83. **Jun'ichi Hase and Hikokichi Ohura** : Syntheses of Higher Fatty Acids. I. Syntheses of ω-Phenyl Fatty Acids.

(Pharmaceutical Faculty, University of Toyama)*

It has been reported by Sabin and co-workers1) that phthionic acid, the fatty acid from tubercle bacilli, causes formation of giant cells in omentum major by intraperitoneal injection in rabbits. Previously, one of the writers (Hase)2) showed that, although arachidic and lignoceric acids caused formation of giant cells by intracutaneous injection in guinea pigs, fatty acids of smaller molecules, those below stearic acid, failed to cause such formation. These evidences lead to the assumption that such formation of giant cells is caused by fatty acids which, being unable to undergo metabolism, becomes a foreign body.

In order to examine the relationship between the structure and cutaneaus reaction of fatty acids, syntheses of normal series fatty acids substituted in α- or ω-, or in both α- and ω-positions, with phenyl group to give them metabolic hindrance, were attempted. Of these fatty acids, α-phenyl acids have been prepared by Tamemasa,3) that ω-phenyl acids (V) of normal series were prepared and are described in this paper.

There are two existing methods for the syntheses. One is the condensation4,5) of the half-ester chloride or dichloride of aliphatic α,ω-dicarboxylic acids and benzene by the Friedel-Crafts reaction and then reduction of the product to (V). The other is the condensation6) of ω-phenylalkyl bromide and diethyl sodiomalonate, followed by decarboxylation, or the condensation7) of ethyl sodio-ω-carbethoxydecylacetoacetate and ω-phenyl acid chlorides and derived to (V) through the keto acid by the usual method. There is a limit to the size of the molecule of the aliphatic dicarboxylic acids used in the first method and the yield markedly deceases in the case of larger molecules. The

Table I. Method of Preparing ω-Phenyl Fatty Acids

(I)	(II)	(III) C_6H_5-$(CH_2)_m$-CO-$(CH_2)_n$-$COOC_2H_5$			(IV)	(V) C_6H_5-$(CH_2)_n$-COOH	
m	n	m	n	Compd. No.		n	Compd. No.
2	2	2	2	(1)	(14)	5	(27)
3	2	3	2	(2)	(15)	6	(28)
2	4	2	4	(3)	(16)	7	(29)
3	4	3	4	(4)	(17)	8	(30)
2	6	2	6	(5)	(18)	9	(31)
2	7	2	7	(6)	(19)	10	(32)
2	8	2	8	(7)	(20)	11	(33)
4	7	4	7	(8)	(21)	12	(34)
4	8	4	8	(9)	(22)	13	(35)
2	12	2	12	(10)	(23)	15	(36)
4	12	4	12	(11)	(24)	17	(37)
2	16	2	16	(12)	(25)	19	(38)
4	16	4	16	(13)	(26)	21	(39)

---

* 5 Okuda, Toyama (長谷純一, 大浦彦吉).

1) F. R. Sabin, *et al.* : J. Exptl. Med., **52**, Supplement No. 3(1930).

2) H. Koida : J. Japan. Pathol. Soc., **40**, 308 (1951); N. Kusano, J. Watanabe, J. Hase : *Ibid.*, **41**, 119(1952).

3) O. Tamemasa : J. Pharm. Soc. Japan, **70**, 622(1950).

