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The Synthesis and Reactions of Pyridotropolones

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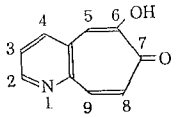
Abstract

Investigations of the synthesis and reactions of pyridotropolones are summarized and discussed. Contents: 1. Introduction 2. Synthesis of pyridotropolones 3. The bromo compounds of pyrido [3, 2-*d*] tropolones and their rearrangement reaction to 6-quinolinols 4. Nitroso and quinoxalo compounds of pyrido[3, 2-*d*]tropolones and *α*-thujaplicine 5. Formation of 2-styryl-pyrido[3, 2-*d*]tropolones and isopropyl-pyrido[3, 2-*d*]indolo-[2, 3-*b*]tropones 6. The reaction of pyridotropolones and their methyl ether 7. Conclusion 8. References.

1 Introduction

Colchicine, which contains tropolone ring, and its allied compounds have the ability to arrest mitosis of plant and animal cells and have found important applications in horticulture and cancer research.[1] Many troponoid compounds show antibacterial activities and 5-aminotropolone and some other tropolone derivatives exhibit radiomimetic action against cancerous cells.[2] Further, some quinoline derivatives show important pharamacological activities and have been used as chemoterapeutics.

Therefore it is interesting to investigate the synthesis and reactions of pyridotropolones which contain a tropolone ring fused with a pyridine ring. There have been some brief reports[3-5] on pyridotropolones but no detailed studies. In view of the above considerations the author carried out the present investigation and obtained some interesting results. The nomenclature employed is as shown in the following example. Pyridotropolone is numbered as follows:



Pyrido[3, 2-*d*]-tropolone
(6-Hydroxy-7H-cyclo-hepta[*b*]pyridin-7-one)

2 Synthesis of Pyridotropolones

2-1 Application of Skraup quinoline synthesis

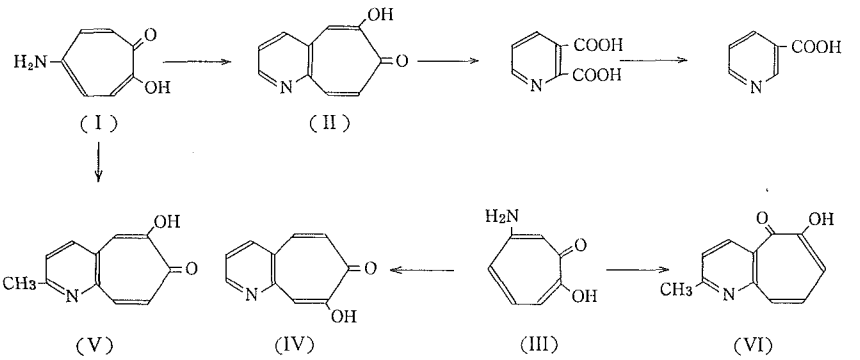
COOK et al[3] synthesized pyrido[3, 2-*d*]tropolone (II) from 5-aminotropolone (I) by the usual Skraup quinoline synthesis method, and then II was oxidized with concentrated nitric acid to quinolinic acid, which on sublimation gave nicotinic acid. The author[6,7] applied the

same procedure to 5-amino compounds of α-thujaplicine, hinokitiol, 4-methyl- and 3-bromo-tropolone, and obtained the corresponding pyrido[3, 2-*d*]tropolones. Moreover, it was found that pyridotropolones were obtained in good yield[8] by the reaction of 5-aminotropolones with α-bromoacrolein.[9] 9-Methyl- and 9-isopropyl-pyrido[3, 2-*d*]tropolones were thus obtained. These compounds were not obtained by the usual Skraup synthesis. DOI[10] obtained pyrido[2, 3-*d*]tropolone (IV) in poor yield, applying the usual Skraup synthesis method to 4-aminotropolone (III).

2-2 Application of Doebner-Miller quinoline synthesis

SLACK et al[4] obtained 2-methyl-pyrido[3, 2-*d*]tropolone (V) from 5-amino-tropolone by the application of Doebner-Miller quinoline synthesis. AKROYD et al[5] obtained 2, 9-dimethyl-pyrido[3, 2-*d*]tropolone from 5-amino-4-methyl-tropolone by the same method. The author[6,7] obtained the corresponding pyrido[3, 2-*d*]-tropolones from 5-amino compounds of α-thujaplicine, hinokitiol and 3-bromo-tropolone by the same reaction. Two directions of the cyclization in the Skraup-, Doebner-Miller- and Gould-Jacobs quinoline synthesis of 5-amino-α-thujaplicine and 5-amino-3-bromotropolone are possible. As for 5-amino-α-thujaplicine, it was obtained a kind of product in both cases, and these products were assumed to be 8-isopropyl-pyrido[3, 2-*d*]tropolones from the consideration of their steric hindrance of the isopropyl group. As for Skraup quinoline synthesis of 5-amino-3-bromotropolone, it was obtained a kind of monobromo compound, and two kinds of monobromo compound were obtained by Doebner-Miller quinolin synthesis. The monobromo compounds which were obtained by the reaction of II and V with one equivalent of NBS, were classified as 5-bromo compound, and the others as 8-bromo compound. DOI[10] obtained 2-methyl-pyrido[3, 2-*c*]tropolone (VI) from 4-aminotropolone. KIKUCHI and MUROI[11] obtained V in good yield using paraldehyde in phosphoric acid instead of hydrochloric acid.

