[Chem. Pharm. Bull. 16(10)1918—1926(1968)]

UDC 547.594.3.07.02 : 541.63

Preparations and Stereochemistries of Ethyl 3α- and 3β-Methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylates and Related Compounds

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(Received January 26, 1968)

The Michael condensation of ethyl 2-oxo-5-methylcyclohexanecarboxylate with acrolein proceeded stereospecifically to afford, upon intramolecular Aldol-type cyclization followed by dehydration, ethyl 3β-methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carboxylate (IV), which was hydrogenated to 3β-methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylate (V). The corresponding 3α-methyl derivative (XIX)was obtained from the Michael adduct of ethyl 2-oxocyclohexanecarboxylate with methacrolein. Configurations and conformations of the compounds prepared were established from the consideration of chemical and NMR evidences.

The bicyclo(3,3,1)nonane ring system has been gaining keen interests not only from the chemistry itself, but also from the point that this ring system is the main structural feature found common in the lycopodium alkaloids.[2] In view of the possibility of total syntheses of these alkaloids *via* the route first forming bicyclo(3,3,1)nonane ring system, we have so far investigated synthetic approach toward these alkaloids *via* the above route, which was rationalized by the recent report by Raphael and his coworkers.[3]

The present paper deals with the preparations and the stereochemistries of the cyclization products of Michael adduct of ethyl 2-oxo-5-methyl cyclohexane carboxylate with acrolein and related compounds.

Intramolecular Aldol condensation of β-(1-ethoxycarbonyl-2-oxo-5-methylcyclohexyl)-propionaldehyde (II), which was obtained from the reaction of ethyl 2-oxo-5-methylcyclohexanecarboxylate (I) with acrolein in the presence of catalytic amount of sodium ethoxide at −60°, underwent smoothly with hydrochloric acid in acetone to afford the cyclized products (III) quantitatively, which showed two spots on thin-layer chromatography.

Oxidation of III with Jones reagent[4] gave the diketo-ester (IX) and dehydration of III on heating their mesylates with γ-collidine gave the unsaturated keto-ester (IV). Both IX and IV behaved as stereochemically homogeneous materials on gas-liquid (GLC) and thin-layer chromatographies (TLC), suggesting III as a mixture of epimeric 6-alcohols and excluding the possibility of the contamination of an epimer due to methyl configuration. Therefore, the Michael condensation of I with acrolein must have proceeded stereospecifically to give the product having the fixed methyl configuration to the newly introduced alkyl group.

Generally, the alkylation of enol or enalate anion is regarded to proceed by either parallel or antiparallel attack of the alkyl group on the intermediary enolate, depending on the relative energies of the transition state and the relative degree of steric hindrance to be overcome. In this case, it may be presumed that the intermediary enolate exists in an equilibrium mixture of structures (I'e) and (I'a) and the incoming alkyl group will attack the enolate predominantly

1) Location: *Toneyama, Toyonaka, Osaka.*
2) K. Wiesner, *Fortschr. Chem. Org. Naturstoffe*, **20**, 271 (1962).
3) E. Colvin, J. Martin, W. Parker, and R.A. Raphael, *Chem. Commun.*, **1966**, 596.
4) A. Bowers, T.G. Halsall, E.R.H. Jones, and A.J. Lemin, *J. Chem. Soc.*, **1953**, 2548.

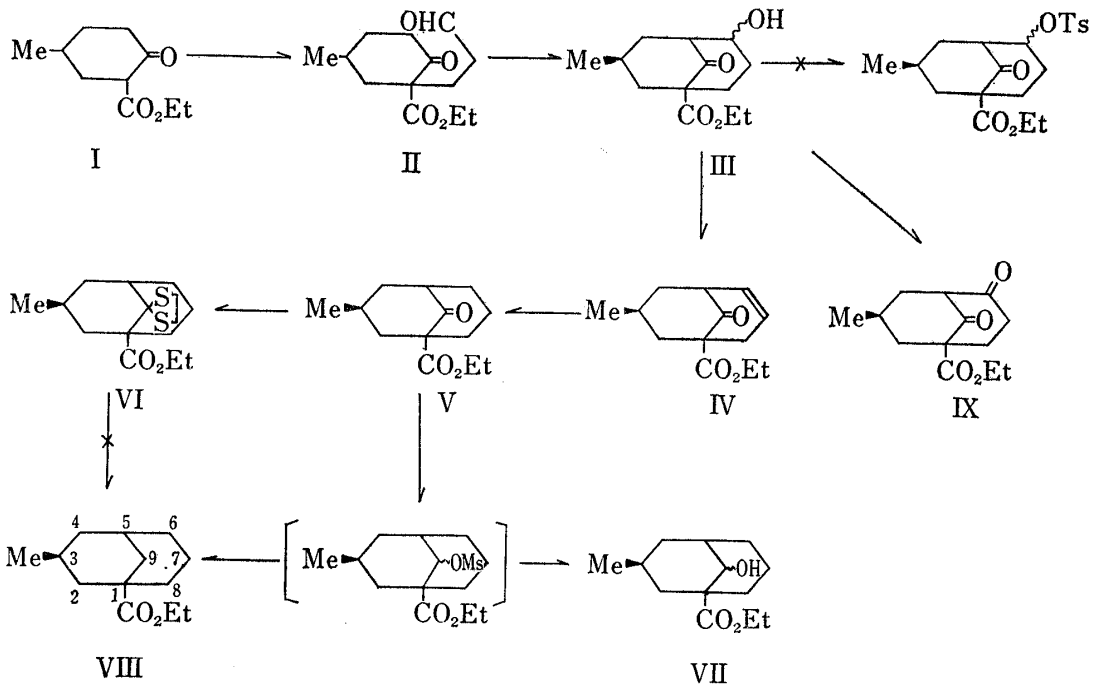

Chart 1

in the direction best suited for maximum overlap with the *n*–orbital of the enolate double bond, that is, perpendicular attack from either *α*– or *β*–sides of the enolates.[5–7]

