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.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

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.

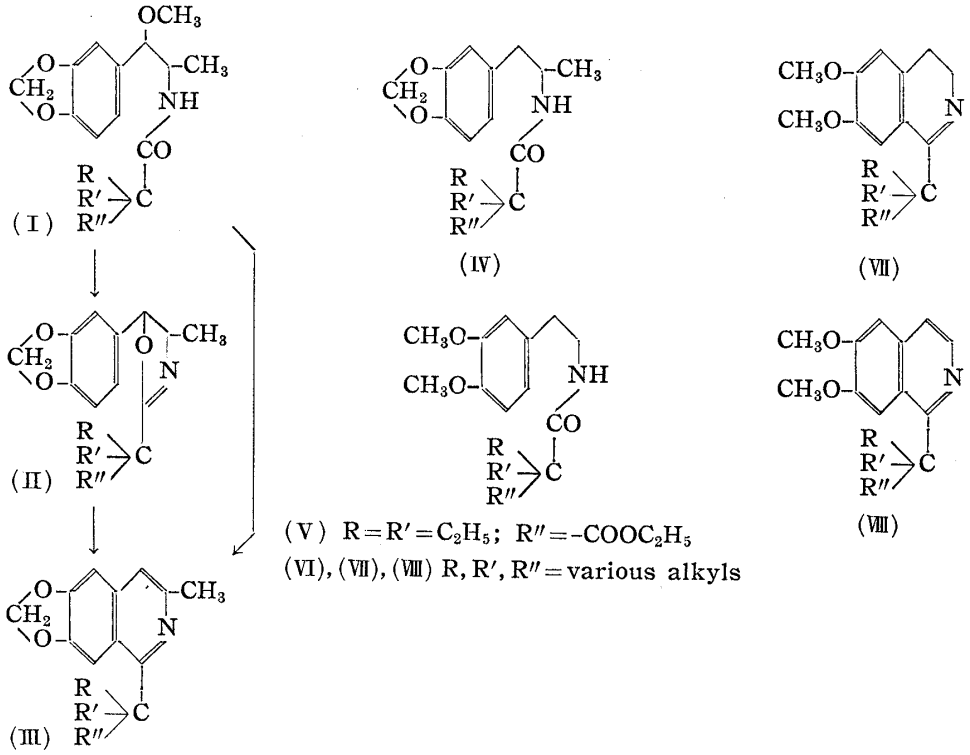
In continuation of the preceding work[3] this paper describes the synthesis of 1-*tert*-alkyl-6,7-dimethoxyisoquinolines as a possible spasmolytic agent.

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.

In the preceding paper it was reported that the compound (V) could be cyclized with an excellent result, and this fact induced the author to attempt the cyclization of α,α,α-trialkyl-N-(3,4-dimethoxyphenethyl)acetamides of the general formula (VI). The corresponding 1-*tert*-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolines (VII) were produced in high yields, regardless of the size of trialkylmethyl portion of the starting amides. This result is in striking contrast to that of Sugasawa and Yoshida, whose failure, therefore, appears to be ascribed to the presence of methyl group on the α-carbon atom of nitrogen of the starting amides.



For the preparation of trialkylacetic acids are known the method of Zielger,[7] Sperber,[8] and some others.[9] Among these Sperber's method seems to be excellent for the preparation of trialkyacetic acid with the same three alkyl groups, otherwise the purity of the product is not always satisfactory.

For the present purpose the reaction was started from a certain alkylacetic acid, R-CH_2-COOH, which was converted into alkylcyanoacetate (A), to which the first alkyl group (R′) could be introduced with ease, giving dialkylcyanoacetate (B). The latter was hydrolyzed, decarboxylated, and the resulting dialkylacetonitrile (C) was alkylated (R″) for the second time, furnishing trialkylacetonitrile (D), which could be hydrolyzed to the corresponding acetic acid (F) via the amide (E). Though somewhat tedious this method gives pure compounds in satisfactory yields on each stage, as can be seen from Tables I, II, and III.

The trialkylacetyl chlorides (Table IV) were prepared as usual from the acids and were condensed with 3,4-dimethoxyphenethylamine giving the corresponding amides (VI) in excellent yields (Table V). Since most of the amides did not solidify, they were directly cyclized by treating with phosphoryl chloride in boiling toluene or xylene, forming 3,4-dihydroisoquinolines (VII) again in good yields (Table VI).

The dehydrogenation of the dihydro compounds was only successful when they were

7) K. Ziegler, H. Ohlinger: Ann., **495**, 84(1932).
8) N. Sperber, D. Papa, E. Schwenk: J. Am. Chem. Soc., **70**, 3091(1948).
9) e.g. T. Reichstein, H. Rosenberg, R. Eberhardt: Helv. Chim. Acta, **18**, 721(1935).