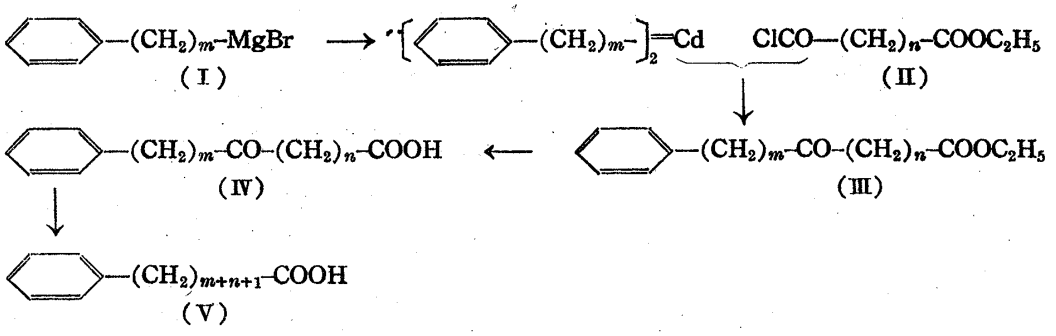
4) H. S. Raper, E. J. Wayne : Biochem. J., **22**, 195(1928).

5) W. Borsche : Ber., **52**, 2084(1919).

6) H. Staudinger, F. Müller : Ber., **56**, 714(1923).

7) G. M. Hills, R. Robinson : J. Chem. Soc., **1936**, 281.

second method is rather tedious. In general[8], lengthening of a straight chain can be effected by the condensation of the half-ester chloride (II) of aliphatic α,ω-dicarboxylic acid and the cadmium compound obtained by the application of cadmium chloride to the Grignard reagent and the product (III) thereby formed is saponified and submitted to reduction. Utilization of such a method on ω-phenylalkylmagnesium bromide (I) should give (V). Actually, Soffer[9] reported on the syntheses of (33)** by this method where $m=2$ and $n=8$. By the use of this method, it would be possible to obtain (V) with any desired number of carbon atoms by changing m and n. Moreover, this method is generally reported to give a comparatively goood yield that this method was adopted for the present series of experiments.



In this condensation, the larger the size of m, the poorer became the yield of the Grignard reagent, with incomplete progress of the reaction. Higher fatty acids were, therefore, prepared by leaving the m small, at $m=2\sim4$, and the size of n was made large. In the case of $m=2$, the yield of (III; 1, 3, 5, 6, and 7) was 60~73%, while in the case of $m=3$ and 4, the yield of (III; 2, 4, and 9) fell to 39~58%. Further, when $m=2$ and the half-ester chloride was small, such as $n=2$, 4, and 8, the yield of (III; 1,3, and 7) was good but when it was larger, such as $n=16$, the yield of (III; 12) fell to 39%. Saponification and reduction of the condensation product (III) went well. The analytical data and properties of the ω-phenyl fatty acids and related compounds thereby synthesized are shown in Table II. Relationship between carbon numbers of the normal chain and melting temperature of (V) is shown in Fig. 1. The curve of melting points becomes lowest at six and seven carbon atoms and with larger molecules the curve appears as a dentate, as that of normal fatty acid series, but that of the smaller molecules show the specific curve by the influence of the ω-phenyl group.

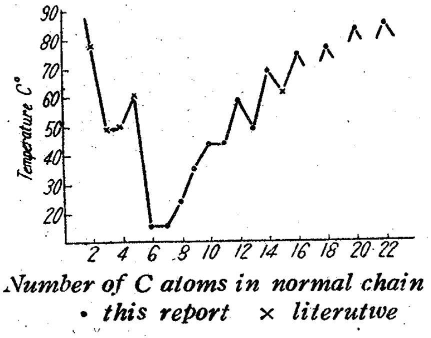


Fig. 1.
Melting Temperature of ω-Phenyl Fatty Acids

Histological studies on these acids are being carried out.

Just before submitting this manuscript, it has come to the notice of the present wri-

---

** Arabic numerals in parentheses are the number of the substances listed in Table I.

[8] H. Gilman, J. F. Nelson: Chem. Zentr., **1937**, I, 334; J. Cason: J. Am. Chem. Soc., **68**, 2078 (1945).; Org. Syntheses, 28, 75 (1948); Chem. Revs., **40**, 15 (1947).