In the structure (I'e), the reaction will proceed through the pre–twist transition state when *β*–attack occurs, while through the pre–chair transition state at *α*–attack. Since the latter transition state would be energetically more stable than the former, the alkylation will occur preferentially at *α*–side of the molecule, leading to the product in which the methyl group is *trans* to the alkyl group. On the other hand, in the structure (I'a), *β*–side attack is suppressed by steric hindrance of axial methyl group which make improbable to go through the pre–chair transition state. Therefore, if the reaction occur *via* the structure (I'a), the possibility would be *α*–attack to form the pre–twist intermediate, which also resulted *trans* configuration of the groups. Hence, the prediction is obvious and is that the above mentioned Michael condensation proceeds mostly through *α*–attack on the enolate (I'e), giving a stereochemically homogeneous product in which the methyl group is *trans* to the alkyl group and further, the configuration of methyl group in these bicyclo(3,3,1)nonane derivatives is presumably *β*–equatorial.

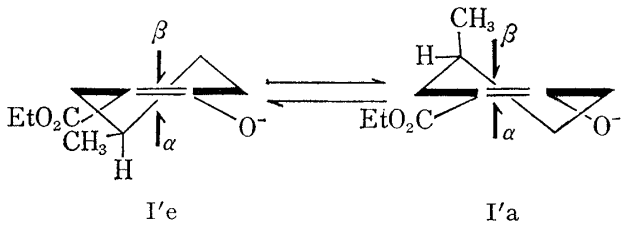

Chart 2

In order to secure concrete proof on the orientation of the methyl group, we now converted III into a series of derivatives which could be identified by their alternative syntheses.

The unsaturated ketone (IV) was obtained *via* their mesylates of III in 50 to 60% yield, although direct dehydration of III with phosphorus oxychloride in pyridine was unsuccessful. Catalytic hydrogenation of IV in the presence of platinum oxide followed by oxidation with Jones reagent gave the saturated keto-ester (V).

5) L. Velluz, J. Vallis, and G. Nominé, *Angew. Chem.*, **77**, 185 (1965).
6) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley and Sons. Inc., New York, 1965, p. 307.
7) N.L. Allinger and C.K. Riew, *Tetrahedron Letters*, **1966**, 1269.

Succeedingly, the keto–ester (V) was converted into the saturated ester (VIII) as follows. The thioketal, obtained from the keto–ester (V) in the usual manner, resisted to desulfurization with Raney nickel (W–2) under various conditions. Reduction of V with sodium borohydride followed by treatment of methanesulfonyl chloride in pyridine gave the mesylates. Reduction of the mesylates with lithium aluminum hydride in tetrahydrofuran, to obtain 3–methylbicyclo(3,3,1)nonane–1–methanol, gave the diol (VII) instead, while hydrogenolysis of the mesylates under vigorous condition[8] gave the desired saturated ester (VIII) though in poor yield. Compounds (V) and (VIII) were homogeneous on GLC and TLC.

Now, we have investigated alternative syntheses of the derivatives (V) and (VIII) or their configurational isomers of methyl group to confirm the stereospecificity of the Michael condensation.

