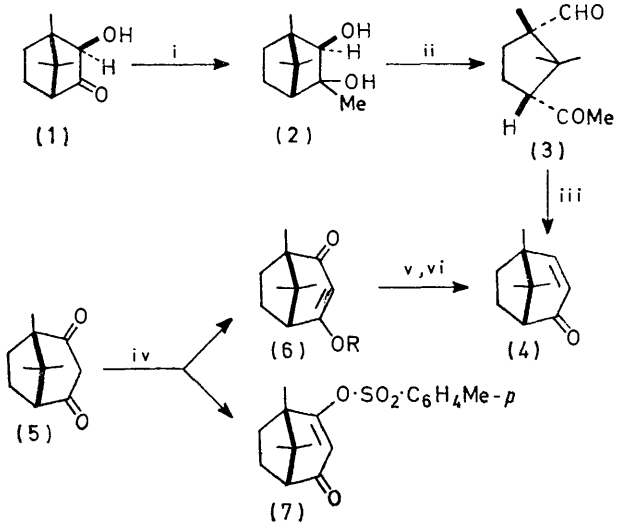
A Synthesis of (−)-(*R*)-*trans*-β-(1,2,3-Trimethylcyclopent-2-enyl)acrylic Acid

By **Ian Fleming,***† and **R. B. Woodward,** Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.

The synthesis of the title compound (21) from *exo*-2-hydroxybornan-3-one (1) is described. One stage, the Beckmann rearrangement of the oxime (8) of 5,8,8-trimethylbicyclo[3.2.1]oct-3-en-2-one into the lactam, 6,9,9-trimethyl-2-azabicyclo[4.2.1]non-4-en-3-one (12), was carried out in good yield, in spite of the fact that the ratio of the geometrical isomers present in the oxime mixture was unsuitable for rearrangement in this direction. The technique used involved the equilibration, in a mixture of hydrochloric and acetic acids at 95°, of the mixture of oxime toluene-*p*-sulphonates (9) and (10). Under these conditions, the minor oxime sulphonate gave the lactam (12) directly, whereas the major and more stable oxime sulphonate did not rearrange directly to a lactam. Instead, the major oxime sulphonate rearranged to the minor oxime sulphonate, which then rearranged to give more of the desired lactam (12).

In an earlier paper [1] we described the synthesis of *exo*-2-hydroxybornan-3-one (1). This compound was made as an early intermediate in a synthesis of the acid (21). We here describe that synthesis, the first useful one of the acid (21), which was, in its turn, an early intermediate in a larger enterprise.[2,3] Subsequently another synthesis of this acid was developed,[2] which proved to be marginally superior (19% based on camphor, compared to 17%) to the one described here. However, in the course of the present work an unexpected and new reaction was observed when the diazoalkane (14) was allowed to decompose in the absence of mineral acid. The new reaction is the subject of the following three papers.

exo-2-Hydroxybornan-3-one (1), prepared from (−)-camphor in 81% yield,[1] was treated with methylmagnesium iodide and the resulting diol (2) was cleaved,



(1) (2) (3) (4) (5) (6) (7)

Reagents: i, MeMgI; ii, $NaIO_4$; iii, NaOH; iv, $MeC_6H_4{\cdot}SO_2Cl$–C_5H_5N; v, $LiAlH_4$; vi, H_2O

without purification, to give the keto-aldehyde (3). On treatment with alkali, this gave the αβ-unsaturated ketone (4), which had previously been prepared [4] by reduction, followed by hydrolysis, of the enol methyl ether (6; R = Me).

In imitation of this route, we had earlier found that the enol toluene-*p*-sulphonate (6; R = $SO_2{\cdot}C_6H_4Me$-*p*) was easier to handle than the corresponding methyl ether, and that it gave the αβ-unsaturated ketone (4) in a pure state and in high yield. The enol toluene-*p*-sulphonate (6; R = $SO_2{\cdot}C_6H_4Me$-*p*), like the enol ether, had been prepared from 1,8,8-trimethylbicyclo[3.2.1]octane-2,4-dione (5) using toluene-*p*-sulphonyl chloride in pyridine, and was consequently contaminated with its isomer (7), from which it could be separated with ease. However, the losses, both in the synthesis of the dione (5) from bornane-2,3-dione, and in the recovery of the dione (5) from the unwanted enol toluene-*p*-sulphonate (7), made this route marginally less attractive than that from the hydroxybornanone (1). The route from the hydroxybornanone gave the unsaturated ketone (4) in 74% yield based on camphor, whereas the route from the dione (5) gave the unsaturated ketone in 56% yield based on camphor. The difference in these yields appears to be substantial but the unsaturated ketone prepared by the latter route was evidently in a purer state. Thus in the subsequent work described below the purer ketone prepared from the dione (5) gave the lactam (12) in 75% yield, whereas the unsaturated ketone prepared from the hydroxybornanone (1) gave the lactam (12) in only 62% yield. Overall, therefore, the lactam (12) was obtained from camphor by the latter route in 46% yield compared to 42% by the former route. The lactam (12) was, after the hydroxybornanone (1), the first intermediate which could readily be purified by recrystallisation: thus it is the yield of this intermediate which is important.

