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28. Sadao Ohki, Fumiko Hamaguchi, Tokuko Yanagi, and Motoyo Yoshino : Cyclization towards Carbon-Carbon Double Bond. III.*1 A New Synthesis of 1-Pyrroline Derivatives and a Synthesis of 1,2-Dialkyl-3-diphenylmethylenepyrrolidine Alkyl Halide, an Anti-acetylcholine Substance.

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(A) Synthesis of 3-Diphenylmethylene-1-pyrrolines

Some time ago, 1-pyrroline derivatives (I and II) were synthesized by Sugasawa and others[1] by the Bischler-Napieralski reaction and also by the application of Ritter's N-alkylamide synthesis.[2] One of the present writers (F. H.) reported recently the syntheses of 3-diphenylmethylene-1-pyrroline (IIIa) and its 2-phenyl derivative (IIIb) from the acyl derivative (IV) of 4,4-diphenyl-3-butenylamine by Sugasawa's method.[3]

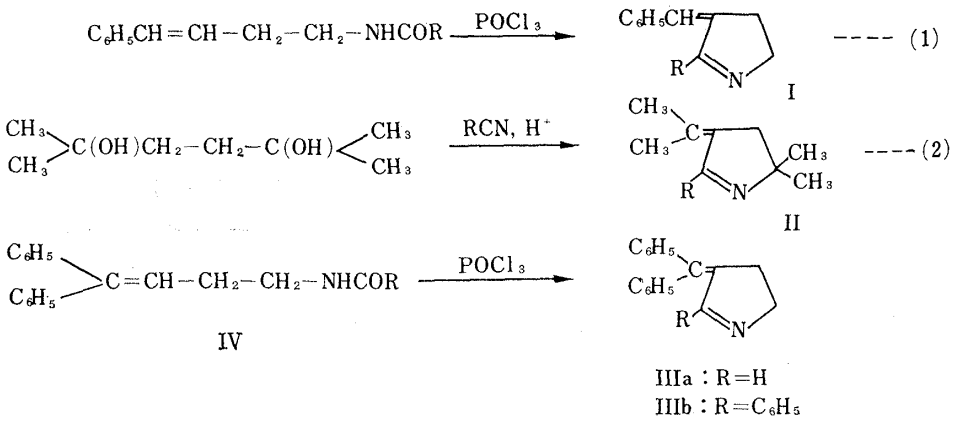

Chart 1.

These synthetic reactions are valuable since various kinds of pyrrolidine derivatives and other compounds can be derived from compounds of the types I, II, and III.[3,4] 2-Alkyl-3-diphenylmethylene-1-pyrroline (III) can also afford 1,2-dialkyl-3-diphenylmethylenepyrrolidine alkyl halide, which showed a comparatively strong anti-acetylcholine activity, as will be described later.

For these reasons, it seemed necessary to find a new synthetic route to these three types of compounds, especially a new and simple method for preparing the III-type compounds.

Lora-Tamayo and others[5] had reported the synthesis of 3,4-dihydroisoquinolines by the reaction of 2-chloroethylbenzene and nitrile-stannic chloride complex, and had

*1 Part II. S. Ohki, F. Hamaguchi : Yakugaku Zasshi, **85**, 971 (1965).

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1) S. Sugasawa, S. Ushioda : Tetrahedron, **5**, 48 (1959); Cf. T. Fujisawa, S. Sugasawa : *Ibid.*, **7**, 185 (1959).

2) A. I. Meyers, J. J. Ritter : J. Org. Chem., **23**, 1918 (1958).

3) F. Hamaguchi : Yakugaku Zasshi, **82**, 1088 (1962).

4) T. Mizoguchi : Chem. Pharm. Bull. (Tokyo), **9**, 818 (1961), **10**, 366 (1962); A. I. Meyers, W. Y. Libans : J. Org. Chem., **26**, 1682 (1962); cf. A. I. Meyers, *et al.* : *Ibid.*, **28**, 2944 (1963).

5) M. Lora-Tamayo, R. Maronero, G. G. Munoz : Chem. Ber., **93**, 289 (1960); cf. M. Lora-Tamayo, R. Madronero, G. G. Munoz, J. M. Marzal, M. Stud : *Ibid.*, **94**, 199 (1961).