[9] M. D. Soffer: J. Am. Chem. Soc., **69**, 1684 (1947).

ters that Huisgen and his collaborators[10] synthesized (V; 32, 33, 34, and 35) by the same method as the present one, during the course of the syntheses of cyclic ketones.

The authors' thanks are due to Prof. Yokota of the University of Toyama and Prof. Ishiguro of the University of Kyoto for their review of this manuscript and to Dr. Kusano of the University of Tokyo for his advice on this work. The authors also thank the members of the Analytical Laboratory of the Government Institute for Infectious Diseases, University of Tokyo, and Mr. Iwaki of this Faculty, for microanalytical data.

Experimental

General Method for ω-Phenylketo Acid Esters $C_6H_5-(CH_2)_m-CO-(CH_2)_n-COOC_2H_5$—ω-Phenylalkyl bromides were prepared by refluxing the corresponding alcohols with 48% HBr. $m=2$, b.p$_{15}$ 100°, yield, 90.2%; $m=3$, b.p$_{16}$ 110~111°, yield, 82.6%; $m=4$, b.p$_{15}$ 124~126°, yield, 87%.

Aliphatic α,ω-dicarboxylic acid half-esters were prepared by the partial saponification of the diesters, and their conversion by $SOCl_2$ at room temperature to half-ester chlorides (II). Boiling points and yields of these compounds are as follows: Half-esters: $n=2$, b.p$_5$ 106~108°, yield, 78%; $n=4$, b.p$_{15}$ 167~168°, yield, 56%; $n=6$, b.p$_{16}$ 185~188°, yield, 50.5%; $n=7$, b.p$_{15}$ 192~194°, yield, 46.1%; $n=8$, b.p$_{15.5}$ 205°, yield, 55.1%; $n=12$, b.p$_6$ 204~207°, yield, 65.5%; $n=16$, m.p. 70~71°, yield, 59.5%. Half-ester chlorides (II): $n=2$, b.p$_{17}$ 89.5~91.5°, yield, 95%; $n=4$, b.p$_{15}$ 122~123°, yield, 97%; $n=6$, b.p$_{16}$ 146~148°, yield, 68%; $n=7$, b.p$_{14}$ 152~155°, yield, 88%; $n=8$, b.p$_{15}$ 169~171°, yield, 92.4% $n=12$, b.p$_2$ 170~171°, yield, 94%; $n=16$, b.p$_{0.3}$ 203~205°, yield, 71%.

(III) were prepared by the following procedures[8]: To a mixture of Mg turnings (0.1 g.-atom) and 20 cc. dry ether was added under stirring a solution of pure ω-phenylalkyl bromide (0.1 mole) in 40 cc. dry ether and the mixture was refluxed for 15 mins. To the cold mixture was added 0.054 mole of anhyd. $CdCl_2$ in several portions. After refluxing for 1 hr., ether was distilled off and then 35 cc. of dry benzene was added to the residue. Distillation of benzene was continued until the whole became dark and viscous under stirring. At this point, a second 35 cc. of dry benzene was added to the flask, and the mixture was refluxed with vigorous stirring for a few minutes. (II) (0.08 mole) in 20 cc. of dry benzene was added to the above cadmium compound from the dropping funnel. Heating and stirring were continued for 1 hr. (4 hrs. in the case of higher series of III). The reaction mixture was decomposed by the addition of ice water, followed by 2*N* H_2SO_4 to give two clear layers. The benzene layer was washed with water, aq. Na_2CO_3, and water, and then dried over anhyd. Na_2SO_4. After removal of benzene the residue was distilled in vacuum. In the case of larger molecules, the reaction mixture was fractionated by esterification and low-pressure distillation in order to remove acid components instead of washing with aq. Na_2CO_3.

