A Synthesis of an Octahydrophenanthrene Derivative[1]

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In the previous paper[2] synthesis of 2-methoxy-5-hydroxy-1-naphthylacetic acid and unsuccessful attempts to prepare therefrom 1, 2, 3, 4-tetrahydro-2-oxo-5-methoxy-1-naphthyl acetate (IIIb) were described. This paper reports a successful synthesis of the acetate IIIb from 5-methoxy-2-tetralone (I) and of a hydrophenanthrene derivative IX, a promising intermediate in the synthesis of certain diterpenoid skeletons, from IIIb.

The monoalkylation of β-tetralones had been in general difficult to achieve by direct alkylation since they tend to undergo partial or exclusive dialkylation[3]. However, the difficulty was recently overcome by the ingeneous procedure of Stork[4], which is concerned with alkylation of enamine derivatives of ketones with alkyl halides. In this study, the Stork method was adopted. The reaction of 5-methoxy-2-tetralone with pyrrolidine in boiling benzene afforded a previously undescribed enamine II, m. p. 78.5~79.5°C, in almost quantitative yield. II was then alkylated in benzene with ethyl bromoacetate and the intermediary ammonium salt was hydrolysed with water. Ethyl 1, 2, 3, 4-tetrahydro-2-oxo-5-methoxy-1-naphthyl acetate (IIIb), thus obtained in 74% yield, is a viscous liquid, boiling at 150~151°C (0.05 mmHg). Piperidine enamine of the methoxytetralone, on being treated in the same way, afforded a poor yield of IIIb. Hydrolysis of the ester IIIb with aqueous sodium hydroxide gave the acid IIIa, m. p. 172~173°C.

In hope of preparing a tricyclic $\alpha\beta$-unsaturated ketone V, the authors next examined the reaction of IIIb with 1-(*N*, *N*-diethylamino)-butan-3-one methiodide in benzene in the presence of potassium ethoxide. After chromatography on acid alumina, there could be isolated from the reaction mixture a compound $C_{19}H_{24}O_5$, m. p. 134~135°C, as the main product. The infrared spectrum (Fig. 1; nujol mull) of this compound exhibited absorption bands at 3400 (broad; OH), 1700 (six-membered ring ketone) 1735 and 1175 cm^{-1} (ester). The authors supposed at this stage that they had ketol IV in hand. In several instances, the Robinson annelation reaction has been shown[5] to lead to intermediary ketol of type IV, which affords $\alpha\beta$-unsaturated ketone of type V by a β-elimination process. On treatment with isopropenyl acetate in the presence of *p*-toluenesulfonic acid, the ketol IV afforded an acetate

1) Approaches to the Synthesis of Diterpenoid Alkaloid Models, Part III. A portion of Ph. D. Dissertation (Hokkaido University) of Akira Suzuki. Read in part before the 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959 and outlined in part in the preliminary communication; T. Matsumoto and A. Suzuki, This Bulletin, 33, 862 (1960).

2) T. Matsumoto and A. Suzuki, ibid., 32, 1283 (1959).