TABLE I. $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\cdot CN$

No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	b.p. (°C/mm. Hg)	Yield (%)	Solvent*	Reaction time (hr.)
1	7	CH_3	CH_3	C_4H_9	75.5/30	74	B	4.4
2		CH_3	C_2H_5	C_3H_7	83/40	61	T	3.5
3		C_2H_5	C_2H_5	C_2H_5	60~64/10	60	B	4.0
4	8	CH_3	CH_3	C_5H_{11}	79~81/18	70	B	4.0
5		CH_3	C_2H_5	C_4H_9	84~86/21	70	B	6.5
6		C_2H_5	C_2H_5	C_3H_7	81~82/18	40	T	3.5
7	9	CH_3	C_2H_5	C_5H_{11}	99~100.5/19	81	B	4.0
8		C_2H_5	C_2H_5	C_4H_9	81.5/9.5	54.5	B	5.5
9	10	C_2H_5	C_2H_5	C_5H_{11}	113~115.5/18	77.5	B	7.0
10		C_2H_5	C_3H_7	C_4H_9	110~112/18	72	T	5.0
11		C_3H_7	C_3H_7	C_3H_7	104~106/14	61	T	6.5
12	13	C_4H_9	C_4H_9	C_4H_9	127~129/5	79	T	7.0

* B: Benzene T: Toluene

TABLE II. $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\cdot CONH_2$

No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	b.p. (°C/mm. Hg)	m.p. (°C)	Yield (%)	Crystal Form
1	7	CH_3	CH_3	C_4H_9	141~142/17	93~93.5	70.5	faint yellow plates
2		CH_3	C_2H_5	C_3H_7	140~141/17	40~43	70	faint yellow prisms
3		C_2H_5	C_2H_5	C_2H_5	148~149/21	106~108	69	colorless dices
4	8	CH_3	CH_3	C_5H_{11}	153~154/20	100~102	73	faint yellow prisms
5		CH_3	C_2H_5	C_4H_9	149.5~150/19	24~25	60	faint yellow prisms
6		C_2H_5	C_2H_5	C_3H_7	148.5~149/17	68.5~70	86	faint yellow prisms
7	9	CH_3	C_2H_5	C_5H_{11}	163~164/19	15~17	93	colorless needles
8		C_2H_5	C_2H_5	C_4H_9	157.5~158/17	67.5~69	92	faint yellow dices
9	10	C_2H_5	C_2H_5	C_5H_{11}	133~134/3	43~45	93	colorless prisms
10		C_2H_5	C_3H_7	C_4H_9	133~134/3	39~41	86	colorless prisms
11		C_3H_7	C_3H_7	C_3H_7	133~134/2.5	69	96	colorless prisms
12	13	C_4H_9	C_4H_9	C_4H_9	—	58~60	84	colorless prisms

TABLE III. $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\cdot COOH$

No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	b.p. (°C/mm. Hg)	m.p. (°C)	Yield (%)	Crystal Form
1	7	CH_3	CH_3	C_4H_9	115~117/15	—	87	colorless oil
2		CH_3	C_2H_5	C_3H_7	118~119.5/15	—	95	colorless oil
3		C_2H_5	C_2H_5	C_2H_5	117~118/14	38~39	85	colorless prisms
4	8	CH_3	CH_3	C_5H_{11}	128~130.5/15	—	87	colorless oil
5		CH_3	C_2H_5	C_4H_9	131~133/16	—	91	colorless oil
6		C_2H_5	C_2H_5	C_3H_7	129~130.5/15	—	94	colorless oil
7	9	CH_3	C_2H_5	C_5H_{11}	147~148/18.5	—	97	colorless oil
8		C_2H_5	C_2H_5	C_4H_9	140~142/15	—	96.5	colorless oil
9	10	C_2H_5	C_2H_5	C_5H_{11}	153~154/15.5	—	94.5	colorless oil
10		C_2H_5	C_3H_7	C_4H_9	150~150.5/15	—	91	colorless oil
11		C_3H_7	C_3H_7	C_3H_7	150~151/15	65	93	colorless prisms
12	13	C_4H_9	C_4H_9	C_4H_9	135~138/3	35~36	80.5	colorless prisms

$$R\text{-}CH_2\text{-}COOH \longrightarrow R\text{-}CHBr\text{-}COOCH_3 \longrightarrow R\text{-}CH\begin{matrix} COOCH_3 \\ CN \end{matrix} \quad (A) \longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>\!C\begin{matrix} COOCH_3 \\ CN \end{matrix} \quad (B)$$

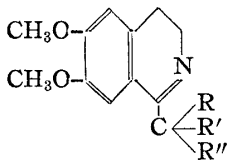
$$\longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>\!CH\text{-}CN \quad (C) \longrightarrow \begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\text{-}CN \quad (D) \longrightarrow \begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\text{-}CONH_2 \quad (E) \longrightarrow \begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\text{-}COOH \quad (F)$$

