*Syntheses of α-, β- and γ-Dolabrins**

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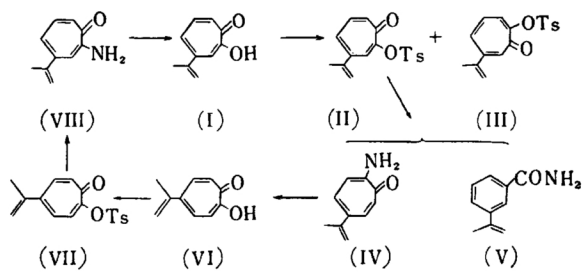
It is already known that hinokitiol (β-thujaplicin) and α-thujaplicin are present as tropolonic constituents in the essential oil of *Thujoposis dolabrata Sieb. et Zucc*[1]. Recently, the presence of β-dolabrin (4-isopropenyltropolone) in this oil was revealed in this laboratory[2], and more recently, it was also found in other species[3,4]. β-Dolabrin is the first of natural tropolones to possess a double bond in the side chain conjugated to the tropolone ring and it is interesting not only from the point of biogenesis of natural tropolones but also in the study of the chemical nature of such troponoids. For example, oxidation of β-dolabrin easily affords 4-acetyltropolone** in a high yield[2] which is an important starting material for synthesizing colchicine and its allied compounds[5].

Since there are a number of conifers containing α-, β- and γ-thujaplicines, though on different combinations according to species and habitat, there is still a possibility that α- and γ-isomers (3- and 5-isopropenyltropolones) of β-dolabrin might exist in nature[6]. In the present paper will be described the syntheses of isomeric (α-, β- and γ-) dolabrins.

According to Sato[7] in this laboratory, it is possible to convert 4-substituted tropolones to 5-substituted tropolones by utilization of the abnormal substitution of *p*-toluenesufonate of tropolones. Its reverse conversion is also possible. This reaction was applied to β-dolabrin (I). I forms two kinds of tosylates, one of m. p. 128°C and the other of m. p. 82°C, in a good yield. It is certain from the following series of experiments that the tosylate of m. p. 128°C has the structure of II and that of m. p. 82°C, the structure III. Reaction of II with methanol saturated with ammonia gives two kinds of products (IV and V), both corresponding to $C_{10}H_{10}ON$. IV turns green with ferric chloride and forms a picrate. Together with evidence of its ultraviolet spectrum (Fig. 1), IV is known to be an aminotropone derivative, while the ultraviolet spectrum of V (Fig. 1) shows it to be a benzenoid compound formed by rearrangement. Reduction of V affords *m*-cumic acid amide and, therefore, V is 3-isopropenylbenzamide. When II reacts with liquid ammonia, IV is obtained in a good yield but the rearrangement product is not



* Presented at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958.

1) T. Nozoe, A. Yasue and K. Yamane, *Proc. Japan Acad.*, **27**, 15 (1951).

2) T. Nozoe, K. Takase and M. Ogata, *Chem. & Ind.*, **1957**, 1070.

3) J. A. F. Gardner and G. M. Barton, *Can. J. Chem.*, **36**, 1612 (1958).

4) E. Zavarin, R. M. Smith and A. B. Anderson, *J. Org. Chem.*, **24**, 1318 (1959).

** Friedel-Crafts type acylation does not occur in tropolones; Cf. Ref. 6 and P. L. Pauson, *Chem. Revs.*, **55**, 43 (1955).

5) T. Nozoe, K. Takase, J. Shin, Y. Kitahara and K. Doi, Paper presented at the 132nd Convention of the American Chemical Society, New York, September, 1957.

6) T. Nozoe, *Fortsch. Chem. org. Naturstoffe*, **13**, 232 (1956).

7) T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1058 (1959).

obtained. Hydrolysis of IV with alcoholic alkali gives a tropolone derivative (VI), $C_{10}H_{10}O_2$ as colorless scaly crystals, m. p. 101°C, and its reduction affords γ-thujaplicin, indicating that VI is the objective 5-isopropenyltropolone, which may be called γ-dolabrin. pK_a value of VI is 7.17 at 25°C***.

γ-Dolabrin (VI) so obtained can be led back to β-dolabrin by the same process. VI affords only one kind of tosylate (VII) whose reaction with liquid ammonia gives 2-amino-4-isopropenyltropone (VIII) and 4-isopropenylbenzamide (IX). VIII turns green with ferric chloride and is hydrolyzed in alcoholic alkali to β-dolabrin. The structure of IX was also confirmed by its reduction to *p*-cumic acid amide. Reaction of VII with methanolic ammonia gives a small amount of methyl 4-isopropenylbenzoate (X), besides VIII and IX. The ultraviolet spectra of VIII and IX are shown in Fig. 1.

