

duced an additional 0.8 g. of the salt with rotation and melting point identical with those above and this material was added to the main portion. The total yield was 68% for this diastereoisomer.

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.12; H, 6.52.

*L- α -Acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt.* During the isolation of *D- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt from 18.8 g. of *DL- α -acetamido- γ -*p*-nitrophenylbutyric acid (0.0707 mole) and 8.55 g. (+)- α -phenylethylamine (0.0707 mole) when the mother liquors were combined and evaporated to a small volume, two types of crystals were observed to form on cooling. One type was light yellow plates which were the *D- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt and very fine, long, almost colorless needles. By repeated recrystallizations from a minimum of 95% ethanol these two types of crystals were separated and there was obtained 1.4 g. of the *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt (10%) as fine, faintly yellow needles with $[\alpha]_D^{25} -38 \pm 2^\circ$ (c, 1.29 in methanol) and melting point 196–200° (dec.), the rotation of which was not changed by further recrystallization from ethanol.****

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.22; H, 6.63.

*L- α -Acetamido- γ -*p*-nitrophenylbutyric acid (-)- α -phenylethylamine salt.* The mother liquors from the isolation of 9.3 g. of the *D- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt and 1.4 g. of the *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt from 18.8 g. of the racemic acid (0.0707 mole) and 8.55 g. of the amine (0.0707 mole) were evaporated to dryness at reduced pressure (water pump) and there was obtained 16.3 g. of solid material. To this material suspended in 100 ml. of water was added concentrated aqueous sodium hydroxide until the solid was dissolved and the α -phenylethylamine was completely separated as an oil. The amine was removed from the aqueous solution by washing with three 60-ml. portions of ether. On acidification (pH 1) of the aqueous solution with concentrated hydrochloric acid, the partially resolved acid separated as a crystalline solid; and after cooling overnight at 0°, 10.8 g. (0.0406 mole) was collected by filtration. To the acid dissolved in 170 ml. of hot 95% ethanol was added 4.91 g. of (-)- α -phenylethylamine¹³ (0.0406 mole) dissolved in 30 ml. of hot 95% ethanol, and**

the solution was allowed to cool slowly overnight at room temperature. On cooling light yellow plates were deposited and after filtration and one recrystallization from 95% ethanol, there was obtained 8.2 g. of the *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (-)- α -phenylethylamine salt (67% corrected for the *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt obtained above) as light yellow plates with $[\alpha]_D^{25} -44 \pm 2^\circ$ (c, 1.23 in methanol) and m.p. 203–207° (dec.), the rotation of which was not altered by further recrystallization from ethanol.**

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50. Found: C, 62.10; H, 6.68.

*D- α -Acetamido- γ -*p*-nitrophenylbutyric acid (IIIb).* To 52.2 g. of the *D- α -acetamido- γ -*p*-nitrophenylbutyric acid (+)- α -phenylethylamine salt (0.135 mole) suspended in 300 ml. of water was added concentrated aqueous sodium hydroxide until the solid was completely dissolved and the (+)- α -phenylethylamine was completely separated from the aqueous solution. The amine was removed by washing with three 200-ml. portions of ether and, on acidification (pH 1) of the aqueous solution with concentrated hydrochloric acid, the organic acid precipitated. After cooling the mixture overnight at 0°, filtration, and recrystallization, there was obtained 33.3 g. of *D- α -acetamido- γ -*p*-nitrophenylbutyric acid (92.8%) with properties as shown in Table I.**

*L- α -Acetamido- γ -*p*-nitrophenylbutyric acid (IIIb).* In the same way as with its enantiomorph, 26.5 g. of the *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (-)- α -phenylethylamine salt (0.0684 mole) was decomposed with aqueous sodium hydroxide to 14.2 g. of *L- α -acetamido- γ -*p*-nitrophenylbutyric acid (78.9%) with properties as shown in Table I.**

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Santonin and Related Compounds. XVI.¹ C-Methylation of the Δ^4 -3-Octalone Systems²

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The reaction of 9-methyl- Δ^4 -3-octalone (I) with methyl iodide and potassium *tert*-butoxide readily yielded the 4,4,9-trimethyl ketone (II), as the chief product. In addition, 2,4,4,9-tetramethyl (III) and 4,9-dimethyl ketone (IV) were both obtained in minute amounts. Similar methylation of the dimethyl ketone (IV) proceeded much less readily leading to lower yield of the trimethyl ketone (II). A possible explanation is offered for these methylation reactions.

