-CH_2CH_2N<^{Me}_{Me}$	188—190(HCl)	10
28	*m*-NO_2	H	$-CH_2CH_2OCH_2CH_2CH_3$	$-CH_2CH_2N<^{Me}_{Me}$	165—167(HCl)	10
29	*m*-NO_2	H	$-CH_2-$	$-CH_2CH_2N<^{Me}_{Me}$	135—141(HCl)	10
30	*m*-NO_2	H	Me	$-CH_2CH_2-$	185—187(HCl)	10
31	*m*-NO_2	H	Me	$-CH_2CH_2N<^{Mt}_{Mt}$	128(HCl)	10
32	*m*-NO_2	H	$-CH<^{Me}_{Me}$	$-CH_2CH_2N<^{Me}_{Et}$	113—120(HCl)	10

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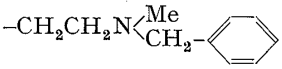
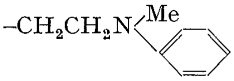
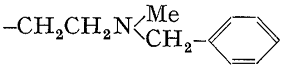
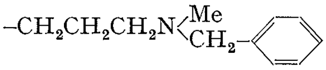
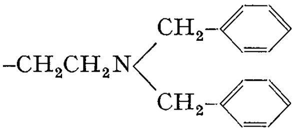
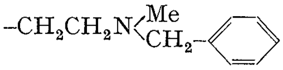
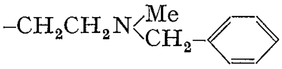
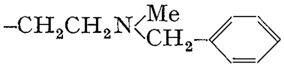
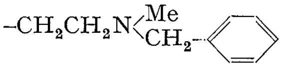
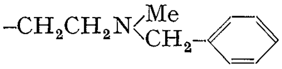
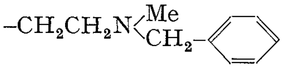
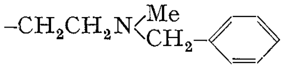
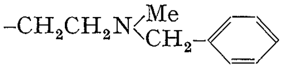
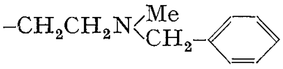
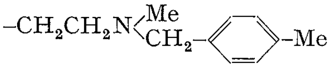
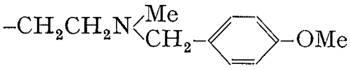
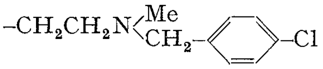
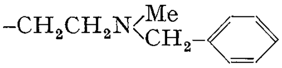
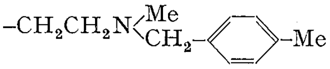
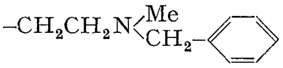
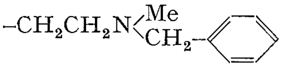
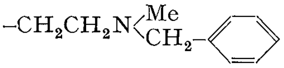
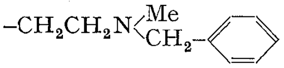
12) L.I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

13) H. Gilman, J. Tolman, F. Yeoman, L.A. Woods, D.A. Shireley, and S. Avakin, *J. Am. Chem. Soc.*, **68**, 426 (1946).

	X	R	R′	R″	mp (C°)	Potency
33	*m*-NO_2	H	Me		135—138(HCl)	30
34	*m*-NO_2	H	Me		170—181(HCl)	200 YC-93
35	*m*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$		132—135(HCl)	200
36	*m*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$		166—168(HCl)	200
37	*m*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$			30
16	*m*-NO_2	H	$-\mathrm{CH_2CH_2N}{<}^{\mathrm{Me}}_{\mathrm{Me}}$	$-\mathrm{CH_2CH_2N}{<}^{\mathrm{Me}}_{\mathrm{Me}}$	95— 97(2HCl)	1
38	*m*-NO_2	H	$-\mathrm{CH_2CH_2N}{<}^{\mathrm{Me}}_{\mathrm{Me}}$			10
39	*m*-NO_2	H				10
40	*p*-NO_2	H	Me		181—183(HCl)	1
41	*o*-NO_2	H	Me			200
34	*m*-NO_2	H	Me		170—181(HCl)	200
42	*m*-NO_2	H	Et		168—169(HCl)	200
35	*m*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$		171—173(HCl)	200
43	*o*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$		208—210(HCl)	200
44	*m*-NO_2	H	$-\mathrm{CH}{<}^{\mathrm{Me}}_{\mathrm{Me}}$			200
45	*m*-NO_2	H	Et			200
46	*m*-NO_2	H	Et		135—139(HCl)	200
47	*m*-CF_3	H	Me		148—152(HCl)	30
48	*m*-CF_3	H	Me		130—132(HCl)	30
49	*m*-CF_3	H	Et			30
50	*o*-CF_3	H	Me		196—200(HCl)	30
51	*o*-SCH_3	H	Me		210—213(HCl)	30
52	H	H	Me		201—202(HCl)	1

As shown in Table V, the introduction of an N-benzyl-N-methylaminoethyl group into an asymmetric ester of dihydropyridine significantly increased the vasodilating activity, which was more than 10 to 20 times that of compounds with an N,N-dialkylaminoethyl group (compound **31** *vs.* **34**; **26** *vs.* **35**). Among them, 2-(N-benzyl-N-methylamino)ethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (**34**) (YC-93) was the most active. Thus, several other synthetic routes for these compounds were examined; the results are summarized in Chart 5.

