Synthesis of Potential Hypnotics

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Several 2,2-disubstituted *cyclo*hexanones were prepared and a number of their corresponding oximes was subjected to Beckmann rearrangement in order to obtain ε,ε-disubstituted caprolactams believed to possess hypnotic activity.

It was believed that lactams containing a quaternary carbon atom adjacent to the lactam moiety, *i.e.* the grouping —CO—NH—CRR'— within a cyclic system, might possess hypnotic activity. Such compounds would be available from 2,2-dialkyl-*cyclo*hexanones, for example, through Beckmann rearrangement of the corresponding oximes.

It has been shown [1] that such rearrangement leads exclusively to the above grouping rather than to the isomeric (—CRR'—CO—NH—) one. It was also expected [2] that the disubstituted caprolactams would be less prone to polymerization than caprolactam itself. However, this expectation was not realized. In fact, although some of the products synthesized did indeed possess hypnotic activity, polymerization occurred so readily that preparation of this type of compound was abandoned as impractical.

The difficulties in preparing 2,2-disubstituted *cyclo*hexanones in one step are well known. However, the availability of Stork's excellent method for the synthesis of monoalkyl*cyclo*hexanones [3] afforded the possibility of alkylating the latter derivative in the presence of sodium hydride in reasonable overall yield. The purification of the liquid products was effected by distillation through the efficient column described by Clauson-Kaas and Limborg [4].

The oximes were prepared in high yield by the pyridine procedure [5] and were rearranged by means of polyphosphoric acid [6]. The disubstituted caprolactams thus obtained polymerized very readily during distillation or even upon standing. Purification with lower loss of material could be effected chromatographically.

In the attempt to prepare 6,6-dialkylpyridones from the corresponding oximes of 2,2-disubstituted *cyclo*pentanones, the following approach was attempted but failed.

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Table 1. 2,2-Disubstituted

2,2-Disubstituted cyclohexanone	Yield %	B. p.		n_D^{30}	C=O I.R. ν cm^{-1}	Empirical formula	Analysis Calc.		
		°C	mm				C	H	O
Et, Et	61	83— 85	12	1.4560	1 708	$C_{10}H_{18}O$	77.9	11.8	10.4
Et, Allyl	76	115—124	19	1.4694	1708	$C_{11}H_{18}O$	79,5	10.9	9.6
Et, i-Pr	41	110—112	20	1.4559	1 700	$C_{11}H_{20}O$	78.5	12.0	9.5
Et, n-Bu	49	123—125	20	1.4568	1 695	$C_{12}H_{22}O$	79.1	12.2	8.8
Et, i-Bu	61	118—120	20	1.4560	1 695	$C_{12}H_{22}O$	79.1	12.2	8.8
Et, Ph	80	99—105	0.2	1.5305	1 705	$C_{14}H_{18}O$	83.1	9.0	7.9
Me, n-Bu	62	96	12	1.4525	1 698	$C_{11}H_{20}O$	78.5	12.0	9.5
Allyl, i-Pr	56	120—124	20	1.4725	1 695	$C_{12}H_{20}O$	79.9	11.2	8.9

Chlorination of 2-ethylcyclopentanone with sulfuryl chloride afforded 2-chloro-2-ethylcyclopentanone. Treatment of the latter with diethyl cadmium indeed effected alkylation by replacement of the chlorine atom with an ethyl group without attack of the carbonyl group but unfortunately this cadmium alkyl was a sufficiently strong base so as to effect dehydrochlorination and 2-ethyl-cyclopent-2-enone was formed concomitantly. Perhaps a different metal alkyl might be employed successfully but this was not pursued further.