Table II. Analytical Data, Melting Points, and Properties of Phenyl-Fatty Acids and Related Intermediate Compounds

Compd.	Mol. formula	Analytical data Calcd. C			Found			m.p. or (b.p./mm. Hg)°C	Properties
		C	H	-COOH or N	C	H	-COOH or N		
(1)	$C_{14}H_{18}O_3$	—	—	—	—	—	—	(144-6/2)	c.O.
(2)	$C_{15}H_{20}O_3$	—	—	—	—	—	—	(139-41/0.5)	c.O.
(3)	$C_{16}H_{22}O_3$	—	—	—	—	—	—	(146-8.5/0.5)	c.O.
(4)	$C_{17}H_{24}O_3$	—	—	—	—	—	—	(169-70/4)[a]	c.O.
(5)	$C_{18}H_{26}O_3$	—	—	—	—	—	—	(197-8/4.5)	c.O.
(6)	$C_{19}H_{28}O_3$	—	—	—	—	—	—	(177-80/0.6)	c.O.
(7)	$C_{20}H_{30}O_3$	75.43	9.49	—	75.65	9.85	—	(202-3/2), 34[b]	c.W.M.
(8)	$C_{21}H_{32}O_3$	—	—	—	—	—	—	(183-5/0.25)	c.O.
(9)	$C_{22}H_{34}O_3$	—	—	—	—	—	—	(189-90/0.06)[d]	c.O.
(10)	$C_{24}H_{38}O_3$	76.95	10.22	—	76.72	10.40	—	(242-5/2), 49-50	c.Po.M.
(11)	$C_{26}H_{42}O_3$	77.56	10.51	—	77.55	10.70	—	(205-6/0.002), 39-40	c.W.M.
(12)	$C_{28}H_{46}O_3$	78.09	10.77	—	78.28	10.90	—	(227/0.001), 64.5-65.5	c.Po.M.
(13)	$C_{30}H_{50}O_3$	78.55	10.99	—	78.16	11.41	—	(239-40/0.002), 45.5	c.Po.M.
(14)	$C_{12}H_{14}O_3$	69.88	6.84	(C) 21.83	69.74	6.60	21.94	90.5[e]	c.N.A.
(14)-S	$C_{13}H_{17}N_3O_3$	59.29	6.51	(N) 15.96	59.30	6.52	15.85	166.5	c.N.A.
(15)	$C_{13}H_{16}O_3$	70.82	7.32	—	71.12	7.49	—	75.5~76.5	c.N.A.
(15)-S	$C_{14}H_{19}N_3O_3$	60.63	6.90	(N) 15.15	60.38	7.00	15.22	161.5~163.5	c.N.A.
(16)	$C_{14}H_{18}O_3$	71.77	7.74	(C) 19.22	71.63	7.65	19.22	55~56	c.N.A.

---

10) V. R. Huisgen, W. Rapp, I. Ugi, H. Walz, I. Glogger; Ann., **586**, 52 (1954).

