

SOME CHEMICAL TRANSFORMATIONS OF PUMMERER'S KETONE

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(Received in UK 22 February 1980)

Abstract—The relative proportions of the epimeric alcohols obtained by reducing Pummerer's Ketone with a range of reagents have been determined, and the stereochemistries of these alcohols confirmed by europium shift studies. The reactions of Pummerer's Ketone with phenylcuprate, N,N-diethylaminopropyne, tosmic and hydrazoic acid have been investigated.

The synthesis of molecules having simplified morphine structures has been the basis of many efforts to produce analgesics with more acceptable properties than morphine and its congeners. An omission from the various types of molecular structure subjected to detailed study has been the hexahydrodibenzofuran ring system which constitutes a substantial portion of the morphine skeleton. This is particularly surprising since a facile synthetic entry into this ring system is provided by the oxidative coupling of phenols and the present investigations were prompted by our own success in effecting oxidative coupling of dissimilar phenols.¹

At the commencement of our studies analgetic activity had been claimed² for compounds such as **2** obtained by acylation of the pyrrolidine enamine of Pummerer's Ketone (**1**). Subsequently, compound **3** was reported³ to have comparable antitussive activity to codeine. The principal aim of the present studies was to convert Pummerer's Ketone (**1**) into compounds with a nitrogen bearing function at C₁ thereby providing a reasonable approximation to the morphine skeleton.

The first approach examined⁴ was the conversion of the alcohols **4** and **5** into the corresponding dimethylamides **6** and **7** by reaction with N,N-dimethylacetamide dimethylacetal and concurrent Claisen rearrangement. These transformations and the reduction of the amides to the corresponding amines have been described subsequently by other workers.⁵ However, some incidental observations are of interest. The alcohol **5** had been prepared previously⁶ in admixture with the epimer **4** by LAH reduction of **1**. In order to avoid the tedious

separation of **5** from **4** a survey of the proportions of the epimeric alcohols resulting from reduction of **1** with various reducing agents was conducted.

The ratio of **4** to **5** observed was 13:1 with aluminium isopropoxide and isopropanol, 4.3:1 using sodium dihydro-bis(2-methoxyethoxy) aluminate, 1:3.9 with LAH, and 1:13 employing NaBH₄ in ethanol. In apparent contrast to observations⁷ made with other $\alpha\beta$ -unsaturated ketones the reduction of **1** with NaBH₄ in ethanol in the presence of a molar equivalent of cerous chloride led to a diminishment in the proportion of the more sterically hindered alcohol formed, the observed ratio of **4** to **5** being 1:2. This fell to 1:1.5 if excess cerous chloride were added, and to 1:1 when methanol was substituted for ethanol. No saturated alcohols resulting from 1,4-reduction were encountered in any of the foregoing reactions.

The relative stereochemistries of the alcohols **4** and **5** were originally assigned⁶ on the basis of the observance of intramolecular H-bonding between the OH group and ether oxygen in **5** and not in **4**. Additional evidence for the correctness of these assignments was obtained from a quantitative investigation of the influence of tris(2,2,6,6-tetramethylheptane-3,5-dionato) europium-(Eu(THD)₃) on the ¹H NMR spectra of these epimers. The gradients (G) of plots of shift of individual peaks in ppm vs the molar ratio of Eu(THD)₃ to alcohol are summarised in Table 1. Plots of log₁₀G vs the log₁₀ of the distance (τ) of the respective protons from the OH group measured on Dreiding models gave satisfactory linear correlations of slope -1.95 for **4** and -2.19 for **5**. Less

