β-Thujone (II); $[\alpha]_D^{26.5}$ +68.0 (±2°) (c=1.000, $CHCl_3$); ORD (c=0.636, CH_3OH), $[\phi]_{311}^{peak}$ +1152, $[\phi]_{272}^{trough}$ −431, a=+16; UV: $\lambda_{max}^{heptane}$ 274 mμ (ε 20.5).

The author is very grateful to Dr. K. Takeda, Director of this laboratory, and Dr. H. Minato for their advice and to Dr. T. Nakagawa for his interest on this work. He wishes to thank Dr. S. Sumimoto and coworkers for the gas chromatographic separation of the samples used and also Dr. K. Kuriyama and Mr. M. Yamakawa for their kind measurements of the ORD and UV spectra and helpful discussion.

Summary

Full interpretation of the proton magnetic resonance spectra of α- and β-thujones by using the solvent effect revealed that they take a boat-like envelope conformation. This conclusion was also supported by ultraviolet spectroscopy.

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197. Issei Iwai, Tadahiro Iwashige, Yasuo Yura, Norio Nakamura,*1 and Kiyoshi Shinozaki*2 : Studies on Acetylenic Compounds. XXXIX.*3 The Addition Reaction of Cyanogen Bromide to Acetylenic Compounds.

(*Research Laboratories, Sankyo Co., Ltd.*1 and Technical Research Laboratory, Nihon Nyukazai Co., Ltd.*2*)

Addition of cyanogen halide to a double bond has been studied by Cowen and Dixon.[1] They carried out the reaction in the solution of carbon disulfide to obtain β-halonitriles using mixture of aluminum chloride and nitromethane as a catalyst. However, only one paper on the addition of cyanogen halide to a triple bond has been published : Dutcher obtained 3-chloroacrylonitrile by the reaction of cyanogen chloride with acetylene in the presence of cuprous ammonium chloride in the acidic aqueous medium.[2]

It has been known that a triple bond is more active than a double bond as concerns addition reaction of nucleophilic reagents. The difference between these unsaturated bonds is considerably great, especially in the addition reaction. On the other hand, it has been reported that acid chlorides easily adds to a triple bond in the presence of aluminum chloride.[3] Then, cyanogen halide would be expected to add to a triple bond in the similar way.

In this paper authors wish to report the addition reaction of cyanogen bromide to a triple bond activated by an adjacent phenyl group. Phenylacetylene reacted with a mixture of cyanogen bromide and aluminum bromide in tetrachloroethane or in carbon

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*1 Nishishinagawa, Shinagawa-ku, Tokyo (岩井一成, 岩重忠博, 由良靖雄, 中村紀雄).
*2 Kawasaki-shi, Kanagawa-ken (篠崎 清).
*3 Part XXXVIII : This Bulletin, **12**, 1094 (1964).

1) F. M. Cowen, J. K. Dixon : Brit. Pat., 686,692 (C. A., **48**, 8251 (1953)).
2) H. A. Dutcher : U. S. Pat., 2,419,488 (C. A., **41**, 5145f (1947)).
Recently, it was reported that only *cis*-3-chloroacrylonitrile was obtained by this method. F. Scotti, E. J. Frazza : J. Org. Chem., **29**, 1800 (1964).
3) M. Julia : Ann. chim. (Paris), **5**, 595 (1950); *Idem* : Bull. soc. chim. France, **18**, c 13 (1951); C. C. Price, J. A. Pappalardo : J. Am. Chem. Soc., **72**, 2613 (1950); J. W. Kroeger, F. J. Sowa, J. A. Nieuwland : J. Org. Chem., **1**, 163 (1936).

disulfide to afford a nitrile compound (I) of m.p. 41～42° and b.p_2 115～117°, whose infrared spectrum showed absorption at 2222 cm^{-1} due to the nitrile group. Treatment of the nitrile (I) with aqueous ammonia gave an amino compound, which was identical to β-aminocinnamonitrile (II) prepared from benzonitrile and acetonitrile.[4] Hydrolysis of I with 98% sulfuric acid gave a corresponding acid amide (III) which showed no depression of melting point on admixture with an authentic sample of *trans*-β-bromocinnamamide prepared by Auwers' method.[5] From these results I was confirmed to be *trans*-β-bromocinnamonitrile.

