Summary

Solubilities of the molecular compound of sulfanilamide and sulfathiazole in aqueous solutions containing varying amounts of sulfanilamide were determined. It was found from the results that the solubility product principle can be applied to such mixtures. Based on the principle, a method for calculating the value of the saturated concentration of the compound was proposed.

Besides, the influence of each one of the sulfonamides to the solubility of the other was investigated. Using all these data, the phase diagram of the system of sulfanilamide, sulfathiazole and water was constructed which indicates that the system belongs to the type where a one-to-one molecular compound is formed but is decomposed by water. It was also confirmed that the metastable solubilities of the compound observed in water and in the sulfanilamide solution can be represented by the points on the extention of the saturation curve of the molecular compound in the diagram.

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39. Tetsuo Hiraoka and Issei Iwai : Studies on Acetylenic Compounds. XLII.*1 Total Synthesis of Estrone by the Double Cyclization of Acetylenic Compounds.*2

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Recently much attention has been focused on the total synthesis of 19-nor-steroids from an industrial standpoint since useful pharmacological activities of 19-nor-steroids have been found. Hughes and Smith[1] succeeded in the synthesis of estrone by a very short route which greatly contributed to its industrialization.[2] These kinds of approaches was followed by Torgov, *et al.* who skillfully synthesized estrone starting from methoxy-tetralone.[3] The successive notable total synthesis on the industrial scale was developed by Velluz, *et al.* who resolved a racemic intermediate in an earlier stage.[4] Even in 1964 the total syntheses of steroidal skeletons were a target for

*1 Part XLI : I. Iwai, J. Ide : This Bulletin, **13**, 663 (1965).

*2 Presented at the 8th annual simposium of the Chemistry of the Natural Products (Nagoya, Japan) (1964).

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1) G. A. Hughes, H. Smith : Proc. Chem. Soc., **1960**, 74; *Idem* : Chem. & Ind., **1960**, 1022; H. Smith, G. A. Hughes, *et al.* : J. Chem. Soc., **1963**, 5072; H. Smith, G. A. Hughes, *et al.* : *Ibid.*, **1964**, 4472, 4492.

2) Chem. Eng. News, Aug. 26, 1963, Page 32; *Ibid.*, March 2, 1964, Page 42.

3) S. N. Ananchenko, I. V. Torgov : Dokl. Akad. Nauk. S. S. S. R., **127**, 553 (1959); *Ibid.*, **135**, 73 (1960); Tetrahedron Letters, **1963**, 1553; *Ibid.*, **1964**, 171; V. E. Limanov, S. N. Ananchenko, I. V. Torgow: Izvest. Akad. Nauk. S. S. S. R., Ser. Khim, **1964**, 1814; K. K. Koskoev, S. N. Ananchenko, A. V: Platonov, I. V. Torgov : Izvest. Akad. Nauk. S. S. S. R., Otdel. Khim. Nauk., **1963**, 2058; I. V. Torgov, T. I. Sorkina, I. I. Zaretskaya : Angew. Chem., **76**, 794 (1964); A. V. Zakharychev, S. N. Ananchenko, I. V. Torgov : Steroids, **4**, 31 (1964).

4) L. Velluz, G. Nominé, J. Mathieu : Angew. Chem., **72**. 725 (1960); L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, A. Pierdet : C. R. Hebd. Seances Acad. Sci., **250**, 1084 (1960); L. Velluz, G. Nominé, E. Toromanoff, D. Bertin, R. Bucourt, J. Tessier : *Ibid.*, **250**, 1293 (1960); L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, M. Vignau, J. Tessier : *Ibid.*, **250**, 1510 (1960); L. Velluz, G. Nominé, G. Amiard, V. Torelli, J. Cérede : Compt. rend., **257**, 3086 (1963).

organic chemists.[5~8] Recent progress in the syntheses of 19-nor-steroids has been reviewed by Windholz, *et al.*[9] and Velluz, *et al.*[10]

This paper deals with a synthesis of estrone which is a key intermediate for 19-nor-steroids.