(16)-S	$C_{15}H_{21}N_3O_3$	61.83	7.26	(N) 14.42	62.13	7.04	14.17	157	c.N.A.
(17)	$C_{15}H_{20}O_3$	72.55	8.12	—	72.87	8.07	—	42~43	c.N.A.
(17)-S	$C_{16}H_{23}N_3O_3$	62.92	7.59	(N) 13.76	63.08	7.51	14.06	120~121	c.Pr.A.
(18)	$C_{16}H_{22}O_3$	73.25	8.45	(C) 17.16	73.28	8.66	17.43	59.5	c.Pl.A.
(18)-S	$C_{17}H_{25}N_3O_3$	63.92	7.88	(N) 13.15	64.02	7.40	13.44	121	c.Pr.A.
(19)	$C_{17}H_{24}O_3$	73.87	8.83	(C) 16.41	74.36	8.40	16.67	63	c.Pl.A.
(19)-S	$C_{18}H_{27}N_3O_3$	64.83	8.16	(N) 12.60	65.09	8.29	12.99	124.5	c.Gr.A.
(20)	$C_{18}H_{26}O_3$	74.44	9.02	(C) 15.50	74.36	8.86	14.64	67[f]	c.Pl.A.
(20)-S	$C_{19}H_{25}N_3O_3$	65.67	8.41	(N) 12.09	65.64	8.51	11.77	104~105	c.Gr.A.
(21)	$C_{19}H_{28}O_3$	74.96	9.27	—	74.66	9.09	—	60.5~61.5	c.Pr.A.
(21)-S	$C_{20}H_{31}N_3O_3$	66.45	8.64	(N) 11.62	66.13	8.48	11.80	125.5~126.5	c.Gr.A.
(22)	$C_{20}H_{30}O_3$	75.43	9.49	(C) 14.13	75.59	9.32	14.25	73.5[g]	c.Pl.A.
(22)-S	$C_{21}H_{33}N_3O_3$	67.16	8.86	(N) 11.19	67.12	8.49	10.91	96.5	c.N.A.
(23)	$C_{22}H_{34}O_3$	76.08	9.89	—	75.74	9.76	—	80.5~81.5	c.Pr.A.
(23)-S	$C_{23}H_{37}N_3O_3$	68.43	9.24	(N) 10.41	68.66	9.04	10.21	102~103	c.Gr.A.
(24)	$C_{24}H_{38}O_3$	76.95	10.22	—	77.19	10.48	—	74.5~75.5	c.Bl.A.
(24)-S	$C_{25}H_{41}N_3O_3$	69.56	9.57	(N) 9.73	69.25	9.36	10.03	86.5~88	c.N.A.
(25)	$C_{26}H_{42}O_3$	77.56	10.52	—	77.49	10.88	—	92~93	c.Bl.A.
(26)	$C_{28}H_{46}O_3$	78.09	10.77	—	78.18	10.63	—	84~85	c.Bl.A.
(27)	$C_{12}H_{16}O_2$	74.96	8.45	(C) 23.41	75.04	8.17	23.15	(185~187/12), 15~16[h]	c.O.
(28)	$C_{13}H_{18}O_2$	75.69	8.79	(C) 21.82	75.90	8.87	22.18	(157~158/2.5), 15~16[i]	c.O.
(29)	$C_{14}H_{20}O_2$	76.32	9.15	(C) 20.43	76.31	9.01	20.94	(205~208/13), 23~24[j]	c.O.
(30)	$C_{15}H_{22}O_2$	76.88	9.46	(C) 19.13	76.68	9.60	19.04	34.5~35.5[k]	c.Pl.A.
(31)	$C_{16}H_{24}O_2$	77.33	9.73	(C) 18.07	77.38	9.77	18.07	43.5~44[l,r]	c.Pl.Pe.
(32)	$C_{17}H_{26}O_2$	77.82	9.98	(C) 17.16	77.94	9.73	16.89	43~44[m,r]	c.Pl.Pe
(33)	$C_{18}H_{28}O_2$	78.21	10.21	(C) 16.28	78.46	10.05	16.15	58~59[n]	c.Pl.Pe
(34)	$C_{19}H_{30}O_2$	78.57	10.41	(C) 15.50	78.63	10.50	15.53	48~49[o]	c.Pl.Pe
(35)	$C_{20}H_{32}O_2$	78.89	10.59	(C) 14.78	78.86	10.51	14.79	68~69[p]	c.Pl.Pe
(36)	$C_{22}H_{36}O_2$	79.46	10.91	(C) 13.53	79.46	11.04	13.85	73.5~74.5	c.Bl.Pe
(37)	$C_{24}H_{40}O_2$	79.94	11.18	(C) 12.20	80.23	10.99	11.99	76~77	c.Bl.Pe
(38)	$C_{26}H_{44}O_2$	80.35	11.41	(C) 11.58	80.36	11.75	11.36	82.5~83.5	c.Bl.Pe
(38)-E	$C_{28}H_{48}O_2$	80.71	11.61	—	80.62	11.64	—	57~58	c.Bl.A.
(39)	$C_{28}H_{43}O_2$	80.71	11.61	(C) 10.80	81.10	11.92	10.83	84~85[q]	c.Bl.Pe