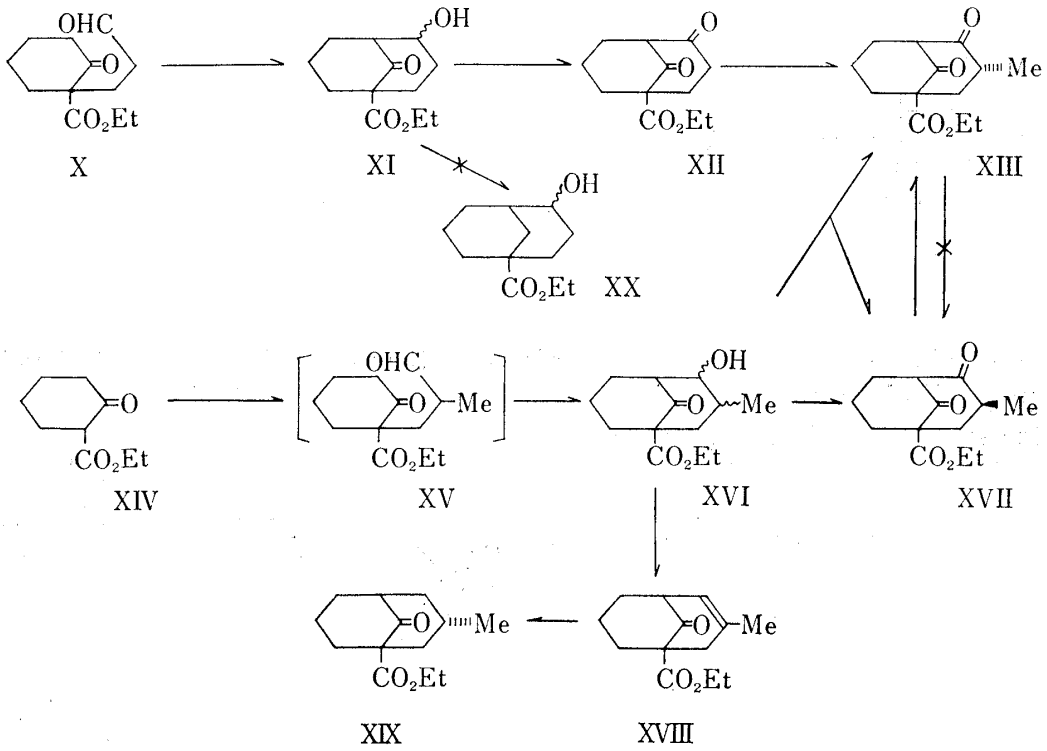

Chart 3

The keto–aldehyde (X), prepared according to the method reported by Cope and his coworkers,[9] was cyclized quantitatively to give a mixture of epimeric hydroxyketones (XI). To avoid complex side reaction arising from the 9–keto group, we first attempted in vain to remove this functional group under various hydrogenolytic conditions. The diketone (XII), prepared from the hydroxyketone (XI) by Jones oxidation, was converted into the methyl diketone (XIII) as a single product through the pyrrolidine enamine in only 6.3% yield. Due to poor yield of the above enamine process, it was neccessary to exploit an alternative route to XIII. The Michael adduct of ethyl 2–oxocyclohexanecarboxylate (XIV) with freshly distilled methacrolein was subjected to intramolecular Aldol cyclization giving the cyclized products (XVI), which showed four spots on TLC and was oxidized with Jones reagent to give a mixture of the diketones (XVII as a major and XIII as a minor), which showed two spots on TLC but not separated on GLC. And one of the products (XIII) was found to be identical with the sample obtained by the route *via* the enamine procedure and the other (XVII) was isomerized rapidly in acidic media to the former (XIII), whereas no isomerization occurred

8) E. Fujita, T. Fujita, H. Katayama, and M. Shibuya, *Chem. Commun.*, **1967**, 252.
9) A.C. Cope and M.E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950).

from XIII to XVII. Therefore, the compounds (XIII) and (XVII) are epimers regarding methyl configuration, the former being the more stable isomer.

Again, all attempts to convert XIII and XVII into either V or VIII, by removing the carbonyl groups at C-4 and C-9 positions, were unsuccessful.

Finally, hydrogenation of the unsaturated ester (XVIII), which was obtained by dehydration of the keto-alcohols (XVI), has been examined. Hydrogenation of XVIII with platinum oxide underwent smoothly to give the saturated keto-ester (XIX) in 70% yield, which was homogeneous on TLC and different from the corresponding saturated ester (V) on the behaviors of IR, TLC, GLC, NMR, and melting points of their 2,4-dinitrophenylhydrazone, suggesting XIX as an epimer of V as to the methyl configuration.

Configurations and conformations of epimeric compounds (XIII) and (XVII) were clearly elaborated by examination of their NMR spectra, in comparison with those of IX and XII, shown in Table I.

Table I. The NMR Spectra of the Bridgehead Proton of the Diketonic Compounds IX, XII, XIII and XVII

Compd. No.	Solvent	Chemical shift (τ)	Coupling constant (cps)
XII	$CDCl_3$	6.83 (t)	4
IX	$CDCl_3$	6.87 (t)	4
XIII	C_5H_5N	6.82 (t)	4
XVII	CCl_4	6.87 (t)	4
	C_6H_6	6.77 (t)	4
	C_5H_5N	6.55 (t)	4

NMR spectra of the compounds (IX), (XII) and (XVII), exhibited triplet signals of similar pattern near 6.87 τ, which were the lowest signal of protons on the bicyclo(3,3,1)nonane ring and might be assigned to the bridgehead proton neighboring to both carbonyl groups from the following reasons. First, this signal was greatly shifted to lower field when measured in the solvents such as benzene and pyridine, and secondly, the bridgehead proton is coplanar with two carbonyl groups respectively, shown by the Dreiding model, only when the compound has the twin-chair conformation, thus inducing shift of the signal to lower field and this was further proved by double resonance experiment on XIII in pyridine. Decoupling of the C-5 proton from the adjacent methylene group by bombarding the signal at 7.89 τ collapsed the triplet into the singlet, demonstrating firmly the signal at 6.55 τ for the bridgehead proton.[10] On the other hand, NMR spectra of XIII in carbon tetrachloride and benzene exhibited no distinguishable signal from other ring protons in the 6 to 7 τ region, but the triplet signal appeared at 6.82 τ when measured in pyridine, thus suggesting that XIII has a different conformation from that of XVII.

Thus, from these chemical and NMR evidences and in addition, the reports on the conformation of some bicyclo(3,3,1)nonane derivatives,[11] it can be concluded that these compounds (IX), (XII), and (XVII) have the same twin-chair conformation as in (XVII') and the methyl orientation in XVII is β-equatorial. On the structure of XIII, three conformations (XIIIa, XIIIb, XIIIc) are considered as shown in Chart 4. Validity of conformations XIIIb and XIIIc are excluded from their coplanarity of the bridgehead proton with both carbonyl groups, which can not explain NMR behavior on the bridgehead proton, while such coplanarity

10) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 63, 159.

11) W.A.C. Brown, J. Martin, and G.A. Sim, *J. Chem. Soc.*, **1965**, 1844; R.A. Appleton and S.H. Graham, *Chem. Commun.*, **1965**, 205.

is absent in the conformation (XIIIa). Thus, XIII would have the chair–boat conformation (XIIIa) with the methyl group in α–equatorial orientation.

With structures thus established, we now could explain the stereochemical aspects of the reactions, *i.e.*, catalytic hydrogenation of XVIII and the isomerization from XVII to XIII in term of steric interference present between 3– and 7–positions. Steric congestion in α–side of the bicyclo(3,3,1)nonane derivatives by the interaction of C–3 and C–7 methylene groups might restrict approach of the reagent from α–side, to the great extent, thus permitting the exclusive β–side attacks of hydrogen onto the olefinic double bond in XVIII, and of protonation on the enol (E) in the isomerization from XVII to XIII. Therefore, the methyl configuration in XVII might be also β–equatorial.

