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BECKMANN REARRANGEMENT OF α,β-UNSATURATED KETOXIMES IN CYCLIC SYSTEMS

MIGRATORY APTITUDE OF OLEFINIC GROUPS

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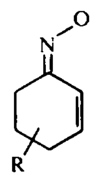
Abstract—Several cyclic α,β-unsaturated ketoximes, or their tosylates were subjected to the Beckmann rearrangement. With all compounds except **8b**, groups located *anti* to the leaving group migrated efficiently, irrespective as to whether the migrating group was alkyl or olefinic. The olefinic group in **8b**, however, resisted the migration and this was interpreted in terms of the steric effect in the transition state.

SEVERAL investigations on the Beckmann rearrangement of cyclic α,β-unsaturated ketoximes have been reported. The general trend is that, while *syn*-oximes (**1**)* undergo the facile rearrangement to lactams of type **3**, *anti*-isomers (**2**) resist the rearrangement under similar conditions, thus indicating that the olefinic group cannot migrate as effectively as an alkyl group.[1] Only a few cases have been observed where the migration of the olefinic group proceeds to a similar extent to the alkyl migration in the Beckmann rearrangement in cyclic system.[2] The effect of ring size in the Beckmann rearrangement of *anti*-benzocycloalkanone oxime derivatives (**4**) on ease of rearrangement was interpreted in accord with the stability of the tricyclic



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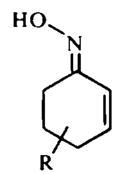

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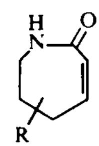

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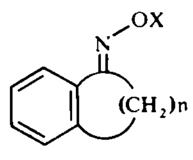

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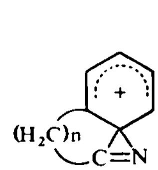

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phenonium ion intermediates (**5**).[3] In the case of the indene system, no *syn-anti* steric regulation has been observed and only a single product (alkyl migration) has been isolated from a mixture of oxime isomers or even from *anti*-oximes.[4] The mechanism

* The prefix *syn* implies oxime OH group and C—C double bond are on the same side of C—N double bond.

through an imminium ion intermediate has been proposed for the reaction. Alkyl migration products through similar imminium ion intermediates have been obtained as major products by the rearrangement of indanone oximes, while aryl migration products have been isolated from tetralone oximes.[5]

It has been well established that the aryl group migrates preferentially to the alkyl group in rearrangements in electron-deficient systems, and the phenonium ion, in which the aryl ring lies at right angles to the migrating axis, has been proposed as an intermediate.[6] With a similar argument it could be expected that an olefinic group would migrate more efficiently than an alkyl group, but experimental results mentioned above are evidently contradictory with this expectation.

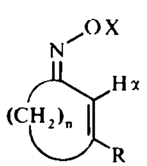
With the intention of obtaining information on the migratory aptitude of olefinic groups, the Beckmann rearrangement was carried out on some cyclic α,β-unsaturated ketoximes.

RESULTS

3-Methyl-2-cyclohexenone oxime system

Since the assignments of *syn* and *anti* configurations of oximes in older literature leads sometimes to erroneous conclusions, we tried to prepare oximes having definite configuration.

3-Methyl-2-cyclohexenone (**6**) was reacted with hydroxylamine hydrochloride in alkaline solution according to the method reported by Knoevenagel.[7] The product which has been described as "Labiles Oxim" was actually found to be a 1:2 mixture of *syn*- (**7a**) and *anti*- (**8a**) oximes, because its NMR spectrum showed two signals in the olefinic region at δ 6·5 (1/3 H) and δ 5·8 (2/3 H). It has been demonstrated[8] that the olefinic proton in the *syn*-oxime system resonates at lower field than that in the *anti*-isomer, and hence, it was concluded that the major product had *anti*-configuration. Treatment of the mixture with TsCl in pyridine afforded a tosylated product. The product was again shown to be a mixture of two components as revealed from two spots on TLC and two C=N bands in the IR spectrum. It was found that one isomer went into solution when refluxed in EtOH, while the other isomer was stable and



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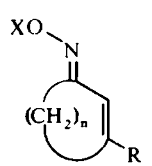

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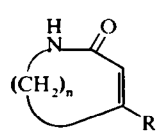

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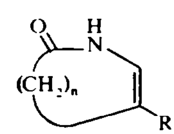

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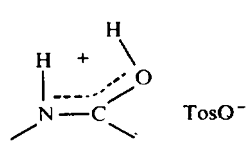
a: R = CH_3, n = 3, (X = H)
b: R = CH_3, n = 3, (X = Tos)
c: R = H, n = 5, (X = H)



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recrystallizable from MeOH. The MeOH-stable isomer thus isolated showed an NMR signal at δ 6·0 (olefinic proton) appearing at higher field than that of the other isomer (δ 6·6, *vide infra*) and the *anti*-structure (**8b**) was assigned for the compound. The MeOH-unstable isomer was obtained in a pure state in the following way. The ketone (**6**) was treated with hydroxylamine hydrochloride under acidic condtion according to the method leading to "Stabiles Oxim" reported by Harries.[9] The product (isolated as hydrochloride) showed a single signal in the olefinic region in the NMR spectrum at δ 6·6. Tosylation with TsCl in pyridine afforded a tosylate which showed an olefinic proton signal at δ 6·6 and *syn*-structure **7b** was assigned to this compound.