In the previous paper of this series an intramolecular cyclization reaction involving a triple bond and benzene nucleus was reported.[11]

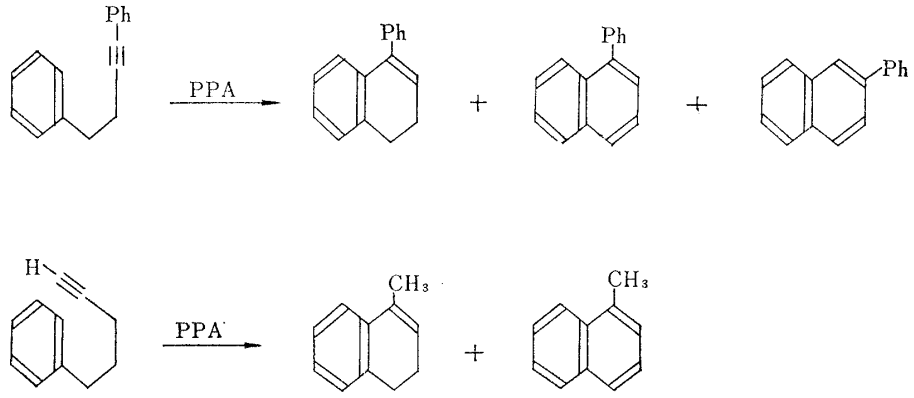

Chart 1.

This reaction was partially accompanied by dehydrogenation to give aromatic naphthalene derivatives. It is conceivable that if the reaction is conducted under milder conditions, the dehydrogenation might be prevented. Then the double bond in dihydronaphthalene derivatives can become useful for further cyclization if it is located near a functional group such as an aromatic carbonyl or hydroxyl function. This thought leads us to use an acetylenic grouping as a key function of the double cyclization to give a tetracyclic compound.

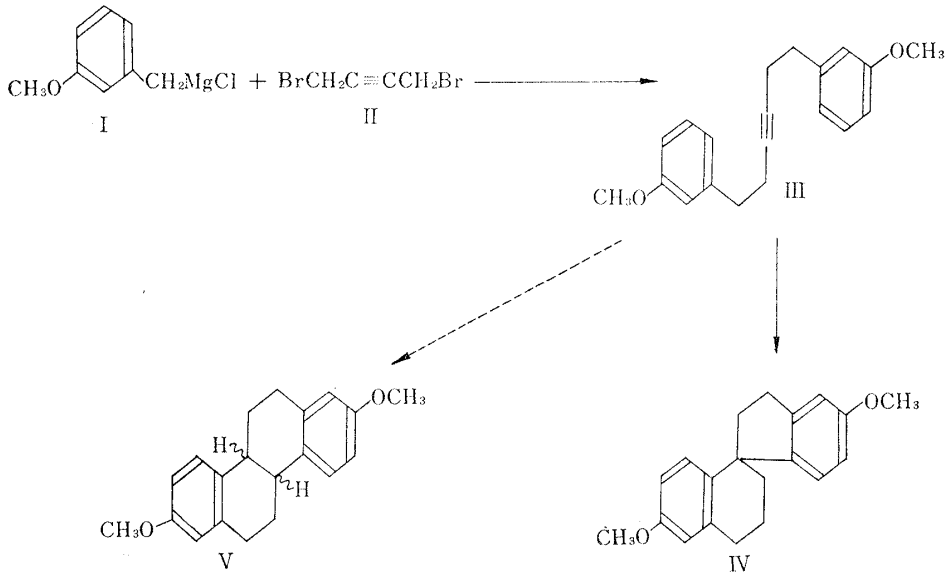

Chart 2.

