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BRIDGED RING SYSTEMS—II

REARRANGEMENTS IN THE BICYCLO[3:3:1]NONANE SERIES

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Abstract—Treatment of β-(1-ethoxycarbonyl-2-keto-3-methylcyclohexyl)-propionaldehyde with concentrated sulphuric acid furnishes not only the expected ethyl 5-methylbicyclo[3:3:1]non-3-en-9-one-1-carboxylate (II), but also two rearranged products, 7-methylindan-4-carboxylic acid (VI) and ethyl 2-acetylbicyclo[3:3:0]oct-1(2)-ene-5-carboxylate (IX).

IN another approach[1] to the synthesis of clovene, an alternative route to a suitably substituted bicyclo[3:3:1]nonane derivative has been examined involving the acid-catalysed cyclization of β-(1-ethoxycarbonyl-2-keto-3-methylcyclohexyl)propionaldehyde (I). By analogy with previously described examples[2] the product expected was ethyl 5-methylbicyclo[3:3:1]non-3-en-9-one-1-carboxylate (II). This in fact was obtained in acceptable yield and constituted the main component of the mixture produced. The structure assigned to this main product was confirmed by its light absorption and general chemical properties. It did not react with 2,4-dinitrophenylhydrazine or semicarbazide acetate in the cold, but gave a crystalline pyrazolone (III) by treatment with hydrazine. The crystalline keto-acid derived by hydrolysis could be reduced by the Clemmensen technique with retention of the double bond to furnish the acid (IV). Catalytic reduction of this product gave the saturated bicyclo-acid (V) identical with that obtained by an alternative route.[1] The position of the double bond in II and IV was assigned by consideration of the mode of formation of II; rigorous corroboration of this point will be described in a future publication.

The presence of two other products from the cyclization of I was indicated by the light absorption properties. One of these by-products was acidic and was readily extractable with base; the second formed a semicarbazone with great ease and could therefore be simply separated from the main product (II) which reacted very sluggishly with semicarbazide acetate.

The crystalline acidic by-product, $C_{11}H_{12}O_2$, possessed the light absorption characteristics of a substituted benzoic acid. The melting point of the acid and of its derived amide and nitrile tallied exactly with those recorded[3] for 7-methylindan-4-carboxylic acid (VI). Further confirmation was provided by lithium aluminium hydride reduction of the corresponding methyl ester followed by hydrogenolysis of the alcohol to 4-7-dimethylindan, identified by its physical properties and characteristic infra-red and ultra-violet spectra.[4] (Formulae I–VI.)

The liquid ketonic by-product, $C_{13}H_{18}O_3$, showed absorption bands in the infra-red at 1725 (ester) and 1667 cm^{-1} (conjugated C=O) and at 252 mμ (ε 12,000) in the

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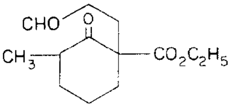
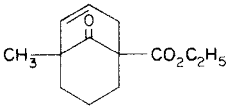
[1] R. D. H. Murray, W. Parker and R. A. Raphael, *Tetrahedron* **16**, 74 (1961).
[2] A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.* **72**, 5228 (1950).
[3] L. F. Fieser and A. M. Seligman, *J. Amer. Chem. Soc.* **58**, 2481 (1936).
[4] J. Entel, *Analyt. Chem.* **26**, 612 (1954).



I



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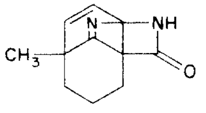

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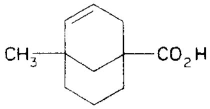

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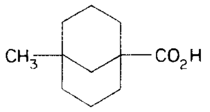

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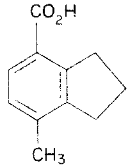
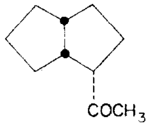
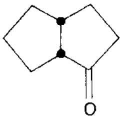


