The Synthesis of 4-Substituted Tropolones from 3-Phenoxytropolone

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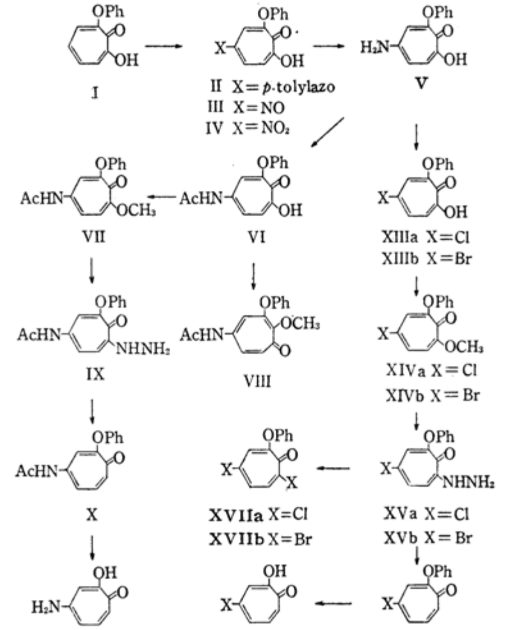
In a previous paper,[1] it was described how 2-phenoxytropone has been synthesized from 3-phenoxytropolone through a hydrazinotropone derivative. This reaction has now been extended to 5-substituted 3-phenoxytropolones in order to synthesize some 4-substituted tropolones, such as 4-amino-, 4-chloro- and 4-bromotropolone, which are fundamental compounds in troponoid and are interesting in their chemical natures.

The azo-coupling of 3-phenoxytropolone (I)[1] with *p*-tolyldiazonium chloride afforded a *p*-tolylazo compound (II). On the other hand, the nitrosation of I with sodium nitrite in acetic acid afforded a nitroso compound (III), and the nitration of I with fuming nitric acid afforded a nitro compound (IV). By catalytic reduction all of these compounds (II, III and IV) gave the same amino compound (V.) From the general tendency in the electrophilic substitution of tropolones, which suggests that azo and nitroso groups are located at the 5-position of the tropolone ring,[2] II and III are assumed to be 5-(*p*-tolylazo)- and 5-nitroso-3-phenoxytropolone respectively; consequently, IV and V are 5-nitro- and 5-amino-3-phenoxytropolone respectively.

The acetylation of V gave a monoacetate (VI), which is assumed to be 5-acetamido-3-phenoxytropolone from its acidic nature, its positive color reaction with ferric chloride, and its infrared spectrum, which shows an absorption at 1683 cm^{-1} (C=O of amide). The methylation of VI with diazomethane afforded two methyl ethers (VII and VIII.) When heated with hydrazine, one of these methyl ethers, VII, gave a hydrazinotropone derivative (IX,) in which the methoxyl group was replaced with hydrazine. The oxidative decomposition of IX with copper sulfate in acetic acid afforded a dehydrazinated compound (X,) which is assumed to be 4-acetamido-2-phenoxytropone from its infrared spectrum, which shows absorptions at 1704 cm^{-1} (C=O of amide) and 827 cm^{-1}.[3] The alkaline hydrolysis of X afforded an amino compound, which was identical with the 4-aminotropolone (XI) obtained from 4-acetyltropolone by a Schmidt reaction[4] or from 3-iodotropolone by an abnormal substitution reaction in liquid ammonia.[4] On the basis of these results, it is established that IX and X are 4-acetamido-7-hydrazino-2-phenoxytropone and 4-acetamido-2-phenoxytropone respectively, and that, consequently, methyl ether VII and VIII are 4-acetamido-7-methoxy-2-phenoxytropone and 5-acetamido-2-methoxy-3-phenoxytropone respectively.