EXPERIMENTAL PART *

2-Ethylcyclohexanone. A mixture of freshly distilled cyclohexanone (108 g, 1.1 mole), pyrrolidine (156 g, 2.1 mole) and dry thiophene-free benzene (500 ml) was heated and stirred in a nitrogen atmosphere [7]. The water formed during the preparation of the enamine was collected in a calibrated moisture trap. Most of the benzene and excess pyrrolidine were removed at atmospheric pressure and the rest at the water pump. The flask containing the residual yellow oil was cooled to room temperature and ethyl iodide (187 g, 1.2 mole) was slowly added, causing a strong exothermic reaction. When stirring became difficult due to the thickness of the reaction mixture, absolute ethanol (125 ml) was added. After addition of the ethyl iodide was complete the mixture was heated under reflux overnight (under nitrogen).

The ethanol was removed at reduced pressure and the resulting crystalline mass was heated under reflux with water (200 ml) for 3 h. After cooling and separation of the oily phase, the aqueous phase was extracted twice with ether. The aqueous phase was then subjected to steam distillation; the distillate was saturated with sodium chloride and was extracted several times with ether. The oil and combined ether extracts were dried

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* M.p.'s and b.p.'s are uncorrected. Infrared spectra were measured in chloroform solution with a Perkin Elmer Model 21 Spectrophotometer using sodium chloride optics.

ketones and their oximes.

Found			Oxime m.p. or b. p. (°C)	Empirical Formula	Analysis					
					Calc.			Found		
C	H	O			C	H	N	C	H	N
77.2	12.1	10.6	46—48	$C_{10}H_{19}ON$	71.0	11.3	8.3	70.8	11.2	8.0
79.6	10.7	9.7	100—103/0.2	$C_{11}H_{19}ON$	72.9	10.6	7.7	72.6	10.4	7.7
78.3	11.8	10.0	90—94/0.1	$C_{11}H_{21}ON$	72.1	11.6	7.6	71.7	11.1	7.7
78.7	12.2	9.1	48—49; 98—103/0.2	$C_{12}H_{23}ON$	73.0	11.8	7.1	73.0	11.6	7.0
78.4	12.0	9.2	80; 100—105/0.01	$C_{12}H_{23}ON$	73.0	11.8	7.1	72.7	11.7	7.0
82.9	8.9	7.8	149—150	$C_{14}H_{19}ON$	77.4	8.8	6.5	77.8	8.9	6.5
78.4	12.2	9.8	40—41; 85—88/0.05	$C_{11}H_{21}ON$	72.1	11.6	—	72.1	11.4	—
79.6	11.5	9.1	76—77	$C_{12}H_{21}ON$	73.8	10.8	7.2	73.6	10.6	7.1

(magnesium sulfate) and the ether was removed, leaving a brownish oil (140 ml) which when distilled through an efficient column [4] afforded 2-ethyl*cyclo*hexanone as a colorless oil, b. p. 88°/50 mm, n_D^{30} 1.4464 (71 g, 63 % based on unrecovered *cyclo*hexanone). Lit.[8] reports b. p. 67°/12 mm, n_D^{15} 1.4543.

2-Allylcyclohexanone. This ketone was similarly prepared from *cyclo*hexanone (49 g, 0.5 mole), pyrrolidine (71 g, 1 mole) in dry benzene (500 ml) and freshly distilled allyl bromide (73 g, 0.6 mole). Dry *n*-butanol was used instead of ethanol. The ketone had b. p. 90—98°/20 mm, n_D^{30} 1.4647 (42 g, 60 %). Lit.[9] reports b. p. 91—94°/12 mm.