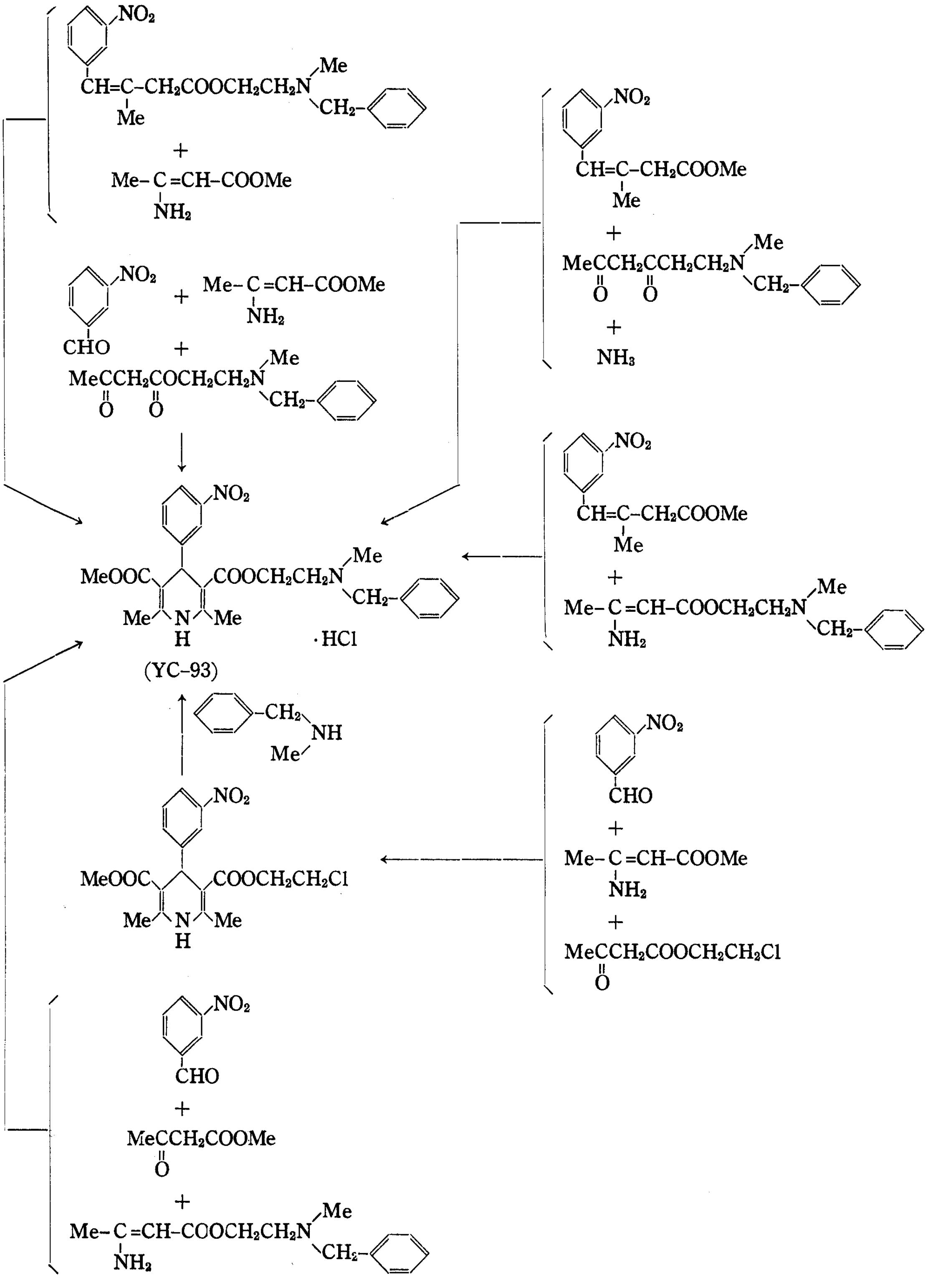
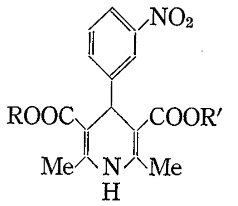


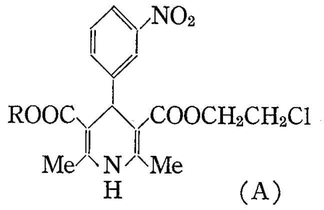
Chart 5

Alkyl 2-chloroethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylates (A), one of which already figured as an intermediate of **34** (YC-93) in Chart 5, are new compounds prepared by the modified Hantzch reaction from 2-chloroethyl acetoacetate, aminocrotonic acid ester, and an aldehyde in good yields. These compounds are useful for preparing amino-substituted asymmetric esters of dihydropyridine by substitution reactions with several kinds of amines. Such reactions are useful for the preparation of compounds containing a secondary amine in the ester moiety, which are difficult to prepare by means of the usual condensation reaction. Compounds prepared by this method are summarized in Table VI.

TABLE VI. Dihydropyridines prepared from Chloro-esters (A)



	R	R′	mp (°C)	Potency
57	Me	$CH_2CH_2NHCH_2$-⌬	128—130(HCl)	30
34	Me	-$CH_2CH_2N{<}^{Me}_{CH_2}$-⌬	170—181(HCl)	200
58	Me	CH_2CH_2NHMe		1
9	Me	$CH_2CH_2N{<}^{Me}_{Me}$	110—114(HCl)	10
59	Et	$CH_2CH_2N{<}^{CH_2CH_2OH}_{CH_2CH_2OH}$		1
60	-$CH{<}^{Me}_{Me}$	$CH_2CH_2N{<}^{Et}_{CH_2}$-⌬	130—135(HCl)	200



(A)

	R	mp (°C)	Potency
61	Me	130	100
62	Et	164—165	100
63	-$CH{<}^{Me}_{Me}$	143—145	100

[6-^{14}C]YC-93 was also prepared by the route shown in Chart 6, for further biological studies of absorption, distribution, metabolism, and excretion.[14]

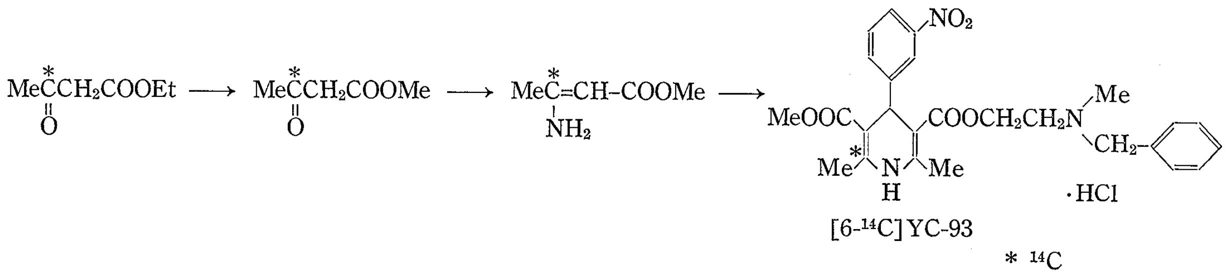


Chart 6

Another kind of dihydropyridine with one of the ester groups replaced by an acetyl group was prepared by the reaction of acetylacetone with the appropriate disubstituted aminocrotonate and aldehyde (Table VII). Replacement of one of the ester groups in dihydropyridines with an acetyl group decreased the potency (compound **34** *vs.* **54**; **46** *vs.* **55**).