4-Chlorotropolone (XIIa) and 4-bromotropolone (XIIb) were synthesized from 5-amino-3-phenoxytropolone (V) as described in the following sequence. By a Sandmeyer reaction, V was converted to 5-chloro-3-phenoxytropolone (XIIIa) and 5-bromo-3-phenoxytropolone (XIIIb), which in turn gave crystalline methyl ethers, 4-chloro-7-methoxy-2-phenoxytropone (XIVa) and 4-bromo-7-methoxy-2-phenoxytropone (XIVb) with diazomethane respectively. The heating of methyl ethers, (XIVa and XIVb) with hydrazine afforded



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[1] K. Takase, This Bulletin, 37, 1288 (1964).

[2] T. Nozoe, *Fortsh. Chem. org. Naturstoffe*, 13, 273 (1956).

[3] 2, 4-Disubstituted tropones show the characteristic absorption in the 810~840 cm^{-1} range (T. Nozoe, K. Takase and M. Yasunami, to be published).

[4] K. Doi, This Bulletin, 34, 497, 501 (1961).

4-chloro-7-hydrazino-2-phenoxytropolone (XVa) and 4-bromo-7-hydrazino-2-phenoxytropone (XVb) respectively, in both of which the methoxyl group was replaced with hydrazine. The oxidative decomposition of hydrazino compounds, (XVa and XVb,) with copper sulfate in acetic acid afforded 4-chloro-2-phenoxytropone (XVIa) and 4-bromo-2-phenoxytropone (XVIb), the alkaline hydrolysis of which gave the known 4-chlorotropolone (XIIa)[6] and 4-bromotropolone (XIIb)[5,6] respectively. By the oxidative decomposition of hydrazino compounds, (XVa and XVb,) with copper sulfate in concentrated hydrochloric acid or hydrobromic acid, 4, 7-dichloro-2-phenoxytropone (XVIIa) and 4, 7-dibromo-2-phenoxytropone (XVIIb) were obtained. The above-mentioned results confirm that 4-substituted tropolones were synthesized from 3-phenoxytropolone.

Experimental[7]

5-(*p*-Tolylazo)-3-phenoxytropolone (II).—Into a solution of 3-phenoxytropolone (I) (420 mg.) in a N potassium hydroxide solution (10 ml.), *p*-tolyldiazonium chloride solution prepared from *p*-toluidine (240 mg.) was stirred. The mixture was then stirred for a further 2 hr. and acidified with 6 N hydrochloric acid. The crystals (640 mg.) m. p. 141~143°C, so obtained were recrystallized from benzene, affording II (520 mg.) as red needles, m. p. 156~157°C.

λ_{max}^{MeOH} mμ (log ε) ; 232 (4.32), 300 (4.11), 402 (4.38).

Found : C, 72.43 ; H, 5.10 ; N, 8.52. Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28 ; H, 4.85 ; N, 8.43%.

5-Nitroso-3-phenoxytropolone (III).—To a stirred solution of I (4.28 g.) in glacial acetic acid (28 ml.), a solution of sodium nitrite (4.0 g.) in water (8 ml.) was added over a 1 hr. period at 0~5°C. The mixture was stirred for a further hour, and then allowed to stand overnight in an ice-box. The crystals thereby obtained were collected by filtration and washed with water, affording III (3.57 g.), m. p. 198°C (decomp.). Recrystallization from a large amount of ethanol afforded yellowish orange rhombo prisms, m. p. 202°C (decomp.).

λ_{max}^{MeOH} mμ (log ε) ; 250 (3.93), 298 (4.05), 460 (3.50).

Found : C, 64.07 ; H, 3.68 ; N, 5.64. Calcd. for $C_{13}H_9O_4N$: C. 64.20 ; H, 3.73 ; N, 5.76%.

5-Nitro-3-phenoxytropolone (IV).—To a solution of I (210 mg.) in glacial acetic acid (2 ml.), fuming nitric acid (0.05 ml.) was added under cooling, and the mixture was then stirred for 1 hr. The addition of water to the mixture gave IV (70 mg.) as yellow crystals, m. p. 139~142°C, which were recrystallized from methanol, affording yellow needles, m. p. 143~144°C.

λ_{max}^{MeOH} mμ (log ε) ; 245 (4.25), 390 (4.17), 432 (4.25).

