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Studies on Reactions of Isoprenoids. XI.1) Stereochemistry of the Ritter Reaction Products of Camphene with Unsaturated Nitriles

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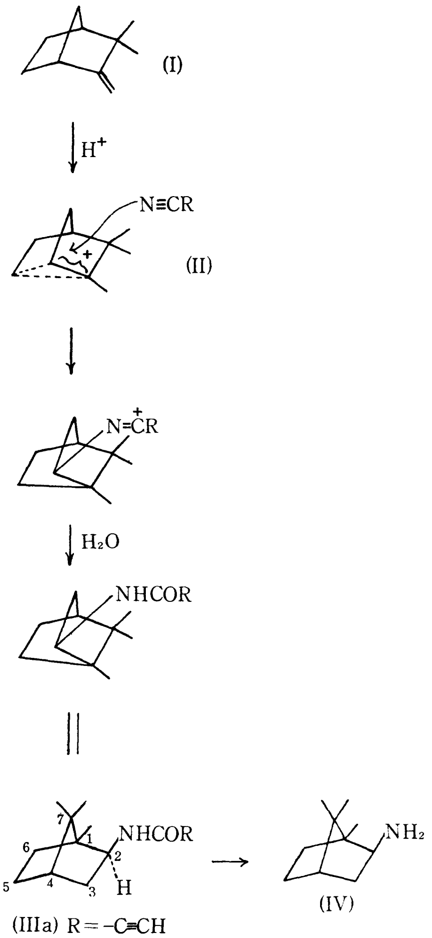
The Ritter reactions of camphene (I) with various nitriles except unsaturated nitriles have been studied mainly from the interest in the pharmacological activities of the products.2) We have recently reported the Ritter reactions of I with cyanoacetylene and chlorocyanoacetylene as the first examples of the Ritter reactions with acetylenic nitriles.3) However, the stereochemistry of the corresponding products was not described in detail. This note describes the structural elucidation of the Ritter reaction products of I with cyanoacetylene and chlorocyanoacetylene as well as that with acrylonitrile on the basis of their analytical, IR and NMR data in comparison with the NMR data of *N*-acetylisobornylamine (IIId),2a) and of their hydrolysis produdts.

The Ritter reactions were carried out with the ratio, I : nitrile : sulfuric acid = 1 : 2 : 4. The yields of IIIa from I and cyanoacetylene, and IIIb from I and chlorocyanoacetylene were both improved to 41 and 61% as compared with the previous values 15 and 40%. The Ritter reaction of I with acrylonitrile proceeded similarly to afford an unsaturated amide (IIIc) in 49% yield. The yields, mps and analyses of these products are summarized in Table 1.



(IIIa) $R=-C\equiv CH$
(IIIb) $R=-C\equiv CCl$
(IIIc) $R=-CH=CH_2$

In the NMR spectra (Table 2) of these products (IIIa—c), a common characteristic double triplet signal for one proton appeared in the range τ 6.00—6.08. A similar pattern signal was also observed at τ 6.07 in the spectrum of IIId,2a) suggesting that IIIa—c have the same configuration as IIId at C-2 position. Thus, the structures of IIIa—c were assigned as *N*-propioloylisobornylamine, *N*-chloropropioloylisobornylamine, and *N*-acryloylisobornylamine respectively. These assignments were supported by hydrolyses of IIIa—c to afford the same isobornylamine (IV) in the yields

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1) Part X of this series: T. Sasaki and S. Eguchi, This Bulletin, **42**, 2736 (1969).

2) a) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948); b) F. R. Benson and J. J. Ritter, *ibid.*, **71**, 4128 (1949); c) J. J. Ritter, U.S. 2573673 (1951); *Chem. Abstr.*, **46**, 9584h (1952); d) N. K. Kochetkov, A. Ya. Khorlin and K. I. Lopatina, *J. Gen. Chem. USSR* (*Eng. Transl.*), **29**, 77 (1959); *Chem. Abstr.*, **53**, 22058i (1959); e) C. A. Stone, M. L. Torchiana, K. L. Meckelburg, J. Stavorski, M. Sletzinger, G. A. Stein, W. V. Ruyle, D. F. Reinhold, W. A. Gaines, H. Arnold and K. Pfister, III, *J. Med. Pharm. Chem.*, **5**, 665 (1962); *Chem. Abstr.*, **57**, 12341c (1962); f) P. L. de Bennevile, U.S. 2632766 (1953); *Chem. Abstr.*, **47**, 6686c (1953).

3) T. Sasaki, S. Eguchi and K. Shoji, *J. Chem. Soc.*, *C*, **1969**, 406.