The route from the unsaturated ketone (4) to the lactam (12) presented a special problem, the solution to which is of general interest. The formation of the oxime of the ketone was unremarkable, except that the product was recrystallisable only when it had been prepared from very pure ketone. Usually, purification was not even attempted but instead the crude oxime was converted directly into the mixture of toluene-*p*-sulphonates (9) and (10). When this mixture of the two geometrical isomers was recrystallised from ethanol, one

† *Present address:* University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

[1] I. Fleming and R. B. Woodward, *J. Chem. Soc.* (*C*), 1968, 1289.

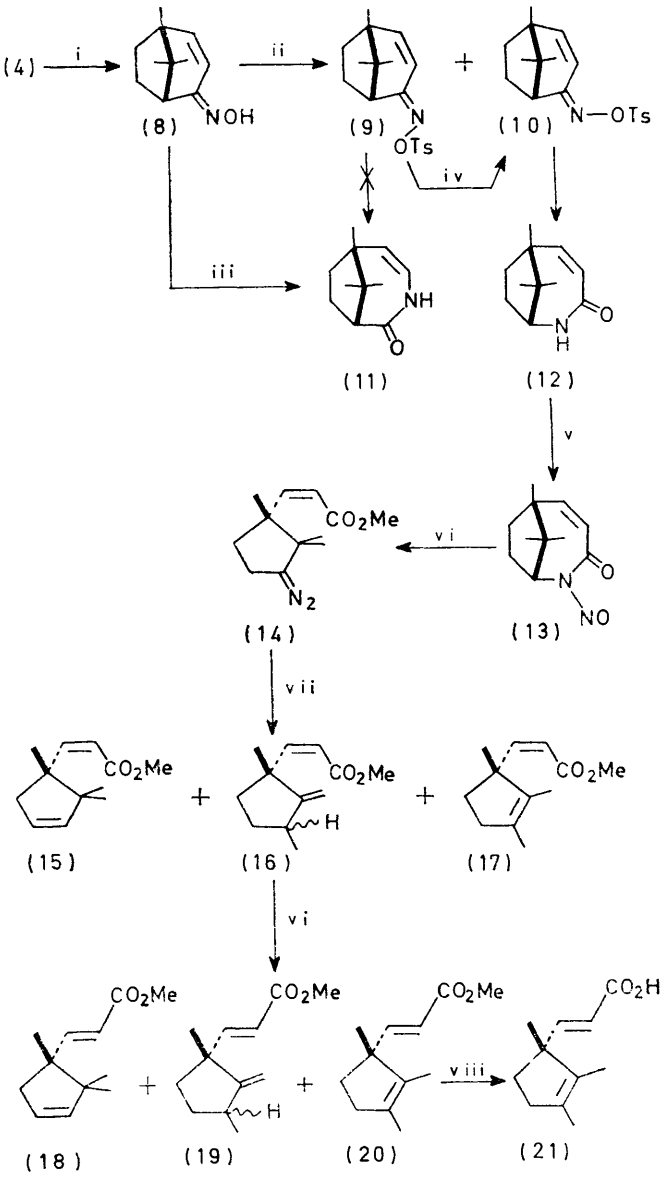
[2] R. B. Woodward, *Pure Appl. Chem.*, 1968, **17**, 519.

[3] R. B. Woodward, *Pure Appl. Chem.*, 1971, **25**, 283; *ibid.*, **1973**, **33**, 145.

[4] H. Favre, B. Marinier, and J.-C. Richer, *Canad. J. Chem.*, 1956, **34**, 1329.

of the isomers (9) separated out pure, but the other rearranged and gave the desired lactam (12), which stayed in solution. These two products were isolated in 57 and 26% yield, respectively.[5] This ratio of yields reflects the ratio of the geometrical isomers present in the original oxime (8): a direct Beckmann rearrangement of this oxime, using phosphoric acid, had given a mixture of the lactams (11) and (12) in a similar (and also unsuitable) ratio. We were therefore faced with the problem of how to direct the Beckmann rearrangement to give the desired lactam (12), when the oxime mixture was so composed that it favoured the formation of the other lactam (11). The solution of this problem depended on the fact that the oxime sulphonate (9) is extraordinarily stable. It survives many hours' boiling in ethanol, unlike its isomer (10), which evidently rearranges, even after the brief heating used to get the freshly prepared mixture into solution. It is stable enough to allow alkaline hydrolysis to give the corresponding oxime, geometrically pure. It even survived, at least in part, a distillation taking place over several minutes at 200° and 0·3 mmHg. We therefore reasoned that any mild reaction conditions which allowed the interconversion of the oxime sulphonates (9) and (10) would give the desired lactam (12). In exploratory work we found that the stable oxime sulphonate (9) in the presence of acid in a nucleophilic solvent (hydrochloric acid in acetic acid was satisfactory) indeed gave the lactam in good yield. Applied to the original mixture of oxime sulphonates (9) and (10), these conditions gave the lactam (12) in 82% yield based on pure oxime.