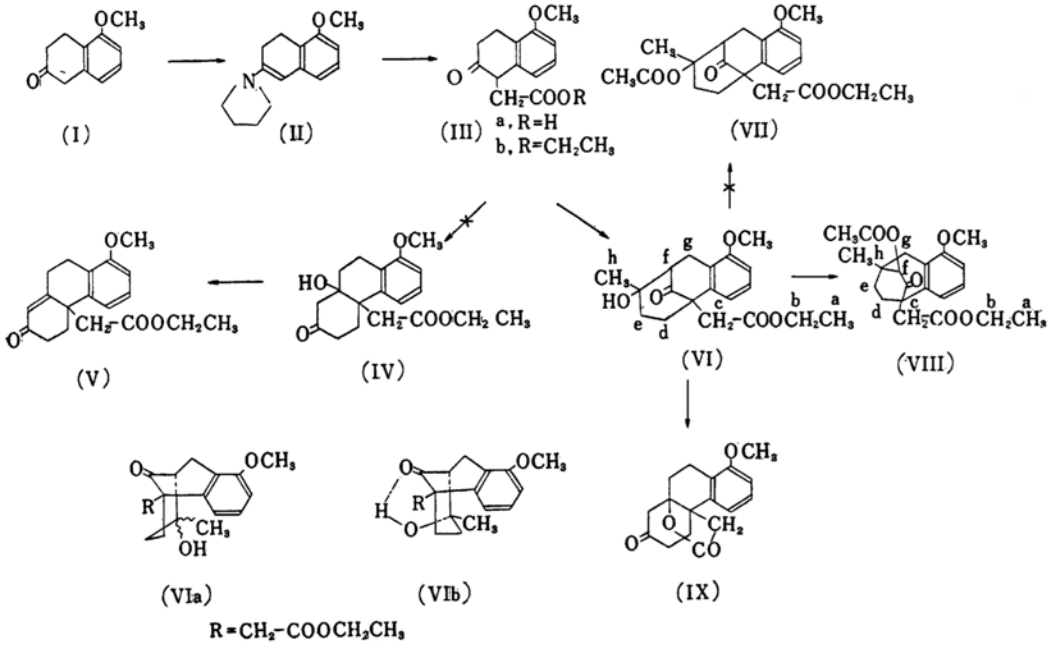
3) J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 1942, 689; C. A. Grob and W. Jundt, *Helv. Chim. Acta*, 31, 1691 (1948); J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1946, 676; J. D. Chanely, *J. Am. Chem. Soc.*, 70, 244 (1948); M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson and E. A. Bowler, ibid., 72, 3704 (1950); G. Stork, ibid., 73, 4748 (1951).

4) G. Stork, R. Terrell and J. Szmuszkovicz, ibid., 76, 2024 (1954); E. D. Bergmann and R. Ikan, ibid., 78, 1482 (1956); S. Hunig, E. Benzing and E. Lucke, *Ber.*, 90, 2833 (1957).

5) C. Mannich, W. Koch and F. Borkowsky, ibid., 70, 355 (1937); P. Wieland, H. Neberwasser, G. Anner and K. Misscher, *Helv. Chim. Acta*, 36, 1231 (1953); C. Georgian, *Chem. & Ind.*, 1954, 930; J. Colonge, J. Dreux and J. P. Kehlstadt, *Bull. soc. chim. France*, 1954, 1404; G. Stork, ibid., 1955, 256; F. J. McQuillin, *J. Chem. Soc.*, 1955, 528; R. Howe and F. J. McQuillin, ibid., 1955, 2423; W. S. Johnson, J. Ackerman. J. F. Eastham and H. A. Dewalt, Jr., *J. Am. Chem. Soc.*, 78, 6302 (1956).

having a m. p. 97.5～98.5°C. Contrary to expectation, attempted pyrolytic elimination of acetic acid from the acetate to the $\alpha\beta$-unsaturated ketone did not occur, even though the reaction temperature was raised to 300°C.

Eventually, through the aid of N. M. R. spectroscopy, the ketol was shown to be actually a bridged ring compound VI. The N. M. R.



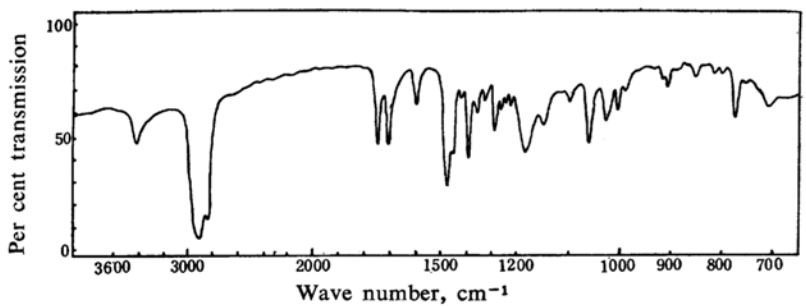


Fig. 1. Infrared spectrum of VI.