Found : C, 60.03 ; H, 3.60 ; N, 5.54. Calcd. for $C_{13}H_9O_5N$: C, 60.23 ; H, 3.50 ; N, 5.40%.

5-Amino-3-phenoxytropolone (V).—*a) From 5-(p-Tolylazo)-3-phenoxytropolone (II)*.—A suspension of II (150 mg.) in methanol (10 ml.) was shaken with hydrogen in the presence of 5% palladium on carbon (20 mg.) ; 23 ml. of hydrogen (23°C, 760 mmHg) was absorbed during 5 hr. The catalyst was then removed and the solvent evaporated, affording a mixture of crystals and an oily substance. Benzene was added to this mixture, and soluble part was decanted off. The residue was recrystallized from methanol to give V (70 mg.) as yellow needles, m. p. 90~94°C, which showed the same melting point upon further recrystallization from the same solvent.

λ_{max}^{MeOH} mμ (log ε) ; 235 (4.38), 358 (4.24).

Found : C, 65.03, 64.88 ; H, 5.52, 5.34 ; N, 5.57, 5.54. Calcd. for $C_{13}H_{11}O_3N \cdot CH_3OH$: C, 64.36 ; H, 5.79 ; N, 5.36%.

b) From 5-Nitroso-3-phenoxytropolone (III). — When a suspension of III (2.43 g.) in methanol (40 ml.) was hydrogenated in the presence of 5% palladium on carbon (200 mg.), 490 ml. of hydrogen (20°C, 760 mmHg) was absorbed during 1 hr. The catalyst was then filtered off and the filtrate concentrated to give V (1.91 g.) as yellow needles, m. p. 92~94°C.

The hydrogenolysis of III in the presence of platinum oxide also gave V.

c) From 5-Nitro-3-phenoxytropolone (IV).—When a solution of IV (60 mg.) in methanol (5 ml.) was hydrogenated in the presence of platinum oxide, V (30 mg.) was obtained as yellow needles, m. p. 90~93°C, after the treatment described in b).

5-Acetamido-3-phenoxytropolone (VI).—When a mixture of V (1.86 g.) and acetic anhydride (3.7 ml.) was heated for 5 min. and then cooled, it afforded VI (1.55 g.) as yellow needles, m. p. 190~191°C.

λ_{max}^{MeOH} mμ (log ε) ; 242 (4.38), 348 (4.18).

Found : C, 66.76 ; H, 4.94 ; N, 5.10. Calcd. for $C_{15}H_{13}O_4N$: C, 66.41 ; H, 4.83 ; N, 5.16%.

4-Acetamido-7-methoxy-2-phenoxytropone (VII) **and 5-Acetamido-2-methoxy-3-phenoxytropone** (VIII).—To a stirred suspension of VI (1.35 g.) in a mixture of ether (2.5 ml.) and ethyl acetate (5 ml.), an ethereal solution of diazomethane (10 ml.) was added under cooling with ice-water. After the mixture had been stirred for a further 6 hr., the crystals (940 mg.), m. p. 191~194°C, so obtained were collected by filtration and recrystallized from methanol, affording VII (540 mg.) as pale yellow prisms, m. p. 216~218°C.

λ_{max}^{MeOH} mμ (log ε) ; 245 (4.34), 343 (4.15), 368 (4.12).

Found : C, 67.31 ; H, 5.68 ; N, 4.80. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36 ; H, 5.30 ; N, 4.91%.

All the filtrates were combined, the solvent was removed, and the residue was dissolved in ethyl acetate and chromatographed through and alumina column. The first effluent gave crystals (470 mg.), m. p. 120~124°C, which were then recrystallized

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[5] K. Doi, ibid., **34**, 504 (1961).

[6] T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Npipon Kagaku Zasshi*), **80**, 1171 (1959).

[7] All melting points are uncorrected.

from ethyl acetate, affording VIII as yellow scaels, m. p. 126∼127°C.

λ_{max}^{MeOH} mμ (log ε); 245 (4.35), 340 (4.18).

