CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 10 No. 2 February 1962

UDC 547.538.2

13. Issei Iwai and Tetsuo Hiraoka : Studies on Acetylenic Compounds. XX.*1 Carbon-Carbon Alkylation with Acetylenic Mannich Base.

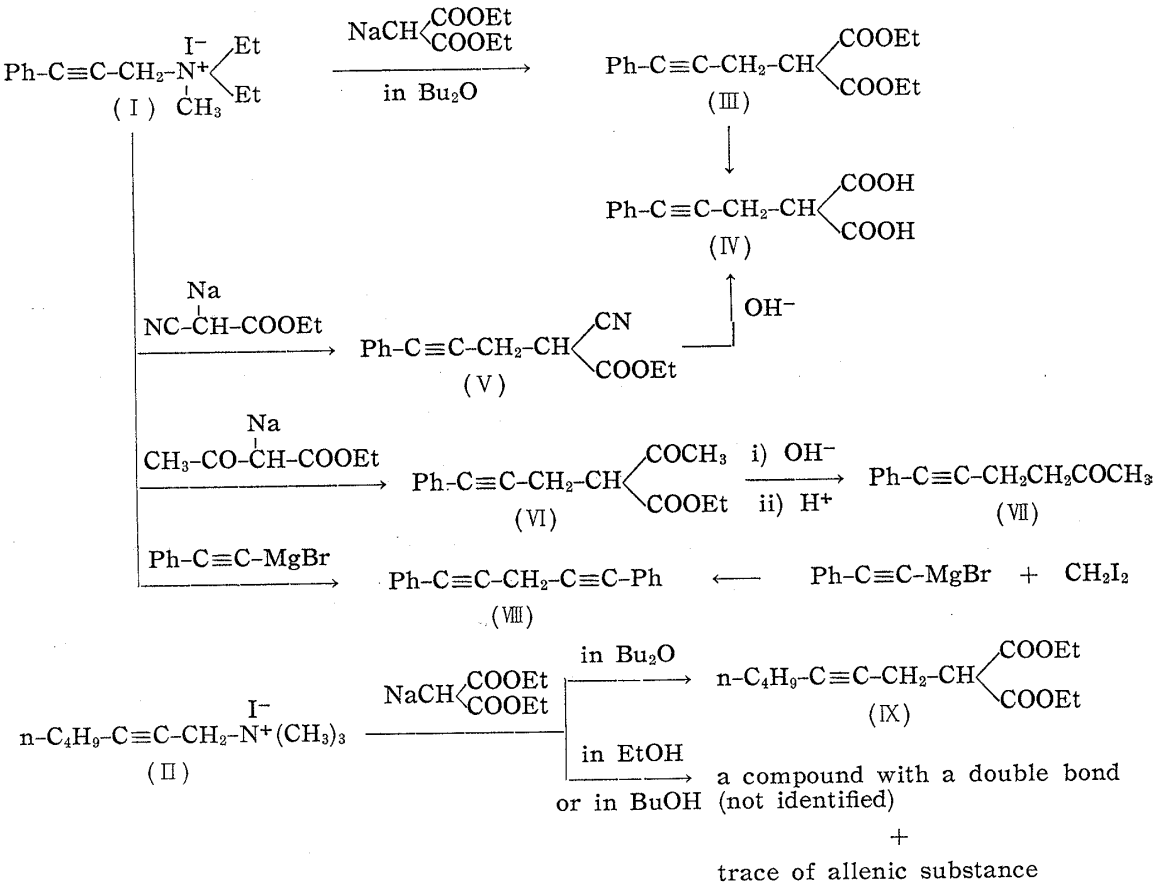
(*Takamine Laboratory, Sankyo Co., Ltd.**2)