The *syn*-tosylate (**7b**) afforded a lactam tosylate (**9a**·TosOH) in a good yield on refluxing in MeOH. The salt type structure was deduced from the bands at 1230 and 1140 cm^{-1} in the IR spectrum.* The NMR spectrum of this compound showed two signals at lower field (δ 12·0 and 10·9), indicating that the actual structure was **11**. The NMR spectrum also showed a signal for the protons adjacent to nitrogen at δ 3·6, and thus the alternative structure **10a** with the migration of olefinic group was eliminated.

The *anti*-isomer (**8b**) was stable in refluxing MeOH. On heating with Et_3N or piperidine in DMF, the reaction conditions considered as the most effective for the Beckmann rearrangement of oxime tosylates,[10] **8b** suffered extensive polymerization and no product was identified.

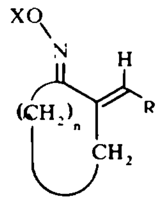
2-Benzylidenecyclohexanone oxime system

The oxime (**12a**) was prepared from the corresponding ketone (*trans*-configuration† was assigned for the compound in view of the steric repulsion between Ph and oxygen atom) and hydroxylamine hydrochloride in the presence of NaOH. As revealed from the NMR spectrum and TLC, the oxime was found to consist of a single isomer, the *anti*-configuration being preferable in view of the steric effect of the benzylidene group. The *anti*-configuration has also been assigned as the most probable structure in several 2-substituted cyclohexanone oximes.[11] When the oxime was treated with TsCl in anhydrous pyridine, yellow crystals of pyridinium tosylate (**16**) were obtained. A similar pyridinium tosylate has been suggested as the possible intermediate in the Beckmann rearrangement of 2-arylcyclohexanone oxime tosylate from the NMR investigation of the reaction mixture.[12] Compound **16**, on treating with dilute H_2SO_4 under mild conditions afforded lactam **13a** as sole product. When the lactam (**13a**) was heated in dilute AcOH, an open-chain amide (**14a**) was obtained, thus eliminating the alternative structure with the alkyl migration for the compounds **13a** and **16**. With stronger acid at higher temperature, compound **16** also afforded **14a**.

Recently the stereochemistry of vinyl groups in the reaction involving cationic vinyl species has been studied.[13] It seemed of interest to determine whether or not the benzylidene group maintained the geometric configuration of the starting material during migration, and the product identification in the reaction mixture was examined in detail. We found that when the mixture of the oxime **12a** and TsCl in pyridine was

* All compounds of p-toluenesulfonic acid salt type we examined showed SO_2 bands at 1230–1200 and 1150–1050 cm^{-1}, while compounds of p-tolylsulfonyl type showed bands at 1380–1350 and 1180–1170 cm^{-1}.

† The prefix *trans* implies that Ph and carbonyl groups are on the other sides of C—C double bond.



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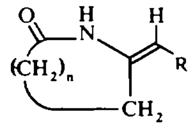

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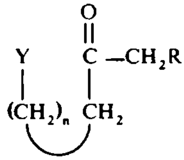

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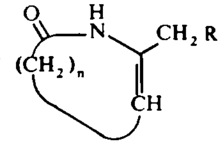

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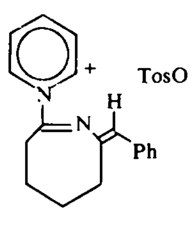
a: R = Ph, n = 3, (X = H, Y = $CONH_2$)
b: R = Ph, n = 2, (X = H, Y = $CONH_2$)
c: R = Ph, n = 2, (X = Tos)
d: R = CH_3, n = 3, (X = H, Y = CN)
e: R = CH_3, n = 3, (Y = $CONH_2$)
f: R = Ph, n = 5, (X = H)



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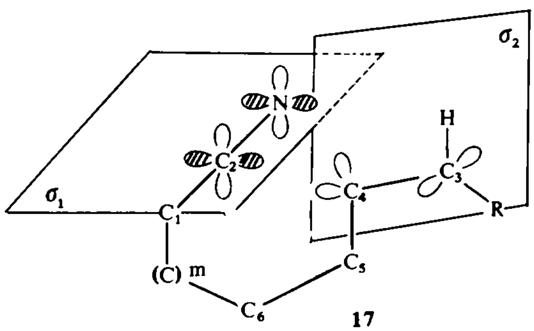

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treated directly with dilute H_2SO_4, the lactam **13a** was obtained as exclusive product in a yield of 75% along with 25% of starting oxime (**12a**).* No other product was detected, and evidently, no *cis–trans* isomerization of the olefinic group occurred during the reaction.

2-Benzylidenecyclopentanone oxime system

The oxime **12b** was prepared in the same way as for the six-membered ring system. In contrast with **12a**, however **12b** afforded a stable oxime tosylate **12c** in a good yield.

* The result was obtained in the following way: We found that a quantitative yield of product was obtained when the mixture of oxime **12a** and TsCl in pyridine was treated directly with dilute H_2SO_4. The product (A), obtained as quite crystals of m.p. 93–105° was found to be a 1:1 mixture of the lactam **13a** and a molecular complex of **13a** and **12a** (1:1) from the following observations. TLC of A showed two spots at R_f 0·5 and 0·7. Recrystallization of A from acetone–water afforded lactam **13a** and crystals of m.p. 122° (B). Although **13a** showed a single spot of R_f 0·5 on TLC, crystal B showed again two spots at R_f's 0·5 and 0·7. Recrystallization of B, however, did not result any change in m.p., NMR spectrum and R_f values on TLC. The separation of two components from B was accomplished with chromatography on silica gel. The IR spectrum and TLC showed that the first eluent was identical with the oxime **12a** and the second eluent with the lactam **13a**. The IR (KBr) and NMR ($CDCl_3$) spectra of B were not a simple algebraic summation of the component spectra. However, the NMR spectrum became a simple summation of two sets of spectra of **12a** and **13a** of identical intensity when measured in acetone. From these facts, it was concluded that B was a 1:1 molecular complex of **12a** and **13a**. A also showed a simplified NMR spectrum in acetone and from the integration, composition of **12a** and **13a** in A was estimated as approximately 1:3.