Found: C, 67.48; H, 5.27; N, 4.86. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91%.

From the second effluent, VII (250 mg.) was obtained, m. p. 214∼216°C after recrystallization from methanol.

4-Acetamido-7-hydrazino-2-phenoxytropone (IX). —A mixture of VII (540 mg.), ethanol (1.5 ml.) and 80% hydrazine hydrate (0.2 ml.) was warmed for 2 min. and then cooled to give IX (460 mg.) as yellow needles, m. p. 210°C (decomp.).

λ_{max}^{MeOH} mμ (log ε); 258 (4.37), 360 (4.27), 428 (3.99).

Found: C, 63.13; H, 5.13; N, 15.10. Calcd. for $C_{15}H_{15}O_3N_3$: C, 63.15; H, 5.30; N, 14.73%.

Acetate: M. p. 247°C (decomp.), pale yellow needles (from ethanol).

λ_{max}^{MeOH} mμ (log ε); 252 (4.39), 355 (4.29), 410 (4.01).

Found: C, 62.17; H, 5,01; N, 12.59. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.24; N, 12.84%.

4-Acetamido-2-phenoxytropone (X).—A solution of IX (200 mg.) in a mixture of glacial acetic acid (3 ml.) and water (1 ml.) was heated at about 100°C; to this, a 30% copper sulfate solution (1.2 ml.) was added in one lot and heating was continued for 2 min. The reaction mixture was then diluted with water (15 ml.) and extracted with chloroform, and the chloroform solution was passed through a short alumina column. The evaporation of the solvent from the effluent left crystals (130 mg.), m. p. 168∼171°C, which were recrystallized from a mixture of chloroform and ethyl acetate to give X as colorless needles, m. p. 174∼175°C.

λ_{max}^{MeOH} mμ (log ε); 268 (4.25), 358 (4.05).

Found: C, 70.16; H, 5.45; N, 5.47. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49%.

4-Aminotropolone (XI).—A mixture of X (120 mg.) in ethanol (2 ml.) and a 2 N potassium hydroxide solution (1 ml.) was heated under reflux for 2 hr. and then neutralized to pH 7 with 2 N hydrochloric acid and extracted with chloroform. After the evaporation of the solvent, the residue was sublimed in vacuo and recrystallized from methanol to give XI (40 mg.) as colorless needles, m. p. 187∼188°C, which showed no depression of melting point on admixture with an authentic specimen.⁴⁾

N-Acetate: M. p. 167°C; pale brown prisms (from ethanol).

λ_{max}^{MeOH} mμ (log ε); 267 (4.56), 335 (3.75), 365 (3.85).

Found: C, 60.51; H, 5.00; N, 7.74. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82%.

5-Chloro-3-phenoxytropolone (XIIIa). — To a stirred mixture of V (920 mg.) in 50% aqueous dioxane (10 ml.) containing concentrated sulfuric acid (0.6 ml.), a solution of sodium nitrite (360 mg.) in water (1 ml.) was added over a 30 min. period at 0∼5°C. After being stirred for an additional hour, the mixture was stirred into a solution of cuprous chloride (1.4 g.) in concentrated hydrochloric acid (7.5 ml.); stirring was then continued for one hour. Water was added, and the copper chelate thereby obtained was collected by filtration and dried. Into a suspension of this copper chelate in chloroform, hydrogen sulfide gas was passed, and the copper sulfide thereby formed was filtered off. The evaporation of the solvent from the filtrate gave XIIIa (710 mg.), m. p. 100∼103°C, which was recrystallized from methanol, affording pale yellow prisms, m. p. 106∼107°C.

λ_{max}^{MeOH} mμ (log ε); 248 (3.40), 342 (4.09), 385 (3.77), 416 (3.68).

Found: C, 62.95; H, 3.96. Calcd. for $C_{13}H_9O_3Cl$: C, 62.79; H, 3.65%.