Table IV. $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C\cdot COCl$

No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	b.p. (°C/mm. Hg)	Yield (%)	Form
1	7	CH_3	CH_3	C_4H_9	75~78/25	quant.	colorless oil
2		CH_3	C_2H_5	C_3H_7	82~84/33	90	colorless oil
3		C_2H_5	C_2H_5	C_2H_5	67~68/17	84.5	colorless oil
4	8	CH_3	CH_3	C_5H_{11}	93~95/26	quant.	colorless oil
5		CH_3	C_2H_5	C_4H_9	97~100/28	quant.	colorless oil
6		C_2H_5	C_2H_5	C_3H_7	97~98/26	92.5	colorless oil
7	9	CH_3	C_2H_5	C_5H_{11}	108~109/23	98	colorless oil
8		C_2H_5	C_2H_5	C_4H_9	117~118/29	90	colorless oil
9	10	C_2H_5	C_2H_5	C_5H_{11}	115~117/16	quant.	colorless oil
10		C_2H_5	C_3H_7	C_4H_9	109~110/11	98	colorless oil
11		C_3H_7	C_3H_7	C_3H_7	111~114/14	94.5	colorless oil
12	13	C_4H_9	C_4H_9	C_4H_9	140~141/14	92.5	colorless oil

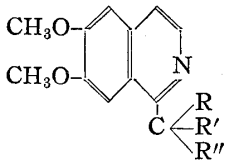
Table V. $(CH_3O)_2C_6H_3\text{-}CH_2\cdot CH_2\cdot NH\cdot CO\cdot C\!<\!\begin{matrix} R \\ R' \\ R'' \end{matrix}$

No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	m.p. (°C)	Yield (%)	Crystal Form
1	7	CH_3	CH_3	C_4H_9	—	91	faint brown vitreous
2		CH_3	C_2H_5	C_3H_7	—	97	faint yellow vitreous
3		C_2H_5	C_2H_5	C_2H_5	65~67	84	colorless needles
4	8	CH_3	CH_3	C_5H_{11}	—	quant.	yellow brown vitreous
5		CH_3	C_2H_5	C_4H_9	—	quant.	faint yellow vitreous
6		C_2H_5	C_2H_5	C_3H_7	—	96	faint yellow vitreous
7	9	CH_3	C_2H_5	C_5H_{11}	—	quant.	faint yellow vitreous
8		C_2H_5	C_2H_5	C_4H_9	—	95	faint yellow vitreous
9	10	C_2H_5	C_2H_5	C_5H_{11}	46~47	98	colorless needles
10		C_2H_5	C_3H_7	C_4H_9	—	97	faint yellow vitreous
11		C_3H_7	C_3H_7	C_3H_7	73~75	quant.	colorless scales
12	13	C_4H_9	C_4H_9	C_4H_9	93~94	95	colorless needles

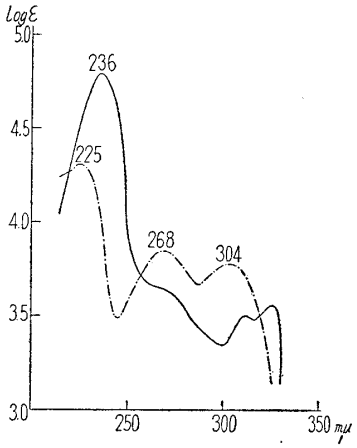
Table VI. 

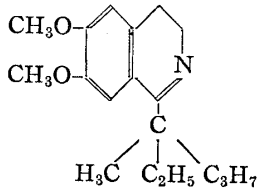
No.	No. of C in $\begin{matrix} R \\ R' \\ R'' \end{matrix}\!\!>\!C-$	R	R′	R″	b.p. (°C/mm. Hg)	m.p. (°C)	Picrate m.p. (°C)	Picrate Crystal Form	Yield (%)
1	7	CH_3	CH_3	C_4H_9	144~146/0.4	—	142.5~143.5	yellow plates	91
2		CH_3	C_2H_5	C_3H_7	139~141/0.09	—	149.5~151.5	yellow needles	90
3		C_2H_5	C_2H_5	C_2H_5	—	62	173~174	yellow needles	82
4	8	CH_3	CH_3	C_5H_{11}	138~142/0.05	—	117~119	yellow scales	88
5		CH_3	C_2H_5	C_4H_9	145~147/0.06	30~32	114~116	yellow pillars	87
6		C_2H_5	C_2H_5	C_3H_7	140~143/0.06	—	133~134	yellow prisms	85
7	9	CH_3	C_2H_5	C_5H_{11}	150~152/0.05	—	122~124	yellow needles	85
8		C_2H_5	C_2H_5	C_4H_9	150~152/0.05	—	160~161	yellow dices	82.5
9	10	C_2H_5	C_2H_5	C_5H_{11}	159~162/0.07	46~47	114~115	yellow needles	92
10		C_2H_5	C_3H_7	C_4H_9	160~163/0.05	35	125~127	yellow prisms	84.5
11		C_3H_7	C_3H_7	C_3H_7	—	82.5~83	129~131	yellow plates	88
12	13	C_4H_9	C_4H_9	C_4H_9	—	42~44	142~143	yellow scales	88

Table VII.

