This substance was esterified with CH_2N_2 in Et_2O and the product was recrystallized from Me_2CO-Et_2O mixture to colorless waxy substance, m.p. 68~70°. *Anal.* Calcd. for $C_{83}H_{166}O_4$: C, 81.16; H, 13.62; mol. wt., 1228. Found: C, 81.02; H, 13.68; mol. wt. (Rast), 1256, 1170.

Separation of the Neutral Substances—Fractions 1 to 3 from the above chromatography were combined and rechromatographed over 20 g. of alumina, separating the effluent into following fractions:

Fract. No.	Eluant (100 cc.)	Residue (mg.)	Fract. No.	Eluant (100 cc.)	Residue (mg.)
1	Petr. ether	40	11	Petr. ether-benzene (1:1)	60
2	〃	25	12	〃	65
3	〃	20	13	〃	22
4	〃	27	14	Benzene	50
5	Petr. ether-benzene (9:1)	30	15	〃	60
6	〃	3	16	Benzene-Et_2O (3:1)	22
7	〃	2	17	〃	30
8	Petr. ether-benzene (4:1)	32	18	〃	15
9	〃	22	19	Benzene-Et_2O (1:1)	3
10	〃	27	20	〃	2
			21	Et_2O	trace
				Total	557 mg.

Fraction 1 was recrystallized from Et_2O-EtOH to colorless crystalline powder, m.p. 71~73°. U.V. λ_{max}^{hexane} mμ (log ε): 222 (2.74), 267 (2.43), 271 (2.57). I. R. λ_{max}^{Nujol} μ: 5.80 (ester), 5.88 (-CO-), 6.10 (-C=C-). *Anal.* Calcd for $C_{84}H_{164}O_3$ (XI): C, 82.55; H, 13.53. Found: C, 82.45; H, 13.73.

Fraction 12 was recrystallized from Et_2O-EtOH to colorless crystalline powder, m.p. 69~70.5°. U.V. λ_{max}^{hexane} mμ (log ε): 222 (2.64), 267 (2.34), 271 (2.40). I.R. λ_{max}^{Nujol} μ: 3.0 (OH), 5.75 (ester), 5.82 (-CO-). *Anal.* Calcd. for $C_{84}H_{166}O_4$ (XII): C, 81.35: H, 13.49. Found: C, 81.64; H, 13.83.

Fraction 14 was recrystallized from Et_2O-EtOH to colorless crystalline powder, m.p. 72~74°. U.V. λ_{max}^{hexane} mμ (log ε): 222 (2.46), 266 (1.85), 270 (2.08). I. R. λ_{max}^{Nujol} μ: 3.0 (OH), 5.75 (ester), 6.10 (-C=C-). *Anal.* Calcd. for $C_{84}H_{166}O_3$ (XIII): C, 82.41; H, 13.67. Found: C, 82.47; H, 13.82.

Fraction 18 was recrystallized from Et_2O-EtOH to colorless crystalline powder, m.p. 72.5~73°. U. V. λ_{max}^{hexane}: Nil. I. R. λ_{max}^{Nujol}: 3.0 μ (OH). *Anal.* Calcd. for $C_{82}H_{166}O_3$ (XIV): C, 82.06; H, 13.94. Found: C, 81.75; H, 13.66.

Summary

Condensation of 2-hexacosyl-3-acetoxytriacontanoic acid chloride and ethyl benzyl tetracosylmalonate gave ethyl 2-tetracosyl-3-oxo-4-hexacosyl-5-acetoxydotriacontanoate whose reduction with sodium borohydride finally afforded the objective 2-tetracosyl-3, 5-dihydroxy-4-hexacosyldotriacontanoic acid, $C_{82}H_{164}O_4$.

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UDC 547.821.41 : 547.732 : 547.722.2

89. Tetsuji Kametani, Keiichiro Fukumoto, and Yukio Nomura: Studies on the Syntheses of Heterocyclic Compounds. XLV.* Synthesis of the Methyl Derivatives of Heterocyclic Compounds by the Hydrogenolysis of their Phenylurethans from Primary Alcohol.