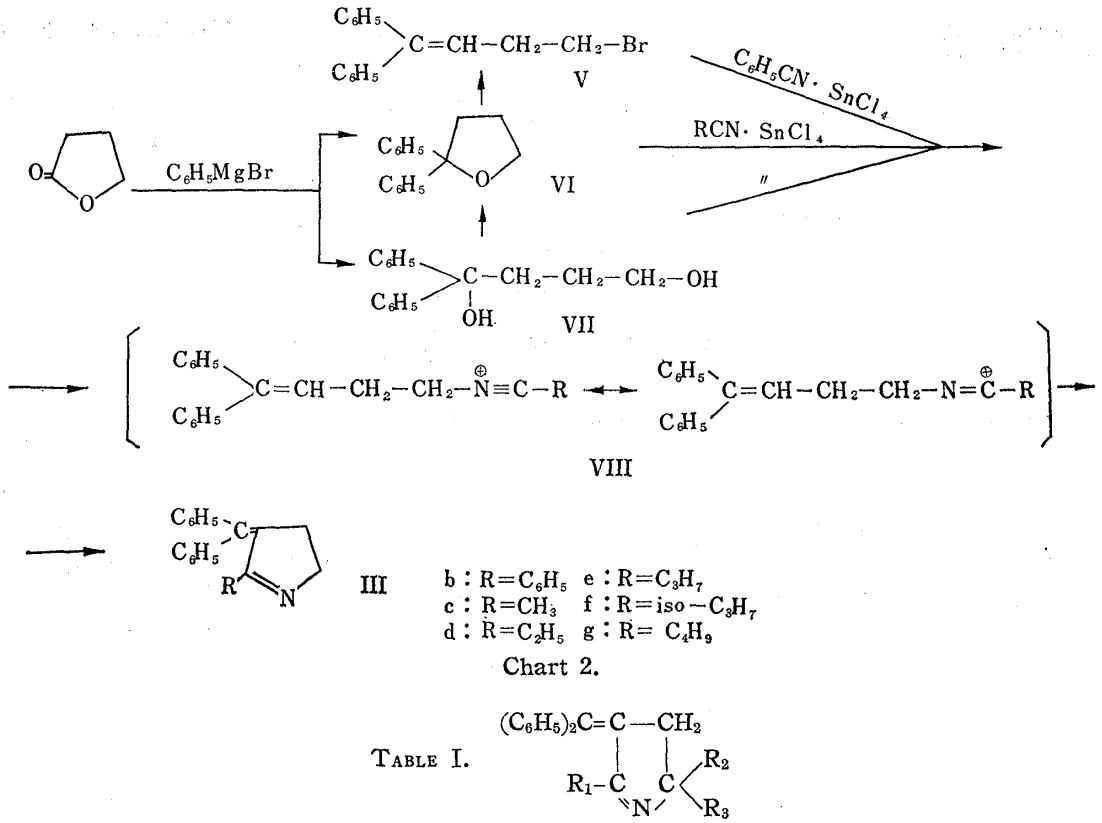


Chart 2.

TABLE I.

Compound	R_1	R_2	R_3	m.p.[b] (°C) (b.p. °C/mm. Hg)	Yield (from III) (%) without $POCl_3$	Yield (from III) (%) with $POCl_3$	IR ($\nu_{C=N}$) (cm^{-1})
Ia[a]	H	H	H	115～116			1565
Ib[a]	C_6H_5	〃	〃	157～158	62		1550
Ic	CH_3	〃	〃	119 164 (picrate)	41	62	1587
Id	C_2H_5	〃	〃	89 (131～136/4)	68	68	1590
Ie	C_3H_7	〃	〃	60 (152/4) 166 (picrate)	47	68	1585
If	iso-C_3H_7	〃	〃	104～105 (171～173/7)		69	1585
Ig	C_4H_9	〃	〃	49 (116/0.3) 167 (picrate)	43		—
XI	CH_3	CH_3	〃	(158/3) 178～179 (picrate)		48	1585
XII	〃	〃	CH_3	92～93		29	1587