Table 1. Eu(THD)₃ shift measurements on alcohols **4** and **5**

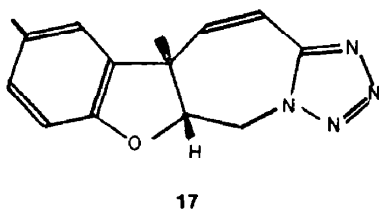
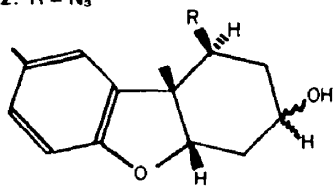
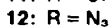
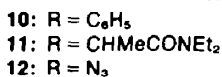
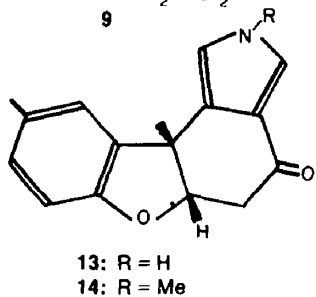
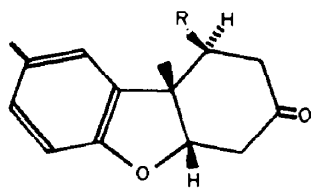
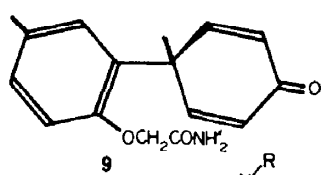
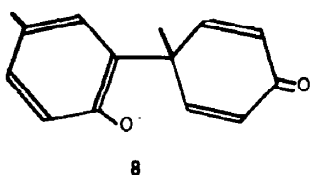
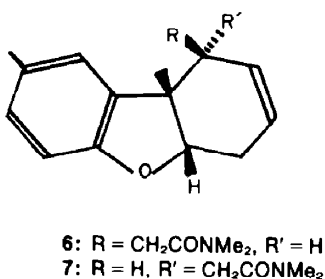
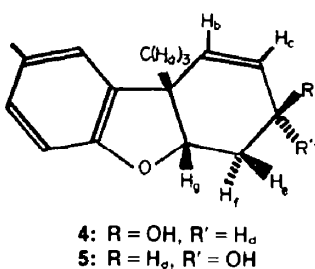
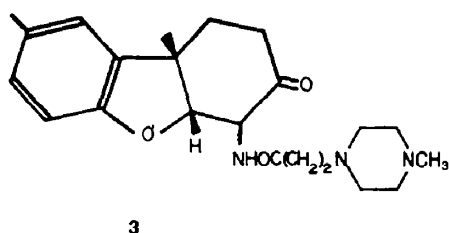
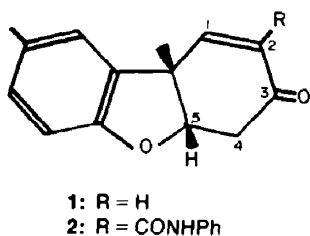
Proton	Alcohol 4		Alcohol 5	
	log ₁₀ G	τ	log ₁₀ G	τ
H _A	0.60	5.36	0.60	5.12
H _B	0.73	4.44	0.76	4.00
H _C	1.20	2.52	1.14	2.92
H _D	1.41	2.04	1.42	2.04
H _E	1.25	2.68	0.95	3.40
H _F	1.12	2.76	1.18	2.80
H _G	0.74	4.56	0.83	3.72

satisfactory correlations resulted if the converse stereochemistries were assumed.

The foregoing method of side-chain introduction resulted in the loss of the C.3 oxygen function which could be important for biological activity and thus addition reactions of the α,β -unsaturated ketonic system were investigated. Direct Michael additions of addends such as nitromethane could not be effected probably because of the competing ring opening of **1** to the phenoxide anion⁸ **8**. This phenomenon also thwarted attempts to make use of the facile rearrangement² of 4-substituted derivatives of **1** to the isomeric 2-substituted ones. Thus base promoted alkylation of **1** with chloroacetamide yielded the dienone **9**. The cuprous chloride mediated addition of phenylmagnesium iodide to

1 provided the anticipated product **10** of conjugate addition, but we were unable to effect analogous reactions with several potential organolithium addends. In view of these observations it was surprising that the base-catalysed reaction of **1** with tosylmethyl isocyanide yielded the anticipated pyrrole **13** which underwent base-mediated N-methylation to **14**.