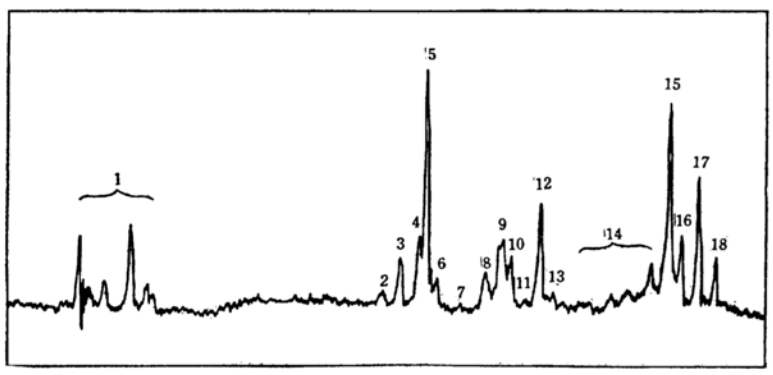


Fig. 2. N. M. R. spectrum of VI in $CDCl_3$

TABLE I. ASSIGNMENTS OF THE N. M. R. SPECTRUM OF VI

Peak number in Fig. 2	Chemical shift c. p. s. (stand. benzene)	Proton type	Number of protons	
			Calcd. for VI	Obs. from peak area
1	−21	Aromatic H	3	3.0
2, 3, 4, 6	100	b-H	2	2.5
5	105	O-CH_3	3	2.9
8, 9, 10	136	f, g-H and OH	4	3.5
12	151	c-H	2	1.7
15	203	h-H	3	3.4
16, 17, 18	215	a-H	3	3.0
14 and others		d, e-H		

spectrum[6] of the ketol (Fig. 2) showed one sharp maximum at a high applied magnetic field, characteristic of proton resonance for the $-\overset{|}{\underset{|}{C}}-CH_3$ group (203 c. p. s.; standard, benzene). This observation is clearly incompatible with structure IV, and the spectrum is completely accounted for in terms of structure VI (see Table I). A formula such as VIII and Xa would also explain the resonance line at 203 c. p. s., but would not give any explanation for the other lines. The formation of a bridged ketol system similar to VI through the Robinson annelation-reaction was first disclosed only quite recently by Johnson and his coworkers[7].

In order to elucidate the conformation the authors further examined the O-H stretching absorption band of the ketol in the 3300 cm^{-1} region. The spectrum was measured in 0.0046 M[8] tetrachloroethylene solution[9] and as indicated in Fig. 3, was found to exhibit two bands at 3430 and 3590 cm^{-1}. The latter band corresponds to the vibration of aliphatic free OH group[10] while the former band may be attributed to OH group bonded to the carbonyl oxygen atom[11]. In structure VIa, in which the cyclohexanone ring takes a boat form, the hydroxyl group, be it either axial or equatorial, is unable to form an intramolecular hydrogen bond[12].

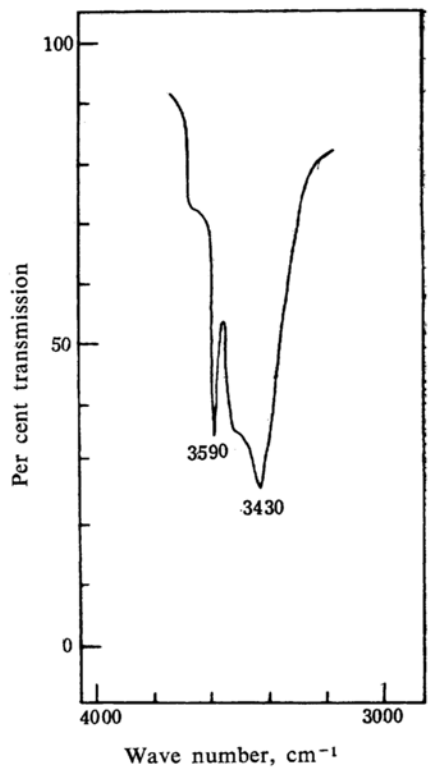


Fig. 3. ν O-H absorption of VI in tetrachloroethylene (0.0046 M).

