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SOME CHEMICAL TRANSFORMATIONS OF PUMMERER'S KETONE

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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 claimed[2] for compounds such as **2** obtained by acylation of the pyrrolidine enamine of Pummerer's Ketone (**1**). Subsequently, compound **3** was reported[3] 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 C_1 thereby providing a reasonable approximation to the morphine skeleton.

The first approach examined[4] 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 previously[6] 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 $NaBH_4$ in ethanol. In apparent contrast to observations[7] made with other $\alpha\beta$-unsaturated ketones the reduction of **1** with $NaBH_4$ 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 assigned[6] 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 $\log_{10}G$ vs the $\log_{10}$ of the distance (r) 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

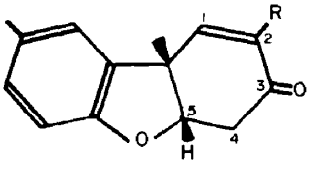
Table 1. $Eu(THD)_3$ shift measurements on alcohols **4** and **5**

Proton	Alcohol 4		Alcohol 5	
	$\log_{10}$ G	r	$\log_{10}$G	r
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

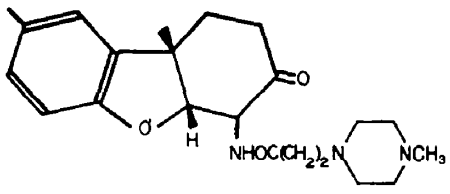
satisfactory correlations resulted if the converse stereochemistries were assumed.

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 anion[8] **8**. This phenomenon also thwarted attempts to make use of the facile rearrangement[2] 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 examples[9] 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,



1: R = H
2: R = CONHPh



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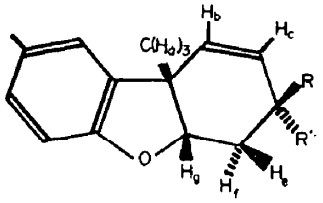
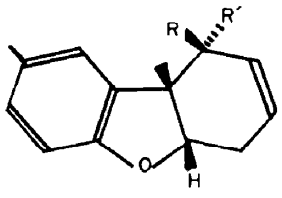
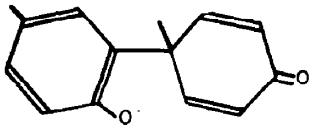


4: R = OH, R′ = H_d
5: R = H_d, R′ = OH



6: R = CH_2CONMe_2, R′ = H
7: R = H, R′ = CH_2CONMe_2



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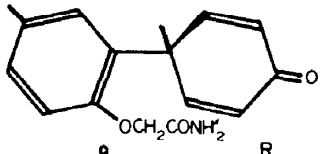

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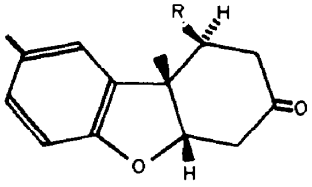
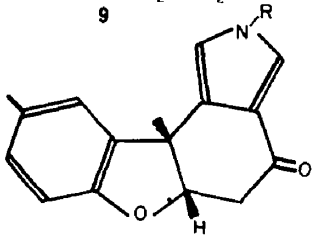
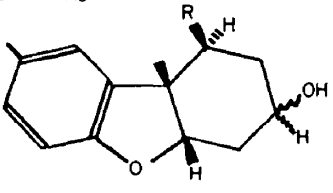


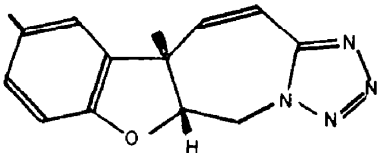
10: R = C_6H_5
11: R = $CHMeCONEt_2$
12: R = N_3



13: R = H
14: R = Me



15: R = $CHMeCONEt_2$
16: R = $CHMeCH_2NEt_2$



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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 rearrangement[8] under the strongly acidic conditions normally required for appropriate ring expansion reactions. Suitable conditions for Beckman 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 BF_3 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 $CDCl_3$ solns 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 $NaBH_4$ (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 $CeCl_3 \cdot 6H_2O$ and (ii) 10 g of $CeCl_3 \cdot 6H_2O$ in 5 ml EtOH prior to addition of $NaBH_4$. It was also conducted in MeOH with 10 g of $CeCl_3 \cdot 6H_2O$.