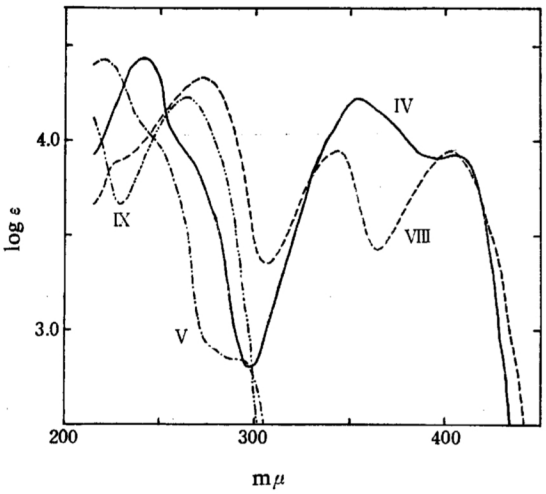


Fig. 1. Ultraviolet absorption spectra of IV, V, VIII and IX in methanol.

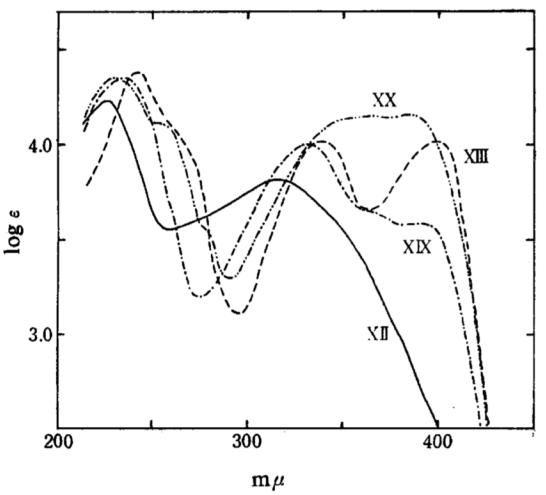


Fig. 2. Ultraviolet absorption spectra of XII, XIII, XIX and XX in methanol.

Reaction of III with liquid ammonia produces an oily substance containing aminotropone and a rearrangement product, 3-isopropenylbenzamide (V). The oily substance was not induced to crystallize or led to form a crystalline derivative such as a picrate but its hydrolysis with alcoholic alkali afforded a small amount of a tropolone derivative (XI) whose copper complex was found by mixed fusion to be identical with the copper complex of α-dolabrin which will be described below. Reaction of III with methanolic ammonia afforded V but the aminotropone derivative was not isolated. The results of the amination of III show that the large steric hindrance of the 7-position to undergo abnormal substitution in III makes it difficult to be attacked by ammonia and rearrangement product V should be formed in a larger amount.

Alkaline hydrolysis of tosylate II gives β-dolabrin and rearrangement product 3-isopropenylbenzoic acid, however acidic hydrolysis of II and III gives β-dolabrin.

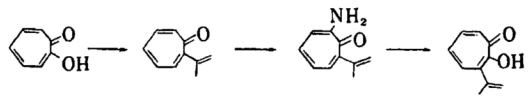
Tropolone is known to form the corresponding 2-alkyltropones by the action of alkyllithium or Grignard reagents[8,9] and this process was attempted for the introduction of isopropenyl group into the tropone ring. Reaction of excess of isopropenyllithium to tropolone afforded an oily substance (XII), $C_{10}H_{10}O$, whose ultraviolet spectrum (Fig. 2) indicated two absorption maxima corresponding to those of tropone[9]. Moreover, the maximum absorption of XII showed a bathochromic shift of 3 and 16 mμ respectively, from those of tropone and it seems appropriate to consider that this shift originates in the conjugation of the side chain double bond with the tropone ring. The infrared spectrum of XII supports the structure as 2-isopropenyltropone. XII is the first tropone derivative with a double bond in the side chain conjugated to the tropone ring and examination of its chemical properties appeared of interest. XII is fairly labile and increased its viscosity when left in the air. Attempted distillation at a reduced pressure resulted in resinification. XII forms an oily hydrochloride but does not produce distinct picrate or 2, 4-dinitrophenylhydrazone.

Attempted amination of XII with hydrazine[10]

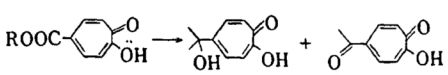
*** pK_a value was measured by Dr. N. Yui of the Institute of Applied Science, Faculty of Technology, Tohoku University, to whom the authors are deeply indebted.