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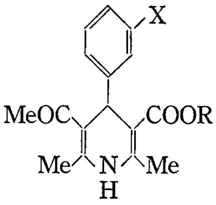
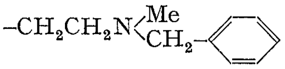
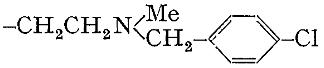
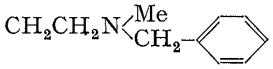
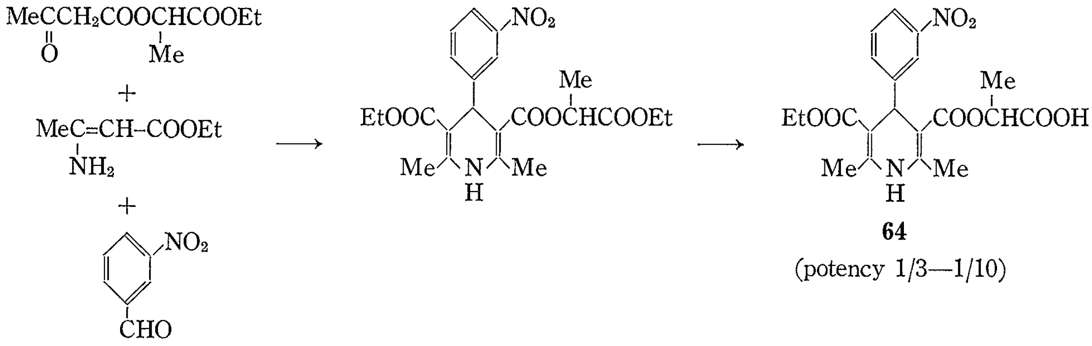
[14] *a*) S. Higuchi, H. Sasaki, Y. Shiobara, and T. Sado, *Xenobiotica.*, 7, 469 (1977); *b*) S. Higuchi, H. Sasaki, Y. Shiobara, and T. Sado, *Yamanouchi Kenkyujyo Hokoku.*, 3, 175 (1977).

Table VII. Dihydropyridines having an Acetyl Group in the Ester Moiety



	X	R	mp (°C)	Potency
53	*m*-NO_2	$-CH_2CH_2N<^{Me}_{Me}$	233—236(HCl)	10
54	*m*-NO_2		154—157(HCl)	30—100
55	*m*-NO_2		145—150(HCl)	30—100
56	*m*-CF_3		168—169(HCl)	

Condensation of 1-ethoxycarbonylethyl acetoacetate, ethyl aminocrotonate, and *m*-nitrobenzaldehyde, followed by mild alkaline hydrolysis, gave a different type of water-soluble dihydropyridine, 1-carboxyethyl 2,6-dimethyl-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**64**) (Chart 7).



64

(potency 1/3—1/10)

Chart 7

The vasodilating activities of various water-soluble dihydropyridines prepared in this study were evaluated; its results demonstrated that the nature of the substituent in the 4-phenyl ring has a significant effect on the potency.

The activity increases in order of $H \ll CF_3$, $SCH_3 < NO_2$ (compound **52** *vs.* **51**, **50** *vs.* **41**) (Table V). There is little difference in potency with variation in the position of the nitro group (*ortho* or *meta*) on the phenyl ring, but *meta* substitution results in reduced toxicity. A substituent in the *para* position on the phenyl ring caused a marked decrease in the activity (compound **40** *vs.* **41** *vs.* **34**). It is difficult to see a clear relationship between vasodilating activity and water solubility from the data in this study,[15,16] but some features can be seen. For instance, bis(2-dimethylamino)ethyl ester (**16**) of dihydropyridine, one of the most water-soluble compounds in this study, showed only a modest activity, whereas **34** (YC-93), one of the most active compounds in this study, had a rather low water solubility, although its solubility was more than 100 times that of Bayer 1040 or SKF 24260. This suggests that

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15) M. Iwanami, M. Murakami, K. Takahashi, M. Fujimoto, T. Shibanuma, R. Kawai, and T. Takenaka, Jpn. Patent (Kokai) 109384 (1974).

16) T. Takenaka, *Kiso to Rinsho.*, **8**, 51 (1974).

compounds having a high water solubility have weak activity, and compounds having moderate water solubility may be more desirable. We selected **34** (YC-93) as the most attractive candidate for a water-soluble dihydropyridine vasodilator in view of its activity and bioavailability.

Experimental

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with a JEOL MH-100 spectrometer (100 MHz) using Me_4Si as an internal standard. The following abbreviations are used; s singlet, d doublet, t triplet, m multiplet. Silica gel 60 F_{254} (Merck) TLC plates were used. For column chromatography, silica gel (Wakogel C-200) was used. Organic soluvents were dried over anhyd. $MgSO_4$ and all evaporations were carried out *in vacuo*. The cerebral vasodilating activities of the present compounds were measured by the following method. Adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg, *i.v.*) and artificially ventilated. Vertebral blood flow was measured with an electromagnetic flow meter (Nihon Koden Co., Ltd. MF-5) positioned around the vessel.

Sodium 2-[2,6-Dimethyl-3,5-bis(ethoxycarbonyl)-4-(*m*-nitrophenyl)-1,4-dihydropyridine-1-yl]ethylsulfate (2)——NaH (5.2 g, 50% dispersion in mineral oil) was added in small portions to a solution of 4.0 g of diethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate in 160 ml of THF at room temperature. After stirring for 30 min at this temperature, the mixture was cooled to −10 to −20°, and 20 g of ethylene sulfate in 80 ml of THF was added in small portions. After 1 hr of stirring at −10°, the reaction mixture was allowed to come to room temperature and then a further 4.0 g of NaH (50% dispersion in mineral oil) was added. After 3 hr of stirring, the reaction mixture was cooled to −10°, and 5.0 g of ethylene sulfate was added in small portions. After stirring for 1 hr at room temperature, the reaction mixture was diluted with 800 ml of ether and washed with 100 ml of H_2O. The ether layer was concentrated, and chromatographed on a silica gel column (12 × 50 cm). A small amount of starting material was eluted with AcOEt–MeOH. After removal of the solvent by evaporation, 3.5 g of **2** was obtained as crystals by the addition of 30 ml of H_2O to the residue. This compound was recrystallized from H_2O. *Anal.* Calcd. for $C_{21}H_{25}N_2NaO_{10}S$: C, 48.11, H, 4.69; N, 5.27. Found: C, 48.65; H, 4.84; N, 5.38. NMR ($CDCl_3$) δ: 1.20 (6H, t, $-CH_2C\underline{H}_3$), 2.40 (6H, s, $C_{2,6}-CH_3$), 4.06 (8H, $-C\underline{H}_2CH_3+\rangle NC\underline{H}_2C\underline{H}_2O-$), 5.10 (1H, s, C_4-H).