Scheme 1



2-3 Application of Gould-Jacobs quinoline synthesis

5-(β, β-dicarbethoxyvinylamino)-tropolone (VII), which was obtained by condensing ethoxymethylenemalonic ester with 5-aminotropolone, gave 3-carbethoxy-4-hydroxy-pyrido[3, 2-*d*]tropolone (VIII) when heated in boiling Dowtherm. Acid hydrolysis of VIII gave carboxylic acid (IX). (SLACK et al[4]). The author[6,7] obtained the corresponding pyrido[3, 2-*d*]tropolones by the application of the

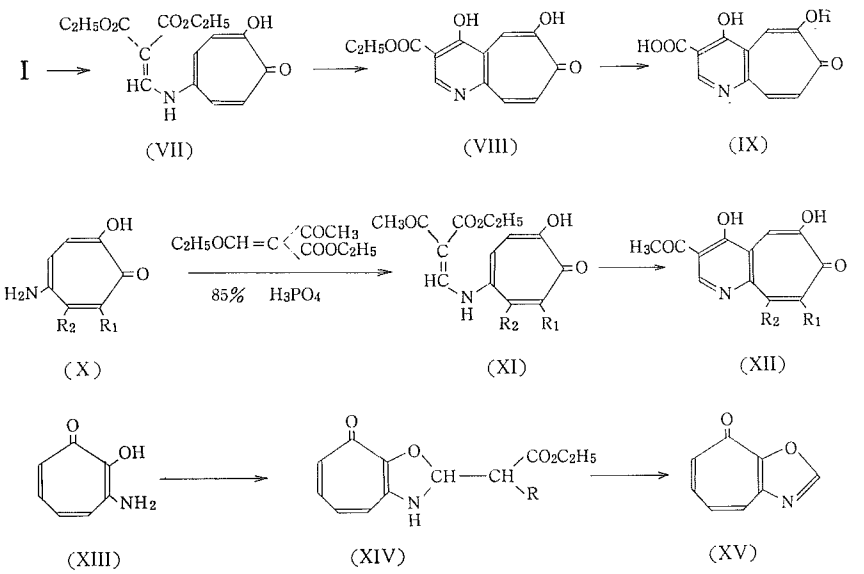
Table 1 Pyridotropolones synthesized by the Skraup reaction and the Doebner–Miller reaction.

Pyridotropolones	m.p. (°C)	Reference
Pyrido[3, 2-*d*]tropolone	165–166	6, 8)
	168–169	3)
2-Methyl-	198	4, 6)
	195–196	14)
9-Methyl-	183	8)
2, 9-Dimethyl-	192–193	5)
8-Isopropyl-	160–161	6, 8)
8-Isopropyl-2-methyl-	128–129	6)
9-Isopropyl-	137.5–138	8)
9-Isopropyl-2-methyl-	170–170.5	6)
8-Bromo-	212–213	7)
5-Bromo-2-methyl-	164.8–165.3	7)
8-Bromo-2-methyl-	204–205	7)
Pyrido[2, 3-*d*]tropolone	208–209	10)
2-Methyl-pyrido [3, 2-*c*] tropolone	187–188	10)

same method to 5-amino compounds of 3-isopropyl-, 4-isopropyl-, 4-methyl- and 3-bromotropolone. Doi[10] obtained corresponding pyrido[2, 3-*d* or 3, 2-*c*]tropolone by the same reaction of 4-aminotropolone.

The author[12] synthesized 3-acetyl-4-hydroxy-pyrido[3, 2-*d*]tropolones (XII) by thermal ring closure of the condensation products (XI) of 5-aminotropolones (X) with ethoxymethyleneacetoacetic ester.[13] The attempt at thermal ring closure of

Scheme 2



the condensation products of 4-amino- and 5-aminotropolone with ethoxymethylenecyanoacetic ester ended in failure, as did also the attempt at thermal ring closure of the condensation product of 5-aminotropolone with chloromalonedialdehyde.[7]

Neither the application of ethoxymethylenemalonic ester[14] nor of ethoxy-

Table 2 Pyridotropolones synthesized

Aminotropolone	Reagent	Condensation Product m.p.(°C)
5-Amino-tropolone	$C_2H_5OCH=C(COOC_2H_5)_2$	171
5-Amino-4-methyl-	〃	155–156
5-Amino-3-isopropyl-	〃	125–126
5-Amino-4-isopropyl-	〃	123–124
5-Amino-3-bromo-	〃	155–156
5-Amino-	$C_2H_5OCH=C(COCH_3)(COOC_2H_5)$	163–164
5-Amino-4-methyl-	〃	168–169
5-Amino-3-isopropyl-	〃	114.5–115.5
5-Amino-4-isopropyl-	〃	119–120
5-Amino-3-bromo-	〃	175–176
4-Amino-	$C_2H_5OCH=C(COOC_2H_5)_2$	136–137
5-Amino-3-isopropyl-	$C_2H_5OCH=C(CN)(COOC_2H_5)$	190–192
5-Amino-4-isopropyl-	〃	181–182
4-Amino-	〃	202–203
5-Amino-	$Cl-C(CHO)=CHOH$	227–228(dec.)
5-Amino-3-isopropyl-	〃	193.5–194

