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Studies on Nitrogen-containing Heterocyclic Compounds. XL.[1] Syntheses of 2-Alkylcyclopropa[*c*]quinolines

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Addition of methanol or water to the N-cyano group in 3-cyano-1,1-dichloro-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline (**1a**) afforded the corresponding N-imino ester or N-carboxamide compounds under alkaline (sodium hydroxide) conditions. Hitherto unknown N-unsubstituted 2-alkyl (or aryl)-1a,2,3,7b-tetrahydro-1H-cyclopropa-[*c*]quinolines were obtained in excellent yields by the reaction of **1a** with Grignard reagents (RMgX: R=Me, Et, *n*-Pr, iso-Pr, *n*-Bu, $PhCH_2$, Ph, X=Cl, Br, I) in an ethereal medium. Ring expansion to produce benzazepine derivatives did not take place.

Keywords——pseudo-base; the Grignard reaction; addition; alkylation; the von Braun reaction

In the course of investigations on mono- and di-aza-naphthalenes and related heterocycles, the present authors have developed a new synthesis of cyclopropa[*c*]quinolines *via* pseudo-base.[1,3] The reactions of dihalocarbene towards 1,2-dihydroquinolines to produce tetrahydrocyclopropa[*c*]quinolines have been reported by several authors.[1,3,4]

In this report, hitherto unknown N-unsubstituted 2-alkyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinolines were synthesized in two steps from the bromocyan adducts of quinoline. Thus, the adduct was allowed to react with dihalocarbene to produce 3-cyano-1,1-dichloro-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline,[3] which was subsequently treated with Grignard reagents. However, the expected ring expansion reaction to produce benzazepine derivatives did not take place, and instead, the 2-alkyl derivatives were produced *via* nucleophilic attack of the Grignard reagents on the α-carbon atom.

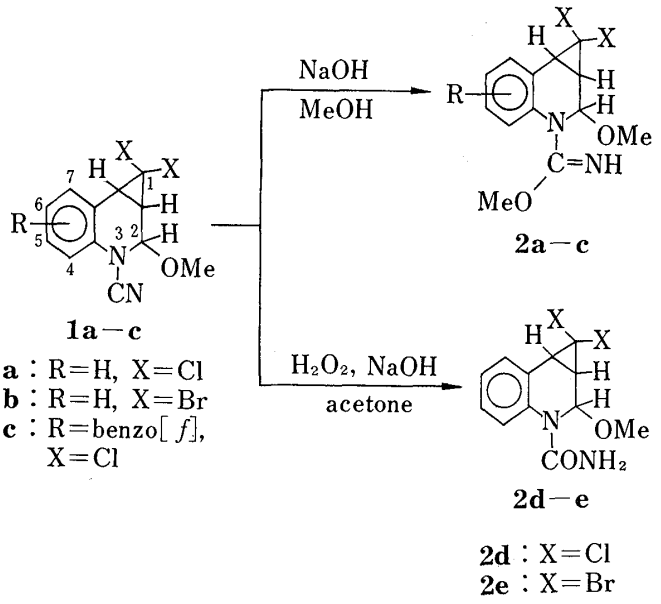

Chart 1

The ring expansion of 1,1-dihalo-1a,2,3,7b-tetrahydro-1H-cyclopropa-[*c*]quinolines usually proceeds in basic media to yield the corresponding benzazepine derivatives.[4] There fore, 3-cyano-1,1-dihalo-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa-[*c*]quinoline (**1a**) was treated with a

1) Part XXXIX: Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **99**, 493 (1979).
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3) Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **99**, 471 (1979).
4) A. Cromarty, K.E. Haque, and G.R. Proctor, *J. Chem. Soc.* (*C*), **1971**, 3536; T. Greibrokk, *Tetrahedron Lett.*, **1972**, 1663.

methanol solution of sodium hydroxide in the expectation of obtaining benzazepine derivatives. However, nucleophilic addition of methanol to the C=N bond occurred, producing the imino ester (**2a**) as a sole product. In the same manner, 3-cyano-1,1-dibromo-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline (**1b**) and 3-cyano-1,1-dichloro-2-methoxy-1a,2,3,9c-tetrahydro-1H-cyclopropa[*c*]benzo[*f*]quinoline (**1c**)[3] reacted with methanol in basic media to yield the imino esters (**2b**) and (**2c**), respectively. Again, benzazepins were not produced in measurable quantities. Similarly water reacted with **1a** and **1b**, producing the corresponding carboxamides **2d** and **2e**, respectively (see Chart 1). In these reactions, the nucleophiles selectively attacked the N-cyano bonds[5] leaving the halogen atoms on the cyclopropane rings intact. The inert nature of the halogen-carbon bonds in the cyclopropa-[*c*]quinoline derivative might be due to the increasing s-character of the carbon bonding orbital, which decreases the polarity of the carbon-halogen bonds.

