dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on Florisil. Estriol 16,17-dicaproate (Vc, 700 mg.) was obtained from Et_2O eluates as an oily substance. It failed to crystallize but it was analytically pure and IR spectrum showed that it was estriol 16,17-dicaproate (Vc). $[\alpha]_D^{20}$: $-6°$(c=0.84, dioxane). *Anal.* Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found : C, 73.98; H, 9.24.

Estradiol 17-Acetate (Xa)——A solution of $NaBH_4$ (1.0 g.) in MeOH (24 ml.) was added to a solution of estradiol diacetate (IXa, 1.0 g.) in MeOH (80 ml.). The solution was stirred at 40° for 45 min., and poured into 2% AcOH. The product was extracted with Et_2O, and the ethereal extract was washed with 5% Na_2CO_3 and H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from MeOH to give estradiol 17-acetate (Xa, 850 mg., m.p. 212~215°), the IR spectrum of which was the same as that of authentic sample.

Estradiol 17-Valerate (Xb)——Estradiol 3-benzoate 17-valerate (IXb, 60 mg.) was treated with $NaBH_4$ as described above and estradiol 17-valerate (Xb, m.p. 142~144°) was obtained.

We are very grateful to Dr. I. Chuman, Director of this laboratory for valuable advices, and Dr. F. Ueno and Dr. H. Tajima for their encouragement throughout this work.

Summary

Estriol 16-monoacylates were obtained from estriol (I) by refluxing or warming estriol with carboxylic acids. A more drastic condition afforded estriol 16,17-diacylates. Transesterification gave the same results. The reactions of estriol triacylates and estradiol diacylates with sodium borohydride gave estriol 16,17-diacylates and estradiol 17-acylates, respectively. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate (III) was transformed into estriol 16-acetate (IIa) by treatment with sodium borohydride. A milder condition afforded estriol 3,16-diacetate (VI).

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92. Toshihiko Okamoto and Hiroaki Takayama : The Reaction of N-Alkoxypyridinium Derivatives. (6).[1,2] The Reaction of N-Methoxyquinolinium Salt with Ketones.

(Faculty of Pharmaceutical Sciences, University of Tokyo[*1])

Reactions of N-alkoxypyridinium salt with nucleophilic reagents have been reported by several authors. N-Alkoxypyridinium derivative gave picolinonitrile and isonicotinonitrile when it was reacted with cyanide ion.[3] This reaction also proceeds with quaternary salts of quinoline-,[3] isoquinoline-,[3] phenanthridine-[4] and quinine N,N′-dioxides.[5] Further, 2-alkylpyridine was obtained by the reaction of N-alkoxypyridinium salt and alkyl magnesium halogenide.[6] The mechanism of these reactions have been established to be as follows.

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1) Part (5) : H. Tani : Yakugaku Zasshi, **81**, 182 (1961).

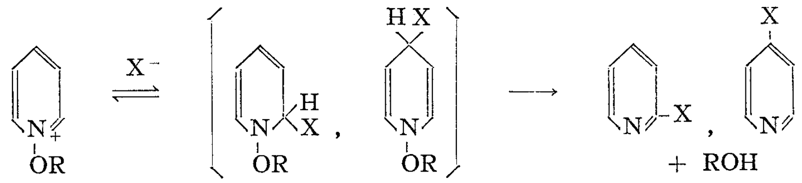
2) This paper constitute Part IV of a series entitled Reaction Mechanism in Aromatic Heterocyclic Compounds by T. Okamoto. Part III : This Bulletin, 8, 892 (1960).

3) T. Okamoto, H. Tani : This Bulletin, **7**, 130, 925 (1959); H, Tani : *Ibid.*, **7**, 930 (1959); W, E. Feely, E.M. Beavers : J. Am. Chem. Soc., **81**, 4004 (1959); Y. Kagawa : J. Biochem., **47**, 104 (1960).

4) E. Hayashi, Y. Hotta : Yakugaku Zasshi, **80**, 834 (1960).

5) T. Okamoto, H. Takayama : *Ibid.*, **82**, 1076 (1962).

6) O. Cervinka : Chem. & Ind. (London), 1482 (1960).



