NHCO). *Anal.* Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.77; H, 6.07; N, 12.96.

2-(N-Phenylcarbamoylanilino)-3-methylpyridine (XIIa)——A mixture of X (1.80 g, 0.01 mol) and IIa (2.40 g, 0.02 mol) was heated at 90°C for 3 h with stirring. After cooling, the reaction mixture was treated in the same manner as described for XIIa, mp 134—135°C as colorless needles in 93% yield. UV λ_{max}^{EtOH} nm (log ε): 250 (4.56). IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1655 (C=O). NMR (in $CDCl_3$, 60 MHz) τ: 1.70 (1H, d-d, $J_{6-5}=4.8$ Hz, $J_{6-4}=1.8$ Hz, pyridine C_6–H), 2.33—3.27 (13H, m, pyridine C_4 and C_5–H, 2 phenyl C–H, N–H) in which range one proton signal due to the N–H disappeared upon the addition of D_2O, 7.79 (3H, s, CH_3). MS *m/e*: 303 (M^+), 211 ($M^+-C_6H_5NH$), 183 ($M^+-C_6H_5NHCO$). *Anal.* Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.44; H, 5.48; N, 14.05.

Acknowledgement The authors are grateful to the staff of the Analytical Department of this Faculty for the microanalyses and spectral measurements. The authors are also grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co., Inc., for the supply of several chemicals.

References and Notes

1) Part III: T. Hisano, M. Ichikawa, T. Matsuoka, H. Hagiwara, K. Muraoka, T. Komori, K. Harano, Y. Ida, and A.T. Christensen, *Chem. Pharm. Bull.*, **27**, 2261 (1979).
2) *a*) R.A. Abramovitch, I. Shinkai, and R.V. Dahn, *J. Heterocycl. Chem.*, **13**, 171 (1976); *b*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Chem. Pharm. Bull.*, **24**, 533 (1976).
3) *a*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Heterocycles*, **2**, 163 (1974); *b*) T. Hisano, T. Matsuoka, M. Ichikawa, and M. Hamana, *Heterocycles*, **14**, 19 (1980); *c*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Org. Prep. Proced. Int.*, **6**, 243 (1974).
4) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 256; A.R. Katrizky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press Inc., London, 1971, p. 330.
5) *a*) R. Huisgen, *Proc. Chem. Soc.*, **1961**, 357; *b*) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
6) Y. Takahashi, S. Otsuka, H. Masuda, M. Hirota, Y. Ito, and Y. Hamada, *Bull. Chem. Soc. Jpn.*, **49**, 2770 (1976).
7) R.A. Abramovitch and G.M. Singer, *J. Org. Chem.*, **39**, 1975 (1974).
8) R.R. Burtner, U.S. Patent 2802008 (1957) [*C.A.*, **52**, 1280*g* (1958)].

[Chem. Pharm. Bull. 29(12)3712—3715(1981)]

Mannich Reaction of 1,4-Dihydroquinoline Derivatives

JIRO ARITOMI,* SHOZO UEDA, and HARUKI NISHIMURA

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka 564, Japan

(Received June 3, 1981)

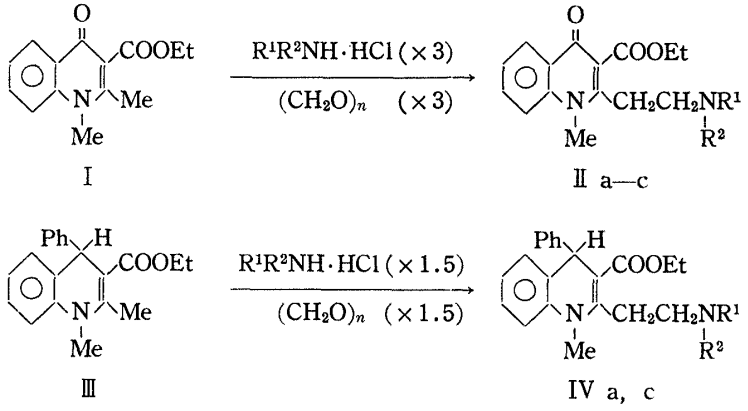
Two ethyl 1,2-dimethyl-1,4-dihydroquinoline-3-carboxylate derivatives (I, III) were subjected to the Mannich reaction to give 1-methyl-2-(2-disubstituted aminoethyl) derivatives (II, IV). They are additional examples of the Mannich reaction at the γ-carbon atom of enaminoester compounds.

