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SYNTHESIS OF FLUORINE-CONTAINING AROMATIC HETEROCYCLIC COMPOUNDS

5. REACTIONS OF 3,5-DINITRO-4-CHLOROBENZOTRIFLUORIDE AND 2-CHLORO-5-TRIFLUOROMETHYLPHENYL ISOCYANIDE DICHLORIDE WITH GOSSYPOL AND APOGOSSYPOL

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SUMMARY

The synthesis of fluorine-containing derivatives of gossypol such as 5,5'-diisopropyl-6,6',7,7'-tetra-O-di(2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-1,1'-dihydroxy-2,2'-binaphthalene (4) and 5,5'-diisopropyl-1,1',6,6',7,7'-hexa-O-tri (2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-2,2'-binaphthalene (5) is described. The structures were confirmed by IR, NMR, Analysis and Mass spectroscopy. The reactivity of gossypol with fluorine-containing electrophiles is discussed.

INTRODUCTION

Gossypol is a major toxic ingredient of cottonseed. It has many valuable biological activities being used as an anticancer agent, antibiotic and pesticide [1][2]. The report of Chinese investigators that the cottonseed pigment gossypol was an effective male antifertility agent has spawned enormous interest [3]. Because fluorine-organic chemistry has made a significant impact in the biomedical and health-related sciences, we initiated a

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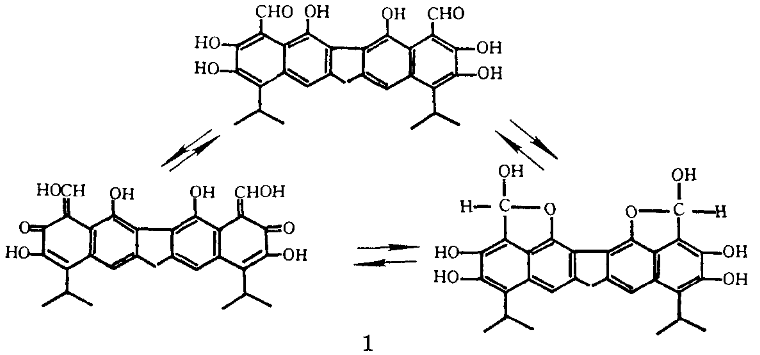
program to synthesize more active biological fluorine-containing derivatives or analogues of gossypol Recently the synthesis of a fluorine-containing gossypol Schiff base and its dynamic study by NMR was reported from our laboratory [4] [5] In this paper we describe the reaction of apogossypol with fluorine-containing electrophiles

RESULTS AND DISCUSSION

Reactions of gossypol (1) with 2-chloro-5-trifluoromethyl phenyl isocyanide dichloride (A) or 3,5-dinitro-4-chlorobenzotrifluoride (B) gave complicated mixtures, which were difficult to separate due to the isomerism of 1 as below