5-Bromo-3-phenoxytropolone (XIIIb).—A diazotized solution of III (920 mg.), as in the above experiment, was treated with a solution of cuprous bromide (1.4 g.) in concentrated hydrobromic acid (7.5 ml.). The copper chelate so obtained was treated with hydrogen sulfide gas to give XIIIb (870 mg.), m. p. 93∼96°C. Recrystallization from methanol afforded pale yellow needles, m. p. 100∼101°C).

λ_{max}^{MeOH} mμ (log ε); 250 (4.42), 342 (4.17), 390 (3.75), 416 (3.79).

Found: C, 53.34, H, 2.09. Calcd. for $C_{13}H_9O_3Br$: C, 53.26; H, 3.10%.

4-Chloro-7-methoxy-2-phenoxytropone (XIVa).— To a stirred suspension of XIIIa (950 mg.) in ether (8 ml.), an ethereal solution of diazomethane (6.5 ml.) was added while it was being cooled with ice-water; then the mixture was stirred for 3 hr. and allowed to stand overnight. The crystals so obtained were collected by filtration and recrystallized from ethanol, affording XIVa (430 mg.) as pale yellow needles, m. p. 133∼134°C.

λ_{max}^{MeOH} mμ (log ε); 248 (4.37), 330 (4.05), 362 (3.91).

Found: C, 63.96; H, 3.99. Calcd. for $C_{14}H_{11}O_3Cl$: C, 64.01; H, 4.23%.

The removal of the solvent from the filtrate gave an oily substance, which was then dissolved in benzene and chromatographed through an alumina column. The first effluent gave an oily substance (300 mg.), while the second effluent gave XIVa (100 mg.).

4-Bromo-7-methoxy-2-phenoxytropone (XIVb).— The same treatment of XIIIb (1.03 g.) with diazomethane as in the above experiment and recrystallization from ethanol afforded XIVb (470 mg.) as pale yellow needles, m. p. 155∼156°C.

λ_{max}^{MeOH} mμ (log ε); 428 (4.42), 330 (4.05), 360 (3.94).

Found: C, 54.92; H, 3.09. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.74; H, 3.61%.

The filtrate was chromatographed as in the above experiment, giving an oily substance (300 mg.) and XIVb (70 mg.).

4-Chloro-7-hydrazino-2-phenoxytropone (XVa).— When mixture of XIVa (400 mg.) in ethanol (2 ml.) and 80% hydrazine hydrate (0.2 ml.) was warmed for 2 min., XVa was obtained as yellow needles, m. p. 205°C (decomp.).

λ_{max}^{MeOH} mμ (log ε) ; 256 (4.22), 352 (4.14), 430 (3.92).

Found : C, 59.64 ; H, 3.98 ; N, 10.48. Calcd. for $C_{13}H_{11}O_2N_2Cl$: C, 59.43 ; H, 4.23 ; N, 10.68%.

Acetate : M. p. 155～157°C ; pale yellow needles (from methanol).

λ_{max}^{MeOH} mμ (log ε) ; 255 (4.32), 348 (4.12), 398 (3.94), 414 (3.96).

Found : C, 59.09 ; H, 4.13 ; N, 9.01. Calcd. for $C_{15}H_{13}O_3N_2Cl$: C, 59.12 ; H, 4.33 ; N, 9.19%.

4-Bromo-7-hydrazino-2-phenoxytropone (XVb).—The treatment of XIVb (400 mg.) with hydrazine, as in the above experiment, afforded XVb (340 mg.) as yellow needles, m. p. 199°C (decomp.).

λ_{max}^{MeOH} mμ (log ε) ; 258 (4.19), 355 (4.09), 430 (3.80).

Found : C, 50.69 ; H, 3.74 ; N, 8.90. Calcd. for $C_{13}H_{11}O_2N_2Br$: C, 50.83 ; H, 3.61 ; N, 9.12%.

Acetate : M. p. 185～186°C, yellow needles (from ethanol).

λ_{max}^{MeOH} mμ (log ε) ; 255 (4.33), 348 (4.22), 395 (3.93), 412 (3.95).