8) W. von E. Doering and C. F. Hiskey, *J. Am. Chem. Soc.*, **74**, 5688 (1952).
9) T. Mukai, This Bulletin, **31**, 1547 (1958).
10) T. Nozoe, T. Mukai, J. Minegishi and T. Fujisawa, *Sci. Repts. Tohoku Univ.*, Series I, **37**, 164 (1954).

turned it black and the 2-aminotropone derivative was not isolated. Reaction of XII with hydroxylamine hydrochloride in pyridine[10] afforded the product as a brown viscous substance in the main with a trace of yellow oily substance (XIII), whose ultraviolet absorption spectrum (Fig. 2) indicated a typical curve for 2-aminotropone derivative. Hydrolysis of XIII with alcoholic alkali gave a very minute amount of a tropolone derivative (XIV), m. p. 36°C, which showed coloration with ferric chloride characteristic of tropolones and easily formed a copper complex, $C_{20}H_{18}O_4Cu$. This copper complex showed no depression of the melting point when fused with the copper complex of XI mentioned above. Paper chromatography of XI and XIV also gave spots with identical R_f value.



(XII) (XIII) (XIV)



(XVI~XVIII) (XIX) (XX)

Synthesis of γ-dolabrin was attempted by the Grignard reaction of tropolone-5-carboxylic acid alkylester. Methylmagnesium iodide was applied to tropolone-5-carboxylic acid (XV)[11], its methyl ester, and iron complex, but all these compounds were sparingly soluble in ether and the starting compound was recovered in all cases. In order to increase solubility in ether, amyl (XVI), octyl (XVII), and cyclohexyl (XVIII) esters of tropolone-5-carboxylic acid were prepared. Application of about six molar equivalents of methylmagnesium iodide against these esters afforded 5-α-hydroxyisopropyltropolone (XIX) and 5-acetyltropolon (XX). The ultraviolet absorption spectra of XIX and XX are indicated in Fig. 2. The structure of XIX was confirmed from the fact that dehydration of XIX by heating with potassium hydrogensulfate easily afforded γ-dolabrin (VI). XIX turns green in aqueous layer to ferric chloride but the color does not transfer to benzene or chloroform layer. This is the general behavior of hydroxyl or carboxyl derivatives of tropolone. XIX is easily dehydrated and changes partly into VI on heating with acid or by sublimation. 5-Acetyltropolone (XX) is also obtained by oxidation of VI. XX easily forms an oxime, the same as 4-acetyltropolone as already reported[5], and also undergoes condensation with benzaldehyde derivatives to

11) Y. Kitahara, ibid., 40, 74 (1956).

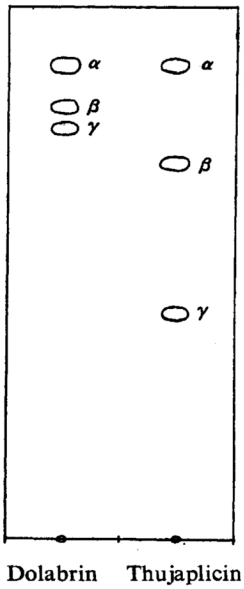


Fig. 3. Paper chromatogram of α-, β- and γ-dolabrin and α-, β- and γ-thujaplicin.

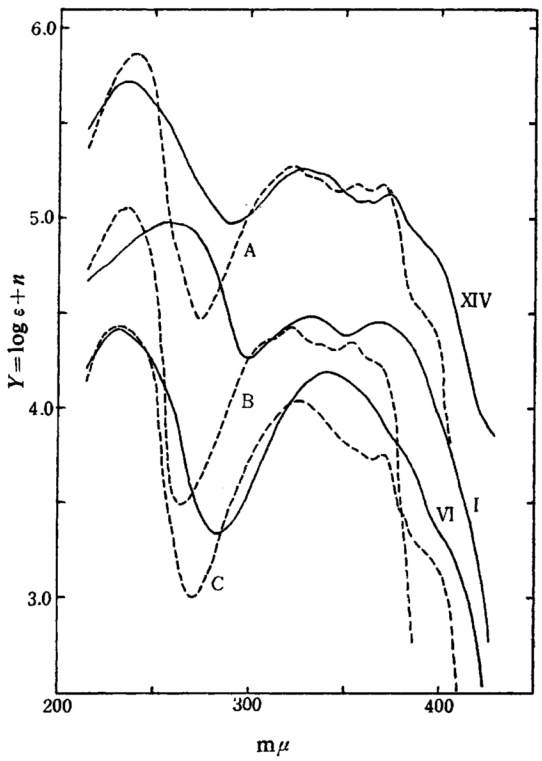


Fig. 4. Ultraviolet absorption spectra of α-, β- and γ-dolabrin (XIV, I and VI), and α-, β- and γ-thujaplicin (A, B and C).