5) D. K. Banerjee, V. Paul, S. K. Balasubramanian, P. S. Murthy : Tetrahedron, **20**, 2487 (1964).
6) S. J. Daum : Diss. Abs., **24**, 4992 (1964).
7) S. L. Gray : *Ibid.*, **25**, 1567 (1964).
8) Abstr. Papers, Am. Chem. Soc., 148. Aug.-Sept. 40S~41S (1964).
9) T. B. Windholz, M. Windholz : Angew. Chem. Internat. Edit., **3**, 353 (1964).
10) L. Velluz, J. Valls, G. Nominé : *Ibid.*, **4**, 181 (1965).
11) I. Iwai, T. Hiraoka : This Bulletin, **11**, 638 (1963).

First, *m*-methoxybenzylmagnesium chloride solution was prepared from *m*-methoxybenzyl chloride and magnesium according to Van Campen's method,[12] however, an appreciable amount of the coupling reaction product, 1,2-bis(*m*-methoxyphenyl)ethane, was obtained in spite of carefully controlled experiments. The reaction of *m*-methoxybenzylmagnesium chloride (I) in tetrahydrofuran with 1,4-dibromo-2-butyne (II) gave 1,6-bis(*m*-methoxyphenyl)-3-hexyne (III), m.p. 41~42°. Treatment of III with polyphosphoric acid (PPA) at 90° afforded an oil b.$p_{0.0002}$ 172~175° (bath temp.), which did not crystallize even after repeated chromatography on alumina. However the homogeneity of this oil was confirmed by gas chromatography. The physical properties listed above do not agree with those of 4,10-dimethoxy-1,2,7,8,14,17-hexahydrochrysene (V)[13] which is a crystalline substance even as a mixture of the *cis* and *trans* form. The NMR spectrum of the oil showed two different methoxy peaks and thus excluded the dimethoxyhexahydrochrysene structure (V) since in V the two methoxy groups should be equivalent in the chemical shift in both the *cis* and *trans* forms. If the double cyclization had proceeded to give a spirane derivative (IV), the NMR spectrum of the product should show four benzylic protons, whereas in the case of V six benzylic protons should be assigned in the NMR. As shown in Fig. 1, the NMR spectrum of the reaction product showed four benzylic protons around τ 7.2 and six aliphatic methylene protons around τ 8. From these facts it could be concluded that the cyclization product obtained from III is 5,6′-dimethoxy-3′,4′-dihydrospiro[indan-1,1′(2′*H*)-naphthalene] (IV).

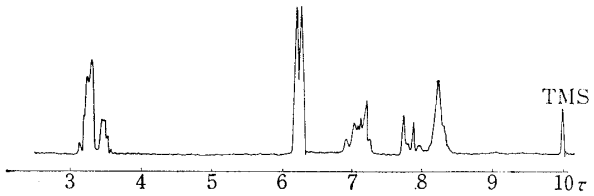

Fig. 1.

This cyclization reaction could reasonably be explained by the following reaction mechanism. The first cyclized intermediate (VI) might be protonated in two ways:

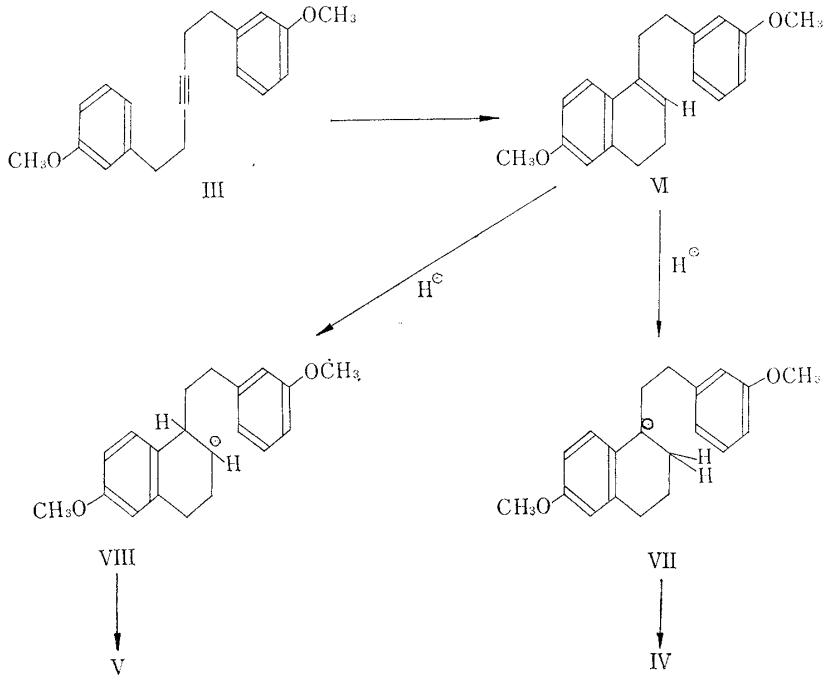

Chart 3.

12) M.G. Van Campen, D.F. Meisner, S.M. Parmerter: J. Am. Chem. Soc., **70**, 2296 (1948).
13) A.J. Birch, H. Smith: J. Chem. Soc., **1951**, 1882.

protonation at the 1 position of 3,4-dihydronaphthalene derivative (Ⅵ) gives an intermediate (Ⅷ) which leads to a chrysene derivative (Ⅴ), whereas protonation at the 2 position affords an intermediate (Ⅶ) which leads to the spirane (Ⅳ). Clearly the intermediate (Ⅶ) is thermodynamically more stable than Ⅷ because the former is a benzyl cation whereas the latter is a phenethyl cation. Therefore in the cyclization reaction of Ⅲ protonation would occur exclusively to give the intermediate (Ⅶ) which would yield the spirane (Ⅳ). In order to prevent the spirane formation and to obtain the steroidal skeleton the intermediate (Ⅵ) should be modified. A hydroxyl or ketone group in the future steroidal D-ring could be utilized advantageously to accomplish the second cyclization to the desired steroidal skeleton, because these oxy groups would be more easily protonated than the double bond of an intermediate such as Ⅵ. Therefore a derivative having a cyclopentane dione ring which would become the steroidal D-ring appeared an attractive intermediate for this purpose.

Treatment of 5-(*m*-methoxyphenyl)-1-pentyne (Ⅸ)[14] with ethyl magnesium bromide followed by hydroxymethylation with formaldehyde afforded 6-(*m*-methoxyphenyl)-2-hexyne-1-ol (Ⅹ), b.$p_{0.0008}$ 124~126°. Bromination of this acetylenic alcohol with phosphorous tribromide in ether gave 1-bromo-6-(*m*-methoxyphenyl)-2-hexyne (Ⅺ), b.$p_{0.0006}$

