

HYDROGEN GAS GENERATED, ML.

Time (min.) Sample	1	2	3	4	5	6	7	10	13
Matrine	8.5	29.3	50.0	65.3	78.0	87.3	—	—	—
Allomatrine	1.1	5.1	10.2	15.2	21.1	26.2	31.0	43.9	54.1
Matridine	0.5	2.1	4.4	7.1	9.1	10.2	11.4	14.0	15.0
Allomatridine	0.4	2.0	4.1	5.2	6.2	7.0	7.2	8.2	—

dioxide stream and the hydrogen gas that generated was determined by azotometer.

Reaction of matrine and allomatrine with cyanogen bromide. A solution of 5 g. of allomatrine²⁹ dissolved in 30 ml. of dry benzene was warmed on a water bath to 60–70° and a solution of 2.3 g. of cyanogen bromide dissolved in 20 ml. of dry benzene was added dropwise. The mixture was heated for 30 min., the solvent was distilled off, and the residue was dissolved in chloroform. The chloroform solution was washed with 10% hydrochloric acid, dried over potassium carbonate, and the solvent distilled off. Addition of acetone to the residue separated some crystals which were washed with acetone and afforded 4.0 g. of bromoallomatrine cyanamide (IX), m.p. 153–157°. Further crystallization from acetone gave plates, m.p. 167–168°.

Anal. Calcd. for C₁₅H₂₂ON₃Br: C, 54.23; H, 6.80; N, 11.86. Found: C, 54.03; H, 6.85; N, 12.00.

The reaction of matrine with cyanogen bromide has already been described.⁵

Reaction of matridine²⁶ and allomatridine²⁷ with methyl

iodide. A solution of 500 mg. of the base dissolved in 2 ml. of methanol and 1 g. of methyl iodide was refluxed for 1 hr., cooled, and crystals that separated out were recrystallized. Allomatridine N⁴,N⁹-dimethiodide (X): plates (from methanol-water), m.p. 293–296° (decomp.).

Anal. Calcd. for C₁₅H₂₆N₂·2CH₃I: C, 38.80; H, 6.58; N, 4.80. Found: C, 39.00; H, 6.41; N, 4.90.

Matridine N⁹-methiodide (XI): white prisms (from acetone), m.p. 238–239°.

Anal. Calcd. for C₁₅H₂₆N₂·CH₃I: C, 50.10; H, 7.71; N, 7.44. Found: C, 50.75; H, 7.75; N, 7.29.

Acknowledgment. We thank Dr. C. Schöpf (Darmstadt) for kindly supplying a sample of *rac*-allomatridine. We are also very grateful to Dr. T. F. Platonov (Moscow), who had generously given us a sample of isoleontine.

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Santonin and Related Compounds. XVII.¹ Reactions of the Bromo Derivatives of 4,9-Dimethyl- Δ^4 -3-octalone-6-acetic Acid with Bases

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The monobromides (IIa and IIb) of the *trans*- and *cis*-ketones (Ia and Ib) mentioned in the title were treated with a variety of bases. In most cases, the $\Delta^{4,5}$ -dienones (IV and V) and the lactones (IIIa and IIIb) were obtained as the expected products. With aqueous alkali, each of the monobromides was converted in low yield to the corresponding α -ketol (VIIa or VIIb) under allylic rearrangement. As other anomalous products, a bromo lactone (VIa) and the $\Delta^{1,4}$ -dienone acid (VIIIa) were obtained from the *trans*-monobromide (IIa) in a few instances. Reactions of the dibromides (IXa and IXb) with bases led predominantly to the bromo lactones (VIa and VIb), respectively. A probable mechanism for the unusual reactions of the monobromides with bases is discussed.

Miki has reported² that treatment of the 5-bromo compound (II) of the keto acid (I) with alkali led to a liquid lactone (III) in unspecified yield. Gunstone and Tulloch³ have disclosed the isolation of a solid lactone (III) in low purity from the same monobromide (II) on reaction with sodium ethoxide. Ishikawa⁴ has reported that the enol acetate of the malonate analog of the acetic acid compound (I), which was said to be a precursor for I, was treated with peracid followed by hydrolysis-decarboxylation of the resulting lactone ester to give two solid isomers of III. The melting

points reported for these solid lactones were rather different. The starting keto acid (Ia), at that time regarded as *cis*, was recently revised to be *trans*, possessing the acetic acid side chain axial.⁵ From steric considerations, it is obvious that the result of Ishikawa⁴ is most unlikely. The purpose of this investigation was to reexamine the reaction of the *trans*-monobromide (Ia) with base and to study, for comparison purposes, the behavior of the *cis*-monoenone (Ib)⁵ upon bromination and subsequent treatment with bases.

It has been reported^{2,3} that monobromination of the *trans*-monoenone (Ia) with *N*-bromosuccinimide afforded a good yield of the 5-bromo compound (IIa). The simpler procedure using one equiv-

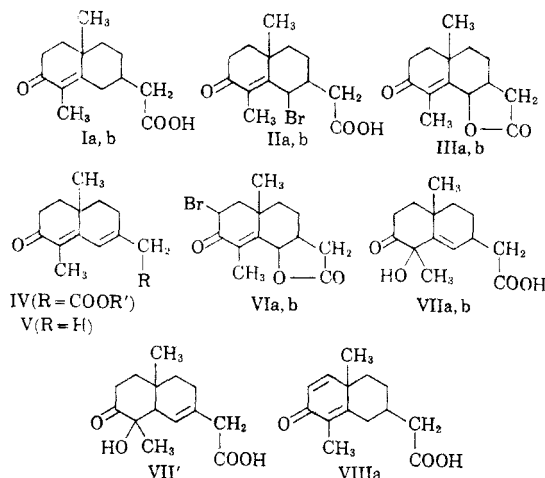
(1) Part XVI, M. Yanagita, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 841 (1958).