A satisfactory solution to this synthetic problem was provided by the addition of *N,N*-diethylaminopropyne to **1** which, after hydrolysis of the intermediary cyclobutene, gave the amide **11**. Analogy with other examples⁹ suggests that addition occurs preferentially to the less hindered face of **1** leading to the depicted stereochemistry for **11**. LAH reduction of **11** only proceeded as far as the alcohol (**15**) even under fairly vigorous conditions,



and complete reduction to the amino alcohol (16) was eventually effected with diborane. The stereochemical disposition of the OH group in 15 and 16 has not been established.

The introduction of a N atom into the cyclohexenone ring of 1 was also of interest since it would then become a reasonable approximation to the piperidine ring of morphine. Pummerer's Ketone undergoes a dienone-phenol type rearrangement⁸ under the strongly acidic conditions normally required for appropriate ring expansion reactions. Suitable conditions for Beckmann rearrangement of the oxime of 1 or its dihydro derivative could not be established but treatment of 1 with hydrazoic acid in the presence of BF₃ etherate provided not only the anticipated tetrazole (17) but also the azide (12).

EXPERIMENTAL

IR spectra were recorded for Nujol mulls on a Unicam SP200 spectrophotometer. NMR spectra were measured for CDCl₃ solutions with internal TMS on a Perkin-Elmer R12B spectrometer. Mass spectra were obtained either by the P.C.M.U., Harwell or by the ULIRS Mass Spectrometry Service at Q.E.C. (MS30) or the School of Pharmacy (MS9).

Reduction of 1

(a) Pummerer's Ketone (0.5 g) was dissolved in EtOH (10 ml) and NaBH₄ (0.5 g) added portionwise over 2 min. The mixture was stirred for 1 hr and the excess borohydride decomposed with 2M HCl. The product was isolated by ether extraction. The reaction was repeated adding (i) 0.8 g CeCl₃·6H₂O and (ii) 10 g of CeCl₃·6H₂O in 5 ml EtOH prior to addition of NaBH₄. It was also conducted in MeOH with 10 g of CeCl₃·6H₂O.

(b) Pummerer's Ketone (0.5 g) in xylene (10 ml) was added to a 70% soln of sodium dihydro-bis(2-methoxyethoxy) aluminate in toluene (3.9 g) and stirred for 12 hr. Then 2M HCl was added and the products isolated by ether extraction.

(c) Reductions with LAH₄ and isopropanol-aluminium isopropoxide were carried out as previously described.⁶

The mixtures were analysed using a Pye series 104 gas chromatograph fitted with a 10% P.E.G. on celite column, at 190–200°.

The addition of N,N-diethylaminopropylene to 1

N,N-Diethylaminopropylene (1.99 g) was added to a soln of 1 (4.28 g) in anhyd. acetonitrile (20 ml) and THF (40 ml). The mixture was heated under reflux for 24 hr and the solvents then evaporated. The residue was taken up in EtOH (25 ml) containing a few drops of 2N NaOH and allowed to stand overnight. The keto-amide 11 (55%) was isolated by dilution with water and CHCl₃ extraction, m.p. 103–105° from benzene. (Found: C, 73.6; H, 8.4; N, 3.9. Calc. for C₂₁H₂₉NO₂: C, 73.5; H, 8.5; N, 4.1%); IR 1720, 1640 cm⁻¹; NMR δ 0.91 (t, 3H, CH₃), 1.05 (t, 3H, CH₃), 1.45 (d, 3H, CH₃, J = 6 Hz), 1.65 (s, 3H, CH₃), 1.8–3.5 (m, 10H with superimposed singlet at 2.32 for CH₃), 3.8–4.25 (br, 1H, CH), 4.55–4.7 (m, 1H, CH), 6.5–7.2 (m, 3H, ArH); MS *m/e* 343(9), 199(8), 186(33), 159(27), 146(79), 129(100), 113(16), 100(67).