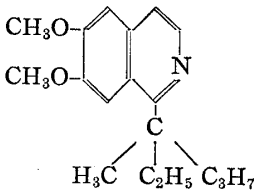


No.	No. of C in R, R′, R″>C-	R	R′	R″	b.p. (°C/mm. Hg)	m.p. (°C)	Picrate m.p. (°C)	Picrate Crystal Form	Yield (%)
1	7	CH_3	CH_3	C_4H_9	153~154/0.04	—	138~139	yellow needles	80.5
2		CH_3	C_2H_5	C_3H_7	150~153/0.04	—	165.5~167.5	yellow prisms	79
3		C_2H_5	C_2H_5	C_2H_5	—	74	201~202	yellow prisms	67
4	8	CH_3	CH_3	C_5H_{11}	163~165/0.05	47~48	111~112.5	yellow rhombs	81
5		CH_3	C_2H_5	C_4H_9	157~158/0.03	—	149~151	yellow needles	78
6		C_2H_5	C_2H_5	C_3H_7	155~158/0.035	56~57	188~189	yellow needles	80
7	9	CH_3	C_2H_5	C_5H_{11}	163~164/0.02	—	141~142.5	yellow prisms	81
8		C_2H_5	C_2H_5	C_4H_9	162~163/0.04	56~57	175~175.5	yellow needles	94
9	10	C_2H_5	C_2H_5	C_5H_{11}	164~165/0.035	—	151.5~152.5	yellow needles	75.5
10		C_2H_5	C_3H_7	C_4H_9	162~163/0.03	—	139~140	yellow needles	67.5
11		C_3H_7	C_3H_7	C_3H_7	—	93~94.5	176~177	yellow needles	94
12	13	C_4H_9	C_4H_9	C_4H_9	—	88	142.5~143	yellow pillars	61





10.1164 γ/cc. in EtOH



4.027 γ/cc. in EtOH

Fig. 1. Ultraviolet Absorption Spectra

heated with 30% Pd-C in boiling ethyl cinnamate, which served as a solvent and also as a hydrogen acceptor, furnishing isoquinolines (VIII) in fair to good yields (Table VII).

The ultraviolet absorption curves of (VII: R=CH_3, R′=C_2H_5, R″=C_3H_7) and (VIII: R, R′, R″ as above) shown in Fig. 1 will serve to show the successful dehydrogenation.

Pharmacological experiments of (VII) and (VIII) are now under progress and the results will be published in due course.

The author thanks Professor Sugasawa for his interest in this work.

Experimental

(1) **Preparation of Trialkylacetic Acids**—Each stage will be shown with one example.

Methyl α-Ethyl-α-propyl-α-cyanoacetate (B : R=C_2H_5, R′=C_3H_7)—To a cold methanolic MeONa solution (10 g. of Na in 100 cc. of MeOH), methyl α-ethyl-α-cyanoacetate (A : 50 g.) was added, followed

Table VIII. R, R′>C<CN, $COOCH_3$

No.	R	R′	b.p. (°C)	Yield (%)	Analyses (%)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	CH_3	CH_3	185~190	77	$C_6H_9NO_2$	56.7	7.1	11.0	56.5	7.3	11.3
2	CH_3	C_2H_5	190~193	81	$C_7H_{11}NO_2$	59.6	7.8	9.9	59.2	7.5	9.5
3	C_2H_5	C_2H_5	199~204	86.5	$C_8H_{13}NO_2$	61.9	8.4	9.0	62.4	8.4	9.2

by dropwise addition of PrBr (55 g.). The whole was then refluxed on a steam bath for 5 hrs., when the solution became neutral. After evaporating MeOH, water was added to the residue, separating an oily substance, which was extracted with ether, washed, dried, and evaporated. The residue distilled at 215~218°; yield, 55 g.(83%). *Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.9; H, 8.9; N, 8.3. Found: C, 64.3; H, 9.1; N, 8.1 (For other examples see Table VIII).

α-Methyl-α-ethylacetonitrile (C : $R=CH_3$, $R'=C_2H_5$)—Methyl α-methyl-α-ethyl-α-cyanoacetate (124 g.) was mixed with methanolic KOH-solution prepared from 64 g. of KOH dissolved in 200 cc. of MeOH. The mixture was allowed to stand overnight at room temp. and then refluxed on a steam bath for 4 hrs. MeOH was then removed *in vacuo* and the residue was mixed with water, separating an oily layer, which was taken up in ether, washed, dried, and evaporated. The viscous syrupy residue was distilled by heating in an oil bath kept at 180°; vigorous evolution of CO_2 being observed. The distillate was dissolved in ether, washed with dil. Na_2CO_3 solution, dried, and evaporated. The residue distilled over P_2O_5 at 122~126° as a colorless oil; yield, 50 g.(65%). *Anal.* Calcd. for C_5H_9N: C, 72.3; H, 10.8; N, 16.9. Found : C, 72.7; H, 10.4; N, 17.25. (cf. Table IX for other examples).

