218. *Some Reactions of Thiacyclohexan-4-one and 1-Alkyl-4-piperidones.*

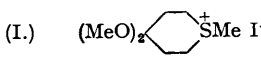
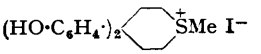
By H. M. E. Cardwell.

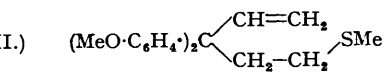
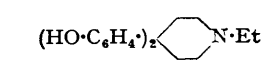
Thia*cyclo*hexan-4-one and 1-alkyl-4-piperidones react readily with methanol and methyl iodide to give dimethyl ketals. The reactions of these ketones with phenol and with phenylmagnesium bromide are described. The products showed no significant pharmacological activity.

Thia*cyclo*hexan-4-one on treatment with methyl iodide at room temperature slowly gives the methiodide (Bennett and Scorah, *J.*, 1927, 194). In an attempt to hasten the reaction these reactants were heated under reflux in methanol for 3 hours. The major product, however, was the ketal, 4 : 4-*dimethoxythia*cyclo*hexane methiodide* (I). At room temperature, in methanol, the major product was thia*cyclo*hexan-4-one methiodide.

Thia*cyclo*hexan-4-one methiodide was recovered unchanged after prolonged heating under reflux with methanol and methyl iodide. Evidently there are two independent reactions with different temperature coefficients, one reaction leading to thia*cyclo*hexanone methiodide which does not react further, and one leading presumably to the ketal sulphide which then reacts further with methyl iodide to give (I). The conversion of the ketone into the ketal sulphide, which may not be the rate-controlling step in the second reaction, is probably catalysed by traces of iodine or hydrogen iodide from the methyl iodide.

With the analogous 4-piperidones there was no evidence of two such independent reactions, for 1-ethyl-4-piperidone on being heated under reflux in methanol and methyl iodide gave a quantitative yield of 4 : 4-*dimethoxy*-1-*methyl*-1-*ethylpiperidinium iodide*, whilst 4-keto-1 : 1-dimethylpiperidinium iodide on similar treatment gave a good yield of 4 : 4-*dimethoxy*-1 : 1-

(I.)  (II.) 

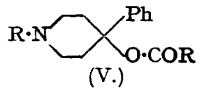
(III.)  

dimethylpiperidinium iodide. Substitution of ethyl iodide for methyl iodide in these reactions led to complex mixtures. Addition of methyl iodide to a refluxing solution of thia*cyclo*hexanone or the piperidones in ethanol also gave complex mixtures, but in the former case some 4 : 4-*diethoxythia*cyclo*hexane methiodide* was isolated. In *iso*propanol the piperidones react normally with methyl iodide to give ketone methiodides (Cardwell and McQuillin, *J.*, 1949, 708) but with ethyl iodide complex mixtures were obtained and in the experiment with 1-ethyl-4-piperidone a *substance* of empirical formula $C_{18}H_{36}O_3N_2I_2$ (corresponding to two molecules of 4-keto-1 : 1-diethylpiperidinium iodide plus an atom of oxygen) was isolated in low yield. Since the completion of this work McElvain and McMahon (*J. Amer. Chem. Soc.*, 1949, **71**, 901) have reported that 4-ketopiperidine hydrochloride on recrystallisation from ethanol–ether gives 4 : 4-diethoxypiperidine hydrochloride.

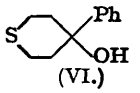
Thia*cyclo*hexan-4-one on being heated with phenol and methyl iodide gave a moderate yield of 4 : 4-*di*-p-*hydroxyphenylthia*cyclo*hexane methiodide* (II). The structure of this compound was confirmed by its independent preparation from thia*cyclo*hexan-4-one and phenol in the presence of concentrated hydrochloric acid, followed by treatment of the phenolic fraction with methyl iodide. In an attempt to prepare the dimethyl ether of this compound by treating it with diazomethane and subsequently with methyl iodide and potassium carbonate the only isolated product was 5-*methylthio*-3 : 3-*di*-p-*methoxyphenylpent*-1-*ene* (III).

1-Ethyl-4-piperidone with phenol and concentrated hydrochloric acid similarly gave 4 : 4-*di*-p-*hydroxyphenyl*-1-*ethylpiperidine* (IV) (cf. von Braun, *Annalen*, 1929, **472**, 1) which was characterised as the *acetate*, *methiodide*, and the *methiodide* of the diacetyl derivative.