It has been known that the compounds shown by the general formula aryl-CH_2-$\overset{+}{N}$-($R_1R_2R_3$) or RCO-CH_2CH_2-$\overset{+}{N}$($R_1R_2R_3$) are easily alkylated with active methylene compounds by losing $NR_1R_2R_3$. In the case of β-aminoketone ($RCOCH_2CH_2$-$\overset{+}{N}$($R_1R_2R_3$)) the reaction is considered to be effected by elimination mechanism,[1] while in the case of aryl-CH_2-$\overset{+}{N}$-($R_1R_2R_3$), its reaction mechanism has not been clarified yet. By the reaction of aryl-CH_2-$\overset{+}{N}$($R_1R_2R_3$) with active methylene compounds, C-N bond of these compounds is easily cleaved and the rather stable resonance type of aryl-$\overset{+}{C}H_2$ would be an intermediate, which must be an essential structural requirement for this reaction. From these points of view, the acetylenic Mannich base of R-C≡C-CH_2-$\overset{+}{N}$($R_1R_2R_3$) is expected to undergo this alkylation reaction. The present paper describes the alkylation of acetylenic Mannich base.

Some time after the start of this investigation, Schlögl and Orgler[2] reported that acetylenic Mannich base did not react with active methylene compounds but did not react with potassium cyanide to yield unexpected tricarboxylic acid, and they also reported that alkyl-C≡C-CH_2-$\overset{+}{N}$($R_1R_2R_3$) afforded a tricarboxylic acid, whereas Ph-C≡C-$CH_2\overset{+}{N}$($R_1R_2R_3$) gave only polymeric substance. In the present series of work, alkylation of acetylenic Mannich base with active methylene compounds and also with Grignard compounds was successfully effected.

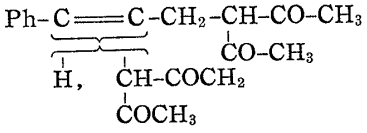
Methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (I)[3] and trimethyl-(2-heptynyl)-ammonium iodide (II)[4] were employed as the acetylenic Mannich base. On the reaction of methyldiethyl-(3-phenyl-2-propynyl)ammonium iodide (I) with sodium diethylmalonate in dibutyl ether, diethyl 4-phenyl-3-butyne-1,1-dicarboxylate (III) was obtained in 30% yield, but this reaction did not proceed in dehyd. ethanol solution and the starting material was recovered. (III) was hydrolyzed to 4-phenyl-3-butyne-1,1-dicarboxylic acid (IV), m.p. 139~141°. Analogously, (I) afforded ethyl 1-cyano-4-phenyl-3-butyne-1-carboxylate (V) and ethyl 1-acetyl-4-phenyl-3-butyne-1-carboxylate (VI) respectively, by reaction with ethyl cyano-acetate sodium salt and ethyl acetoacetate sodium salt in dibutyl ether. (V) was converted into 4-phenyl-3-butyne-1,1-dicarboxylic acid (IV), m.p. 139~141°, by alkaline hydrolysis,

*1 Part XIX : This Bulletin, **9**, 976 (1961).
*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (岩井一成, 平岡哲夫).
1) J.H. Brewster, E.L. Eliel : Org. Reactions, **VII**, 99 (1953).
2) K. Schlögl, Kh. Orgler : Monatsh., **90**, 306 (1959).
3) C. Mannich, F. Chang : Chem. Ber., **66**, 418 (1933).
4) A. Marszak-Fleury, *et al.* : Bull. soc. chim. France, **1950**, 1305.



which showed no depression in melting point on admixture with the compound prepared via (III). (VI) was converted by hydrolysis and decarboxylation into 6-phenyl-5-hexyn-2-one (VII), which formed 2,4-dinitrophenylhydrazone of m.p. 138~140°. The infrared spectra of (III), (V), and (VI) showed no absorption in the region of 2100~2250 cm^{-1}, which is characteristic to the acetylenic bond. This should be due to location of the triple bond near the center of the compound and the absence of this absorption of the triple bond has been observed in many cases.[5] However, the structure of these three compounds was confirmed by the fact that ultraviolet spectra of these substances showed the same absorption as that of methylphenylacetylene and that these compounds absorbed two moles of hydrogen by catalytic hydrogenation in the presence of platinum dioxide.