Diethyl 2,6-Dimethyl-1-(2-dimethylamino)ethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5)——Method a: NaH (1.3 g as a 50% dispersion in mineral oil) was added to a solution of 3.0 g of diethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dissolved in 12 ml of THF at room temperature. To this mixture, 3.26 g of dimethylaminoethyl methanesulfonate was added at −10° with stirring. The mixture was allowed to come to room temperature when the addition was completed. The residue was dissolved in H_2O and chromatographed on a silica gel column. After elution of a small amount of the starting material with AcOEt, elution with 1:1 AcOEt–MeOH afforded 2.5 g of **5**, mp 129—130°. Its hydrochloride was obtained by acidification with EtOH–HCl. *Anal.* Calcd. for $C_{23}H_{31}N_3O_6$: C, 62.01; H, 7.01; N, 9.43. Found: C, 62.01; H, 7.20; N, 9.42. NMR ($CDCl_3$) δ: 1.24 (6H, t, $-CH_2C\underline{H}_3$), 2.18 (4H, q, $-C\underline{H}_2CH_3$), 2.22 (6H, s, $\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\rangle N-$), 2.31 (2H, t, $-CH_2N\langle$), 2.52 (6H, s, $C_{2,6}-CH_3$), 3.83 (2H, t, C_1-H), 5.1 (1H, s, C_4-H).

Method b: NaH (0.173 g as a 50% dispersion in mineral oil) was added to a solution of 1.12 g of diethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dissolved in 5 ml of abs. THF at room temperature. The mixture was cooled to −10°, and 0.699 g of dimethylaminoethyl bromide-HBr suspended in 2.5 ml of THF was added. After stirring overnight at room temperature, the reaction mixture was diluted with ether and washed with H_2O. The ether layer was dried over anhyd. $MgSO_4$ and evaporated down to a small volume; 1.0 g of **5** was deposited from the solution upon cooling, as crystals of mp 129—130°.

3,5-Bis(ethoxycarbonyl)-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridin-1-ylacetic Acid (4)——A mixture of 3.0 g of *m*-nitrobenzaldehyde, 4.2 g of ethyl acetoacetate, and 2.8 g of glycine ethyl ester hydrochloride in 10 ml of pyridine was heated at 100° with stirring for 5 hr. When the reaction was over, the mixture was poured into H_2O and extracted with $CHCl_3$.

The $CHCl_3$ layer was concentrated, and the residue was chromatographed on silica gel with $CHCl_3$. Ethyl [3,5-bis(ethoxycarbonyl)-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridin-1-yl]acetate was isolated, mp 111° (0.5 g). This compound (0.5 g) was added to a mixture of EtOH and 1 N NaOH (1:1) (4 ml), and the mixture was refluxed for 3 hr. After cooling, EtOH was evaporated off and 50 ml of H_2O was added. After washing with benzene, the aqueous layer was acidified to pH 1—2 with 2 N HCl and extracted with benzene. The benzene layer was washed with H_2O. Concentration of the solvent gave 0.4 g of **4** in crystalline form, mp 125—127°. NMR ($CDCl_3$) δ: 1.26 (6H, t, $-CH_2C\underline{H}_3$), 2.46 (6H, s, $C_{2,6}-CH_3$), 4.16 (4H, q, $-C\underline{H}_2CH_3$), 4.50 (2H, s, $\rangle NCH_2-$), 5.10 (1H, s, C_4-H), 9.56 (1H, s, $-COOH$).

2-Dimethylaminoethyl Ethyl 1-Ethoxymethyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7) and Bis(2-dimethylamino)ethyl 1-Ethoxymethyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydro-

pyridine-3,5-dicarboxylate (8)——Benzene (50 ml) was added to a solution of 50 ml of 2-dimethylaminoethanol containing 3.5 g of **1** with stirring. After stirring for 1 hr at room temperature, the mixture was cooled, and 50 ml of ether and 20 ml of H_2O were added. The ether layer was separated and the aqueous layer was extracted twice with 20 ml of ether. The combined ether extract was dried over anhyd. $MgSO_4$. The solvent was evaporated off, and the residue was dissolved in a small amount of AcOEt then chromatographed on a silica gel column (4×28 cm) with AcOEt. From the first fraction, checked by silica gel TLC (eluent, AcOEt) 2.1 g of **7**, was isolated, mp 90—92°. *Anal.* Calcd. for $C_{24}H_{33}N_3O_7$: C, 60.62; H, 6.99; N, 8.84. Found: C, 60.62; H, 6.81; N, 8.57. NMR ($CDCl_3$) δ: 1.24 (6H, t, $-COOC\underline{H}_2CH_3$), 1.24 (3H, t, $-CH_2OCH_2C\underline{H}_3$), 2.24 (6H, s, $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!N-$), 2.90 (6H, s, $C_{2,6}-CH_3$), 2.56 (2H, t, $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!N-CH_2-$), 3.48 (2H, q, $-CH_2OC\underline{H}_2CH_3$), 4.20 (2H, t, $-COOCH_2-$), 4.86 (2H, s, $>NCH_2O-$), 5.20 (1H, s, C_4-H).

