plex is formed by the combination of free amino group in pepsin and sulfate groups in ROS-S or heparin.

The author expresses his deep gratitude to Prof. Emeritus M. Ishidate and Prof. Y. Ito of Faculty of the Pharmaceutical Sciences, University of Tokyo, for their invaluable help and suggestion. He is also deeply grateful to Dr. S. Hayashi, Managing Director of this Company, and to Mr. G. Tatsui, Director of this Laboratory, for their permission to submit this report.

Summary

It was confirmed that the complex of pepsin with ROS-S and heparin is formed in an acid solution (pH 1.5~4.4) and that the complex is dissociated at the pH above 5.2. The isolated complex has no proteolytic activity, but it was almost completely recovered by removing ROS-S or heparin as the barium salt or protamine complex. It was confirmed that the inhibitory action of polysaccharide sulfates on proteolytic action of pepsin is caused by the formation of inactive complex of pepsin with the sulfates.

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31. Masazumi Kawanishi : Synthesis of 1-Alkyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-one Derivatives.

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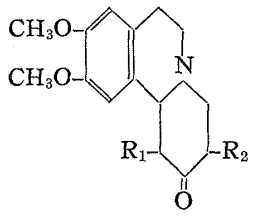
Though it is more than 40 years ago since Pyman[1] had correctly proposed benzoquinolizine as the fundamental skeleton for the Ipecachuanha group of alkaloids, it has never been met in synthetic medicinals until quite recently Schnider, *et al.*[2] ascribed a tranquilizing property to their synthetical products, 3-alkyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-ones (B), whose 3-isobutyl derivative was introduced into the clinical field by the Hoffmann La-Roche Inc. as Nitoman.



(A) R_1=alkyl, R_2=H
(B) R_1=H, R_2=alkyl

The present writer, who for some time has been engaged in the study related to rotundine, was interested with the above report and decided to synthesize a series of 1-alkyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-one derivatives (A) for pharmacological evaluation.

For this objective, it seemed pertinent to develop the method of Ban,[3] which he

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*1 Toda-machi, Kita-adachi-gun, Saitama-ken (川西正純).
1) W. H. Brindley, F. L. Pyman : J. Chem. Soc., **130**, 1067 (1927).
2) A. Brossi, H. Lindlar, M. Walter, O. Schnider : Helv. Chim. Acta, **41**, 119 (1958).
3) Y. Ban : This Bulletin, **6**, 312 (1958).

worked out to synthesize 3-ethyl-9, 10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]-quinolizin-2-one (B : $R_2=C_2H_5$, $R_1=H$) as an intermediate for the synthesis of emetine. By an alternative route, Schnider, *et al.*[2] also synthesized two of A-type compounds ($R_1=C_2H_5$ and iso-C_4H_9, $R_2=H$).