(2) T. Miki, *J. Pharm. Soc. Japan*, **75**, 399 (1955).

(3) F. D. Gunstone and A. P. Tulloch, *J. Chem. Soc.*, 1130 (1956).

(4) H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 494 (1956).

(5) M. Yanagita, S. Inayama, N. Hirakura, and F. Seki *J. Org. Chem.*, **23**, 690 (1958).



alent of bromine was found to give the same result. Also, bromination of the *cis*-keto acid (Ib) was well effected with *N*-bromosuccinimide to form the corresponding monobromide (IIb) in comparable yield. However, bromination of Ib with bromine proceeded much more slowly, as compared with that of the *trans* isomer (Ia). When the reaction of Ib with one equivalent of bromine was accelerated by exposure to sunlight, the dibromide (IXb) was isolated in appreciable amount, with recovery of the unchanged starting ketone. This relative inertness of Ib to bromine may be attributed to an increase in steric hindrance due to the combined effects of the two *cis*-substituents at the 6- and 9-positions, which may prevent an axial approach of bromine to the carbon at the 5-position.

Reactions of each isomer of the monobromides (IIa and IIb) with a variety of bases were carried out under relatively mild conditions, and the products, except crystalline compounds, were isolated as 2,4-dinitrophenylhydrazones by reaction with Brady's reagent.⁶ When the *trans*-monobromide (IIa) was heated with anhydrous sodium acetate in glacial acetic acid, the known *trans*-keto lactone (IIIa) was chiefly obtained, along with a small amount of the $\Delta^{4,5}$ -dienone (V), from the neutral fraction. With Brady's reagent, the acidic fraction formed a 2,4-dinitrophenylhydrazone of the ethyl ester (IV, R' = C₂H₅) of the $\Delta^{4,5}$ -dienone acid, indicating the presence of IV (R' = H) in the reaction mixture. On the contrary, the *cis*-monobromide (IIb) on acetolysis furnished predominantly the dienone (V), together with a minute amount of the crystalline *cis*-keto lactone (IIIb).⁷ The structure for the *cis*-keto lactone was inferred from its behavior with alkali and the ultraviolet spectrum, $\lambda_{\text{max}}^{\text{EtOH}}$ 244 m μ (log ϵ 4.13), being rather close to those reported for the similar

lactones.⁸ Assignments of the structures (IV, R' = H and R' = C₂H₅) to the dienone acid and its ester rest mainly on the ultraviolet spectra of the compounds and their 2,4-dinitrophenylhydrazones, resembling respectively those of bicyclic $\Delta^{4,5}$ -3-ketones and their hydrazone derivatives.^{5,9} On warming with ethanol, the hydrazone of the *cis*-keto lactone (IIIb) was transformed into the same derivative of the ethyl ester (IV, R' = C₂H₅) of the dienone acid, affording support for the above structures. That the neutral dienone which is probably a secondary product of the dienone acid (IV, R' = H) possesses the structure V is evidenced by the ultraviolet spectrum and by its formation from IV (R' = H) on heating.

It is of interest that treatment of the *trans*-monobromide (IIa) with aqueous sodium bicarbonate led chiefly to the known 2-bromo lactone (VIa),² accompanied with a small amount of the dienone acid (IV, R' = H). On the other hand, the *cis*-monobromide (IIb) with bicarbonate gave in a good yield the crystalline dienone acid (IV, R' = H), along with lesser amount of the dienone (V). When the *trans*-monobromide was dissolved in 10% aqueous sodium hydroxide, the dienone acid (IV, R' = H), the bromo lactone (VIa), and the keto lactone (IIIa) were obtained. In addition, a new acid was isolated in minute amount from the less-soluble crop. On similar treatment with alkali, the *cis*-monobromide afforded a corresponding isomer of this new acid. Both are isomeric with the hydroxy acid resulting from hydrolysis of the keto lactone (III), but exhibit no ultraviolet absorption bands corresponding to that of the α,β -unsaturated ketones. Their infrared spectra possess bands at 3374 or 3367 cm.⁻¹ (OH), 1733 cm.⁻¹ (COOH), 1715 cm.⁻¹ (C=O in six-membered rings), and 1681 and 813 cm.⁻¹ (R₁R₂C=CHR₃).¹⁰ With Brady's reagent, these acids formed no precipitates at room temperature, but when warmed, both were converted to the same 2,4-dinitrophenylhydrazone of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅). These results indicated that the new acids could have either the α -ketol structure VII or VII', but the latter structure (VII') was excluded by the formation of different ketols from IIa and IIb.

Reaction of the *trans*-monobromide (IIa) with 2,4-dinitrophenylhydrazine in hot acetic acid furnished the hydrazones of the dienone acid (IV, R' = H) and of the dienone (V). In contrast, the *cis*-monobromide (IIb) on similar treatment was converted to the hydrazones of the *cis*-keto lactone (IIIb) and the parent acid (Ib). Refluxing of the

(6) A saturated ethanolic solution of 2,4-dinitrophenylhydrazine and concentrated sulfuric acid.