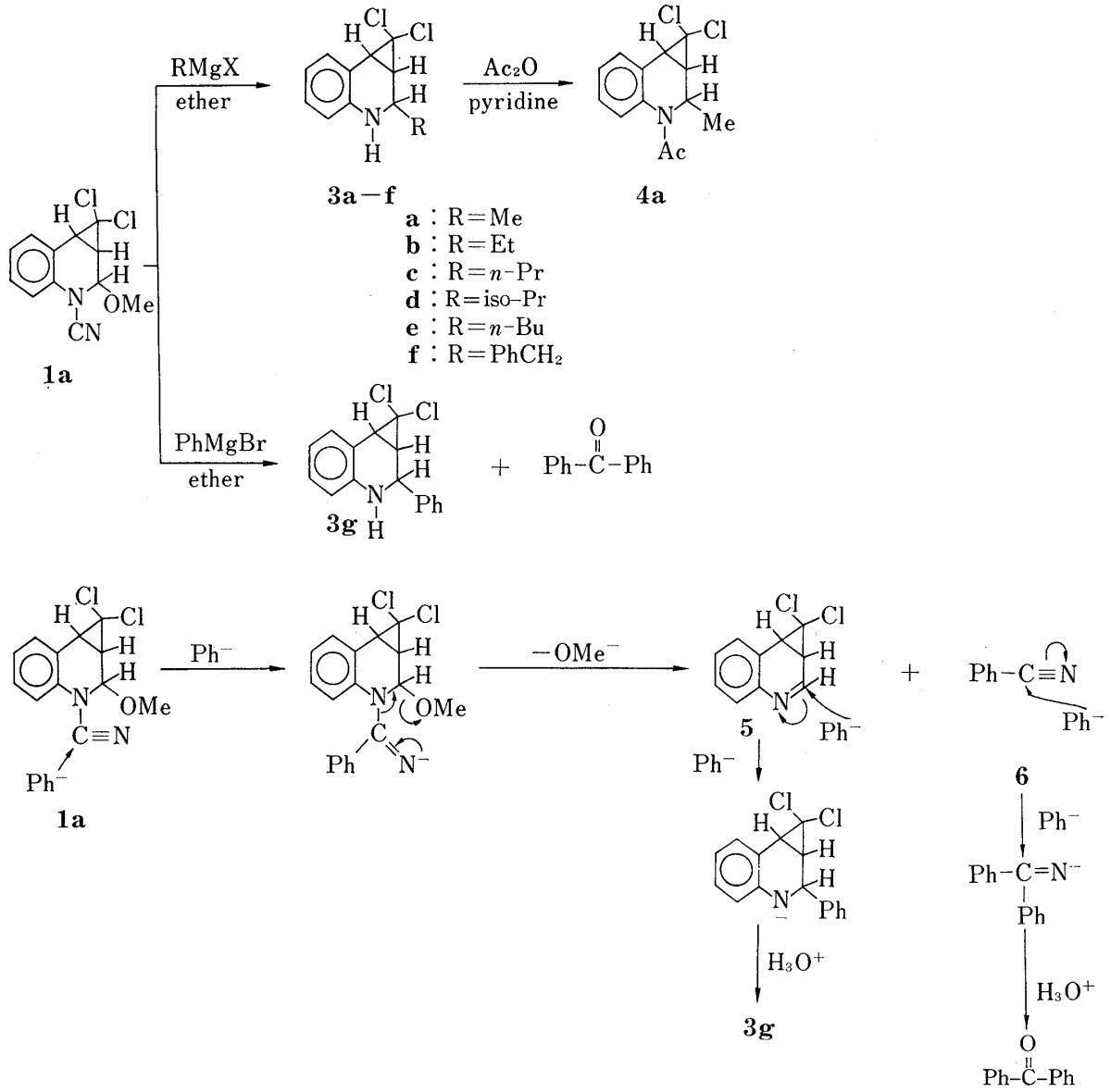


Chart 2

5) Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **98**, 1 (1978); *idem*, *ibid.*, **98**, 1081 (1978); *idem*, *Chem. Pharm. Bull.* (Tokyo), **26**, 3682 (1978); Y. Hamada, M. Sugiura, and M. Hirota, *Yakugaku Zasshi*, **98**, 1361 (1978).