The oxime tosylate was unchanged when refluxed in MeOH, but it afforded a lactam (**13b**) as a sole identifiable product in low yield, when refluxed (7 hr) in MeOH containing piperidine. The alternative structure with alkyl migration was eliminated because **13b**, on hydrolysis, afforded an open-chain amide **14b**.

2-*Ethylidenecyclohexanone oxime system*

Only a single oxime was obtained* by oximation of the corresponding ketone, and the *trans-anti* structure **12d** was presented from the analogy of the previous result. When **12d** was treated with TsCl in pyridine, a nitrile (**14d**), an amide (**14e**) and a lactam (**15d**) were obtained. The structure with endocyclic double bond in **15d** was deduced from the NMR spectrum which showed signals at δ 5·1 (triplet, 1H for $=C\underline{H}—$) and at δ 1·1 (triplet, 3H for $—CH_2C\underline{H}_3$). The expected product **13d** would have ring strain largely owing to the transannular steric interaction and to eclipsed bonds. It is reasonable to assume that the reaction would proceed as it did, so as to afford products with partial or complete relief of the ring strain (**14d**, **14e** and **15d**). While it has generally been accepted that the Beckmann fragmentation (abnormal reaction) overcomes the normal reaction in cases when the migrating carbon atom is particularly stabilized as a carbonium ion, our result shows that the steric effect could also induce the abnormal Beckmann reaction. The exclusive formation of the unfavorable ring system in the case of **13a** could be rationalized because the otherwise unstable ring system would be stabilized by conjugation with a phenyl ring.

2-*Cyclooctenone oxime system*

The oxime was prepared from 2-cyclooctenone and hydroxylamine hydrochloride in the presence of $NaHCO_3$. The product showed complicated NMR signals in the olefinic region and was assumed to be a mixture of *syn* and *anti* isomers. From the integrated area of a doublet appearing at the downfield edge of the olefinic region of the NMR spectrum, which was assignable as an AB doublet of syn-H_α, the ratio of *syn* to *anti* was estimated as approximately 1:3. The oxime showed two peaks on GLC, but the clean separation on a preparative scale could not be effected. When the oxime mixture was treated with TsCl in pyridine at −30°, two crystals (D, mp 64–65° and E, mp 64–67°) were obtained. The solid D was identified as **10c** from the elemental analysis and spectroscopic data. The NMR spectrum showed no signals assignable as methylene protons adjacent to nitrogen (δ 3·0–4·0). The solid E was identified as a 1:1 complex of **9c** and **10c**, because the NMR spectrum displayed a simple algebraic summation of the spectrum of D and another spectrum which was assignable as that of **9c**; namely it showed absorption of methylene protons adjacent to nitrogen at δ 3·35. The solid E showed a single spot on TLC, and separation into components was unsuccessful.

2-*Benzylidenecyclooctanone oxime system*

The oxime, represented as *trans-anti* structure **12f** (*vide supra*), was unexpectedly unreactive with TsCl in pyridine, the starting material being recovered. The lack of reactivity of the oxime OH toward TsCl could be attributable to the steric inhibition by methylene hydrogens of the puckered ring. The oxime, however, reacted with

* Although the oxime was evidently free from any isomers as revealed by simple pattern for the olefinic proton in the NMR spectrum, it contained 20% of unidentifiable contaminant which could not be removed.

PCl_5 in ether at $-10°$, and afforded a lactam (**15f**). The structure with an endocyclic double bond was deduced from the NMR spectrum; namely a triplet at δ 6·2, (1H for =CH—), and a singlet at δ 3·2, (2H for —CH_2Ph). Presumably, the similar effect of ring strain as with the ethylidenecyclohexanone oxime system would be operating in this case.

DISCUSSION

As a summary of the present investigation, we can arrange compounds in order of the ease with which they undergo the Beckmann rearrangement as follows (Fig. 1.). **a**–**d** Were too reactive to permit isolation, while **e**–**h** were isolable, **e** being stable only at low temperature.[14] **e** and **f** underwent the Beckmann rearrangement in MeOH, while **g** did only in the presence of piperidine. **h** was unreactive under various conditions. Evidently, most of the olefinic groups migrated as effectively as alkyl groups and we must therefore regard the failure of the olefinic migration in **h** as abnormal. We feel that the results are most consistent with the intermediacy of a bridged ion (**17**) for the migration of olefinic group. The evidence that the migrating group approaches the migrating terminus (N) from the side opposite the leaving group strongly suggest that the developing p-orbital of C_2 and N (shaded) will be at right angles to the existing p-orbital (contributing to C—N double bond) and the bonds C_1—C_2—N will tend