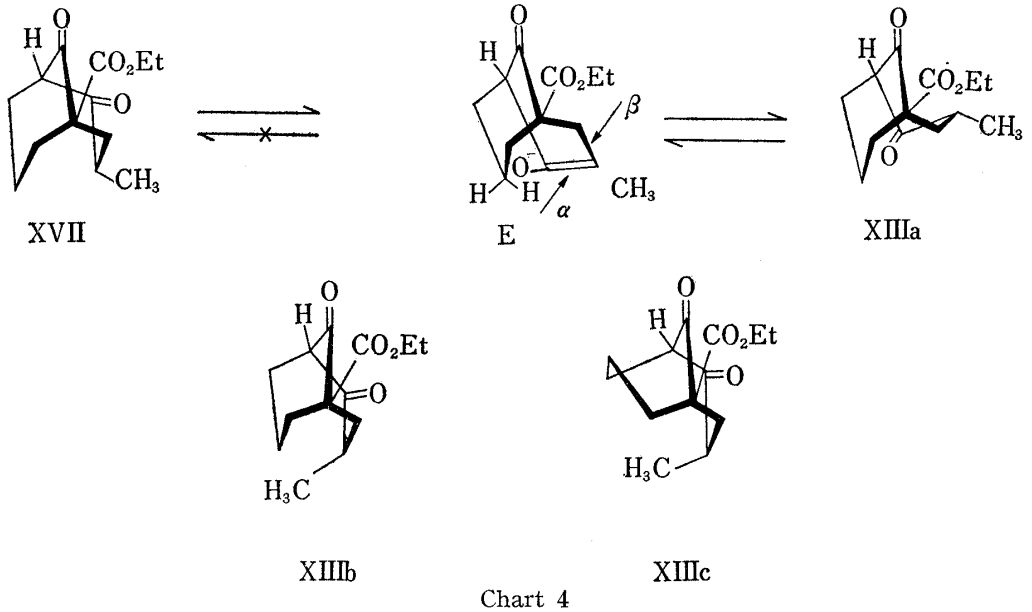

Chart 4

Thus, the methyl group in IV has the same configuration as lycopodium alkaloids and IV is now being incorporated into sequences designed to prepare the alkaloids, *i.e.*, lycopodine,[12] obscurines[13] and sauroxine.[14]

Experimental

Melting points and boiling points are uncorrected. Gas–liquid chromatography were measured on Perkin–Elmer gas chromatograph model 800, employing SE–30 column, unless otherwise mentioned. The NMR spectra were taken on Hitachi Perkin–Elmer H–60 type spectrometer at 60 Mc, tetramethylsilane serving as internal reference.

β-(1-Ethoxycarbonyl-2-oxo-5-methylcyclohexyl)propionaldehyde (II)——A stirred ethereal solution (100 ml) of 19.6 g (0.35 mole) of freshly distilled acrolein and 46 g (0.25 mole) of ethyl 2–oxo–5–methylcyclohexanecarboxylate (I) was added dropwise at −60° to an alcoholic solution (150 ml) of sodium ethoxide prepared from 100 mg of Na, containing 200 mg of hydroquinone, over a period of 2 hr. The resulting mixture was allowed to keep at the same temperature for another one hr, and then to room temperature. Neutralization with AcOH followed by removal of the solvent under reduced pressure left the brown residue, which was dissolved in 200 ml of ether. The ether layer was washed successively with brine, satd. $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 67 g of the viscous brown residue, which was distilled, bp 120—130° (0.1—0.08 mmHg) to give 32.2 g (58%) of colorless oil. *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.00; H, 8.33. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2717 (CHO), 1727, 1715 (sh) (C=O). NMR τ $CDCl_3$: 0.23 (1H, s, $-C\underline{H}O$), 5.81 (2H, q, $J=8$ cps, $-CO_2\underline{CH_2}CH_3$), 8.72 (3H, t, $J=8$ cps, $-CO_2CH_2\underline{CH_3}$), 8.95 (3H, diffused d, $J=5$ cps, $>CH-\underline{CH_3}$).

12) D.B. Harrison and W.A. McLean, *Chem. Ind.* (London), **1960**, 261.
13) W.A. Ayer, J.A. Berezowsky, and G.G. Iverach, *Tetrahedron*, **18**, 567 (1962).
14) W.A. Ayer and T.E. Habgood, *Tetrahedron*, **21**, 2169 (1965).

Ethyl 6α- and 6β-Hydroxy-3β-methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylates (III)——A solution of 33.25 g (0.138 mole) of II in 400 ml of acetone containing 40 ml of 6 N HCl was heated under reflux in nitrogen stream for 40 min. After removing acetone, the residue was dissolved in 200 ml of AcOEt. The AcOEt layer was washed successively with brine, satd. $NaHCO_3$, and brine and dried. Evaporation of the solvent gave 30.5 g (92%) of the residue, which gave two spots on TLC and one peak on GLC and was used to the next step without further purification. A sample for analysis was obtained by distillation, bp 150—155° (0.01 mmHg) (bath temp.), as colorless oil. *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.84; H, 8.35. IR ν_{max}^{film} cm^{-1}: 3425 (–OH), 1715 (–C=O). NMR τ $CDCl_3$: 5.83 (2H, q, J=7.5 cps, $-CO_2\underline{CH_2}CH_3$), 8.72 (3H, t, J=7.5 cps, $-CO_2CH_2\underline{CH_3}$), 9.05 (3H, d, J=5.5 cps, $>\underline{CH}-CH_3$).

Ethyl 3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carboxylate (IV)——To a solution of 22 g (0.192 mole) of CH_3SO_2Cl in 100 ml of dry pyridine was added dropwise a solution of 30.5 g (0.127 mole) of III in 100 ml of dry pyridine over a period of 45 min and the solution was stirred for 1 hr under ice-cooling and then allowed to stand at room temperature overnight. The resulting mixture was poured into an ice-water containing 230 ml of conc. HCl and extracted thoroughly with three 200 ml portions of AcOEt. The AcOEt layer was washed with brine, dried and evaporated to give 38.5 g of the residue. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1368 and 1183 ($-OSO_2-$). To this brown residue was added 150 ml of γ-collidine and the mixture was heated under reflux for 10 hr. After cooling, the mixture was poured into ice-chilled 6 N HCl with stirring and extracted with three 200 ml portions of AcOEt. The AcOEt layer was washed thoroughly with brine and dried. Evaporation of the solvent gave 25 g of the residue, which was distilled, bp 107—115° (0.05 mmHg) to give 14.9 g (53%) of colorless oil, which on cooling solidified, mp 57—58°, and recrystallized from petr. ether to afford colorless plates, mp 59—59.5°. *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.26; H, 8.05. IR ν_{max}^{KBr} cm^{-1}: 1730, 1715 (–C=O), 1647 (C=C). NMR τ $CDCl_3$: 4.20 (2H, m, $-C\underline{H}=C\underline{H}-$), 5.77 (2H, q, J=8 cps, $-CO_2\underline{CH_2}CH_3$), 8.70 (3H, t, J=8 cps, $-CO_2CH_2\underline{CH_3}$), 9.01 (3H, d, J=6 cps, $>CH-\underline{CH_3}$).