This paper treats the reactions of the N-alkoxyquinolinium salt with some ketones. To the solution of N-methoxyquinolinium methosulfate in water-methanol mixture, a ketone and alkali carbonate or alkali hydroxide was added. Then, the reaction mixture was left to stand over night at room temperature. The reaction products were extracted with chloroform and separated by alumina chromatography using benzene-hexane mixture as the solvent. The first eluate was quinoline and the second was proved to be quinaldyl ketone. The results of the reactions with several ketones are summarized in the Table I.

TABLE I. Reaction of N-methoxyquinolinium Methosulfate with Ketone

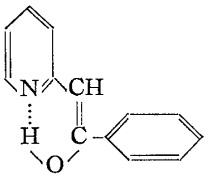
Ketone	Product				
	Quinaldyl ketone	Yield a) (%)	m.p. (°C) b.p. (°C/mm. Hg)	Picrate m.p.	Quinoline Yield (%) a)
Acetone	Methyl quinaldyl ketone	38	79.5∼80.5 (78∼79)7,10)	182∼183 (182∼183)7)	16
2-Butanone	Ethyl quinaldyl ketone	8	$75\sim85/_{0.003\sim0.005}$ $(142\sim143/_{1.4})$7)	179∼183 (181∼182)7)	48
Acetophenone	Phenyl quinaldyl ketone	4	119∼120 (115∼116)	177 (172∼173)	55

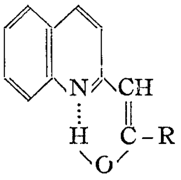
a) Calculated from the N-oxide

The structure of the methyl quinaldyl ketone thus obtained was proved by the admixture with the sample synthesized from quinaldyl lithium and ethyl acetate.7) The ethyl quinaldyl ketone was reduced to the corresponding 2-butyl quinoline by Huang-Minlon's method. The picrate of the latter showed no depression on the admixture with that of 2-butylquinoline obtained from quinoline and butyl lithium.8) The structure of the phenyl quinaldyl ketone obtained by the reaction was confirmed from the melting points of its free base and picrate.7) Following chemical and physical behaviors of these ketones also support their quinaldyl ketone structures.

These products were positive to Zimmermann's test for active methylene groups. However, these showed no absorption band corresponding to carbonyl grouping in the infrared spectra and intensive green colors were developed forming chelate complexes when ferric ion was added to the alcoholic solutions of these compounds. Further, the alcoholic solution of the compounds showed absorptions in the region of unusually long wave length in the ultraviolet spectra as are shown in Fig. 1 and Fig. 2.

As already was pointed out in the case of 2-phenacyl pyridine9) above results support the enol structures of these ketones and also the existences of intramolecular hydrogen bondings between these enol hydrogens and the nitrogens. In acidic solutions, the spectra of these compounds were normal and similar to that of quinaldine.





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7) N.N. Goldberg, R. Levine : J. Am. Chnm. Soc., **74**, 5217 (1952).
8) K. Ziegler, H. Zeiser : Ann., **485**, 174 (1931).
9) R.F. Brauch : Nature, **177**, 671 (1956).

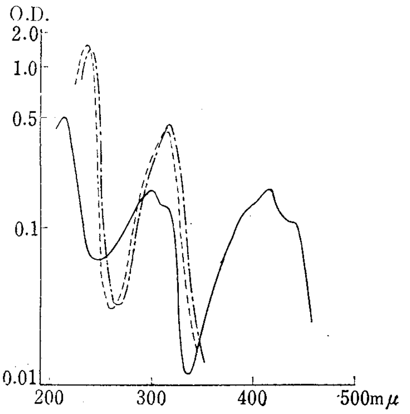
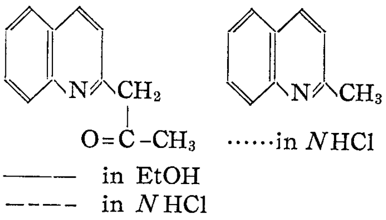


Fig. 1.