As described in the preceding paper of this series,¹ it became necessary to introduce one methyl group

(1) Part XV, M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

into the 4-position of Δ^4 -3-octalone compounds. It had been previously reported³ that the direct methylation of either Δ^4 - or Δ^5 -cholesten-3-one with

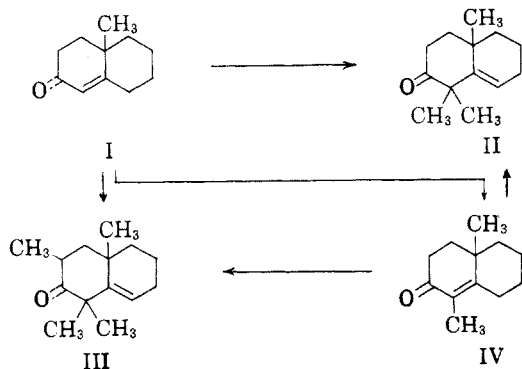
(3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol readily afforded the 4,4-dimethyl derivative in good yield. As our model experiment, the methylation of 9-methyl- Δ^4 -3-octalone (I) with these reagents was explored.

Since this work was initiated, several papers⁴ have appeared describing similar dimethylation of the Δ^4 -3-octalone systems in steroids and others, in some of which but unrewarding efforts^{4b,d,e} to prepare the 4-monomethyl derivative by this procedure have been mentioned. It seems of interest to compare the methylation of the Δ^4 -3-ketosteroids with that of the simplest analog such as I.

9-Methyl- Δ^4 -3-octalone (I) was treated with 3 equivalents of potassium *tert*-butoxide and excess of methyl iodide in *tert*-butyl alcohol at refluxing temperature for 5 min. On chromatographic separation of the crude product on alumina, the expected 4,4,9-trimethyl ketone (II) was in 46% yield obtained, which was characterized as a 2,4-dinitrophenylhydrazone ($\lambda_{\max}^{\text{CHCl}_3}$ 369.5 m μ , log ϵ 4.24). The evidence for the structure (II) was based on the analysis of the hydrazone derivative and on the lack of the ultraviolet absorption band corresponding to the α,β -unsaturated ketone.⁵

The more readily eluted fraction gave a small amount of an oil, which formed a 2,4-dinitrophenylhydrazone different from the same derivative of the trimethyl ketone (II). The analytical figures of the hydrazone showed that this oily ketone possibly possesses the tetramethyl structure III. This assign-



(4) (a) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955). (b) G. D. Meakins, O. R. Rodig, *J. Chem. Soc.*, 4679 (1956). (c) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, B. Sturgeon, *J. Chem. Soc.*, 4490 (1956). (d) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957). (e) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957). (f) J. D. Cocker and T. G. Halsall, *Chem. & Ind. (London)*, 1275 (1956). (g) F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.*, **79**, 2906 (1957). Cf. since the preparation of this manuscript was completed, N. W. Atwater has announced in his communication to the Editor [*J. Am. Chem. Soc.*, **79**, 5315 (1957)] that direct methylation of the Δ^4 -3-ketosteroids with the same reagents under the suitable conditions gave a satisfactory yield of the 4-monomethyl derivative.

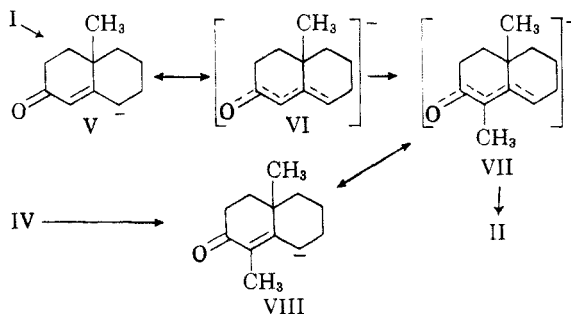
(5) During the later stages of this investigation, F. E. King, C. F. Ritchie, and C. J. Timmons [*Chem. & Ind. (London)*, 1230 (1956)] reported the preparation of the trimethyl compound (II) by the similar method, but no experimentation was described.

ment was supported by the ultraviolet absorption band ($\lambda_{\max}^{\text{CHCl}_3}$ 370 m μ , log ϵ 4.35) of the hydrazone, which is practically identical with that of the same derivative of II. From the later elution, the desired 4,9-dimethyl- Δ^4 -3-octalone (IV), along with the starting material (I), was isolated in a small amount, as the 2,4-dinitrophenylhydrazone.