Keywords——1,2-dimethyl-1,4-dihydroquinoline-3-carboxylic acid; Mannich reaction; enaminoester; γ-substitution; 1-methyl-2-(2-disubstituted aminoethyl)-1,4-dihydroquinoline-3-carboxylic acid

In the previous papers,[1] we reported the Mannich reaction of dialkyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives, and found that their 2-(and 6-)methyl carbons react easily. They are the first examples of the Mannich reaction at the γ-carbons of cyclic enaminoester compounds, so it seemed interesting to investigate the generality of γ-substitution

in the Mannich reaction with enaminoester compounds. Two ethyl 2-methyl-1,4-dihydroquinoline-3-carboxylate derivatives(I, III) were prepared and subjected to the Mannich reaction; the results of the experiments are described here.

A mixture of ethyl 1,2-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate(I), 3 molar equivalents of paraformaldehyde and diethylamine hydrochloride was boiled in dioxane for 20 h. Treatment of the basic fraction of the reaction mixture with ethanolic hydrogen chloride gave colorless prisms of the hydrochloride(IIb·HCl), mp 186—187°C.



I II a—c III IV a, c

	R^1	R^2
a:	Me	Me
b:	Et	Et
c:	Me	$PhCH_2$

Chart 1

The structure of IIb was concluded to be that of the expected Mannich reaction product on the basis of elemental analysis and the proton magnetic resonance(PMR) spectrum. That is, the PMR spectrum of IIb shows signals of protons of two new Et groups of the diethylamino group. The signal of 2-methyl protons of the starting material is lost in the spectrum of the product, and instead, signals of the two consecutive methylene protons are observed at δ 2.70—3.12 (ppm) in a typical, symmetrical A_2B_2 pattern. The spectra of the products with other amines are also similar with regard to the substituted aminoethyl groups (Table II).

Table I. Reaction Products

Product	Yield (%)	mp (°C) Recrystn.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
IIa	41	76—80 Et_2O–Hex.	$C_{17}H_{22}N_2O_3$	67.52 (67.31	7.33 7.34	9.27 8.99)	
IIb·HCl	70	186—187 EtOH	$C_{19}H_{26}N_2O_3\cdot HCl$	62.20 (62.05	7.42 7.38	7.64 7.61	9.66 9.53)
IIc	60	100—102 Tol.–Pet. Ether	$C_{23}H_{26}N_2O_3$	72.99 (72.82	6.93 7.15	7.40 7.26)	
IVa	49[b]	151—152[c] EtOH–Et_2O	$C_{23}H_{28}N_2O_2\cdot(COOH)_2$	66.06 (66.06	6.65 6.66	6.16 6.27)	
IVc	22[b]	170—173[c] EtOH–Et_2O	$C_{29}H_{32}N_2O_2\cdot(COOH)_2$	70.17 (69.99	6.46 6.64	5.28 5.32)	

a) Hex.=Hexane, Tol.=Toluene, Pet.Ether=Petroleum Ether.
b) Yield of crude oil.
c) Crystallized and analyzed as the hydrogen oxalate.

Treatment of ethyl 1,2-dimethyl-4-phenyl-1,4-dihydroquinoline-3-carboxylate(III) with the Mannich reagents afforded IV, although the yields were slightly lower than those in the case of I.

Clearly, the reactivity of the γ-carbon atoms of cyclic enaminoester compounds with the Mannich reagents is not restiricted to dihydropyridine derivatives.

Table II. PMR Spectral Data[a] for II and IV

Compd.	NR^1R^2	CH_2CH_2N	1-Me	COOEt	4-H	Ph
IIa[b]	2.32 6H, s	2.44—3.20[c] 4H, m	3.78 3H, s	1.40 3H, t 4.42 2H, q	—	8.43 1H, dd 7.16—7.73 3H, m
IIb	1.06 6H, t 2.61 4H, q	2.70—3.12[c] 4H, m	3.82 3H, s	1.40 3H, t 4.42 2H, q	—	8.40 1H, dd 7.26—7.74 3H, m
IIc	2.35 3H, s 3.55 2H, s	2.58—3.12[c] 4H, m	3.52 3H, s	1.38 3H, t 4.39 2H, q	—	8.18 1H, dd 7.16—7.72 8H, m
IVa	2.34 6H, s	2.45—2.66 2H, m 3.16—3.42 2H, m	3.44 3H, s	1.27 3H, t 4.18 2H, q	5.22 1H, s	6.90—7.32 9H, m
IVc	2.32 3H, s 3.58 2H, s	2.56—2.85 2H, m 3.20—3.50 2H, m	3.29 3H, s	1.25 3H, t 4.16 2H, q	5.20 1H, s	6.84—7.40 14H, m

a) δ (ppm), number of protons and appearance of the signal are shown.
b) 60 MHz.
c) A_2B_2 pattern.