Compound	UV λ_{max}^{EtOH} mμ (log ε)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia[a]	235 (4.24), 297 (4.32)							
Ib[a]	237 (4.44), 306 (4.32)							
Ic	231 (4.09), 287 (4.17)	$C_{18}H_{17}N$	87.4	6.9	5.7	87.5	6.3	5.5
		$C_{18}H_{17}N \cdot C_6H_3O_7N_3$	60.5	4.2	11.8	60.1	4.5	12.2
Id	231 (4.20), 287 (4.20)	$C_{19}H_{19}N$	87.3	7.3	5.4	87.0	7.1	5.5
Ie	231 (4.16), 287 (4.16)	$C_{20}H_{21}N$	87.2	7.7	5.1	86.7	6.9	5.0
		$C_{20}H_{21}N \cdot C_6H_3O_7N_3$	61.9	4.8	11.1	62.3	5.0	11.2
If	230 (4.23), 288 (4.22)	$C_{20}H_{21}N$	87.2	7.7	5.9	87.5	7.7	5.2
Ig	231 (4.23), 287 (4.23)	$C_{21}H_{23}N \cdot C_6H_3O_7N_3$	62.5	5.05	10.8	62.5	4.6	10.5
XI	228 (4.12), 287 (4.12)	$C_{19}H_{19}N \cdot C_6H_3O_7N_3$	61.5	4.1	11.5	61.0	4.6	11.2
XII	229 (4.17), 287 (4.20)	$C_{20}H_{21}N$	87.2	7.7	5.1	87.5	7.85	5.2

a) Ref. (5). *b*) m.p.s are uncorrected.

stated that the reaction probably proceeded *via* the nitrilium salt. Since the mechanism of this reaction seems to be very similar to that of the Bischler-Napieralski reaction, this reaction was applied to the synthesis of Ⅲ.

Treatment of 4-bromo-1,1-diphenyl-1-butene[3] (Ⅴ) with benzonitrile-stannic chloride complex, Ⅲb was obtained in a fair yield and its structure was proved by direct comparison with Ⅲb prepared previously.[3] The same compound (Ⅲb) was also obtained by the reaction of benzonitrile-stannic chloride complex with 2,2-diphenyltetrahydrofuran[3,6] (Ⅵ) or with 1,1-diphenyl-1,4-butanediol[3,6] (Ⅶ), both are precursors of Ⅴ.[3] The nitrilium salt (Ⅷ) may be the common intermediate in these reactions, as shown in Chart 2.

The compound most easy to obtain, Ⅶ, was reacted with stannic chloride complex of acetonitrile, propionitrile, butyronitrile, and valeronitrile to afford the corresponding 1-pyrrolines in a comparatively good yield (Table I). In this reaction, addition of phosphoryl chloride generally improved the yield and made isolation of the product easier. Since the starting materials, Ⅴ, Ⅵ, and Ⅶ, prepared from butyrolactone and Grignard reagent,[3,6] can be obtained much more readily than Ⅳ and the yield of these reaction is fairly good, the present method seems to be a convenient and advantageous method for the synthesis of Ⅲ.

In this reaction, the nitrile-stannic chloride complex seemed to have reacted with the primary alcoholic group in Ⅶ to form the nitrilium salt (Ⅷ). This fact contrasts with the Ritter reaction[2] (equation 2 in Chart 1) in which the reaction most easily takes place with the tertiary alcoholic group. Therefore, secondary alcohol (Ⅸ) and tertiary alcohol (X) were prepared and their reaction with acetonitrile-stannic chloride complex was compared with the reaction of primary alcohol (Ⅷ).

The secondary alcohol (Ⅸ) was prepared by the Grignard reaction of γ-methylbutyrolactone, obtained by the reduction of methyl levulate with sodium borohydride, and phenylmagnesium bromide. The tertiary alcohol (X) was also prepared by the Grignard reaction of γ,γ-dimethylbutyrolactone, obtained from methyl levulate and