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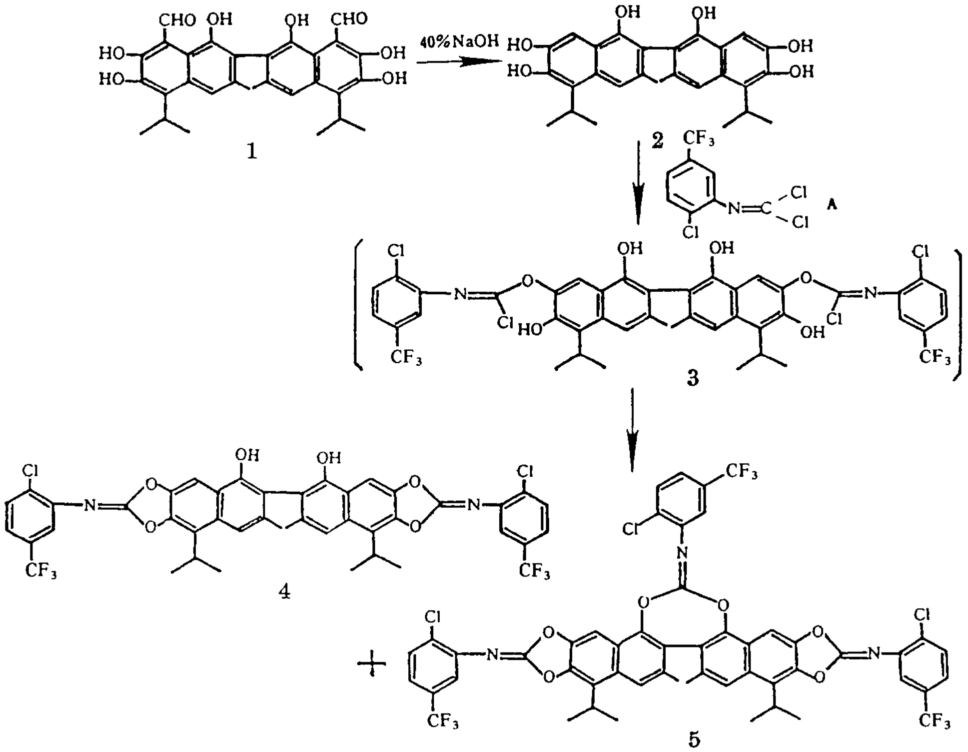
Thus gossypol (1) was treated with base to provide apogossypol (2) which readily reacted with (A) to furnish 5,5'-diisopropyl-6,6',7,7'-tetra-O-di(2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-1,1'-dihydroxy-2,2'-binaphthalene (4) and 5,5'-diisopropyl-1,1',6,6',7,7'-hexa-O-tri(2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-2,2'-binaphthalene (5), with the latter as major product (Scheme 1)

Treatment of 1 with 2,6-dinitro-4-trifluoromethyl phenylhydrazine (c) afforded the 5,5'-diisopropyl-1,1',6,6',7,7'-hexahydroxyl-3,3'-dimethyl-8,8'-di(2,6-dinitro-4-trifluoromethyl phenylhydrazone)-2,2'-binaphthalene (7), which further reacted with (B) furnishing 5,5'-diisopropyl-6,6',7,7'-tetra-O-di(3-nitro-5-trifluoromethylphenyl)-8,8'-di(2,6-dinitro-4-trifluoromethylphenylhydrazone)-3,3'-dimethyl-2,2'-binaphthyl -1,1'-diol (8) Likewise, treatment of 2 with (B) afforded

5,5'-diisopropyl-6,6',7,7'-tetra-O-di(3-nitro-5-trifluoromethylphenyl)-3,3'-dimethyl-2,2'-binaphthyl-1,1'-diol (6)
(Scheme 2)