VI

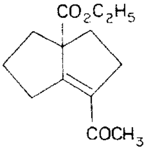
ultra-violet. Catalytic reduction showed the presence of one carbon–carbon=. The reduction product was hydrolysed to a saturated keto-acid which was stable to heat, gave a strong iodoform reaction and formed a mono-piperonylidene derivative. Mild hydrolysis of the by-product itself gave an unsaturated keto-acid which was readily decarboxylated by heat to a mixture of conjugated and non-conjugated ketones; this behaviour suggested the presence of a vinylogous β-keto-ester system. Catalytic reduction of this ketonic mixture gave a single saturated ketone (VII) whose semicarbazone melted very close to the value recorded for the semicarbazone of *cis*, endo-2-acetylbicyclo[3:3:0]octane[5]. Further identification was obtained by oxidation of VII with pertrifluoracetic acid followed by hydrolysis and oxidation to the well-known *cis*-bicyclo[3:3:0]octan-2-one (VIII)[6] whose semicarbazone showed no depression of melting point on admixture with an authentic sample kindly provided by Professor A. C. Cope. (Formulae VII–XII.) The above results are fully compatible with the structure IX for the ketonic by-product, but do not exclude the alternative structure X. However, structure IX is favoured both on mechanistic grounds (see below) and also from examination of the proton magnetic resonance spectrum. This showed no



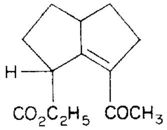
VII



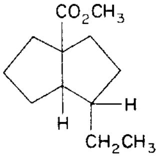
VIII



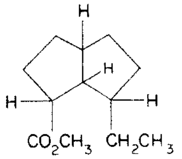
IX



X



XI



XII

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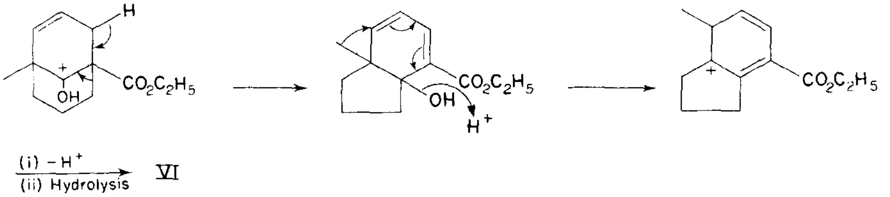
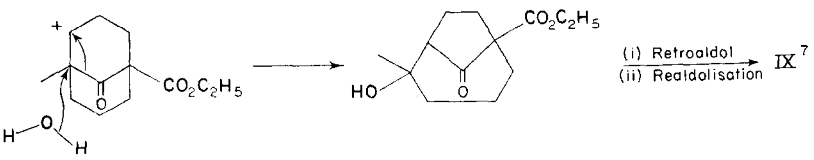
[5] A. C. Cope, M. Brown and H. E. Petree, *J. Amer. Chem. Soc.* **80**, 2852 (1958).

[6] A. H. Cook and R. P. Linstead, *J. Chem. Soc.* 955 (1934); A. C. Cope and W. R. Schmitz, *J. Amer. Chem. Soc.* **72**, 3056 (1950); J. D. Roberts and W. F. Gorham, *Ibid.* **74**, 2278 (1952).

absorption peaks in region $\tau = 6{\cdot}5$–$7{\cdot}0$ which would be expected from the hydrogen atom indicated in structure X. The exclusion of structure X is further substantiated by the spectrum of the fully reduced methyl ester XI. The corresponding alternative structure XII would require peaks from three protons in the region $\tau = 7{\cdot}5$–$8{\cdot}0$ and also peaks from one proton in the region $\tau = 6{\cdot}5$–$7{\cdot}0$. Whereas structure XI requires peaks from two protons in the region $\tau = 7{\cdot}5$–$8{\cdot}0$. The observed spectrum indeed showed only peaks clustered around $\tau = 7{\cdot}75$ from two protons and no trace of absorption in the region $\tau = 6{\cdot}6$–$7{\cdot}0$.

The detailed mechanism of these and allied rearrangements is now being studied. Of many possibilities, the two following schemes seem worthy of consideration.





EXPERIMENTAL

The m.ps. were determined on a Kofler block and are corrected, but b.ps. are uncorrected. The U.V. spectra were determined in ethanol solution and the I.R. spectra were determined as liquid films unless stated otherwise.