Compound: Numbers are the same as in Table I. –S semicarbazone, –E ethyl ester. Analytical data: (C) for carboxylic group and (N) for nitrogen. m.p. and b.p.: All melting points and boiling points are uncorrected. *a*) reported b.p.$_{0.002}$ 138~142°[10]. *b*) Reported m.p. 45.5~46.5° (methyl ester)[9]. *d*) Huisgen[10] reported b.p.$_{0.003}$ 185~195°. *e*) Reported m.p. 89° by Erdmann (Ann., **258**, 131). *f*) Soffer[9] reported m.p. 71.3~71.5°, Huisgen[10] did not report. *g*) Synthesized by Huisgen, but m.p. not reported. *h*) Reported m.p. 11°, b.p.$_{11}$ 186~188°, by Grateau (Compt. rend., **191**, 947), m.p. 22~24°, b.p.$_{12}$ 186° by Staudinger[6], b.p.$_{30}$ 206~208° by Borsche[5], b.p.$_{17}$ 180~190° by Braun (Ber., **44**, 2873) *i*) b.p.$_{17}$ 205~210° by Braun (*loc. cit.*), bp.$_{12}$ 191~193° by Huisgen[10]. *j*) Huisgen[10] reported b.p.$_{11}$ 204~206°, Borsche[5], b.p.$_{14}$ 209~210°. *k*) Reported m.p. 29~30°, b.p.$_{12}$ 215° by Raper[4], m.p. 39~40° by Huisgen[10]. *l*) Reported m.p. 42° by Raper[4], m.p. 41° by Borsche[5], and not reported by Huisgen[10]. *m*) Reported[10] m.p. 44.5~45.5°. *n*) Reported m.p. 60.5~61.5° by Soffer and m.p. 57~58° by Huisgen. *o*) Reported[10] m.p. 52~53°. *p*) Reported[10] m.p. 69.5~70°. *q*) Reported m.p. 81° by Robinson[7]. *r*) Depression, 10°. Properties: c- colorless, O- oil, W- wax, Po- crystalline powder, N- needles, Pr- prisms, Gr- granules, Pl- plates, Bl- blades, M- recrystallized from MeOH, A- from EtOH, Pe- from petroleum ether.

Properties of (III) are shown in Table II, and the yield (%) was as follows: (1) 61, (2) 58, (3) 73, (4) 39, (5) 69, (6) 60, (7) 71, (8) 66, (9) 50, (10) 56, (11) 39, (12) 39, (13) 21.

Saponification and Reduction of (III)—The keto-acid ester (III) was saponified with ethanolic KOH, and reduced by the Clemmensen method in EtOH solution to (V). To the EtOH solution of the keto-acid (IV) (0.01 mole) saturated with HCl gas, amalgamated Zn (29 g.) was added and the mixture was boiled under reflux for 20 hrs. Further quantities of amalgamated Zn (20 g.) was then added and the mixture was boiled under reflux for a further 24 hrs., while repeatedly passing HCl gas into the solution until saturation. Yield, 80~90%.

Reduction of (IV; 26) was effected by the Wolff-Kishner method as modified by Huang-Minlon.[11] A mixture of 0.3 g. keto-acid (26), 1 g. KOH, 1 cc. of 81% hydrazine hydrate, and 6 cc. of diethylene glycol was refluxed for 1 hr. The condenser was removed until the temperature of the reaction mixture reached 200° by the slow evaporation of water. The reflux condenser was replaced and refluxing

---

[11] Huang-Minlon: J. Am. Chem. Soc., **68**, 2487(1946).

was continued at a higher temperature for 3 hrs. The mixture was cooled to about 100° and poured into 50 cc. of water. To this was added with stirring dil. HCl. The thick, gelatinous, colorless solid that separated was digested for 1 hr., collected by filtration, washed with water, and dried. A crude yield of 93% was obtained. m.p. 84~85°. Mixed with the keto-acid (26), m.p. 84~85°, the depression was only 2°.