The conformation VIb with chair cyclohexanone ring and axial OH group is the only one in which the formation of an intramolecular hydrogen bond is possible.

6) The N. M. R. spectra were taken on a Varian 40 MC instrument at the University of Illinois through the courtesy of Drs. Ben Shoulder and Masaji Ohno, to both of whom the authors are pleased to express their sincere thanks.

7) W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Am. Chem. Soc.*, 82, 614 (1960).

8) At this dilution the association of the solute molecule is neglegible. N. D. Coggeshall, *J. Chem. Phys.*, 18, 978 (1958); F. A. Smith and E. C. Creitz, *J. Research Natl. Bur. Standards*, 46, 145 (1951).

9) The infrared spectrum was taken with a Hilger H 800 infrared spectrophotometer with calcium fluoride optics. The authors wish to express their gratitude to Assistant Professor Sanjuro Matsushita and Miss Hisako Nakato of the Physical Chemistry Laboratory for the infrared spectral measurement. For the absence of interaction between hydroxyl group of solute and π-electrons of tetrachloroethylene, see L. L. Ingraham, J. Corse, G. F. Bailey and F. Stitt, *J. Am. Chem. Soc.*, 74, 2297 (1952).

10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen and Co., Ltd., London (1958), p. 96.

11) In general, an intramolecularly bonded OH group exhibits a sharp band. The rather broad absorption band at 3430 cm^{-1} might be caused by the overlapping of the absorption due to intramolecular hydrogen bond between the OH group and the ethoxy carbonyl oxygen atom (see formula VIb) and or by the rotatory isomerism of the hydroxyl group. For the latter effect, see R. Piccolini and S. Winstein, *Tetrahedron Letters*, No. 13, 4 (1959); M. Kahn, N. Lüttke and R. Mecke, *Z. anal. Chem.*, 170, 106 (1959).

12) For example, L. Hunter, W. Klyne's "Progress in Stereochemistry", Vol. 1, Butterworths Scientific Publications, London (1954), p. 223.

TABLE II. ASSIGNMENTS OF THE N. M. R. OF VIII

Peak number in Fig. 5	Chemical shift c. p. s. (stand. benzene)	Proton type	Number of protons	
			Calcd. for VIII	Obs. from peak area
1	−22	Aromatic H	3	3.0
2, 3, 4, 6	100	b-H	2	2.2
5	104	O-CH_3	3	2.9
8	129	g-H	2	1.8
9	138	c-H	2	1.7
11	178	$COCH_3$	3	3.8*
13	190	h-H	3	3.1
15, 16, 17	212	a-H	3	3.0
10, 12, 14 and others		d and e-H		

* Absorption due to d and e-H may be overlapped.

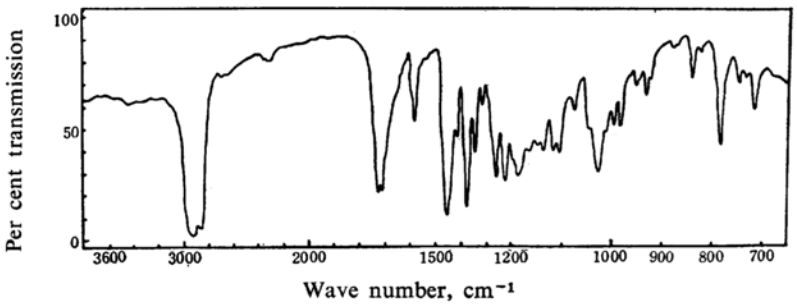


Fig. 4. Infrared spectrum of VIII.