3 The bromo compounds of pyridotropolones and their rearrangement reactions to 6-quinolinols.[15]

The bromination of 8-isopropyl-pyrido[3, 2-*d*]tropolone (XVI, R=H) and 2-methyl homolog (XVI, R=CH_3) gave 5-bromo compounds (XVII) and 5, 5-dibromo compounds (XVIII) with NBS (N-bromosuccinimide). XVII affords the rearrangement product 7-isopropyl-6-quinolinol and its 2-methyl compound (XIX) when heated in a 2 N potassium hydroxide solution. XVIII were rearranged easily to 5-bromo-7-isopropyl-6-quinolinol derivatives (XX) by heating either in water or

methyleneacetoacetic ester[8,14] nor of ethoxymethylene cyanoacetic ester[14] to 3-aminotropolone (XIII) would yield pyridotropolone, but 2-substituted 2, 3-dihydrooxazolo [5, 4-*b*]tropones (XIV) (R=$CO_2C_2H_5$, $COCH_3$, CN), afforded oxazolo[5, 4-*b*]tropone (XV) on thermal treatment. Pyridotropolones synthesized from aminotropolones are listed in Tables 1 and 2.

by Gould Jacobs method.

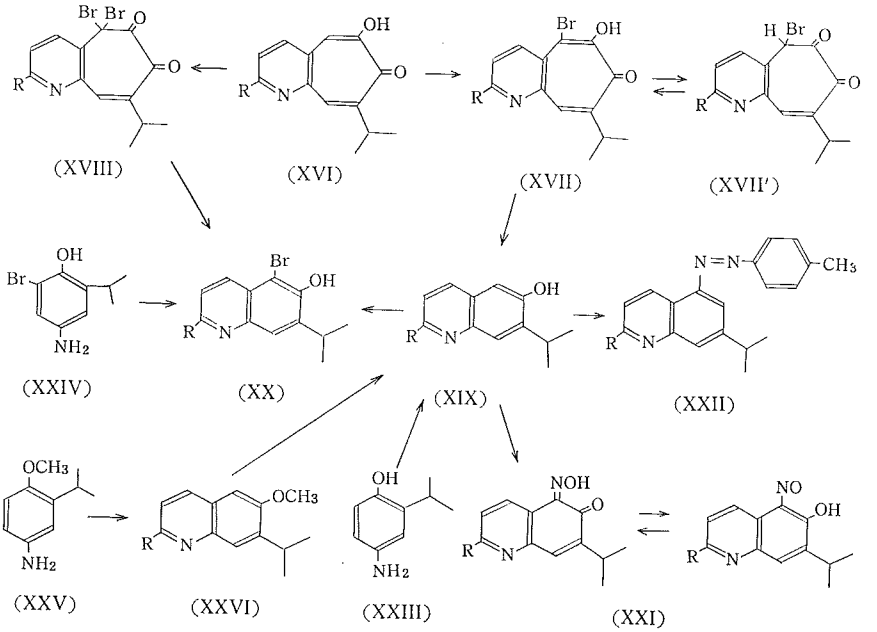
Pyridotropolone	m. p. (°C)	Reference
3-Ethoxycarbonyl-4-hydroxy-pyrido[3, 2-*d*]tropolone	>260	4)
3-Carboxy-4-hydroxy-	>280	4)
3-Ethoxycarbonyl-4-hydroxy-9-methyl-	265-268(dec.)	7)
3-Ethoxycarbonyl-4-hydroxy-8-isopropyl-	277-278(dec.)	6)
3-Ethoxycarbonyl-4-hydroxy-9-isopropyl	173-174	6)
3-Ethoxycarbonyl-4-hydroxy-(5 or 8)-bromo-	>280	7)
3-Acetyl-4-hydroxy-	>280	12)
3-Acetyl-4-hydroxy-9-methyl-	245-247	7)
3-Acetyl-4-hydroxy-8-isopropyl-	>290	12)
3-Acetyl-4-hydroxy-9-isopropyl-	169-169.7	12)
———	——	7)
3-Ethoxycarbonyl-4-hydroxy-pyrido[2, 3-*d* or 3, 2-*c*]tropolone	>270	10)
———	——	6)
———	——	6)
———	——	10)
———	——	7)
———	——	7)

in a dilute solution of acid or base. XIX afforded nitroso compound (XXI) and azo compound (XXII) and also XX on bromination. 7-Isopropyl-6- quinolinol (XIX, R=H) was synthesized by the Skraup reaction using α-bromoacrolein, and the 2-methyl homolog (XIX, R=CH_3) was obtained from 4-amino-2-isopropylphenol (XXIII) by the Doebner-Miller reaction using α-bromocrotonaldehyde. 5-Bromo-7-isopropyl-6-quinolinol (XX, R=H) was obtained from 4-amino-6-bromo-2-isopropylphenol (XXIV). XXVI (R=H and R=CH_3) were obtained from methoxyquinolines (XXVI, R=H and R=CH_3) by heating with hydroiodic acid. XXVI were