2-n-Butyl-2-methylcyclohexanone. In a 1-liter 3-necked flask equipped with mechanical stirrer, reflux condenser and dropping funnel, a mixture of 2-methyl*cyclo*hexanone (56 g, 0.5 mole), dry toluene (500 ml) and sodium hydride (13.2 g, 0.55 mole) was heated and stirred under reflux for 15 h under nitrogen. The suspension of sodio-derivative was then cooled and *n*-butyl bromide (67.5 g, 0.5 mole) was added with stirring during 10 min and then heated under reflux for 2—3 h. After cooling to *ca.* 50°, the precipitated sodium bromide was removed by filtration and the salt was washed with two portions (50 ml) of dry ether. The solvents were removed at the water pump from the combined filtrates. The light yellow residue (*ca.* 90 ml) was distilled through an efficient column [4] affording 2-*n*-butyl-2-methyl*cyclo*hexanone, b. p. 96°/12 mm) n_D^{30} 1.4525 (52 g, 62 %) and 2,6-di-*n*-butyl-2-methyl*cyclo*hexanone, b. p. 144—145°/12 mm, n_D^{30} 1.4560 (9.0 g, 8 %). (Found: C 80.2; H 12.3; O 7.5. Calc. for $C_{15}H_{28}O$: C 80.3; H 12.6; O 7.1.)

The disubstituted ketone gave an orange 2,4-dinitrophenylhydrazone, m. p. 144—145° (from ethanol-ethyl acetate). (Found: C 58.5; H 6.9; N 16.6. Calc. for $C_{17}H_{24}O_4N_4$: C 58.6; H 6.9; N 16.1.) The trisubstituted ketone did not form the analogous derivative, presumably for steric reasons.

Other 2,2-disubstituted cyclohexanones. These were prepared analogously employing the corresponding 2-substituted *cyclo*hexanone and alkyl bromide or iodide. The 2-ethyl-, 2-allyl- and 2-methyl-compounds served as starting materials except in the case of the preparation of 2-ethyl-2-phenyl*cyclo*hexanone, when 2-phenyl*cyclo*hexanone was alkylated as described above, with ethyl bromide. 2-Allyl-2-ethyl*cyclo*hexanone was prepared by alkylation of 2-allyl*cyclo*hexanone with ethyl iodide.

Oximes. The pyridine procedure was used. The ketone was heated under reflux with an equal weight of hydroxylamine hydrochloride in pyridine-absolute ethanol [5] for 3 h. The crystalline oximes were recrystallized from aqueous methanol and the liquid oximes were distilled in a high vacuum. They were obtained pure in at least 70—80 % yield.

The data pertinent to the ketones and oximes are summarized in Table 1.

ε,ε-Disubstituted caprolactams. It was found in this case that 85 % sulfuric acid and boron trifluoride [10] were inferior to polyphosphoric acid [6] as catalysts for Beckmann rearrangement of the oximes. The best experimental conditions found were the following.
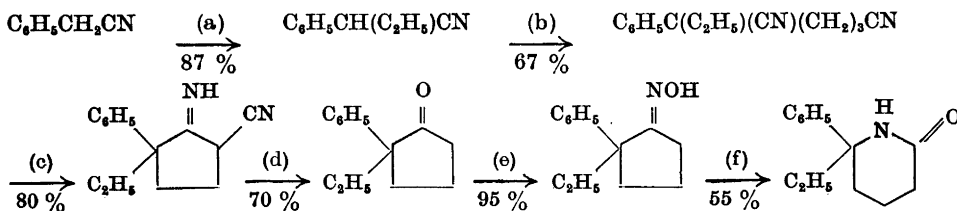
In a 3-necked flask provided with a teflon-blade stirrer, calcium chloride tube and a flask with a connecting rubber sleeve containing phosphorus pentoxide (30 g) was placed orthophosphoric acid (85 %, 30 g). The solid pentoxide was added in small portions with vigorous stirring during 15 min. Its container was then replaced by a thermometer. The polyphosphoric acid thus prepared was heated in an oil bath to 100° and the oxime (2 g) was added, causing the temperature to rise to *ca.* 115° during the first minute after addition. When the temperature had dropped to 105°, the reaction mixture was heated to 115° and thus maintained for 10 min. After cooling to 90°, the slightly yellow mixture was poured on to cracked ice (150 g). The resulting turbid solution was cooled to —10° in an ice-salt bath and aqueous potassium hydroxide (40 %, 100 ml) was added dropwise with vigorous stirring, keeping the temperature below —5°. The pH was then *ca.* 6.5 and the lactam was readily extracted with chloroform-ethyl acetate (10:1; 150 ml + 100 ml). The bright yellow solution was dried (magnesium sulfate) under nitrogen in the refrigerator. A change of color to red indicates occurrence of polymerization. The solvents were removed at water pump pressure under nitrogen and the residual oil was dissolved in carbon tetrachloride in order to remove any insoluble polymer which may have formed. Removal of the solvent from the filtrate under nitrogen at water pump pressure usually affords a dark oil which can be further purified either by distillation of small portions (2 g) in a high vacuum or by chromatography. In the latter case a solution of the lactam in carbon tetrachloride is poured on to a column of florex-celite (5:1) with successive elution by carbon tetrachloride-benzene and chloroform. Analytically pure lactam is present in the chloroform fractions.