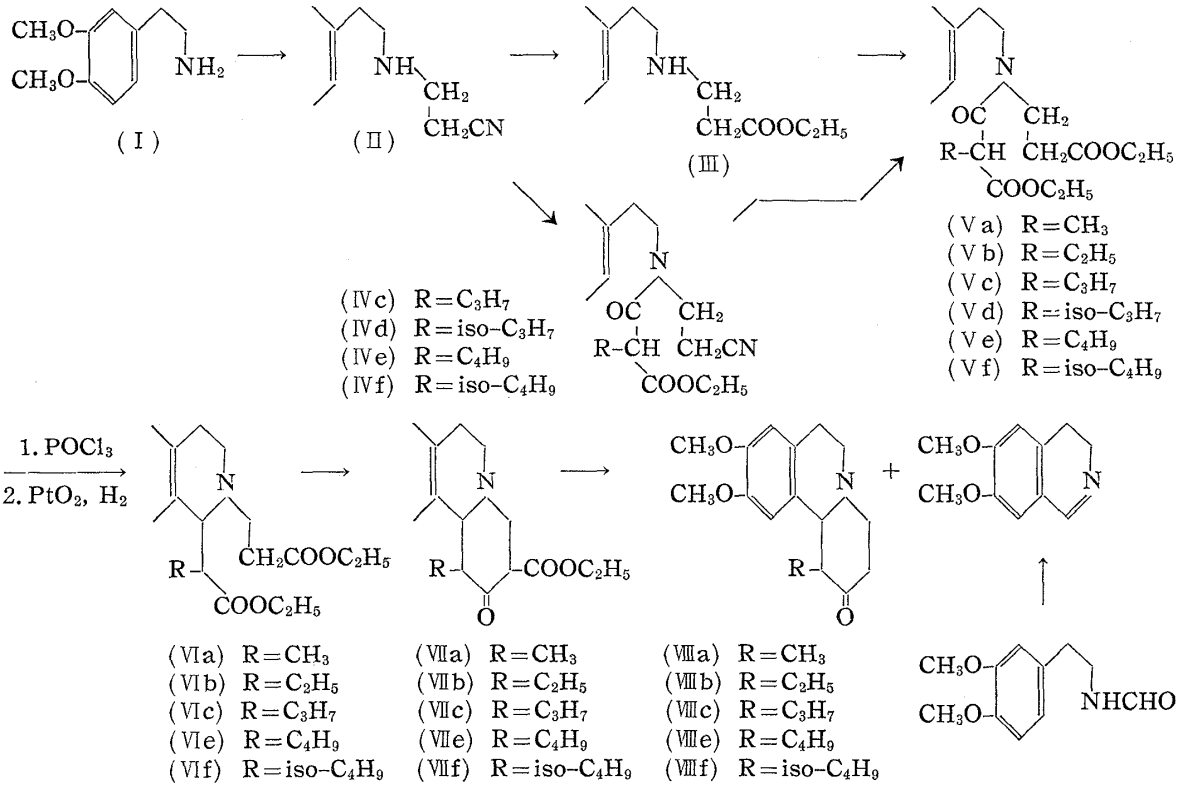

Chart 1.

3-(3,4-Dimethoxyphenethylamino) propionitrile (II), prepared according to the method of Yamazaki,[4] was converted into the corresponding ethyl ester by the conventional method. This esterification reaction gave only a poor yield (16~18%) of the desired product, recovering a considerable amount of the starting phenethylamine, probably due to the retro-Michael reaction during esterification.

In order to avoid this drawback, the aminopropionitrile (II) was acylated with the chloride of ethyl hydrogenalkylmalonate, followed by esterification of the product to give the diethyl ester-amide (V). When the intensity of the ester band (1740 cm^{-1}) and the amide band (around 1650 cm^{-1}) of (IV) and (V) was compared, a distinct increase of intensity was observed in the ester band of (V), which fact also lent support that complete esterification took place giving a good yield of (V).

Cyclization of the ester amide (V) thus obtained was then attempted with phosphoryl chloride in benzene, but the result was unsatisfactory, giving a poor yield of the cyclized product together with a considerable amount of the recovered starting material. Refluxing with phosphoryl chloride alone gave a better result and this cyclization method was therefore adapted for the whole series of the compound (V). From the cyclization mixture phosphoryl chloride was removed and the aqueous extract of the residue, treated once with decolorizing charcoal, was again evaporated. The residue dissolved in ethanol furnished the reduction product (VI) on being reduced catalytically. (Vd) (R= iso-C_3H_7) was, however, found to be quite refractory to the cyclization and even the combination of polyphosphoric acid-phosphoryl chloride proved to be ineffective to promote

4) T. Yamazaki : Yakugaku Zasshi, **79**, 1017 (1959).

the cyclization, either recovering the starting material or giving rise to a resinous product, when the reaction was conducted for an extended period of time. This failure may be ascribed to the steric effect of the isopropyl group.

All bases (VI) thus obtained formed a viscous oil, which distilled in a high vacuum with partial decomposition and also failed to afford any crystalline salts through which the purification seemed possible.

Dieckmann cyclization of the crude (VI) proceeded smoothly with sodium hydride in pure toluene, heated in an oil-bath kept at 120~125°, to yield the cyclized product (VII), whose solubility in aqueous sodium hydroxide solution decreases with increasing size of the alkyl group in 1-position. In conformity with their structure, all (VII) give distinct deep reddish purple ferric chloride color test in alcoholic solution. Schnider, *et al.* also prepared (VIIb) and (VIIf), whose physical constants are in good agreement with those of the present products.

These keto-esters, except (VIIa), which showed a considerable resistance towards ketonic fission probably due to its high melting point (177~178°), underwent smooth fission on being boiled with 10% hydrochloric acid, generating carbon dioxide to yield 1-alkyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-one derivatives (VIII). Inspection of infrared absorption spectra of the crude products (VIII) revealed that, besides a band at 1710 cm^{-1} ascribable to CO-group, there is a weak but distinct band at 1660 cm^{-1}, which may probably be assigned to the contaminating 6,7-dimethoxy-3,4-dihydroisoquinoline, the by-product in the ketonic fission reaction. Schnider, *et al.* also pointed out the presence of the said isoquinoline in their crude (VIIIb) and (VIIIf), both of which they obtained in a poor yield.