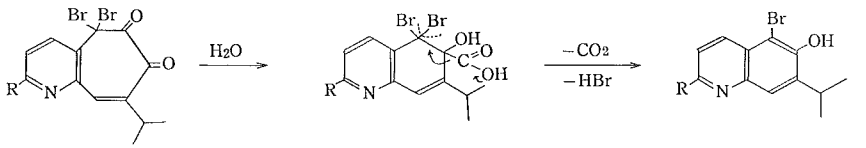
prepared from 4-amino-2-isopropylanisol (XXV). The 7-isopropyl-6-quinolinols thus synthesized were identical with the corresponding rearrangement products of brominated 8-isopropyl-pyrido[3, 2-*d*]tropolones.[16]

It is thought that the mechanism of this interesting rearrangement of XVIII to 5-bromo-7-isopropyl-6-quinolinols (XX) goes on first through benzillic acid rearrangement, followed by decarboxylation and dehydrobromination as shown in Scheme 4. In the case of the reaction of 5-bromo-8-isopropyl-pyrido[3, 2-*d*]-tropolones (XVII) to 7-isopropyl-6-quinolinols (XIX) in a potassium hydroxide solution, it is thought that XVII undergoes rearrangement in the same manner as XVIII *via* its tautomeric structure XVII'.

Scheme 3



Scheme 4.



The author[7] obtained 5-bromo-pyrido[3, 2-*d*]tropolone (XXVII) by the reaction of II with NBS, but detailed studies on the bromo compounds of II were carried out by KIKUCHI and MUROI.[11] The reaction of II with the equivalent of 2 moles of bromine gave a 5, 8-dibromo compound (XXVIII), which was obtained by the bromination of XXVII. Bromination of II with the equivalent of 2 moles of bromine afforded a 5, 5-dibromo compound (5, 5-dibromo-5H-cyclohepta[*b*]-

pyridine-6, 7-dione) (XXIX) which rearranged to 5-bromo-6-quinolinol (XXX) and a small amount of XXVII on heating in a dilute hydrochloric acid solution. II and XXVIII afforded tribromo compounds (5, 5, 8-tribromo-5H-cyclohepta[*b*]-pyridine-6, 7-dione) (XXXI) on reaction with a large excess of bromine in acetic acid. XXXI rearranged easily to 5, 7-dibromo-6-quinolinol (XXXII) on heating in dilute hydrochloric acid. The reaction of 2-methyl-pyrido[3, 2-*d*]tropolone with thionyl chloride afforded a 5-chloro compound which was also obtained by a bromochloro exchange reaction of 5-bromo compound with conc. hydrochloric acid. The halogen derivatives of pyridotropolones are shown in Table 3 except for the compounds that appeared in Tables 1 and 2.

Scheme 5

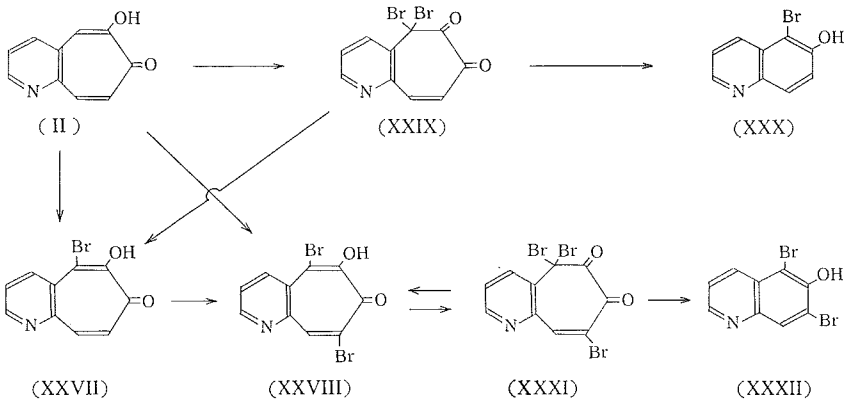


Table 3 Halogen derivatives of pyridotropolones.