$Y = \log + 1.5$ (for α-series)
$Y = \log + 0.7$ (for β-series)
$Y = \log + 0$ (for γ-series)

form 5-cinnamoyltropolone derivatives.

The work described in this paper has completed the total syntheses of α-, β- and γ-dolabrins, and 4-, and 5-acetyltropolones.

The paper chromatogram**** of α-, β- and γ-dolabrins so obtained is shown in Fig. 3, and their ultraviolet absorption spectra, together with those of corresponding thujaplicins are given in Fig. 4. The spectra of dolabrins show a bathochromic shift from those of corresponding thujaplicins, due to conjugation of the isopropenyl group with the tropolone ring. The absorption of γ-dolabrin in the longer wavelength region differs from that of α- and β-isomers.

Experimental[12]

p-Toluenesulfonate (II and III) of β-Dolabrin (I).—To a solution of 1 g. of β-dolabrin dissolved in 1.5 ml. of pyridine, 1.4 g. of p-toluenesulfonyl chloride was added and the mixture was allowed to stand for about 1 hr. The colorless needles that precipitated out by addition of 4 ml. of ethanol were collected by filtration. Recrystallization of crude crystals, m. p. 124~126°C, from ethanol afforded 820 mg. of II as colorless plates, m. p. 127~128°C. Ethanol was evaporated from the filtrate left after removal of II, water was added to the residue, and the solution was extracted with benzene. The benzene extract was dried, passed through a chromatographic column of alumina, and eluted with benzene. 850 mg. of crystals, m.p. 72~74°C, thereby obtained were recrystallized from ethanol to III as pale yellow scales, m. p. 81~82°C.

Found (for II): C, 64.67; H. 4.66. Found (for III): C, 64.64; H, 4.96. Calcd. for $C_{17}H_{16}O_4S$: C, 64.55; H, 5.10%.

Reaction of 2-Tosyloxy-4-isopropenyltropone (II) and Ammonia a) A solution of 300 mg. of II dissolved in 30 ml. of methanol saturated with ammonia was allowed to stand at room temperature for 4 days. Methanol was evaporated under reduced pressure and the residue was treated with benzene, from which 165 mg. of ammonium p-toluenesulfonate was obtained as the insoluble portion. The benzene soluble portion was chromatographed over alumina and eluted with benzene, affording 70 mg. of yellow crystals m. p. 99~102°C. Subsequent elution with ethyl acetate gave 30 mg. of crystals, m. p. 119~123°C. Recrystallization of the former from benzene-cyclohexane mixture afforded IV as yellow needles, m. p. 110~112°C, while that of the latter from benzene-cyclohexane gave V as colorless scales, m. p. 126~126.5°C.

Found (for IV): C, 74.34; H, 6.90; N, 8.09. Found (for V): C, 74.29; H, 6.93; N, 8.75. Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69%.

IV forms a picrate of yellow prisms, m. p. 174~175°C (decomp.).

Found: C, 48.80; H, 3.26; N, 14.42. Calcd. for $C_{16}H_{14}O_8N_4$: C, 49.23; H, 3.62; N, 14.36%.

b) A mixture of 200 mg. of II and 13 ml. of liquid ammonia was allowed to stand at room temperature for 2 days and ammonia was evaporated. The residue was extracted with benzene and 60 mg. of IV was obtained. Purification of its filtrate by chromatography afforded 30 mg. of IV but none of V.

γ-Dolabrin (VI) from 2-Amino-5-isopropenyltropone (IV).—A mixture of 200 mg. of IV and 500 mg. of sodium hydroxide in 3 ml. of 30% ethanol was refluxed. The yellow crystals that precipitated out were collected, dissolved in water, and the solution was neutralized with 2 N hydrochloric acid, from which 150 mg. of colorless crystals, m. p. 94~96°C, was obtained. Recrystallization from benzene-cyclohexane mixture afforded VI as colorless scales, m. p. 100~101°C.

Found: C, 73.72; H, 5.86. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22%.

I. R. Spectrum: $\tilde{\nu}$ (O-H, C=O, C=C) 3215, 1606, 1595, δ (=CH_2) 907 cm^{-1}. (in KBr disk).

Copper complex: Green needles, m. p. over 290°C.