Outstanding analgesic activity has been discovered in compounds of the general formula (V) by Jensen and Lundquist (*Dansk Tidsskr. Pharm.*, **1943**, **17**, 173); preparation of the sulphur analogue would have been of interest. Phenylmagnesium bromide and thia*cyclo*hexan-4-one gave a good yield of 4-*hydroxy*-4-*phenylthia*cyclo*hexane* (VI). Attempts to prepare the corresponding acetoxy-compound were fruitless, acetic anhydride in the cold giving 4-phenylthia*cyclo*hex-3-ene (characterised as the *methiodide*), whilst acetyl chloride and pyridine in the cold gave an intractable mixture of products. Similarly phenylmagnesium bromide and



(V.)



(VI.)

$(NMe_2 \cdot CH_2 \cdot CH_2)_2 > CPh \cdot OR$

(VII.)

bis-2-dimethylaminoethyl ketone dihydrochloride gave a good yield of 1 : 5-*bisdimethylamino*-3-*phenylpentan*-3-*ol* (VII; R = H). On treatment of this with acetyl chloride in cold acetone 1 : 5-*bisdimethylamino*-3-*acetoxy*-3-*phenylpentane dihydrochloride* (VII; R = Ac) was obtained.

Dr. White of the Biological Division of these Laboratories reports that the phenol (IV) and its derivatives were devoid of significant pharmacological activity, unlike the related 3-piperidino-1 : 1-diphenylpropane (Schaumann, *Med. und Chem.*, **1942**, **4**, 229). The methiodide of (VI) and the dihydrochloride of (VII) (R = Ac) were also of little pharmacological interest.

Experimental.

(M. p.s are uncorrected. Micro-analyses are by Mr. A. Bennett.)

*Reaction of Thia*cyclo*hexan-4-one with Methyl Iodide and Methanol.*—(a) *At the boiling point.* Thia*cyclo*hexan-4-one (2 g.) in refluxing methanol (20 c.c.) was treated with methyl iodide (10 c.c.). After being heated under reflux for 2½ hours the hot, red solution was diluted with ether until crystallisation started. 4 : 4-*Dimethoxythia*cyclo*hexane methiodide* (4·1 g., 78%), m. p. 119—120°, was collected; it recrystallised from ethanol in colourless rods or needles, m. p. 123—125° (decomp.) (Found: C, 31·9; H, 5·5; S, 10·5; I, 41·8. $C_8H_{17}O_2SI$ requires C, 31·6; H, 5·6; S, 10·5; I, 41·8%). On further dilution of the mother liquors with ether, thia*cyclo*hexan-4-one methiodide (0·45 g., 7·5%), m. p. 80—85°, was obtained (Cardwell, *J.*, 1949, 715, gives m. p. 82—85°).

(b) *At room temperature.* Thia*cyclo*hexan-4-one (2 g.) was set aside at room temperature for 5 days with methanol (20 c.c.) and methyl iodide (10 c.c.). The solid (2·9 g.), m. p. 86—87°, which separated was collected by filtration. A further quantity (1·9 g.), m. p. 75—76°, was obtained on dilution with ether. One recrystallisation raised the melting point of this second crop to 84—86°; these two crops did not depress the melting point of an authentic specimen of thia*cyclo*hexan-4-one methiodide. On further dilution of the mother liquors with ether a very small quantity of impure 4 : 4-dimethoxythia*cyclo*hexane methiodide, m. p. 99—104°, was obtained. One recrystallisation from *n*-propanol raised the melting point to 121—123°.

4 : 4-*Dimethoxythia*cyclo*hexane Methiodide* (alternative preparation).—Thia*cyclo*hexan-4-one (2 g.), methyl orthoformate (5 c.c.), and toluene-*p*-sulphonic acid (0·5 g.) were mixed and set aside at room temperature for 24 hours. A small quantity of anhydrous potassium carbonate was added, and the mixture was filtered, the residue being washed with dry ether. The solvents were removed from the filtrate under reduced pressure on the steam-bath. The residue was triturated with ether and filtered, and the filtrate after removal of the ether *in vacuo* was treated with excess of methyl iodide. After 24 hours at room temperature the methiodide was collected and crystallised from *n*-propanol. The resulting colourless needles melted at 120—121°, alone or mixed with 4 : 4-dimethoxythia*cyclo*hexane methiodide prepared as in (a) above. The sample (a) on treatment with dilute aqueous hydriodic acid followed by removal of solvent under reduced pressure and crystallisation of the residue from methanol gave colourless prisms of thia*cyclo*hexan-4-one methiodide, m. p. 81—84° alone or mixed with an authentic specimen.