β-(1-Ethoxycarbonyl-2-keto-3-methylcyclohexyl) propionaldehyde (I). A mixture of 2-ethoxycarbonyl-6-methylcyclohexanone (5·52 g) and redistilled acrolein (1·98 ml) was added dropwise to a stirred solution of sodium (0·032 g) in anhydrous ethanol (20 ml) chilled to −70° containing hydroquinone (0·035 g) and the mixture stirred for 1 hr. Acetic acid was then added till the reaction mixture was at pH 7. Removal of the ethanol furnished a red oil which was dissolved in ether and washed with water, dil sodium bicarbonate solution, water and dried. Distillation of the residual oil after removal of the solvent gave the aldehyde (I) b.p. 130°/0·4 mm, (Found: C, 64·85; H, 8·15. $C_{13}H_{20}O_4$ requires: C, 65·0; H, 8·4%). The corresponding bis-2,4-dinitrophenylhydrazone crystallized from acetic acid in needles m.p. 200–201°. (Found: C, 49·15; H, 4·45; N, 18·45. $C_{25}H_{28}O_{10}N_8$ requires: C, 50·0; H, 4·45; N, 18·65%).

Ethyl 4-hydroxy-5-methylbicyclo[3:3:1]*nonan-9-one-1-carboxylate.* A mixture of the above aldehyde (3·0 g), acetic acid (12 ml), conc hydrochloric acid (3·0 ml) and water (6 ml) was heated on a steam-bath for 15 min and then held at room temp for 18 hr. The crude product was distilled to give ethyl 4-hydroxy-5-methylbicyclo[3:3:1]nonan-9-one-1-carboxylate (2·4 g), b.p. 130°/0·05 mm, n_D^{20} 1·4934. (Found: C, 64·65; H, 8·7. $C_{13}H_{20}O_4$ requires: C, 64·95; H, 8·4%).

Ethyl 5-methylbicyclo[3:3:1]*non-3-en-9-one-1-carboxylate* (II). The aldehyde (367 g) was added dropwise to conc sulphuric acid (1 l.), held at 0°, the reaction mixture stirred at room temp overnight and then diluted with ice-water (15 l.) and thoroughly extracted with ether (2 × 5 l.). The combined ethereal extracts were washed with sodium carbonate solution,* water and dried. Removal of the solvent followed by distillation gave a clear oil (204 g) b.p. 120°/0·25 mm–140°/0·8 mm, which was treated with excess of a conc solution of semicarbazide acetate in ethanol and allowed to stand at 0°

* See Acidification of alkaline extracts* p. 58.

[7] Since treatment of ethyl 4-hydroxy-5-methylbicyclo[3:3:1]nonane-9-one-1-carboxylate with conc sulphuric acid gave the same mixture of products, it is probable that this alcohol is the key intermediate in the formation of II, VI, and IX from I.

overnight. The precipitated semicarbazone† (21·25 g) was collected, the filtrate concentrated under red press, diluted with a large volume of water and extracted with ether. The crude product was then distilled to give *ethyl 5-methylbicyclo*[3:3:1]*non-3-en-9-one-*1-*carboxylate* (II) as a clear oil (135 g) b.p. 115°/0·2 mm, $n_D^{21·5}$ 1·4900. (Found: C, 69·8; H, 8·15. $C_{13}H_{18}O_3$ requires: C, 70·25; H, 8·15%). The corresponding *pyrazolone* (III crystallized from benzene–pet ether (60–80°) in needles m.p. 149–150°. (Found: C, 69·35; H, 7·35. $C_{11}H_{14}ON_2$ requires: C, 69·45; H, 7·40%).

Acidification of the alkaline extracts* gave 7-methylindan-4-carboxylic acid, VI, (10 g) which crystallized from ethyl acetate in stout prisms m.p. 228–229°. (Found: C, 75·15; H, 7·0. Calc. for $C_{11}H_{12}O_2$: C, 75·0; H, 6·85%). The corresponding methyl ester crystallized from aqueous methanol in needles m.p. 45–47°. (Found: C, 75·5; H, 7·4. $C_{12}H_{14}O_2$ requires: C, 75·75; H, 7·4%). 7-Methylindan-4-carboxamide, prepared from the aromatic acid chloride by trituration with 0·88 ammonia, crystallized from ethyl acetate in needles m.p. 179–179·5°. (Found: C, 75·2; H, 7·5; N, 7·9. Calc. for $C_{11}H_{13}ON$: C, 75·4; H, 7·5; N, 8·0%). 7-Methyl-4-cyanoindan, prepared by phosphorus pentoxide dehydration of the corresponding amide, crystallized from pet ether (40–60°) in plates m.p. 71–73°. (Found: N, 8·65. Calc. for $C_{11}H_{11}N$: N, 8·9%).