TABLE IX. $\begin{matrix}R\\R'\end{matrix}\!\!>\!CH\cdot CN$

No.	R	R′	b.p. (°C)	Yield (%)		Analyses (%) Calcd. C	H	N	Found C	H	N
1	C_2H_5	C_2H_5	144~148	81	$C_6H_{11}N$	74.2	11.3	14.4	74.3	11.5	15.0
2	C_2H_5	C_3H_7	164~165	75	$C_7H_{13}N$	75.7	11.7	12.6	75.4	12.0	12.9

α-Methyl-α-ethyl-α-butylacetonitrile (D : $R=CH_3$, $R'=C_2H_5$, $R''=C_4H_9$)—α-Ethyl-α-methylacetonitrile (17 g.) and BuBr (31 g.) were dissolved in benzene (30 cc.) and to this solution a suspension of powdered $NaNH_2$ (9 g.) in 40 cc. of benzene was added during 1.5 hrs. with stirring and heating at 80~90°. After about 5 hrs.' heating the evolution of NH_3 almost ended. The product was worked up as usual, giving a colorless oil of $b.p_{21}$ 84~86°. Yield, 20 g.(70%). *Anal.* Calcd. for $C_9H_{17}N$: C, 77.6; H, 12.2; N, 10.1. Found : C, 77.9; H, 12.0; N, 10.3 (cf. Tables I and X).

TABLE X. $\begin{matrix}R\\R'\\R''\end{matrix}\!\!>\!C\cdot CN$

No.	R	R′	R″		Analyses (%) Calcd. C	H	N	Found C	H	N
1	CH_3	CH_3	C_4H_9	$C_8H_{15}N$	76.8	12.0	11.2	77.1	11.83	11.5
2	CH_3	C_2H_5	C_3H_7	$C_8H_{15}N$	76.8	12.0	11.2	76.4	11.77	10.9
3	C_2H_5	C_2H_5	C_2H_5	$C_8H_{15}N$	76.8	12.0	11.2	76.3	12.45	11.1
4	CH_3	CH_3	C_5H_{11}	$C_9H_{17}N$	77.62	12.2	10.1	77.6	12.5	10.2
5	C_2H_5	C_2H_5	C_3H_7	$C_9H_{17}N$	77.6	12.2	10.1	77.7	11.86	9.7
6	CH_3	C_2H_5	C_5H_{11}	$C_{10}H_{19}N$	78.4	12.4	9.1	78.6	12.5	9.3
7	C_2H_5	C_2H_5	C_4H_9	$C_{10}H_{19}N$	78.4	12.4	9.1	78.2	12.3	9.5
8	C_2H_5	C_2H_5	C_5H_{11}	$C_{11}H_{21}N$	79.0	12.6	8.4	78.6	12.6	8.8
9	C_2H_5	C_3H_7	C_4H_9	$C_{11}H_{21}N$	79.0	12.6	8.4	79.2	12.3	8.1

TABLE XI. $\begin{matrix}R\\R'\\R''\end{matrix}\!\!>\!C\cdot CONH_2$

No.	R	R′	R″		Analyses (%) Calcd. C	H	N	Found C	H	N
1	CH_3	CH_3	C_4H_9	$C_8H_{17}ON$	67.1	11.9	9.8	67.4	12.1	9.6
2	CH_3	C_2H_5	C_3H_7	$C_8H_{17}ON$	67.1	11.9	9.8	67.2	11.8	9.8
3	CH_3	CH_3	C_5H_{11}	$C_9H_{19}ON$	68.8	12.1	8.9	68.5	11.7	8.7
4	CH_3	C_2H_5	C_4H_9	$C_9H_{19}ON$	68.8	12.1	8.9	69.2	12.3	8.8
5	C_2H_5	C_2H_5	C_3H_7	$C_9H_{19}ON$	68.8	12.1	8.9	69.1	11.8	9.1
6	CH_3	C_2H_5	C_5H_{11}	$C_{10}H_{21}ON$	70.2	12.3	8.2	70.5	11.9	8.0
7	C_2H_5	C_2H_5	C_4H_9	$C_{10}H_{21}ON$	70.2	12.3	8.2	69.9	11.9	7.8
8	C_2H_5	C_3H_7	C_4H_9	$C_{11}H_{23}ON$	71.3	12.4	7.6	71.3	12.5	7.8

α,α-Diethyl-α-amylacetamide (E : $R=R'=C_2H_5$, $R''=C_5H_{11}$)—A mixture of α,α-diethyl-α-amylacetonitrile (20 g.) and H_2SO_4(200 g. of 80%) was heated on a steam bath for 12 hrs. with vigorous stirring. The reaction mixture was diluted with water, separating a brown oil, which was taken up in benzene, washed, and evaporated. The residue was distilled *in vacuo*, furnishing an almost colorless vitreous substance of $b.p_3$ 133~134°, which soon solidified on standing. Colorless prisms of m.p. 43~45°. Yield, 20.5 g.(93%). *Anal.* Calcd. for $C_{11}H_{23}ON$: C, 71.3; H, 12.4; N, 7.6. Found: C, 71.3; H, 12.9; N, 7.1 (cf. Tables II, and XI).