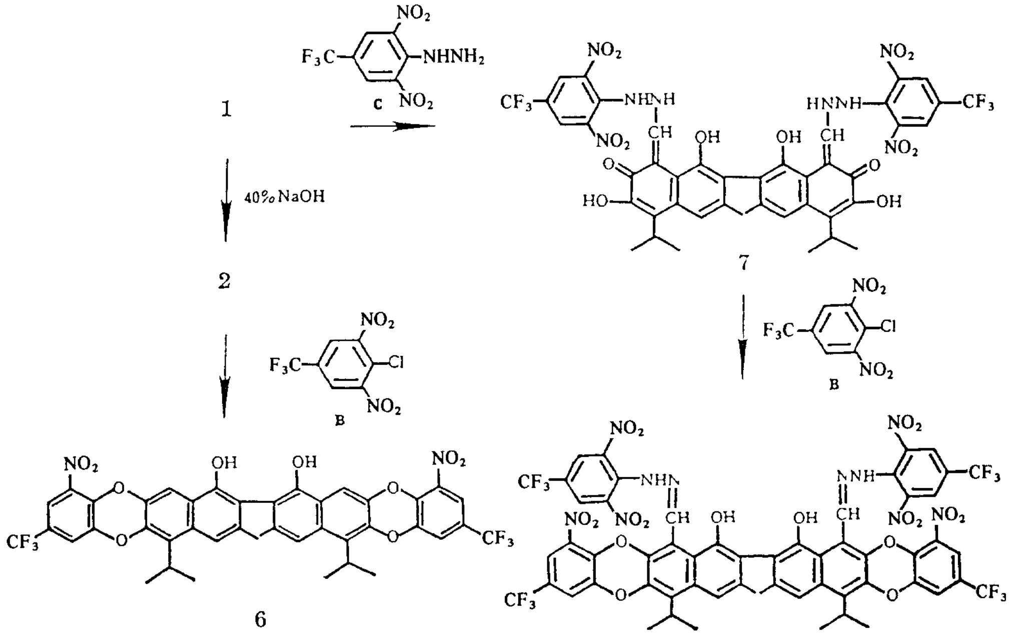


Scheme 1

The interesting structure of 5 was deduced from examination of spectroscopy data The parent ion was found at 1072 by FAB mass spectroscops and elemental analyses supported the molecular formula $C_{52}H_{33}Cl_3F_9N_3O_6$ Lack of absorption in the infrared spectrum at $3200-3500cm^{-1}$ indicates that all of OH-groups have reacted The strong absorption at $1080cm^{-1}$ showed the formation of an Ar-O-C bond ^1H NMR displays a series of signals at 1 51ppm showing that 5 contains four CH_3-groups in two $CH(CH_3)_2$-groups The presence of a multiplet at 3 98ppm is consistent with tertiary hydrogen atom coupled to a adjacent methyl group The aromatic methyl resonances of 5 appeared at

2 51 and 2 55ppm, showing two Ar-CH_3 groups, while gossypol displays only a signal at 2 04ppm Probably the downfield shift (<u>ca</u> 0 5ppm) of the aromatic methyls result from a deshielding effect of the naphthalene ring due to the formation of a 7-member ring, which places the two methyl groups in different steric environments The multiple signals at 6 77-7 88 were clear indications of the phenyl and naphthalene rings The remaining signals at 8 14-8 32 are characteristic of a phenyl ring on a 1,1'-position This leaves 5 as the reasonable structure consistent with the observed data

The structure of 4,6,8 could be deduced similarly It should be pointed out that compound 8 shows one compound on TLC but four compounds on HPTLC Elemental analyses and mass spectra demonstrated that the four compounds have the same molecular weight, and isomerism is probably due to the cis-trans configurational isomers of NO_2 groups with the 2,6-dinitro-4-trifluoromethylphenyl hydrazone groups



Scheme 2

Evidence suggests that the 1,1',6,6',7,7'-OH have similar nucleophilic reactivity toward (A) and the distorted angle is beneficial to the formation of the seven membered ring in addition to two five member rings in 4 However, by using (B) instead of (A), only one product (6) was obtained, 1,1'-OH groups still remain Interestingly, no monosubstituted product (3) has been found even by using excess of (A), demonstrating that the intramolecular ring-closure reaction of 3 is more ready than the intermolecular disubstituted reaction with (A) Probably this is due to the steric hindrance of 3 or the increased stability of the second phenol ion (1,1'-OH), which immediately underwent nucleophilic attack at the carbocation of 3 forming 4 and 5

EXPERIMENTAL

Melting points were determined on a X-4 melting point apparatus and were uncorrected Routine NMR spectra were recorded on Varian XL-200 spectrometer, TMS being used as internal reference, acetone-d_6 as solvents Infrared spectra were obtained on a Perkin Elmer 983 spectrometer Mass spectra were measured on Finnigan 4021 spectrometer

5,5'-Diisopropyl-3,3'-dimethyl-1,1',6,6',7,7'-hexahydroxyl-2,2'-binaphthalene (2) [6]