Ethyl 3β-Methyl-6,9-dioxobicyclo(3,3,1)nonane-1-carboxylate (IX)——A solution of 444 mg (1.8 mmoles) of III in 5 ml of purified acetone was cooled to 0° and stirred while 1 ml of standard chromic acid reagent[4] was slowly added. After 10 min MeOH was added to discharge the red color followed by adding water. The ether extract of the reaction mixture was washed successively with brine, satd. $NaHCO_3$, and brine and dried. Evaporation of the solvent gave 330 mg (74.6%) of the oily residue, homogeneous on both TLC and GLC. A sample for analysis was obtained by distillation, as colorless oil, bp 125—130° (0.05 mmHg) (bath temp.). *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.13; H, 7.53. IR ν_{max}^{film} cm^{-1}: 1730—1720 (–C=O). NMR τ $CDCl_3$: 5.72 (2H, q, J=7.5 cps, $-CO_2\underline{CH_2}CH_3$), 6.87 (1H, t, J=4 cps, bridgehead H), 8.72 (3H, t, J=7.5 cps, $-CO_2CH_2\underline{CH_3}$), 9.05 (3H, diffused d, $>CH-\underline{CH_3}$).

Treatment of III with *p*-TsCl——a) To an ice cooled solution of 240 mg (1 mmole) of III in dry pyridine was added portionwise 500 mg of crystalline *p*-TsCl and the mixture was allowed to stand at room temperature overnight. The mixture was poured into ice and extracted with three 40 ml portions of ether. The ether layer was washed with brine, satd. $NaHCO_3$, 10% HCl, brine and dried. Evaporation of the solvent gave the residue, which was identified as the starting material from IR and TLC behaviors.

b) A solution of 500 mg (2.1 mmoles) of III and 1.0 g (5.3 mmoles) of *p*-TsCl in 20 ml of dry pyridine was warmed on a boiling water bath for 7 hr. After cooling, the mixture was poured into ice and extracted with three 50 ml portions of AcOEt. The combined AcOEt extracts were washed successively with brine, 10% HCl, and brine and dried and evaporated. The residue, weighing 570 mg, was identified as the starting material on examination of TLC.

Ethyl 3β-Methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylate (V)——Five hundred milligram (2.2 mmoles) of the unsaturated keto-ester (IV) was subjected to catalytic hydrogenation over 100 mg of PtO_2 in 20 ml of EtOH under ordinary condition. The reaction was stopped at the point where about 1.5 equivalent amount of hydrogen was absorbed. The catalyst was filtered off and the solvent was evaporated to give 533 mg of the residue, which had OH absorption near 3480 cm^{-1} in IR. This residue was dissolved in 10 ml of purified acetone and treated with Jones reagent as usual. The AcOEt extract of the reaction mixture, after washed and dried, gave 530 mg of the residue, which was distilled, bp 107—109° (0.01 mmHg) (bath temp.) to give 475 mg (94%) of colorless oil, homogeneous on TLC. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1733, 1718 (sh) (–C=O). NMR τ $CDCl_3$: 5.79 (2H, q, J=7.5 cps, $-CO_2\underline{CH_2}CH_3$), 8.71 (3H, t, J=7.5 cps, $-CO_2CH_2\underline{CH_3}$), 9.04 (3H, d, J=5.5 cps, $-CH-\underline{CH_3}$). 2,4-Dinitrophenylhydrazone, mp 115—116°, yellow needles, recrystallized from EtOH. *Anal.* Calcd. for $C_{19}H_{24}O_6N_4$: C, 56.43; H, 5.98; N, 13.86. Found: C, 56.70; H, 6.05; N, 13.76. IR ν_{max}^{KBr} cm^{-1}: 3306 (–NH), 1713 (–COOEt), 1613 (–C=N).

Thioketalization of V——A mixture of 320 mg (1.4 mmoles) of V in 5 ml of glac. AcOH, 0.2 ml of $BF_3 \cdot Et_2O$ and 0.32 ml (3.8 mmoles) of ethanedithiol was warmed on a boiling water bath for 3 hr. After cooling, the mixture was poured into cold water neutralized with $NaHCO_3$ and extracted with three 50 ml portions of AcOEt. The combined AcOEt extracts were washed with brine, dried and evaporated to give 540 mg of the residue, which was chromatographed on silicagel. Fraction eluted by *n*-hexane gave 210 mg (50%) of the thioketal (VI), homogeneous on TLC, and distilled, bp 118—124° (0.01 mmHg) (bath temp.), to give colorless oil. *Anal.* Calcd. for $C_{15}H_{24}O_2S_2$: C, 59.98; H, 8.05. Found: C, 60.08; H, 7.95. IR ν_{max}^{film} cm^{-1}: 1715 ($-CO_2Et$). NMR τ CCl_4: 5.97 (2H, q, J=7.5 cps, $-CO_2\underline{CH_2}CH_3$), 6.85 (4H, s, $-S-C\underline{H_2}-C\underline{H_2}-S-$), 8.76 (3H, t, J=7.5 cps, $-CO_2CH_2\underline{CH_3}$), 9.11 (3H, d, J=5.5 cps, $>CH-\underline{CH_3}$).