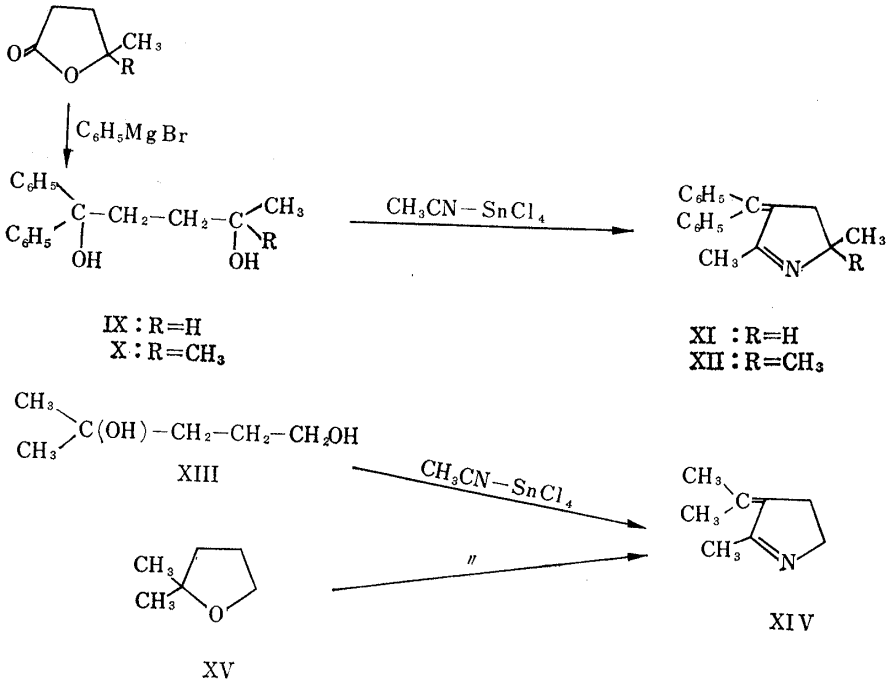


Chart 3.

6) J. F. Vozza : J. Org. Chem., 24, 1720 (1959).

methylmagnesium iodide, and phenylmagnesium bromide.

Reaction of Ⅶ, Ⅸ, ane Ⅹ with acetonitrile-stannic chloride complex under the same condition afforded the corresponding 1-pyrrolines (Ⅲc, Ⅺ, and Ⅻ) in 62, 48, and 29% yield.*3 This result indicates that reaction becomes more difficult in the order of primary, secondary, and tertiary alcohols. The fact that the only nitrogen-containing product from the reaction of 4-methyl-1,4-pentanediol (XIII) with acetonitrile-stannic chloride complex was 2-methyl-3-isopropylidene-1-pyrroline (XIV) shows that the reaction preferentially takes place with aliphatic primary alcohol over tertiary alcohol in the same molecule, and more clearly represents the above relationship.

From the result of these reactions, it is considered that the formation of a nitrilium salt from nitrile-stannic chloride complex follows the S_N2 reaction and the formation of a nitrilium salt by the Ritter reaction follows the S_N1 reaction.

The structure of XIV was confirmed from elemental analytical values of its picrate, from its ultraviolet absorption maximum (in ethanol) at 246 mμ, and similarity of its infrared absorptions at 1658 ($\nu_{C=C}$) and 1590 ($\nu_{C=N}$) cm^{-1} with those of Ⅱ.[2] The compound (XIV) was also obtained by the same reaction of 2,2-dimethyltetrahydrofuran (XV).

Infrared and ultraviolet spectra, and analytical data of the compounds obtained by these reactions are summarized in Table I. The stretching vibration of C=N in 2-alkyl-1-pyrrolines (Ⅲc~g, Ⅺ, and Ⅻ) was observed in higher frequency region than that of 2-unsubstituted compounds. This may be due to the steric effect of the substituent in 2-position on the coplanarity between the double bond of diphenylmethylene group and the pyrroline ring, and this effect partially destroyed the conjugation between C=C and C=N, as was described by Meyers[7] in the case of 2-substituted 3-isopropylidene-1-pyrrolines. This effect was also observed in the ultraviolet spectra of these compounds. In the case of Ⅲa, in which the coplanarity of C=C and C=N is not affected by the substituent in 2-position, absorption maximum was observed in a longer wave-length region than that of 2-substituted compounds. A substituent in 5-position (Ⅺ and Ⅻ) showed little effect on ultraviolet spectra.