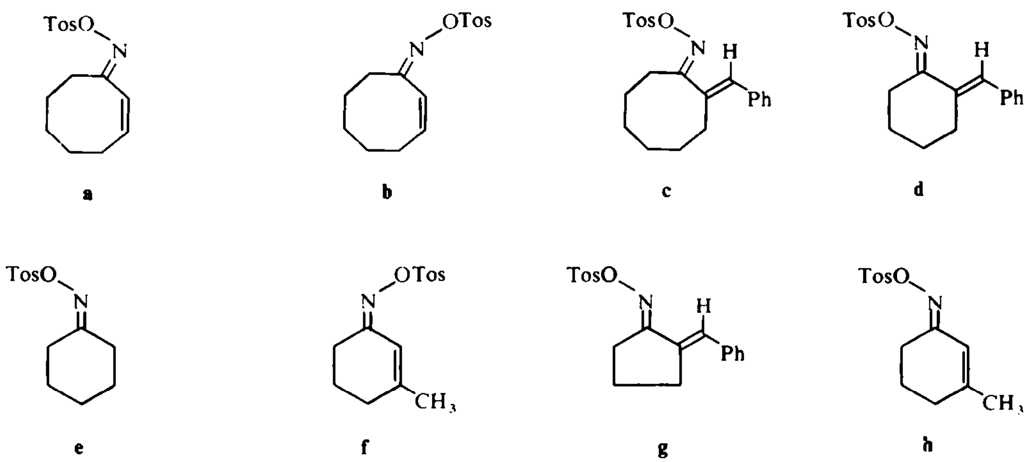

FIG 1.

to be on a straight line. It is conceivable that the developing orbital on migrating carbon atom (C_4) would partly overlap with the p-orbital on C_3, and partly with the developing vacant p-orbital of C_2 and N, thus stabilizing the bridged ion **17**. In order for the stabilization to be effective, both plane σ_1 and σ_2 should be perpendicular to each other, from the analogy with the case of the phenonium ion. Molecular models demonstrate that the orientation can be achieved well with compounds **a**, **c** and **d**, but strain increases with **g**, and no such an orientation is possible with the *endo*-cyclic double bond system of a six-membered ring (**h**), because in the last system, C_5 (now having p-orbital) and C_6 should be on σ_2

With the present picture for the mechanism of the rearrangement, it is obvious that the geometrical configuration of the olefinic group should be retained, because the migrating group does not become completely detached from the C_2 and N atoms.

The argument ascribing the failure of the olefinic carbon atom to migrate in the *anti*-cyclohexanone oxime system to the charge-deficient character of the intermediate complex[15] was incompatible with the present results.

EXPERIMENTAL

IR spectra were obtained on a Jasco IRS and a Hitachi EPI-G_3 spectrometers. NMR spectra were measured on a Jeol MH-60 (60 MHz) spectrometer and chemical shifts are represented in δ values (TMS). Mass spectra were measured on a Hitachi RMS-4 spectrometer.

Mixture of syn- *and* anti-3-*methyl-2-cyclohexenone oximes* (**7a** *and* **8a**). To a soln of 3-methyl-2-cyclohexenone[16] (14 g, b.p. 65–66°/5 mm) in MeOH (80 ml) and 10 ml water was added $NH_2OH \cdot HCl$ (9 g) and NaOH (5·2 g). The mixture remained for 1 day at room temp and solvent was evaporated *in vacuo*. MeOH was added and NaCl filtered off. On evaporation of MeOH an oil was obtained, and distilled to give a 1:2 mixture of *syn*- and *anti*-oximes (12 g), b.p. 93–95°/3 mm. (Lit[7]: b.p. 130–131°/18 mm). ν (neat): 3150 (s), 2890 (vs), 1635 (s), 1435 (s), 975 (vs) and 960 cm^{-1} (vs); NMR (CCl_4): δ 6·5 (s, 1/3 H), 5·8 (s, 2/3 H), 2·5 (t, 2H), 2·0 (m, 4H) and 1·9 (s, 3H).

The ratio of *syn*- and *anti*-oximes was unchanged when the mixture was refluxed in MeOH for 5 hr.

anti-3-*Methyl-2-cyclohexenone oxime tosylate* (**8b**). A soln of TsCl (19 g) in pyridine (30 ml) was added to a soln of the oxime mixture obtained above (12·5 g) in 17 ml pyridine with stirring at 0°. The soln was stirred for an additional 2 hr at 0°, and poured onto crushed ice containing 20 ml H_2SO_4. The solid was collected and refluxed in 100 ml EtOH. On cooling a solid separated which was recrystallized from MeOH to afford 13 g of **8b**, m.p. 100·5–101°. ν (KBr): 1640 (m), 1370 (s), 1180 (vs), 855 (s), 810 (s), 680 (s) and 550 cm^{-1} (s); NMR ($CDCl_3$): δ 7·9 (d, 2H), 7·4 (d, 2H), 6·0 (s, 1H), 2·7 (t, 2H), 2·6 (s, 3H), 2·4–1·7 (m, 4H) and 2·0 (s, 3H). (Found: C, 60·3; H, 6·4; N, 4·8. $C_{14}H_{17}NO_3S$ requires: C, 60·2; H, 6·1; N, 5·0%).

syn-3-*Methyl-2-cyclohexenone oxime hydrochloride*. A mixture of 3-methyl-2-cyclohexenone (22 g), $NH_2OH \cdot HCl$ (14 g), 100 ml MeOH and 4 ml conc HCl was refluxed for 4·5 hr. After standing overnight at room temp, the solvent was evaporated *in vacuo*. On addition of a small amount of acetone the oxime hydrochloride separated. This was collected and washed with acetone to give 12 g, m.p. 142–145°. (Lit[9]: m.p. 158–159°). ν (KBr): 1610 (vs), 1070 (m) and 855 cm^{-1} (m); NMR ($CDCl_3$): δ 11·8 (s, 1H), 6·6 (s, 1H), 2·8 (t, 2H), 2·3 (t, 2H), 2·0 (s, 3H) and 1·8 (m, 2H).