Treatment of VI with Raney Nickel (W-2)——A suspension of 210 mg (0.7 mmole) of VI, 10 ml of abs. EtOH and 1.5 g of Raney nickel (W-2) was heated under reflux on steam bath with stirring. Additional portions of Raney nickel were added at one hour interval. From careful inspections of IR and TLC, only the starting material was recovered even after 20 hr heating.

9-Hydroxy-3β-methylbicyclo(3,3,1)nonane-1-methanol (VII)——To an ice-cooled solution of 2.1 g (9.4 mmoles) of V in 20 ml of EtOH was added 400 mg (10.5 mmoles) of $NaBH_4$ portionwise and the mixture was stirred for one hr and allowed to stand at room temperature for 2.5 hr. After removing EtOH, was added dil. HCl to decompose excess reducing agent and extracted with three 50 ml portions of AcOEt. The AcOEt layer was washed with brine, $NaHCO_3$, and brine, and dried. Evaporation of the solvent gave 2.05 g of the residue. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 (–OH), 1705 (COOEt). A solution of 500 mg (3.5 mmoles) of this crude alcohols in 10 ml of dry pyridine was added to an ice-cooled solution of 400 mg (3.5 mmoles) of CH_3SO_2Cl in 10 ml of dry pyridine with stirring over a period of 20 min and the mixture was allowed to stand at room temperature overnight, poured into ice-water containing 20 ml of conc. HCl and extracted with three 50 ml portions of AcOEt. The combined organic extracts were washed with water, dried and evaporated to give 670 mg of the residue, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1370 and 1180 (–OSO_2–), which was dissolved in 20 ml of dry tetrahydrofuran and 550 mg (14.4 mmoles) of $LiAlH_4$ was added. The resulting mixture was refluxed for 9 hr. After ice-cooling, was added AcOEt to decompose excess $LiAlH_4$ and extracted with AcOEt. The AcOEt layer was washed with water and dried. Evaporation of the solvent gave 670 mg of the oily residue, which was subjected to chromatography on silicagel. Fraction eluted by $CHCl_3$ gave 160 mg of colorless oil (overall yield 40%), which soon solidified on cooling and recrystallized from *n*-hexane—benzene to afford colorless leaflets, mp 108—110°. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.48; H, 10.78. IR ν_{max}^{KBr} cm^{-1}: 3344 and 3279 (–OH). NMR τ $CDCl_3$: 4.36 (1H, d, J=2.5 cps, –C<u>H</u>–OH), 4.64 (2H, s, >C<u>H_2</u>OH), 4.90 (2H, broad s, –OH, which disappeared by D_2O exchange), 9.10 (3H, d, J=6 cps, >CH–C<u>H_3</u>).

Ethyl 3β-Methylbicyclo(3,3,1)nonane-1-carboxylate (VIII)——A mixture of 1.21 g (4.0 mmoles) in 50 ml of abs. EtOH and 500 mg of Raney nickel (W-2) was catalytically hydrogenated in an autoclave under the condition of 60 atmospheric pressure and at 90° for 15 hr. After removing the catalyst, evaporation of the solvent gave 1.12 g of the residue, which was subjected to chromatography on silicagel. Fraction eluted by CCl_4 gave 165 mg (20%) of oil, almost homogenous on TLC, distilled, bp 75—80° (0.5 mmHg) (bath temp.). *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.88; H, 10.30. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1717 (–COOEt), NMR τ $CDCl_3$: 5.91 (2H, q, J=7.5 cps., –CO_2<u>CH_2</u>CH_3), 8.75 (3H, t, J=7.5 cps, –CO_2CH_2<u>CH_3</u>), 9.11 (3H, d, J=5 cps, >CH–<u>CH_3</u>).

Ethyl 4α- and 4β-Hydroxy-9-oxobicyclo(3,3,1)nonane-1-carboxylates (XI)——To a solution of 8.4 g (37 mmoles) of the keto-aldehyde (X) in 100 ml of acetone was added 10 ml of 6N HCl and the mixture was refluxed under nitrogen stream for 30 min. After removing most of acetone, was added 60 ml of ether. The ether layer was washed successively with brine, $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$ and evaporated. The residue thus obtained, weighing 7.9 g, was distilled, bp 160—175° (0.8 mmHg) (bath temp.), to afford 7.0 g (83%) of colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (–OH), 1730—1720 (–C=O) (lit[9]): bp 170—200° (0.3 mmHg). 50% yield by treatment with H_2O–AcOH—HCl).

Ethyl 4,9-Dioxobicyclo(3,3,1)nonane-1-carboxylate (XII)——A solution of 3.4 g (15 mmoles) of XI in 15 ml of purified acetone was cooled to 0° and stirred while 4.0 ml of standard chromic acid reagent was added. The mixture was treated with MeOH to decompose excess oxidizing agent, followed by extraction with ether. The organic layer was washed with brine, satd. $NaHCO_3$ and brine, dried and evaporated to give 2.2 g of the oily residue, which was distilled, bp 125—130° (0.01 mmHg) (bath temp.), to afford 1.85 g (55%) of colorless oil, which on standing solidified and was recrystallized from petr. ether to give colorless needles, mp 54.5—55.5°. *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.27. IR ν_{max}^{KBr} cm^{-1}: 1734 (sh), 1716 (sh), 1707 (–C=O). NMR τ $CDCl_3$: 5.74 (2H, q, J=7.5 cps, –CO_2<u>CH_2</u>CH_3), 6.83 (1H, t, J=4 cps, bridgehead H), 8.67 (3H, t, J=7.5 cps, –CO_2CH_2<u>CH_3</u>).