Next, the reactions of **1a** with carbanions were examined. An ethereal solution of **1a** was added to a solution of methylmagnesium iodide, yielding a product, $C_{11}H_{11}Cl_2N$, in 88.5 % yield. Its IR spectrum showed an NH absorption at 3440 cm^{-1}, indicating the existence of a free secondary amine function. Together with the NMR data in Table I, these data showed the product to be 1,1-dichloro-2-methyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline (**3a**). The compound **3a** was sensitive to air and readily became colored or polymerized on standing. However, the N-acetyl derivative **4a** consisted of colorless crystals stable in air. On the other hand, methylation using methyllithium as a nucleophile proceeded in only fair yield (33%), and a side reaction yielding an undesired polymerized product was predominant. Reaction of **1a** with an excess of phenylmagnesium bromide similarly gave 1,1-dichloro-2-phenyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline (**3g**) in 90% yield. In the course of this reaction, benzophenone was formed in 78% yield as a by-product. Introduction of a 2-alkyl (or aryl) group together with the formation of the ketone can be explained by assuming the mechanism illustrated in Chart 2. The first step of this reaction may be the nucleophilic attack of organomagnesium halide on the carbon atom of the N-cyano group, which induces elimination of the nitrile (**6**) and methoxide anion, yielding the 1,2-dehydro product (imine **5**). Both the nitrile and the imine then react normally with the organomagnesium halide to form the final products (**3g** and benzophenone) after hydrolysis. Alternatively, the reaction in the second step may proceed concertedly or in an S_N2 fashion, without producing the intermediate imine (**5**). In any case, 3 mol of the organomagnesium halide was consumed to produce 1 mol of **3g**. The procedure was extended to a variety of alkylmagnesium halides, and various alkyl groups were introduced on the carbon atom adjacent to the endcyclic nitrogen atom of the tetrahydro-1H-cyclopropa[*c*]quinoline derivative (**1a**). Thus, the action of alkylmagnesium halides (RMgX: where R=Et, *n*-Pr, iso-Pr, *n*-Bu and $PhCH_2$; X=Cl, Br, or I) on **1a** in an ethereal medium gave **3b**—**f**, respectively, in excellent yields as listed in Table I. These products were identified by spectroscopic and chemical methods.

In conclusion, The reaction offers a general method to synthesize 2-alkyl(or aryl)-1,1-dichloro-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinolines from quinoline other readily accessible starting materials.

Experimental

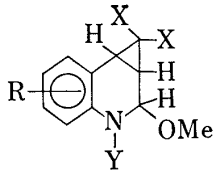
Gas chromatography was carried out with a JGC 20KFP machine, using an FID detector (Japan Electron Optics Lab., Tokyo), with a stainless steel column of 3 mm × 1 m; liquid phase, 10% SE-30, 10% OV-17; stationary phase, Chromosorb W-AW-DMCS, 60—80 mesh; carrier gas, N_2 at 50 ml/min. Nuclear magnetic resonance (NMR) spectra were taken with a JEOL PS-100 machine (Japan Electron Optics Lab., Tokyo), using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were taken with a Hitachi M-52 spectrometer, and infrared spectra (IR) with a JASCO IRA-I spectrometer (Japan Optics).

1,1-Dichloro (or Dibromo)-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline-3-carboxylic Acid Imino Methyl Ester (2a, b) and 1,1-Dichloro-2-methoxy-1a,2,3,9c-tetrahydro-1H-cyclopropa[*c*]benzo[*f*]-quinoline-3-carboxylic Acid Imino Methyl Ester (2c)——NaOH (20% aqueous solution, 4 ml) was added dropwise to a methanolic solution (0.01 mol in 30 ml) of **1a**, **1b** or **1c** with stirring and the mixture was kept at room temperature for 3 hr. The whole was poured into water, extracted with CH_2Cl_2, and the organic layer was dried over anhyd. $MgSO_4$. The solvent was distilled off, and **2a**, **2b** or **2c** was obtained as a residual solid. The yields and physical properties of these products are given in Table I.