Although vinyl (and phenyl) groups are usually apt to migrate with ease to electron-deficient centres,[6] in this case a vinyl group is markedly reluctant to migrate. The low rate of migration in this case is probably caused by geometrical factors which prevent the overlap of the *p*-orbitals of the vinyl group and the emptying orbital created on the nitrogen atom by the loss of the sulphonate group. When vinyl (and phenyl) groups do migrate with ease it is generally because a new bond to the electron-deficient atom can be formed first.[7] We now see an unusually clear case in which such bonding is difficult; the consequence is that the higher migratory aptitude of alkyl groups—higher, that is, than vinyl groups in *concerted* migrations—is exceptionally well demonstrated.[8] In our later work[9] we had further need to direct the Beckmann rearrangement in a similar way in several other αβ-unsaturated ketoximes. In each case the technique used here was successful. This technique could



Reagents: i, NH_2·OH; ii, MeC_6H_4·SO_2Cl–C_5H_5N; iii, H_3PO_4; iv, HCl–AcOH; v, N_2O_4; vi, NaOMe; vii, H_3O^+; viii, NaOH

well prove useful in other syntheses—thus it might be possible to avoid the separation of oximes [10] or lactams [11]

[5] For related observations, see R. H. Mazur, *J. Org. Chem.*, 1963, **28**, 248; C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J. Chem. Soc.*, 1962, 1050; C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, *ibid.*, 1965, 5868; F. Kohen, *Chem. and Ind.*, 1966, 1378; M. S. Ahmad and A. H. Siddiqi, *Austral. J. Chem.*, 1968, **21**, 1371; and especially Y. Tamura, Y. Kita, and M. Terashima, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 529.

[6] For comparison with the examples of ref. 5, see especially G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 1956, **21**, 520.

[7] For evidence in favour of this theory in the Beckmann reaction series, see R. Huisgen, J. Witte, H. Walz, and W. Jura, *Annalen*, 1957, **604**, 191.

[8] For a selection of other cases of alkyl or vinyl migration bearing on this problem, see refs. 6, 13, and 14, and G. Seidl, R. Huisgen, and J. H. M. Hill, *Tetrahedron*, 1964, **20**, 633; E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, 1964, **86**, 478; J. Wiemann, N. Thoai, and N. Kirpalani, *Bull. Soc. chim. France*, 1967, 3923; C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *J. Amer. Chem. Soc.*, 1967, **89**, 3940; H. W. Whitlock and P. Fuchs, *Tetrahedron Letters*, 1968, 1453; M. Tomita, S. Minami, and S. Uyeo, *J. Chem. Soc.* (*C*), 1969, 183; R. M. Pinder, *ibid.*, p. 1690; J. E. McMurry, *J. Amer. Chem. Soc.*, 1969, **91**, 3676; J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Shultenover, and W. J. Wagner, *J. Org. Chem.*, 1969, **33**, 694; T. Sato, H. Wakatsuka, and K. Amano, *Tetrahedron*, 1971, **27**, 5381.

[9] E. H. Billett, I. Fleming, and S. W. Hanson, *J.C.S. Perkin I*, 1973, 1661.

[10] As used by, for example, K. Oka and S. Hara, *Chem. and Ind.*, 1969, 168.

[11] See, for example, C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 1961, 3641; G. Habermehl and A. Haaf, *Tetrahedron Letters*, 1969, 3815, and references therein.

used in some syntheses; and it could probably have been used in a recent synthesis of quinine.[12] Its usefulness is enhanced by the development of a complementary technique [13] which induces vinyl migration to electron-deficient nitrogen.