Reduction of the N,N-diethylacetamide (11)

(a) The amide 11 (1.2 g) in dry ether (25 ml) was added to an ethereal soln (50 ml) of LAH (2 g) and the stirred mixture heated under reflux for 2.5 hr. The excess LAH was decomposed by cautious addition of water and the granular ppt of alumina filtered off and washed with warm ether. The combined ethereal solns were washed with water, dried (Na₂SO₄) and evaporated to give 15 (82%) m.p. 112–114° from EtOH. (Found: C, 72.8; H, 8.9; N, 4.3. Calc. for C₂₁H₃₁NO₂: C, 73.0; H, 9.0; N, 4.1%); IR 3400, 1645 cm⁻¹; NMR δ 0.9 (t, 3H, CH₃), 1.05 (t, 3H, CH₃), 1.4 (d, 3H, CH₃, J = 6.5 Hz), 1.49 (s, 3H, CH₃), 2.0–3.5 (m, 10H with superimposed singlet at δ 2.31 for CH₃), 3.8–4.25 (br, 1H, CH), 4.35–4.55 (m, 1H, CH), 6.6–7.2 (m, 3H, ArH); MS *m/e* 345(8),

326(7), 307(21), 199(8), 186(33), 159(27), 156(17), 146(80), 129(100), 113(16), 100(67).

(b) BF₃-etherate (6 ml) was added dropwise over 30 min to a stirred soln of 11 (0.5 g) and NaBH₄ (1.2 g) in diglyme (25 ml) under N₂. The temp was kept at 20–25° for a further hr and then water (25 ml) added dropwise. After 1 hr the mixture was extracted with ether. The extracts were washed thoroughly with water, dried (Na₂SO₄) and evaporated. The residue was treated with a methanolic soln of HCl to give the hydrochloride of 16 m.p. 167–169° from alcohol. (Found: C, 68.8; H, 9.3; N, 3.6. Calc. for C₂₁H₃₄ClNO₂: C, 68.6; H, 9.2; N, 3.8%).

Reaction of 1 with phenylmagnesium iodide

To a stirred ethereal soln (50 ml) of PhMgBr, prepared from iodobenzene (19.2 g) and Mg (1.8 g), under N₂ was added successively THF (80 ml) and a soln of 1 (4 g) and cuprous chloride (0.4 g) in THF (40 ml). Additional THF (80 ml) was added to facilitate stirring. After 30 min the mixture was cooled to 0° and satd NH₄Cl aq added. The mixture was extracted with ether and the ethereal extract washed in turn with Na₂S₂O₃ aq, NH₄Cl aq and water. The extract was dried (Na₂SO₄) and evaporated. Column chromatography of the residue on silica and elution with toluene-EtOAc (1:1) provided 10 (40%), m.p. 192–194° from EtOH. (Found: C, 82.0; H, 6.7. Calc. for C₂₀H₂₆O₂: C, 82.2; H, 6.8%); IR 1720 cm⁻¹; NMR δ 1.28 (s, 3H, CH₃), 2.0–2.4 (m, 4H with superimposed singlet at 2.3 for CH₃), 2.95 (dd, 1H, CH, J = 6 Hz), 4.75 (m, 1H, CH), 6.75–7.45 (m, 8H, ArH); MS *m/e* 292(40), 277(15), 246(10), 225(10), 170(100), 157(40), 156(35), 116(50), 102(44).

Reaction of 1 with tosmic

A soln of 1 (2.14 g) and tosmic (1.95 g) in a mixture of anhyd. ether (40 ml) and dimethyl sulphoxide (20 ml) was added slowly to a stirred suspension of NaH (1.2 g) in ether (25 ml), and stirring continued for an additional 30 min. Water was then added cautiously followed by KOH aq and the products isolated by ether extraction. The residue obtained by evaporation of the dried ethereal extracts was chromatographed over silica gel with toluene-EtOAc (7:3) as eluent. After separation of unchanged P.K. the more polar fraction was crystallised from MeOH to yield 13 (25%), m.p. 145–147°. (Found: C, 75.5; H, 6.1; N, 5.7. Calc. for C₁₆H₁₅NO₂: C, 75.9; H, 5.9; N, 5.5%); IR 3300, 1650 cm⁻¹; NMR δ 1.70 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.96 (d, 2H, CH₂, J = 4 Hz) 4.76 (t, 1H, CH, J = 4 Hz) 6.5–7.5 (m, 6H, ArH and NH); MS *m/e* 253(90), 238(100), 213(70), 151(40), 148(50), 118(25).