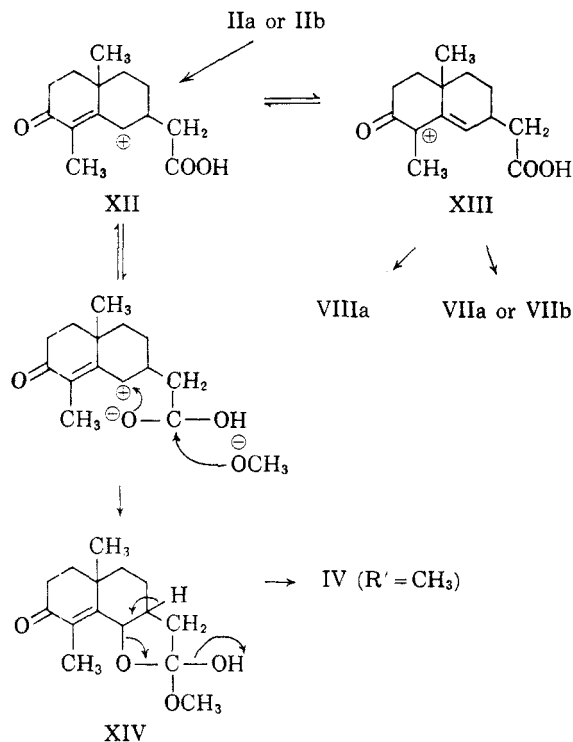
(7) The melting point reported by Miki² for the hydrazone of the *trans*-keto lactone (IIIa) is 10° lower than that of our sample, but identical with that of the same derivative of the *cis*-isomer (IIIb).

(8) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953); Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).

(9) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1439 (1952).

(10) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 33.

ion (XII) would be intramolecularly attacked by carboxyl-oxygen to form XIV, which then could be



dehydrated to the ester. It is conceivable, however, that the monobromides would be eliminated to the $\Delta^{4,5}$ -dienone acid (IV, $R' = H$), which then would be esterified directly. This possibility was excluded by the result that on refluxing with methanol under the conditions employed for methanolysis of II, IV ($R' = H$) gave only the dienone (V) together with the recovered acid. In the aforementioned reactions of the monobromides with bases, the *trans*-isomer (IIa) showed a greater tendency to form the lactone ring, while the *cis*-isomer (IIb) was more readily dehydrobrominated to the $\Delta^{4,5}$ -dienone compound (IV or V). These observations are consistent with the configurations of IIa and IIb, in which the axial substituent at the 6-position more readily participated in the above reactions.

EXPERIMENTAL¹⁶

All temperatures are uncorrected.

Bromination of *trans*-4,9-dimethyl- Δ^4 -3-octalone-6-acetic acid (Ia). (a) *With N-bromosuccinimide.* According to the procedure reported previously,^{2,3} 0.37 g. of the *trans*-monoeneone⁵ (Ia) in 70 cc. of carbon tetrachloride was refluxed with 0.28 g. of *N*-bromosuccinimide in the presence of traces of benzoyl peroxide. After about 3 min., bromination was completed, considerably reducing the reported reflux time (30 min.² or 2 hr.³). The bromide (IIa), amounting to 0.27 g. (55%), was recrystallized from ethyl acetate to give colorless prisms, m.p. 134–136°: $\lambda_{\text{max}}^{\text{EtOH}}$ 255.5 μ ($\log \epsilon$ 4.07); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1695 (COOH), 1661 (C=O), and 1597

cm^{-1} (C=C). Reported, m.p. 135°² and 126–129°:³ $\lambda_{\text{max}}^{\text{EtOH}}$ 246 μ ($\log \epsilon$ 4.12).²

The bromide remained unaffected on standing with hydrobromic acid in acetic acid overnight.

(b) *With one equivalent of bromine.* The *trans*-monoeneone (Ia, 0.945 g.) was treated with 0.65 g. of bromine in 4 cc. of chloroform at room temperature in the usual manner. The bromine uptake took place somewhat slowly. There was obtained 0.8 g. (63%) of the crude product (IIa), which was recrystallized from ethyl acetate by addition of petroleum ether to give colorless prisms, m.p. 125–127° and mixed m.p. 128–134°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{BrO}_3$: C, 53.32; H, 6.08. Found: C, 53.13; H, 6.11.

(c) *With two equivalents of bromine.* By the procedure described above, 0.945 g. of the *trans*-monoeneone (Ia) was brominated with 1.3 g. of bromine to give 1.16 g. (73%) of the dibromide (IXa), m.p. 129–132°. Recrystallization from ethyl acetate-methanol by addition of petroleum ether gave colorless prisms, m.p. 130–132°: $\lambda_{\text{max}}^{\text{EtOH}}$ 260 μ ($\log \epsilon$ 4.04); $\gamma_{\text{max}}^{\text{CHCl}_3}$ 1684 cm^{-1} (C=O). Reported, m.p. 122°² and 123–125°:³ $\lambda_{\text{max}}^{\text{EtOH}}$ 242 μ ($\log \epsilon$ 4.08)² and 253 μ ($\log \epsilon$ 4.04).³

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_3$: C, 42.65; H, 4.61. Found: C, 42.15; H, 4.58.

Bromination of *cis*-4,9-dimethyl- Δ^4 -3-octalone-6-acetic acid (Ib). (a) *With N-bromosuccinimide.* By the procedure described above, the *cis*-monoeneone (Ib) was treated with *N*-bromosuccinimide. After refluxing of the mixture for 10–15 min., the bromination was completed. The monobromide, m.p. 135–140°, obtained in 60% yield, was recrystallized from ethyl acetate to give colorless prisms, m.p. 141–142°: $\lambda_{\text{max}}^{\text{EtOH}}$ 256 μ ($\log \epsilon$ 4.15); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1701 (COOH), 1663 (C=O), and 1597 cm^{-1} (C=C).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{BrO}_3$: C, 53.32; H, 6.08. Found: C, 53.66; H, 6.12.