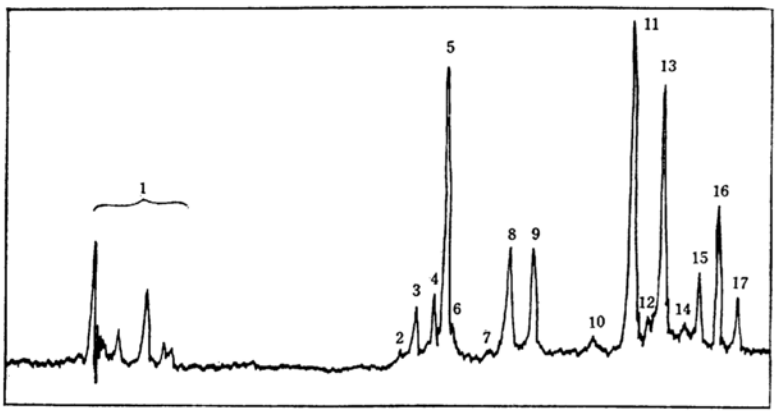


Fig. 5. N. M. R. spectrum of VIII in $CDCl_3$.

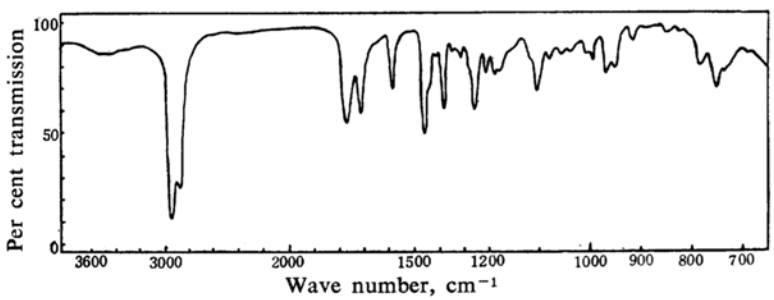
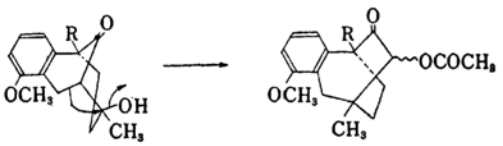


Fig. 6. Infrared spectrum of IX.

Next, examination was made of the structure of the acetylation product with m. p. 98.5°C (vide supra). The infrared spectrum (Fig. 4) of the acetate showed complete absence of hydroxyl function and presence of the following groups: saturated ester (1730 and 1175 cm^{-1}), acetate (1730 and 1230 cm^{-1}) and six-membered cyclic ketone (1715 cm^{-1}). Therefore a structural formula VII may be considered for this compound. Invalidity of this structure was however concluded from the N. M. R. spectrum, which is depicted in Fig. 5. The paramagnetic shift of the peak due to presence of $CH_3-\overset{|}{C}-$ protons to 190 c. p. s., disappearance of the peak at 151 c. p s. due to $-\overset{|}{C}-CH_2-CO_2$ protons and appearance of a new peak at 138 c. p. s. suggest a fundamental change in the framework of VI. The acetate may then be expressed by VIII, since an attack of proton upon the hydroxyl function of compound VIc would result in the formation of structure VIIIa through the well known 1, 2-shift as follows:



(VIc) (VIIIa)

R=$CH_2-COOCH_2CH_3$

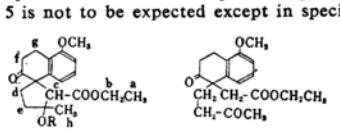
This structure is consistent with the N. M. R. spectrum; the interpretation of the spectrum in terms of formula VIII is summarized in Table II. The structure also explains the stability of the acetate to pyrolitic treatment, since in formula VIII elimination of an element of acetic acid would be impossible. Further, convincing evidences in favor of the formula VIII were provided by positive reactions with triphenyltetrazolium chloride and with the Tollens' reagent. On the basis of these findings the structure of the acetate may be concluded to be VIII[13].