The next stage of the synthesis was the nitrosation of the lactam (12). The nitroso-lactam (13) was then treated with concentrated methanolic sodium methoxide to give a solution of the diazoalkane (14). When this solution was poured into an excess of dilute aqueous sulphuric acid, the red colour was instantly discharged, and the major products were the three esters (15)—(17), produced by successive *C*-protonation of the diazoalkane, loss of nitrogen with and without rearrangement, and loss of a proton. The three esters, which we shall call the ' solvolysis products,' were formed approximately in the ratio 14 : 25 : 53, together with 8% of a bicyclic isomer.[14] The mixture of esters was boiled with sodium methoxide in methanol, to convert the *cis* double bond in the side chain to a *trans* double bond, and then with toluene-*p*-sulphonic acid in benzene, to convert the isomer (19) into the desired ester (20). At this stage the esters (18) and (20) were present in the ratio 11 : 81, together with about 8% of a tricyclic ester, of unknown structure, derived from the bicyclic ester. Alkaline hydrolysis and fractional crystallisation gave the desired acid (21) in 27% yield based on nitroso-lactam. The mother liquors from the fractional crystallisation were re-esterified. The mixture of esters was boiled again, but for a longer time, with toluene-*p*-sulphonic acid in benzene, probably to rearrange the ester (18) to the ester (21) but possibly simply to destroy the ester (18). The mixture was then fractionally distilled, to remove the tricyclic ester, and hydrolysed to a mixture of acids. Fractional crystallisation gave a second crop of the desired acid (21). Repetition of this sequence, but with the fractional distillation omitted, gave a third crop of the acid. The combined yield of the acid (21) was 39% based on nitroso-lactam. Based on camphor, the yield was 17%, which represents an average yield over 16 steps of 90%, counting as a step the formation of an isolable, though not necessarily isolated, intermediate.

EXPERIMENTAL

cis-3-*Acetyl*-1,2,2-*trimethylcyclopentanecarbaldehyde* (3).—(+)-*exo*-2-Hydroxybornan-3-one [125 g; prepared [1] from (−)-camphor] in dry ether (500 ml) was added dropwise over 45 min to a stirred solution of methylmagnesium iodide [from magnesium (46 g) and methyl iodide (130 ml)] in ether (1·2 l) cooled in ice. The mixture was heated under reflux for 2 h, cooled in ice, and then poured during 10 min into a vigorously stirred slurry of ice and water (2·5 l) and ammonium chloride (150 g). The aqueous layer was separated and washed with ether; the combined ether layers were washed with water, dried (Na_2SO_4), and evaporated to give the crude diol (2). The diol was dissolved in ethanol (1 l) and cooled to 0°. A solution of sodium periodate (175 g) in water (1·3 l) was added over 30 min with stirring, under nitrogen, and with cooling in ice. Sodium iodate was precipitated and, after the mixture had been kept at 0° for a further 2 h, was filtered off. Most of the ethanol was distilled off at reduced pressure. The residue was taken up in ether, washed with water, and dried (Na_2SO_4), and the ether was distilled off at reduced pressure. The residue was combined with the product from two similar runs on the same scale and the combined product was fractionally distilled to give the *keto-aldehyde* (374·2 g, 91·5%), b.p. 96—98° at 2—3 mmHg, 129—132° at 10 mmHg, 86° at 0·7 mmHg, $[\alpha]_D^{25}$ −93° (*c* 0·8 in EtOH), n_D^{21} 1·4765 (Found: C, 72·45; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·50; H, 9·95%), $\nu_{max.}$ (CCl_4) 1725 cm^{-1}, τ 0·33 (1H, s, CHO), 7·85 (3H, s, Ac), 8·73, 8·90, and 9·18 (each 3H, s, CMe). The *bis-semicarbazone* formed prisms, m.p. 225—226° (from EtOH) (Found: C, 52·7; H, 8·45. $C_{13}H_{24}N_6O_2$ requires C, 52·7; H, 8·15%).

5,8,8-*Trimethylbicyclo*[3.2.1]*oct*-3-*en*-2-*one* (4).—*First preparation.* The keto-aldehyde (3) (374·2 g) was added dropwise over 30 min to an ice-cooled mixture of ethanol (700 ml), sodium hydroxide (31 g), and water (310 ml) under nitrogen and then kept at room temperature for 60 h. The ethanol was evaporated off at reduced pressure; the residue was taken up in ether, washed with water, and dried (Na_2SO_4), and the ether was distilled off to leave the ketone as a solid mass (100%, crude), m.p. 160—167°. This product showed i.r. and n.m.r. spectra and t.l.c. behaviour identical with those of an authentic sample.[4] The intermediate, 4-*hydroxy*-5,8,8-*trimethylbicyclo*[3.2.1]*octan*-2-*one*, was obtained (18%) in one experiment when potassium acetate in methanol was used; m.p. (sealed tube) 236—238° (decomp.) (from cyclohexane) (Found: C, 72·3; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%), $\nu_{max.}$ (CCl_4) 3700, 3550, and 1720 cm^{-1}.