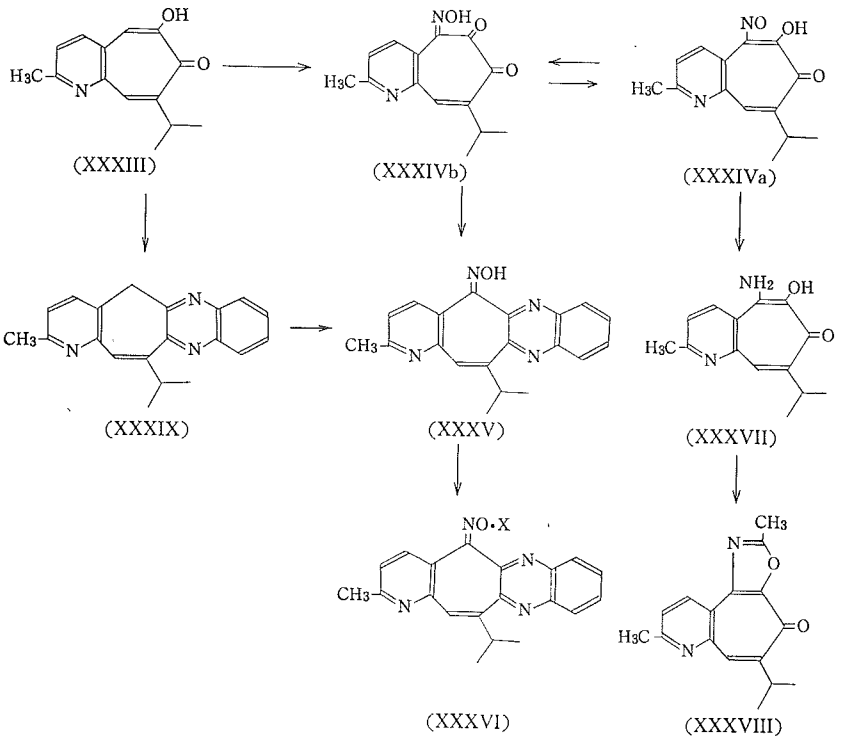
Pyrido[3, 2-*d*]tropolone	m. p. (°C)	Reference
5-Bromo-	198(dec.)	7, 11)
8-Bromo-	213	7)
5, 8-Dibromo-	232-234(dec.)	11)
5, 5-Dibromo comp. (5, 5-Dibromo-5H-cyclohepta[*b*]-pyridine-6, 7-dione)	122-124(dec.)	11)
5, 5, 8-Tribromo comp. (5, 5, 8-Tribromo-5H-cyclohepta-[*b*]pyridine-6, 7-dione)	148-150(dec.)	11)
5-Bromo-2-methyl-	166	7)
8-Bromo-2-methyl-	205	7)
5-Bromo-2, 9-dimethyl-	151	7)
5-Bromo-8-isopropyl-	156	15)
5, 5-Dibromo-8-isopropyl comp. (5, 5-Dibromo-8-isopro-pyl-5H-cyclohepta[*b*]pyridine-6, 7-dione)	143	15)
5-Bromo-8-isopropyl-2-methyl-	145.5	15)
5, 5-Dibromo-8-isopropyl-2-methyl comp. (5, 5-Dibromo-8-isopropyl-2-methyl-5H-cyclohepta[*b*]pyridine-6, 7-di-one)	175-177	15)

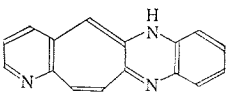
4 Nitroso- and Quinoxalo compounds of pyrido[3, 2-*d*]-tropolones and α-thujaplicine.[17]

5-Nitroso compound (XXXIV) was obtained quantitatively by the reaction of 2-methyl-8-isopropyl-pyrido[3, 2-*d*]tropolone (XXXIII) with sodium nitrite in acetic acid. Though XXXIV contains one molecule of crystalline water, it gave a quinoxalo compound XXXV on condensing with *o*-phenylenediamine. Since the infrared spectra of the acetate (XXXVI, X=$OCCH_3$) and benzoate (XXXVI, X=OCC_6H_5) exhibit carbonyl absorption (acetate, 1775, 1217 cm^{-1}; benzoate, 1760, 1243 cm^{-1}), these are not N-compounds but O-acetate or O-benzoate as shown in Scheme 6. 5-Amino compound (XXXVII) was obtained by the catalytic reduction of nitroso compound XXXIV, and gave oxazolo compound XXXVIII on heating with acetic anhydride.

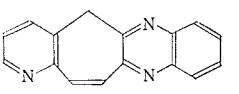
Pyrido[3, 2-*d*]tropolone (II) and 2-methyl homolog (V) have α-diketonic

Scheme 6





(A)

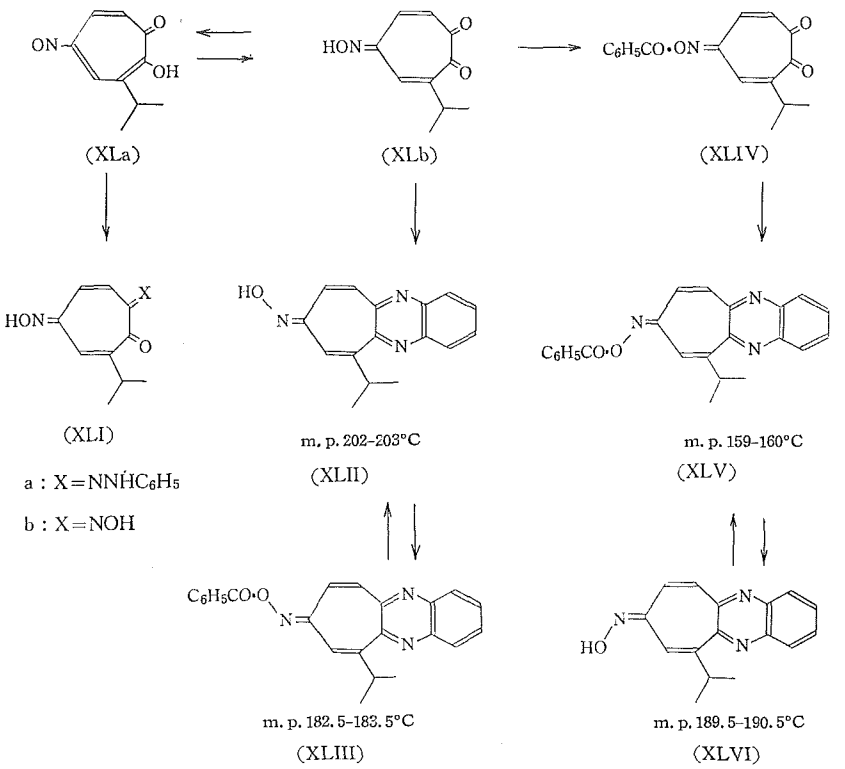


(B)

Table 4 Quinoxaline derivatives of pyrido[3, 2-*d*]tropolones.

