UDC 547.833.8.07

31. **Masao Murayama**: Synthesis of 1-Isoquinolylacetic Acid Derivatives.

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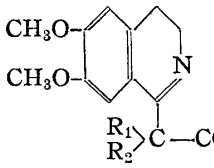
In view of the fact that trialkylacetic acids[1] and the amides[2] thereof with higher alkyl groups are potent antispasmodics, it appeared worth while to synthesize 1-isoquinolyl acetic acid derivatives of general formula (I), where R_1 and R_2 represent various alkyl groups, for pharmacological testing. In our knowledge none of this type of trisubstituted acetic acids is known in the literature. 2-Diethylaminoethyl ester (Ⅶ) of (I) was also prepared for the same purpose.



(I)

3,4-Dimethoxyphenethylamine was acylated with chlorides of several malonic monoesters, yielding the corresponding amides (Ⅱ). The latter were then treated with phosphorus pentoxide in boiling toluene, giving rise to the cyclization products (Ⅲ). The results are listed in Table I.

Table I. Cyclization of Amides (Ⅱ)

Product: Ethyl α,α-R_1,R_2-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate

R_1	R_2	Yield (%)	Appearance of crude product	b.p. (°C/mm. Hg)	Pure product		Picrate		Hydrochloride m.p.(°C)
					Appearance	m.p.(°C)	Appear.	m.p.(°C)	
H	H	69	Reddish brown		Faint yellow rhombs	81	Yellow needles	170~171	
H	C_2H_5	82	Yellowish brown	170~175/0.04	Vitreous		Yellow prisms	113~114.5	134.5~135
CH_3	CH_3	78.5	Colorless	179~181/0.5	Colorless needles	74.5~76	Sandy grains	141~142	
C_2H_5	C_2H_5	91.5	〃	160~163/0.02	Colorless prisms	65~67	Dice	163~165	159(decomp.)

Contrary to expectation, the cyclization of disubstituted amides, in which the isoquinoline formation appeared to be most difficult by steric reason,[3] proceeded most smoothly, the reaction mixture remained colorless throughout the reaction, and the products were isolated at once in colorless state of high purity and yield. The cyclization of amido-ester (Ⅱ: R_1, R_2=H) was already recorded by Openshaw, *et al.*[4] and in this case the reaction mixture assumed a dark reddish brown color, from which the product (ethyl ester of (I): R_1, R_2=H) was obtained pure only after repeated recrystallization.

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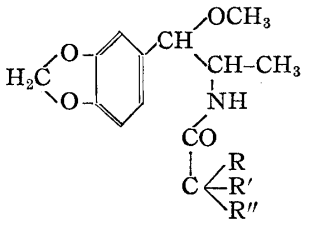
1) N. Sperber, R. Fricano: J. Am. Chem. Soc., **71**, 3352(1949).

2) Frdl. Fortschr. Teerfarb.-Fabrik., **24**, 413; U.S. Pat. 2,186,976; 2,429,835; Deut. med. Wochschr., **64**, 671(1938); Arch. exptl. Pathol. Pharmakol., **186**, 552(1937).

3) The yield of cyclization product of the following compound decreases rapidly with the bulkiness of R, R′, and R″. cf. S. Sugasawa, N. Yoshida: Yakugaku Zasshi, **74**, 625(1954).

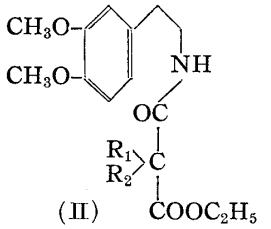


4) A.R. Battersby, H.T. Openshaw, C.S. Wood: J. Chem. Soc., **1953**, 2465.

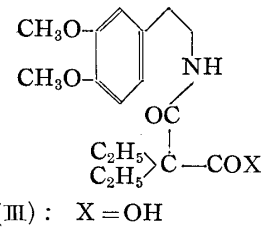
In order to synthesize 2-diethylaminoethyl ester (Ⅶ) the transesterification of the ethyl ester of (I: $R_1, R_2 = C_2H_5$) with 2-diethylaminoethanol was attempted under a variety of conditions, but without success, always recovering the original ester. This result is not surprising from the tertiary nature of the ester group, which was also proved quite resistant toward hydrolysis.

When however, the amido-ester (Ⅱ: $R_1, R_2 = C_2H_5$) was allowed to stand with ethanolic potassium hydroxide solution at room temperature, the ester group was hydrolyzed smoothly and the corresponding acid (Ⅲ: $R_1, R_2 = C_2H_5$) was obtained in a good yield, which was then treated with thionyl chloride to yield the chloride (Ⅳ).