From the next fraction, 1.0 g of **8**, mp 95—97° was isolated. *Anal.* Calcd. for $C_{26}H_{38}N_4O_7$: C, 60.22; H, 7.39; N, 10.80. Found: C, 60.25; H, 7.38; N, 10.50. NMR ($CDCl_3$) δ: 1.22 (3H, t, $-OCH_2C\underline{H}_3$), 2.24 (12H, s, $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!N-$), 2.55 (6H, s, $C_{2,6}-CH_3$), 2.55 (4H, t, $>NCH_2-$), 3.47 (2H, q, $-OC\underline{H}_2CH_3$), 4.20 (4H, t, $-COOCH_2$), 4.86 (2H, s, $>NCH_2O-$), 5.20 (1H, s, C_4-H).

2-Dimethylaminoethyl Ethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (11) and Bis(2-dimethylamino)ethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (16)——Benzene (50 ml) was added to a solution of 50 ml of 2-dimethylaminoethanol containing 3.5 g of **1** with stirring. After stirring for 40 min at room temperature, the mixture was concentrated, the residue was treated with 20 ml of ice-cold water, and the resulting solution was acidified with conc. HCl. After standing for 30 min, the solution was extracted three times with 50 ml each of $CHCl_3$. This organic phase (A) contained compound **11**, and the water phase (B) contained compound **16**. These compounds were isolated by the following procedure. The organic phase was extracted three times with H_2O, then the combined aqueous extracts was made alkaline with NaOH, and extracted twice with 50 ml portions of $CHCl_3$. The organic solvent was concentrated and the residue was dissolved in a small amount of acetone, followed by acidification with EtOH–HCl. The hydrochloride of **11** crystallized from the solution upon cooling (1.5 g). *Anal.* Calcd. for $C_{21}H_{28}ClN_3O_6$: C, 55.57; H, 6.22; Cl, 7.81; N, 9.26. Found: C, 55.54; H, 6.31; Cl, 7.66; N, 9.08. NMR ($CDCl_3$) δ: 1.24 (3H, t, $-COOCH_2CH_3$), 2.24 (6H, s, $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!N-$), 2.36 (6H, s, $C_{2,6}-CH_3$), 2.54 (2H, t, NCH_2-), 4.16 (2H, q, $-COOC\underline{H}_2CH_3$), 4.16 (2H, q, $-COOC\underline{H}_2CH_3$), 4.16 (2H, t, $>NCH_2C\underline{H}_2O-$), 5.15 (1H, s, C_4-H), 6.86 (1H, s, C_1-H).

The water phase (B) was made alkaline with NaOH and extracted three times with 20 ml portions of $CHCl_3$. The combined extracts was dried over anhyd. $MgSO_4$ and concentrated. From the residue, 1.7 g of **16** was obtained. Acidification of this compound in $CHCl_3$ with EtOH–HCl gave its hydrochloride, mp 248°. *Anal.* Calcd. for $C_{23}H_{34}Cl_2N_4O_6$: C, 51.67; H, 6.60; Cl, 13.09; N, 10.39. Found: C, 51.79; H, 6.42; Cl, 13.29; N, 10.50. NMR ($CDCl_3$) δ: 2.20 (12H, s, $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!N-$), 2.35 (6H, s, $C_{2,6}-CH_3$), 2.54 (4H, t, $>NCH_2-$), 4.14 (4H, t, $-COOCH_2-$), 5.15 (1H, s, C_4-H), 6.25 (1H, s, C_1-H).

3-Ethoxycarbonyl-1-ethoxymethyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-5-carboxylic Acid (20)——Na (0.7 g) was added to a solution of 1-dimethylamino-2-propanol (10 ml) containing about 2% of water, then 1.0 g of **1** in 10 ml of benzene was added. After stirring for 1 hr at room temperature, the reaction mixture was diluted with 40 ml of H_2O, and acidified to pH 1—2 with conc. HCl. The solution was extracted with $CHCl_3$ and the extract was concentrated. The residue was chromatographed on silica gel with benzene–acetone (10: 1). The product (**20**) crystallized on concentration of the eluent (0.4 g) and was recrystallized from ether–petroleum ether, mp 175—176°. *Anal.* Calcd. for $C_{20}H_{24}N_2O_7$: C, 59.40, H, 5.98; N, 6.93. Found: C, 59.35; H, 6.02; N, 6.78. NMR ($CDCl_3$) δ: 1.23 (3H, t, $-CH_2OCH_2C\underline{H}_3$), 1.26 (3H, t, $COOCH_2C\underline{H}_3$), 2.54 (3H, s, C_3-CH_3), 2.58 (3H, s, C_5-CH_3), 3.48 (2H, q, $-CH_2OC\underline{H}_2CH_3$), 4.17 (2H, q, $COOC\underline{H}_2CH_3$), 4.86 (2H, s, $>NCH_2-$), 5.20 (1H, s, C_4-H).

Dihydropyridines by Condensation Reaction——General Procedure: The aldehyde (1 mol), the substituted acetoacetic acid ester (1 mol), and the aminocrotonic acid ester (1 mol) were dissolved in iso-PrOH (5—6 volume) and refluxed for 6 hr with stirring. The reaction mixture was concentrated and the residue was chromatographed on silica gel with an appropriate solvent. The dihydropyridines isolated usually crystallized as the hydrochloride upon addition of EtOH–HCl.

2-(N-Benzyl-N-methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate Hydrochloride (34) (YC-93)——Method a: A mixture of 1835 g of 2-N-benzyl-N-methylaminoethyl acetoacetate (about 95% purity), 823 g of methyl 3-aminocrotonate, and 1069 g of *m*-nitrobenzaldehyde in 5 l of iso-PrOH was refluxed for 6 hr with stirring. The reaction mixture was diluted with 7 l of $CHCl_3$ and washed with 4.7 l of dilute HCl (700 ml of conc. HCl diluted with 4 l of H_2O) then washed twice with 3 l each of H_2O. The $CHCl_3$ layer was dried over anhyd. $MgSO_4$ and concentrated. The residue was dissolved in 10 l of AcOEt and this solution was stirred overnight with cooling below 5°. The crystals that separated were collected by filtration. This compound (**34**) (**YC-93**) was isolated in two crystalline forms (α and β forms).

The α and β forms have different mp, IR, and X-ray diffraction patterns.

Procedure a: The crude product (130 g) was dissolved in 500 ml of MeOH and the solvent was removed completely *in vacuo*. The residue was dissolved in 600 ml of acetone and this solution was stirred overnight with cooling below 5°.

The crystals that separated were collected by filtration and washed with acetone, mp 168—170° (91 g, β form).