Found: C, 62.02; H, 4.49. Calcd. for $C_{20}H_{18}O_4Cu$: C, 62.24; H, 4.70%.

Reduction of γ-Dolabrin (VI) and 3-Isopropenylbenzamide (V).—a) A solution of 20 mg. of VI dissolved in 4 ml. of ethanol, added with 5 mg. of palladium-carbon, was submitted to hydrogenation and 3 ml. of hydrogen was absorbed. Ethanol was evaporated and the crystalline residue was sublimed under reduced pressure. Recrystallization of the sublimate from cyclohexane afforded colorless needles, m. p. 77~78°C, which showed no depression on admixture with γ-thujaplicin, m. p. 80°C.

b) Fifteen mg. of V was hydrogenated by the same way as above to afford 7 mg. of colorless scales, m. p. 94~95°C after recrystallization from benzene-cyclohexane, which showed no depression on admixture with m-cumic acid amide m. p. 95~95.5°C.

p-Toluenesulfonate (VII) of γ-Dolabrin (VI),—To a solution of 260 mg. of γ-dolabrin dissolved in 0.5 ml. of pyridine, 360 mg. of p-toluenesulfonyl chloride was added and the mixture was allowed to stand. After about 1.5 hr. 2 ml. of ethanol was added to it and 410 mg. of crystals m. p. 121~124°C was obtained. The filtrate was evaported and the residue was poured into water, separating 70 mg. of crystals m. p. 119~124°C. The combined crystals were recrystallized from ethanol to VII as pale yellow prisms, m. p. 125~126°C.

Found: C, 64.74; H, 5.04. Calcd. for $C_{17}H_{16}O_4S$: C, 64.55; H, 5.10%.

Reaction of 2-Tosyloxy-5-isopropenyltropone (VII) and Ammonia.—a) A mixture of 320 mg. of VII dissolved in 15 ml. of liquid ammonia was allowed to stand for 5 days at room temperature,

**** Chromatography is carried out on the paper treated with 17% aqueous solution of phosphoric acid, and benzene used as developing solvent.

12) M. p. are uncorrected. The microanalyses were carried out by Messrs Shin-ichi Ohyama, Kazuyoshi Azumi and Miss Ayako Iwanaga, and infrared spectra were measured with Perkin-Elmer Model 21 double beam spectrophotometer by the member of Prof. Kinumaki's laboratory of the Chemical Research Institute of Non-aqueous solutions, to whom the authors' acknowledgements are hereby extended.

then ammonia was evaporated, and the residue was extracted with benzene. The benzene solution was passed through an alumina layer. The first elution with benzene-ethyl acetate afforded 100 mg. of yellow crystals, m. p. 90~97°C, and subsequent elution with ethyl acetate afforded 30 mg. of colorless crystals, m. p. 181°C. Recrystallization of the former from benzene-petroleum ether afforded VIII as yellow needles, m. p. 100~101°C. The latter was recrystallized from a mixture of ethyl acetate and petroleum ether, affording IX as colorless plates, m. p. 180.5~182°C. Catalytic reduction of IX with polladium-carbon afforded colorless crystals, m. p. 152°C, which showed no depression on admixture with *p*-cumic acid amide, m. p. 153°C.

Found (for VIII): C, 74.17; H, 6.41; N, 8.92. Found (for IX): C, 74.33; H, 6.62; N, 8.62. Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69%.

Picrate of VIII: m. p. 130~131°C.

Found: C, 49.72; H, 3.48; N, 14.41. Calcd. for $C_{16}H_{14}O_8N_4$: C, 49.23; H, 3.62; N, 14.36%.

b) A solution of 400 mg. of VII dissolved in 50 ml. of methanol saturated with ammonia was allowed to stand for 4 days at room tepmerature and then the methanol was evaporated. The residue was extracted with benzene, and the benzene-insoluble portion was extracted with water. The insoluble residue was 100 mg. of crystals melting at 180°C. The sparingly soluble portion of benzene extract afforded 30 mg. of the same crystals. Both lots of crystals corresponded to IX. The benzene-soluble portion was chromatographed over alumina and elution with benzene gave 5 mg. of crystals X, m. p. 50~53°C, which showed no depresseon on admixture with methyl *p*-isopropenylbenzoate. The portion eluted with ethyl acetate affored 15 mg. of β-dolabrin, m.p. 51°C, by the same hydrolysis as below.