In the case of 2-phenyl derivative (Ⅲb), the stretching vibration of C=N was observed in a lower frequency region than that of 2-alkyl derivatives, and ultraviolet absorption maximum was in a longer wave-length region by the increase of a cross conjugation of the phenyl group.

(B) Synthesis of 1-Methyl-2-alkyl-3-diphenylmethylene-pyrrolidine Methiodide and its Pharmacological Activity

The methiodies of Ⅲa to Ⅲg were reduced by sodium borohydride to the corresponding 1-methyl-2-alkyl-3-diphenylmethylenepyrrolidines (XVIa~g) (Table Ⅱ).

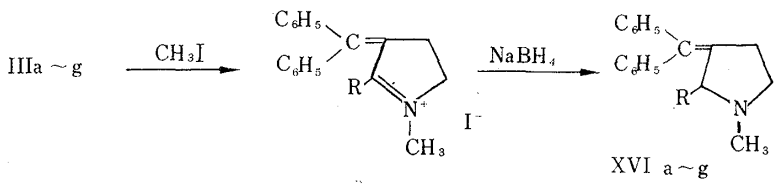
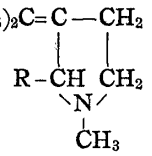


Chart 4.

*3 Treatment of Ⅶ, Ⅸ and Ⅹ by the Ritter reaction conditions (reaction with the nitrile in conc. sulfuric acid at room temperature) failed to afford 1-pyrrolines, either recovering the starting material or giving non-nitrogenous product of unknown structure.

7) A. L. Meyers : J. Org. Chem., 24, 1233 (1959).

Table II.



Compound	R	m.p. (°C) (b.p. °C/mm. Hg)	Yield (from III) (%)	m.p. of deriv. (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XVIa	H	69 (135/5)	—	207 (methiodide)	$C_{18}H_{19}N$ (free base) $C_{19}H_{22}NI$	86.7 58.3	7.7 5.7	5.6 3.6	86.75 58.15	7.9 5.6	5.6 3.5
XVIb	C_6H_5	88～89	92		$C_{24}H_{23}N$ (free base)	88.6	7.1	4.3	88.8	7.4	4.1
XVIc	CH_3	(120～121/0.1)	71	264～265 (HCl-salt) 105～107 (methiodide)	$C_{19}H_{21}N \cdot HCl$ $C_{20}H_{24}NI \cdot \frac{1}{2}H_2O$	76.1 57.9	7.35 6.1	4.7 3.4	76.4 58.2	7.2 5.9	4.3 3.7
XVId	C_2H_5	(128/0.5)	83	118～119 (picrate) 203 (methiodide)	$C_{20}H_{23}N \cdot C_6H_3O_7N_3$ $C_{21}H_{26}NI \cdot H_2O$	61.65 57.7	5.2 6.4	11.1 3.2	61.9 57.9	5.35 6.4	10.95 3.3
XVIe	C_3H_7	(133.5/0.1)	54	122～123 (picrate) 245～246 (methiodide)	$C_{21}H_{25}N \cdot C_6H_3O_7N_3$ $C_{22}H_{28}NI$	62.3 61.0	5.4 6.5	10.8 3.2	62.1 60.5	5.45 6.2	10.3 3.2
XVIf	iso-C_3H_7	(143/4)	72	234～235 (methiodide)	$C_{22}H_{28}NI$	61.0	6.5	3.2	61.25	6.7	3.2
XVIg	C_4H_9	72～74 (128～129/0.5)	88	175～176 (picrate) 230～232 (methiodide)	$C_{22}H_{27}N \cdot C_6H_3O_7N_3$ $C_{23}H_{30}NI$	62.9 61.7	5.7 6.7	10.5 3.15	63.1 61.8	5.6 6.4	10.6 3.2

The free base and methiodide of XVI was examined for anti-acetylcholine, anti-histamine, and anti-barium activities by the Magnus method, using smooth muscle of an excised intestine from mice and guinea pigs.*4 The strongest anti-acetylcholine activity was found in the methiodide of XVIc, which showed about one-quarter the activity of atropine sulfate. Anti-histamine action was found in the methiodide of XVId, which was about 1/1.5 of diphenhydramine hydrochloride. The compound (XVIe) had an anti-barium action about 19 times stronger than that of papaverine hydrochloride. Details of these pharmacological activities will be reported elsewhere. Further examinations are also being made on the pharmacological activity of various derivatives of this series of compounds.