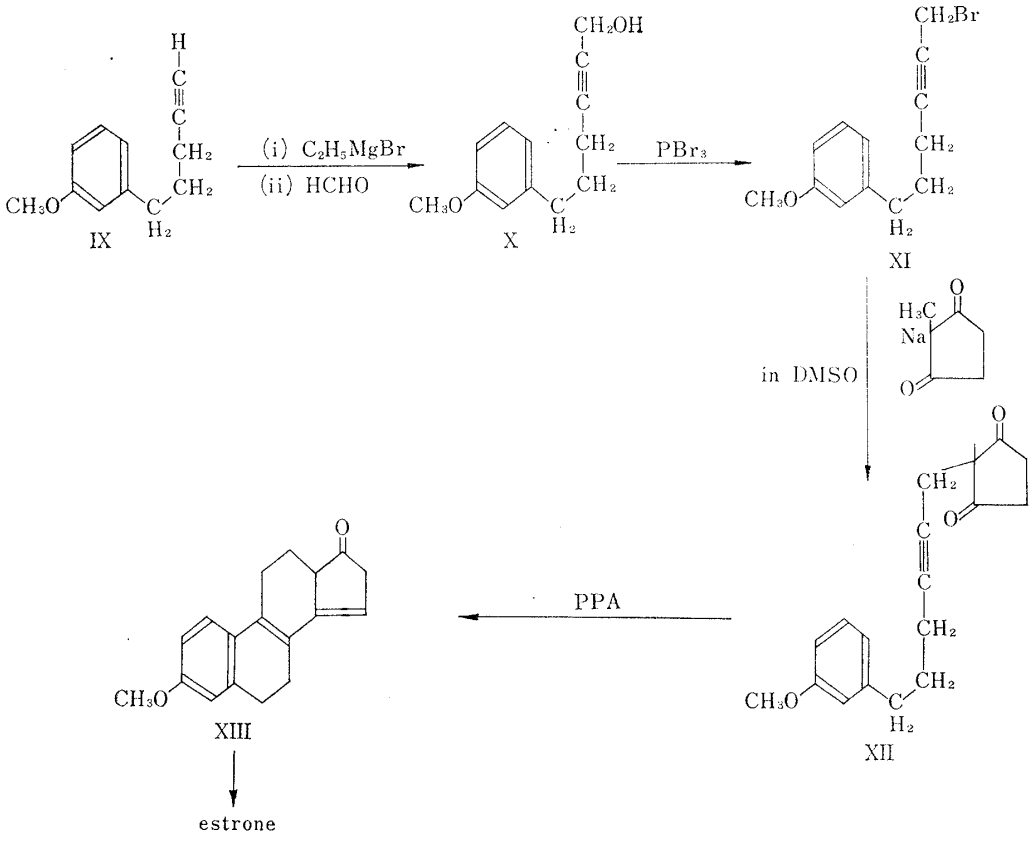

Chart 4.

114~115°. The reaction of this bromo derivative (Ⅺ) with 2-methyl-1,3-cyclopentanedione[15] encountered with great difficulties. When this reaction was carried out in methanol in the presence of sodium methoxide an unexpected carboxylic acid methyl ester was obtained. This showed in the NMR spectrum a methyl ester peak at τ

14) H. Smith, *et al.*: J. Chem. Soc., **1963**, 5072.
15) J. J. Panouse, C. Sannié: Bull. soc. chim. France, **1955**, 1036.

6.25 resulting from the ring opening of the cyclopentane moiety. This type of ring opening in a cyclic 1,3-dione derivative has been reported by Stetter, *et al.*[16]

This condensation reaction of the acetylenic bromo derivative (XI) with 2-methyl-1,3-cyclopentanedione was repeated using dioxane and acetone as solvents without success. Crispin and Whitehurst have reported that the reaction of 2-methyl-1,3-cyclopentanedione with an allylic bromo derivative gave a desired condensation product only in poor yield.[17] It is known that the reactivity of propargyl bromide derivatives in the S_N-2 type reactions is retarded owing to the inductive effect of the triple bond.[18] However it was found that the reaction proceeded well if the sodium salt of 2-methyl-1,3-cyclopentanedione was reacted in dimethyl sulfoxide. Thus the desired product, 2-methyl-2-[6-(*m*-methoxyphenyl)-2-hexynyl]-1,3-cyclopentanedione (XII), b.$p_{0.0006}$ 175~180° (bath temperature) n_D^{22} 1.5356, was obtained in 67% yield. Then XII was submitted to cyclization reaction according to the previously established method[11]; namely, treatment of XII with PPA at room temperature gave 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (XIII), m.p. 109.5~110.5°, in 63% yield whose UV and IR spectra were identical with those reported.[19] Conversion of XIII into estrone has been known,[20] and thus the total synthesis of estrone was achieved. A reasonable reaction mechanism for this double cyclization of the acetylenic derivative (XII) is shown in Chart 5.