4 : 4-*Diethoxythia*cyclo*hexane Methiodide.*—Thia*cyclo*hexan-4-one (2 g.) and methyl iodide (10 c.c.) in ethanol (20 c.c.) were refluxed for 3½ hours. On cooling in ice a solid (1·9 g.) separated; it was difficult to purify and analyses were variable. It was probably a mixture of ketals and ketone methiodide. On dilution of the mother-liquors with ether a further quantity (1·0 g.) (m. p. 102—105° with shrinking from 80°) was obtained. After four crystallisations from *n*-propanol 4 : 4-*diethoxythia*cyclo*hexane methiodide* was obtained in low yield as colourless slender prisms, m. p. 120—120·5° (decomp.) (Found: C, 36·3; H, 6·1; S, 10·0; I, 38·3. $C_{10}H_{21}O_2SI$ requires C, 36·2; H, 6·3; S, 9·6; I, 38·3%).

4 : 4-*Dimethoxy*-1 : 1-*dimethylpiperidinium Iodide.*—4-Keto-1 : 1-dimethylpiperidinium iodide (5 g.) was heated under reflux for 6 hours with methanol (100 c.c.) and methyl iodide (15 c.c.). On dilution of the solution with ether a solid (4·7 g.) was obtained; this crystallised from methanol–ether with varying quantities of methanol of crystallisation. From *n*-propanol 4 : 4-*dimethoxy*-1 : 1-*dimethylpiperidinium iodide* crystallised in colourless prisms, m. p. 180—181° (decomp.) (Found: C, 35·8; H, 6·6. $C_9H_{20}O_2NI$ requires C, 35·9; H, 6·6%). A mixture with 4-keto-1 : 1-dimethylpiperidinium iodide (m. p. 190—191°) melted at 168—170°.

4 : 4-*Dimethoxy*-1-*methyl*-1-*ethylpiperidinium Iodide.*—Methyl iodide (10 c.c.) was added to a refluxing solution of 1-ethyl-4-piperidone (3·5 g.) in methanol (25 c.c.), and heating under reflux was continued for 4½ hours. Dilution with ether gave an oil which soon crystallised (yield, 8·0 g.); recrystallisation from *iso*propanol gave 4 : 4-*dimethoxy*-1-*methyl*-1-*ethylpiperidinium iodide* as pale yellow prisms (7·1 g.), m. p. 159—161° (Found: N, 4·3; I, 40·2. $C_{10}H_{22}O_2NI$ requires N, 4·4; I, 40·3%). On treatment with

dilute hydriodic acid and removal of the solvent under reduced pressure this ketal gave a solid from which, on extraction with hot *iso*propanol, 4-keto-1-methyl-1-ethylpiperidinium iodide, m. p. 183—184° alone or mixed with an authentic specimen, was obtained. A mixture of this ketone with 4-keto-1 : 1-dimethylpiperidinium methiodide (m. p. 194—195°) melted at 184—186°; mixed melting points in this series are not therefore of much significance.

4 : 4-*Di*-p-*hydroxyphenylthia*cyclo*hexane Methiodide.*—(*a*) Thia*cyclo*hexan-4-one (2 g.), phenol (20 g.), and methyl iodide (10 c.c.) were heated under reflux on a steam-bath for 4 hours. The hot, red solution was diluted with ether, the resulting red gum was triturated with hot ethanol, and the cream-coloured solid (3·2 g.) was filtered off. 4 : 4-*Di*-p-*hydroxyphenylthia*cyclo*hexane methiodide* crystallised from methanol in colourless spear-shaped prisms, m. p. 200—201° (decomp.) (rapid heating) (Found : C, 50·6; H, 5·2; S, 7·6; I, 29·6. $C_{18}H_{21}O_2SI$ requires C, 50·5; H, 4·9; S, 7·5; I, 29·7%).

(*b*) Thia*cyclo*hexan-4-one (2·0 g.), phenol (3·2 g.), acetic acid (1 c.c.), and concentrated hydrochloric acid (1 c.c.) were mixed and heated at 50° for 9 hours. The solvent was removed under reduced pressure, and the residue was shaken with ether and 2N-sodium hydroxide. The aqueous layer was acidified and extracted with ether, the ethereal layer was dried (Na_2SO_4), and the residue, obtained by evaporation of the ether, was treated with excess of methyl iodide. After 12 hours at room temperature the excess of methyl iodide was decanted. The residue crystallised from methanol in colourless prisms, m. p. 203° (decomp.) alone or mixed with the sample prepared by method (*a*).