α-Ethyl-α-propyl-α-butylacetic Acid (F : $R=C_2H_5$, $R'=C_3H_7$, $R''=C_4H_9$)—The amide with the same alkyl substituents (17 g.) was dissolved in glacial AcOH(90 cc.) and to this solution was introduced a stream of dry HCl-gas during 15 mins., followed by an addition of butyl nitrite (20 g.) during 1 hr. with cooling. The mixture was stirred for additional 2 hrs. at room temp. and then further 2 hrs. on a steam bath. AcOH was now evaporated *in vacuo*, and the residue was dissolved in dil. NaOH solution, which was washed with benzene. The aqueous layer was acidified with dil. HCl, separating an oily substance, which was taken up in benzene. The residue obtained after evaporation of benzene was distilled, giving almost colorless oil of $b.p_{15}$ 150~150.5°. Yield, 15.5 g. (91%). *Anal.* Calcd. for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9. Found : C, 70.5; H, 11.75 (cf. Tables III and XII).

TABLE XII. $R, R', R''>C\cdot COOH$

No.	R	R′	R″		Analyses (%) Calcd. C	Calcd. H	Found C	Found H
1	CH_3	CH_3	C_4H_9	$C_8H_{16}O_2$	66.6	11.2	66.5	11.2
2	CH_3	C_2H_5	C_3H_7	$C_8H_{16}O_2$	66.6	11.2	66.2	11.2
3	CH_3	CH_3	C_5H_{11}	$C_9H_{18}O_2$	68.3	11.5	68.0	11.6
4	CH_3	C_2H_5	C_4H_9	$C_9H_{18}O_2$	68.3	11.5	68.4	11.8
5	C_2H_5	C_2H_5	C_3H_7	$C_9H_{18}O_2$	68.3	11.5	68.1	11.8
6	CH_3	C_2H_5	C_5H_{11}	$C_{10}H_{20}O_2$	69.7	11.7	69.5	11.8
7	C_2H_5	C_2H_5	C_4H_9	$C_{10}H_{20}O_2$	69.7	11.7	69.5	11.6
8	C_2H_5	C_3H_7	C_4H_9	$C_{11}H_{22}O_2$	70.9	11.9	70.6	12.0

(2) Preparation of N-(3,4-Dimethoxyphenethyl)-α,α,α-trialkylacetamides

N-(3,4-Dimethoxyphenethyl)-α,α,α-tripropylacetamide (VI : $R=R'=R''=C_3H_7$)—To a stirred mixture of 3,4-dimethoxyphenethylamine (4.5 g.), benzene (10 cc.), and Na_2CO_3 solution (20 cc. of 10%) a benzene solution of tripropylacetyl chloride (5 g.) (prepared from the acid and $SOCl_2$ as usual) was added with cooling in ice water. Worked up as usual. A faint yellow vitreous substance was obtained, which solidified on standing to colorless scales (from ligroine), m.p. 73~75°. Yield, 8.7 g. or almost quantitative. *Anal.* Calcd. for $C_{21}H_{35}O_3N$: C, 72.2; H, 10.1; N, 4.0. Found : C, 72.6; H, 10.4; N, 4.5.

All other amides were prepared analogously. Those which did not solidify were used as such directly for the next stage (cf. Tables V and XIII).

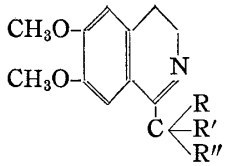
TABLE XIII. CH_3O-(C$_6$H$_3$)-$CH_2\cdot CH_2\cdot NH\cdot CO\cdot C(R,R',R'')$ (2 CH_3O groups)

No.	R	R′	R″		Analyses (%) Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
1	CH_3	CH_3	C_4H_9	$C_{18}H_{29}O_3N$	—	—	4.6	—	—	4.3
2	CH_3	C_2H_5	C_3H_7	$C_{18}H_{29}O_3N$	—	—	4.6	—	—	4.8
3	C_2H_5	C_2H_5	C_2H_5	$C_{18}H_{29}O_3N$	70.3	9.5	4.6	70.4	9.4	4.7
4	CH_3	CH_3	C_5H_{11}	$C_{19}H_{31}O_3N$	—	—	4.4	—	—	4.5
5	CH_3	C_2H_5	C_4H_9	$C_{19}H_{31}O_3N$	—	—	4.4	—	—	4.0
6	C_2H_5	C_2H_5	C_3H_7	$C_{19}H_{31}O_3N$	—	—	4.4	—	—	4.1
7	CH_3	C_2H_5	C_5H_{11}	$C_{20}H_{33}O_3N$	—	—	4.2	—	—	4.4
8	C_2H_5	C_2H_5	C_4H_9	$C_{20}H_{33}O_3N$	—	—	4.2	—	—	3.9
9	C_2H_5	C_2H_5	C_5H_{11}	$C_{21}H_{35}O_3N$	72.2	10.1	4.0	71.9	9.8	3.9
10	C_2H_5	C_3H_7	C_4H_9	$C_{21}H_{35}O_3N$	—	—	4.0	—	—	3.8
11	C_4H_9	C_4H_9	C_4H_9	$C_{24}H_{41}O_3N$	73.6	10.55	3.6	73.8	10.3	3.8

(3) Cyclization

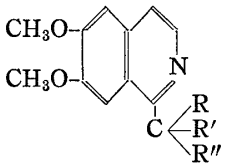
1-Tributylmethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VII : $R=R'=R''=C_4H_9$)—The amide

TABLE XIV.