(*Pharmaceutical Faculty, University of Osaka***)

Many methods are known for obtaining methyl derivatives by the reduction of a hydroxyl group in primary alcohols, such as by red phosphorus and hydrogen iodide,[1,2] sodium and alcohol,[3] zinc dust distillation,[4] or sodium and ammonia,[5] but these methods

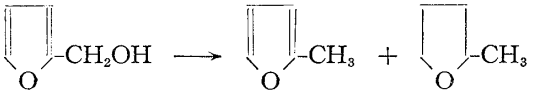
* Part XLIV: Yakugaku Zasshi, **76**, 753(1956).
** Hotarugaike, Toyonaka, Osakafu (亀谷哲治, 福本圭一郎, 野村幸雄).
1) P. S. Bailey, G. Nowlin: J. Am. Chem. Soc., **71**, 732(1949).
2) R. G. Jones: *Ibid.*, **71**, 383(1949).
3) H. de Pommereau: Compt. rend., **174**, 685(1922).
4) A. Klages: Ber., **39**, 2587(1906).
5) A. J. Birch: J. Chem. Soc., **1954**, 809.

generally give a poor yield.

Recently, a method has been reported by Johnson *et al.*[6] in which the chloride obtained from the alcohol is treated with lithium aluminum hydride and lithium hydride in the presence of tetrahydrofuran, but their method has not yet been examined in the case of heterocyclic compounds.

$$RCH_2OH \longrightarrow RCH_2Cl \longrightarrow RCH_3$$

In addition to the above-mentioned facts, two kinds of products, 2-methylfuran and 2-methyltetrahydrofuran, are obtained in the hydrogenation of furfuryl alcohol[7].



Therefore, examinations were made on a method of changing the alcoholic hydroxyl to a methyl group by way of a phenylurethan derivative and the objective methyl derivatives of heterocyclic compounds, pyridine, thiophene and furan, were found to be produced in a quantitative, good yield. Further the yield from this method was compared with that from the catalytic hydrogenation of heterocyclic chloromethyl derivatives.

As one of the methods for determination of alcoholic hydroxyl group, the formation of urethan by reaction between alcohol and phenyl isocyanate has hitherto been known. It is also well known that urethans are hydrolyzed to the mixture of aniline, alcohol, and carbon dioxide by the Curtius reaction.[8]

$$RCH_2OH + C_6H_5\text{-}N{=}C{=}O \longrightarrow RCH_2OOC\text{-}NHC_6H_5$$
$$C_6H_5NHCOOCH_2R \longrightarrow RCH_2OH + CO_2 + C_6H_5NH_2$$

In this case, if the urethan is hydrogenated in the presence of calculated amount of alkali agent, the methyl derivative must be obtained besides alkali carbamate. By making use of this reaction, attempt was made to synthesize methyl derivatives of heterocyclic compounds. In the case of Curtius reaction, the alcoholic group is not so important, but the other fragment of amino group is of importance.

At first catalytic hydrogenation of urethan was tried by using only palladium-black in the presence of a suitable solvent such as methanol, water, dioxane, etc. It was found that the absorption of hydrogen was not sufficient due to the formation of carbon dioxide, from free carbamic acid. This carbamic acid is thought to be unstable and decomposes instantly into aniline and carbon dioxide, and the absorption of hydrogen is hindered by the carbon dioxide formed during the hydrogenation.

$$RCH_2OOC\text{-}NHC_6H_5 \longrightarrow RCH_3 + HOOCNHC_6H_5$$
$$C_6H_5NHCOOH \longrightarrow C_6H_5NH_2 + CO_2$$

Accordingly, urethan was reduced after dissolving the calculated amount of sodium hydroxide into the solvent in order to prevent the decomposition of carbamic acid by derivation to a sodium salt. As a result hydrogen was absorbed quantitatively and the objective methyl derivative was produced. A white crystalline powder, which was thought to be the sodium salt of carbamic acid, was also obtained after the reaction.

$$RCH_2OOC\text{-}NHC_6H_5 + NaOH \longrightarrow RCH_3 + NaOOC\text{-}NHC_6H_5$$

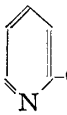
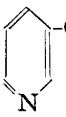
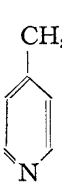
In order to compare the present results (Table I) with the yield of the reduction method in case of chloromethyl derivatives (Table II), reduction of the chlorides was carried out.