1,1-Dichloro (or Dibromo)-2-methoxy-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline-3-carboxylic Acid Amide (2d, e)——H_2O_2 (10%, 20 ml) was added dropwise to a methanolic solution of **1a** or **1b** (0.01 mol in 30 ml) and 10% aqueous NaOH solution (1 ml), with cooling in an ice bath. After standing for 1 hr at room temperature, the reaction mixture was treated as described for **2a**, and **2d** or **2e** was obtained. The yields and physical properties of these products are given in Table I.

2-Alkyl (or Aryl)-1,1-dichloro-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinolines (3a—g)——A typical example of the experimental procedure used to obtain **3** is as follows. Under a nitrogen atmosphere, an ethereal solution of **1a** or **1b** (0.005 mol in 50 ml) was added gradually to a stirred phenylmagnesium bromide solution prepared *in situ* from magnesium (0.02 g atom) and bromobenzene (0.021 mol) in ether (50 ml),

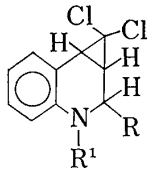
TABLE I. Yields and Physical Properties of Products of the Reaction with MeOH or H_2O



Starting material Compd. No.	Compd. No.	R	X	Y	Yield (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} NH, NH_2	IR C=N–	IR –CO–N<	IR –O–	NMR[a] (10% solution in $CDCl_3$) δ C_2–H (d)	C_{1a}–H (d–d)	C_{7b}–H (d)	NH, NH_2 (b–s)	O–CH_3 (s)	Formula	*Anal.* (%) Calcd. (Found) C	H	N
										$J_{1a,2}$=2 Hz,		$J_{1a,7}$ =10 Hz						
1a	**2a**	H	Cl	–C(=NH)–OMe	93.0	3340	1640	1060		5.72	2.70	2.90	5.72	3.28 3.80	$C_{13}H_{14}Cl_2N_2O_2$[b]	51.82 (51.77	4.68 4.41	9.30 9.09)
1b	**2b**	H	Br	–C(=NH)–OMe	90.5	3340	1640	1070		5.76	2.80	3.02	5.06	3.28 3.80	$C_{13}H_{14}Br_2N_2O_2$	40.03 (39.87	3.62 3.41	7.18 6.91)
1c	**2c**	Benzo[*f*]	Cl	–C(=NH)–OMe	91.9	3340	1630	1070		5.80	2.86	3.54[c]	5.84	3.36 3.84	$C_{17}H_{16}Cl_2N_2O_2$	58.12 (58.21	4.59 4.73	7.97 8.11)
1a	**2d**	H	Cl	$-CONH_2$	86.4	3430 3530	1670	1070		6.00	2.66	2.90	5.38	3.26	$C_{12}H_{12}Cl_2N_2O_2$	50.18 (49.92	4.21 4.41	9.75 9.57)
1b	**2e**[d]	H	Br	$-CONH_2$	85.1	3430 3530	1670	1070		6.14	2.84	3.06	5.22	3.44	$C_{12}H_{12}Br_2N_2O_2$	38.33 (38.22	3.22 3.09	7.45 7.51)

a) s: singlet; d: doublet; d-d: doublet of doublets; b-s: broad singlet.
b) MS: *m/e* 300 (M^+).
c) C_{9c}–H: $J_{1a,9c}$=10 Hz.
d) mp 200—202° (dec.).

TABLE II. Yields and Physical Properties of 2-Alkyl(or Aryl)-1,1-dichloro-1a,2,3,7b-tetrahydro-1H-cyclopa[*c*]quinoline Derivatives (**3a—g**, **4a**, **g**)