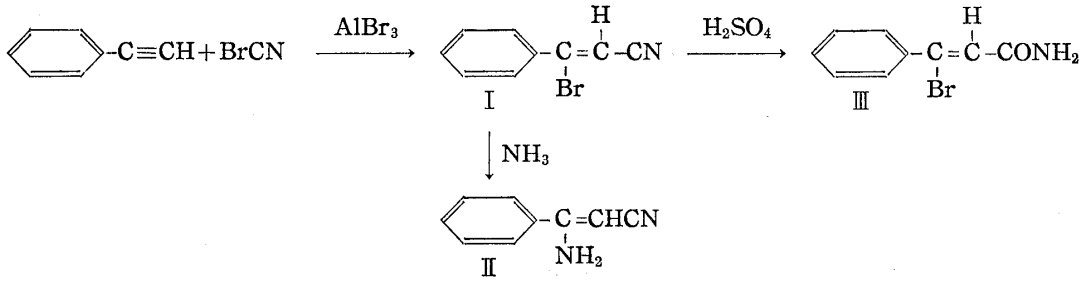
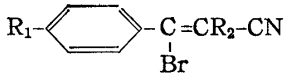


Chart 1.

Other substituted phenylacetylene compounds such as *p*-bromo- and *p*-methoxyphenylacetylene, tolane and methylphenylacetylene similarly reacted with cyanogen bromide to give corresponding cinnamonitrile derivatives (Table I). *p*-Nitrophenylacetylene,

Table I. α-Bromocinnamonitrile Derivatives



No.	R_1	R_2	b.p. °C/mm. Hg	m.p. (°C)	UV λ_{max}^{EtOH} mμ (log ε)	Yield (%)
I	H	H	115～117/2[5]	41～42	274 (4.27)	34.9
IV	Br	〃	——	76～77	282 (4.32)	5.3
V	CH_3O	〃	——	78～79	228 (4.47) 305 (4.75)	3.7
VI	H	C_6H_5	——	85～86.5	224 (3.84) 294 (3.70)	8.3
VII	〃	CH_3	101～103/0.3	42～43	261 (4.22)	33.1

however, did not react with cyanogen bromide and the starting material was recovered under the same reaction conditions. In the case of *p*-bromo and *p*-methoxyphenylacetylene, small amount of nitrogen-free compounds of m.p. 253～256° and of m.p. 128～148° were obtained, respectively. The former was considered to be a trimerized product of *p*-bromophenylacetylene from the results of its elemental analysis and molecular weight determination. These compounds, however, were not further investigated.

α-Methyl-β-bromocinnamonitrile (VII) is somewhat different from I in their chemical behavior. The compound (VII) did not react with aqueous ammonia or even with sodium amide, but reacted with guanidine to give a cyclized product, 5-methyl-6-phenyl-2,4-diaminopyrimidine of m.p. 196～197°.[6] (The similar type of cyclization reaction will be reported in another paper.). Hydrolysis of VII with 70% sulfuric acid gave the corresponding acid amide (IX), which was further hydrolized to the carboxylic acid (X) (m.p.

4) Holzwart: J. Prakt. Chem., (2) **39**, 242 (1889).
5) K. v. Auwers, E. Wolter: Ann., **492**, 283 (1932). The nitrile was described as oil.
6) G. H. Hittings, P. B. Russel, F. A. Falco: U. S. Pat., 2,688,019 (C. A., **50**, 1931i (1956)).

129~130°) by treatment with conc. hydrochloric acid under drastic condition. The carboxylic acid (X), however, showed depression in m.p. (96~108°) on admixture with α-methyl-β-bromocinnamic acid (XI) (m.p. 128~129°) prepared by Körner's method.[7] Furthermore, ultraviolet absorption spectrum of X showed the maximum at 255 mμ (log ε 3.74), while that of XI exhibited the maximum at 261 mμ (log ε 3.73). The methyl