Various pyridylmethanols used as the starting material were prepared as follows: In the case of 3- and 4-pyridylmethanol, each ester was prepared by reduction with lithium aluminum hydride.[9~11] 2-Pyridylmethanol was synthesized by the method of Boekelheide and

6) J. E. Johnson, R. H. Blizzard, H. W. Carahrt: J. Am. Chem. Soc., **70**, 3664(1948).
7) Beilstein's Handbuch, **17**, 112.
8) Th. Curtius: Ber., **23**, 3023(1890).
9) H. Gilman, H. S. Broadbent: J. Am. Chem. Soc., **70**, 2757(1948).
10) R. G. Jones, E. C. Kolnfeld: *Ibid.*, **73**, 107(1951).
11) H. S. Mosher, J. E. Tessieri: *Ibid.*, **73**, 4925(1951).

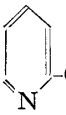
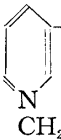
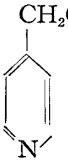
Linn[12] by way of 2-picoline N-oxide and 2-pyridylmethanol acetate. In the case of 2-thenyl alcohol, the 2-thiophenealdehyde was prepared from thiophene by using N-methylformanilide in the presence of phosphoryl chloride[13] and then 2-thiophenealdehyde submitted to the crossed-Cannizzaro reaction.[14] In a similar manner furfuryl alcohol was prepared from furfural by the crossed-Cannizzaro reaction.[14]

Table I. Preparation of Methyl Derivatives of Heterocyclic Compounds by Reduction of Phenylurethans in the Presence of Pd-Black

Starting material	(g.)	Absorption of H_2 (cc.) (%)	Yield (g.)	Yield (%)	Solvent
	2	196/198 (100)	0.8	98	MeOH
	2	197/198 (100)	0.8	98	〃
	2	198/198 (100)	0.8	98	〃
	4	390/398 (ca. 100)	1.3	94.2	〃
	2.5	400/477 (83.3)	0.81	80	Dioxane

Each urethan was prepared in the following way: In the case of 2-, 3-, and 4-pyridylmethyl carbanilate, equivalent moles of pyridylmethanol (1 mole) and phenyl isocyanate (1 mole) were mixed, the mixture was allowed to stand, and the solid urethans obtained were

Table II. Preparation of Methyl Derivatives of Heterocyclic Compounds by Reduction of Chlorides in the Presence of Pd-Black

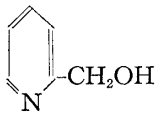
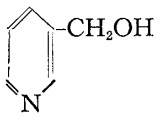
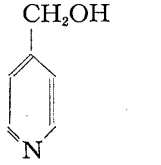
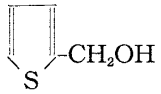
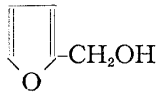
Starting material	(g.)	Absorption of H_2 (cc.) (%)	Yield (g.)	Yield (%)	Solvent
	2	230/345 (66)	0.65	42.8	EtOH
	1.2	140/200 (66)	0.2	30	H_2O
	3	275/500 (55)	0.4	23.5	H_2O
	2.5	300/458 (66)	0.8	42.1	EtOH
	3	260/550 (47.3)	0.45	21.03	Dioxane

12) V. Boekelheide, W. J. Linn: *Ibid.*, **76**, 1286(1954).
13) Org. Syntheses, **31**, 108 (1951).
14) F. W. Dunn, K. Dittmer: J. Am. Chem. Soc., **68**, 2561, 2562(1946).

determined by elemental analyses. These reactions were exothermic. 2-Thenyl carbanilate[14] was obtained by mixing equal moles of 2-thenyl alcohol and phenyl isocyanate, and heating the mixture on a water bath for 0.5 hour. The product agreed with an authentic sample produced by the method of Dunn and Dittmer.[14] In the case of furfuryl carbanilate, furfuryl alcohol and phenyl isocyanate were refluxed for 2 hours in dehyd. benzene. In all cases, the yield was quantitative.