Procedure b: The crude product (100 g was treated as described above, and the resulting acetone solution was left to stand overnight at room temperature. The crystals were isolated as the α form, mp 179—181° (68 g). *Anal.* Calcd. for $C_{26}H_{30}ClN_3O_6$: C, 60.52; H, 5.86; Cl, 7.00; N, 8.14. Found: C, 60.76; H, 5.86; Cl, 6.87; N, 8.14. NMR (base) (d_6-DMSO): 2.21 (3H, s, $-N\langle\begin{smallmatrix}\underline{CH}_3\\CH_2-\end{smallmatrix}$), 2.36 (6H, s, $C_{2,6}$–CH_3), 2.66 (2H, t, $-CH_2N\langle$), 3.53 (2H, s, $-C\underline{H}_2-C_6H_5$), 4.21 (2H, t, $-COOCH_2-$), 5.18 (1H, s, C_4–H), 6.1 (1H, s, $\rangle$N–H).

Method b: A mixture of 1.5 g of 2-(N-benzyl-N-methylamino)ethyl 2-(*m*-nitrobenzylidene)acetoacetate and 0.452 g of methyl 3-aminocrotonate in 7 ml of iso-PrOH was refluxed for 6 hr with stirring. On cooling, the mixture was diluted with 50 ml of $CHCl_3$ and washed with 10 ml of 2 N HCl then twice with 10 ml each of H_2O. The $CHCl_3$ layer was evaporated and the residue was dissolved in 7 ml of AcOEt. After stirring this solution overnight at room temperature the crystals of the product was collected by filtration (1.4 g). It was recrystallized from acetone and identified by comparison with the IR of the standard compound prepared by method a, mp 170°.

Method c: A mixture of 2.49 g of methyl 2-(*m*-nitrobenzylidene)acetoacetate and 2.48 g of 2-(N-benzyl-N-methylamino)ethyl 3-aminocrotonate in 8 ml of iso-PrOH was refluxed for 6 hr, the reaction mixture was treated by method b, and 2.0 g of the same product, mp 170°, was obtained.

Method d: A mixture of 1.1 g of 2-(N-benzyl-N-methylamino)ethyl 2-(*m*-nitrobenzylidene)acetoacetate, 0.34 g of methyl acetoacetate, and 0.35 g of 28% NH_3 in 5 ml of EtOH was refluxed for 5 hr with stirring. The reaction mixture was treated by method b and 0.33 g of the same product, mp 170°, was obtained.

Method e: A mixture of 2.0 g of 2-chloroethyl methyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, and 1.3 g of N-methylbenzylamine in 6 ml of toluene was refluxed for 5 hr. From the reaction mixture, 1.7 g of the same product, mp 170°, was obtained by method b.

2-Dimethylaminoethyl Ethyl 1,2,6-Trimethyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (18)——A mixture of 2.6 g of ethyl acetoacetate and 1.35 g of $MeNH_2 \cdot HCl$ dissolved in 10 ml of pyridine was stirred for 20 hr at room temperature. To the reaction mixture, 3.0 g of *o*-nitrobenzaldehyde and 3.45 g of 2-dimethylaminoethyl acetoacetate were added, and the solution was heated at 90° for 30 min. The solvent was evaporated off and the residue was chromatographed on silica gel with AcOEt–acetone mixture (4: 1). The product (**18**) was isolated by concentration of the eluate (2.5 g). Its hydrochloride was obtained by acidification with EtOH–HCl. *Anal.* Calcd. for $C_{22}H_{30}ClN_3O_6$: C, 56.47; H, 6.46; Cl, 7.58; N, 8.98. Found: C, 56.22; H, 6.65; Cl, 7.62; N, 8.80. NMR ($CDCl_3$) δ: 1.24 (3H, t, $-COOCH_2C\underline{H}_3$), 2.44 (3H, s, $C_{2,6}$–CH_3), 2.48 (3H, s, $\rangle N-CH_3$), 2.84 (6H, s, $-N\langle\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 3.30 (3H, s, $\rangle NCH_3$), 3.46 (2H, t, $-C\underline{H}_2N\langle\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 4.50 (2H, q, $-COOC\underline{H}_2CH_3$), 5.72 (1H, s, C_4–H).

2-(N-Benzyl-N-methylamino)ethyl 3-Acetyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-5-carboxylate (54)——Method a: A mixture of 1.0 g of acetylacetone, 1.6 g of *m*-nitrobenzaldehyde, 2.5 g of 2-(N-benzyl-N-methylamino)ethyl acetoacetate, and 0.74 g of 28% NH_3 in 5 ml of EtOH was heated at 90° for 4 hr. After concentration, 20 ml of AcOEt was added to the residue and extracted with 2 N HCl. The aqueous phase was neutralized with $NaHCO_3$ and extracted with AcOEt. The solvent was concentrated and the residue was dissolved in 3 ml of EtOH, followed by acidification with 2N EtOH–HCl. A small amount of AcOEt was added to this EtOH solution until the solution became turbid. After cooling at 0° for 20 hr, **54** was obtained as crystals (1.4 g), mp 154—157°. *Anal.* Calcd. for $C_{26}H_{30}ClN_3O_5$: C, 62.46; H, 6.05; Cl, 7.09; N, 8.22. Found: C, 62.75; H, 6.21; Cl, 6.99; N, 8.22. NMR (d_6-DMSO) δ: 2.28 (3H, s, $-COCH_3$), 2.40 (6H, s, $C_{2,6}$–CH_3), 3.50 (2H, s, $-C\underline{H}_2-C_6H_5$), 4.40 (2H, t, $COOC\underline{H}_2CH_2-$), 4.56 (2H, t, $\rangle NCH_2-$), 5.24 (1H, s, C_4–H), 9.60 (1H, s, $\rangle$N–H).

Method b: A mixture of 5.0 g of 2-(N-benzyl-N-methylamino)ethyl 3-aminocrotonate, 3.1 g of *m*-nitrobenzaldehyde, and 2.0 g of acetylacetone in 15 ml of iso-PrOH was heated at 85° for 4 hr with stirring. The reaction mixture was diluted with 40 ml of AcOEt and extracted three times with excess dilute HCl and 40 ml of H_2O. The combined aqueous extract was saturated with NaCl and the resulting oily products were extracted with $CHCl_3$. Removal of $CHCl_3$ by evaporation gave 5.0 g of **54** by method a.