When acetylacetone was reacted with (I), an unexpected product of m.p. 56~57° was obtained and its analytical data suggested that 2 moles of acetylacetone had been introduced into (I). Infrared spectrum of this substance showed strong absorption at 840 cm^{-1}, which is characteristic to *para*-substituted benzene derivatives. However, oxidation of this compound with alkaline potassium permanganate gave benzoic acid, which fact excluded the possibility of a *para*-substituted benzene derivative. Therefore, the strong absorption at 840 cm^{-1} must be due to the bending vibration of $R_1R_2C{=}CHR_3$. From the results of infrared and ultraviolet absorptions, and from analytical data, the most probable structure of this compound would be as follows :



5) cf. L. J. Bellamy : "The Infra-red Spectra of Complex Molecules," 60 (1958), Methuen & Co., London.

(I) was also expected to react with a Grignard reagent and in fact, when (I) was treated with phenylacetylenemagnesium bromide, 1,5-diphenyl-1,4-pentadiyne (Ⅷ), m.p. 85~86°, was isolated in a very low yield and the main reaction product was polymerized tarry non-distillable substance. The compound (Ⅷ) was independently synthesized by the Grignard method[6] from methylene iodide and phenylacetylenemagnesium bromide, also in a low yield. Both compounds obtained here showed no depression in mixed melting point.

2-Nitropropane did not afford the expected product in the reaction with (I) and distillation of the reaction mixture caused serious decomposition, the compounds isolated in a very low yield were unidentified substances of m.p. 202~204° and m.p. 127~128° (decomp.).

In the reaction of trimethyl(2-heptynyl)ammonium iodide (Ⅱ) with diethyl malonate sodium salt, it was found that the reaction carried out in dibutyl ether gave the expected product, diethyl 3-octyne-1,1-dicarboxylate (Ⅸ), while the reaction carried out in alcohol gave another substance possessing a double bond and a trace of allenic compound. When dehyd. butanol was used as the solvent, the reaction temperature could be raised and the reaction was accomplished more smoothly, but the reaction products were too complicated to be identified. (Ⅸ) was converted into the known 3-octyne-1,1-dicarboxylic acid[7] (X), m.p. 92~93°, by alkaline hydrolysis.

According to Schlögl and Orgler,[2] the reaction of acetylenic Mannich bases with potassium cyanide in hydrous alcohol proceeds by S_N-1 mechanism and they advocated the reaction mechanism as shown in Chart 1.

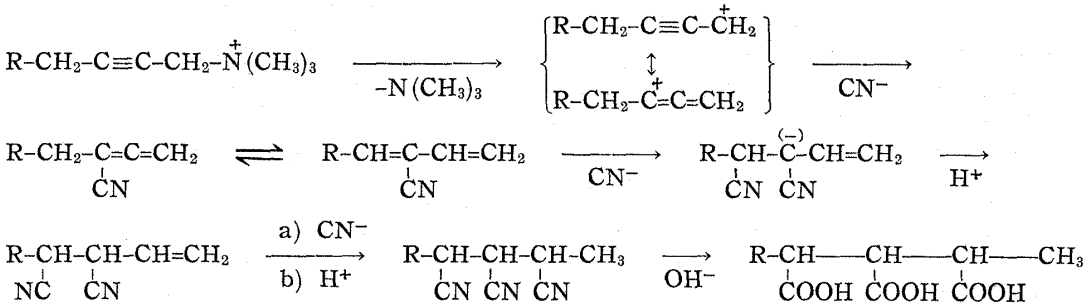


Chart 1.

The present series of experiments showed that, when the reaction is carried out in an ethanolic medium, the compound showing a double-bond absorption in the infrared spectrum and a trace of allenic substance are obtained. Therefore, alkylation of acetylenic Mannich base in ethanol is most likely to proceed by S_N-1 mechanism, as Schlögl concluded. On the other hand, when the reaction is carried out in dibutyl ether, as in the present work, the reaction mechanism could be considered as S_N-2, because only the compound having triple bond was obtained.

Experimental*3

Diethyl 4-Phenyl-3-butyne-1,1-dicarboxylate (III) and 4-Phenyl-3-butyne-1,1-dicarboxylic Acid (IV)——To powdered sodium (0.65 g.: 0.0304/1.1 *M*) in n-Bu_2O (50 cc.), diethyl malonate (12.2 g.: 0.0304 × 2.5 *M*) was added and this mixture was stirred at room temperature for 6 hr. To the resulting paste methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (10 g. : 0.0304 *M*) was added and this reaction mixture was heated, with continuous stirring, on an oil bath at 110° for 2 hr. and at 145°

*3 All melting points are uncorrected.