Table 2 records the data pertinent to the lactams.

Table 2. ε,ε-Disubstituted caprolactams.

Lactam	Yield	B. p. °C	mm	C=O I.R. $\nu(cm^{-1})$	Emperical Formula	Analysis Calc. C	H	N	Found C	H	N
Et, Et	29	101—104	0.05	1 650	$C_{10}H_{19}ON$	71.0	11.3	8.3	71.6	11.0	7.9
Et, n—Bu	33	115—117	0.01	1 650	$C_{12}H_{23}ON$	73.0	11.8	7.1	72.3	11.3	7.3
Et, i—Bu	17	120—132	0.01	1 670	$C_{12}H_{23}ON$	73.0	11.8	7.1	72.8	11.6	7.2
Et, Ph	62	150—160	0.01	1 665	$C_{14}H_{19}ON$	77.4	8.8	6.5	77.0	8.6	6.4

6-Ethyl-6-phenyl-2-piperidone. This compound was prepared *via* the following reaction scheme:[11]

$C_6H_5CH_2CN$ $\xrightarrow[87\ \%]{(a)}$ $C_6H_5CH(C_2H_5)CN$ $\xrightarrow[67\ \%]{(b)}$ $C_6H_5C(C_2H_5)(CN)(CH_2)_3CN$

$\xrightarrow[80\ \%]{(c)}$ [structure with NH, CN, C6H5, C2H5] $\xrightarrow[70\ \%]{(d)}$ [structure with O, C6H5, C2H5] $\xrightarrow[95\ \%]{(e)}$ [structure with NOH, C6H5, C2H5] $\xrightarrow[55\ \%]{(f)}$ [piperidone structure with C6H5, C2H5, N—H, O]

(a) The procedure was exactly analogous to the synthesis of the corresponding methyl derivative [11]. The product had b. p. 115—120°/12 mm.

(b) The alkylation was carried out with γ-iodobutyronitrile (b. p. 72—73°/0.5 mm, n_D^{30} 1.5180), prepared from the γ-bromocompound [11].

The product was obtained after a forerun (b. p. 70—134°/0.01 mm), as an oil, b. p. 135.5—138°/0.01 mm, n_D^{30} 1.5040. (Found: C 78.7; H 7.5. Calc. for $C_{14}H_{16}N_2$: C 79.2; H 7.6.)

(c) Cyclization was effected by means of sodamide in dry benzene [11]. The major portion of the crystalline imine had m. p. 122° but an additional small amount of light brown crystals from the mother liquor, m. p. 112—116°, was sufficiently pure for further work. (Found: C 78.7; H 7.5; N 12.9. Calc. for $C_{14}H_{16}N_2$: C 79.2; H 7.6; N 13.2.)

(d) Hydrolysis of the imine (12.1 g) was effected by heating under reflux with acetic acid (100 ml), concentrated sulfuric acid (6 ml) and water (6 ml) for 4 h [11]. After dilution with water (120 ml), extraction with benzene and distillation, 2-ethyl-2-phenyl*cyclo*pentanone was obtained as an oil (7.5 g), b. p. 79—81°/0.01 mm, n_D^{30} 1.5283.