Contrary to the case of acid treatment described above, treatment of VI with dilute aqueous alkali or with sodium ethoxide in ethanol, followed by acidification gave rize to a product $C_{17}H_{18}O_4$, to which a hydrophenanthrene structure IX was assigned on the basis of infrared (Fig. 6) and N. M. R. spectra. Although the product was amorphous and could not be crystallized by chromatography or by any other means, it was regarded homogeneous enough on the basis of the behavior in chromatography and of infrared spectrum. The infrared absorption spectrum showed complete absence of the hydroxyl group and presence of six-membered cyclic ketone (1720 cm^{-1}) and γ-lactone (1770 cm^{-1}). The formation of γ-lactone is impossible from the above mentioned skeletons VI and VIII and is possible only from the structure containing the hydrophenanthrene skeleton IX. The correctness of structure IX is further substantiated by the elemental analysis and by the N. M. R. spectrum. In the spectrum[14], the sharp maximum at high magnetic field characteristic for $-\overset{|}{C}-CH_3$ protons could not be recognized. This type of conversion from skeletons VI to IX by alkaline reagent has been recently described by Johnson and coworkers[7]. The authors were thus able to obtain an intermediate IX which seems to be promising for the synthesis of a certain diterpenoid skeleton.

Experimental[15]

Preparation of Pyrrolidine Enamine (II). — A solution of 4.3 g. (0.0244 mol.) of 5-methoxy-2-tetralone, which was prepared from 2, 5-dimethoxynaphthalene by the procedure of Cornforth and Robinson[16], and 3.5 g. (0.0488 mol.) of freshly distilled pyrrolidine in 40 ml. of dry benzene was refluxed on a water bath while water, distilled off as an azeotropic mixture with benzene, was separated with a Dean-Stark type apparatus[17]. The condensation reaction was completed after 3 hr. After removal of the solvent and excess pyrrolidine, the residue afforded a distillation under reduced pressure

13) In the preliminary report[1] a formula Xb was suggested as the structure of the acetate. The formation of the spirocyclic compound was explained through a reverse aldol condensation and a subsequent aldol condensation of an intermediary diketone XI. Peaks at 129 and 138 c. p. s. were interpreted to be attributable to f and g protons, although in general these four protons constitute an ABCD system and a rather simple absorption pattern as in Fig. 5 is not to be expected except in special cases.



(X)

a. R=H

b. R=$COCH_3$

(XI)

14) The spectrum was taken on a Varian 40 MC instrument at Tohoku University. The authors are very grateful to Professor Genjiro Hazato and his coworkers for the measurement.

15) All melting and boiling points are uncorrected. Unless otherwise specified, infrared spectra were taken in nujol mull on a Koken model DS-301 infrared spectrophotometer with sodium chloride optics. Ultraviolet spectra were measured in 95% ethanol or methanol solutions by means of a Beckmann model DK-2 spectrophotometer. The authors are indebted to Miss Noriko Fujino for microanalysis.

16) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1861.

17) E. W. Dean and D. D. Stark, *Ind. Eng. Chem.*, **12**, 486 (1920); S. Natelson and S. Gottfried, *Org. Syntheses*, **23**, 37 (1943).

5.35 g. (95.5%) of a product, boiling at 159~160°C (0.09 mmHg). The enamine derivative II was a pale yellow viscous liquid, which crystallized on being allowed to stand. Recrystallization from petroleum ether yielded colorless prisms, m. p. 78.5~79.5°C.

ν_{max}^{nujol} [18] 1610, 1590 and 1565 cm^{-1}.

λ_{max}^{MeOH} [18] 243 (ε 13800) and 315 mμ (ε 19300).

Found: C, 78.48; H, 8.21. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35%.