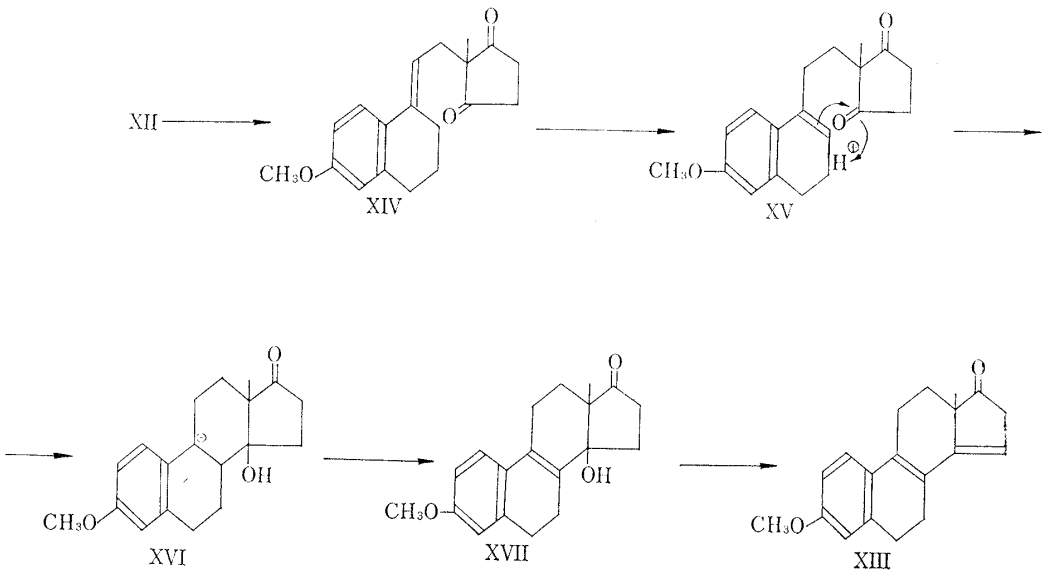

Chart 5.

The exo double bond in the first cyclized intermediate (XIV) would move to an endo position to give XV, and subsequent protonation at one of the carbonyl groups would cause the cyclization to afford XVI. Deprotonation coupled with dehydration of the 14-hydroxy group would give a stable extended conjugated system of the desired substance (XIII). Here the roll of PPA is conveniently described as a source of proton rather than to form PPA complex intermediate.[21]

16) H. Stetter, W. Dierichs : Chem. Ber., **85**, 1061 (1952).
17) D. J. Crispin, J. S. Whitehurst : Proc. Chem. Soc., **1963**, 22.
18) M. S. Newman, J. H, Wotiz : J. Am. Chem. Soc., **71**, 1292 (1949).
19) S. N. Ananchenko, I. V. Torgov : Tetrahedron Letters, **1963**, 1553.
20) G. A. Hughes, H. Smith : Chem. & Ind., **1960**, 1022; S. N. Ananchenko, I. V. Torgov : Dokl. Akad. Nauk. S. S. S. R., **127**, 553 (1959); I. V. Torgov, *et al.* : *Ibid.*, **135**, 73 (1960); *Idem* : Tetrahedron Letters, **1963**, 1553. *Idem* : *Ibid.*, **1964**, 171; T. Miki, K. Hiraka, T. Asako : Proc. Chem. Soc., **1963**, 139.
21) F. Uhlig, H. R. Snyder : "Advances in Organic Chemistry : Methods and Results," p. 43~44, Interscience Publishers, New York.