Experimental*5

2-Phenyl-3-diphenylmethylene-1-pyrroline (IIIb)——Method (a). From 1,1-diphenyl-1,4-butanediol (VII): To a mixture of VII (0.5 g., 0.002 mole), and benzonitrile (0.2 g., 0.002 mole), $SnCl_4$ (0.52 g., 0.002 mole) was added and the mixture was heated at 135° for 3 hr. When cooled, the reaction mixture was decomposed with 20% NaOH and extracted with ether. The ether extract was extracted with 20% HCl, the acid layer was basified with NaOH, and the separated oil was extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from iso-Pr_2O to afford colorless needles, m.p. 156～157°. Yield, 0.38 g. (62%). This compound was identified with an authentic sample[3] obtained previously through admixture and comparison of their infrared and ultraviolet spectra.

*4 Pharmacological action was examined by Mr. M. Hitomi, Osaka Laboratory of Fujisawa Pharmaceutical Ind., Ltd.

*5 All melting points are uncorrected.

Method (b). From 2,2-diphenyltetrahydrofuran (Ⅵ): To a mixture of Ⅵ (0.5 g., 0.0023 mole) and benzonitrile (0.24 g., 0.0023 mole), $SnCl_4$ (0.9 g., 0.0034 mole) was added and the mixture was heated at 130~140° for 3 hr. The reaction mixture was treated as in method (a) and 0.33 g. (50%) of Ⅲb, m.p. 156~157°, was obtained. This compound showed on depression of m.p. on admixture with the sample obtained as above.

Method (c). From 4-Bromo-1,1-diphenyl-1-butene (Ⅴ): A mixture of Ⅴ (1.0 g., 0.004 mole), benzonitrile (0.41 g., 0.004 mole), and $SnCl_4$ (1.04 g., 0.004 mole) was treated as in method (a) and the same Ⅲb was obtained as colorless needles (0.6 g., 50%), identified with the authentic sample by admixture.

2-Alkyl-3-diphenylmethylene-1-pyrroline (IIIc~g) (cf. Table I)——To a mixture of Ⅶ (0.1 mole) and $POCl_3$ (30~50 g.), the nitrile (0.4 mole) and $SnCl_4$ (0.3 mole) were added and the mixture was heated at 130~140° for 3 hr. After removal of $POCl_3$ and unreacted nitrile *in vacuo*, the residue was treated as in method (a).

1,1-Diphenyl-1,4-pentanediol (IX)——A solution of 11.8 g. (0.118 mole) of γ-methylbutyrolactone in dry ether was slowly added to the Grignard solution, prepared from 37 g. (0.236 mole) of bromobenzene and 5.7 g. (0.236 g. atom) of Mg in dry ether with stirring at 0°. The stirring was continued for 2 hr. at 0° and for 30 min. at room temperature. The reaction mixture was allowed to stand overnight and treated with 2.05*M* HCl. The ethereal layer was separated and treated successively with H_2O, 5% NaOH, and saturated NaCl solution. After being dried over Na_2SO_4, the solvent was evaporated, the crude solid product was washed with hexane, and recrystallized from acetone-iso-Pr_2O mixture to colorless crystals, m.p. 72~73°. Yield, 25.8 g. (85%). *Anal.* Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.9; Found: C, 79.5; H, 7.8.

1,1-Diphenyl-4-methyl-1,4-pentanediol (X)——By the same procedure as described above, starting with γ,γ-dimethylbutyrolactone, X was obtained as colorless crystals, m.p. 127~128° (from acetone-iso-Pr_2O). Yield, 12.4%. *Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.8; H, 8.1.

2,5-Dimethyl-3-diphenylmethylene-1-pyrroline (XI) (Table I)——By the procedure described for the synthesis of IIIc~g, XI was obtained as colorless oil (48% yield) from the reaction of Ⅸ and CH_3CN-$SnCl_4$ complex.