Piperidine enamine of 5-methoxy-2-tetralone was obtained under the same condition. The condensation of 5 g. (0.0284 mol.) of the tetralone with 5 g. (0.0588 mol.) of the amine in 30 ml. of dry benzene was complete in 3 hr.; yield 4.6 g. (67%), b. p. 135~140°C (0.001 mmHg).

Found: C, 79.16; H, 8.54. Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70%.

Ethyl 1,2,3,4-Tetrahydro-2-oxo-5-methoxy-1-naphthyl Acetate (IIIb).—At room temperature and during 45 min., 3.9 g. of ethyl bromoacetate in 5 ml. of benzene was added to a solution of 5.3 g. of 3,4-dihydro-2-(*N*-pyrrolidyl)-5-methoxy naphthalene (II) in 10 ml. of benzene. After refluxing for 3 hr. on a water bath (ca. 70°C), the solution was cooled to room temperature and 20 ml. of water was added.

The whole was vigorously stirred for one hour at room temperature and the organic layer was separated; the water layer was extracted twice with benzene. The combined organic layer was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure; b. p. 150~151°C (0.05 mmHg.), colorless viscous liquid, yield 4.5 g. (74%).

ν_{max}^{film} 1725 (ketonic carbonyl) and 1735 cm^{-1} (ester carbonyl).

Found: C, 68.36; H, 6.59. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%.

The keto ester IIIb was also prepared from the piperidine enamine derivative by the same procedure. The yield, however, was lower than the above case; there was obtained 2 g. (41%) of IIIb from 4.5 g. of the piperidine enamine and 3.1 g. of ethyl bromoacetate.

Hydrolysis of the Ethyl Ester IIIb.—A mixture of 300 mg. of IIIb, 3 ml. of 60% sodium hydroxide and 3 ml. of ethanol was heated on a water bath for one hour. The solution was then diluted with 5 ml. of water, acidified with 6 N hydrochloric acid and extracted with ethyl acetate three times. The combined extracts were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo left an oily pale brown residue, from which on trituration with ether, a crystalline material was obtained. For analysis the product was recrystallized from benzene to afford colorless prisms, m. p. 172~173°C.

ν_{max}^{nujol} 1695 (carboxylic carbonyl) and 1710 cm^{-1} (ketonic carbonyl).

λ_{max}^{MeOH} 271 (ε 2200) and 278 mμ (ε 2220).

Found: C, 66.77; H, 6.00. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02%.

Condensation of IIIb with 1-(*N*, *N*-Diethylamino)-butan-3-one Methiodide. — Diethylaminobutanone (4.2 g.), prepared according to the Wilds and Shunk method[19] was swirled gently in a 200 ml. flask and cooled with ice during the addition of methyl iodide (4.2 g) in portions for 15 min. The swirling was regulated, so as to obtain crystalline methiodide as an even coating on the walls of the flask. When no more liquid remained, the flask was kept in ice for one hour. A solution of the keto ester IIIb (7 g.) in dry thiophen-free benzene (40 ml.) was added, air was expelled from the flask by dry nitrogen, and a solution of potassium (1.7 g.) in absolute ethanol (25 ml.) was added with ice cooling during 5 min. Swirling was continued until the methiodide had all dissolved (about one hour) and was replaced by a precipitate of potassium iodide. After it had been kept in ice for another hour, the mixture was heated gently for 30 min. An excess of 3 N sulfuric acid was then added and the nitrogen gas was stopped. After addition of enough water (60 ml.) to dissolve the potassium sulfate the benzene layer was separated and the aqueous layer extracted three times with ether. The united extracts were washed with water, cleared with a little sodium sulfate, and concentrated in vacuo to leave 3.5 g. of an oil which was chromatographed through a column of acid-washed alumina[20] (50 g.) packed and washed with benzene. The portions eluted with benzene-chloroform (volume ratio 1 : 1, 450 ml.) and with chloroform only (400 ml.) were viscous oils and gave no crystalline products. The fraction obtained by elution to a total of 450 ml. of ethanol, contained 1.8 g. (20.3%) of a solid, m. p. 124~130°C; recrystallization from ligroin yielded a pure sample of the bridged ring ketol VI as colorless prisms, m. p. 134~135°C.