Hydrolysis of 2-Amino-4-isopropenyltropone (VIII).—A solution of 30 mg. of VIII dissolved in a mixture of 150 mg. of potassium hydroxide, and 1 ml. of 50% methanol was refluxed for 3.5 hr. The methanol was then evaporated, 2 ml. of water was added to the residue, and this was extracted with benzene to remove an unreacted substance, the mother liquor was acidified, extracted with benzene, and benzene was evaporated after drying. Recrystallization of its residue from cyclohexane afforded 23 mg. of pale yellow needles, m. p. 54~56°C, which showed no depression on admixture with β-dolabrin

Reaction of 2-Tosyloxy-6-isopropenyltropone (III) and Ammonia.—a) A mixture of 2 g. of III and about 20 ml. of liquid ammonia was allowed to stand for 2 days at room temperature. The ammonia was evaporated and the residue was extracted with benzene. The benzene solution was washed with water, dried, and chromatographed over alumina. Elution with benzene afforded 490 mg. of yellow oil (A), and subsequent elution with ethyl acetate afforded 220 mg. of (V), m. p. 124°C. A was refluxed with a mixture of 1 g. of potassium hydroxide, and 5 ml. of 50% ethanol for 8 hr. Ethanol was then evaporated, 5 ml. of water was added to the residue, and this was extracted with benzene. Mother liquor was acidified and extracted with benzene, affording a minute quantity of oil (XI), and this was derived to a copper complex by reaction with copper sulfate solution and 50 mg. of green crystals was obtained. Recrystallization from chloroform-petroleum ether afforded greenish yellow needles, m. p. 250°C (decomp.).

b) A solution of 2 g. of III dissolved in 200 ml. of methanol saturated with ammonia was allowed to stand for 3 days at room temperature and the solvent was evaporated. The residue was dissolved in benzene and 220 mg. of V m. p. 124°C was obtained. The filtrate was evaporated and the residue was refluxed for 2 hr. with a solution of 1 g. of sodium hydroxide in 5 ml. of 50% ethanol. The colorless needles, $C_{10}H_{13}O_2N$, m. p. 179.5~180.5°C (after recrystallization from benzene) were obtained by neutralization of the solution. However, the structure of this acidic substance was not defined.

Found (for m. p. 179.5°C): C, 66.97; H, 7.11; N, 7.73. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%.

Synthesis of 2-Isopropenyltropone (XII) from Tropolone. — A solution of 6.4 g. (0.053 mol. eq.) of 2-bromopropene dissolved in 10 ml. of ether was added dropwise into 0.65 g. (0.093 mol. eq.) of lithium in 12 ml. of ether with stirring in nitrogen atmosphere and the mixture was refluxed for 2 hr. After removal of residual lithium pieces, a solution of 1.15 g. (0.0093 mol. eq.) of tropolone dissolved in 50 ml. of ether was added dropwise with stirring and the mixture was stirred for 1 hr. The solution was cooled with ice and 20 ml. of 2 N sulfuric acid was added, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether solution was washed with sodium chloride solution, passed through an alumina layer to remove unreacted tropolone, and the ether was evaporated from the effluent, leaving 1.5 g. of pale reddish brown oil. Bromination of this oil in glacial acetic acid failed to produce any crystalline derivative. The oil was dissolved in benzene and dry hydrogen chloride gas was passed through this solution. The oily hydrochloride that separated out was collected, decomposed with water, and extracted with ether. The ether extract was washed with water, dried, and passed through a column of alumina. Evaporation of ether from the effluent afforded a reddish brown oil, n_D^{25} 1.6978, which was submitted to elemental analyses and spectral measurement.

Found: C, 81.33; H, 7.01. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90%.

I. R. spectrum: $\tilde{\nu}$ (C=O, C=C) 1627, 1570~1600, δ (=CH_2) 897 cm^{-1} (in KBr disk).

Reaction of 2-Isopropenyltropone and Hydroxylamine: (Synthesis of α-Dolabrin (XIV)). — A solution of 0.2 g. of 2-isopropenyltropone and 0.3 g. of hydroxylamine hydrochloride dissolved in a mixture of 1.5 ml. of dehydrated ethanol and 1.5 ml. of pyridine was refluxed for 2 hr. Ethanol was then evaporated, water was added to the residue, and the solution was extracted with benzene. The benzene extract was washed with water and passed through an alumina layer. First elution with benzene

afforded 20 mg. of red oil (A) and subsequent elution with chloroform and ethanol respectively afforded 10 mg. of yellowish oil (B) and 50 mg. of yellowish brown oil (C). A part of A underwent crystallization but was not purified and it was assumed to be an oxime from its ultraviolet spectrum. λ_{max}^{MeOH} mμ (log ε): 223 (4.17), 299 (3.71), 390～400 (3.11).