syn-3-*Methyl-2-cyclohexenone oxime tosylate* (**7b**). A soln of TsCl (5·7 g) in 12 ml pyridine was added to a soln of the oxime hydrochloride obtained above (4·8 g) in 12 ml pyridine with stirring and cooling by ice-salt. The mixture was stirred at 0° for 2 hr, and poured onto crushed ice containing 8 ml H_2SO_4. The solid was filtered and recrystallized from $CHCl_3$ – pet ether, m.p. 88–94° (dec). ν (KBr): 1635 (m), 1365 (s), 1355 (s), 1185 (vs), 790 (vs), 660 (s), 584 (s) and 555 cm^{-1} (s); NMR ($CDCl_3$): δ 7·9 (d, 2H), 7·4 (d, 2H), 6·6 (s, 1H), 2·5 (s, 3H), 2·4–2·2 (m, 4H), 2·0 (s, 3H) and 2·0–1·8 (m, 2H). (Found: C, 59·9; H, 6·3; N, 5·2. $C_{14}H_{17}NO_3S$ requires: C, 60·2; H, 6·1; N, 5·0%).

Beckmann rearrangement of **7b**. A soln of *syn*-oxime tosylate **7b** (1 g) in 20 ml MeOH and 2 ml water was refluxed for 1 hr. The solvent was evaporated *in vacuo*, the residue solidified, a small amount of acetone was added and the residue filtered. The solid (0·8 g) was recrystallized from dioxane to afford 0·4 g of pure sample of **9a**·TosOH; m.p. 142–143°. ν (KBr): 1680 (m), 1625 (m), 1230 (vs), 1140 (s), 998 (vs), 680 (s) and 570 cm^{-1} (s); NMR ($CDCl_3$): δ 12·0 (s, 1H), 10·9 (b, 1H), 7·9 (d, 2H), 7·3 (d, 2H), 6·05 (s, 1H), 3·7–3·5 (m, 2H), 2·7 (t, 2H), 2·5 (s, 3H), 2·1 (s, 3H) and 2·3–2·0 (m, 2H). (Found: C, 56·5; H, 6·2; N, 4·6. $C_{14}H_{19}NO_4S$ requires: C, 56·6; H, 6·4; N, 4·7%).

Beckmann rearrangement of **12a**. (a) A soln of TsCl (3·8 g) in pyridine (15 ml) was added to a soln of **12a**[17] (4 g, m.p. 126°) in pyridine (10 ml) with stirring at 0°. The soln was stirred for 2 hr at 0° and an additional 30 min at room temp, poured onto crushed ice containing 10 ml conc H_2SO_4 and the mixture extracted with C_6H_6 (100 ml). The soln was dried (Na_2SO_4) and concentrated *in vacuo*. A solid (3·9 g) was obtained which was recrystallized from ligroin. m.p. 93–105°. Further recrystallization of this material from aqueous acetone afforded two crystals (B and C). The solid B (crystallizing out first) showed two spots on TLC and was chromatographed on silica gel. Elution with ligroin afforded crystals of m.p. 126° which did not depress the m.p. of the starting oxime **12a** on admixture. IR spectrum was also identical with that of **12a**. Elution with acetone afforded crystals identical with the solid C and identified as lactam **13a**, m.p. 124°, ν (KBr): 3140 (m), 3050 (m), 2900 (m), 1655 (vs), 1620 (s), 1385 (s), 695 (s) and 516 cm^{-1} (m): NMR ($CDCl_3$): δ 8·45 (b, 1H), 7·0 (s, 5H), 6·0 (s, 1H), 2·6–2·4 (m, 4H) and 1·9–1·6 (m, 4H). (Found: C, 77·6: H, 7·5: N, 7·0%).

(b) A soln of TsCl (1·9 g) in 7 ml pyridine was added to a soln of oxime **12a** (2 g) in 5 ml pyridine with stirring at −5°. The mixture was stirred at this temp for 2 hr and then at room temp for 30 min. The soln was freeze-dried, water (10 ml) was added to the residue and the soln placed in a refrigerator overnight. Orange-yellow crystals of **16** were obtained which were recrystallized from water (temp. below 60°). m.p. 108–109°, 2·7 g. ν (KBr): 3450 (b, w), 1683 (w), 1610 (w), 1467 (s), 1220 (vs), 1177 (vs), 1010 (s) and 680 cm^{-1} (vs); NMR ($CDCl_3$): δ 9·7 (d, 2H), 8·7 (m, 1H), 8·3 (m, 2H), 7·8 (d, 2H), 7·4 (s, 5H), 7·2 (d, 2H), 6·8 (s, 1H), 3·5–3·3 (m, 2H), 2·8–2·6 (m, 2H), 2·3 (s, 3H) and 2·1–1·9 (m, 4H). (Found: C, 69·2; H, 6·1; N, 6·5. $C_{25}H_{26}N_2O_3S$ requires: C, 69·1; H, 6·0; B, 6·5%).

The compound **16** (2 g) was added to a mixture of 0·7 ml conc H_2SO_4 and 7 g of ice and extracted rapidly with C_6H_6 (10 ml). The soln was dried (Na_2SO_4) and the solvent removed *in vacuo*; m.p. 124°. The compound was identical with the lactam **13a** (m.m.p. and IR).

When a soln of the compound **16** (0·2 g) in 90% $AcOH_{aq}$ (3 ml) reacted at room temp for 3 hr, and the solvent was removed *in vacuo*, a solid remained, recrystallized from C_6H_6-ligroin to afford **14a**, m.p. 109°. ν (KBr): 3180 (m), 1700 (vs), 1630 (vs), 1615 (vs), 1416 (s) and 700 cm^{-1} (s); NMR ($CDCl_3$): δ 7·1 (s, 5H), 5·5 (b, 2H), 3·6 (s, 2H), 2·4 (t, 2H), 2·1 (t, 2H) and 1·6–1·4 (m, 4H). (Found: C, 71·4; H, 7·9; N, 6·2. $C_{13}H_{17}NO_2$ requires: C, 71·2; H, 7·8; N, 6·4%).