When the residue of the benzene solution of each of crude (VIII) was treated with dilute hydrochloric acid, there first separated one and the same faint yellow prisms of m.p. 75~76°, which decomposed at 198~201° on further heating. This hydrochloride showed a distinct infrared absorption band at 1650~1660 cm^{-1} (Nujol) ascribable to $C{=}\overset{+}{N}$, while no band was recognized in the ketone region. Direct comparison with the authentic specimen[5] confirmed the identity of the above salt with the hydrochloride of 6,7-dimethoxy-3,4-dihydroisoquinoline. Thus, the competitive formation of this isoquinoline with the desired product (VIII) was confirmed to be common in the ketonic fission reaction of all keto-esters (VII), affecting the yield of the ketones (VIII). Each of (VIII) was isolated from the hydrochloride filtrate and was characterized either as the hydrochloride or as a phenylhydrazone.

The route via which Schnider, *et al.* prepared (VIIIb) and (VIIIf) started from condensation of α-alkyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline acetate with acrylonitrile according to the Michael method, which reaction required a long time for completion. As mentioned above, this drawback was avoided in the present method, but the Bischler-Napieralski cyclization was possible only with simultaneous formation of a considerable amount of a by-product, which rendered purification of the product difficult and hence the preparation of its derivatives for characterization impossible. Thus, for the preparation of the final product it appears difficult to choose one in preference to the other.

Experimental*2

Ethyl α-Alkyl-2-(2-ethoxycarbonylethyl)-6,7-dimethoxy-3,4-dihydro-1-isoquinoline Acetate(Va~f)——i) Preparation from N-(3,4-Dimethoxyphenethyl)-β-alanine Ethyl Ester (III) (Va~b): The compound (III) (1 mole), dissolved in 3 volumes of benzene, was mixed with 10% Na_2CO_3 solution (1.1 mole)

*2 A Nippon Bunko Model IR-S spectrophotometer was used for the determination of the infrared spectra.

5) F. L. Pyman: J. Chem. Soc., **95**, 1618 (1909); E. Späth, H. Epstein: Ber., **59**, 2796 (1926).

and to this mixture, a solution of chloride of ethyl hydrogen alkyl malonate (1.1 mole) in 3 volumes of benzene was added dropwise with ice-cooling and stirring. After being stirred for 1 hr. at room temperature, the benzene layer was separated, washed successively with H_2O, 5% HCl, and 5% $NaHCO_3$ solution, dried over anhyd. Na_2SO_4, and the solvent was distilled off, leaving a viscous residue in a fairly good yield. This product was used without further purification for the following reaction.

Table I.

Compound R	IR $\nu_{C=O}^{liquid}$ (cm^{-1})	
	Ester	Amide
Me (Va)	1735	1650
Et (Vb)	1730	1650

ii) Preparation from 3-(3,4-Dimethoxyphenethylamino)propionitrile (II): a) Ethyl N-(2-Cyanoethyl)-N-(3,4-dimethoxyphenethyl)-2-alkylmalonamate (IVc~f): Aminopropionitrile (II) (1 mole), dissolved in 3 volumes of benzene, was mixed with 10% Na_2CO_3 solution (1.1 mole) and to this mixture, a benzene solution of chloride of ethyl hydrogen alkyl malonate (1.1 mole) was addeddropwise with ice-cooling and stirring. The reaction mixture was treated as above. The crude product (IVc~f) was obtained in a good yield and was used for the following reaction without further purification.

Table II.

Compound R	IR $\nu_{C\equiv N}^{liquid}$, $\nu_{=O}^{liquid}$ (cm^{-1})		
	Nitrile	ester	Amide
Pr (IVc)	2290	1740	1650
iso-Pr (IVd)	2290	1735	1650
Bu (IVe)	2285	1735	1650
iso-Bu (IVf)	2290	1740	1655

b) Esterification of (IVd~f): The solution of the foregoing compound (IVa~f) dissolved in 3 volumes of dehyd. EtOH was saturated with dry HCl with ice-cooling, during which time the solution became faintly green. The mixture was gently warmed to about 65°(bath temp.), when the green color disappeared and NH_4Cl deposited out. After being kept at 65~70° for 10 min., the reaction mixture was allowed to stand at room temperature overnight, filtered from NH_4Cl, and the filtrate was concentrated *in vacuo*. The syrupy residue was extracted with benzene, which was washed successively with H_2O, 5% $NaHCO_3$, and H_2O, dried, and the solvent was distilled off, leaving a pale yellow brownish syrup. The yield of the crude product (Vd~f) was fairly good in each case.