The bromide remained unaffected on standing with hydrobromic acid in acetic acid overnight.

(b) *With one equivalent of bromine.* Under the same conditions as described for the *trans*-isomer (Ia), 0.708 g. of the *cis*-monoeneone⁵ (Ib) was treated with 0.49 g. of bromine in 3 cc. of chloroform. When about two fifths of the bromine had been added, the bromine uptake became considerably slower. The remaining bromine was added with exposure to sunlight for 1.5 hr. Evaporation of the light brown reaction mixture left a red-brown viscous oil which soon partly solidified. By trituration with a little ether, 0.4 g. (39%) of the dibromide (IXb), m.p. 134–135°, was obtained. Recrystallization from ethyl acetate gave colorless prisms, m.p. 139–140°: $\lambda_{\text{max}}^{\text{EtOH}}$ 261 μ ($\log \epsilon$ 4.10); $\gamma_{\text{max}}^{\text{CHCl}_3}$ 1683 cm^{-1} (C=O). It showed obvious depression of the melting point (10–15°) on admixture with the above monobromide (IIb) of the *cis*-monoeneone.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_3$: C, 42.65; H, 4.61. Found: C, 42.52; H, 4.70.

The mother liquor of the dibromide gave 0.15 g. (21%) of the starting ketone (Ia), m.p. and mixed m.p. 135–138°.

Acetolysis of the *trans*-5-bromo compound (IIa). The above *trans*-monobromide (IIa, 0.70 g.) was heated with 3 g. of anhydrous sodium acetate in 10 cc. of glacial acetic acid on a boiling water bath for 2 hr. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed successively with sodium bicarbonate, sodium hydroxide solution, and water. The bicarbonate solution gave a small amount (0.04 g.) of a light brown oil, which with Brady's reagent formed in low yield a 2,4-dinitrophenylhydrazone mixture. Repeated recrystallizations from ethyl acetate-methanol gave deep red scales, m.p. 168–170°, undepressed on admixture with the hydrazone of the $\Delta^{4,5}$ -dienone ethyl ester (IV, $R' = \text{C}_2\text{H}_5$) described below.

The above ether solution remaining from the alkali extraction was dried and evaporated to leave a red-orange viscous oil (0.30 g.), $\lambda_{\text{max}}^{\text{EtOH}}$ 246 μ ($\log \epsilon$ 4.03) and 300 μ

(16) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurements by Miss M. Suzuki, both of this school.

(log ϵ 3.30). This oil formed almost quantitatively a 2,4-dinitrophenylhydrazone mixture, which on repeated recrystallization from ethyl acetate gave the derivative of the *trans*-keto lactone (IIIa) as red fine needles, m.p. 236–238° (dec.); $\lambda_{\max}^{\text{CHCl}_3}$ 262 m μ (log ϵ 4.22), 293 m μ (log ϵ 4.03) (inf.), and 385 m μ (log ϵ 4.50). Reported, m.p. 228°.²

Anal. Calcd. for C₂₀H₂₂N₄O₆: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.94; H, 5.37; N, 13.30.

The mother liquor of recrystallization of the hydrazone of IIIa afforded dark red crystals, melting in the range 251–265° (dec.). Purification by passing through a neutral alumina column in chloroform solution gave the derivative of the $\Delta^{4,5}$ -dienone (V) as lustrous deep red plates, m.p. 269–271°. Recrystallization from benzene raised the melting point to 271–273°; $\lambda_{\max}^{\text{CHCl}_3}$ 266 m μ (log ϵ 4.22), 316 m μ (log ϵ 4.17), and 411 m μ (log ϵ 4.54).

Anal. Calcd. for C₁₉H₂₂N₄O₄: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.23; H, 5.56; N, 15.01.

Acetolysis of the cis-5-bromo compound (IIb). The *cis*-monobromide (IIb, 0.4 g.) was treated with sodium acetate by the procedure described above for the *trans*-isomer (IIa). The neutral product (0.17 g.), a pale yellow oil, partly solidified on treatment with a little ether. The *cis*-keto lactone (IIb, 0.02 g.), m.p. 159–162°, so obtained, was recrystallized from ethyl acetate by addition of petroleum ether to give colorless prisms, m.p. 167–169°; $\lambda_{\max}^{\text{EtOH}}$ 244 m μ (log ϵ 4.14); $\nu_{\max}^{\text{CHCl}_3}$ 1669 cm.⁻¹ (C=O).

Anal. Calcd. for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.49; H, 7.74.

It formed a 2,4-dinitrophenylhydrazone, which was recrystallized from ethyl acetate to give silky yellow needles, m.p. 225–227°; $\lambda_{\max}^{\text{CHCl}_3}$ 260 m μ (log ϵ 4.09), 290 m μ (log ϵ 3.85) (inf.), and 380 m μ (log ϵ 4.35).

Anal. Calcd. for C₂₀H₂₂N₄O₆: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.62; H, 5.21; N, 13.74.

The mother liquor of crystallization of IIIb gave a yellow oil (0.13 g.), which was twice fractionated to an almost colorless oil, b.p. 122–125° at 1 mm.; $\lambda_{\max}^{\text{EtOH}}$ 298 m μ (log ϵ 4.36). It consisted mainly of the $\Delta^{4,5}$ -dienone (V), forming its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°.