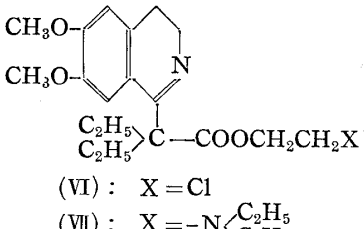
When treated with 2-chloroethanol the latter furnished 2-chloroethyl ester (Ⅴ), which could also be prepared by esterifying the acid (Ⅳ) with 2-chloroethanol by the agency of dry hydrogen chloride. Since (Ⅴ), regardless of its preparation, was not induced to crystallize, it was cyclized to (Ⅵ) directly, which was then treated with an excess of diethylamine, giving the 2-diethylaminoethyl ester (Ⅶ) as a faint yellow syrup and was characterised by its crystalline dipicrate.



(Ⅱ)



(Ⅲ): X = OH
(Ⅳ): X = Cl
(Ⅴ): X = $-OCH_2CH_2Cl$



(Ⅵ): X = Cl
(Ⅶ): X = $-N(C_2H_5)_2$

Dehydrogenation of the ethyl esters of (I: $R_1, R_2 = CH_3$ or C_2H_5), even under forced conditions, e. g. boiling with ethyl cinnamate in the presence of 30% Pd-C, was not successful, recovering the starting ester quantitatively. Potassium permanganate solution was also proved to be of no use for dehydrogenation purpose. Synthesis of (I) and (Ⅶ) with higher alkyl groups is now under progress and the results of their pharmacological assays will be published in due course.

Experimental

Preparation of esters of α,α-diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetic acid is described as a typical example.

α,α-Diethyl-α-ethoxycarbonyl-N-(3,4-dimethoxyphenethyl)acetamide (Ⅱ : $R_1 = R_2 = C_2H_5$)—3,4-Dimethoxyphenethylamine (10 g.) in pure Et_2O(50 cc.) was acylated with chloride of monoethyl malonate (10 cc. in Et_2O) with stirring and cooling. After 5 hrs.' stirring the hydrochloride of the starting amine that separated was filtered off, the ethereal filtrate was successively washed with dil. HCl, dil. Na_2CO_3 solution, and water, dried and evaporated. The solid residue formed colorless needles of m.p. 75~76.5°, when purified from a mixture of benzene-petr. ether. Yield, 8.8 g.(90%). *Anal.* Calcd. for $C_{19}H_{29}O_5N$: C, 64.9; H, 8.3; N, 4.1. Found: C, 65.3; H, 8.7; N, 4.1.

α-Ethyl-α-ethoxycarbonyl-N-(3,4-dimethoxyphenethyl)acetamide(Ⅱ : $R_1 = H$, $R_2 = C_2H_5$)—Colorless needles of m.p. 64~67°. Yield, 90%. *Anal.* Calcd. for $C_{17}H_{25}O_5N$: C, 63.15; H, 7.4; N, 4.6. Found: C, 63.0; H, 7.5; N, 4.8.

α,α-Dimethyl-α-ethoxycarbonyl-N-(3,4-dimethoxyphenethyl)acetamide(Ⅱ: $R_1 = R_2 = CH_3$)—Vitreous substance which could not be induced to crystallize. Yield, 90.5%.

Ethyl α,α-Diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate (I : $R_1 = R_2 = C_2H_5$)—The foregoing amide (Ⅱ) (4.7 g.) in pure toluene (75 cc.) was heated and to this solution P_2O_5(27.6 g.) was now added in three portions with stirring, every 15 mins., during which the reaction mixture remained colorless all through, the whole was cooled, and the excess of P_2O_5 was decomposed with ice water. The supernatant toluene layer was separated and shaken twice with cold dil. HCl. The HCl-acid solution was combined with the original aqueous layer and basified. The free base that separated was collected in Et_2O. The extract was washed, dried, and Et_2O was evaporated, leaving a nearly colorless syrup, which solidified on standing. The base distilled at 160~163°(0.02 mm.), which formed colorless prisms of m.p. 65~67° from petr. ether. Yield, 4.1 g.(91.5%). *Anal.* Calcd. for

$C_{19}H_{27}O_4N$: C, 68.4; H, 8.2; N, 4.2. Found : C, 68.6; H, 7.7; N, 4.3.

Picrate : Yellow dice (from EtOH), m.p. 163~165°. *Anal.* Calcd. for $C_{25}H_{30}ON_4$: C, 53.4; H, 5.3; N, 10.0. Found : C, 53.3; H, 5.6; N, 10.0.