Hoping to raise the yield of the dimethyl ketone (IV), the methylation of I was effected by employing one equivalent of potassium *tert*-butoxide. However, it did not improve the yield of IV and gave chiefly II in 25% yield. The use of two equivalents of potassium *tert*-butoxide resulted only in a better yield of II.

From the present and earlier works,^{4b,d,e,g} it may be deduced that ready methylation of the Δ^4 -3-octalone systems by the above procedure normally does not proceed through the dimethyl ketone (IV). To examine this deduction, the methylation of IV was carried out with two equivalents of potassium *tert*-butoxide under similar conditions. Expectedly, the methylation took place much less readily than that of I, and refluxing of the solution required 7 hr. for completion of the reaction. There was obtained, together with traces of III, the trimethyl ketone II in a rather low yield.

During this investigation, an improvement was made in preparation of the dimethyl ketone IV, which was hitherto obtained by the condensation of 2-methylcyclohexanone and diethylaminopentan-3-one methiodide with sodamide in ether.⁶ Use of the free Mannich base in place of its methiodide with sodium at higher temperature, as reported for the preparation of I,⁷ was found to raise the yield of IV from 46% to 65–74%. This provided a more simple and economical method for preparing IV.



On the basis of the foregoing results, a possible explanation is proposed for the formation of the trimethyl ketone II from I or IV. Extraction of a proton at the 4-position by a base may give the carbanion V, for which a resonating structure VI can be written. The electrophilic attack by methylation on VI would give the dimethyl anion VII, which would be immediately converted to II by further methylation. It may be assumed that in the

(6) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).

(7) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

carbanion VIII from the dimethyl ketone IV, the electron release properties of the methyl group at the 4-position would suppress the distribution of π -electrons of the Δ^4 -double bond to the carbon at the 3-position, preventing VIII from assuming the mesomeric form VII. This may account for the considerable difficulty encountered in the methylation of IV, compared with that of I.

EXPERIMENTAL⁸

All temperatures were uncorrected.

Methylation of 9-methyl- Δ^4 -3-octalone (I) by methyl iodide.

(a) *With 3 equivalents of potassium tert-butoxide.* To a paste of potassium tert-butoxide prepared from 1.20 g. of potassium metal and 15 cc. of tert-butyl alcohol was added a solution of 1.64 g. of the ketone (I) in 2 cc. of benzene. Methyl iodide (6.0 g.) was added, with stirring, to the deep brown solution at room temperature, and was heated to reflux for 5 min. The solution faded in color and became completely neutral to the litmus paper. After removal of potassium salt by filtration, the reaction was evaporated under reduced pressure. The residual oil was dissolved in ether, and washed successively with dilute hydrochloric acid, aqueous sodium carbonate, and water. A brown oil from the dried ether solution was fractionated to a colorless oil (1.52 g.), b.p. 137–147° at 22 mm., which was chromatographed on alumina (30 g.). Each fraction was eluted with 20 cc. of the solvent: fractions 1–6, petroleum ether; fractions 7–11, petroleum ether-ether (1:1); fraction 12, ethanol.

Fractions 2–3 gave an oil (0.83 g.) which was again chromatographed on alumina (25 g.). Early elution with petroleum ether yielded 0.30 g. of an oil, consisting mainly of the tetramethyl ketone (III). It formed a 2,4-dinitrophenylhydrazone (0.43 g., 77%), melting in the range of 162–175°. Recrystallization from ethanol-ethyl acetate gave orange plates, m.p. 177.5–178°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 370 m μ ($\log \epsilon$ 4.35).

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.06; H, 6.78; N, 14.80.

The later elution with petroleum ether and elution with petroleum ether-ether furnished 0.47 g. of the trimethyl ketone (II), white leaflets, m.p. 31.5–32.5°. It formed quantitatively a 2,4-dinitrophenylhydrazone, m.p. 156–158°, which was recrystallized from ethanol to yellow plates, m.p. 159–160°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 369.5 m μ ($\log \epsilon$ 4.24).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_4$: C, 61.27; H, 6.48; N, 15.05. Found: C, 61.18; H, 6.28; N, 15.16.

Fractions 4–7 yielded 0.24 g. of the trimethyl ketone (II), m.p. and mixed m.p. 31–32° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160°).