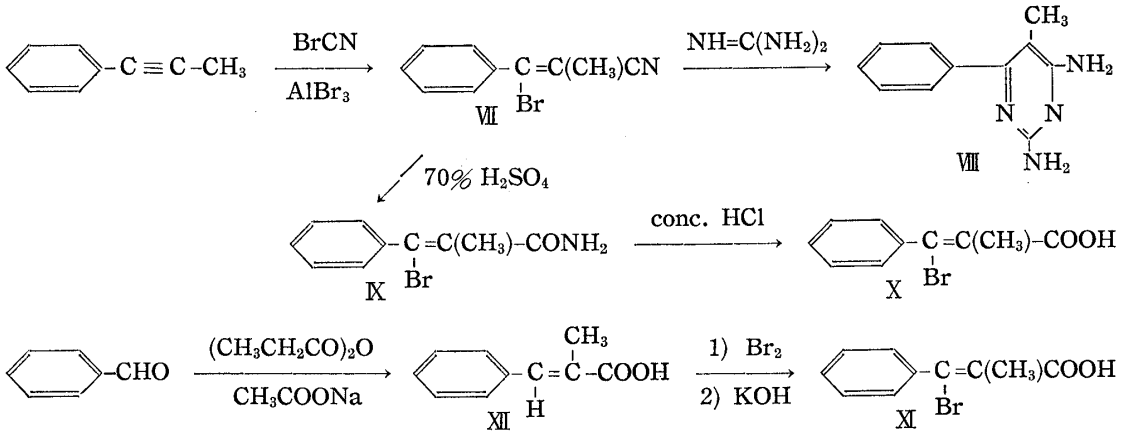


Chart 2.

group of α-methylcinnamic acid (XII), which is prepared from benzaldehyde and propionic anhydride by Perkin reaction, is *trans* to the olefinic hydrogen.[8] Bromination of XII should give the *erythro* dibrom compound (XIII), and dehydrobromination of XIII with alkali should yield *cis*-α-methyl-β-bromocinnamic acid (XI) by *trans*-elimination.[9,10] (See Chart III.)

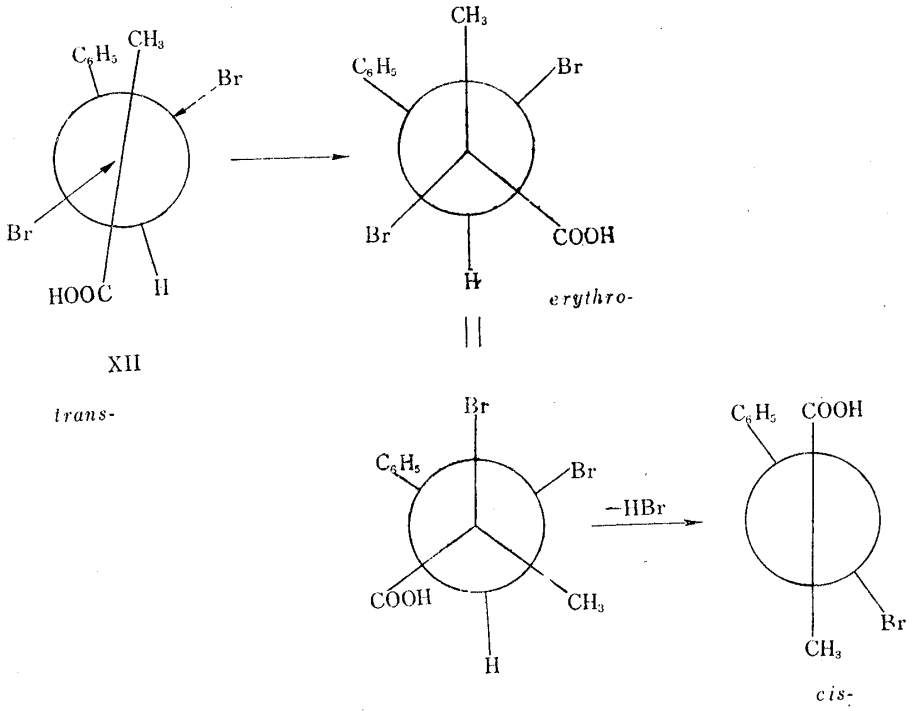
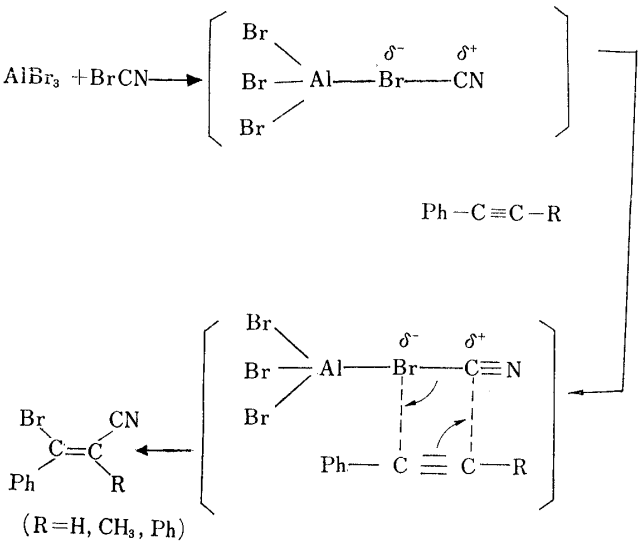