Each chloride in case of pyridylmethyl isomers was synthesized by the reaction between the corresponding alcohol and phosphoryl chloride, in the presence of ethyl acetete, by the method of Itai and Ogura.[15] In the case of thiophene and furan, thionyl chloride was used as the chlorination agent and dehyd. ether as a solvent, but in the latter case, some drops of pyridine were added into the mixture of dehyd. ether and furfuryl alcohol. The yield is shown in Table III.

TABLE III. Preparation of the Chlorides of Heterocyclic Compounds by Chlorination of Alcohols

Material	Solvent	Reagent	Yield (%)
	AcOEt	$POCl_3$	80
	AcOEt	$POCl_3$	85.5
	AcOEt	$POCl_3$	71
	Et_2O	$SOCl_2$	58.3
	Et_2O	$SOCl_2$	25

Synthesis of the methyl derivatives of heterocyclic compounds from primary alcohol can be effected by hydrogenation of its chloride, the yield from alcohol to the chloride being about 70% and that of the reduction of the chloride, almost 40%. Therefore, the over-all yield is approximately 30%, which is below that from the present method, the yield of the heterocyclic phenylurethan and its methyl derivatives in this case being quantitative.

Therefore, if the methyl derivatives are not obtained easily but the hydroxymethyl derivative is, then the present method will be an efficient procedure. Furthermore, in case of furan derivatives, an unnecessary by-product hydrogenated in the heterocyclic ring, i.e. tetrahydrofuran derivative, is also obtained if they are reduced drastically and the present method seems to be convenient. In the case of furan derivatives, it is not easy to prepare its chloride, but the furfuryl alcohol can be obtained very easily from furfural by the crossed-Cannizzaro reaction, so that the preparation of furfuryl alcohol is thought to be easier than that of furfuryl chloride. The chloride is obtained only by chlorination of the alcohol and, in addition, its yield is rather poor because of the sensibility of furan ring to acidic reagents.

Experimental[16]

2-Pyridylmethyl Carbanilate—Nine grams of 2-pyridylmethanol and 8.5 g. of phenyl isocyanate were

15) T. Itai, H. Ogura: Yakugaku Zasshi, **75**, 296(1955).
16) All m.p. s are uncorrected. Analyses were by Mr. Fukuda, Pharmaceutical Faculty, University of Osaka.

mixed, by which heat generated and color of the solution turned brownish. On standing, the mixture turned into a solid and was recrystallized from dil. EtOH, m.p. 99.5°. Yield, 17.5 g. (100%). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$ (2-Pyridylmethyl carbanilate): C, 68.41; H, 5.30. Found: C, 68.49; H, 5.25. Picrate: m.p. 187.5° (decomp).

2-Picoline—i) Preparation from 2-pyridylmethyl carbanilate: A mixture of 0.2 g. of Pd-black and 50 cc. of MeOH was hydrogenated, absorbing 72 cc. of H_2. Then 2 g. of 2-pyridylmethyl carbanilate dissolved in MeOH and 0.4 g. of NaOH dissolved in MeOH were added into the above-mentioned mixture, and the whole mixture was catalytically hydrogenated at room temperature and atmospheric pressure. When the absorption of hydrogen ceased, Pd-black was removed by filtration and its filtrate was concentrated on a water bath to a small volume, a mixture of white crystals and orange solution being formed. This mixture was extracted with Et_2O, the extract was dried over KOH pellets, and evaporated. The residue was distilled and a colorless substance of b.p. 126~130° was obtained. Yield, 0.8 g. (98.16%). The picrate showed the m.p. of 166°. This agreed with an authentic sample of 2-picoline. At the same time, 1 g. of sodium carbamate was obtained as a by-product. The yield of the carbamic acid was 99%.

(ii) Preparation from 2-pyridylmethyl chloride: A solution of 2 g. of 2-chloromethylpyridine in 30 cc. of EtOH was added to the mixture of 50 cc. of MeOH and a catalyst, prepared from 0.2 g. of $PdCl_2$ and 4 g. of activated charcoal. The reaction mixture was treated as usual and 0.65 g. of 2-picoline was obtained. Yield, 42.8%.