5,8,8-*Trimethyl*-4-*oxobicyclo*[3.2.1]*oct*-2-*en*-2-*yl Toluene*-p-*sulphonate* (6; R = $SO_2{\cdot}C_6H_4Me$-*p*) *and its* 1,8,8-*Trimethyl Isomer* (7).—1,8,8-Trimethylbicyclo[3.2.1]octane-2,4-dione (5) (18 g) [prepared (81%) by the method of Quinkert [15]] dissolved in pyridine (25 ml), was stirred at 2—4° while toluene-*p*-sulphonyl chloride (19·5 g) in pyridine (30 ml) was added dropwise over 1 h. The mixture was stirred at 2—4° for 30 min, allowed to come to room temperature over 3 h, and then shaken with ether and ice-cold sulphuric acid (100 ml; 6N). The ether layer was washed with water, alkali, and water again, and then evaporated. The residue was crystallised from ethanol to give the *enol sulphonate* (6) (14·88 g, 45%), prisms, m.p. 118—119° (from ethanol) (Found: C, 64·5; H, 6·7. $C_{18}H_{22}O_4S$ requires C, 64·7; H, 6·6%), $\nu_{max.}$ (KBr) 1670, 1630, and 1580 cm^{-1}, τ 2·0—2·8 (4H, AB system, *J* 8 Hz), 4·25 (1H, d, *J* 1·5 Hz), and 7·55, 9·0, 9·1, and 9·2 (each 3H, s). The mother liquors from the crystallisation, the sodium hydroxide extract, and more sodium hydroxide (to make a total of 70 ml at a concentration of 10%) were heated under reflux for 4 h, cooled, acidified, and extracted with ether. Evaporation of the extract and crystallisation of the residue gave unchanged dione (5) (7·7 g, 43%). Thus the yield of the enol sulphonate, based on starting material consumed, was 78%.

If, instead of hydrolysing the alcoholic mother liquors, we added water, crystals slowly separated. Recrystallisation gave the other *enol sulphonate* (7) (37%), prisms, m.p. 63°

[12] M. Uskokovic, J. Gutzwiller, and T. Henderson, *J. Amer. Chem. Soc.*, 1970, **92**, 203.

[13] D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1971, 945.

[14] E. H. Billett and I. Fleming, following paper.

[15] G. Quinkert, A. Moschel, and G. Buhr, *Chem. Ber.*, 1965, **98**, 2742.

(from aqueous ethanol and then benzene–n-hexane) (Found: C, 64·8; H, 6·6%), $\nu_{max.}$ (KBr) 1670 and 1610 cm^{-1}, τ 2·1—2·8 (4H, AB system, J 8 Hz) 4·1 (1H, s) and 7·56, 8·95, 9·11, and 9·15 (each 3H, s).

5,8,8-*Trimethylbicyclo*[3.2.1]*oct*-3-*en*-2-*one* (4).—*Second preparation.* The enol sulphonate (6; R = $SO_2 \cdot C_6H_4Me$-*p*) (25·6 g) in dry ether (900 ml) and methanol (100 ml) was stirred at 2—4° with sodium borohydride (10 g) for 2 h. Ice-cold water was added, the mixture was stirred for a further 15 min, and the ether layer was washed with water (3 × 100 ml), whereupon the washings became acidic. The combined ether layers were evaporated and the residue was heated on a steam-bath with water (20 ml) for 8 min, cooled, and filtered. The filtrate was extracted with ether, the extract evaporated, and the residue combined with the residue of the filtration. The combined residues were sublimed (0·1 mmHg) to give the ketone (4) (12·2 g, 97%), identical with the compound prepared by the known route.[4] This route [by way of the methyl ether (6; R = Me)] and another [by way of the slightly more amenable ethyl ether [16] (6; R = Et)] were comparable in yield but rather less convenient. Other routes, which were less efficient, were tried: these included the preparation of the enamine (6; NMe_2 for OR), the isopropyl ether, the benzoate ester, and the trimethylsilyl ether.

5,8,8-*Trimethylbicyclo*[3.2.1]*oct*-3-*en*-2-*one Oxime* (8).—The crude ketone [prepared from the keto-aldehyde (3)] in pyridine (800 ml) was stirred with hydroxylamine hydrochloride (210 g added in four equal portions at hourly intervals) at room temperature for 18 h. The mixture was dissolved in ether and washed with water, and the ether and pyridine were evaporated off at reduced pressure to leave the oxime as a solid cake which could not be recrystallised. A pure sample prepared (92%) from the ketone derived from the enol sulphonate, had m.p. 90—91° (from aqueous methanol) (lit.,[4] m.p. 91°). This was still a mixture of the geometrical isomers. One of the isomers, obtained pure by alkaline hydrolysis of the toluene-*p*-sulphonate (9) had m.p. 101—102°.