TABLE 1. THE RITTER REACTIONS OF CAMPHENE (I) WITH UNSATURATED NITRILES[a]

Nitrile	Product (Yield, %)	Mp (°C)	Analysis (%) Found C	H	N	Calcd[d] C	H	N
NC-C≡CH	IIIa (41)	142—143[b]						
NC-C≡CCl	IIIb (61)	131—132[c]	64.80	7.76	5.69	65.05	7.56	5.84
NC-CH=CH$_2$	IIIc[e] (49)	135—136	74.91	10.04	6.83	75.31	10.21	6.76

a) All reactions were carried out using 0.01 mol of I, 0.02 mol of nitrile, and 0.04 mol of concentrated sulfuric acid in 30 m*l* of acetic acid at *ca.* 30°C for 20 hr.

b) Lit,[3] mp 141°C.

c) Previous value, mp 106°C.[3] The compound seems still somewhat impure though its IR spectrum was superimposable on that of IIIb.

d) (IIIb): $C_{13}H_{18}NOCl$. (IIIc): $C_{13}H_{21}NO$.

e) The IR spectrum (KBr) had absorption bands at 3310, 1650, 1615, 1520, 960 and 903 cm^{-1}.

TABLE 2. NMR DATA OF IIIa—d (CDCl$_3$, 60 MHz)

	IIIa τ	IIIb τ	IIIc τ	IIId τ
NH	4.10 (1H, broad s)	4.10 (1H, broad s)	4.15—4.55* (*ca.* 1H, broad s)	4.50 (1H, broad s)
C-2-*endo*-H	6.05 (1H, double t, J=5.5 and 9.0 Hz)	6.08 (1H, double t, J=5.5 and 9.0 Hz)	6.00 (1H, double t, J=5.5 and 9.0 Hz)	6.07 (1H, double t, J=5.5 and 9.0 Hz)
Isobornyl ring protons	7.88—8.95 (7H, m)	7.90—9.00 (7H, m)	7.80—8.92 (7H, m)	7.70—9.01 (7H, m)
Methyl protons	9.08, 9.13, 9.17 (9H, each s)	9.08, 9.13, 9.16 (9H, each s)	9.06, 9.17 (9H, each s)	9.08, 9.15 (9H, each s)
Other protons	7.21 (-C≡CH) (1H, s)		3.70—4.53(CH=CH$_2$) (*ca.* 3H, ABX type m)	8.03 (COCH$_3$) (3H, s)

* This signal was overlapped with the signals of vinyl protons.

46, 10,[4] and 50%, respectively. This was identified as a phenylurea derivative with an authentic specimen[5] by means of mixed melting point determination and IR spectral comparison.

From the results it was concluded that the Ritter reactions of I with unsaturated nitriles at *ca.* 30°C afford the corresponding unsaturated amide derivatives after the Wagner-Meerwein rearrangement of I as observed in these reactions with certain saturated nitriles, though this type of rearrangement is known to be dependent on the reaction temperature as well as on nitriles (Scheme 1).[2d]

Experimental[6]

General Procedure for the Ritter Reactions. A mixture of 0.01 mol of I and 0.02 mol of nitrile was added to an ice-cooled mixture of 0.04 mol of concentrated sulfuric acid (sp. gr., *ca.* 1.84) and 30 m*l* of glacial acetic acid with stirring. Stirring was continued for 20 hr at room temperature (*ca.* 30°C) and the mixture was poured onto ice-water (200 g). The product was taken in chloroform and recrystallized from *n*-hexane or *n*-hexane-dichloromethane to give the corresponding amide derivatives (see Table 1).

General Procedure for the Hydrolyses of IIIa—c. *Ca.* 0.2 g of IIIa (or IIIb, and or IIIc) was heated in a mixture of 10 m*l* of ethanol and 20 m*l* of 6N hydrochloric acid under refluxing for 2 days.[4] After removal of ethanol under reduced pressure, the reaction mixture was washed with ether (30 m*l*×3). The water layer was made alkaline with 10% aqueous solution of sodium hydroxide and extracted several times with ether (30 m*l*×5). The combined ether extracts were dried over

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[4] IIIb was very stable to acidic hydrolysis; only 10% conversion to IV was observed together with an 80% recovery of IIIb after refluxing for 10 days under the conditions given in Experimental.

[5] L. S. Luskin, A. J. McFaul and G. E. Geutest, *J. Org. Chem.*, **21**, 1430 (1956).

[6] All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Yanagimoto C. H. N. Corder Model MT-1. The IR spectra were recorded on a JASCO Model IR-S IR spectrophotometer and NMR spectra were obtained with a Varian A-60 spectrometer at 60 MHz using TMS as an internal reference.

sodium sulfate and the solvent was removed under reeduced pressure to give clorless solids of IV which were directly treated with phenyl isocyanate in dry benzene (10 m*l*) to afford a phenylurea derivative of IV, mp 255.5—258°C (dec.) (from aqueous ethanol, lit,5) mp 252—255°C (dec.)).