The semicarbazone† (21·25 g) when shaken with dil mineral acid, gave *ethyl-*2-*acetylbicyclo-*[3:3:0]*oct-*1(2)-*ene-*5-*carboxylate* (IX; 15·5 g), b.p. 107–112°/0·175 mm, n_D^{21} 1·5002. (Found: C, 70·35; H, 7·7. $C_{13}H_{18}O_3$ requires: C, 70·25; H, 8·15%). The I.R. spectrum of this material showed maxima at 1728 and 1667 cm^{-1} and the U.V. spectrum showed a maximum at 252 mμ (ε 12,000).

The corresponding 2,4-*dinitrophenylhydrazone* crystallized from methanol in plates m.p. 138–140°. (Found: C, 56·7; H, 5·6; N, 14·5. $C_{19}H_{22}O_6N_4$ requires: C, 56·7; H, 5·5; N, 13·9%) with U.V. maximum, in chloroform solution, at 390 mμ (ε 14,000). The *semicarbazone* crystallized from methanol in needles m.p. 195–196°. (Found: C, 60·3; H, 7·7; N, 14·7. $C_{14}H_{21}O_3N_3$ requires: C, 60·2; H, 7·6; N, 15·05%).

Treatment of ethyl 4-hydroxy-5-methylbicyclo[3:3:1]nonane-9-one-1-carboxylate with conc sulphuric acid gave the same mixture of products.

5-*Methylbicyclo*[3:3:1]*non-*3-*en-*9-*one-*1-*carboxylic acid.* Hydrolysis of II with methanolic potassium hydroxide gave the required *carboxylic acid* which crystallized from pet ether (60–80°) in needles m.p. 139–140°. (Found: C, 68·4; H, 7·0. $C_{11}H_{14}O_3$ requires: C, 68·0; H, 7·3%). The corresponding *methyl ester* crystallized from methanol in cubes m.p. 83–84°. (Found: C, 69·4; H, 7·0. $C_{12}H_{16}O_3$ requires: C, 69·2; H, 7·75%).

5-*Methylbicyclo*[3:3:0]*non-*3-*ene-*1-*carboxylic acid* (IV). Zinc amalgam was prepared by shaking zinc powder (400 g), mercuric chloride (40 g), conc hydrochloric acid (20 ml) and water (200 ml) for 5 min and then decanting the aqueous layer. The keto-acid (40 g), prepared above, xylene (200 ml), conc hydrochloric acid (400 ml) and water (200 ml) were added to the zinc amalgam and the mixture heated under reflux for 12 hr. Further portions of conc hydrochloric acid (250 ml) were added at intervals of 4 hr. The cold reaction mixture was saturated with ammonium sulphate, thoroughly extracted with ethyl acetate and the combined extracts washed with water and saturated sodium carbonate solution. Acidification of these alkaline extracts followed extraction with ethyl acetate and removal of the solvent gave the crude olefinic acid IV. Treatment with diazomethane then furnished the corresponding methyl ester (25 g) which, after treatment with sodium borohydride (one molar equivalent) in methanol, was adsorbed on alumina (grade H, 350 g) from pet ether (60–80°). Elution with the same solvent gave *methyl* 5-*methylbicyclo*[3:3:1]*non-*3-*ene-*1-*carboxylate* (13·2 g) b.p. 55°/0·1 mm, n_D^{21} 1·4825. (Found: C, 74·05; H, 9·4. $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·35%). Hydrolysis with potassium hydroxide in methanol then gave 5-*methylbicyclo*[3:3:0]*non-*3-*ene-*1-*carboxylic acid* (IV) which crystallized from pet ether (40–60°) in elongated needles m.p. 109–111°. (Found: C, 73·55; H, 9·1. $C_{11}H_{16}O_2$ requires: C, 73·3; H, 8·95%).