10 0g(0 017mol) of Gossypol acetic acid (1) was heated in 40% aqueous sodium hydroxide (80ml) at 90^{o}C under a nitrogen atmosphere for 3h The reaction mixture was poured onto ice containing concentrated sulfuric acid The resultant precipitate was extracted with ether, and the combined extracts were washed with water, dried and concentrated in vacuo to gave 8 0g of crude apogossypol (2) in near quantitative yield This product was not further purified but used directly in the next reaction

5,5'-diisopropyl-6,6',7,7'-tetra-O-di(2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-1,1'-dihydroxyl-2,2'-binaphthalene (4) and 5,5'-diisopropyl-1,1',6,6',7,7'-hexa-O-tri(2-chloro-5-trifluoromethylphenylisocyanide)-3,3'-dimethyl-2,2'-binaphthalene (5)

To a stirring solution containing 0 4g(0 87mmol) of apogossypol (2) and 0 53g(1 9mmol) of 2-chloro-5-trifluoromethylphenyl isocyanide dichloride in 20ml THF, 0 5g(4 9mmol) of triethylamine was added dropwise The mixture was stirred at room temperature under N_2 for 3h and then refluxed for 7h The precipitated white solids were removed by filtration and the cake was washed with acetone Combined filtrates were concentrated under reduced pressure and the residual oil was dissolved in ether, washed with 0 5M HCl and water, dried with Na_2SO_4 This solution was concentrated in vacuo and the residue was separated through a column (30x2cm) which was eluted with a linear gradient of light petroleum and 10% ethyl acetate in light petroleum Then using TLC (silica gel, 10% ethyl acetic acid in light petroleum, four times) 60mg of a light yellow solid (4) was obtained in 8% yield m p 164-166°C IR (KCl) 3200(w, OH), 1750, 1736(s, N=C), 1625, 1579(m,ArH), 1129-1246(s, C-F)cm^{-1} ^{1}HNMR δH(CD_3COCD_3) 1 40-1 51(12H, m, 2x-CH$(CH_3)_2$), 2 14(6H, s, 2xAr-CH_3), 3 06(2H, s, 2xOH), 3 93(2H, m, 2x-CH$(CH3)_2$), 7 50-7 55(2H, m, Ar-H), 7 73-7 77(6H, m, Ar-H), 7 96(2H, s, Ar-H)ppm Anal calcd for $C_{44}H_{32}Cl_2F_6N_2O_6$ C, 60 76, H, 3 68, N, 3 22 M^+, 869 Found C, 60 97, H, 3 81, N, 3 25 M^+,869

180mg of a white solid (5) was obtained in 20% yield m p 160-162°C IR(KCl) 1740, 1760(s, N=C), 1625, 1579(m, ArH), 1240(s, F-C), 1080(s, ArOC)cm^{-1} ^{1}H NMR δH(CD_3COCD_3) 1 51(12H, m, 2x-CH$(CH_3)_2$), 2 51(3H, s, Ar-CH_3), 2 55(3H, s, Ar-CH_3), 3 98 (2H, m, 2x-CH$(CH_3)_2$), 6 77-7 88(10H, m, ArH), 8 14-8 32(3H, m, ArH)ppm Anal calcd for $C_{52}H_{33}Cl_3F_9N_3O_6$ C, 58 18, H, 3 08, F, 15 94, N, 3 91, M^+, 1072 Found C, 58 54 H, 3 12, F, 15 64, N, 3 81 M^+,1072

5,5'-Diisopropyl-6,6',7,7'-tetra-O-di(3-nitro-5-trifluoromethylphenyl)-3,3'-dimethyl-2,2'-binaphthyl-1,1'-diol (6)