Experimental*3

1,6-Bis(*m*-methoxyphenyl)-3-hexyne (III)——To Mg-turnings (19.5 g. : 0.8 mole) in abs. tetrahydrofuran (250 ml.) was dropwise added a solution of *m*-methoxybenzyl chloride (31.3 g. : 0.2 mole) in abs. tetrahydrofuran (200 ml.) during 6 hr. During the addition the inner temperature was maintained at 50~55° by external heating. After the addition the reaction mixture was heated at 60° for 30 min. Then the excess Mg was filtered off and washed with tetrahydrofuran in N_2 atmosphere. To this Grignard solution was added butynedibromide (18 g.) in abs. tetrahydrofuran (25 ml.) under ice-water cooling. After the addition the reaction mixture was heated at 60°(inner temperature) for 5 hr. Then 10% H_2SO_4 solution (150 ml.) was added dropwise under ice-water cooling. The aqueous layer was separated and extracted with benzene. The combined organic solutions were washed with $NaHCO_3$ solution and with saturated NaCl solution until neutral to litmus, dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue was purified by chromatography using silica gel (550 g.). Elution with hexane-benzene (1:1) and recrystallization from 95% EtOH gave 1,6-bis(*m*-methoxyphenyl)-3-hexyne (III) as prisms of m.p. 41~42°(5.41 g.). *Anal.* Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found : C, 81.57; H, 7.50. UV λ_{max}^{EtOH} mμ (log ε) : 273.5 (3.59), 280 (3.57).

5,6′-Dimethoxy-3′,4′-dihydrospiro[indan-1,1′(2′*H*)-naphthalene] (IV)——A mixture of 1,6-bis(*m*-methoxyphenyl)-3-hexyne (III) (1.0 g.) and PPA (10.5 g.) was heated at 90° with continuous mechanical stirring for 3.5 hr. Then ice-water was added and extracted with ether. The combined ether extracts were washed with $NaHCO_3$ solution and with water until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oil, which was purified by Al_2O_3 chromatography(Woelm Al_2O_3, grade II, 30 g.) Elution with hexane and evaporation of the solvent gave an oil which did not crystallize. This oil was submitted to vacuum distillation to give pure 5,6′-dimethoxy-3′,4′-dihydrospiro[indan-1,1′(2′*H*)-naphthalane] (IV) (900 mg.) of $b.p_{0.0002}$ 172~175° (bath temperature). *Anal.* Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found : C, 81.36; H, 7.32. $n_D^{16.5}$ 1.6000. NMR spectrum was shown on page 264 (Fig. 1).

6-(*m*-Methoxyphenyl)-2-hexyn-1-ol (X)——An ethylmagnesium bromide solution was prepared from Mg (16 g.), EtBr (71.8 g.) and abs. tetrahydrofuran (400 ml.) in the usual manner. To this solution was added 5-(*m*-methoxyphenyl)-1-pentyne (IX) (114 g.) in abs. tetrahydrofuran (250 ml.) under ice-water cooling. After the addition the reaction mixture was heated at 60°(bath temperature) for 3.5 hr. The 200 ml. of abs. ether was added, and formaline gas (generated from 28 g. of paraformaldehyde by pyrolysis) was introduced at room temperature. The resulting reaction mixture was stirred at room temperature for 2 hr. and allowed to stand overnight. NH_4Cl (70 g.) in H_2O (1 L.) was added dropwise under ice-water cooling. The aqueous layer was separated and extracted with ether. The combined extracts were washed successively with 10% H_2SO_4 solution, $NaHCO_3$ solution and H_2O until neutral to litmus. After drying over Na_2SO_4 and evaporation of the solvent the redidue was distilled under reduced pressure to give 6-(*m*-methoxyphenyl)-2-hexyn-1-ol (X) of $b.p_{0.0008}$ 124~126°(102 g.). *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found : C, 75.94; H, 7.77. IR ν_{max}^{liquid} cm^{-1} : 2220, 2290 (-C≡C-), 3400 (-OH).

1-Bromo-6-(*m*-methoxyphenyl)-2-hexyne (XI)——To a solution of 6-(*m*-methoxyphenyl)-2-hexyn-1-ol (X) (97.7 g.) in abs. ether (250 ml.) and pyridine (6.5 ml.) was added PBr_3 (64.8 g.) at such a rate that the solution gently refluxed. After the addition was completed the reaction mixture was heated under reflux for 2 hr. Then the solution was poured into ice-water and extracted with ether. The combined extracts were washed with $NaHCO_3$ solution and with H_2O until neutral to litmus, dried over Na_2SO_4 and evaporated. Distillation of the residue gave 1-bromo-6-(*m*-methoxyphenyl)-2-hexyne (XI) of $b.p_{0.0006}$ 114~115°(112 g.). *Anal.* Calcd. for $C_{13}H_{15}OBr$: C, 57.77; H, 5.51. Found : C, 58.00; H, 5.60. IR ν_{max}^{liquid} cm^{-1} : 2220, 2290 (-C≡C-).