5-*Methylthio*-3 : 3-*di*-p-*methoxyphenylpent*-1-*ene.*—4 : 4-Di-*p*-hydroxyphenylthia*cyclo*hexane methiodide (479 mg.) in methanol (10 c.c.) was treated with ethereal diazomethane (6—8 mols.). After 3 hours at room temperature the solvents were evaporated in a stream of air. The residue still gave a positive diazo-coupling reaction and was therefore heated under reflux in methanol with excess of methyl iodide and potassium carbonate for 2½ hours. The solution was filtered, diluted with ether, and filtered again. The filtrate was evaporated to dryness, and the residue was extracted with ethanol and filtered. After evaporation of the ethanol the residue was crystallised from *n*-propanol; colourless needles (189 mg.), m. p. 91—93°, were obtained. Recrystallisation of these from *iso*propanol gave rosettes of colourless needles of 5-*methylthio*-3 : 3-*di*-p-*methoxyphenylpent*-1-*ene*, m. p. 92—93° (Found : C, 73·6; H, 7·0; S, 9·8; I, nil. $C_{20}H_{24}O_2S$ requires C, 73·2; H, 7·3; S, 9·8; I, nil%).

4 : 4-*Di*-p-*hydroxyphenyl*-1-*ethylpiperidine.*—1-Ethyl-4-piperidone (6·3 g.), phenol (10 g.), acetic acid (25 c.c.), and concentrated hydrochloric acid (15 c.c.) were mixed and heated on the steam-bath for 15 hours. Excess of solvent was removed under reduced pressure, and the residue was digested with dilute hydrochloric acid and then cooled. Filtration gave a white crystalline hydrochloride (13·9 g., 83%), which was shaken with ammonia solution (*d* 0·88) and chloroform. Evaporation of the chloroform layer gave 4 : 4-*di*-p-*hydroxyphenyl*-1-*ethylpiperidine* which crystallised from aqueous ethanol in pale pink prisms (8·9 g., 60%), m. p. 234—235° (decomp.) (Found : C, 76·8; H, 8·2; N, 4·9, 4·5. $C_{19}H_{23}O_2N$ requires C, 76·8; H, 7·7; N, 4·7%).

The *acetate* was prepared by dissolving the base in acetone and adding acetic acid. It crystallised from ethyl acetate–ethanol in fine, colourless needles, shrinking from 110° and effervescing at 140° (Found : N, 4·0. $C_{19}H_{23}O_2N,C_2H_4O_2$ requires N, 3·9%). The *methiodide* crystallised from ethanol–ether in colourless prisms, m. p. 230—232° (decomp.) (Found : N, 3·1. $C_{20}H_{26}O_2NI$ requires N, 3·2%). The *diacetyl methiodide* crystallised from methanol in colourless needles, m. p. 279—280° (decomp.) (Found : N, 2·8; I, 23·3. $C_{24}H_{30}O_4NI$ requires N, 2·7; I, 24·3%).

4-*Hydroxy*-4-*phenylthia*cyclo*hexane.*—Thia*cyclo*hexan-4-one (11·6 g.) in ether (60 c.c.) was added slowly with stirring to an ice-cold Grignard solution prepared from bromobenzene (23·6 g.), magnesium turnings (3·7 g.), and ether (30 c.c.). After ½ hour at 0° the solution was heated under reflux for one hour, cooled to 0°, and decomposed with ice, ammonium chloride, and acetic acid. The ethereal extract was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and distilled. The fraction boiling at 118—128°/0·05 mm. rapidly solidified (yield 12·8 g.). 4-*Hydroxy*-4-*phenylthia*cyclo*hexane* crystallised from *cyclo*hexane in colourless prisms, m. p. 75—76° (Found : C, 67·9; H, 7·2; S, 16·5. $C_{11}H_{14}OS$ requires C, 68·0; H, 7·2; S, 16·5%). The *methiodide* crystallised from methanol in colourless prisms, m. p. 165—166° (decomp.) (Found : S, 9·3; I, 37·7. $C_{12}H_{17}OSI$ requires S, 9·5; I, 37·8%).