6) V. Grignard, L. Lapayre : Compt. rend., **192**, 250 (1931).

7) M. S. Newman, J. H. Wotiz : J. Am. Chem. Soc., **71**, 1292 (1949).

for 5 hr. in N_2 atmosphere. The cooled solution was poured into cold 10% HCl solution and extracted with Et_2O. The extract was washed three times with H_2O, dried over Na_2SO_4, and evaporated. n-Bu_2O and excess of diethyl malonate were removed by vacuum distillation. Distillation of the residue gave a crude diethyl 4-phenyl-3-butyne-1,1-dicarboxylate (III), which showed b.$p_{0.2}$ 133~135° and it weighed 2.5 g. (30% yield). IR : $\lambda_{max}^{CCl_4}$ 5.75 μ(COOR).

The crude substance (III) obtained as above (1 g.) was heated with 20% KOH solution (5 cc.) on a steam bath for 7 hr. and during this time, the solution became homogeneous. The cooled solution was acidified with 15% HCl solution and extracted with Et_2O. The combined Et_2O extracts were washed three times with saturated NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The oily residue crystallized on standing overnight, it was triturated with benzene, and dried; weighing 350 mg. It melted at 86~125°. Recrystallization from H_2O gave 4-phenyl-3-butyne-1,1-dicarboxylic acid (IV) of m.p. 139~141°. *Anal.* Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.04; H, 4.61. IR λ_{max}^{Nujol} μ : 3.25, 3.75(OH), 5.85(CO). UV λ_{max}^{EtOH} mμ(log ε) : 239.5(4.38), 250.5(4.35).

Ethyl 1-Cyano-4-phenyl-3-butyne-1-carboxylate (V) and 4-Phenyl-3-butyn-1,1-dicarboxylic Acid (IV)——Ethyl cyanoacetate (8.6 g.) was added to finely powdered Na (0.65 g.) in n-Bu_2O (50 cc.) and the mixture was stirred for 6 hr. at room temperature. After allowing it to stand overnight, methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (10 g.) was added to the resulting paste and the reaction mixture was heated at 100° for 1 hr. and at 145° for 3 hr. The cooled reaction mixture was poured into cold 10% HCl solution and extracted with Et_2O. The combined Et_2O extract was washed once with $NaHCO_3$ solution and three times with saturated NaCl solution, dried, and evaporated. Distillation of the residue gave crude ethyl 1-cyano-4-phenyl-3-butyne-1-carboxylate (V), b.$p_{0.04}$ 108~118°, weighing 1 g. IR $\lambda_{max}^{CCl_4}$ μ : 4.49(CN), 5.75(COOR). UV λ_{max}^{EtOH} mμ(log ε) : 238(3.97), 249(3.91).

The crude substance (V) (0.5 g.) obtained as above was dissolved in EtOH (1 cc.), 15% KOH solution (2.5 cc.) was added to this solution and this mixture was refluxed for 10 hr. EtOH was evaporated in a reduced pressure and 10% NaOH solution was added to the residue. After extraction with Et_2O, the aqueous solution was acidified with 10% HCl solution and again extracted with Et_2O. The combined Et_2O extract was washed three times with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The oily residue crystallized on treatment with benzene as needles (20 mg.) of m.p. 135~137°. Recrystallization from benzene afforded pure 4-phenyl-3-butyne-1,1-dicarboxylic acid (IV) of m.p. 139~141°, undepressed on admixture with the sample obtained through (III).

Ethyl 1-Acetyl-4-phenyl-3-butyn-1-carboxylate (VI) and 6-Phenyl-5-hexyn-2-one (VII)——Ethyl acetoacetate (10 g.) was added to finely powdered Na (0.65 g.) in n-Bu_2O (50 cc.) and the mixture was stirred at room temperature for 4 hr. To the resulting paste, finely powdered methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (10 g.) was added and the reaction mixture was heated on an oil bath at 140~145° for 6 hr. 10% HCl solution was added to the cooled solution and extracted with Et_2O. The combined Et_2O extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The brown residue was dissolved in benzene and passed through a short column packed with Al_2O_3 (20 g.). From the eluates, benzene was evaporated in a reduced pressure. Distillation of the residue gave crude ethyl 1-acetyl-4-phenyl-3-butyne-1-carboxylate (VI), b.$p_{0.2}$ 110~130°, weighing 1.4 g. IR $\lambda_{max}^{CHCl_3}$ μ : 5.75(COOR), 5.82(CO).