Chart 3.

7) A. Körner : Ber., **21**, 276 (1898).
8) R. Stoermer, P. Voht : Ann., **409**, 276(1898).
9) A. J. Speziale, C. C. Tung : J. Org. Chem., **28**, 1353 (1963).
10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," 523 (1959); Henly Holt and Co., New York.

Consequently, X is considered to be *trans*-α-methyl-β-bromocinnamic acid, and accordingly, Ⅶ must be *trans*-α-methyl-β-bromocinnamonitrile. Moreover, the fact that ultraviolet spectrum of X showed the absorption maximum at lower frequency than that of Ⅺ is also agreed with the results obtained from *cis*- and *trans*-β-bromocinnamic acid.[11]

These results provide the proof for the fact that *cis*-addition has occurred on the addition of cyanogen bromide to a triple bond. The reaction mechanism for the *cis*-addition could be elucidated as follows : In the transition state, the bromine-carbon bond of cyanogen bromide would be polarized as $Br\overset{\delta^-}{—}CN\overset{\delta^+}{}$ by aluminum bromide. On the other hand, the triple bond of phenylacetylene derivatives would be polarized as $Ph\text{-}C\overset{\delta^+}{\equiv}C\text{-}R\overset{\delta^-}{}$ because of the inductive effect of phenyl group. Therefore, the cyano group should be located away from the phenyl group, so that the illustrated four-centered transition state would be formed. Similar transition states have been used to explain base-catalysed addition of trichlorosilanes to olefins and acetylenes,[12] disproportionation reactions of hydrogen containing halogenosilanes[13] and the reaction of tetramethylsilane with methyl bromide in the presence of aluminum bromide.[14]



Experimental*4

***trans*-β-Bromocinnamonitrile (I)**——Aluminum bromide (25.2 g.) was dissolved in tetrachloroethane (150 ml.) and warmed to 40° on a water bath. To this mixture was added cyanogen bromide (15.0 g.) in tetrachloroethane (50 ml.) over 2 hr. at 40~45°. Colorless precipitate was formed. After additional 30 min. stirring, phenylacetylene (8.2 g.) in tetrachloroethane (50 ml.) was added dropwise over 2 hr. Stirring was continued for 2 hr., and the reaction mixture was poured into about 300 ml. of 10% HCl solution. The organic layer was washed two times with aq. Na_2CO_3, several times with H_2O, and dried over $CaCl_2$. After evaporation of tetrachloroethane under reduced pressure, the residue was distilled. The distillate which passed over 98° at 2 mm. was redistilled to afford *trans*-β-bromocinnamonitrile (I), $b.p_2$ 115~117°, (reported $b.p_{12}$ 161~163°),[5] which crystallised on cooling. Recrystallization from EtOH gave white needles, m.p. 41~42°. Yield, 5.3 g. (34.9%). When carbon disulfide was used as the solvent, the yield was 7.3%. UV : λ_{max} 274 mμ (log ε 4.28). IR : ν_{max} 2222 cm^{-1} (-CN) (Film). *Anal.* Calcd. for C_9H_6NBr : C, 51.93; H, 2.90; N, 6.78; Br. 38.40. Found : C, 51.93; H, 2.90; N, 6.78; Br, 38.72.