Fraction 8 gave 0.29 g. of crystals contaminated with a little oil. On rechromatography on alumina (8 g.) as described above, an additional 0.16 g. (total 46%) of the trimethyl ketone (II), m.p. and mixed m.p. 31.5–32.5° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160°). The later elution with petroleum ether-ether furnished 0.03 g. of an oil (IV), forming a red 2,4-dinitrophenylhydrazone (0.05 g.). Recrystallization from glacial acetic acid gave red plates, m.p. 196–198°, undepressed on admixture with the same derivative, m.p. 198–199°, of the dimethyl ketone (IV) reported previously.⁹

Fraction 9 furnished 0.07 g. of IV (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 197–198°).

Fractions 10–12 gave only traces of an oil which was not examined.

(8) Microanalyses were by Miss C. Shibuya, and the ultraviolet measurements by Miss M. Suzuki.

(9) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(b) *With one or two equivalents of potassium tert-butoxide.* As described in (a), the ketone (I, 0.50 g.) was treated with methyl iodide (0.50 g.) and potassium tert-butoxide prepared from 0.12 g. (1 equivalent) of potassium metal and 5 cc. of tert-butyl alcohol. The crude product, b.p. 124–131° at 13 mm., amounted to 0.38 g., which was chromatographed on alumina (10 g.). The trimethyl ketone (II, 0.15 g., 25%), m.p. and mixed m.p. 31–32°, was obtained from the elution with petroleum ether. A fraction eluted with petroleum ether-ether furnished a small amount (15 mg.) of the dimethyl ketone (IV) (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 195–197°). The starting ketone (I, 0.10 g.) was recovered from the later elution, which was identified as its 2,4-dinitrophenylhydrazone,¹⁰ m.p. and mixed m.p. 169°, after recrystallization from ethanol-ethyl acetate.

The ketone (I, 0.50 g.) was similarly treated with methyl iodide (1 cc.), potassium metal (0.24 g., 2 equivalents), and tert-butanol (10 cc.). The crude product (0.39 g.), b.p. 92–102° at 4 mm., was chromatographed on alumina (10 g.), as described above. There was obtained 0.255 g. (38%) of II, m.p. and mixed m.p. 31.5–32.5°.

4,9-Dimethyl- Δ^4 -3-octalone (IV). This was prepared by effective variation of the earlier method⁶ similarly as described for the preparation of I.

Sodium metal (0.8 g.) was added, in small pieces, to 40.5 g. of 2-methylcyclohexanone under stirring at room temperature (exothermic). After sodium dissolved, 25.0 g. of diethylaminopentan-3-one was added, and the mixture under stirring was slowly heated to 130–140° (oil bath temperature). Soon the separated diethylamine began to reflux. This temperature was maintained for 3 hr. The reaction mixture, consisting of two layers, was acidified with 10% hydrochloric acid and ice, and was extracted with ether. The ether solution was washed with aqueous sodium carbonate, then with water, and dried. A yellow oil from the ether solution was fractionated to the unchanged starting ketone (20.7 g.), and 21.0 g. of the crude octalone (IV), a colorless oil, b.p. 102–116° at 2 mm. Redistillation of the latter fraction afforded 19.5 g. (69%) of IV, b.p. 104–107° at 2 mm.; n_D^{20} 1.5256. Reported,⁶ b.p. 99–100° at 1 mm.; n_D^{20} 1.5260.

It formed quantitatively the 2,4-dinitrophenylhydrazone,^{6,7} m.p. and mixed m.p. 197–198° (after recrystallization from ethanol).

Methylation of 4,9-dimethyl- Δ^4 -3-octalone (IV) with methyl iodide. This was carried out by a similar procedure as described above for I. To a paste of potassium tert-butoxide prepared from 0.44 g. (2 equivalents) of potassium metal and 10 cc. of tert-butyl alcohol was added, dropwise, 1.00 g. of the dimethyl ketone (IV), followed by 5 cc. of methyl iodide. When the mixture was heated to reflux for 7 hr., it became neutral to litmus paper. The crude product, a yellowish oil (1.02 g.), was fractionated to 0.77 g. of a colorless oil, b.p. 106–111° at 4 mm., which was chromatographed on alumina (20 g.) and eluted with benzene. An oil (0.15 g.) from the early elution formed a mixture of 2,4-dinitrophenylhydrazones, which on mechanical separation by picking up and recrystallization from ethyl acetate afforded the derivative of II as yellow plates, m.p. and mixed m.p. 158–160°, and the derivative of III as orange plates, m.p. 173–174° and mixed m.p. 175–176°. The following elution gave the trimethyl ketone (II, 0.26 g., 24%), m.p. and mixed m.p. 31–32° (the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159°). The latter elution gave the unchanged starting ketone (IV, 0.17 g.).

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(10) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).