Ethyl 3α-Methyl-4,9-dioxobicyclo(3,3,1)nonane-1-carboxylate (XIII) from XII——A solution of 1.85 g (8.3 mmoles) of the diketo-ester (XII), 2 ml (40 mmoles) of pyrrolidine and trace of *p*-TsOH in 30 ml of dry C_6H_6 was heated under reflux with the Dean Stark water separator to remove water as it formed for 6 hr. Evaporation of the solvent under reduced pressure gave 2.45 g of the residue, which showed a strong band at 1650 cm^{-1} in IR. This residue was dissolved in 25 ml of C_6H_6 and added 2.4 ml of MeI and the resulting mixture was warmed gently under reflux for 10 hr. During this period additional 2.4 ml portion of MeI was added at every two hours. After removing the solvent, to the residue was added 10 ml of water, 10 ml of 6N HCl and small amount of acetone enough to make the mixture homogeneous and the solution was allowed to stand at room temperature for 6 hr and then refluxed for further 30 min. Evaporation of the solvent under reduced pressure, AcOEt extraction, followed by usual work-up afforded 1.6 g of the residue, which was chromatographed on silicagel. Fraction eluted by CCl_4 afforded 150 mg (6.3%) of the α-methyl derivative (XIII), which was distilled, bp 82—85° (0.01 mmHg) (bath temp.), giving colorless oil, solidified on standing, mp 66—71°, which was homogeneous on TLC and GLC. Recrystallization from petr. ether gave an analytical sample as colorless plates, mp 70.5—71.5°. *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.43; H, 7.47. IR ν_{max}^{KBr} cm^{-1}: 1735 (sh), 1717, 1702 (–C=O). NMR τ $CDCl_3$: 5.77 (2H, q, J=7 cps,

$-CO_2\underline{CH_2}CH_3$), 8.68 (3H, t, $J=7$ cps, $-CO_2CH_2\underline{CH_3}$), 8.86 (3H, d, $J=5$ cps, $>CH-\underline{CH_3}$). Fraction eluted by $CHCl_3$ recovered 1.2 g of the starting material (XII).

Epimeric Mixtures of Ethyl 4-Hydroxy-3-methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylate (XVI)——To an alcoholic solution (100 ml) of sodium ethoxide prepared from 80 mg of Na and 100 mg of hydroquinone was added a mixture of 10 g (59 mmoles) of XIV and 4 g (57 mmoles) of freshly distilled methacrolein at −35 to −40° with stirring over a period of one hr and allowed to keep at the room temperature for further one hr. Neutralization with AcOH at room temperature and evaporation of the solvent under reduced pressure gave the residual oil, which was dissolved in AcOEt. The organic layer was washed successively with brine, satd. $NaHCO_3$, brine and dried over anhydrous $MgSO_4$, and evaporated to give 12.9 g of the residue, which was distilled *in vacuo*, bp 115—128° (0.5 mmHg), to afford 7.2 g (50%) of XV as colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2717 (-CHO), 1715 (-C=O).

A mixture of 7.2 g (30 mmoles) of the aldehyde dissolved in 100 ml of acetone containing 8 ml of 6N HCl was refluxed under nitrogen stream for 30 min. Evaporation of the solvent, extraction with AcOEt, washing and drying were carried out as usual, giving 7.0 g of the residue, which showed four spots on TLC and employed to the next step without further purification. A specimen for analysis was obtained by column chromatography followed by distillation *in vacuo*, bp 135—138° (0.01 mmHg) (bath temp.), as colorless oil. *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: 64.72; H, 8.23. IR ν_{max}^{film} cm^{-1}: 3436 (-OH), 1724—1704 (-C=O).

Oxidation of XVI——A solution of 7.0 g (29 mmoles) of XVI in 25 ml of purified acetone was treated with Jones reagent as in the oxidation of III. Worked up as usual gave 6.7 g of the residue, which showed two spots on TLC ($Rf=0.55$ for the component A and 0.75 for the component B on silicagel with *n*-hexane—ether (1:1)), but a single spot on GLC. The crude mixture (4.5 g) was chromatographed on silica gel using $CHCl_3$–CCl_4 (1:1) as eluent and from the forerunning fraction was separated 540 mg of the component (B), which solidified on cooling, and was recrystallized from petr. ether to colorless crystals, mp 69—70°, homogeneous on TLC, which was identical with the sample obtained by the enamine method in comparison with IR, TLC, mp and mixed mp. Repeated chromatography of the latter fraction afforded the component (A), ethyl 3β-methyl-4,9-dioxobicyclo(3,3,1)nonane-1-carboxylate (XVII) as colorless oil. Distillation *in vacuo*, bp 112—114° (0.05 mmHg), afforded an analytical sample. *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.12; H, 7.40. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1728, 1708 (-C=O). NMR τ CCl_4: 5.78 (2H, q, $J=7$ cps, $-CO_2\underline{CH_2}CH_3$), 6.87 (1H, t, $J=4$ cps, bridgehead H), 8.69 (3H, t, $J=7$ cps, $-CO_2CH_2\underline{CH_3}$), 8.85 (3H, d, $J=6.5$ cps, $>CH-\underline{CH_3}$).

Isomerization of XVII to XIII——To a solution of 200 mg of the 3β-methyl derivative (XVII) in 10 ml of glac. AcOH was bubbled dry HCl gas for 5 min and the mixture was allowed to keep at room temperature. The isomerization was completed within 2.5 hr upon checking with TLC. (The isomerization was found to occur slowly even on standing the mixture at room temperature).

To the mixture was added water and neutralized with $NaHCO_3$, and extracted with AcOEt. The organic extract was washed with water, dried and evaporated to afford 185 mg of the residue. Chromatography on silica-gel using $CHCl_3$—CCl_4 (1:1) as eluent afforded 130 mg of the 3α-methyl derivative (XIII), which was completely identical with XIII on TLC, IR, mp, and mixed mp.

Under the same condition, no isomerization was observed from the 3α-methyl derivative (XIII) to the 3β-methyl derivative (XVII).