B also afforded no crystalline picrate but it was assumed from its ultraviolet spectrum to be 2-aminotropone derivative.

It was considered possible that C contains a 2-aminotropone derivative. Therefore, it was refluxed for 2 hr. with 0.2 g. of sodium hydroxide and 2 ml. of 50% ethanol, the ethanol was evaporated, water was added to the residue, and the solution was extracted with chloroform to remove the neutral portion. The aqueous layer was acidified and extracted with chloroform, affording 20 mg. of a brown oil. Distillation of this oil under a reduced pressure gave pale yellow crystals, m. p. 35～36°C, which was dissolved in petroleum ether and derived to a copper complex. The copper comprex came as greenish yellow crystals, m. p. 250°C (decomp.).

Found: C, 61.56; H, 5.15; Cu, 16.29. Calcd. for $C_{20}H_{18}O_4Cu$: C, 62.24; H, 4.70; Cu, 16.46%.

Synthesis of Esters of Tropolone-5-carboxylic Acid (XV).—*a) Amyl Ester (XVI).*—To a solution of 600 mg. XV dissolved in 10 ml. of amyl alcohol, 0.15 ml. of conc. sulfuric acid was added and the mixture was refluxed for 2 hr. The solution was filtered to remove carbonized material, the filtrate was concentrated, and the residue was allowed to stand with the addition of ethanol. The residue afforded 450 mg. of crystals melting at 60°C which was recrystallized from petroleum ether to XVI as colorless, scales m. p. 61～62°C. This substance turns red with ferric chloride and the color transfers to the chloroform layer.

Found: C, 66.30; H, 6.74. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

Hydrolysis of this mother liquor with alkali resulted in recovery of 150 mg. of XV, m. p. over 250°C.

b) Octyl Ester (XVII). — Obtained by the same method as a) as colorless scales, m. p. 55°C.

Found: C, 69.53; H, 8.12. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

c) Cyclohexyl Ester (XVIII).—To a solution of 600 mg. of XV dissolved in 12 ml. of cyclohexanol, 0.6 ml. of conc. hydrochloric acid was added and the mixture was refluxed for 8 hr. The reaction mixture was filtered while hot, the filtrate was concentrated, and allowed to stand. Evaporation was repeated twice and 800 mg. of crystals of m. p. 85°C was obtained as the first crop, and 140 mg. of crystals of m. p. 90°C as the second crop. The combined crystals were recrystallized from ethanol and 60 mg. of tropolone-5-carboxylic acid, m. p. over 250°C, was obtained from the sparingly soluble portion, and 600 mg. of pale brown plates XVIII, m. p. 94～95°C, from the easily soluble portion. Further recrystallization of the latter raised its melting point to 97～98°C.

Found: C, 67.07; H, 6.23. Calcd. for $C_{14}H_{16}O_4$; C, 67.73; H, 6.50%.

Synthesis of γ-Dolabrin (VI) from the Esters of Tropolone-5-caboxylic Acid.—a) A solution of 0.5 g. (0.0017 mol. eq.) of XVII dissolved in 10 ml. of ether was added with stirring under ice-cooling to the Grignard reagent from 1.6 g. (0.0113 mol. eq.) of methyl iodide, 0.26 g. (0.0104 mol. eq.) of magnesium, and ether, and the mixture was stirred for 3 hr. Ten ml. of 15% ammonium chloride solution was added to this mixture and the whole mixture was extracted thoroughly with ether. The ether was evaporated, the residue was heated with 10 ml. of 6 N sulfuric acid for 10 min. and the mixture, was extracted with three 5-ml. portions of chloroform, affording 250 mg. of dark brown oil A. The mother liquor left after chloroform extraction was extracted with eight 5-ml. portions of ethyl acetate, affording 40 mg. of pale yellow oil (B). A part of B crystallized on being allowed to stand, but its melting point could not be measured. B was submitted to paper chromatography with benzene as a solvent but it did not move with this solvent. A mixture of B and finely divided fused hydrogensulfate was heated for a few minutes at 140°C and the mixture was sublimed under reduced pressure, from which 20 mg. of colorless crystals, m. p. 90～95°C, was obtained. Recrystallization from cyclohexane afforded colorless plates, m. p. 99～100°C, undepressed on admixture with γ-dolabrin. This has indicated that B chiefly contains the objective 5-α-hydroxy-isopropyltropolone (XIX). Some crystals separated out on standing A and 25 mg. of pale yellow crystals, m. p. 178°C, was obtained. It showed no depression of the melting point on admixture with 5-acetyltropolone (XX). The mother liquor left after separation of these crystals was found to contain the octyl ester, XIX, and XX.