2,5,5-Trimethyl-3-diphenylmethylene-1-pyrroline (XII) (Table I)——This compound (XII) was obtained from X and CH_3CN by the same method as above. Colorless crystals, m.p. 92~93°. Yield, 29%.

2-Methyl-3-isopropylidene-1-pyrroline (XIV)——From 4-methyl-1,4-pentanediol[8] (XIII): To a mixture of XIII (1.0 g.) and $POCl_3$ (3 ml.), CH_3CN (1.4 g.) and $SnCl_4$ (3 ml.) were added and the mixture was heated at 125~135° for 3 hr. After removal of $POCl_3$, the residue was treated as described in method (a). Colorless oil (0.29 g., 28%), $b.p_4$ 59°. Picrate: yellow crystals, m.p. 154° (from EtOH). *Anal.* Calcd. for $C_8H_{13}N \cdot C_6H_3O_7N_3$: C, 47.8; H, 4.6; N, 15.9. Found: C, 47.7; H, 5.0; N, 15.1. UV λ_{max}^{EtOH} mμ (log ε): 246 (3.78). IR cm^{-1}: $\nu_{C=C}$ 1658; $\nu_{C=N}$ 1590.

A resinous substance, not containing N, was obtained as a by-product which was not extracted by conc. HCl.

From 2,2-dimethyltetrahydrofuran[9] (XV): A mixture of XV (0.5 g.), CH_3CN (0.8 g.), $POCl_3$ (1.7 ml.), and $SnCl_4$ (1.7 ml.) was heated at 125~135° for 3 hr. and treated in the same way as above. The same XIV was obtained in 0.14 g. yield (24%) as colorless oil and identified with the above sample through infrared and ultraviolet spectra, and by admixture of their picrates.

1-Methyl-2-alkyl-3-diphenylmethylenepyrrolidine (XVI) (Table II)——Excess of CH_3I was added to a solution of III dissolved in MeOH, the mixture was warmed on a water bath for 5 hr., and allowed to stand overnight. MeOH and excess of CH_3I were evaporated under a reduced pressure and the residual crude methiodide of III was dissolved in MeOH. To this solution, ca. 4 equiv. of $NaBH_4$ was added in small portions under stirring and the mixture was stirred for 4 hr. at room temperature. The mixture was acidified with 10% HCl, MeOH was evaporated under a reduced pressure, and the residue was basified with 20% NaOH. The alkaline layer was salted out with K_2CO_3 and extracted with ether. The ether layer was dried over Na_2SO_4, the solvent was evaporated, and distillation of the residue afforded XVI.

Methiodide (Table II): XVI was dissolved in MeOH, excess CH_3I was added, and the mixture was warmed on a water bath for 1 hr. After leaving the mixture to stand overnight, the precipitated crystals were collected and recrystallized from MeOH.

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8) W. F. Baitinger, *et al.*: J. Org. Chem., **29**, 989 (1964).
9) Cf. N. T. Shuikin, *et al.*: Chem. Abst., **60**, 11966 (1964).

Summary

2-Subsituted 3-diphenylmethylene-1-pyrrolines (Ⅲ) were synthesized in one step by the reaction of 1,1-diphenyl-1,4-butanediol (Ⅶ), 2,2-diphenyltetrahydrofuran (Ⅵ), or 4-bromo-1,1-diphenyl-1-butene (Ⅴ) with nitrile-stannic chloride complex. 2,5-Dimethyl (Ⅺ) and 2,5,5-trimethyl-3-diphenylmethylene-1-pyrroline (Ⅻ) were obtained respectively from 1,1-diphenyl-1,4-pentanediol (Ⅸ) and 1,1-diphenyl-4-methyl-1,4-pentanediol (Ⅹ).

The fact that 2-methyl-3-isopropylidene-1-pyrroline (XIV) was obtained from 2-methyl-2,5-pentanediol (XIII) and 2,2-dimethyltetrahydrofuran (XV) by the same reaction was of interest in contrast with preparation of 1-pyrrolines (Ⅱ) by the Ritter reaction.

Reduction of the methiodide of Ⅲ with sodium borohydride gave 1-methyl-2-alkyl-3-diphenylmethylenepyrrolidine. The methiodide of the 2-methyl compound (XVIc) was found to have a comparatively strong anti-acetylcholine activity.

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