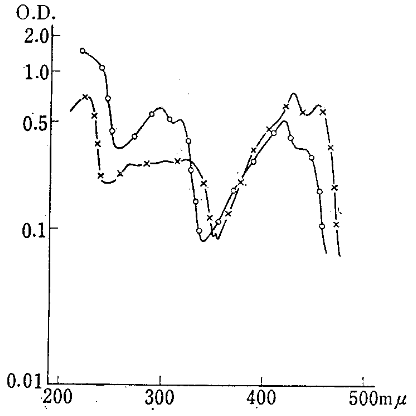
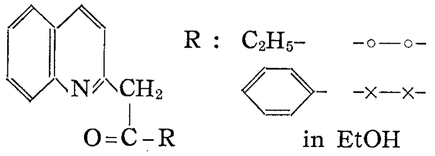
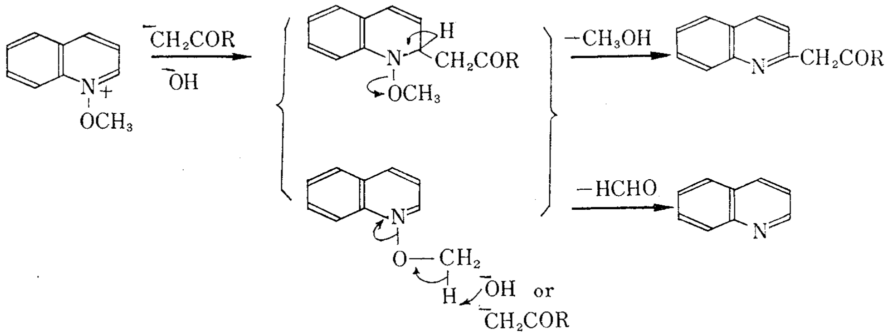


Fig. 2.



The mechanism of the reaction of N-alkoxyquinolinium salt and the ketone should be the same to that of the reaction of cyanide ion or Grignard's reagent and N-alkoxypyridinium salt. It should be written as follows. The reaction was accompanied by partial decomposition of the quaternary salt into the tertiary base and the aldehyde. The N-alkoxyquinolinium salts gave quinaldyl ketone in considerable yield, but only pyridine was recovered in the reactions of the N-alkoxypyridinium salt and the ketones.



Experimental

Reaction of 1-Methoxyquinolinium Methosulfate with Acetone——To a solution of 1.45 g. (0.01 mole) of quinoline N-oxide (b.p$_{3\sim4}$ 163~166°) in benzene (5 cc.), 2 g. of Me_2SO_4 was added and the mixture was allowed to stand over night at room temperature. 3 cc. of H_2O was then added to the reaction mixture and shaken to separate the produced quaternary salt as H_2O layer from benzene. 5.6 g. (0.1 mole) of Me_2CO was added to the above separated quaternary salt solution and a suspension of 2.1 g. (0.02 mole) of Na_2CO_3 in 3 cc. of H_2O was added dropwise during 10 min. at room temperature. The reaction mixture was stirred for 2 hr. and allowed to stand over night. The reaction products were extracted with $CHCl_3$, evaporated to dryness and oily residue was obtained.

The residue was passed through Al_2O_3 column using $CHCl_3$ as the solvent. The $CHCl_3$ eluates were collected and after evaporation of the solvent, 1.035 g. of residue was obtained. This residue was again submitted to alumina chromatography using benzene hexane (4:1) mixture as the solvent.

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From less adsorbing fractions, 210 mg. of quinoline was obtained and its picrate (m.p. 197~199°) showed no depression when mixed with the authentic sample. Yield, 16 % as calcd. from the N-oxide.

From the eluate subsequent to the quinoline fractions, resinous product was obtained which was recrystallized from petr. ether to give yellow needles of m.p. 79.5~80.5°. This was identified as methyl quinaldyl ketone by the admixture with the sample (m.p. 79.5~80.5°) synthesized by a different route. Yield, 700 mg. (38 % as calcd. from the N-oxide). UV λ_{max}^{EtOH} mμ (log ε) : 216 (4.46), 300 (4.16), 413 (4.20). $\lambda_{max}^{N\ HCl}$ mμ : 238, 318. *Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.95; N, 7.56. Found : C, 77.28; H, 5.99; N, 7.32.

Picrate : Yellow needles from EtOH, m.p. 182~183 (decomp.). *Anal.* Calcd. for $C_{18}H_{14}N_4O_8$: C, 52.18; H, 3.41; N, 13.52. Found : C, 51.97; H, 3.66; N, 13.40.

Methyl Quinaldyl Ketone——Synthesized from quinaldyl lithium and AcOEt by the method described by Goldberg and Levine.[7] Yellow needles from petr. ether, m.p. 79.5~80.5°.