b) Reaction of 0.42 g. of the amyl ester (XVI) with 6 molar equivalents of methylmagnesium iodide, as in the case of the above a), was carried out. After completion of the reaction, the product was decomposed with 15 ml. of 6 N sulfuric acid. After separation of the ether layer, the mother liquor was extracted with 20 ml. and 10 ml. of chlololform, and the combined ether and chloroform extracts were washed with eight 10-ml. portions of 8 N sulfuric acid. Evaporation of the solvent from this combined extract left 250 mg. of oil A. Sulfuric acid layer and washings were combined, neutralized to pH 4 with dil. potassium hydroxide solution, and the solution continuously extracted with chloroform for 10 hr. Evaporation of chloroform from this extract afforded 80 mg. of oil which underwent crystallization. The crystals were washed out repeatedly with cyclohexane, the cyclohexane was evaporated, and the residue was sublimed under reduced pressure, affording 40 mg. of pale yellow crystals, m. p. 98～99°C, undepressed on admixture with γ-dolabrin (VI). Paper chromatographic examination showed A to be a mixture of the recovered ester, XIX, and XX.

c) A solution of 0.42 g. of the cyclohexyl ester (XVIII) dissolved in 12 ml. of ether was reacted with 6 molar equivalents of methylmagnesium iodide as in the case of (a), stirring for 1 hr. and

refluxed for 30 min. After it was cooled, 15 ml. of 4 N sulfuric acid was added to effect decomposition, extracted with ether, and the ether was evaporated after washing with water and drying over sodium sulfate, affording 250 mg. of yellow oil (A). The sulfuric acid layer was extracted 5 times with 5 ml. of chloroform each time, and the extract was washed with water, dried, and evaporated, to leave 50 mg. of oil. This crystallized immediately and was found to contain chiefly XIX and a small amount of XX. This substance actually gave green coloration in the aqueous layer and pale reddish brown coloration in the chloroform layer with ferric chloride. There was no suitable solvent for recrystallization of the above crystals but on leaving its ethalolic solution, comparatively large plate crystals, m. p. 101~104°C, separated out on the wall of the vessel. A chromatographic test indicated that A contained the recovered ester, XIX, and XX. Crystals separated out on standing A and 15 mg. of XX, m. p. 178~180°C, was obtained. The benzene solution of filtrate was chromatographed over silica gel but it was not successfully separated into its components.

5-Acetyltropolone (XX) from γ-Dolabrin (VI).—A solution of 770 mg. of VI dissolved in 27 ml. of formic acid, to which was added 6 ml. of 35% hydrogen peroxide, was stirred at 40°C for 3 hr. and formic acid was distilled off under reduced pressure. Further 7 ml. of 1.2 N sodium hydroxide was added and the mixture was stirred at 40°C for 3 hr. This was acidified with 2 N hydrochloric acid and extracted with chloroform. The aqueous layer was cooled with ice, an aqueous solution of 900 mg. of periodic acid dihydrate was added, mixture was stirred, and 590 mg. of crystals was obtained. The same amount of crystals, 70 mg., was obtained from the chloroform layer. The combined crystals were recrystallized from ethanol to XX as yellow plates, m. p. 182~183°C.

Found: C, 65.69; H, 4.49. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91%.

Oxime: Pale yellow plates, m. p. 201~202°C (decomp.).

Found: C, 60.55; H, 4.75; N, 7.81. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.00; N, 7.82%.

Condensation of XX with Benzaldehyde and 3, 4, 5-Trimethoxybenzaldehyde.—a) A mixture of 650 mg. of XX suspended in 10 ml. of methanol to which was added 700 mg. of benzaldehyde, 1.3 ml. of 5% potassium hydroxide solution, and 15 ml. of water was stirred thoroughly and the orange crystals that separated out were collected by filtration. This substance was dissolved in 100 ml. of water, acidified with 2 N hydrochloric acid, and 900 mg. of yellow needles was recrystallized from ethanol to yellow needles, m. p. 158~159°C.

Found: C, 76.04; H, 4.32. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80%.

b) A mixture of 100 mg. of XX and 150 mg. of trimethoxybenzaldehyde afforded 150 mg. of a condensate of m. p. 207.5~208.5°C after recrystallization from acetic acid.

Found: C, 66.16; H, 5.12. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

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