2-Methyl-2-[6-(*m*-methoxyphenyl)-2-hexynyl]-1,3-cyclopentanedione (XII)——To a sodium methoxide solution prepared from Na (822 mg.) and abs. MeOH (25 ml.) was added 2-methyl-1,3-cyclopentanedione (4 g.) in abs. MeOH (60 ml.) and MeOH was evaporated under reduced pressure. Traces of MeOH was removed by codistillation with benzene. To the crystalline residue was added dimethyl sulfoxide (120 ml.) and the solid substance dissolved when warmed. To the resulting solution was added 1-bromo-6-(*m*-methoxyphenyl)-2-hexyne (XI) (9.54 g.) in dimethyl sulfoxide (5 ml.) and the reaction mixture was heated at 85° (bath temperature) for 6.5 hr. Approximately one half of the dimethyl sulfoxide was evaporated under reduced pressure and the residue was poured into H_2O and extracted with ether. The combined extracts were washed with 10% NaOH solution and with H_2O until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oily residue (10.2 g.). This oil was dissolved in 30 ml. of hexane-benzene (1:1) and chromatographed over Al_2O_3 (300 g., Woelm, grade II, neutral). Elution with hexane-benzene (1:1) and evaporation of the solvent gave an oil which could not be crystallized after all efforts. Vacuum distillation of the oil gave 2-methyl-2-[6-(*m*-methoxyphenyl)-2-hexynyl]-1,3-

*3 All melting points are uncorrected.

cyclopentanedione (XII) of b.$p_{0.0006}$ 175~180° (bath temperature) (7.11 g.), n_D^{22} 1.5356. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found : C, 75.66; H, 7.36. IR ν_{max}^{liquid} cm^{-1} : 1740 (CO).

3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one (XIII)——A mixture of 2-methyl-2-[6-(*m*-methoxyphenyl)-2-hexynyl]-1,3-cyclopentanedione (XII) (1.482 g.) and PPA (20 g.) was stirred at room temperature for 6 hr. Then ice-water was added to the reaction mixture and extracted with ether. The combined extracts were washed with $NaHCO_3$ solution and with water until neutral to litmus, dried over Na_2SO_4 and evaporated to give a crystalline substance (1.35 g.). Recrystallization from MeOH gave 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (XIII) as prisms of m.p. 109.5~110.5°(600 mg.). The mother liquor was evaporated under reduced pressure and the oily residue was dissolved in benzene and chromatographed over silica gel (20 g.). Elution with benzene and recrystallization from MeOH gave a further crop of XIII (259 mg.). *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found : C, 81.66; H, 7.19. IR ν_{max}^{Nujol} cm^{-1} : 1745 (CO). UV λ_{max}^{EtOH} mμ (log ε) : 312.6 (4.49).

The authors are grateful to the members of the Analytical Section of this laboratories for elemental analyses and spectral data.

Summary

Total synthesis of estrone by the double cyclization of an acetylenic compound was achieved. This method consists of building up B and C rings of the steroidal skeleton in one step starting from a compound having A and D rings of the future steroidal system. Actually treatment of 2-methyl-2-[6-(*m*-methoxyphenyl)-2-hexynyl]-1,3-cyclopentanedione (XII) with polyphosphoric acid successfully gave 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (XIII) which is a key intermediate to estrone, whereas this type of the double cyclization of a symmetrically disubstituted acetylenic compound, 1,6-bis(*m*-methoxyphenyl)-3-hexyne (III), proceeded in a different way giving the undesirable tetracyclic spirane derivative (IV).

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