The Mixture of 5,8,8-*Trimethylbicyclo*[3.2.1]*oct*-3-*en*-2-*one* O-p-*Tolylsulphonyloxime* (9) *and* 6,9,9-*Trimethyl*-2-*aza-bicyclo*[4.2.1]*non*-4-*en*-3-*one* (12).—Pure oxime (8) (5·0 g) in dry pyridine (8 ml) was swirled in an ice-bath while toluene-*p*-sulphonyl chloride (6·0 g) in dry pyridine (6 ml) was added. The mixture was kept at room temperature for 15 min, ice (50 g) was added, and the mixture was kept at 0°, with occasional stirring, until the precipitate solidified (3—12 h). This mixture of oxime toluene-*p*-sulphonates was filtered off and washed with cold water. Recrystallisation from ethanol caused the one oxime toluene-*p*-sulphonate (10) to rearrange to the lactam, while the other (9) separated (3·88 g). The ethanol was evaporated from the mother liquor and the residue was chromatographed (silica gel; 80% chloroform in n-hexane) to separate more of the *oxime toluene*-p-*sulphonate* (9) (total 5·27 g, 57%), prisms, m.p. 96—97° (from ethanol) (Found: C, 64·9; H, 7·0; N, 4·2. $C_{18}H_{23}NO_3S$ requires C, 64·85; H, 6·95; N, 4·2%), $\nu_{max.}$ ($CHCl_3$) 1620 and 1600 cm^{-1}, τ 2·0—2·8 (4H, AB system, J 8 Hz, ArH), 3·6—4·3 (2H, AB system, J 9·5 Hz, upfield pair finely split, J 1·5 Hz, CH=CH), 6·65br (1H, d, J 6 Hz, CH–C=N), and 8·99, 9·10, and 9·25 (each 3H, s, CMe). The chromatography also gave the *lactam* (12) (1·30 g, 26%), needles, m.p. 208° (from cyclohexane) (Found: C, 73·65; H, 9·55; N, 7·7. $C_{11}H_{17}NO$ requires C, 73·7; H, 9·55; N, 7·8%), $[\alpha]_D^{20}$ −116° (c 1·1 in EtOH), $\lambda_{max.}$ (EtOH) 218·5 nm (ε 10,700), $\nu_{max.}$ (CCl_4) 3250, 1670, and 1610 cm^{-1}, τ 4·0—4·4 (AB system, J 12 Hz, with the upfield pair split into doublets, J 1 Hz, a splitting not observed in $CD_3 \cdot OD$, CH=CH), 6·85br (1H, t, J 8 Hz, CH–N) and 8·9 and 9·0 (6H and 3H, s, CMe).

The assignment of structure (12) to this lactam, and of structure (11) to that obtained by Dr. J. M. Lehn (see later) was aided by the assignments of structure made by Mazur [17] to the corresponding products from isophorone oxime.

6,9,9-*Trimethyl*-3-*azabicyclo*[4.2.1]*non*-4-*en*-2-*one* (11) (*by* Dr. J. M. Lehn).—The oxime (8) (0·1 g) was heated in polyphosphoric acid (3 g) at 125° for 1 h. Water (20 ml) was added, the mixture was extracted with ether (3 × 10 ml), and the extract was evaporated. The residue was separated by t.l.c. on silica gel [ethyl acetate–hexane (3 : 1)]. The faster running material (R_F 0·5) was the *lactam* (11) (40—60 mg), m.p. 200—201° (Found: C, 73·5; H, 9·5; N, 7·85. $C_{11}H_{17}NO$ requires C, 73·7; H, 9·55; N, 7·8%), $\nu_{max.}$ ($CHCl_3$) 1640—1650br cm^{-1}, $\lambda_{max.}$ (EtOH) 248 nm (ε 6600), τ ($CDCl_3$) 4·4—5·4 (ABX system, J_{AB} 10·5 Hz, with J_{AX} 6·5 and J_{BX} 0·8 Hz, the A and B signals being at low and high field respectively; the AX and BX couplings were absent in $CD_3 \cdot OD$).

6,9,9-*Trimethyl*-2-*azabicyclo*[4.2.1]*non*-4-*en*-3-*one* (12).—The whole of the crude oxime (8) from the foregoing preparation was dissolved in pyridine (720 ml) and the solution was divided into three equal portions. Each of the portions was treated as follows. The mixture of oxime toluene-*p*-sulphonates was prepared with toluene-*p*-sulphonyl chloride (130 g) in pyridine (100 ml), as before. The washed mixture was dissolved in hot acetic acid (500 ml) and then concentrated hydrochloric acid (250 ml) was added. The mixture was heated at 90—96° for 15 min, cooled to room temperature, filtered, made alkaline with potassium hydroxide solution (625 g made up to 1·5 l), and cooled to 0°, and a first crop of the lactam was collected. The filtrate from all three runs was combined and extracted with ethyl acetate (7 × 1 l); the combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to give a second crop of lactam. Recrystallisation from cyclohexane gave pure lactam, m.p. 208° (229·4 g, 62% based on keto-aldehyde), identical with the sample prepared before. The overall yield shows that impurities have accumulated from the three stages, since pure oxime was converted into pure lactam by the previous procedure in 82% yield. Purification of the intermediates, however, was not practicable.