Summary

ω-Phenyl-fatty acids, ω-phenyl-caproic, -enanthic, -caprylic, -pelargonic, -capric, -undecanoic, -lauric, -tridecanoic, -myristic, -palmitic, -stearic, -arachidic, and -behenic acids, were prepared.

(Received August 20, 1954)

---

84. **Masao Tomita, Yasuo Inubushi, and Kazuo Ito**: Studies on the Alkaloids of Menispermaceous Plants. CXIX.[1] A Bisected Phenolic Product from the Cleavage of Tetrandrine and Isotetrandrine with Metallic Sodium in Liquid Ammonia.

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

Several years ago, Tomita, Fujita, and Murai reported that on the fission of isotetrandrine (I(−, +))[2] and tetrandrine (I(+, +))[3] with sodium in liquid ammonia, the former yielded as the bisected bases *l*-O,O,N-trimethylcoclaurine (II) and *d*-N-methylcoclaurine (III), and the latter, *d*-O,O,N-trimethylcoclaurine (II) and *d*-N-methylcoclaurine (III), respectively; and that *d*-N-methylcoclaurine (III) thus obtained formed from methanol colorless prisms, m.p. 139~139.5°, $[\alpha]_D^{16}$: +88.51° ($CHCl_3$), which by analyses, were found to be a hemihydrate with an empirical formula $C_{18}H_{21}O_3N \cdot \frac{1}{2}H_2O$.

Very recently, however, Kidd and Walker[4] applied the same mode of fission process to phaeanthine (I(−, −)), an antipode of tetrandrine (I(+, +)), and O,O-dimethylcurine (IV), and reported that of the two bases (II) and (III) obtained, *l*-N-methylcoclaurine (III), a phenolic base, gave colorless prisms (from benzene or toluene), m.p. 176~177°, $[\alpha]_D^{23}$: −69.6° ($CHCl_3$), corresponding to a composition of $C_{18}H_{21}O_3N$.

It is well established that *dl*-N-methylcoclaurine, when derived from the naturally occurring coclaurine by Tomita and Kusuda,[5] as well as when synthesized by Kidd and Walker,[4] has a definite m.p. of 161~162°. However, a doubt has arisen from the fact that of its optically active substances, the *d*-form shows m.p. 139~139.5°, whereas the *l*-form, m.p. 176~177°, and hence it has become necessary to reinvestigate the *d*-form (III).

On the other hand, just prior to the above British investigators, Bick and Clezy[6] also carried out similar cleavage reactions of O,O-dimethylcurine, O,O-dimethylchondrocurine, phaeanthine, and isotetrandrine, but they characterized the bisected bases as the methiodides or O-methyl ether methiodides without isolating them *per se*. As a result, no further records with reference to the m.p. of N-methylcoclaurine (III) of the bisected bases are available.

---

* Yoshida-Konoe-cho, Sakyo-ku, Kyoto (富田真雄, 犬伏康夫, 伊藤一男).

[1] Part CXVIII. Y. Inubushi, M. Kozuka: This Bulletin, **2**, 215(1954).

[2] M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, **71**, 226, 1035(1951).

[3] E. Fujita, F. Murai: *Ibid.*, **71**, 1039(1951).

[4] D. A. A. Kidd, J. Walker: J. Chem. Soc., **1954**, 669.

[5] M. Tomita, F. Kusuda: J. Pharm. Soc. Japan, **72**, 280(1952).

[6] I. R. C. Bick, P. S. Clezy: J. Chem. Soc., **1953**, 3893.