Starting material Compd. No.	Reagents and reaction time (hr)	Products: Compd. No.	R	R¹	Yield (%)	mp (°C) bp (°C) (mmHg)	IR $\nu_{max}^{CHCl_3}$ cm⁻¹ >NH	IR $\nu_{max}^{CHCl_3}$ cm⁻¹ –CO–N<	NMR[a] (10% solution in $CDCl_3$) δ C_2–H (m)	C_{1a}–H (d-d)	C_{7b}–H (d)	NH (b-s) $J_{1a,2}$=2 Hz, $J_{1a,7}$=10 Hz	Formula	*Anal.* (%) Calcd. (Found) C	H	N
1a	MeMgI; 6	**3a**	Me	H	88.5	135—140 (0.05)	3440	—	3.70	1.94	2.68	3.48	$C_{11}H_{11}Cl_2N$[b]	57.89 (57.67	4.86 4.59	6.14 5.99)
1a	MeLi; 1	**3a**[c]	Me	H	33.0											
1a	EtMgI; 6	**3b**	Et	H	86.7	138—140 (0.03)	3450	—	3.40	1.90	2.62	3.62	$C_{12}H_{13}Cl_2N$	59.50 (59.71	5.41 5.39	5.78 5.42)
1a	*n*-PrMgBr; 9	**3c**	*n*-Pr	H	87.0	145—148 (0.03)	3440	—	3.50	1.96	2.65	3.50	$C_{13}H_{15}Cl_2N$	60.93 (61.02	5.90 5.80	5.47 5.33)
1a	iso-PrMgBr; 20	**3d**	iso-Pr	H	84.8	143—145 (0.03)	3450	—	3.42	1.98	2.70	3.64	$C_{13}H_{15}Cl_2N$	60.93 (60.99	5.90 5.72	5.47 5.36)
1a	*n*-BuMgBr; 10	**3e**	*n*-Bu	H	90.0	155—160 (0.04)	3460	—	3.46	1.92	2.62	3.46	$C_{14}H_{17}Cl_2N$	62.21 (62.01	6.34 6.48	5.18 5.41)
1a	$PhCH_2MgCl$; 3	**3f**	$PhCH_2$	H	90.5	168—170 (0.01)	3440	—	3.70	2.06	2.66	3.52	$C_{18}H_{17}Cl_2N$	67.91 (68.12	5.38 5.52	4.40 4.62)
1a	PhMgBr; 6	**3g**	Ph	H	90.0	165—170 (0.01)	3440	—	4.56[d]	2.14	2.70	3.64	$C_{17}H_{15}Cl_2N$	67.10 (67.24	4.97 5.12	4.60 4.37)
		Benzophenone[c]			78.0											
3a	Ac_2O, ryridine	**4a**	Me	Ac	89.0	150—152	—	1630	5.40	2.30	2.84	—[e]	$C_{13}H_{13}Cl_2NO$	57.78 (57.59	4.85 4.83	5.18 5.01)
3g	Ac_2O, ryridine	**4g**	Ph	Ac	92.4	179—181	—	1650	6.44	2.76	3.08	—[f]	$C_{19}H_{17}Cl_2NO$	65.89 (66.13	4.95 5.12	4.04 3.96)
1b	MeMgI; 3	—[g]														

a) b-s: broad singlet; d: doublet; d-d: doublet of doublets; m: multiplet. *b*) MS: *m/e* 227 (M^+). *c*) Identified from IR spectra. *d*) Doublet.
e) CH_3–CO–: 2.10 (s). *f*) CH_3–CO–: 2.14 (s). *g*) Polymelized.

and the reaction mixture was kept at room temperature until no peak of the starting material could be seen on GLC. The mixture was then hydrolyzed with ice-cold sat. NH_4Cl, and the organic layer was separated and dried over anhyd. $MgSO_4$. After removal of the solvent, the residue was fractionated under reduced pressure. Compound **3g** was obtained as a viscous oil. bp 165—170° (0.01 mmHg). From the lower-boiling-point fraction, benzophenone was obtained in 78% yield with respect to **1a**. The reaction is quite general, producing the hitherto unknown N-unsubstituted tetrahydro-1H-cyclopropa[*c*]quinolines in excellent yields. Some of their physical properties are listed in Table II.

3-Acetyl-1,1-dichloro-2-methyl (or phenyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[*c*]quinoline (4a, g)——A mixture consisting of **3a** (or **3g**) (0.005 mol), pyridine (5 ml), acetic anhydride (5 ml), and benzene (10 ml) was heated under reflux for 15 hr. When the reaction was completed, the solution was concentrated, and the deposited crystals were recrystallized from benzene–*n*-hexane (1: 1, v/v). The yields and physical properties are listed in Table II.

Acknowledgement We are grateful to the staff of the Analysis Center of this University for elemental analyses.