λ_{max}^{MeOH} 271 (ε 1410) and 278 mμ (ε 1310).

Found: C, 68.44; H, 7.10. Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28%.

The 2,4-dinitrophenylhydrazone of VI was crystallized from ethanol as orange needles and had m. p. 260°C (decomp.).

Found: C, 58.61; H, 5.43. Calcd. for $C_{25}H_{28}O_8N_4$: C, 58.58; H, 5.51%.

Acetylation of the Ketol VI.—A mixture of 300 mg. of VI, 6 mg. of *p*-toluenesulfonic acid and 3 ml. of isopropenyl acetate (Eastman) was heated on a water bath for 4 hr. After the acid was neutralized with a few drops of pyridine, the solution was concentrated in vacuo to leave a pale yellow brown oil, which on trituration with petroleum benzine completely crystallized; yield 300 mg. (89%), m. p. 77~85°C. Upon recrystallization from petroleum benzine, it formed colorless plates, m. p. 97.5~98.5°C.

Found: C, 67.10; H, 6.94. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00%.

Alkali Treatment of the Ketol VI.—A mixture consisting of 300 mg. of VI, 35 mg. of sodium and 5 ml. of ethanol was refluxed on a water bath for 4 hr. and was then acidified with glacial acetic acid. After removal of most of the ethanol, the residue

18) For the characteristic frequencies of enamine, see G. Opitz, H. Hellmann and H. W. Schubert, *Ann.*, 623, 112 (1959).

19) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, 65, 471 (1943).

20) E. Lederer and M. Lederer. "Chromatography", Elsevier Publishing Company, Amsterdam (1954), p. 22.

was diluted with water and extracted with chloroform three times. The united extracts were washed with an aqueous solution saturated with sodium chloride, dried over anhydrous sodium sulfate and then concentrated in vacuo. There remained a pale brown oil which was chromatographed on acid-washed alumina[20] (ca. 30 g.) packed and washed with benzene. One hundred and six fractions were collected as in the following table.

Fraction No.	Eluant	Residue
1— 15	Benzene-chloroform (1 : 1); 150 ml.	Colorless oil 24 mg.
16— 36	The same; 200ml.	Nil.
37— 46	Benzene-chloroform (1 : 2); 100 ml.	Colorless oil 8 mg.
47— 51	Benzene-chloroform (1 : 2); 100 ml.	Nil.
52— 61	Benzene-chloroform (1 : 3); 100 ml.	Colorless oil 10 mg.
62— 71	The same; 100ml.	Pale orange oil 7 mg.
72— 91	Chloroform, 200 ml.	Nil.
92— 96	Chloroform-ethanol (1 : 1); 50 ml.	Colorless oil 8 mg.
97—101	The same; 50 ml.	Colorless oil 120 mg.
102—106	The same; 50 ml.	Colorless oil 10 mg.

Treatment of the fractions numbered 97 through 101 with ether-petroleum ether yielded an amorphous product which could not be turned into a crystalline substance by any means. The substance was however submitted to elemental, infrared and N. M. R. analysis.

Found: C, 70.64; H, 6.45. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

Infrared absorption spectrum is reproduced in Fig. 6.

Summary

Ethyl 1, 2, 3, 4-tetrahydro-2-oxo-5-methoxy-1-naphthyl acetate (IIIb) has been synthesized. Condensation of IIIb with 1-diethylaminobutan-3-one methiodide afforded an anomalous product VI. Treatment of VI with isopropenyl acetate in the presence of *p*-toluenesulfonic acid gave rise to an acetate VIII, while on treatment with alkali and then with acid, a hydrophenanthrene lactone IX was obtained.

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