6,9,9-*Trimethyl*-2-*nitroso*-2-*azabicyclo*[4.2.1]*non*-4-*en*-3-*one* (13).—The lactam (12) (14·55 g) was added over 5 min to a stirred, ice-cooled mixture of freshly fused sodium acetate (14 g) and a fresh solution of dinitrogen tetroxide (13 ml) in carbon tetrachloride (200 ml). The mixture was stirred for 2 h at 0°. Water (60 ml) was added, and the carbon tetrachloride layer was separated, washed with water (60 ml), dried (Na_2SO_4), and evaporated. The residue was recrystallised from cyclohexane to give the *nitroso-lactam* (16·1 g, 95%), yellow needles, m.p. 105—109° (from ether) (Found: C, 63·5; H, 7·75; N, 13·55. $C_{11}H_{16}N_2O_2$ requires C, 63·4; H, 7·75; N, 13·45%), $[\alpha]_D^{25}$ +19° (c 1·0 in EtOH), $\nu_{max.}$ ($CHCl_3$) 1690 and 1525 cm^{-1}, τ 3·6—4·25 (AB system, J 13 Hz), 5·05 (1H, q), and 8·82, 8·90, and 9·24 (each 3H, s).

(−)-(*R*)-trans-β-(1,2,3-*Trimethylcyclopent*-2-*enyl*)*acrylic Acid* (21).—(i) *Formation of the diazoalkane and of the* cis-

[16] H. Favre and B. Marinier, *Canad. J. Chem.*, 1957, **35**, 278.
[17] R. H. Mazur, *J. Org. Chem.*, 1961, **26**, 1289.

esters. The nitroso-lactam (13) (124·4 g) in dry tetrahydrofuran (300 ml) was added dropwise over 1 h with stirring to an ice-cooled solution of sodium (80 g) in methanol (800 ml), with the temperature kept below 5°. The solution was stirred at 0° for a further 15 min. (There was little evolution of nitrogen during this preparation of a secondary diazoalkane, indicating that the intermediate diazotate had mainly, and unusually, decomposed to diazoalkane, without giving much of the solvolysis products directly.[18]) The solution was poured during 5—10 min into vigorously stirred, ice-cold sulphuric acid (336 ml made up to 2 l with water). The mixture was extracted with ether (2 × 600 ml), and the extract washed with water and evaporated. A solution of the residue in benzene (300 ml) was dried (Na_2SO_4) and evaporated.

(ii) *Conversion of* cis-*esters into* trans-*esters*. The mixture of esters was added to a solution of sodium (45 g) in methanol (600 ml) and heated under reflux under nitrogen for 48 h. The cooled solution was poured into sulphuric acid (600 ml; 6N), extracted with ether and the extract was worked up as for the *cis*-esters. Some hydrolysis of the esters had always taken place in this reaction, so the total products were treated with an excess of ethereal diazomethane; if the amount of this hydrolysis, as judged by the consumption of diazomethane, was large, then the isomerisation was usually found (by n.m.r.) to have been incomplete, and it had to be repeated.

The structures of the esters (18)—(20) were assigned on the basis of their n.m.r. spectra, obtained from samples separated by Dr. S. H. Pine by preparative g.l.c. (10 ft column; 20% Carbowax 20M in Diatoport at 150°). The ester (18), eluted first, had τ (CCl_4) 2·95 and 4·3 (each 1H, d, J 16 Hz), 4·45 (2H, m), 6·3 (3H, s), 7·42 and 7·88 (each 1H, d J 16—17 Hz with further unresolved broadening of each line), and 8·9, 9·0, and 9·1 (each 3H, s). The ester (19), eluted next, had τ (CCl_4) 3·2 and 4·35 (each 1H, d, J 16 Hz), 5·05 (1H, d, J 3 Hz), 5·20 (1H, d, J 3 Hz), 6·3 (3H, s), 8·0—8·8 (5H, m), 8·75 (3H, s), and 8·85 (3H, d). The third ester (20) had τ (CCl_4) 3·2 and 4·45 (each 1H, d, J 16 Hz), 6·3 (3H, s), 7·5—8·2 (4H, m), and 8·35, 8·5, and 8·85 (each 3H, s).

(iii) *Conversion of the ester* (19) *into the ester* (20). The mixture of esters was heated under reflux in a solution of toluene-*p*-sulphonic acid (76·5 g; anhydrous) in benzene (700 ml) for 30 min. The solution was cooled, washed with water, sodium carbonate solution, and water, dried (Na_2SO_4), and evaporated. The residue was distilled and the fraction b.p. 60—65° at 0·1 mmHg (71·6 g, 62%) was collected.