β-Aminocinnamonitrile (II)——To a solution of I (20.6 g.) in 50 ml. fo EtOH, was added 20 ml. of NH_4OH under stirring. After 24 hr. standing, EtOH was evaporated and the residue was extracted with Et_2O. The ethereal layer was washed with H_2O and dried over Na_2SO_4 and Et_2O was evaporated. The residue was recrystallized to white needles of β-aminocinnamonitrile, (II) m.p. 86~87°, which showed no depression on admixture with an authentic sample of m.p. 87~88°, prepared from benzonitrile and acetonitrile according to Holzwart's method.[4] Yield, 6.5 g. IR and UV spectra of II was identical with those of the authentic sample. UV : λ_{max} 290 mμ (log ε 4.06). IR ν_{max} cm^{-1} : 3230, 3350, 3450

*4 All melting points are uncorrected. UV spectra were taken in EtOH.

11) A. Mangini, F. Montanari : Gazz. chim. ital., 88, 1081 (1958).
12) R. A. Pike : J. Org. Chem., 27, 2186 (1962).
13) G. A. Russel : J. Am. Chem. Soc., 81, 4815, 4825 (1959).
14) *Idem* : *Ibid.*, 81, 4831 (1959).

($-NH_2$), 2180 (-CN) (Nujol). *Anal.* Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found : C, 74.90; H, 5.62; N, 19.34.

***trans*-β-Bromocinnamamide (III)**——A mixture of *trans*-β-cinnamonitrile (I) (1.14 g.) and conc. H_2SO_4 (1.50 g.) was stirred at 70~80° for 4 hr. After cooling, the mixture was diluted with ice-water and extracted with Et_2O. The ethereal layer was washed with aq. Na_2CO_3 and H_2O, and dried over Na_2SO_4. After evaporation of Et_2O, the residue was recrystallized from benzene to white needles of *trans*-β-bromocinnamamide (III), m.p. 109~110°, showing no depression on admixture with the authentic sample of m.p. 109~110°, prepared from β-bromocinnamoyl chloride and NH_4OH according to von Auwers' method.[5] Yield, 0.51 g. UV and IR spectra of III and those of authentic sample were superimposable. UV : λ_{max} 262 mμ (log ε 4.13). *Anal.* Calcd. for C_9H_8ONBr : C, 47.81; H, 3.56; N, 6.20. Found : C, 47.96; H, 3.57; N, 6.52.

β,4-Dibromocinnamonitrile (IV)——*p*-Bromophenylacetylene (18.1 g.) was treated with aluminum bromide (26.7 g.) and cyanogen bromide (15.9 g.) as described above. The reaction mixture was washed and dried as before, and the solvent was evaporated. The residue was dissolved in hexane-benzene (1:1) and chromatographed on Al_2O_3 (Woelm, grade III, 500 g.). Elution with the same solvent gave white tufts of needles of β,4-dibromocinnamonitrile (IV), m.p. 76~77° (from hexane). Yield, 1.52 g. (5.3%). UV : λ_{max} 282 mμ (log ε 4.32). IR : ν_{max} 2213 cm^{-1} (-CN) (Nujol). *Anal.* Calcd. for $C_9H_5NBr_2$: C, 37.67; H, 1.76; N, 4.88. Found : C, 37.78; H, 1.76; N, 4.59.

Prior to the elution of IV, black oil was eluted with hexane, and chromatographed again on Al_2O_3 (Woelm, grade I, 200 g.). The first 200 ml. of hexane eluted white needles, m.p. 253~256°, which was believed to be a trimerized product of *p*-bromophenylacetylene, $C_{24}H_{17}Br_3$. *Anal.* Calcd. for $C_{24}H_{17}Br_3$: C, 52.87; H, 3.15; Br, 43.89; M. W., 545. Found : C, 53.46; H, 3.23; Br, 42.98; M. W., 537.*5

β-Bromo-4-methoxycinnamonitrile (V)——Aluminum bromide (26.6 g.), cyanogen bromide (10.6 g.) and *p*-methoxyphenylacetylene (13.2 g.) were warmed in tetrachloroethane as described before. The reaction mixture was treated as before, and the solvent was evaporated *in vacuo*. The residue was dissolved in hexane-benzene (1:1), and chromatographed on Al_2O_3 (Woelm, grade III, 500 g.). The same solvent eluted white tufts of needles of β-bromo-4-methoxycinnamonitrile (V), m.p. 78~79° (from hexane). Yield, 0.88 g. (3.7%). UV λ_{max} mμ (log ε) : 228 (4.47), 305 (4.75). IR : ν_{max} 2232 cm^{-1} (-CN) (CCl_4). *Anal.* Calcd. for $C_{10}H_8ONBr$: C, 50.45; H, 3.39; N, 5.88. Found : C, 50.77; H, 3.41; N, 5.77.