Hydrolysis of **13a**. A soln of **13a** (0·3 g) in AcOH (15 ml) and water (5 ml) was refluxed for 1 hr. The solvent was removed *in vacuo* and a small amount of water added. The solid was filtered and recrystallized from C_6H_6-ligroin to afford a compound of m.p. 109°, identified as the amide (**14a**) from m.m.p. and IR spectrum.

2-Benzylidenecyclopentanone oxime (**12b**). A mixture of 2-benzylidenecyclopentanone[18] (16·7 g, m.p. 66–67°), $NH_2OH \cdot HCl$ (7 g) and NaOH (4 g) in 150 ml MeOH was refluxed for 1 hr. The hot mixture was filtered to remove NaCl, the filtrate concentrated *in vacuo*, and water added. The solid (17·7 g) was recryallized from ligroin or dil. MeOH, m.p. 124°. ν (KBr): 3300–3100 (b), 1605 (m), 1445 (s), 1288 (s), 1262 (s), 1198 (s), 1050 (s), 940 (vs), 755 (s), 685 (s) and 505 cm^{-1} (s); NMR ($CDCl_3$): δ 9·7 (b, 1H), 7·6 (m, 6H), 3·0–2·6 (m, 4H) and 2·1–1·8 (m, 2H). (Found: C, 77·0; H, 7·0; N, 7·5. $C_{12}H_{13}NO$ requires: C, 77·0; H, 7·0; N, 7·5%).

2-Benzylidenecyclopentanone oxime tosylate (**12c**). A soln of TsCl (2 g) in pyridine (7 ml) was added to a soln of **12b** (2 g) in pyridine (5 ml) at 0°. The soln was stirred for 2 hr at 0° and for an additional 30 min at room temp, and poured onto crushed ice containing 7 ml conc H_2SO_4. The solid (2 g) was recrystallized from MeOH to afford a pure sample of **12c**, m.p. 116–117°. ν (KBr): 1595 (m), 1372 (s), 1190 (vs), 1178 (vs), 815 (vs), 690 (vs) and 560 cm^{-1} (s); NMR ($CDCl_3$): δ 7·9 (d, 2H), 7·3 (s, 6H), 7·3 (d, 2H), 3·0–2·6 (m, 4H), 2·5 (s, 3H) and 2·1–1·7 (m, 2H). (Found: C, 66·9; H, 5·6; N, 4·1. $C_{19}H_{19}NO_3S$ requires: C, 66·9; H, 5·6; N, 4·1%).

Beckmann rearrangement of **12c**. A soln of **12c** (1 g) and piperidine (1 ml) in MeOH (80 ml) and water (20 ml) was refluxed for 7 hr. The solvent was removed *in vacuo*, water added and the mixture extracted with ether. The ether was removed and CCl_4 added. A gradual addition of ligroin caused crystallization of solid (mother liquor: G). The solid was recrystallized from CCl_4 to afford a pure sample of the amide **14b**. 0·03 g. m.p. 105–106°. ν (KBr): 3450 (s), 1715 (vs), 1660 (vs), 1630 (vs) and 700 cm^{-1} (s); NMR ($CDCl_3$): δ 7·2 (s, 5H), 5·8 (b, 2H), 3·7 (s, 2H) and 2·7–1·8 (m, 6H). (Found: C, 70·2; H, 7·4; N, 6·8. $C_{12}H_{15}NO_2$ requires: C, 70·2; H, 7·4; N, 6·8%).

Upon removal of solvent from the mother liquor G described above, an oily substance was obtained. A small amount of ligroin was added to the material and the mixture kept in a refrigerator. A solid separated which was recrystallized from ligroin to afford pure lactam **13b**, 0·02 g, m.p. 125–126°. ν (KBr): 1697 (vs), 1640 (s), 1380 (vs), 1175 (m) and 700 cm^{-1} (m); NMR ($CDCl_3$): δ 9·2 (b, 1H), 7·2 (s, 5H), 6·1 (s, 1H), 2·9–2·4 (m, 4H) and 2·1–1·6 (m, 2H). (Found: C, 77·2; H, 6·9; N, 7·5. $C_{12}H_{13}NO$ requires: C, 77·0; H, 7·0; N, 7·5%).

Hydrolysis of **13b**. A mixture of the lactam **13b** (0·02 g), AcOH (2 ml) and water (0·5 ml) was refluxed for 2 hr. The solvent was removed and acetone added. A solid appeared identical with the amide **14b** by m.m.p. and IR spectrum.

2-Ethylidenecyclohexanone oxime (**12d**). To a soln of 2-ethylidenecyclohexanone[19] (5·8 g, 89–90°/12 mm) and $NH_2OH \cdot HCl$ (3 g) in MeOH (40 ml) was added a soln of NaOH (1·8 g) in MeOH (40 ml) with cooling. The soln was stirred at room temp for 288 hr. Solvent was removed *in vacuo*, water added and the mixture extracted with ether. The ether soln was dried (Na_2SO_4) and the ether removed. The residual oil, on distillation, afforded the oxime **12d**, b.p. 94–100°/2 mm. Redistillation, b.p. 96–98°/2 mm. GLC analysis showed that the fraction included 20% of unidentifiable contaminants. ν (neat): 3200 (b, s), 2900 (vs), 2830 (s), 1438 (s), 1084 (s), 965 (s), 938 (s) and 780 cm^{-1} (s); NMR (CCl_4): δ 9·65 (b, 1H), 5·85 (q, 1H), 3·2 (s, probably of contaminants), 2·4 (b, 4H) and 1·65 (d, 7H).