Ethyl α-Ethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate (I : $R_1=H$, $R_2=C_2H_5$)—Yellowish brown syrup, $b.p._{0.04}$ 170~175°. Forms crystalline hydrochloride of m.p. 134.5~135°.

Picrate : Yellow prisms, m.p. 113~114.5°. *Anal.* Calcd. for $C_{23}H_{26}O_{11}N_4$: C, 51.5; H, 4.85; N, 14.8. Found : C, 51.5; H, 5.0; N, 14.9.

Ethyl α,α-Dimethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate (I : $R_1=R_2=CH_3$)—Colorless needles of m.p. 74.5~76°, $b.p._{0.5}$ 179~181°. *Anal.* Calcd. for $C_{17}H_{23}O_4N$: C, 66.9; H, 7.6; N, 4.6. Found : C, 67.4; H, 7.75; N, 4.5.

Picrate : Yellow sandy crystals. *Anal.* Calcd. for $C_{23}H_{26}O_{11}N_4$: C, 51.5; H, 4.85; N, 14.8. Found: C, 51.3; H, 4.7; N, 14.7.

N-(3,4-Dimethoxyphenethyl)-2,2-diethylmalonamic Acid (III)—The ester (II : $R_1=R_2=C_2H_5$, 10 g.) was dissolved in ethanolic KOH solution prepared from KOH (3 g.), H_2O(5 cc.), and EtOH(80 cc.), and the solution was allowed to stand overnight at room temp.(ca. 20°). EtOH was then evaporated and the residue was dissolved in water. The aqueous solution, after once shaken with benzene, was treated with decolorizing charcoal, filtered, and the filtrate was acidified, separating pasty precipitate, which gradually solidified on standing. This formed colorless needles from benzene-petr. ether, m.p. 98~100.5°. Yield, 8.6 g.(93%). *Anal.* Calcd. for $C_{17}H_{25}O_5N$, C, 63.1; H, 7.3; N, 4.3. Found : C, 63.2; H, 7.3; N, 4.4.

β-Chloroethyl N-(3,4-dimethoxyphenethyl)-2,2-diethylmalonamate (V)—(a) A solution of the foregoing amic acid (III) (2 g.) in pure 2-chloroethanol (10 g.) was saturated with dry HCl-gas and the mixture was heated gently on a steam bath for 3 hrs. After cool, the product was poured into cold water and the oil that separated was taken up in benzene, which was washed with cold dil. Na_2CO_3 solution and then with water, dried, and evaporated, leaving orange colored syrup, which could not be induced to crystallize. Yield, 1.8 g.

(b) The amic acid (III) (1 g.) in benzene (8 cc.) was mixed with $SOCl_2$(1 g.) and the whole was gradually warmed so that benzene began to reflux after 2 hrs.' heating. Excess of $SOCl_2$ was then removed *in vacuo*, and to the residue (IV) was added a mixture of 2-chloroethanol (1 g.) and benzene (5 cc.). The mixture was now gradually heated on a water bath for 2 hrs. and then volatile material was removed *in vacuo*, leaving a light yellowish brown syrup. Yield, 1.2 g.

β-Chloroethyl α,α-Diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate (VI)—The foregoing crude amide (1.2 g.) in 100 cc. of xylene was mixed with $POCl_3$(5 g.) and the mixture was refluxed for 4 hrs., forming brown solution. The solvent and the excess of $POCl_3$ were now removed *in vacuo* and to the residue was added ice water. Some undissolved substance was removed by filtration through a wet filter and the clear filtrate was basified with cooling. The free base was taken up in benzene, washed, dried, and evaporated. The vitreous residue solidified on scratching and was purified from benzene-petr. ether, forming colorless prisms of m.p. 72°. Yield, 0.6 g. or 53% based on the carboxylic acid (III). *Anal.* Calcd. for $C_{19}H_{26}O_4NCl$: C, 62.4; H, 7.7; N, 3.9; Cl, 9.7. Found : C, 62.8; H, 7.4; N, 4.2; Cl, 10.1.

Picrate : Yellow needles (from EtOH), m.p. 188~189°. *Anal.* Calcd. for $C_{25}H_{29}O_{11}N_4Cl$: C, 50.3; H, 4.9; N, 9.4; Cl, 5.9. Found : C, 50.45; H, 5.2; N, 9.5; Cl, 6.4.