Prior to the elution of V, hexane eluted a crystalline compound of m.p. 128~140°. IR spectrum of this compound showed no absorption due to cyano group, and not further investigated.

α-Bromo-β-cyanostilbene (VI)——Aluminum bromide (8.9 g.) in 50 ml. of tetrachloroethane, cyanogen bromide (5.3 g.) in 20 ml. of the solvent and tolane (5.9 g.) in 20 ml. of the solvent were mixed as described before and stirred at 45° for 15 hr. The reaction mixture was treated as other examples and the solvent was evaporated *in vacuo*. The residue (7.3 g.) was dissolved in benzene-hexane (7:3), and chromatographed on Al_2O_3 (Woelm, grade II, 146 g.). The same solvent eluted slightly yellow plates of α-bromo-β-cyanostilbene (VI), m.p. 85~86.5° (from hexane). Yield, 0.78 g. (8.3%). UV λ_{max} mμ (log ε) : 224 (3.84), 294 (3.70). IR ν_{max} cm^{-1} : 2213 (-CN) (Nujol). *Anal.* Calcd. for $C_{15}H_{10}BrN$: C, 63,38; H, 3.55; N, 4.93; Br, 28.14. Found : C, 63.18; H, 3.53; N, 4.98; Br, 28.26.

α-Methyl-β-bromocinnamonitrile (VII)——Aluminum bromide (134 g.) in 600 ml. of tetrachloroethane, cyanogen bromide (79 g.) in 200 ml. of the solvent and phenylmethylacetylene (58 g.) in 200 ml. of the solvent were mixed and stirred as described before. The mixture was treated as other examples, and the solvent was evaporated *in vacuo*. The residue was distilled to give α-methyl-β-bromocinnamonitrile (VII), $b.p_{0.3}$ 101~103°, which crystallized on cooling. Recrystallization from hexane gave slightly yellow prisms, m.p. 42~43°. Yield, 36.7 g. (33.1%). UV : λ_{max} 261 mμ (log ε 4.22). IR : ν_{max} 2222 cm^{-1} (-CN) (Film). *Anal.* Calcd. for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31; Br, 35.98. Found : C, 54.13; H, 3.57; N, 6.65; Br, 35.34.

5-Methyl-6-phenyl-2,4-diaminopyrimidine (VIII)——To a solution of Na (0.8 g.) in 30 ml. of abs. EtOH, guanidine hydrochloride (2.8 g.) and α-methyl-β-bromocinnamonitrile (VII) (2.2 g.) in 10 ml. of abs. EtOH were added. The mixture was refluxed for 18 hr. After evaporation of EtOH, the residue was washed with H_2O and Et_2O, and recrystallized from EtOH to afford prisms of 5-methyl-6-phenyl-2,4-diaminopyrimidine (VIII), m.p. 196~197° (reported 196~197°).[13] Yield, 0.65 g. UV λ_{max} mμ (log ε) : 230 (4.13) (shoulder), 289 (3.85). *Anal.* Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found : C, 65.82; H, 6.13; N, 27.91.

α-Methyl-β-bromocinnamamide (IX)——α-Methyl-β-bromocinnamonitrile (VII) (10.0 g.) was warmed with 32 ml. of 70% H_2SO_4 solution at 80°, for 10 hr. After cooled, the mixture was diluted with H_2O, and the white precipitate was filtered off. The filtrate was washed with H_2O and Et_2O, and recrystallized from EtOH to give colorless prisms of α-methyl-β-bromocinnamide (IX), m.p. 215~217°. Yield, 9.2 g. UV : λ_{max} 253 mμ (log ε 3.65) (shoulder). IR ν_{max} cm^{-1} : 3330, 3150 ($-NH_2$), 1650 ($-CONH_2$) (Nujol). *Anal.*

*5 measured by osmometer.