Ethyl 3-Methyl-9-oxobicyclo(3,3,1)non-3-ene-1-carboxylate (XVIII)——To a solution of 2.5 g (21 mmoles) of CH_3SO_2Cl in 10 ml of dry pyridine at 0° was added a solution of 1.5 g (6.3 mmoles) of XVI in 15 ml of dry pyridine over a period of 30 min. The mixture was stirred at 0° for one hr and left at room temperature overnight and poured into ice-water containing 30 ml of conc. HCl. Work up as usual gave 1.7 g of the residue, which was crystallized upon trituration of *n*-hexane to give 1.5 g of solid, showing strong bands at 1370 and 1175 cm^{-1} due to sulfonate group in IR.

The mixture of 760 mg of the crude mesylates and 25 ml of γ-collidine was refluxed for 6 hr. After cooling, the reaction mixture was poured into ice-water containing 25 ml of conc. HCl and extracted with AcOEt. The AcOEt layer was washed with brine, dried and evaporated to give 820 mg of the residue, which was subjected to chromatography on silicagel. Fraction eluted by $CHCl_3$ gave 470 mg of colorless oil, upon distillation *in vacuo*, bp 80—90° (0.01 mmHg) (bath temp.). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.79; H, 8.05. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1733 (sh), 1720 (-C=O), 1676 (-C=C-). NMR τ $CDCl_3$: 4.69 (1H, broad d, $J=7$ cps, $-C\underline{H}=C-CH_3$), 5.77 (2H, q, $J=7.5$ cps, $-CO_2\underline{CH_2}CH_3$) 8.21 (3H, d, $J=1.5$ cps, $-CH=C-\underline{CH_3}$), 8.71 (3H, t, $J=7.5$ cps, $-CO_2CH_2\underline{CH_3}$).

Ethyl 3α-Methyl-9-oxobicyclo(3,3,1)nonane-1-carboxylate (XIX)——One hundred and twenty milligram (0.5 mmole) of XVIII in 20 ml of EtOH was catalytically hydrogenated over 20 mg of PtO_2 under 4.5 atmospheric pressure at room temperature for 4 hr. The catalyst was removed by filtration and EtOH was distilled off to give 125 mg of the residue, showing OH band at 3490 cm^{-1} in IR. This residue was oxidized with Jones reagent and worked up as usual to afford 95 mg of oil, which on distillation afforded 85 mg (70%) of colorless oil, bp 95—100° (0.01 mmHg) (bath temp.). NMR τ $CDCl_3$: 5.78 (2H, q, $J=7.5$ cps, $-CO_2\underline{CH_2}CH_3$), 8.72 (3H, t, $J=7.5$ cps, $-CO_2CH_2\underline{CH_3}$), 9.01 (3H, diffused d, $J=4.3$ cps, $>CH-\underline{CH_3}$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1717, 1708 (-CO).

Both V and XIX gave the same *Rf* value on TLC, but different retention times on GLC (16.2 min for V and 14.2 min for XIX on SE-52 column at 130°). 2,4-Dinitrophenylhydrazone of XIX, yellow plates, mp 108—109° (decomp.) and its IR spectrum was quite different from that of V. *Anal.* Calcd. for $C_{19}H_{24}O_6N_4$: C, 56.43; H, 5.98; N, 13.86. Found: C, 56.23; H, 5.96; N, 13.88. IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 1716 (CO_2Et), 1611 (C=N).

Attempted Reduction of XI to Ethyl 4α- and 4β-Hydroxybicyclo(3,3,1)nonane-1-carboxylate (XX)——a) With Zinc-amalgam: A mixture of 500 mg (2.1 mmoles) of XI, 2 g of zinc-amalgam, 2 ml of conc. HCl, 0.5 ml of H_2O and 2 ml of toluene was heated under reflux for 2 hr and, after cooling, was extracted with three 30 ml portions of toluene. The combined organic layer was washed with brine, $NaHCO_3$ and brine, and dried. Evaporation of the solvent afforded 360 mg of the residue, which however did not give the desired product.

b) With Modified Huang-Minlon Reduction[15]: To a solution of 500 mg (2.1 mmoles) of XI in 20 ml of EtOH was added 400 mg (2.2 mmoles) of *p*-tosylhydrazine and the mixture was refluxed for 4 hr. After cooling, an aliquot was taken from the reaction mixture and identified the formation of the hydrazone. Then to this reaction mixture was added 1.0 g (26 mmoles) of $NaBH_4$ and the mixture was heated under reflux for 6 hr. After removing EtOH, dil. HCl was added to decompose the excess reducing agent and the mixture was extracted with AcOEt. Evaporation of the dried extract afforded 600 mg of the residue, from which the desired product could not characterize.

Attempted Conversion from XIII and XVII to VIII and Its Epimer——a) Three hundred and sixty milligram (1.5 mmoles) of the α-methyl derivative (XIII) in 10 ml of EtOH was catalytically hydrogenated over 50 mg of PtO_2 under 5.5 atmospheric pressure at room temperature for 5 hr. The catalyst was removed and the solvent was evaporated to give 380 mg of the residue, which showed OH absorption at 3400 cm^{-1} in IR. This residue was dissolved in 10 ml of dry pyridine, cooled to 0° and stirred while a solution of 1.2 g (10 mmoles) of CH_3SO_2Cl in 10 ml of dry pyridine was added. And the reaction mixture was allowed to stand at room temperature overnight and poured into ice-water containing 20 ml of conc. HCl and extracted with AcOEt. The combined organic extracts were washed thoroughly with water, dried and evaporated to give 850 mg of the residue which showed strong bands at 1380 and 1180 cm^{-1} due to sulfonate group. The crude mesylates in 20 ml of EtOH were subjected to catalytic hydrogenation in the presence of Raney nickel (W-2) under 80 atmospheric pressure at 80° for 15 hr. The catalyst was removed and the solvent was evaporated to afford 520 mg of the residue, which was characterized as the starting mesylates from IR inspection and no desoxo derivative was observed.

b) With 700 mg (2.9 mmoles) of the 3β-methyl derivative (XVII), the similar treatment as in a) for desulfurization was attempted but without success.

15) L. Caglioti, *Chem. Ind.* (London), **1964**, 153.