β-Diethylaminoethyl α,α-Diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate (VII)—An intimate mixture of the above chloro ester (VI) (0.75 g.) and diethylamine (0.8 g.) was heated in a sealed tube at 100~120° for 10 hrs. The light brown slurry obtained was mixed with benzene and dil. HCl. The whole was shaken vigorously and the aqueous layer was separated and basified. Light

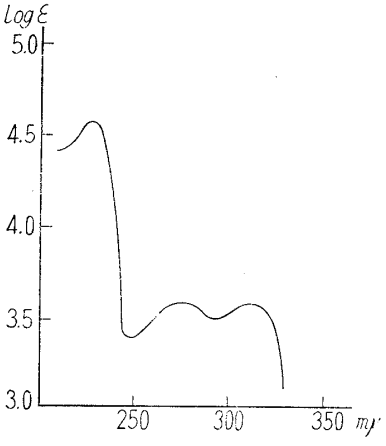
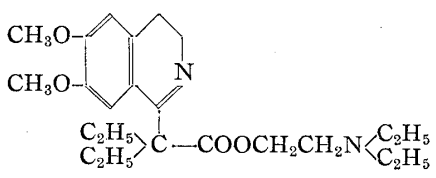


Fig. 1.
Ultraviolet Absorption Spectrum
(in EtOH, 10.02 γ/cc.)



brownish oil that separated was taken up in benzene, washed, dried, and evaporated. The residue formed a faint yellow syrup, which did not solidify. Yield, 0.75 g.(91%).

Dipicrate : Yellow scales (from EtOH), m.p. 131~132.5°(decomp.). *Anal.* Calcd. for $C_{35}H_{42}O_{18}N_8$: C, 48.7; H, 4.9; N, 13.0. Found : C, 48.8; H, 5.2; N, 13.2.

Fig. 1 is the ultraviolet absorption spectrum of the ester of the free base which shows the characteristic maxima of dihydroisoquinoline at 228, 272, and 307 mμ.

Summary

Isoquinoline cyclization of N-(3,4-dimethoxyphenethyl)-2-ethoxycarbonylacetamide and 2-alkyl and 2-dialkyl derivatives was studied. Contrary to expectations, the cyclization of dialkyl-substituted acetamide derivatives proceeded most smoothly with excellent yield of the product. One of such products, ethyl α,α-diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate, resisted all attempts at dehydrogenation and the starting dihydro base was recovered quantitatively. β-Diethylaminoethyl α,α-diethyl-α-(6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)acetate was also prepared for pharmacological evaluation.

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32. **Masao Murayama** : Synthesis of 1-*tert*-Alkyl-6,7-dimethoxyisoquinolines.

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Trialkyl-substituted acetamides of general formula RR′R″C-$CONH_2$[1] with number of carbon atoms of 12~17 in their alkyl portion are reported to have strong spasmolytic activity. More recently it was revealed that trialkyl-substituted acetic acids with number of carbon atoms of 16~18[1] are far stronger antispasmodics. Trialkyl-substituted alkylpyridine-carboxamides[2] are also known to work analogously.

In continuation of the preceding work[3] this paper describes the synthesis of 1-*tert*-alkyl-6,7-dimethoxyisoquinolines as a possible spasmolytic agent.

Attempts to synthesize this type of isoquinolines are not without precedence. Sugasawa, Sugiura, and Kawanishi[4] prepared 1-*tert*-butyl- and 1-(β,β-dimethyl)propyl-6,7-methylenedioxy-3-methylisoquinolines, which, however, were found to be devoid of spasmolytic activity. Later their work was developed by Sugasawa and Yoshida[5] who found that the cyclization of (I)-type of amides to isoquinolines (III) proceeds via oxazoline derivatives (II), which could be isolated in substance. They have also shown that the yield of (III) decreases rapidly with increasing bulkiness of *tert*-alkyl group in (I). For instance 1-*tert*-butylisoquinoline can be obtained in 69% yield, whereas the yield of 1-tripropylmethyl- and 1-tributylmethyl-isoquinolines did not exceed 10%. Their attempt at the synthesis of (III) via its 3,4-dihydro derivative, the cyclization product of (IV), reportedly failed at the cyclization stage.[6]

* Hongo, Tokyo (村山正雄).

1) N. Sperber, R. Fricano : J. Am. Chem. Soc., **71**, 3352(1949).
2) N. Sperber, D. Papa, E. Schwenk : *Ibid.*, **72**, 2012(1950).
3) M. Murayama : This Bulletin, **6**, 183(1958).
4) S. Sugasawa, T. Sugiura, M. Kawanishi : Yakugaku Zasshi, **65**, 450(1945).
5) S. Sugasawa, N. Yoshida : *Ibid.*, **74**, 625(1954).
6) S. Sugasawa, N. Yoshida : Unpublished result. The present author repeated their work and confirmed their result.