Experimental

Melting points are uncorrected. PMR spectra were recorded with a Varian HA-100D spectrometer (100 MHz) or a Varian EM-360A spectrometer (60 MHz), in $CDCl_3$ solution using tetramethylsilane as an internal standard. Ultraviolet spectra were measured with a Shimadzu MPS-5000 spectrometer.

Ethyl 1,2-Dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (I)——Crude diethyl (1-phenylaminoethylidene)malonate[2] (70 g) was added to 350 ml of Dowtherm A[3] and the mixture was heated at 210 to 225°C for 30 min. After the reaction mixture had cooled to room temperature, hexane (1100 ml) was added to the mixture and precipitated crystals were filtered off. Recrystallization of the crystals from EtOH gave 22.1 g (38%) of ethyl 4-hydroxy-2-methyl-quinoline-3-carboxylate (V), mp 234—235°C (lit.[4] mp 229—230°C). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.58; H, 5.49; N, 5.91. UV λ_{max}^{EtOH} nm (log ε): 234 (4.28), 245 (4.26), 254 (sh), (4.10), 315 (4.05), 327 (4.00).

A mixture of 22 g of V, 27 g of methyl iodide, 26 g of K_2CO_3 and 220 ml of dimethyl formamide (DMF) was heated at 80°C with stirring for 2 h. After removal of insoluble materials by filtration, the solvent was distilled off *in vacuo*. Water was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and the solvent was distilled off to give 14.7 g of crystalline solid. Recrystallization of the solid from EtOH gave 13.0 g (56%) of I, mp 144.5—146°C. *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.37; H, 6.04; N, 5.62. PMR (60 MHz) (δ): 1.40 (3H, t, $OC\underline{H}_2C\underline{H}_3$), 2.45 (3H, s, 2-$C\underline{H}_3$), 3.67 (3H, s, $NC\underline{H}_3$), 4.40 (2H, q, $OC\underline{H}_2CH_3$), 7.13—7.80 (3H, m, Ph), 8.37 (1H, dd, Ph(5)). UV λ_{max}^{EtOH} nm (log ε): 244 (4.32), 296 (sh) (3.69), 323 (4.13), 335 (4.15).

Ethyl 1,2-Dimethyl-4-phenyl-1,4-dihydroquinoline-3-carboxylate (III)——Ethyl 2-methyl-4-phenyl-1,4-dihydroquinoline-3-carboxylate (VI) was synthesized according to the patent of Bayer A.G..[5] A mixture of 38 g of α-(2-aminophenyl)benzyl alcohol, 29.8 g of ethyl acetoacetate, 1 g of *p*-toluenesulfonic acid and 340 ml of toluene was refluxed for 2 h, with azeotropic removal of water. The mixture was washed with water and the solvent was distilled off to give an oily residue. The residue was crystallized by adding hexane. The crystals were filtered off and recrystallized from toluene–hexane to give 31.5 g (56%) of VI, mp 146—148°C. *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.97; H, 6.68; N, 4.67. PMR (60 MHz) (δ): 1.19 (3H, t, $OCH_2C\underline{H}_3$), 2.43 (3H, s, 2-$C\underline{H}_3$), 4.09 (2H, q, $OC\underline{H}_2CH_3$), 5.20 (1H, s, 4-H), 6.26 (1H, s, NH), 6.5—7.4 (9H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 230 (4.18), 334 (4.10).