3-Pyridylmethyl Carbanilate—From a mixture of 1.4 g. of phenyl isocyanate and 1.4 g. of 3-pyridylmethanol, 2.8 g. of 3-pyridylmethyl carbanilate was obtained by a similar manner as for 2-pyridylmethyl carbanilate. Needles, m.p. 137°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$ (3-Pyridylmethyl carbanilate): C, 68.41; H, 5.30. Found: C, 68.14; H, 5.23.
Picrate: m.p. 206~207°.

4-Pyridylmethyl Carbanilate—A mixture of benzene solution (10 cc.) of 1.4 g. of 4-pyridylmethanol and 1.4 g. of phenyl isocyanate dissolved in 10 cc. of benzene was refluxed on a water bath for 2.5 hrs. and 2.5 g. of white crystals were obtained by filtration. From the filtrate 0.2 g. of the objective urethan was separated. Total yield, 2.7 g. (93%). This product melted at 125~126° after recrystallization from benzene. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$ (4-Pyridylmethyl carbanilate): C, 68.41; H, 5.30. Found: C, 68.34; H, 5.29.

3- and 4-Picoline—By the same procedure used in the case of 2-picoline, both pyridylmethyl carbanilate and chloride were hydrogenated and in each case 3- or 4-picoline was obtained. Their boiling point and the melting point of picrate agreed with those of the authentic samples. Their yield are shown in Tables I and II.

2-Methylthiophene—(i) Preparation from 2-thenyl carbanilate: Four grams of 2-thenyl carbanilate was added to MeOH solution of 0.8 g. of NaOH containing 0.2 g. of Pd-black, and the mixture was hydrogenated. After sufficient absorption of hydrogen, it was treated as usual and 1.3 g. of 2-methylthiophene was obtained as colorless oil, b.p. 108~113°. Yield, 94.2%.

(ii) Preparation from 2-thenyl chloride: EtOH solution of 2.5 g. of 2-thenyl chloride was hydrogenated over Pd-black and 0.8 g. of 2-methylthiophene was obtained. Yield, 42.1%.

Furfuryl Alcohol—To a solution of 25 cc. of 35% HCHO and 40 cc. of MeOH, 19.2 g. of furfural was added with cooling, 25 cc. of 50% NaOH solution was dropped into this mixture at a temperature below 20° while stirring, and the mixture was stirred with cooling during 2.5 hrs. The reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with alkaline solution, dried, and evaporated. Distillation of the residue gave 15.2 g. of furfuryl alcohol, $b.p_{15}$ 75~76°. Yield, 77.5%.

Furfuryl Carbanilate—A mixture of 10 g. of phenyl isocyanate added to 7.5 g. of furfuryl alcohol in dehyd. benzene was refluxed for 2 hrs. Benzene was removed under a reduced pressure and the residue was allowed to stand, affording 16 g. of white needles, m.p. 47°, after recrystallization from petr. ether. Yield, 85%.

Furfuryl Chloride—Solution of 13 g. of $SOCl_2$ dissolved in 10 cc. of dehyd. Et_2O was added dropwise to the mixture of 9.6 g. of furfuryl alcohol, 9.5 g. of pyridine, and 10.5 g. of dehyd. Et_2O at 2~3° with stirring. The mixture was stirred at 10° for about 5 mins., the ether layer was separated, washed with KOH solution, dried, and distilled. Thus 3 g. of furfuryl chloride, $b.p_{15}$ 52°, was obtained.

2-Methylfuran—(i) Preparation from furfuryl carbanilate: A mixture of 0.2 g. of Pd-black suspended in 50 cc. of dioxane was hydrogenated, 70 cc. of H_2 being absorbed. Saturated dioxane solution of 2.5 g. of urethan and 0.5 g. of NaOH were added to the above solution, the mixture was hydrogenated, and the mixture was filtered to remove the catalyst. The solution was diluted with water, extracted with ether, and the extract was evaporated. The residue was distilled by using a Widmer distillation apparatus and 0.81 g. of 2-methylfuran was obtained[17] as colorless oil, b.p. 62~66°. This showed a red color on pine splinter moistened with mineral acid.