The pyrrole 13 (1.3 g) was added slowly to a stirred soln of t-BuOK (1.2 g) in DMSO (25 ml). MeI (1.8 g) was then added dropwise and the mixture heated at 80–85° for 2 hr. The mixture was poured into ice-water and the products isolated by ether extraction. The crude material thus obtained was chromatographed on silica gel with toluene-EtOAc (4:1) as eluent to give 14 (35%), m.p. 132–134° from MeOH. (Found: C, 76.3; H, 6.4; N, 5.0. Calc. for C₁₇H₁₇NO₂: C, 76.4; H, 6.4; N, 5.2%); IR 1670 cm⁻¹; NMR δ 1.63 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.8–2.95 (m, 2H, CH₂), 3.5 (s, 3H, NCH₃), 4.6–4.8 (m, 1H, CH), 6.45–7.3 (m, 5H, ArH); MS *m/e* 267(60), 252(100), 224(55), 159(22), 146(57), 145(15), 128(15), 115(20), 91(22).

Reaction of 1 with chloroacetamide

Compound 1 (4.8 g) was added slowly to a stirred soln of t-BuOK (2.8 g) in dry DMSO (150 ml). Subsequently chloroacetamide (2.1 g) was added slowly then the mixture heated at 85–90° for 3 hr. The resulting mixture was poured into water and ether extracted. The ethereal soln was washed with water, dried (Na₂SO₄) and evaporated. The product was chromatographed on silica gel and the principal product 9 (55%) eluted with toluene-EtOAc (3:2), m.p. 118–120° from alcohol. (Found: C, 70.5; H, 6.3; N, 4.9. Calc. for C₁₆H₁₇NO₂: C, 70.8; H, 6.3; N, 5.2%); IR 3420, 3350, 1700, 1650 cm⁻¹; NMR δ 1.69 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 4.41 (s, 2H, CH₂), 6.4 (d, 2H, 2X-CH = , J = 11 Hz), 6.8–7.4 (m, 5H, ArH and -CH =), MS *m/e* 271(17), 227(20), 214(47), 211(45), 209(100), 199(43), 197(35), 183(25), 169(19), 142(33), 141(38), 128(30), 115(43).

Reaction of 1 with hydrazoic acid

BF₃-etherate (3.2 ml) was added to a stirred CHCl₃ soln of hydrazoic acid¹⁰ (200 ml, 0.21N) cooled to 0–5°, and then dropwise a CHCl₃ soln (50 ml) of 1 (2.14 g) over a period of 4 hr. After a further 35 hr at room temp the soln was washed with water, dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica in toluene which eluted 12 (22%) as an oil. (Found: M⁺ 257.1175. Calc. for C₁₄H₁₅N₃O₂: M⁺ 257.1164); IR 2100, 1720 cm⁻¹; NMR δ 1.55 (s, 3H, CH₃), 2.2–2.5 (m, 5H, CH₂ and CH₃), 2.85 (d, 2H, CH₂, J = 3 Hz), 3.95 (dd, 1H, CH, J = 3 Hz), 4.72 (dd, 1H, CH, J = 3 Hz), 6.6–7.4 (m, 3H, ArH); MS *m/e* 257(10), 229(100), 214(55), 199(45), 186(30), 171(25), 159(90), 146(74), 128(25), 115(33). Elution with toluene EtOAc (8:2) provided 17 (35%), m.p. 207–209° from CHCl₃-ether. (Found: C, 66.4; H, 5.7; N, 22.1. Calc. for C₁₄H₁₄N₄O: C, 66.1; H, 5.5; N, 22.0%); IR 1650, 1610 cm⁻¹; NMR δ 1.65 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 5.05 (m, 3H, CH and CH₂), 6.54 (d, 1H, –CH=, J 11 Hz), 6.58–7.17 (m, 4H, ArH and –CH=); MS *m/e* 254(90), 239(22), 211(41), 183(100), 159(15).

Acknowledgements—We thank Dr. R. F. Newton for his encouragement, Glaxo-Allenburys Research Ltd and the S.R.C.

for a CASE award (D.R.T.), and the company for a research scholarship ((Y.-P.S.C.).

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