The crude substance (VI) (500 mg.) obtained as above was stirred with 5% NaOH solution (4 cc.) at room temperature for 22 hr. The solution was extracted with Et_2O, the aqueous solution was acidified with dil. H_2SO_4 (1:1), and extracted with Et_2O. The combined Et_2O extract was washed with H_2O, dried, and evaporated. Distillation of the residue afforded 6-phenyl-5-hexyn-2-one (VII), b.p_5 110~140° (oil bath temperature), weighing 45 mg.
2,4-Dinitrophenylhydrazone : m.p. 138~140°. *Anal.* Calcd. for $C_{18}H_{16}O_4N_4$: C, 61.36; H, 4.58; N, 15.90. Found : C, 61.38; H, 4.47; N, 16.06.

The distillation residue was dissolved in EtOH and treated with charcoal. EtOH was evaporated in a reduced pressure. The slightly yellow residue crystallized on standing, which was expected to be Ph-C≡C-CH_2-CH_2-COOH, but the sample was too small to be identified.

1,5-Diphenyl-1,4-pentadiyne (VIII) from Methyldiethyl(3-phenyl-2-propynyl)ammonium Iodide (I) and Phenylacetylenemagnesium Bromide——The Grignard solution of EtMgBr was prepared from Mg (0.4 g.), EtBr (1.83 g.), and Et_2O (20 cc.) as usual. To this solution phenylacetylene (1.7 g.) in dehyd. EtOH (15 cc.) was added, the solution was refluxed for 2 hr., n-Bu_2O (25 cc.) was added and Et_2O was removed by evaporation. To the resulting solution methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (I) (5 g.) was added and the mixture was heated on an oil bath (150°) for 17.5 hr. with continuous mechanical stirring. The cooled solution was poured into 10% HCl solution and extracted with Et_2O and $CHCl_3$. The combined extract was washed four times with saturated NaCl solution and dried over Na_2SO_4. Evaporation of the organic solvents gave a black oil, which was taken up in hot benzene, passed through a short column packed with Al_2O_3, and eluted with benzene. From the eluates, benzene was evaporated to leave a brown oil, which was submitted to distillation and the oily distillate between 105° and 190° (oil bath temp.) at 0.0005 mm. Hg was collected.

It was dissolved in petr. ether (5 cc.) and absorbed on Al_2O_3 (10 g.). Elution of the column with petr. ether afforded an oil which, on treatment with MeOH, crystallized. It melted at 84~85° and weighed 20 mg. Recrystallization from MeOH gave a sample of m.p. 85~86°, which showed no depression in melting point on admixture with the authentic sample prepared from methylene iodide and phenylacetylenemagnesium bromide. *Anal.* Calcd. for $C_{17}H_{12}$: C, 94.41; H, 5.59. Found: C, 93.97; H, 5.44. IR $\lambda_{max}^{CHCl_3}\mu$: 4.53, 4.68(C≡C). UV λ_{max}^{EtOH} mμ(log ε): 228(4.53), 247(4.52), 259.7(4.51), 271(4.21), 287(4.39), 296(4.31), 305(4.57) 316(4.21), 327(4.54).