Table III.

Compound R	IR $\nu_{C=O}^{liquid}$ (cm^{-1})	
	Ester	Amide
Pr (Vc)	1735	1650
iso-Pr (Vd)	1730~1735	1650
Bu (Ve)	1735	1655
iso-Bu (Vf)	1735	1655

Ethyl α-Alkyl-2-(2-ethoxycarbonylethyl)-6,7-dimethoxy-3,4-dihydro-1-isoquinoline Acetate (VIa~f)——The diester-amide (Va~f) was gently refluxed with 3 volumes of freshly distilled $POCl_3$ in an oil bath, vigorous evolution of HCl gas being observed. After the gas evolution had subsided, excess $POCl_3$ was removed *in vacuo* at 80~85°(bath temp.) to leave a dark viscous syrupy residue. The residue was extracted with hot H_2O, the aqueous extract was treated twice with active carbon, and concentrated *in vacuo*.

The residual syrup was dissolved in about 3 volumes of EtOH and directly reduced catalytically under atmospheric pressure over the Adams Pt (1/50 part by weight of the starting diester-amide). In every case, 60~70% of the theoretical amount of H_2 was absorbed. The filtrate from the catalyst was concentrated *in vacuo* and the residue was freed from H_2O by azeotropic distillation with EtOH and benzene to dryness. The residue was redissolved in about 5 volumes of dehyd. EtOH, saturated with dry HCl gas, allowed to stand overnight at room temperature, and the solvent was distilled off. The residue was dissolved in H_2O and the solution was shaken with benzene to remove insoluble material. The resultant aqueous layer was filtered, the filtrate was slightly basi-

fied with K_2CO_3, and extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 and Na_2SO_4. and concentrated *in vacuo*. The residue was again dissolved in benzene and purified by chromatography through Al_2O_3 column. The pure sample was obtained through distillation in a reduced pressure.

Table IV.

Compound R	Amt. of (Va~f) used(g.)	Reaction temp. (bath) (°C)	Reaction time. (hr.)	b.p. (°C/0.1 mm. Hg)	Yield of crude product (g.)	IR $\nu_{C=O}^{liquid}$ (cm^{-1}) ester
Me (VIa)	11.6	130~135	2.5	198~205	5.31	1730
Et (VIb)	17.0	125~130	1.5	198~210	7.97	1730
Pr (VIc)	10.0	125~130	1.5	221~226	3.7	1730
Bu (VIe)	31.5	125~130	4.0	222~228	14.4	1730
iso-Bu (VIf)	20.0	125~130	3.5	224~228	9.2	1730

Ethyl 1-Alkyl-2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-3-carboxylate(VIIa~f)——A small portion of the solutio nof the diester (IVa~f) (1 mole) in 3 volumes of dehyd. toluene was added to the suspension of NaH (2.5 mole) in 20 volumes of dehyd. toluene, previously heated in an oil bath kept at 120°. The reaction soon set in with a vigorous generation of H_2. Further addition of the diester solution was controlled so as to carry on the reaction smoothly. After the H_2 evolution became weak, the bath temperature was raised to 130~140° to complete the reaction. To the cooled reaction mixture 10% AcOH (3 mole) solution in benzene was added slowly under ice-cooling to decompose excess NaH and to dissolve the precipitated Na compound of (VII). The solution was basified with $NaHCO_3$, the supernatant benzene layer was separated, dried, and concentrated. The residue was dissolved in 10% HCl with ice-cooling. After the insoluble material was removed by extraction with benzene, the aqueous solution was filtered, the filtrate was basified with Na_2CO_3, and extracted with benzene. The benzene solution was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH.

Table V.

Compound R	Amt. of (Va~f) used (g.)	Reaction temp. (bath) (°C)	Reaction time (hr.)	m.p. (°C)	Yield (g.)	IR $\nu_{C=O}^{Nujol}$ (cm^{-1}) keto-ester
Me (VIIa)	5.31	130~135	6	177~178	2.01	1660
Et (VIIb)	7.97	120~125	2	107~108*	4.65	1655
Pr (VIIc)	3.72	120~125	2	113~114	1.36	1655
Bu (VIIe)	14.48	120~125	3	85~ 86	5.99	1660
iso-Bu (VIIf)	9.2	120~125	2	Hydrochloride 185~186*	Hydrochloride 3.72	Hydrochloride 1670

* Agreed with the melting point reported.[1)]

Table VI.