Reaction of the trans-5-bromo compound (IIa) with methanolic potassium hydroxide. The *trans*-monobromide (IIa, 0.1 g.) was dissolved in 1 cc. of 10% methanolic potassium hydroxide and allowed to stand in a stream of nitrogen at room temperature for 2 days. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in water, acidified, and extracted with ether. After shaking with bicarbonate and then with potassium hydroxide solution, the ether solution was dried and evaporated to give an oil (20 mg.), which formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 237–239°, of the *trans*-keto lactone (IIIa). Its ultraviolet spectrum was superimposable on that of the above sample.

With Brady's reagent, the alkali- (5 mg.) and the bicarbonate-soluble fractions (20 mg.) formed, respectively, the 2,4-dinitrophenylhydrazones of IIIa and of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅).

Reaction of the trans-5-bromo compound (IIa) with sodium bicarbonate solution. A solution of 50 mg. of the *trans*-monobromide (IIa) in chloroform-ethyl acetate was shaken with a saturated sodium bicarbonate solution. The shaking was maintained until no more turbidity appeared in the aqueous layer on standing. The organic layer was separated, washed with water, dried, and evaporated to leave a pale yellow oil (35 mg.), which gave crystals, m.p. 109–110°, from ethyl acetate solution by addition of petroleum ether. Further recrystallizations from ethyl acetate formed colorless prisms, m.p. 110–112° (dec.), undepressed on admixture with the *trans*-bromo lactone (VIa) described below. The acidic fraction formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 176–178°, of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅).

Another run was carried out in the absence of the organic solvent. The *trans*-monobromide (IIa, 0.2 g.) was added to 4 cc. of saturated bicarbonate solution and the mixture was stirred at room temperature for 30 min. The separated oil was taken up in ether, and evaporation of the dried ether solution gave a pale yellow oil (0.118 g.), which could not be induced to crystallize. Distillation under reduced pressure gave a little oil (V) identified through the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°.

Reaction of the cis-5-bromo compound (IIb) with aqueous sodium bicarbonate. By the procedures described above for IIa, the *cis*-monobromide (IIb) was treated with sodium bicarbonate. After shaking 50 mg. of IIb in the organic solvent with aqueous bicarbonate, the bicarbonate solution was acidified to precipitate 15 mg. of the $\Delta^{4,5}$ -dienone acid (IV, R' = H) as yellowish prisms, m.p. 129–132°, which was not raised on further recrystallization from ethyl acetate-hexane. It had $\lambda_{\max}^{\text{EtOH}}$ 294 m μ (log ϵ 4.48).

Anal. Calcd. for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.39; H, 7.34.

With Brady's reagent, it formed a 2,4-dinitrophenylhydrazone, m.p. 250–251°, after recrystallization from ethyl acetate. It showed no depression of melting point of the same derivative of the free acid (IV, R' = H) described below.

It is to be noted that with Brady's reagent, the acid (IV, R' = H) in crystalline state formed only the hydrazone of the free acid, while, when it was contained in the acid fraction of the reaction products of II, the hydrazone of the ester (IV, R' = C₂H₅) was always obtained.

This acid on pyrolysis was converted to the $\Delta^{4,5}$ -dienone (V) identified through the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°. Also, refluxing of this acid with methanol for 4 hr. gave in 50% yield $\Delta^{4,5}$ -dienone (V), along with recovery of the unchanged acid (40%).

A solution of 0.10 g. of the *cis*-monobromide (IIb) in aqueous bicarbonate was allowed to stand at room temperature overnight. The nearly clear bicarbonate solution was acidified to give a pale yellow oil, which solidified on standing in a refrigerator. There was obtained 0.06 g. (80%) of the dienone acid (IV, R' = H), melting in the range 100–112° (dec.). Recrystallization from ethyl acetate-hexane gave pale yellow prisms, m.p. and mixed m.p. 128–131°; $\lambda_{\max}^{\text{EtOH}}$ 294 m μ (log ϵ 4.48).

From the mother liquor of this acid, the $\Delta^{4,5}$ -dienone (V) was isolated as the 2,4-dinitrophenylhydrazone.

Reaction of the trans-5-bromo compound (IIa) with aqueous potassium hydroxide. The *trans*-monobromide (IIa, 0.7 g.) was dissolved in 7 cc. of 10% potassium hydroxide solution and the undissolved oil was taken up in ether. The ether solution gave traces of the bromo lactone (VIa), m.p. 105–108° and mixed m.p. 111–112°. The alkaline solution, after standing for 4 hr., was acidified under cooling, and the separated oil was taken up in ether. On standing in a refrigerator, the ether solution deposited 0.05 g. of the *trans*-ketol (VIIa) as white crystals, m.p. 190–195°. Recrystallization from ethyl acetate-petroleum ether gave fine white prisms, m.p. 201–203°; ν_{\max}^{KBr} 3364, 1733, 1715, and 1681 cm.⁻¹ It showed no ultraviolet absorption bands corresponding to that of the α,β -unsaturated ketones.

Anal. Calcd. for C₁₄H₂₀O₄: C, 66.64; H, 7.99. Found: C, 66.70; H, 7.61.

This formed no hydrazone on standing with Brady's reagent at room temperature for 2 weeks. When warmed with this reagent, however, the ketol (25 mg.) was converted to the 2,4-dinitrophenylhydrazone (ca. 20 mg.), melting in the range 140–155°, of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅). Recrystallization from ethyl acetate-ethanol gave deep red scales, m.p. and mixed m.p. 173–175°.