(iv) *Saponification of the esters*. The mixture of esters was heated under reflux in a solution of sodium hydroxide (9 g) in water (80 ml) and methanol (360 ml) for 30 min. Sodium hydroxide (9 g) in water (80 ml) was added and boiling was continued for a further 3 h. The methanol was evaporated off and the residue, cooled in ice, was acidified with dilute hydrochloric acid. The product was extracted into ether; the extract was washed with water, dried (Na_2SO_4), and evaporated. Two crystallisations from pentane (150 ml) cooled with solid carbon dioxide in a Dewar flask, gave a first crop (28·6 g, 27%).

(v) *The second and third crops*. The mother liquors from the crystallisation could not be induced to give any more crystalline product [and recrystallisation of the mixture of *benzylisothiuronium salts*, m.p. 139—141° (from aqueous ethanol) (Found: C, 65·6; H, 7·7; N, 8·0. $C_{19}H_{26}N_2O_2S$ requires C, 65·9; H, 7·6; N, 8·1%) did not cause any change in the proportions of the acids present]. The mixture of acids was combined with a similar one from another run (from 100 g of nitroso-lactam), which had given 24 g of the acid (28%). The combined mixture was remethylated by heating under reflux in methanol (350 ml) with sulphuric acid (20 ml) for 5 h. The mixture of esters (64·6 g) was worked up in the usual way [it consisted of 5% of the tricyclic ester, 17% of (18), and 78% of (20)]. The mixture was then heated under reflux in a solution (which had been dried azeotropically by use of a Dean and Stark head) of toluene-*p*-sulphonic acid (70 g; monohydrate) in benzene (1 l) for 21 h. The mixture, consisting now of 13% of the tricyclic ester, 3% of (18), and 80% of (2), was distilled through a spinning band column (bath temperature 90°; drip ratio 1 : 20) to give the tricyclic ester, b.p. 80° at 10·5 mmHg, 103° at 13 mmHg (8·4 g, 4%), and then the mixture of esters (18) and (20), b.p. 103—109° at 13—13·5 mmHg (30·7 g). Saponification of this mixture and two crystallisations of the product gave a second crop of acid (21·3 g). The mother liquors of this crystallisation were recycled by use of the same procedure as before, but without the careful distillation; a third crop (2·4 g) was thus obtained. The total yield of *acid* was 76·4 g (from 224·4 g of nitrosolactam) (39%), m.p. 52—54° (clusters from n-pentane cooled in solid carbon dioxide) (Found: C, 73·2; H, 8·95. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%), $[\alpha]_D^{31}$ −157° (*c* 2·5 in EtOH), $\nu_{max.}$ (CCl_4) 1695 and 1640 cm^{-1}, τ 2·9—4·6 (2H, AB system, J 15 Hz), 8·83br and 8·45br (each 3H, s), and 8·85 (3H, s). The corresponding *anilide* had m.p. 128—131° (needles from cyclohexane) (Found: C, 79·95; H, 8·25; N, 5·4. $C_{17}H_{21}NO$ requires C, 79·95; H, 8·3; N, 5·5%), and the *benzylammonium salt* had m.p. 95—98° (fine needles from water or ether) (Found: C, 75·25; H, 9·05; N, 4·8. $C_{18}H_{25}NO_2$ requires C, 75·2; H, 8·8; N, 4·9%). Careful, laborious, and inefficient recrystallisation of the latter derivative did cause some concentration of the desired acid from the mixture of acids, but no other derivative (the amide and *p*-bromophenyacyl ester were tried in addition to those already mentioned) was effective.

A preparation, similar to that just described but on a smaller scale, was also carried out by use of the diazoalkane (14) generated in benzene solution. Decomposition of this solution with toluene-*p*-sulphonic acid under reflux, followed by aqueous work-up, gave a mixture of esters free of the bicyclic isomer. But, after the isomerisation of the *cis*-esters to the *trans*-esters and of the ester (19) to the ester (20), the overall yield of distilled esters was only the same as that obtained before (62%); furthermore the ratio of the ester (18) to the ester (20) now present was less favourable, being 20 : 80, a ratio at which the acid (21) would not crystallise from the corresponding mixture of acids. The diazoalkane (14) also was decomposed in benzene, either at the b.p. or at lower temperatures, but without added acid. The rate was much reduced, but the ratios of the three products (15)—(17), were not significantly affected.

We thank Drs. J. M. Lehn and S. H. Pine for assistance.

[2/2742 *Received*, 4*th December*, 1972]

[18] Compare this observation with, for example, that of H. Hart and J. L. Brewbaker, *J. Amer. Chem. Soc.*, 1969, **91**, 716, where extensive formation of carbonium ion products directly from the diazotate was generally observed; see also ref. 9.