5-*Methylbicyclo*[3:3:0]*nonane-*1-*carboxylic acid* (V). A solution of IV in ethyl acetate was hydrogenated over platinum oxide at room temp; the theoretical uptake of hydrogen being absorbed in 5 min. The product, purified by sublimation as needles, m.p. 141–143°, was identical (m.p., mixed m.p., and I.R. spectrum) with an authentic sample).[1]

4,7-*Dimethylindan.* Lithium aluminium hydride reduction of methyl 7-methylindan-4-carboxylate, prepared above, gave 4-hydroxymethyl-7-methylindan as a thick oil which showed I.R. maxima at 3300, 3000, 1600, 1493 and 1000 cm^{-1} with a strong band a 817 cm^{-1}. Catalytic hydrogenolysis of this alcohol over reduced platinum oxide in acetic acid solution, containing a few drops of perchloric acid, gave 4,7-dimethylindan n_D^{22} 1·5290, which showed strong maxima in the I.R. at 1493 and 807 cm^{-1} with weak bands at 2995 and 1600 cm^{-1}. The product also exhibited U.V. absorption at 264 mμ (ε 231) with shoulder maxima at 258 and 272 mμ (cf. ref. 4).

Ethyl 2-acetylbicyclo[3:3:0]*octane-5-carboxylate.* Catalytic hydrogenation of IX (3·05 g) in ethyl acetate over palladium-charcoal (10%) resulted in an uptake of 336 ml of hydrogen (one double equivalent). The crude product was fractionally distilled to give *ethyl 2-acetylbicyclo*[3:3:0]*octane-5-carboxylate* b.p. 88–92°/0·15 mm $n_D^{22\cdot5}$ 1·4722. (Found: C, 69·3; H, 9·65. $C_{13}H_{20}O_3$ requires: C, 69·6; H, 9·0%). This material was transparent in the U.V. but showed I.R. maxima at 1725 and 1712 cm^{-1}. The corresponding 2,4-*dinitrophenylhydrazone* crystallized from methanol in stout needles m.p. 111–112°. (Found: C, 56·6; H, 5·4; N, 14·1. $C_{19}H_{24}O_6N_4$ requires: C, 56·45; H, 5·95; N, 13·85%).

2-*Acetylbicyclo*[3:3:0]*octane*-1-*carboxylic acid.* Hydrolysis of the above ester with potassium hydroxide in methanol gave 2-*acetylbicyclo*[3:3:0]*octane*-1-*carboxylic acid* as a liquid mixture of isomers b.p. 128–130°/0·07 mm, n_D^{18} 1·4980. (Found: C, 67·1; H, 8·4. $C_{11}H_{16}O_3$ requires: C, 67·3; H, 8·2%. C-methyl determination: 6·87% Calc. for 1-C methyl: 7·65%). The corresponding *mono-piperonylidene* derivative crystallized from benzene–pet ether (60–80°) in micro-prisms m.p. 137–139°. (Found: C, 69·3; H, 5·9. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·15%).

2-*Acetylbicyclo*:[3;3:0]*oct*-1(2)-*ene*-5-*carboxylic acid.* A solution of IX (3·93 g) and potassium hydroxide (1·27 g) in methanol (30 ml) was allowed to stand at room temp for 4 days and then evaporated to dryness, the residue dissolved in water, extracted with ether and then the aqueous layer acidified to congo red with dil sulphuric acid. Ether extraction followed by washing of the organic layer with water, drying and removal of the solvent gave 2-*acetylbicyclo*[3:3:0]*oct*-1(2)-*ene*-5-*carboxylic acid* (2·46 g) which crystallized from ethyl acetate in stout prisms m.p. 98–102° (decomp). (Found: C, 68·4; H, 7·05. $C_{11}H_{14}O_3$ requires: C, 68·0; H, 7·25%).

2-*Acetylbicyclo*[3:3:0]*oct*-1-(2)-*ene and* 2-*acetylbicyclo*[3:3:0]*oct*-1(5)-*ene.* The keto-acid (2·09 g) obtained above, was heated at 120–140° for 1 hr. Isolation of the neutral product gave a mixture of the conjugated and non-conjugated ketones (1·14 g) b.p. 114–124°/18 mm, n_D^{21} 1·5018–1·5135. Treatment of this mixture with 2,4-dinitrophenylhydrazone in methanolic sulphuric acid gave the 2,4-*dinitrophenylhydrazone* of 2-*acetylbicylo*[3:3:0]*oct*-1(2)-*ene* which crystallized from ethanol in dark red plates m.p. 172–174°. (Found: C, 57·95; H, 5·3; N, 16·9. $C_{16}H_{18}O_4N_4$ requires: C, 58·15; H, 5·5; N, 16·95%).