Pyrido[3, 2-*d*]tropolone	Quinoxaline derivatives m. p. (°C)		Reference
Pyrido[3, 2-*d*] tropolone	178–180		11)
2-Methyl-	178–179		11)
8-Isopropyl-	133–134		18)
8-Isopropyl-2-methyl-	149. 5–150. 5		18)
9-Isopropyl-	158. 5–159		18)
8-Isopropyl-2-methyl-5-nitroso-	238–238. 5		17)
	picrate	224–225(dec.)	
	picrolonate	228–229	
	acetate	156–158	
	benzoate	169–170	
	HCl salt	261–261. 5(dec.)	

Scheme 7



property as shown by KIKUCHI and MUROI[11] who obtained quinoxaline derivatives from them by condensing with *o*-phenylenediamine. The author[18] obtained quinoxalo compounds from 8-isopropyl-, 8-isopropyl-2-methyl- and 9-isopropyl-pyrido-[3, 2-*d*]tropolone by the same reaction. The same compound XXXV described above was obtained by the reaction of amyl nitrite to the quinoxalo compound (XXXIX) of 8-isopropyl-2-methyl-pyrido[3, 2-*d*]tropolone. Although the two formulas A and B are possible for the quinoxalo compound, the results described above and the infrared absorption spectra support formula B and eliminate A. Quinoxaline derivatives of pyrido[3, 2-*d*]tropolones are listed in Table 4.

The author[17] studied also the quinoxalo compound of 5-nitroso-α-thujaplicine (XL)[19] and obtained some interesting results. 5-Nitroso-α-thujaplicine (XL) gave phenylhydrazone (XLIa) and oxime (XLIb). Considering the steric effect of the isopropyl group, the structures shown in Scheme 7 are proposed. XL and *o*-phenylenediamine gave quinoxalo compounds (XLII) in good yield on heating in alcohol. Benzoylation of XLII by the Schotten-Baumann method gave benzoate (XLIII). Hydrolysis of XLIII on heating with 2 N sodium hydroxide solution regenerated 3-isopropyl-quinoxalo[*d*]tropone oxime XLII. Benzoylation of 5-nitroso-α-thujaplicine by the Schotten-Baumann method afforded benzoate (XLIV), which gave a quinoxalo compound (XLV) on heating with *o*-phenylenediamine in absolute alcohol. XLV gave compound XLVI by hydrolysis on heating in a 2 N sodium hydroxide solution. The infrared spectra of the benzoates exhibit strong absorption peaks (XLIV, 1761 and 1235 cm^{-1}; XLIII, 1745 and 1230–1250 cm^{-1}; and XLV, 1762 and 1240, 1258 cm^{-1}). These facts and the analytical value indicate that the two compounds XLIII and XLV are *O*-benzoate of 3-isopropyl-quinoxalo[*d*]tropone oxime and the two compounds XLII and XLVI are 3-isopropyl-quinoxalo[*d*]tropone oxime. It is noticeable that a melting point depression is observed in the admixture of XLIII and XLV and also in the admixture of XLII and XLVI. The author considers the compounds XLIII and XLV and also XLII and XLVI to be pairs of geometrical isomers arising from the double bond, -N=C< as illustrated in Scheme 7. The symmetry of the molecule and their melting points suggest the configuration shown in Scheme 7.

5 Formation of 2-styryl-pyrido[3, 2-*d*]tropolones and isopropyl-pyrido[3, 2-*d*]indolo[2, 3-*b*]tropones

KIKUCHI and MUROI[11] obtained 2-styryl-pyrido[3, 2-*d*]tropolone by condensing 2-methyl-pyrido[3, 2-*d*]tropolone with benzaldehyde under the presence of zinc chloride, and obtained acetate of 2-(*m*-nitrostyryl)-pyrido[3, 2-*d*]tropolone (XLVII) by condensing V with *m*-nitrobenzaldehyde in acetic anhydride, and XLVII by hydrolysis of the acetate. The author[18] obtained 2-styryl compounds from 8-isopropyl-2-methyl- and 9-isopropyl-2-methyl-pyrido[3, 2-*d*]tropolone by the same reaction. 2-Styryl-pyrido[3, 2-*d*]tropolones are listed in Table 5.

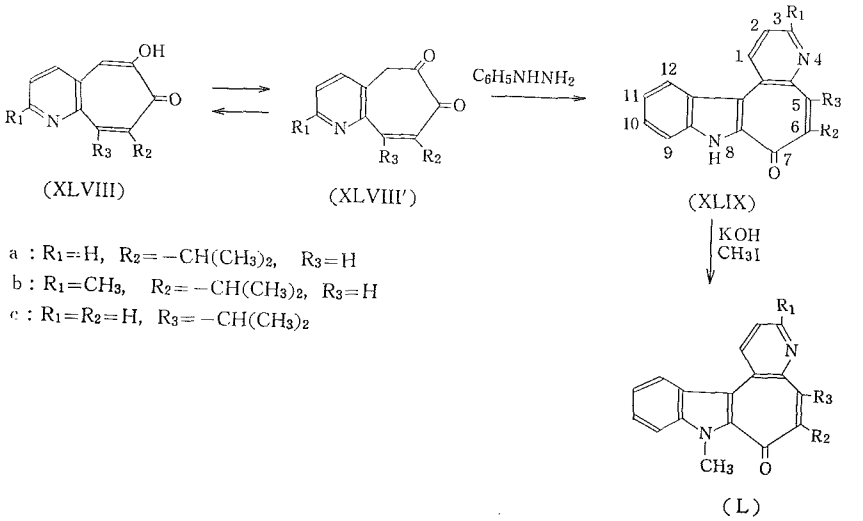
The reaction of 8-isopropyl-2-methyl-pyrido[3, 2-*d*]tropolone (XLVIIIb) with

Table 5 2-Styryl-pyrido[3, 2-*d*]tropolones.