1,5-Diphenyl-1,4-pentadiyne (VIII) from Phenylacetylenemagnesium Bromide and Methylene Iodide[*4]——EtMgBr solution was prepared from Mg (17.9 g.), EtBr (80.4 g.), and Et_2O (500 cc.) as usual. To this Grignard solution phenylacetylene (75.4 g.) in dehyd. Et_2O (100 cc.) was added and this mixture was refluxed for 2.5 hr. During this time, phenylacetylenemagnesium bromide separated as an oil in the underlayer. Then methylene iodide (99 g.) in Et_2O (100 cc.) was added under ice-water cooling and the solution was refluxed for 13 hr. with mechanical stirring. However, oily Grignard reagent did not disappear and therefore, tetrahydrofuran (300 cc.) was added to this solution and Et_2O was distilled off until vapour-phase temperature reached 57°. Then the reaction mixture was refluxed for additional 3 hr. NH_4Cl (40 g.) in H_2O (200 cc.) and 10% H_2SO_4 solution were added under ice-water cooling. The solution was extracted with Et_2O and the combined Et_2O extract was washed with $Na_2S_2O_3$ solution to remove free iodine and further washed with saturated NaCl solution. After drying over Na_2SO_4, Et_2O and tetrahydrofuran were evaporated, and unreacted phenylacetylene and methylene iodide were removed by distillation in a reduced pressure. The residue was distilled at 5×10^{-4} mm. Hg and the distillate between 105° and 145° (oil bath temp.) was collected, which crystallized on standing. It melted at 82~84°. Recrystallization from MgOH gave needles of m.p. 85~86°, weighing 220 mg. *Anal.* Calcd. for $C_{17}H_{12}$: C, 94.41; H, 5.59. Found: C, 94.46; H, 5.11.

Reaction of Methyldiethyl(3-phenyl-2-propynyl)ammonium Iodide (I) with Acetylacetone——To finely powdered sodium (0.65 g.) in n-Bu_2O (50 cc.), acetylacetone (7.6 g.) was added and the mixture was stirred at room temperature for 11.5 hr. Finely powdered methyldiethyl(3-phenyl-2-propynyl)ammonium iodide (10 g.) was added to this solution and the mixture was heated on an oil bath at 145° for 7 hr. with mechanical stirring. The cooled solution was poured into cold 10% HCl solution and extracted with Et_2O. The combined extract was washed with 10% HCl solution, $NaHCO_3$ solution and H_2O. After drying over Na_2SO_4, Et_2O and n-Bu_2O were evaporated in a reduced pressure. The residue was distilled to give a substance of $b.p_{0.5}$ 95~98° (1 g.), which solidified on standing. It melted at 55~57°. Recrystallization from n-hexane gave needles of m.p. 56~57°. From IR and UV spectra, and analytical data, the most probable structure of this compound would be 3,7-diacetyl-4-phenylnona-4-ene-2,8-dione. *Anal.* Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.85; H, 7.31. IR λ_{max}^{Nujol} μ: 6.18, 6.25 (β-diketone), 6.39 (aromatic ring), 11.9 ($R_1R_2C{=}CHR_3$).

The higher distillate was not investigated.

Diethyl 3-Octyne-1,1-dicarboxylate (IX) and 3-Octyne-1,1-dicarboxylic Acid (X)——Ethyl malonate (6.26 g.) was added to finely powdered sodium (0.82 g.) in n-Bu_2O (75 cc.) and the mixture was stirred at room temperature for 3 hr. to form a pasty solution. To this solution trimethyl(2-heptynyl)-ammonium iodide (II) (10 g.) was added and the mixture was heated on an oil bath at 145~150° for 54 hr. with mechanical stirring. The cooled solution was poured into cold 5% HCl solution and extracted with Et_2O. The combined extract was washed four times with H_2O, dried over Na_2SO_4, and evaporated. n-Bu_2O was removed in a reduced pressure. Distillation of the residue gave a crude diethyl 3-octyne-1,1-dicarboxylate (IX), $b.p_{0.4\sim0.5}$ 100~103°. It weighed 3.0 g. IR: $\lambda_{max}^{CCl_4}$ 5.75 μ (COOR).