Cis, endo-2-*Acetylbicyclo*[3:3:0]*octane* (VII). Hydrogenation of the above mixture of unsaturated ketones (0·98 g) over palladium-charcoal (10%) in ethyl acetate solution resulted in the uptake of one molar equivalent of hydrogen with the formation of 2-acetylbicyclo,[3:3:0]octane (0·7 g) b.p. 108–110°/ 20 mm, n_D^{23} 1·4748. (Found: C, 78·55; H, 10·65. $C_{10}H_{16}O$ requires: C, 78·0; H, 10·6%).

The corresponding 2,4-*dinitrophenylhydrazone* crystallized from methanol in yellow needles m.p. 118·5–120°. (Found: C, 58·2; H, 5·9; N, 17·0. $C_{16}H_{20}O_4N_4$ requires: C, 57·8; H, 6·05; N, 16·85%). The corresponding semicarbazone crystallized from methanol in plates m.p. 162–164°. (Found: C, 63·35; H, 8·85; N, 20·3. Calc. for $C_{11}H_{19}ON_3$: C, 63·1; H, 9·15; N, 20·1%). The physical properties of this ketone and its derivatives corresponded with the values given by Cope *et al.*[5]

cis endo-Bicyclo[3:3:0]*octan*-2-*ol.* 2-Acetylbicyclo[3:3:0]octane (0·304 g) was added to a chilled suspension of anhydrous disodium hydrogen phosphate (1·3 g) in methylene chloride (3 ml), the mixture treated dropwise with a solution of hydrogen peroxide (0·32 mm, 80%) and pertrifluoroacetic acid (2·1 ml) in methylene chloride, and then heated under reflux for 30 min. The reaction mixture was then filtered and washed with dil sodium carbonate solution, water and dried. Removal of the solvent gave crude bicyclo[3:3:0]octan-2-ol acetate (0·29 g) which on hydrolysis with methanolic potassium hydroxide gave bicyclo3:3:0octan-2-ol as a thick oil. The corresponding phenylurethane crystallized from pet ether (60–80°) in needles m.p. 87·5–89°. (c.f. Cope *et al.*[5]). (Found: C, 72·95; H, 7·3; N, 6·14. Calc. for $C_{15}H_{19}O_2N$: C, 73·45; H, 7·8; N, 5·7%).

cis-Bicyclo[3:3:0]*octan*-2-*one* (VIII). Oxidation of the above alcohol with chromium trioxide in acetone–dil sulphuric acid, furnished cis-bicyclo[3:3:0]octan-2-one as a sweet-smelling oil. Repeated recrystallization of the corresponding 2,4-dinitrophenylhydrazone from a variety of solvents failed to produce a sharply melting sample; it crystallized from methanol in yellow needles m.p. 110–133°. (Found: C, 55·5; H, 5·05; N, 18·36. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·25; H, 5·3; N, 18·4%). Previous workers have reported that this derivative is generally found as a mixture of *syn* and *anti* forms.[6]

The corresponding semicarbazone crystallized from aqueous methanol in plates m.p. 171–173° and showed no depression of m.p. on admixture with an authentic sample.[6] The I.R. spectrum of this semicarbazone (nujol mull) was identical to that of the authentic specimen. The I.R. spectrum of this sample of cis-bicyclo[3:3:0]octan-2-one (liquid film) agreed with the published spectrum (Roberts and Gorham[6]).

Methyl 4-*ethylbicyclo*[3:3:0]*octane*-1-*carboxylate* (XI). 2-Acetylbicyclo[3:3:0]octane-5-carboxylic acid (2 g) was refluxed with a mixture of zinc amalgam (12 g), water (75 ml) and conc hydrochloric acid (100 ml) for 24 hr. The cooled reaction mixture was then extracted with ether and the ethereal extracts washed with water, dried and the solvent removed to give a thick oil (1·38 g) which was treated with diazomethane and then with a solution of sodium borohydride (excess) in methanol. The crude product (1·1 g) from this reaction sequence was then adsorbed on alumina (grade 1) from pet ether (60–80°). Elution with the same solvent followed by distillation gave *methyl* 4-*ethylbicyclo*-[3:3:0]*octane*-1-*carboxylate* (0·4 g) b.p. 114–118°/22 mm, n_D^{22} 1·4645. (Found: C, 73·15; H, 10·65. $C_{12}H_{20}O_2$ requires: C, 73·45; H, 10·3%).

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