Method c: A mixture of 7.7 g of 2-(N-benzyl-N-methylamino)ethyl acetoacetate, 2.9 g of 4-amino-3-pentene-2-one, and 4.41 g of *m*-nitrobenzaldehyde in 20 ml of iso-PrOH was refluxed for 6 hr. The reaction mixture was treated by method a, and 8.6 g of the hydrochloride of **54** was obtained.

2-Chloroethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (61)——A mixture of 3.0 g of chloroethyl acetoacetate, 3.3 g of *m*-nitrobenzaldehyde, and 2.3 g of methyl 3-aminocrotonate in 5 ml of iso-PrOH was refluxed for 4 hr. After concentration, a small amount of AcOEt was added to the residue and the mixture was chromatographed on a silica gel column (3.2 × 20 cm) with AcOEt. The product **61**, mp 130—131°, was isolated by concentration of the eluate (2.0 g). *Anal.* Calcd. for $C_{18}H_{19}ClN_{20}O_6$: C, 54.76; H, 4.85; Cl, 8.98; N, 7.10. Found: C, 54.43; H, 4.74; Cl, 9.18; N, 6.91. NMR ($CDCl_3$)

δ: 2.36 (6H, s, $C_{2,6}$–CH_3), 3.62 (3H, s, –$COOCH_3$), 3.62 (2H, t, –CH_2Cl), 4.28 (2H, t, –$COOCH_2$–), 5.08 (1H, s, C_4–H), 5.90 (1H, s, $\rangle$N–H).

2-(N-Benzylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**57**)——A mixture of the chloroester (**61**) (2.0 g) and 1.2 g of benzylamine in 6 ml of toluene was refluxed for 3 hr. After concentration, the residue was chromatographed on silica gel. After elution of a small amount of impurities with 1 : 10 acetone–benzene mixture, elution with AcOEt afforded 0.8 g of **57**. Its hydrochloride, mp 128—130°, was obtained by acidification with EtOH–HCl. *Anal.* Calcd. for $C_{25}H_{27}N_3O_6$ (base): C, 64.50; H, 5.85; N, 9.03. Found: C, 64.41; H, 5.72; N, 8.85. NMR ($CDCl_3$) δ: 2.35 (6H, s, $C_{2,6}$–CH_3), 2.84 (2H, t, –$CH_2N\langle$), 3.64 (3H, s, –$COOCH_3$), 3.74 (2H, s, –$C\underline{H}_2$–C_6H_5), 4.16 (2H, t, –$COOCH_2$–), 5.09 (1H, s, C_4–H), 6.28 (1H, s, $\rangle$N–H).

2-Diethanolaminoethyl Ethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**59**)——A mixture of 5.0 g of diethanolamine and 3.0 g of 2-chloroethyl ethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate was heated at 110—120° for 5 hr. The mixture was diluted with 50 ml of ether and washed with 20 ml of H_2O. After drying over anhyd. $MgSO_4$, the ether solution was concentrated. The residue was dissolved in a small amount of AcOEt and chromatographed with AcOEt. Compound **59** was obtained as a crystalline powder (1.1 g). NMR ($CDCl_3$) δ: 1.23 (3H, t, –$COOC\underline{H}_2CH_3$), 2.36 (6H, s, $C_{2,6}$–CH_3), 2.70 (6H, $-C\underline{H}_2N\langle\begin{smallmatrix}C\underline{H}_2-\\ C\underline{H}_2-\end{smallmatrix}$), 3.56 (4H, –$C\underline{H}_2OH$), 4.15 (2H, q, –$COOC\underline{H}_2CH_3$), 4.15 (2H, t, –$COOC\underline{H}_2CH_2N\langle$), 5.12 (1H, s, C_4–H), 7.24 (1H, s, $\rangle$N–H).

Bis[2-(N-benzyl-N-methylamino)]ethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**39**)——A mixture of 2.0 g of 2-(N-benzyl-N-methylamino)ethyl acetoacetate, 2.0 g of 2-(N-benzyl-N-methylamino)ethyl 3-aminocrotonate and 1.2 g of *m*-nitrobenzaldehyde in 12 ml of iso-PrOH was heated at 85° for 6 hr. After cooling, the reaction miuture was extracted with 30 ml of AcOEt, and the extract was washed with excess of dilute HCl then washed three times with 20 ml of H_2O. The combined water phase was made alkaline with dilute NaOH, and extracted with $CHCl_3$. After concentration, the residue was chromatographed on silica gel with AcOEt. The product **39** was obtained as its hydrochloride by acidification with EtOH–HCl (3.0 g). *Anal.* Calcd. for $C_{35}H_{42}Cl_2N_4O_6$: C, 61.31; H, 6.17; Cl, 10.34; N, 8.17. Found: C, 61.06; H, 6.20; Cl, 10.22; N, 7.95. NMR ($CDCl_3$) δ: 2.15 (6H, s, $-N\langle\begin{smallmatrix}CH_3\\ CH_3\end{smallmatrix}$), 2.29 (6H, s, $C_{2,6}$–CH_3), 2.60 (4H, t, –$CH_2N\langle$), 3.44 (4H, s, –$CH_2N\langle$), 4.12 (4H, t, $COOC\underline{H}_2CH_2$–), 5.08 (1H, s, C_4–H), 6.20 (1H, s, $\rangle$N–H).

1-Carboxyethyl Ethyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**64**)——A mixture of 6.0 g of 1-ethoxycarbonylethyl acetoacetate, 3.84 g of ethyl 3-aminocrotonate, and 4.5 g of *m*-nitrobenzaldehyde in 10 ml of iso-PrOH was refluxed for 5 hr. After condensation, the residue was diluted with 20 ml of EtOH. 1-Ethoxycarbonylethyl ethyl 2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate crystallized upon cooling (4.5 g).