4-*Phenylthia*cyclo*hex*-3-*ene Methiodide.*—4-Hydroxy-4-phenylthia*cyclo*hexane (4·0 g.) was suspended in acetic anhydride (5 c.c.). A few drops of concentrated sulphuric acid were added with cooling, and the mixture was set aside for 24 hours, then poured on ice, and extracted with chloroform. After the solution had been washed with aqueous sodium hydrogen carbonate and dried (Na_2SO_4), the solvent was removed *in vacuo*. The residue was crystallised from *n*-hexane at a low temperature and gave 4-phenylthia*cyclo*hex-3-ene, m. p. 49·5—50·5°. Before this sample could be analysed it decomposed into a deep-brown liquid. Immediate treatment of the crystalline solid with methyl iodide gave the 4-*phenylthia*cyclo*hex*-3-*ene methiodide* which crystallised from ethanol in prisms, m. p. 159—160° (decomp.) (Found : S, 10·4; I, 40·5. $C_{12}H_{15}SI$ requires S, 10·1; I, 39·9%).

1 : 5-*Bisdimethylamino*-3-*phenylpentan*-3-*ol.*—Bis-2-dimethylaminoethyl ketone diyhydrochloride (Cardwell, preceding paper) (12·3 g.) was added slowly with stirring to an ice-cold Grignard solution prepared from bromobenzene (39·3 g.), magnesium turnings (6·1 g.), and ether (500 c.c.). After one hour at 0° the mixture was heated under reflux for ½ hour, cooled, and poured on ice and ammonium chloride. The mixture was acidified with acetic acid and extracted with ether, and the aqueous layer was cooled to 0°, made alkaline with aqueous sodium hydroxide, and treated with about half the quantity of potassium carbonate needed for saturation. The mixture was extracted several times with ether, and the extract was dried and the solvent removed, whereupon the residue (7 g.) crystallised. After several recrystallisations from light petroleum (b. p. 40—60°) at about −50°, 1 : 5-*bisdimethylamino*-3-*phenylpentan*-3-*ol* was obtained in colourless prisms, m. p. 93—94° (Found : C, 72·0; H, 10·3; N, 10·8. $C_{15}H_{26}ON_2$ requires C, 72·0; H, 10·4; N, 11·2%). The *di*(*hydrogen oxalate*) crystallised from aqueous ethanol in colourless needles, m. p. 160—162° (Found : N, 6·5. $C_{15}H_{26}ON_2,2C_2H_2O_4$ requires N, 6·5%). The *dimethiodide* crystallised from methanol–ether in colourless prisms, m. p. 195—198° (decomp.) (Found : N, 5·4; I, 47·5. $C_{17}H_{32}ON_2I_2$ requires N, 5·2; I, 47·6%).

1 : 5-*Bisdimethylamino*-3-*acetoxy*-3-*phenylpentane Dihydrochloride.*—1 : 5-Bisdimethylamino-3-phenyl-

pentan-3-ol (4·5 g.) in dry acetone (50 c.c.) was treated dropwise with acetyl chloride (1·19 c.c.). After 2½ hours at room temperature the mixture was filtered, and the white solid was crystallised twice from *iso*propanol. 1 : 5-*Bisdimethylamino*-3-*acetoxy*-3-*phenylpentane dihydrochloride* formed colourless, glistening plates, m. p. 204—205° (slow heating; if the solid was inserted at 190°, it effervesced, resolidified, and finally melted at 198—200°) (Found: N, 7·9; Cl, 19·7. $C_{17}H_{28}O_2N_2,2HCl$ requires N, 7·7; Cl, 19·5%).

Abnormal Product from the Reaction of 1-*Ethyl*-4-*piperidone with Ethyl Iodide.*—1-Ethyl-4-piperidone (51 g.), *iso*propanol (100 c.c.), and ethyl iodide (75 c.c.) were heated under reflux on the steam-bath for 3 hours. On cooling an oil separated; this oil was extracted with hot ethanol, and the undissolved solid was crystallised several times from methanol. The resulting pale-yellow prisms did not melt below 300°. Analysis suggested that the substance contained two molecular proportions of 4-keto-1 : 1-diethylpiperidinium iodide to one atomic proportion of oxygen (Found: C, 37·3; H, 6·1; N, 4·5; I, 43·6. $C_{18}H_{36}O_3N_2I_2$ requires C, 37·2; H, 6·2; N, 4·8; I, 43·6%). This substance represented only a small fraction of the 1-ethyl-4-piperidone used. Dilution of the *iso*propanol and ethanol mother-liquors with ether gave large quantities of an intractible oily mixture of ethiodides.

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