The ketol remained unchanged on standing with 5% sulfuric acid at room temperature, but, when the mixture was warmed for 2 hr., there was obtained the $\Delta^{4,5}$ -dienone

(V) identified through the 2,4-dinitrophenylhydrazone, m.p. 260–265° and mixed m.p. 265–268°.

The ether filtrates from the ketol were shaken with aqueous bicarbonate. Acidification of the bicarbonate solution gave an oil (0.34 g.), forming a 2,4-dinitrophenylhydrazone mixture which was fractionally recrystallized from ethyl acetate. The less-soluble crop was further recrystallized from the same solvent to give the hydrazone, m.p. and mixed m.p. 236–238°, of the *trans*-keto lactone (IIIa). The more-soluble crop was further recrystallized from ethyl acetate-ethanol to give the hydrazone, m.p. 162–164° (mixed m.p. 170–172°), of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅). It had $\lambda_{\text{max}}^{\text{EtOH}}$ 266 m μ (log ϵ 4.20), 315 m μ (log ϵ 4.17), and 405 m μ (log ϵ 4.49). The discrepancy of the melting points of the hydrazones of IV (R' = C₂H₅) may be due to dimorphism.

Anal. Calcd. for C₂₂H₂₆N₄O₆: C, 59.72; H, 5.92. Found: C, 59.31; H, 5.89.

Reaction of the cis-5-bromo compound (IIb) with aqueous potassium hydroxide. By the procedure described above for IIa, 0.4 g. of the *cis*-monobromide (IIb) was treated with 4 cc. of 10% potassium hydroxide solution. The alkaline reaction solution, in which, unlike the above case, no turbidity appeared on standing at room temperature, was acidified and extracted with ether. The ether solution, which gave no precipitates on standing in a refrigerator, was repeatedly shaken with aqueous sodium bicarbonate. Acidification of the combined bicarbonate solutions gave a viscous oil (0.34 g.), which on treatment with a little ether gave 0.045 g. of the *cis*-ketol (VIIb) as fine white crystals, m.p. 227–229°. Recrystallization from ethyl acetate-petroleum ether did not alter the melting point: $\nu_{\text{max}}^{\text{KBr}}$ 3367, 1733, 1715, and 1681 cm.⁻¹ It showed no ultraviolet absorption bands corresponding to that of the α,β -unsaturated ketones.

Anal. Calcd. for C₁₄H₂₀O₄: C, 66.64; H, 7.99. Found: C, 67.03; H, 8.23.

As described with VIIa, the *cis*-ketol (VIIb) was warmed with Brady's reagent to form the hydrazone of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅).

The oily residue from the mother liquor of the *cis*-ketol formed in 40% yield the 2,4-dinitrophenylhydrazone of the *cis*-keto lactone (IIIb) as silky yellow needles, m.p. and mixed m.p. 237–239° (after chromatography on alumina and recrystallization from ethyl acetate-ethanol).

Reaction of the trans-5-bromo compound (IIa) with 2,4-dinitrophenylhydrazine. The *trans*-monobromide (IIa, 63 mg.) was heated with 40 mg. of 2,4-dinitrophenylhydrazine and 17 mg. of anhydrous sodium acetate in 1 cc. of glacial acetic acid in an oil bath (120–140°) for 10 min. On cooling, the solution deposited 15 mg. of the hydrazone of the $\Delta^{4,5}$ -dienone acid (IV, R' = H), m.p. 232–240°. Recrystallization from ethyl acetate and then from acetic acid furnished red scales, m.p. 250–255° (dec.): $\lambda_{\text{max}}^{\text{CHCl}_3}$ 267 m μ (log ϵ 4.05), 315 m μ (log ϵ 4.07), and 411 m μ (log ϵ 4.38).

Anal. Calcd. for C₂₀H₂₂N₄O₆: C, 57.96; H, 5.35. Found: C, 57.75; H, 5.86.

The mother liquor of this hydrazone gave the same derivative, m.p. and mixed m.p. 268–270°, of the $\Delta^{4,5}$ -dienone (V) (after chromatography on alumina and recrystallization from ethyl acetate).

Reaction of the cis-5-bromo compound (IIb) with 2,4-dinitrophenylhydrazine. By the procedure described above for IIa, 25 mg. of the *cis*-monobromide (IIb) was treated with 15 mg. of the hydrazine. On cooling, the reaction solution deposited crystals (10 mg.), melting in the range 200–223°. Recrystallization from ethyl acetate gave deep red scales, m.p. 239–243°, undepressed on admixture with the same derivative of the parent monoenone (Ib).⁵ Its ultraviolet spectrum is superimposable on that of the sample reported previously.⁵ The mother liquor of this derivative gave the hydrazone, m.p. and mixed m.p. 225–227°, of the *cis*-keto lactone (IIIb) (after recrystallization from ethyl acetate-ethanol).

On warming with a small amount of ethanol on the water bath, the hydrazone of the lactone (IIIb) was converted to the same derivative of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅).

Reaction of the trans-5-bromo compound (IIa) with methanol. A solution of 0.45 g. of the *trans*-monobromide (IIa) in 10 cc. of absolute methanol was heated to reflux for 4 hr. Evaporation of the solvent under reduced pressure left an oil, which was mixed with water and extracted with ether. The ether solution was shaken successively with aqueous sodium bicarbonate, 2% sodium hydroxide, and water. Acidification of the bicarbonate solution afforded a pale yellow oil (20 mg.), which with Brady's reagent formed the hydrazone, m.p. and mixed m.p. 174–175°, of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅) (after recrystallization from ethyl acetate).