Beckman rearrangement of **12d**. A soln of TsCl (5·3 g) in 10 ml pyridine was added dropwise to a soln of **12d** (4·3 g) in 6 ml pyridine at −15–−12°. Pyridine (14 ml) was added and the mixture stirred for 2 hr and poured onto crushed ice containing conc H_2SO_4 (12 ml) and $CHCl_3$ (20 ml). The organic layer was separated and the aqueous soln extracted with $CHCl_3$. The combined $CHCl_3$ soln was washed with water, dried (Na_2SO_4) and solvent removed. On an addition of ether a small amount of solid separated (mother liquor: H). The solid was recrystallized from C_6H_6 to afford the amide **14e**. m.p. 96–97°. ν (KBr): 3390 (s), 3190 (s), 1690 (vs), 1653 (vs), 1613 (vs), 1410 (m) and 1110 cm^{-1} (m). (Found: C, 61·3; H, 98·; N, 8·7. $C_8H_{15}NO_2$ requires: C, 61·1; H, 9·6; N, 8·9%).

From the mother liquor (H) the solvent was removed and the residual oil distilled. From the oil, b.p. 62·5–95°/1 mm, seven fractions were obtained by prep GLC, of which the nitrile **14d**, the amide **14e** and the lactam **15d** were identified.

14d (main fraction), MS: *m/e* 139 $(M)^+$, 110 $(M—29)^+$, 82 $(M—57)^+$, 57 $(M—82)^+$; ν (neat): 2926 (s), 2225 (w), 1700 (vs), 1452 (s), 1409 (s), 1367 (s) and 1108 cm^{-1} (s); NMR (CCl_4): δ 2·4 (q, 6H), 1·7 (m, 4H) and 1·0 (t, 3H).

14e, IR spectrum and retention time on gas chromatography were identical with the product obtained above.

15d, MS: *m/e* 139 $(M)^+$, 124 $(M—15)^+$, 101 $(M—28)^+$, 96 $(M—43)^+$ and 84 $(M—55)^+$; ν (neat): 3190 (s), 2950 (s), 2900 (s), 1645 (vs), 1380 (b, s) and 1200 cm^{-1} (s); NMR (CCl_4): δ 8·8 (b, 1H), 5·1 (t, 1H), 2·5–1·6 (m, 8H) and 1·1 (t, 3H).

Mixture of syn- *and* anti-*2-cyclooctenone oximes* (**7c** *and* **8c**). To a soln of 5·5 g of 2-cyclooctenone[20] in MeOH (30 ml) was added $NH_2OH \cdot HCl$ (3·4 g) with stirring at 0°. After $NH_2OH \cdot HCl$ had dissolved, a sat $NaHCO_{3aq}$ was added until the soln became neutral to litmus. The mixture was kept at 0° for 20 min, water was added and the mixture shaken with ether. After removal of solvent, the residual oil was distilled. The oxime (4·3 g) was obtained as a pale yellow viscous oil, b.p. 84–91°/4 mm. ν (neat): 3250 (b), 2920 (s), 1450 (m), 980 (m) and 935 cm^{-1} (m); NMR (CCl_4): δ 9·6 (s, 1H), 6·4 (d, 0·25H), 6·05–5·3 (m, 1·75H), 2·9–2·1 (m, 4H) and 1·55 (s, 4H).

Beckmann rearrangement of the mixture of **7c** *and* **8c**. A soln of TsCl (4 g) in 10 ml pyridine was added dropwise to a soln of oxime mixture (**7c** and **8c**, 2 g) in 25 ml pyridine at −30–−32° over a period of 1·5 hr, and the mixture was stirred for 1·5 hr at this temp. A solid, which was assumed to be a product from TsCl and pyridine, was removed and the filtrate treated with a mixture of conc H_2SO_4 (30 ml), ice (200 g) and $CHCl_3$ (50 ml). The $CHCl_3$ layer was separated and the water layer extracted with $CHCl_3$. The combined $CHCl_3$ soln was washed successively with sat $NaHCO_{3aq}$ and with sat $NaCl_{aq}$, and dried ($MgSO_4$). Evaporation of solvent afforded a pale yellow viscous oil which partially crystallized on standing. The material was washed with pet ether several times and separated into pet ether–soluble solid (D) and pet ether–insoluble oil (F). Solid D was recrystallized from pet ether to afford **10c**, m.p. 64–65°. ν (KBr): 3410 (m), 3180 (m), 3020 (m), 2910 (s) and 1636 cm^{-1} (vs); NMR (CCl_4): δ 8·7 (b, 1H), 6·1 (d, 1H), 5·6 (q, 1H), 2·25 (b, 4H) and 1·65 (m, 4H). (Found: C, 69·4; H, 9·6; N, 10·2. $C_8H_{13}NO$ requires: C, 69·0; H, 9·4; N, 10·1%).

The oil F crystallized when its $CHCl_3$ soln was passed through an alumina column. The solid was recrystallized from ligroin–pet ether to afford a complex of **9c** and **10c**, m.p. 64–67°. ν (KBr): 3500 (m), 3260 (m), 2890 (s), 1657 (vs), 1636 (vs) and 1430 cm^{-1} (m); NMR (CCl_4): δ 8·7 (b, 0·5H), 8·4 (b, 0·5H), 6·1 (d, 0·5H), 5·6 (q, 0·5H), 5·65 (s, 1H), 3·35 (m, 1H), 2·3 (m, 3H) and 1·65 (m, 4H). (Found: C, 69·5; H, 9·5; N, 10·2. $C_8H_{13}NO$ requires: C, 69·0; H, 9·4; N, 10·1%).