Found : C, 51.74 ; H, 3.65 ; N, 7.79. Calcd. for $C_{15}H_{13}O_3N_2Br$: C, 51.59 ; H, 3.75 ; N, 8.02%.

4-Chloro-2-phenoxytropone (XVIa).—A solution of XVa (180 mg.) in a mixture of glacial acetic acid (2 ml.) and water (1 ml.) was heated at about 100°C ; to this, a 30% copper sulfate solution (1.5 ml.) was added in one lot and heating was continued for 15 min. The mixture was then diluted with water and extracted with chloroform, and the chloroform solution was passed through a short alumina column. The removal of the solvent from the effluent left crystals (110 mg.), m. p. 80～83°C, which were recrystallized from a mixture of benzene and cyclohexane to give XVIa as colorless prisms, m. p. 85～86°C.

λ_{max}^{MeOH} mμ (log ε) ; 238 (4.37), 332 (3.95).

Found : C, 66.52 ; H, 3.61. Calcd. for $C_{13}H_9O_2Cl$: C, 67.11 ; H, 3.90%.

4-Bromo-2-phenoxytropone (XVIb). — The same treatment of XVb (210 mg.) with a copper sulfate solution, as in the above experiment, and recrystallization from a mixture of benzene and cyclohexane afforded XVIb (100 mg.) as colorless prisms, m. p. 94～95°C.

λ_{max}^{MeOH} mμ (log ε) ; 242 (4.37), 332 (4.00).

Found : C, 56.40 ; H, 3.23. Calcd. for $C_{13}H_9O_2Br$: C, 56.34 ; H, 3.27%.

4-Chlorotropolone (XIIa).—A solution of XVIa (70 mg.) in a mixture of ethanol (1 ml.) and a 2 N potassium hydroxide solution (1 ml.) was heated under reflux for 2 hr. and then acidified with 6 N hydrochloric acid and extracted with benzene. The benzene layer was shaken with a 2 N potassium carbonate solution, and the carbonate layer was acidified and extracted with chloroform. The removal of the solvent from the extract and the sublimation of the residue in vaccuo afforded colorless crystals, m. p. 68～71°C. Recrystallization from ethanol gave XIIa, m. p. 79～80°C, as colorless needles, which showed no depression of melting point on admixture with an authentic specimen.⁶⁾

4-Bromotropolone (XIIb). — The hydrolysis of XVIb (70 mg.), as in the above experiment, afforded colorless crystals (40 mg.), m. p. 80～83°C. Recrystallization from ethanol gave XIIb, m. p. 87～88°C, as colorless needles, which showed no depression of melting point on admixture with an authentic specimen.⁵,⁶⁾

4, 7-Dichloro-2-phenoxytropone (XVIIa).—A suspension of XVa (100 mg.) in concentrated hydrochloric acid (2 ml.) was heated at about 100°C ; to this, a 20% copper sulfate solution (2 ml.) was added in one lot, and heating was continued for 2 min. The mixture was then diluted with water and extracted with chloroform. The solvent was evaporated, and the residue was passed through a short almina column in a benzene solution to give XVIIa (70 mg.), m. p. 112～115°C. Recrystallization from methanol afforded colorless needles, m. p. 115～116°C.

λ_{max}^{MeOH} mμ (log ε) ; 248 (4.42) ; 340 (3.99).

Found : C, 58.19 ; H, 3.08. Calcd. for $C_{13}H_8O_2Cl_2$: C, 58.45 ; H, 3.02%.

4, 7-Dibromo-2-phenoxytropone (XVIIb). — The treatment of XVb (100 mg.) in concentrated hydrobromic acid with a copper sulfate solution, as in the above experiment, afforded XVIIb (50 mg.), m. p. 112～114°C. Recrystallization from methanol afforded pale yellow needles, m. p. 117～119°C.

λ_{max}^{MeOH} mμ (log ε) ; 262 (4.33), 345 (3.99).

Found : C, 43.68 ; H, 2.75. Calcd. for $C_{13}H_8O_2Br_2$: C, 43.54 ; H, 2.26%.

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