The crude substance (IX) (200 mg.) obtained as above was stirred with KOH (1 g.) in H_2O (1 cc.) at room temperature for 24 hr. During this time a small amount of fine needles separated (it would be potassium salt of the carboxylic acid). After addition of H_2O (1 cc.) to dissolve the crystals, the solution was stirred further at room temperature for 5 hr. The solution was extracted with Et_2O, aqueous layer was acidified with 10% HCl solution, and again extracted with Et_2O, saturating the aqueous solution with NaCl. The combined Et_2O extract was washed three times with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue (120 mg.) crystallized on standing. It showed m.p. 83~86° with previous softening. Recrystallization from benzene afforded 3-octyne-1,1-dicarboxylic acid[7] (X) as prisms, m.p. 89~91°, weighing 51 mg. One more recrystallization from the same solvent gave a sample of m.p. 92~93°. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.86; H, 7.10. IR $\lambda_{max}^{CHCl_3}$ μ: 2.80, 3.25, 3.78(OH), 5.80(COOH).

[*4] V. Grignard and L. Lapayre reported (Compt. rend., **192**, 250 (1931)) that 1,5-diphenyl-1,4-pentadiyne was prepared from phenylacetylenemagnesium bromide and methylene iodide. However, detailed experimental data were not given.

The authors are grateful to Mr. M. Matsui, Director of this Laboratory, and Prof. K. Tsuda of the University of Tokyo for encouragement throughout this work. The measurement of infrared and ultraviolet spectra were carried out by Messrs. O. Amakasu, H. Higuchi, N. Higosaki, and Miss N. Sawamoto. Microanalyses were made by Messrs. T. Onoe and H. Nagashima, and Misses C. Furukawa and H. Ohtsuka.

Summary

It was found that methyl iodide of acetylenic Mannich base reacted with active methylene compounds to form alkylated acetylenic compounds with a loss of tertiary amine. Various acetylenic compounds may be prepared by this method. It seems likely that such alkylation reactions proceed mainly by S_N-1 mechanism in alcohol and mainly by S_N-2 mechanism in dibutyl ether.

(Received January 23, 1961)

UDC 615.7[547.581]-092.21

14. Hisao Tsukamoto*1 and Seisuke Terada*2 : Metabolism of Drugs. XXVI.*3 Metabolic Fate of *p*-Hydroxybenzoic Acid and its Derivatives in Rabbit. (2).*4

(*Institute of Pharmaceutical Sciences, Faculty of Medicine, Kyushu University**1 *and Hygienic Research Laboratory of Nagasaki Prefecture**2)

In the previous paper,[3] it was reported that the ether-type glucuronide of *p*-hydroxybenzoic acid was isolated as the methylacetyl derivative on methylation and acetylation of the glucuronide fraction which was separated by lead acetate[1] from the urine of rabbits receiving methyl *p*-hydroxybenzoate, and its structure had been established as methyl (*p*-methoxycarbonylphenyl 2,3,4-tri-O-acetyl-*β*-D-glucopyranosid)uronate (I).

In the present investigation, five metabolites; *p*-hydroxybenzoic acid, *p*-hydroxyhippuric acid, *p*-carboxyphenyl glucuronide(ether-type glucuronide), *p*-hydroxybenzoyl glucuronide(ester-type glucuronide), and *p*-carboxyphenyl sulfate, were identified in the urine of rabbits receiving methyl *p*-hydroxybenzoate. The three main metabolites, the ether-type glucuronide, *p*-hydroxyhippuric acid, *p*-hydroxybenzoic acid, were isolated as crystalline materials. In the present series of work, structure of the ether-type glucuronide was established as *p*-carboxyphenyl-*β*-D-glucopyranosiduronic acid by identification with the authentic sample prepared by saponification of (I).

Experimental

Separation of the Metabolite Fraction from the Urine of Rabbits——The animals used were male rabbits weighing 2.6~3.2 kg. They were housed in metabolism cages and fed "Okara" (soybean curd residue). A total dose of 7.2 g· of methyl *p*-hydroxybenzoate (0.8 g./kg. body wt.) was administered as a 12% solution in the form of Na salt to 3 rabbits by a stomach tube.

---

*1 Katakasu, Fukuoka (塚元久雄).
*2 Nakagawa-cho, Nagasaki (寺田精介).
*3 Part XXV. H. Tsukamoto, M. Yoshimura : This Bulletin, **9**, 584 (1961).
*4 Part (1). H. Tsukamoto, S. Terada : *Ibid.*, 8, 1066 (1960).
1) I. A. Kamil, J. N. Smith, R. T. Williams : Biochem. J., **50**, 235 (1951).