To a stirring solution containing 0 8g(1 7mmol) of apogossypol (2) and excess of 4-chloro-3,5-dinitrotrifluoromethylbenzene in 40ml of THF, 1 3g(11mmol) of triethylamine was added dropwise The reaction mixture was stirred at room temperature under N_2 for 3h and under reflux for 7h The precipitated solids were removed by filtration and the cake washed with acetone The combined organic extracts were evaporated in vacuo and the residual oil was dissolved in chloroform, washed with 0 5M HCl and water, dried with Na_2SO_4 This solution was concentrated in vacuo and the residue was separated through a column(80X2cm) which was eluted with a linear gradient of light petroleum and 10% ethyl acetate in light petroleum (200ml each) 160mg of a rhombic orange crystalline solid (6) was obtained in 11% yield m p 212-214°C IR(KCl) 3526(s, OH), 1613, 1580(w, ArH), 1545(s, $-NO_2$), 1277, 1230(s, C-F)cm^{-1} ^1H NMR $\delta H(CD_3COCD_3)$ 1 62-1 53(12H, t, 2X-$CH(CH_3)_2$), 2 13(6H, s, 2XAr-CH_3), 3 14(2H, s, 2XOH), 4 05(2H, m, 2X -$CH(CH_3)_2$), 7 64-7 98(8H, m, Ar-H)ppm Anal calcd for $C_{42}H_{30}F_6N_2O_{10}$ C, 60 29, H, 3 59, N, 3 35, F, 13 64 M^+,836 Found C,60 44, H, 3 80, N, 3 54, F, 13 58 M^+, 836

5,5'-Diisopropyl-6,6',7,7'-tetra-O-di(3-nitro-5-trifluoromethylphenyl)-8,8'-di(2,6-dinitro-4-trifluoromethylphenylhydrazone)-3,3'-dimethyl-2,2'-binaphthyl-1,1'-diol (8)

Gossypol diphenyl hydrazone (7) was prepared according to literature [7]

A mixture of 0 5g(0 96mmol) of gossypol and excess of 2,6-dinitro-4-trifluoromethylphenylhydrazine in 70ml ethanol was refluxed for 10h The product was collected by filtration, washed with ethanol and recrystallized from ethanol-acetone 0 75g of purplish red crystalline needles (7) was obtained in 77% yield m p 278-280°C

To a stirring solution containing 0 51g(0 5mmol) of 7 and 1 0g(3 7mmol) of 4-chloro-3,5-dinitrotrifluoromethylbenzene in 20ml THF, 0 48g (4 8mmol) of triethylamine was added dropwise The reaction mixture was stirred under reflux for 24h The solids formed were removed by filtration and the cake was washed with acetone The combined filtrates were evaporated in vacuo and the residual oil was dissolved in ether, washed with 0 5M HCl and water, dried with Na_2SO_4 This solution was concentrated and the residue was separated through a column (30X 2cm) which was eluted with a linear gradient of light petroleum and 10% ethyl acetate in light petroleum (250ml each) 150mg of a pale orange crystalline solid (8) was obtained in 22% yield m p 250^{o}C IR(KCl) 3415(m, NH), 3310(w,OH), 1634(s, ArH), 1551(s, $-NO_2$)cm^{-1} ^{1}H NMR δH(CD_3COCD_3) 1 54-1 73(12H, m, 2X-$CH(CH_3)_2$), 2 38-2 40(6H, d, 2xAr-CH_3), 3 07(4H, s, 2xNH, 2xOH), 4 08-4 40(2H, m, 2X-$CH(CH_3)_2$), 6 61(2H, m, ArH), 7 63 (2H, s, 2xCH=N), 7 92(2H, m, ArH), 8 12(2H, m, ArH), 8 57(2H, m, Ar-H), 8 90(2H, m, Ar-H)ppm Anal calcd for $C_{58}H_{36}F_{12}N_{10}O_{18}$ C, 50 22, H, 2 45, N, 10 00, M$^+$,1386 Found C,50 05, H, 2 33, N, 10 07 M$^+$,1386

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