The neutral product, a light brown oil (0.32 g.), was fractionated to 0.23 g. of a pale yellow oil, b.p. 173–175° at 3 mm. With Brady's reagent, it formed almost quantitatively a hydrazone, m.p. 189–195°, of methyl ester (IV, R' = CH₃) of the $\Delta^{4,5}$ -dienone acid. Recrystallization from ethyl acetate-ethanol gave dark red fine plates, m.p. 206–207°: $\lambda_{\text{max}}^{\text{CHCl}_3}$ 266 m μ (log ϵ 4.19), 315 m μ (log ϵ 4.17), and 402.5 m μ (log ϵ 4.54).

Anal. Calcd. for C₂₁H₂₄N₄O₆: C, 58.87; H, 5.65. Found: C, 59.19; H, 5.45.

The methyl ester, prepared from the acid (IV, R' = H) with diazomethane, formed the same hydrazone, m.p. and mixed m.p. 206–207°.

The above fractionated oil (0.2 g.) was heated to reflux in 1 cc. of 10% methanolic potassium hydroxide for 1 hr. Evaporation of the red-brown solution under reduced pressure left an oil, which was mixed with water and extracted with ether. The ether solution gave a little oil, forming the hydrazone, m.p. and mixed m.p. 265–268°, of the $\Delta^{4,5}$ -dienone (V) (after recrystallization from ethyl acetate). The alkali solution, separated from the neutral product, was acidified under cooling and extracted with ether. The dried ether solution was evaporated to small bulk, and petroleum ether was added. On standing in a refrigerator, the solution deposited two forms of light brown crystals (0.07 g.), which were separated mechanically. One crop (0.035 g.) was recrystallized from ethyl acetate-hexane to give the $\Delta^{4,5}$ -dienone acid (IV, R' = H), light brown prisms, m.p. and mixed m.p. 128–131°. Another crop consisted of 0.01 g. of white prisms, m.p. 183–186°, which was recrystallized from ethyl acetate to raise the melting point to 188–192°: $\lambda_{\text{max}}^{\text{EtOH}}$ 243 m μ (log ϵ 4.05). It showed no depression of the melting point on admixture with the $\Delta^{1,4}$ -dienone acid (VIIIa) kindly furnished by Dr. Miki.¹¹

Anal. Calcd. for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.40.

It formed quantitatively a 2,4-dinitrophenylhydrazone, m.p. 245–250°, which was recrystallized from ethyl acetate to give red plates, m.p. 243–245°: $\lambda_{\text{max}}^{\text{CHCl}_3}$ 259 m μ (log ϵ 4.25), 312 m μ (log ϵ 3.80), and 402 m μ (log ϵ 4.52).

Anal. Calcd. for C₂₀H₂₂N₄O₆: C, 57.95; H, 5.35; N, 13.52. Found: C, 58.24; H, 5.65; N, 13.10.

With diazomethane in ether solution, the acid gave a methyl ester, which formed a 2,4-dinitrophenylhydrazone, m.p. 198–200° (after recrystallization from ethyl acetate-ethanol): $\lambda_{\text{max}}^{\text{CHCl}_3}$ 258 m μ (log ϵ 4.29), 312 m μ (log ϵ 3.85), and 406 m μ (log ϵ 4.58).

Anal. Calcd. for C₂₁H₂₄N₄O₆: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.92; H, 5.55; N, 13.56.

Reaction of the cis-5-bromo compound (IIb) with methanol. By the procedure described above for IIa, 0.27 g. of the *cis*-monobromide (IIb) was treated with 8 cc. of absolute methanol. The neutral oily product (0.18 g.) formed almost quantitatively the 2,4-dinitrophenylhydrazone, melting in the range 175–201°, of the $\Delta^{4,5}$ -dienone methyl ester (IV, R' = CH₃). Recrystallization from ethyl acetate gave dark red plates, m.p. and mixed m.p. 206–208°: $\lambda_{\text{max}}^{\text{CHCl}_3}$ 266 m μ (log ϵ 4.27), 314 m μ (log ϵ 4.29), and 405 m μ (log ϵ 4.61).

Hydrolysis of the above neutral oil gave, along with a small amount of the $\Delta^{4,5}$ -dienone (V), the $\Delta^{4,5}$ -dienone acid (IV, R' = H), but the corresponding $\Delta^{1,4}$ -dienone acid (VIII) could not be detected from the acid fraction.

Reaction of the trans-5-bromo compound (IIa) with γ -collidine. The *trans*-monobromide (IIa, 0.25 g.) was heated with 1.5 cc. of purified γ -collidine (b.p. 169–170°) at 170–180° for 15 min. The reaction mixture was diluted with ether to give a quantitative yield of the collidine hydrobromide. The ether solution was washed successively with dilute hydrochloric acid, water, and aqueous sodium bicarbonate. The neutral fraction, an oil (0.132 g.), which partly solidified, was triturated with ether to give 12 mg. of the *trans*-ketol (VIIa) as light brown crystals, m.p. 183–191°. Recrystallization from ethyl acetate raised the melting point to 200–203° (mixed m.p. 201–203°). The mother liquor of VIIa formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 266–270°, of the $\Delta^{4,5}$ -dienone (V) (after repeated recrystallization from ethyl acetate).

Acidification of the bicarbonate solution gave a pale yellow oil (10 mg.), which formed with Brady's reagent the hydrazone, m.p. and mixed m.p. 170–172°, of the $\Delta^{4,5}$ -dienone ethyl ester (IV, R' = C₂H₅).