Calcd. for $C_{10}H_{10}ONBr$: C, 50.02; H, 4.20; N, 5.83; Br, 33.28. Found : C, 50.29; H, 4.25; N, 5.66; Br, 33.13.

α-Methyl-β-bromocinnamic Acid (X)——A mixture of α-methyl-β-bromocinnamamide (0.505 g.) and conc. HCl (15 ml.) was refluxed for 8 hr, After cooling, the mixture was diluted with H_2O, and made alkaline with 10% NaOH solution. The mixture was extracted with Et_2O to remove unchanged IX, and filtered. The filtrate was acidified with conc. HCl and extracted with Et_2O. The ethereal layer was washed with H_2O, treated with small amount of Norite, filtered and dried over Na_2SO_4. After evaporation of Et_2O, the residue was crystallized from benzene to give colorless prisms of α-methyl-β-bromocinnamic acid (X), m.p. 129~130°. Yield, 0.130 g. X showed depression in m.p. (96~108°) on admixture with authentic α-methyl-β-bromocinamic acid (XI) of m.p. 128~129°, which was prepared by Körner's method[7] and considered to be *cis*-α-methyl-β-bromocinnamic acid. (See Chart III.) UV : λ_{max} 255 mμ (log ε 3.74). IR : ν_{max} 1700 cm^{-1} (-COOH) (Nujol). *Anal.* Calcd. for $C_{10}H_9O_2Br$: C, 49.82; H, 3.76; Br, 33.15. Found : C, 49.74; H, 3.68; Br, 33.58.

The authors express their deep gratitude to Mr. M. Matsui, Director of this laboratory, for his encouragement throughout this work. The measurement of infrared and ultraviolet spectra were carried out by Mr. H. Higuchi, Misses N. Sawamoto and Y. Nakajima. Microanalyses were made by Dr. T. Onoe, Messrs. K. Ono, H. Nagashima and Misses K. Saito, N. Gonda and H. Masuda.

Summary

The addition of cyanogen bromide to an acetylenic bond was studied. Phenylacetylene reacted with cyanogen bromide in the presence of aluminum bromide to afford *trans*-β-bromocinnamonitrile. Similarly, *p*-bromo- and *p*-methoxyphenylacetylene, tolane and methylphenylacetylene yielded corresponding β-bromocinnamonitriles. Nevertheless, *p*-nitrophenylacetylene did not react with cyanogen bromide under the same conditions.

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198. Tadakazu Tsuji, Junzo Kawabata, Sachiko Kobayashi, and Takeo Ueda : Syntheses and Antiviral Effect of *p*-Alkylbenzenesulfonamide Derivatives.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

T. Ueda, *et al.*[1] found that N-dodecanoyl-4-acetamido-1-naphthalenesulfonamide (PANS-610) showed a significant chemotherapeutic effect on Japanese encephalitis virus in mice and human. After that, T. Itoh,[2] one of our group examined compounds of N^1-alkanoyl-N^4-alkanoylsulfanilamide, *p*-alkylbenzenesulfonic acid and N-alkanoyl-4-alkylbenzenesulfonamide related to PANS-610 as to their effect on the Nakayama strain of Japanese encephalitis virus in mice, but could not find any agent more effective than PANS-610. Also, Kawabata, *et al.*[3] found that N-decanoyl-5-acetamido-8-quinolinesulfonamide (I) and N-decanoyl-8-ethoxy-5-quinolinesulfonamide (II) exerted effects stronger than PANS-610 among derivatives of quinolinesulfonamide.

*1 Shinano-machi, Shinjuku-ku, Tokyo (辻 忠和, 川畑潤三, 小林佐知子, 上田武雄).

1) T. Ueda, S. Toyoshima : Keio J. of Med., **5**, 123 (1956).
2) T. Itoh, S. Toyoshima, T. Ueda : Papers read at the Annual Meeting of the Pharmaceutical Society of Japan (1954).
3) J. Kawabata, H. Koibuchi, S. Toyoshima : This Bulletin, 8, 788 (1960); J. Kawabata, H. Koibuchi, T. Itoh, S. Toyoshima : *Ibid.*, 8, 930 (1960).