No.	R	R′	R″	Analyses (%)							Picrate					
					Calcd.			Found				Calcd.			Found		
					C	H	N	C	H	N		C	H	N	C	H	N
1	CH_3	CH_3	C_4H_9	—	—	—	—	—	—	—	$C_{24}H_{30}O_9N_4$	55.6	5.8	10.8	55.9	5.5	10.9
2	CH_3	C_2H_5	C_3H_7	—	—	—	—	—	—	—	$C_{24}H_{30}O_9N_4$	55.6	5.8	10.8	55.7	5.4	11.1
3	C_2H_5	C_2H_5	C_2H_5	$C_{18}H_{27}O_2N$	74.7	9.4	4.9	75.0	9.6	5.1	$C_{24}H_{30}O_9N_4$	55.6	5.8	10.8	55.8	6.0	10.8
4	CH_3	CH_3	C_5H_{11}	—	—	—	—	—	—	—	$C_{25}H_{32}O_9N_4$	56.4	6.1	10.5	56.4	5.7	10.8
5	CH_3	C_2H_5	C_4H_9	$C_{19}H_{29}O_2N$	75.1	9.55	4.6	75.0	9.5	4.4	$C_{25}H_{32}O_9N_4$	56.4	6.1	10.5	56.6	6.1	10.7
6	C_2H_5	C_2H_5	C_3H_7	—	—	—	—	—	—	—	$C_{25}H_{32}O_9N_4$	56.4	6.1	10.5	56.0	6.3	10.6
7	CH_3	C_2H_5	C_5H_{11}	—	—	—	—	—	—	—	$C_{26}H_{34}O_9N_4$	57.1	6.3	10.25	57.2	6.4	10.2
8	C_2H_5	C_2H_5	C_4H_9	—	—	—	—	—	—	—	$C_{26}H_{34}O_9N_4$	57.1	6.3	10.25	57.4	5.9	10.3
9	C_2H_5	C_2H_5	C_5H_{11}	$C_{21}H_{33}O_2N$	76.1	10.0	9.65	76.4	10.2	9.8	$C_{27}H_{36}O_9N_4$	57.8	6.5	10.0	58.0	6.2	10.0
10	C_2H_5	C_3H_7	C_4H_9	$C_{21}H_{33}O_2N$	76.1	10.0	9.65	75.95	10.1	9.6	$C_{27}H_{36}O_9N_4$	57.8	6.5	10.0	57.8	6.4	10.0
11	C_3H_7	C_3H_7	C_3H_7	$C_{21}H_{33}O_2N$	76.1	10.0	9.65	76.3	9.9	9.55	$C_{27}H_{36}O_9N_4$	57.8	6.5	10.0	58.1	6.2	9.9

TABLE XV.



No.	R	R′	R″	Analyses (%)							Picrate					
					Calcd.			Found				Calcd.			Found		
					C	H	N	O	H	N		C	H	N	C	H	N
1	CH_3	CH_3	C_4H_9	—	—	—	—	—	—	—	$C_{24}H_{28}O_9N_4$	55.8	5.5	10.85	55.9	5.5	10.9
2	CH_3	C_2H_5	C_3H_7	—	—	—	—	—	—	—	$C_{24}H_{28}O_9N_4$	55.8	5.5	10.85	56.1	5.7	11.1
3	C_2H_5	C_2H_5	C_2H_5	$C_{18}H_{25}O_2N$	75.2	8.8	4.9	75.3	8.8	4.7	$C_{24}H_{28}O_9N_4$	55.8	5.5	10.85	56.0	5.2	10.5
4	CH_3	CH_3	C_5H_{11}	$C_{19}H_{27}O_2N$	75.7	9.0	4.7	76.0	8.95	4.8	$C_{25}H_{30}O_9N_4$	56.6	5.7	10.6	56.8	6.0	10.6
5	CH_3	C_2H_5	C_4H_9	—	—	—	—	—	—	—	$C_{25}H_{30}O_9N_4$	56.6	5.7	10.6	56.9	5.4	10.8
6	C_2H_5	C_2H_5	C_3H_7	$C_{19}H_{27}O_2N$	75.7	9.0	4.7	75.6	9.2	4.6	$C_{25}H_{30}O_9N_4$	56.6	5.7	10.6	57.0	5.61	10.4
7	C_2H_5	C_2H_5	C_4H_9	$C_{20}H_{29}O_2N$	76.2	9.2	4.4	76.0	9.0	4.8	$C_{26}H_{32}O_9N_4$	57.3	5.9	10.3	57.6	5.8	10.4
8	C_2H_5	C_2H_5	C_5H_{11}	—	—	—	—	—	—	—	$C_{27}H_{34}O_9N_4$	58.0	6.1	10.0	57.8	6.3	10.0
9	C_2H_5	C_3H_7	C_4H_9	—	—	—	—	—	—	—	$C_{27}H_{34}O_9N_4$	58.0	6.1	10.0	58.1	6.2	9.9
10	C_3H_7	C_3H_7	C_3H_7	$C_{21}H_{31}O_2N$	76.6	9.4	4.3	76.3	9.2	4.4	$C_{27}H_{34}O_9N_4$	58.0	6.1	10.0	58.3	6.1	10.0
11	C_4H_9	C_4H_9	C_4H_9	$C_{24}H_{37}O_2N$	77.6	10.0	3.8	77.5	9.8	3.9	$C_{30}H_{40}O_9N_4$	60.0	6.7	9.3	60.3	6.9	9.3