(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 LAH_4, 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-*diethylaminopropyne to* **1**

N,N-Diethylaminopropyne (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 $CHCl_3$ extraction, m.p. 103–105° from benzene. (Found: C, 73.6; H, 8.4; N, 3.9. Calc. for $C_{21}H_{29}NO_3$: C, 73.5; H, 8.5; N, 4.1%): IR 1720, 1640 cm^{-1}; NMR δ 0.91 (t, 3H, CH_3), 1.05 (t, 3H, CH_3), 1.45 (d, 3H, CH_3, J = 6 Hz), 1.65 (s, 3H, CH_3), 1.8–3.5 (m, 10H with superimposed singlet at 2.32 for CH_3), 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 (Na_2SO_4) and evaporated to give **15** (82%) m.p. 112–114° from EtOH. (Found: C, 72.8; H, 8.9; N, 4.3. Calc. for $C_{21}H_{31}NO_3$: C, 73.0; H, 9.0; N, 4.1%): IR 3400, 1645 cm^{-1}; NMR δ 0.9 (t, 3H, CH_3), 1.05 (t, 3H, CH_3), 1.4 (d, 3H, CH_3, J = 6.5 Hz), 1.49 (s, 3H, CH_3), 2.0–3.5 (m, 10H with superimposed singlet at δ 2.31 for CH_3), 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) BF_3-etherate (6 ml) was added dropwise over 30 min to a stirred soln of **11** (0.5 g) and $NaBH_4$ (1.2 g) in diglyme (25 ml) under N_2. 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 (Na_2SO_4) 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 $C_{21}H_{34}ClNO_2$; 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 N_2 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 NH_4Cl aq added. The mixture was extracted with ether and the ethereal extract washed in turn with $Na_2S_2O_3$ aq, NH_4Cl aq and water. The extract was dried (Na_2SO_4) 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 $C_{20}H_{20}O_2$: C, 82.2; H, 6.8%); IR 1720 cm^{-1}; NMR δ 1.28 (s, 3H, CH_3), 2.0–2.4 (m, 4H with superimposed singlet at 2.3 for CH_3), 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 $C_{16}H_{15}NO_2$: C, 75.9, H, 5.9; N, 5.5%); IR 3300, 1650 cm^{-1}; NMR δ 1.70 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.96 (d, 2H, CH_2, 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 $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4; N, 5.2%); IR 1670 cm^{-1}; NMR δ 1.63 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.8–2.95 (m, 2H, CH_2), 3.5 (s, 3H, NCH_3), 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 thd 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 (Na_2SO_4) 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 $C_{16}H_{17}NO_3$: C, 70.8; H, 6.3; N, 5.2%); IR 3420, 3350, 1700, 1650 cm^{-1}; NMR δ 1.69 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 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*

BF_3-etherate (3.2 ml) was added to a stirred $CHCl_3$ soln of hydrazoic acid[10] (200 ml, 0.21N) cooled to 0–5°, and then dropwise a $CHCl_3$ 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 (Na_2SO_4) and evaporated. The residue was chromatographed on silica in toluene which eluted **12** (22%) as an oil. (Found: M^+ 257.1175. Calc. for $C_{14}H_{15}N_3O_2$: M^+ 257.1164); IR 2100, 1720 cm^{-1}; NMR δ 1.55 (s, 3H, CH_3), 2.2–2.5 (m, 5H, CH_2 and CH_3), 2.85 (d, 2H, CH_2, 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 $CHCl_3$–ether. (Found: C, 66.4; H, 5.7; N, 22.1. Calc. for $C_{14}H_{14}N_4O$: C, 66.1; H, 5.5; N, 22.0%); IR 1650, 1610 cm^{-1}; NMR δ 1.65 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 5.05 (m, 3H, CH and CH_2), 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).

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