To a solution of VI (35 g) in 250 ml of DMF, 6.3 g of NaH was added with stirring. After 30 min at room temperature, 20 ml of methyl iodide was added portionwise to the mixture and stirring was continued for 2 h. Insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. Water was added to the residue and the mixture was extracted with $CHCl_3$. After removal of $CHCl_3$, 6.2 g of crystals was obtained. Recrystallization of the crystals from MeOH gave 4.9 g (13%) of III, mp 126—128°C. *Anal.* Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.32; H, 7.03; N, 4.56. PMR (60 MHz) (δ): 1.23 (3H, t, $OCH_2C\underline{H}_3$), 2.58 (3H, s, 2-$C\underline{H}_3$), 3.32 (3H, s, $NC\underline{H}_3$), 4.12 (2H, q, $OC\underline{H}_2CH_3$), 5.12 (1H, s, 4-H), 6.80—7.42 (9H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 230 (sh) (4.09), 331 (4.08).

Mannich Reaction——A representative example is described below. A mixture of 1.0 g (4.1 mmol) of I, 1.34 g (12.2 mmol) of dimethylamine hydrochloride, 0.37 g (12.3 mmol) of paraformaldehyde and 30 ml of dioxane was refluxed for 20 h. After removal of the solvent by evaporation *in vacuo*, water was added to the residue and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with NaCl solution and concentrated *in vacuo*. The oily residue was converted to the HCl salt with EtOH–HCl and recrystallization of the salt from EtOH gave 1.04 g (70%) of IIb·HCl, mp 186—187°C. See Table I.

References and Notes

1) J. Aritomi, S. Ueda, and H. Nishimura, *Chem. Pharm. Bull.*, **28**, 3163 (1980); J. Aritomi and H. Nishimura, *Chem. Pharm. Bull.*, **29**, 1193 (1981).
2) B.P. Bangdiwala and C.M. Desai, *J. Indian Chem.*, **31**, 555 (1954).
3) A eutectic mixture containing 26.5% of diphenyl and 73.5% of diphenyl ether.
4) R.T. Couts and D.G. Wibberley, *J. Chem. Soc.*, **1962**, 2518.
5) Bayer A.G., German Patent 2310746 (1974) [*C.A.*, **82**, 4226*u* (1975)].

[Chem. Pharm. Bull. 29(12)3715—3720(1981)]

Studies on Ketene and Its Derivatives. CVI.[1] Photoreaction of Diketene with *N*-Phenylmaleimide and Dimethyl-*N*-phenylmaleimide

Takuo Chiba, Susumu Tsuchiya, and Tetsuzo Kato*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received June 5, 1981)

Photoreaction of diketene with *N*-phenylmaleimide (**2**) and its dimethyl derivative **3** gave *rel*-(4*R*,5*S*,6*S*)- and *rel*-(4*R*,5*R*,6*R*)-2-oxo-1-oxaspiro[3.3]heptane-5,6-dicarboximides (**4a** and **4b**) and their dimethyl derivatives **5a** and **5b**, respectively. Alcoholysis of compounds **4a** and **4b** with alcoholic hydrogen chloride gave 5-alkoxycarbonyl-4-oxo-*N*-phenyl-1,2-pentanedicarboximides **7** and **8**, which were transformed to the corresponding 5-alkoxycarbonyl-3-oxoheptanedioates **9** and **10** by further alcoholysis. Compounds **4a** and **4b** were hydrolyzed with 10% hydrochloric acid to give 3-carboxy-5-oxohexanoic acid (**11**). Thermolysis of compounds **4a** and **4b** gave 3-methylenecyclobutane-1,2-dicarboximide (**12**).

Keywords——diketene; photoreaction; *N*-phenylmaleimides; 1-oxaspiro[3.3]-heptanedicarboximides; 4-oxo-1,2-pentanedicarboximides; 3-methylenecyclobutane derivatives; decarboxylation

It is reported that radical reaction of diketene with maleic anhydride in the presence of α,α'-azobisisobutyronitrile gave rise to a maleic anhydride-diketene copolymer.[2] In a previous paper of this series,[3] we reinvestigated this reaction under irradiation and obtained different results; that is, photolysis of a solution of diketene and maleic anhydride afforded adducts, *rel*-(4*R*, 5*S*, 6*S*)- and *rel*-(4*R*, 5*R*, 6*R*)-2-oxo-1-oxaspiro[3.3]heptane-5,6-dicarboxylic anhydride (**1a** and **1b**). The present paper reports an extension of our studies to the photoreaction of diketene with *N*-phenylmaleimide (**2**) and dimethyl-*N*-phenylmaleimide (**3**) to give the