Reaction of the cis-5-bromo compound (IIb) with γ -collidine. By the procedure described above for IIa, 0.15 g. of the *cis*-monobromide (IIb) was heated with γ -collidine, forming a quantitative yield of the collidine salt. The neutral oily fraction (0.07 g.) gave 0.015 g. of the *cis*-keto lactone (IIIb) as light brown crystals, m.p. 155–157°, from ether solution by addition of hexane. Recrystallization from ethyl acetate–hexane raised the melting point to 167–169° (mixed m.p.).

The mother liquor of IIIb gave a brown oil (0.05 g.), which formed almost quantitatively the 2,4-dinitrophenylhydrazone, melting in the range 250–265°, of the $\Delta^{4,5}$ -dienone (V). Purification by passing through an alumina column in chloroform solution and recrystallization from ethyl acetate gave a pure sample, m.p. and mixed m.p. 271–273°.

Acetolysis of the trans-2,5-dibromo compound (IXa). By the procedure described above for the *trans*-monobromide (IIa), 0.93 g. of the *trans*-dibromide (IXa) was heated with 3 g. of anhydrous sodium acetate in 12 cc. of glacial acetic acid. The ether solution, containing the neutral products, was dried and concentrated to deposit 0.47 g. (64%) of the *trans*-bromo lactone (VIa) as light brown crystals, m.p. 99–100°. Recrystallization from methanol with charcoal afforded white prisms, m.p. 110–112° (dec.): $\lambda_{\max}^{\text{EtOH}}$ 250 m μ (log ϵ 4.04); $\nu_{\max}^{\text{CHCl}_3}$ 1684 cm.⁻¹ (C=O). Reported,² m.p. 107–112° and $\lambda_{\max}^{\text{EtOH}}$ 242 m μ (log ϵ 4.03).

Anal. Calcd. for C₁₄H₁₇BrO₃: C, 53.67; H, 5.47. Found: C, 53.19; H, 5.42.

The bromo lactone (0.1 g.) was refluxed with 1.0 g. of activated zinc dust in 10 cc. of ethanol containing 0.1 cc. of acetic acid for 15 min. After removal of zinc by filtration, the filtrate was evaporated under reduced pressure to leave a viscous oil, which was mixed with water and extracted with ether. The ether solution was shaken with aqueous sodium carbonate, and the carbonate solution was acidified to separate a brown oil which soon solidified. Recrystallization from methanol gave 0.05 g. (57%) of the starting monoenone (Ia), m.p. and mixed m.p. 132–135°.

Treatment of the bromo lactone with hot collidine in the usual manner formed in 83% yield the collidine salt, but no tractable products were isolated from the reaction mixture.

Acetolysis of the cis-2,5-dibromo compound (IXb). The *cis*-dibromide (IXb, 0.5 g.) was subjected to acetolysis under the conditions described above for IXa. From the neutral fraction, 0.18 g. (45%) of the *cis*-bromo lactone (VIb) was isolated as pale yellow crystals, m.p. 190–193° (dec.), which was recrystallized from ethyl acetate and then methanol to give yellowish prisms, m.p. 180–181° (dec.): $\lambda_{\max}^{\text{EtOH}}$ 248 m μ (log ϵ 4.13); $\nu_{\max}^{\text{CHCl}_3}$ 1686 cm.⁻¹ (C=O).

Anal. Calcd. for C₁₄H₁₇BrO₃: C, 53.67; H, 5.47. Found: C, 54.01; H, 5.81.

The residual oil of the mother liquor of VIb formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°, of the $\Delta^{4,5}$ -dienone (V) (after chromatography on alumina with chloroform elution and recrystallization from ethyl acetate).

Hydrogenation of the *cis*-bromo lactone with zinc dust, as described above for VIa, furnished the starting *cis*-ketone (Ib), m.p. and mixed m.p. 142–144°. Like VIa, VIb could not be dehydrobrominated to the dienone (X) with hot collidine.

Reaction of the trans-2,5-dibromo compound (IXa) with sodium bicarbonate. A solution of 0.05 g. of the *trans*-dibromide (IXa) in ether was shaken with aqueous bicarbonate, as described above for the *trans*-monobromide (IIa). The ether solution, separated from the aqueous layer, gave a light brown oil (0.05 g.), which was again dissolved in a little ether and stored in a refrigerator. There was obtained 0.02 g. of the *trans*-bromo lactone (VIa) as light brown crystals, m.p. 100–105°. Recrystallization from ethyl acetate gave colorless prisms, m.p. and mixed m.p. 110–112°.

Reaction of the trans-2,5-dibromo compound (IXa) with γ -collidine. According to the procedure reported by Gunstone and Tulloch,³ 0.8 g. of the *trans*-dibromide (IXa) was heated with 23 cc. of purified γ -collidine. The crude product, a dark brown oil, was dissolved in ether, and the ether solution was shaken with aqueous sodium bicarbonate and then with 1% sodium hydroxide. The alkaline solution gave only traces of a brown oil. Evaporation of the dried ether solution left a dark brown oil (0.23 g.) which was chromatographed on silica gel (1.5 × 22 cm.) and eluted with chloroform. The early eluted fraction afforded a small amount of the bromo lactone (XI), m.p. 132–135°. Recrystallization from methanol gave colorless plates, m.p. 136–138°: $\lambda_{\max}^{\text{EtOH}}$ 255 m μ (log ϵ 4.12).

Anal. Calcd. for C₁₄H₁₇BrO₃: C, 53.67; H, 5.47. Found: C, 53.23; H, 5.37.

The mother liquor of XI gave no tractable products.

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