Compound R	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
Me (VIIa)	65.68	7.25	4.03	—	65.55	7.31	4.11	—
Et (VIIb)	66.45	7.53	3.87	—	66.41	7.17	3.85	—
Pr (VIIc)	67.17	7.78	3.73	—	67.18	7.48	3.78	—
Br (VIIe)	67.83	8.02	3.59	—	68.18	8.03	3.56	—
iso-Bu (VIIf) Hydrochloride	—	—	3.28	8.32	—	—	3.38	8.03

1-Alkyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-one (VIIIa~f)——The compound (VIIa~f) was refluxed with about 30 volumes of 10% HCl in an oil bath, a vigorous foaming of CO_2 being observed. After cessation of gas effervescence, the reaction mixture was treated with activated carbon and filtered. The filtrate was strongly basified with conc. K_2CO_3 solution and the base liberated was collected in benzene. The benzene solution was dried over anhyd. K_2CO_3 and Na_2SO_4 and concentrated. The residue was redissolved in dehyd. benzene, dry HCl gas was passed through the solution to separate the syrupy, hydrochloride, and the solvent was decanted off. The syrupy residue was washed thoroughly with iso-Pr_2O, dried in a desiccator in a reduced pressure,

and dissolved in dehyd. EtOH. The EtOH solution was added with iso-Pr_2O and allowed to stand in a refrigerator to give 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride as pale yellowish prisms, m.p. 75~76°, b.p. 198~201°.

The mother liquor was concentrated, strongly basified with conc. K_2CO_3 solution, and extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 and concentrated to give the free base. Majority of the bases (Ⅷ) thus obtained were characterized and analyzed as crystalline phenylhydrazones prepared by the conventional method. (Ⅷb : R=Et) gave a crystalline oxime which formed colorless prisms (from 80% EtOH), m.p. 155~156°(decomp.), melting a few degrees higher than 150° cited in the literature. Crystalline hydrochloride was prepared from (Ⅷf : R=iso-Bu), which formed colorless prisms (from EtOH-iso-Pr_2O), m.p. 184~185°(decomp.) as cited in the literature.[2)]

Table Ⅶ.

Compound R	Amt. of (Ⅴa~f) used (g.)	Reaction temp. (bath) (°C)	Reaction time (hr.)	Yield of crude product (g.)	IR $\nu_{C=O}$ (cm^{-1}) ketone
Me (Ⅷa)	2.0	140~145	8	1.36	1710 (in $CHCl_3$)
Et (Ⅷb)	2.5	130~135	1	1.60	1715 (liquid)
Pr (Ⅷc)	1.1	130~135	1.5	0.71	1710 (in $CHCl_3$)
Bu (Ⅷe)	3.0	130~135	1.5	2.02	1710 (in $CHCl_3$)
iso-Bu (Ⅷf)	Hydrochloride 3.4	130~135	50 min.	1.93	1710 (in $CHCl_3$)

Table Ⅷ.

Compound R	Derivative	m.p. (decomp.) (°C)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Me (Ⅷa)	Phenylhydrazone	178~179	72.29	7.44	11.49	72.71	7.09	11.61
Et (Ⅷb)	Oxime	155~156	—	—	9.20	—	—	9.26
Pr (Ⅷc)	Phenylhydrazone	183~184	73.67	8.16	10.31	73.75	8.22	10.61

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Summary

A new synthesis of 1-alkyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizin-2-ones (Ⅷ) (5 specimens) was described. 3-(3,4-Dimethoxyphenethylamino)propionitrile was acylated with the chloride of various ethyl alkylhydrogenmalonates followed by esterification to yield the corresponding diester-amides (Ⅴ), which were cyclized by refluxing with phosphoryl chloride alone. The products were reduced to afford α-alkyl-2-(2-ethoxycarbonylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline acetates (Ⅵ). The latter were cyclized with sodium hydride in boiling toluene according to Dieckmann's method and the products were submitted to ketonic fission to yield the ultimate products in rather a poor yield. 6,7-Dimethoxy-3,4-dihydroisoquinoline was the common by-product produced during the ketonic fission reaction.

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