Pyrido[3, 2-*d*]tropolone	m. p. (°C)	Reference
2-Styryl-	199-201	11)
2-(m-Nitrostyryl)-	258-260	11)
acetate	220-222	
8-Isopropyl-2-styryl-	142-142.5	18)
9-Isopropyl-2-styryl-	182-183	18)

phenylhydrazine in acetic acid gave the unexpected compound $C_{20}H_{18}ON_2$ (XLIX),[18] losing one molecule of ammonia instead of the corresponding phenylhydrazone. The crystal did not react either with carbonyl reagents or with acylating reagents, but N-methyl compound (L) was obtained by a method similar to that used in the case of carbazole. The infrared spectrum of XLIX shows absorption peaks at 1620 and 3300 cm^{-1}. 8-Isopropyl- and 9-isopropyl analoge (XLVIIIa and XLVIIIc) also gave similar compounds (XLIXa and XLIXc) respectively by the same procedure. From these facts, the reaction products are assumed to have the pyrido[3, 2-*d*]indolo[2, 3-*b*]tropone structure. It is interesting that the mother substance, pyrido[3, 2-*d*]tropolone and its 2-methyl homolog gave no pyridoindolotropones. Further studies are now in progress. The mechanism of this condensation reaction seems to be analogous to the Fischer indol syntheses as illustrated in Scheme 9. The pyrido[3, 2-*d*]indolo[2, 3-*b*]tropones obtained are listed in Table 6.

Scheme 8



a : R_1=H, R_2=$-CH(CH_3)_2$, R_3=H
b : R_1=CH_3, R_2=$-CH(CH_3)_2$, R_3=H
c : R_1=R_2=H, R_3=$-CH(CH_3)_2$

Scheme 9

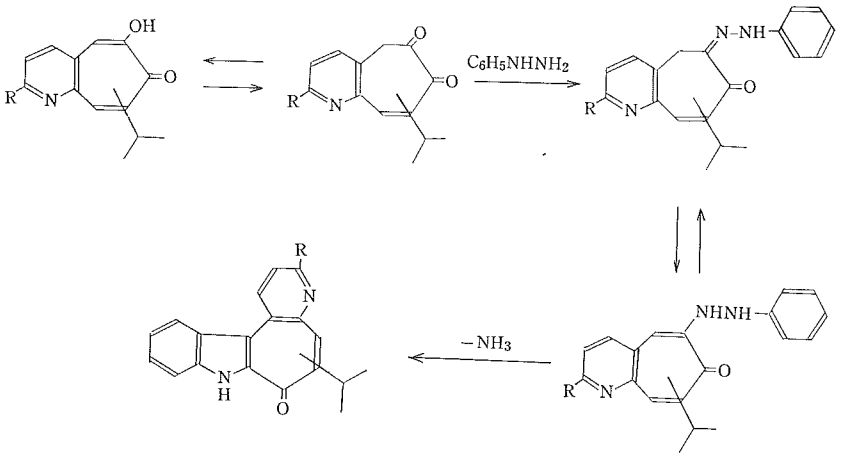


Table 6 Pyrido[3, 2-*d*]indolo[2, 3-*b*]tropones.

Pyrido[3, 2-*d*]indolo[2, 3-*b*]tropones	m. p. (°C)	Reference
6-Isopropyl-	185.5–186.5	18)
6-Isopropyl-3-methyl-	220–221	18)
N-methyl comp.	147–148	
5-Isopropyl-	255	18)

6 The reaction of pyridotropolones and their methyl ethers.

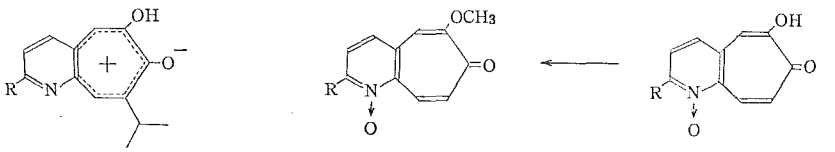
KIKUCHI and MUROI[11] have reported that pyrido[3, 2-*d*]tropolone (II) and its 2-methyl homolog (V) appear to have an *α*-diketone structure, affording dioximes, dihydrazones, osazones and quinoxaline derivatives. The methyl ethers are also reactive toward ketonic reagents and resist acid hydrolysis and anionoid substitution, and these properties are quite different from those of monocyclic tropolones and rather similar to those of benzo-[20] and dibenzotropolones.[21–23] Condensation of 2-methyl-pyrido[3, 2-*d*]tropolone methyl ether with malononitril gave dicyanheptafulven derivative (LI).