(5.5 g.) in pure xylene (120 cc.) was mixed with freshly distilled $POCl_3$ (28 g.) and the whole was refluxed in an oil bath for 6 hrs., giving a light brown solution. Xylene and an excess of $POCl_3$ were removed *in vacuo* and the residue obtained was mixed with ice water containing some HCl. The mixture was once shaken with benzene and the benzene layer was extracted with dil. HCl, which was added to the original aq. acid layer and basified, separating an oily substance. The oil was taken up in benzene, washed and evaporated, leaving a faint brown vitreous substance, which gradually solidified on standing. Purified from petr. ether, it formed colorless prisms of m.p. 42~44°. Yield, 4.6 g.(88%). *Anal.* Calcd. for $C_{24}H_{39}O_2N$: C, 77.2; H, 10.4; N, 3.7. Found : C, 77.5; H, 10.6; N, 3.7

Picrate : Yellow needles (from EtOH), m.p. 142~143°. *Anal.* Calcd. for $C_{30}H_{42}O_9N_4$: C, 59.8; H, 7.0; N, 9.3. Found : C, 60.2; H, 7.1; N, 9.2. (cf. Tables VI, and XIV).

(4) **Dehydrogenation**

1-(Methyl-ethyl-amylmethyl)-6,7-dimethoxyisoquinoline (VIII: R=CH_3, R′=C_2H_5, R″=C_5H_{11})—The dihydro base (3.5 g.), ethyl cinnamate (15 g.), and Pd-C (2.5 g. of 30%) were mixed and the whole was heated in an atmosphere of CO_2 in an oil bath kept at 280~290°. After 8 hrs.' heating the reaction mixture was dissolved in benzene, filtered from the catalyst, and the filtrate was extracted repeatedly with dil aq. HCl. The combined acid solution was basified and the oil separated was extracted with benzene, washed, and evaporated, leaving a colorless syrup, which dilstilled at 163~164°(0.02 mm.). Yield, 2.85 g.(81%).

Picrate : Yellow prisms (from EtOH) m.p. 141~142.5°. *Anal.* Calcd. for $C_{26}H_{32}O_9N_4$: C, 57.3; H, 5.9; N, 10.3. Found : C, 57.0; H, 5.9; N, 10.6. (cf. Tables VII, and XV).

Summary

A series of 1-*tert*-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolines was synthesized in high yields by cyclizing N-(3,4-dimethoxyphenethyl)-2,2,2-trialkylacetamides with phosphoryl chloride. They were dehydrogenated over palladium-carbon only under strenuous conditions to furnish the corresponding isoquinolines. Their spasmolytic activity will be examined. A general procedure for the preparation of trialkylacetic acids of high purity was also described.

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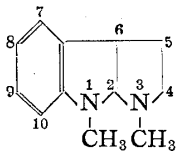
UDC 547.759.07

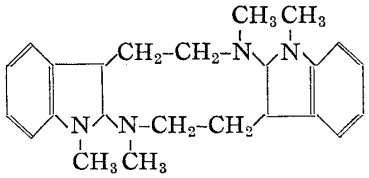
33. Shigehiko Sugasawa and Masao Murayama : Synthesis of *dl*-Esermethole.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

For folicanthine, an alkaloid first isolated from the leaves of *Calycanthus floridus* L. and investigated by Eiter and Svierak,[1,2] two structural formulae (A) and (B) were proposed by Hodson and Smith,[3] of which the former (A) was considered more probable.[4]



(A)



(B)

Many years ago one of the present authors (S. S.) had attempted to synthesize *dl*-esermethole (IX) according to the following scheme :

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* Hongo, Tokyo (菅沢重彦, 村山正雄).

1) K. Eiter, O. Svierak : Monatsh., **82**, 186(1951).
2) *Idem.* : *Ibid.*, **83**, 1453(1952).
3) H.F. Hodson, G.F. Smith : Chem. & Ind.(London), **28**, 740(1956).
4) Based on many experimental results Hodson and Smith later abandoned the formula (A) in favor of (B)(cf. J. Chem. Soc., **1957**, 1877).