Reaction of 1-methoxyquinolinium Methosulfate with 2-Butanone——To the solution of the quaternary salt (obtained from 1.45 g. of quinoline 1-oxide and an excess of Me_2SO_4 as described in the above experiment) (0.01 mole) in 1.5 cc. of H_2O, a mixture of 3.6 g. (0.05 mole) of 2-butanone and 1 cc. of MeOH was added, then a suspension of 2.1 g. (0.02 mole) of Na_2CO_3 in 1.5 cc. of H_2O was added dropwise under ice cooling. The reaction mixture was stirred for about 2 hr. and was allowed to stand over night.

The products mixture was taken up in $CHCl_3$, the residue obtained after evaporation of the solvent was redissolved in $CHCl_3$ and this solution was passed through Al_2O_3 column. The $CHCl_3$ eluate was evaporated and the residue was distilled *in vacuo* to yield two fractions. The first fraction (160 mg.) was identified as quinoline by the admixture of its picrate (m.p. 198~199°) with an authentic sample. The second fraction of $b.p_{0.003\sim0.005}$ 75~85° (160 mg.) was a yellow oil.

This fraction was further purified by alumina chromatography as described in the above experiment. The product still remained as an oil but gave a picrate of m.p. 180~182° (yellow needles from EtOH). *Anal.* Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.29; H, 3.74; N, 13.08. Found : C, 52.98; H, 3.68; N, 12.85.

Reduction of the Reaction Product of the Quaternary Salt and 2-Butanone——To the solution of 100 mg. of the product ($b.p_{0.003\sim0.005}$ 75~85°) in ethylene glycol, 0.5 cc. of hydrazine hydrate (85%) was added and heated for 1 hr. at 110°. Then 90 mg. of powdered KOH was added and the reaction mixture was maintained at 190~200° for 3 hr. After cooling, 5 cc. of H_2O was added, extracted with Et_2O and the Et_2O extract was dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was redissolved in Et_2O and this solution was passed through Al_2O_3 column. The eluate was evaporated to dryness and 36 mg. of yellow oil was obtained.

This oil gave a picrate of yellow needles (from EtOH), m.p. 162~163°. The picrate showed no depression on the admixture with the picrate of 2-butyl quinoline synthesized by a different route. *Anal.* Colcd. for $C_{19}H_{18}N_4O_7$ (picrate) : C, 55.07; H, 4.38; N, 13.52. Found : C, 55.52; H, 4.54; N, 13.15.

2-Butyl Quinoline——Synthesized from quinoline and butyl lithium as described by Ziegler and Zeiser.[8] Oil, $b.p_{3\sim4}$ 105~120°. Picrate : Yellow needles, m.p. 164~166° (from EtOH).

Reaction of 1-Methoxy Quinolinium Methosulfate with Acetophenone——To the solution of the quaternary salt (obtained from 1.45 g. of quinoline 1-oxide and an excess of Me_2SO_4 (0.01 mole) in 1.5 cc. of H_2O, 3.6 g. (0.03 mole) of acetophenone and 1 cc. of MeOH was added. Then, a solution of 0.48 g. (0.012 mole) of NaOH in 1.5 cc. of H_2O was added dropwise under ice cooling. The reaction mixture was stirred for 3 hr. and was allowed to stand over night at room temperature. The reaction products were extracted with $CHCl_3$ and from this solution basic product was shaken into dil. HCl. The acidic solution was basified, and extracted with $CHCl_3$. After evaporation of the solvent the residue was submitted to alumina chromatography using benzene-hexane (9:1) mixture as the solvent. From the first eluate, 710 mg. of quinoline was obtained (55 %, as calcd. from quinoline 1-oxide) and the second eluate gave 100 mg. of crystals after evaporation of the solvent. This was recrystallized from petr. ether to give yellow needles of m.p. 119~120°. UV λ_{max}^{EtOH} mμ : 225, 325, 428, 453. $\lambda_{max}^{N\ HCl}$ mμ : 241, 319. *Anal.* Calcd. for $C_{17}H_{13}NO$: C, 82.59; H, 5.26; N, 5.67. Found : C, 82.81; H, 5.08; N, 5.43.

Picrate : yellow needles from EtOH, m.p. 172~173°. Yield, 4 % as calcd. from quinoline 1-oxide.

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Summary

N-Alkoxyquinolinium salts were reacted with several ketones and corresponding quinaldyl ketones were obtained as the reaction products. This reaction was accompanied by partial decomposition of the quaternary salt into the tertiary base and aldehyde.

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