On the other hand, DOI[10] obtained quinoline-7-carboxylic acid by alkali fusion from the methyl ether of pyrido[2, 3-*d*]tropolone (IV) which had been obtained by methylation with diazomethane.

Efforts to prepare quaternary salts of the pyridine nucleus of 8-isopropyl-pyrido[3, 2-*d*]tropolones by reaction with methyl iodide, ethyl iodide and ethyl *p*-toluenesulfonate were unsuccessful.[18] This was probably due to the low electron density at the nitrogen atom through the contribution of the structure LII. Similar attempts to prepare methiodide from II and V were unsuccessful, but

N-oxide of the methyl ethers was obtained by the reaction of the respective methyl ethers with hydrogen peroxide or by the methylation of the N-oxide (LIV) of II and V.[11] Nitrosation and azocoupling of II produced no certain results. Other derivatives of pyrido[3, 2-*d*]tropolones are summarized in Table 7.

Scheme 10.



(LII) (LIII) (LIV)

Table 7 Other derivatives of pyrido[3, 2-*d*]tropolones.

Pyrido[3, 2-*d*]tropolones		m.p. (°C)	Reference
Pyrido[3, 2-*d*]tropolone	dioxime	219(dec.)	11)
	dihydrazone	205(dec.)	
	osazone	199–202	
	N-oxide	235–236(dec.)	
2-Methyl-pyrido[3, 2-*d*]tropolone	dioxime	227–229(dec.)	11)
	dihydrazone	228–230(dec.)	
	osazone	216–217	
	N-oxide	231(dec.)	
Pyrido[3, 2-*d*]tropolone-methylether		150–152	11)
	oxime	208–209	
	hydrazone	197–198	
	N-oxide	221–222(dec.)	
	〃 hydrazone	243–245(dec.)	
2-Methyl-pyrido[3, 2-*d*]tropolone-methylether		175	4)
		175–176	11)
	oxime	229–231	
	hydrazone	155–156	
	N-oxide	219–229(dec.)	
	〃 hydrazone	220–228(dec.)	
	dicyan-heptafulven deriv.	248–252(dec.)	
Mononitro-pyrido[3, 2-*d*]tropolone		213–218(dec.)	11)

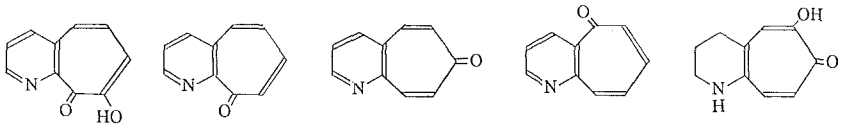
7 Conclusion

Many pyridotropolones and their alkyl derivatives were synthesized as described above. The methods for synthesizing pyridotropolones were improved, and many pyridotropolones were obtained in good yield. Pyridotropolones react undoubtedly as tautomeric forms, one of tropolone type (XLVIII) and the other of α-diketone type (XLVIII'). The reaction of pyridotropolones to ketonic reagents and also with *o*-phenylenediamine show that pyridotropolones have a notably α-diketonic property. The methyl ether of pyrido[3, 2-*d*]tropolones is also reactive toward ketonic reagents and resists hydrolysis and anionoid substitution. These properties are quite different from those of monocyclic tropolones and rather similar to those of benzo-[20] and dibenzotropolones.[21-23] Dibenzotropolones are rearranged into benzillic acid by the action of alkali, but pyrido[3, 2-*d*]tropolones resist such a rearrangement.[11]

The rearrangement reactions of the bromo compounds of pyrido[3, 2-*d*]-tropolones to 6-quinolinol derivatives are interesting. It is known that 3, 4-benzotropolones are easily rearranged to 2, 3-dibromo-1, 4-naphthoquinone by the action of excess bromine,[24] but pyrido[3, 2-*d*]tropolones did not undergo such a rearrangement.

As for monocyclic tropolones, it is known that the 5-position was the one that predominantly submitted to nitrosation, and nitroso compounds of 3, 4- and 4, 5- benzotropolones have not yet been obtained. Nevertheless, in the case of nitrosation of 8-isopropyl-2-methyl-pyrido[3, 2-*d*]tropolone, the ortho position of the tropolone nucleus submitted to nitrosation. But this fact seems to be a peculiar case. Nitrosation of other pyridotropolones is uncertain.

It is interesting that pyrido[3, 2-*d*]indolo[2, 3-*b*]tropone derivatives were obtained by the reaction of isopropyl-pyrido[3, 2-*d*]tropolones and phenylhydrazine, but the parental compound pyrido[3, 2-*d*]tropolone and its 2-methyl homolog did not undergo such a condensation reaction. In the case of 8-isopropyl-pyrido[3, 2-*d*]tropolones, the author considers that phenylhydrazine acts predominantly on the carbonyl group at the 6-position by the steric hindrance of the isopropyl group. Pyridotropolones often show different reactions depending on different substituents, and so it is important to study the reactivity of individual pyridotropolones. It appeared of interest to investigate further the synthesis and reactions of pyrido[3, 2-*f*]tropolones (C), pyridotropones (D, E and F) and also pyridinotropolones (G) which have not yet been obtained. Moreover, it would be interesting to investigate the biological and pharamacological activities of pyridotropolones and their allied compounds.



(C) (D) (E) (F) (G)

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