2-Benzylidenecyclooctanone oxime (**12 f**). A soln of 2-benzylidenecyclooctanone[22] (5 g), $NH_2OH \cdot HCl$ (1·8 g), NaOH (1·0 g) in 50 ml EtOH was stirred for 10 hr at room temp. The solvent was removed *in vacuo* and water added. The solid separated was recrystallized from dil MeOH to afford 3·85 g of **12f**, m.p. 129–133°. ν (KBr): 3200 (b, s), 2900 (vs), 1445 (s), 990 (m), 918 (s), 753 (s) and 699 cm^{-1} (m); NMR ($CDCl_3$): δ 7·3 (s, 5–6H), 6·9 (s, 1H), 2·7 (m, 4H) and 1·7 (m 8H). (Found: C, 78·7; H, 8·4; N, 6·0. $C_{15}H_{19}NO$ requires: C, 78·6; H, 8·4; N, 6·1%).

Beckmann rearrangement of **12f**. Powdered PCl_5 (2 g) was added to a soln of oxime **12f** (0·5 g) in anhyd ether with stirring at −7° over 20 min. The mixture was stirred at this temp for 5 hr and then at room temp for 10 hr, and poured onto crushed ice. The mixture was shaken with ether several times, and the combined ether soln washed successively with sat $NaHCO_{3aq}$ and with water, and dried (Na_2SO_4). On removal of solvent a solid remained which was recrystallized from ligroin–C_6H_6 to give **15f**. m.p. 135–136°. ν (KBr): 2920 (s), 1650 (vs), 1445 (m), 1392 (m), 1300 (m), 750 (s) and 692 cm^{-1} (s); NMR ($CDCl_3$): δ 7·3 (b, 1H, moved on dilution), 6·9 (s, 5H), 5·15 (t, 1H), 3·15 (s, 2H), 2·2–1·6 (m, 4H) and 1·4 (b, s, 6H). (Found: C, 78·4; H, 8·3; N, 6·2. $C_{15}H_{19}NO$ requires: C, 78·6; H, 8·4; N, 6·1%).

REFERENCES

[1] E. C. Horning, V. L. Stromberg and H. A. Lloyd, *J. Am. Chem. Soc.* **74**, 5153 (1952); F. J. Donat and A. L. Nelson, *J. Org. Chem.* **22**, 1107 (1957); C. W. Shoppee, G. Krüger and R. N. Mirrington, *J. Chem. Soc.* 1050 (1962); C. W. Shoppee, R. Lack, R. N. Mirrington and L. R. Smith, *Ibid.* 5868 (1965); F. Kohen, *Chem. and Ind.* 1378 (1966)

[2] R. S. Montgomery and G. Dougherty, *J. Org. Chem.* **17**, 823 (1952); R. H. Mazur, *Ibid.* **26**, 1289 (1961)

[3] R. Huisgen, J. Witte and I. Ugi, *Chem. Ber.* **90**, 1844 (1966)

[4] R. M. Pinder, *J. Chem. Soc.* (*C*) 1690 (1969)

[5] P. T. Landsbury and N. R. Mancuso, *J. Am. Chem. Soc.* **88**, 1205 (1966)

[6] P. A. Smith, *Rearrangements Involving Migration to an Electron-Deficient Nitrogen or Oxygen*, in *Molecular Rearrangements* (P. deMayo, Ed.), p. 457, Interscience Publishers (1963)

[7] E. Knoevenagel and L. Klages, *Liebigs Ann.* **281**, 99 (1894)

[8] G. Slomp and W. J. Wechter, *Chem. & Ind.* 41 (1962); C. W. Shoppee, M. I. Akhtar and R. E. Lack, *J. Chem. Soc.* 3392 (1964)

[9] C. Harries and Jablonski, *Ber. Dtsch. Chem. Ges.* **31**, 1375 (1898)

[10] A. P. Stoll and F. Troxler, *Helv. Chim. Acta* **51**, 1864 (1968)

[11] K. K. Kelly and J. S. Matthews, *Tetrahedron* **26**, 1555 (1970)

[12] A. C. Huitric and S. D. Nelson, Jr., *J. Org. Chem.* **34**, 1230 (1969)

[13] D. R. Kelsey and R. G. Bergman, *J. Am. Chem. Soc.* **92**, 228 (1970)

[14] T. Sato and H. Wakatsuka, *Bull. Chem. Soc. Japan* **42**, 1955 (1969); W. Z. Heldt, *J. Am. Chem. Soc.* **80**, 5880 (1958)

[15] D. N. Kirk, *Steroid Reaction Mechanisms*, in *Reaction Mechanisms in Organic Chemistry* (C. Eaborn and N. B. Chapman, Ed.), p. 343, Elsevier, (1968)

[16] S. Natelson and S. P. Gotteried, *J. Am. Chem. Soc.* **61**, 1001 (1939)

[17] G. Vavon and J. M. Conia, *C.R. Acad Sci., Paris* **234**, 526 (1952)

[18] E. A. Braude and W. F. Forbes, *J. Chem. Soc.* 1755 (1951)

[19] T. G. Halsall and J. M. Mellor, *J. Chem. Soc.* (C) 397 (1966)

[20] A. C. Cope, M. R. Kinter and R. T. Keller, *J. Am. Chem. Soc.* **76**, 2757 (1954)

[21] E. A. Braude, W. F. Forbes, B. F. Gofton, R. P. Houghton and E. S. Waight, *J. Chem. Soc.* 4711 (1957)