(e) A mixture of the above ketone (6.8 g), hydroxylamine hydrochloride (5 g), pyridine (20 ml) and absolute ethanol (20 ml) was heated under reflux for 4 h. After the usual workup, the colorless crystalline oxime (7.0 g) was obtained, m. p. 84—85° (from aqueous methanol). (Found: C 76.6; H 8.2; N 6.7. Calc. for $C_{13}H_{17}ON$: C 76.8; H 8.4; N 6.9.)

(f) Beckmann rearrangement with polyphosphoric acid (see above) gave the desired pyridone as a slightly yellow unstable oil, b. p. 120—125°/0.1 mm. It was best stored in the refrigerator under nitrogen. (Found: C 76.1; H 7.8; N 6.3. Calc. for $C_{13}H_{17}ON$: C 76.8; H 8.4; N 6.9.)

*Attempted preparation of 2,2-diethyl*cyclo*pentanone.* (a) To a solution of 2-ethyl*cyclo*pentanone [12] (22.4 g) in dry carbon tetrachloride (100 ml) was added a solution of sulfuryl chloride (18 ml) in dry carbon tetrachloride (30 ml) during 1 h. Stirring was continued for an additional 2 h and then the mixture was kept in the dark overnight. The solvent was removed at water pump pressure and the desired 2-chloro-2-ethyl*cyclo*pentanone was obtained as a colorless oil (22 g, 73 %), b. p. 78—82/20 mm, n_D^{30} 1.4658, which soon turned yellow. It was used immediately after distillation.

(b) Diethyl cadmium was prepared in the usual way by treating ethyl magnesium bromide (from ethyl bromide (32.7 g, 0.3 mole), magnesium (6.1 g, 0.25 g.atom) in dry ether (200 ml)) with anhydrous cadmium chloride (23.8 g, 0.13 mole). To this solution was added during 10 min a solution of freshly distilled 2-chloro-2-ethyl*cyclo*pentanone (15.1 g) in dry ether (80 ml). After stirring for 10 min at 0°, the dark gray suspension appeared greenish-white. Stirring at ice-bath temperature was continued for an additional 2 h and then the mixture was stirred overnight at room temperature. It was finally heated under reflux for 1 h. Ammonium chloride solution (0.5 M, 100 ml) was added with stirring at 0° followed by hydrochloric acid (10 %, 50 ml). The yellow ether layer was separated and the aqueous phase was extracted with several portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and dried (magnesium sulfate). Distillation gave a mixture of the desired but impure 2,2-diethyl*cyclo*pentanone (66 g), b. p. 82—92°/20 mm, after a forerun of 2-ethyl-*cyclo*pent-2-enone (2.8 g), b. p. 74—82°/20 mm, and higher boiling material (6 g).

Each of the first two fractions was treated with 2,4-dinitrophenylhydrazine. Chromatography of the benzene solutions on basic alumina showed that the first fraction consists mainly of the unsaturated ketone, whose red 2,4-dinitrophenylhydrazone had m. p. 200° (from ethanol-ethyl acetate). (Found: C 53.6; H 4.6; N 19.2. Calc. for $C_{13}H_{14}O_4N_4$: C 53.8; H. 4.9; N. 19.3.) However, this was accompanied by an orange-red 2,4-dinitrophenylhydrazone which formed the main component in the mixture of hydrazones obtained from the second fraction. This was the derivative of 2,2-diethyl*cyclo*pentanone and had m. p. 205° (from ethanol-ethyl acetate). (Found: C 56.2; H 6.2; N 17.5. Calc. for $C_{15}H_{20}O_4N_4$: C 56.2; H 6.3; N 17.5.)

This procedure is therefore impractical for obtaining the pure disubstituted ketone as dehydrochlorination of the starting material accompanied the desired alkylation reaction.

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