(ii) Preparation from furfuryl chloride: The Pd-C catalyst (0.2 g.: 4 g.) was hydrogenated in a mixture of 50 cc. of dioxane and 2 g. of pyridine, a mixture of 3 g. of furfuryl chloride and 50 cc. of

17) The literature records b.p. 86~87° for methyltetrahydrofuran.

dioxane was added, and again hydrogenated. After the reaction, the catalyst was removed by filtration, the filtrate was poured into water, and the solution was extracted with Et_2O. The extract was washed with water, dried, and distilled, affording 0.45 g. of a colorless liquid, b.p. 60~62°. Yield, 21.03%.

Summary

The methyl derivatives of 2-, 3-, and 4-methylpyridine, 2-methylthiophene, and 2-methylfuran were synthesized from the corresponding primary alcohol by way of its phenylurethan by treating the alcohol with phenyl isocyanate and catalytic hydrogenation of the urethan formed, in the presence of palladium-black and sodium hydroxide.

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UDC 547.836.3

90. Keizo Kitahonoki: Azaditerpenoid. V.[1] Syntheses of 8-Azaperhydrophenanthrene Derivatives from Agathenedicarboxylic Acid.

(*Faculty of Pharmaceutical Sciences, University of Tokyo, and Research Laboratory, Shionogi & Co., Ltd.**)

Ruzicka and his co-workers[2,3] obtained a diketo-ester (II) by the ozonolysis of dimethyl agathenedicarboxylate (I) during determination of the structure of this resin acid. In the present paper the syntheses of 8-azaperhydrophenanthrene derivatives from the diketo-ester (II) are described.

When the diketo-ester (II) was treated with methanolic ammonia, pyridine derivative (III), m.p. 145~146°, was obtained in 67% yield. The ultraviolet and infrared absorption spectra of this substance indicated the presence of a pyridine ring (U. V. $\lambda_{max}^{95\%EtOH}$ 272 mμ (log ε 3.78)[4]; I. R. λ_{max}^{Nujol} 6.28, 6.38 μ). In this reaction, presumably an intermediate dihydropyridine ring was first formed and then dehydrogenated to the pyridine derivative.[4]

The pyridine ring in (III) resists catalytic reduction[5] and is neither reduced in acetic acid over Adams' platinum-catalyst at atmospheric pressure nor at 3 atm. using Skita's apparatus. When the pyridine derivative (III) was reduced with sodium and ethanol, it was observed that the pyridine ring was reduced to the piperidine ring, partially with the concomitant reduction of the ester group at C-1 to the alcohol group to give several different reduction products. By chromatography and fractional crystallizations of the basic reduction mixture or its benzoates, four isomeric imino-esters and two isomeric imino-alcohols, corresponding to the formulae (IVa) and (Va), respectively, were obtained in a pure state as a free base or benzoate, as shown in Table I. These isomers are considered to be stereoisomers differing in their spatial configurations about the new asymmetric carbon atoms at 7-, 13-, and 14-positions.

Table I.

Reduction product		m. p. (°C)		
		Free base (IVa)	Benzoate (IVb)	
Imino-ester isomers	A	97~97.5	oil	
	B		113~115	
	C		153~156	
	D		154~156	
		Free base (Va)	O-Benzoate (Vc)	Dibenzoate (Vb)
Imino-alcohol isomers	A	153~155		157~158
	B		146~147	182~183

* Imafuku, Amagasaki, Hyogo-ken (北朴木馨三).

1) Part IV. M. Ohta: This Bulletin, **4**, 273(1956).
2) L. Ruzicka, E. Bernold, A. Tallichet: Helv. Chim. Acta, **24**, 223(1941).
3) cf. R. Zwicky: Dissertation, Eidg. Tech. Hochschule, Zürich(1950).
4) cf. L. Ruzicka, L. Sternbach, O. Jeger: Helv. Chim. Acta, **24**, 504(1941).
5) cf. E. Ochiai: Yakugaku Zasshi, **61**, 298(1941).