NaOH (10 ml) was added to a solution of 2.0 g of the ester in 10 ml of MeOH. After heating at 40—50° for 30 min, the mixture was washed with 10 ml of ether and acidified with 1 N HCl. The solution was extracted with $CHCl_3$, and the $CHCl_3$ extract was dried over anhyd. $MgSO_4$. After removal of the solvent, the product **64** was crystallized by addition of hexane (1.5 g). *Anal.* Calcd. for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.91; H, 5.56; N, 6.54. NMR ($CDCl_3$) δ: 1.20 (3H, t, –$COOCH_2C\underline{H}_3$), 1.40 (3H, d, $-\overset{C\underline{H}_3}{\overset{|}{C}}HCOOH$), 2.35 (6H, s, $C_{2,6}$–CH_3), 4.05 (2H, q, –$COOC\underline{H}_2CH_3$), 4.92 (1H, q, $-\underset{CH_3}{\underset{|}{C}}\underline{H}COOH$), 5.10 (1H, s, C_4–H), 8.10 (1H, s, $\rangle$N–H), 9.30 (1H, –COOH).

Substituted Acetoacetate——General Procedure: Method A: Na (0.2—0.4 mol) was added to a mixture of alkyl acetoacetate (1—1.5 mol) and disubstituted aminoalcohol (1 mol). The reaction mixture was heated at 140—150° for 5 or 6 hr. The alcohol formed during the reaction was removed. From the residue, the product was isolated by distillation.

2-(N-Benzyl-N-methylamino)ethyl Acetoacetate——Na (0.2 g) was added to a mixture of 35 g of ethyl acetoacetate and 44 g of 2-(N-benzyl-N-methylamino)ethanol. The reaction mixture was heated at 140—150° for 5 hr, and EtOH formed during the reaction was evaporated off. The residue was distilled under a vacuum. The product was obtained from the fraction 120—135°/0.5 torr, 7.0 g.

Method B: Diketene (1 mol) was added dropwise with stirring to a solution of disubstituted aminoalcohol (1 mol). The temperature of the reaction mixture was kept between 70—80° during the addition of diketene. When the addition was complete, the temperature was kept at 70—80° for 2—3 hr. The substituted acetoacetate formed was purified by distillation or used directly in the next process.

2-(N-Benzyl-N-methylamino)ethyl Acetoacetate——Diketene (755 g) was added dropwise with stirring to a solution of 1347 g of 2-(N-benzyl-N-methylamino)ethanol, which had been preheated to 75°. The temperature of the reaction mixture was kept at 70—80° during the addition of diketene. When the addition was complete, the temperature was maintained at 70—80° for 2 hr. The crude acetoacetate formed was used for the next reaction. (The distillation was accompanied by partial decomposition: bp 140°/0.5 torr).

Substituted Aminocrotonate——General Procedure: NH_3 gas was bubbled into a solution of substituted acetoacetate in MeOH under cooling in an ice bath. After 5—6 hr, the product was isolated by filtration or by distillation under a vacuum.

Methyl 3-Aminocrotonate——NH_3 gas was bubbled into a solution of 1.0 kg of methyl acetoacetate in 0.5 l of MeOH for 6 hr with cooling. After standing overnight, separated crystals were collected by filtration and washed with MeOH, mp 83—84° (950 g).

2-(N-Benzyl-N-methylamino)ethyl 3-Aminocrotonate——NH_3 gas was bubbled for 6 hr into a solution of 50 g of 2-(N-benzyl-N-methylamino)ethyl acetoacetate in 25 ml of MeOH under cooling in an ice bath. After standing overnight, separated yellow crystals were collected by filtration, mp 59—61° (47 g). Compounds obtained are summarized in Tables III and IV.[17,18]

Methyl 3-Aminocrotonate[3-^{14}C]——Methyl acetoacetate (98.8 mg), MeOH (3 ml) and 0.1 N MeONa (0.83 ml, F=1.206) were added successively to a 3 ml benzene solution of ethyl acetoacetate [3-^{14}C] (2 mCi, 13.5 mCi/mmol, 19.3 mg).[19] The mixture was neutralized with 0.2 N H_2SO_4 in MeOH. The neutralized solution containing methyl acetoacetate [3-^{14}C] was saturated with dry NH_3 below room temperature for 18 hr. The solution was concentrated and the residue was treated with benzene. The benzene solution was concentrated to yield methyl 3-aminocrotonate [3-^{14}C] as pale yellow crystals (115.5 mg).

2-(N-Benzyl-N-methylamino)ethyl Methyl 2,6-Dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine[6-^{14}C]-3,5-dicarboxylate Hydrochloride (^{14}C-YC-93)——A mixture of methyl aminocrotonate [3-^{14}C] (115.5 mg), *m*-nitrobenzaldehyde (151 mg), N-benzyl-N-methylaminoethyl 3-aminocrotonate (249 mg), and iso-PrOH (2 ml) was heated at 90° for 16 hr. The solvent was evaporated off and the residue was purified by silica gel column chromatography (Wakogel C-200, 20 g/benzene) using the following solvents successively; benzene (20 ml), benzene–AcOEt (40: 1, 80 ml), benzene–AcOEt (5: 1, 300 ml) (each fraction was checked by TLC). The desired product was eluted by the last solvent system and 271.9 mg of crystalline ^{14}C-YC-93 was obtained as a free base. The free base was dissolved in 3 ml of acetone and 1 N EtOH–HCl (0.61 ml, F=1.027) was added to the solution. The mixture was concentrated and the residue was crystallized from AcOEt. Filtration and washing with AcOEt gave 255.3 mg of ^{14}C–YC–93 after drying over P_2O_5 under reduced pressure. Specific activity, 3.64 Ci/mg.[20] Total activity: 0.93 mCi. Radiochemical purity, 99.4%.[21] Radiochemical yield, 46.5%. In the second run ^{14}C-YC-93 having a high specific activity and the same radiopurity was obtained starting from 10 mCi/mg of ethyl acetoacetate[3-^{14}C].[22] Specific activity, 29.3 Ci/mg. Total activity, 3.06 mCi.

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17) "Organic Synthesis," Vol. 42, Ed. by Virgil Boeklheide, John Wiley and Sons, Inc., New York, 1963, p. 28.

18) S.A. Glickmann and A.C. Cope, *J. Am. Chem. Soc.*, **67**, 1019 (1954).

19) The radioactive material was provided by Daiichi Pure Chemicals Ltd., Tokyo.

20) The specific activity was determined by liquid scintillation spectroscopy (Tri-Carb 3380, Packard).

21) The radiochemical purity was evaluated by radio-TLC.

22) This radioactive compound was supplied by the Radiochemical Center, Amersham, U .K.