

stimulation. Calycanthine caused a very feeble contraction of the isolated guinea pig's uterus in the concentration of 1:10,000.

SUMMARY

1. The acute toxicity of calycanthine hydrochloride has been determined in mice, rats, rabbits and frogs. Toxic doses cause stimulation in the first three species of animals, but depression and prostration in frogs.

2. Calycanthine hydrochloride induces hyperglycemia in rabbits when injected

intravenously. No apparent changes in the counts of erythrocytes and leucocytes take place.

3. Calycanthine hydrochloride reduces blood pressure and depresses the cardiac contraction in anesthetized cats. Fall of blood pressure has also been observed in anesthetized dogs.

4. Calycanthine hydrochloride produces stimulation of the isolated rabbit's intestines and uterus. It has only slight effect upon the isolated guinea pig's uterus.

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Ketone Alcohols*†

I. Derivatives of 2-Methyl-pentanol-2-one-4

By Clifton Eugene Miller‡

It was reported in a previous paper (1) that preliminary pharmacological tests indicated that the dibromoureide of 2-methyl-pentanol-2-one-4 (diacetone alcohol) possessed hypnotic action. It seemed of interest therefore to prepare other derivatives and

to determine, if possible, whether the degree of hypnosis might be increased or diminished by the substitution of various groups or atoms. This paper presents an introductory report on the preparation of certain acetyl, chlorine, nitrogen and sulfur derivatives of 2-methyl-pentanol-2-one-4.

EXPERIMENTAL

Preparation of 2-Methyl-2-chloro-pentanone-4.—One mole of 2-methyl-pentanol-2-one-4 and three moles of hydrochloric acid, sp. gr. 1.175, were placed

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in a liter separatory funnel and shaken vigorously for 15 min. following the method of Norris (2). The mixture became hot and rapidly assumed a dark red color. The addition of calcium chloride caused two separate layers to be formed. The lower one, which consisted chiefly of water, hydrochloric acid and some acetone, was discarded. The upper layer was carefully washed with a saturated solution of sodium carbonate until neutral to litmus and then dried over anhydrous sodium sulfate. The dried product was distilled in vacuum and the fraction boiling at 45–47° C./25 mm. was collected. This distillate was colorless, had an aromatic odor and gave a positive halogen test. A peculiar phenomenon observed repeatedly at this point was the rapid darkening in the color of the liquid to a deep brownish red. This darkened product possessed a sp. gr. of 0.9712 at 15° C.; $n_{20}^{\circ} = 1.4340$; was insoluble in water and did not react with phenyl isocyanide. A small amount of this product agitated with water gave a positive test for halogen showing possibly a partial hydrolysis in contact with water. Several attempts to remove this brownish red color failed.

Preparation of the Amine of 2-Methyl-2-chloropentanone-4.—A mixture of 21 Gm. of potassium phthalamide (3) and 30 Gm. of 2-methyl-2-chloropentanone-4 was placed in a 500-cc. flask and heated on an oil bath to gentle refluxing for a period of 10 hrs. The mixture gradually solidified after which the solid material was then taken up in 850 cc. of 98% alcohol and refluxed for half an hour on a water bath. The alcoholic liquid which assumed a reddish yellow color was evaporated under reduced pressure and yielded tan-colored crystals melting at 228° C. Repeated recrystallization from dilute alcohol raised the melting point to 234° C. This product upon treatment with carbon disulfide did not yield a residue upon evaporation of the solvent. The nearly colorless crystals mixed with phthalamide melted at 234° C. It is believed, therefore, following the method just outlined, that at present the formation of an amine is not possible.

Preparation of 2-Methyl-2-acetyl-pentanone-4.—Fifty grams of acetyl chloride was added by means of a dropping funnel to 62 Gm. of 2-methyl-pentanol-2-one-4 and the mixture was warmed to about 80° C. on a water bath to start the reaction. Hydrochloric acid gas was given off and a noticeable darkening in color occurred. The resultant mixture was treated with saturated sodium carbonate solution until neutral to litmus, whereupon the upper layer which separated was dried over calcium chloride and then distilled. The physical properties and boiling points are given in the following table.

TABLE I

Tube	B. P., ° C.	Color	Odor
1	44–47/17 mm.	Dark	Sharp
2	44–47/14 mm.	None	Faint
3	50–52/14 mm.	None	Sweet

The distillates of tubes 2 and 3 were combined and redistilled. The fraction boiling at 46–47° C./15 mm. possessed a sweet odor, sp. gr. of 0.9332 at 15° C., and was insoluble in water. A 1.8916-Gm. sample required 0.676 Gm. of KOH for saponification; whereas, calculated for $C_8H_{14}O_3$, 0.671 Gm. of KOH is required.

Preparation of the Thiol Analogue of 2-Methyl-pentanol-2-one-4.—Various methods for the linking of sulfur to carbon are available (4). A survey of these methods and others which presented themselves was carried out in search of a suitable method for introducing atomic sulfur to a carbon chain by the breaking of a C=O group.

The Use of H₂S.—Fifty cubic centimeters of 2-methyl-pentanol-2-one-4 was saturated with hydrogen sulfide until the liquid was light yellow in color. The resultant mixture was then heated to 80° C. on a water bath until the odor of hydrogen sulfide had disappeared and then allowed to cool to room temperature, filtered and poured into a saturated sodium sulfite solution. After vigorous shaking the mixture was filtered, allowed to separate into two layers and the aqueous layer discarded. Distillation of this upper layer showed the product to be a mixture. The fraction boiling at 36–42° C./18 mm. gave a qualitative test for sulfur.

The Use of H₂S and CaCl₂.—In the hope of obtaining more definite results, the above process was repeated with the addition of 10 Gm. of CaCl₂ as a dehydrating agent. This method was discontinued because poor yields were obtained.

The Use of Sulfurated Potash.—Fifty grams of sulfurated potash, calculated as K_2S_3 , was washed once with 95% alcohol and filtered with suction. This moist residue was placed in a 500-cc. flask and a mixture of 50 cc. of benzene and 100 cc. of 2-methyl-pentanol-2-one-4 added. The mixture was then heated under reflux on an electric plate for 6 hrs., during which time the solution gradually darkened to a chocolate-brown, and a gas was evolved. The resulting solution was allowed to cool to room temperature, filtered and the filtrate placed in a salt-ice bath to insure complete precipitation of sulfur. After filtering a second time the liquid was subjected to fractional vacuum distillation to remove benzene and acetone which were discarded.

The high-boiling fraction upon redistillation yielded 40 cc. of a faintly yellow liquid boiling at 70–72° C./22 mm. This liquid had a sp. gr. of 0.9441 at 15° C.; $n_{20}^{\circ} = 1.4247$; was found to be miscible with water, contained at least one double bond inasmuch as it rapidly decolorized a chloroform solution of bromine. The product gave a positive sodium nitroprusside test for sulfur. Degradation with potassium hydroxide and heat yielded acetone, sulfur and possibly isopropyl mercaptan. Further investigation on this product is being carried out and will be reported in a future paper.

CONCLUSIONS

1. Several derivatives of 2-methyl-pentanol-2-one-4 have been prepared and some of their physical properties noted.

2. Efforts to form the amine of 2-meth-

yl-2-chloro-pentanone-4 have thus far been unsuccessful.

3. Some preliminary work on the introduction of sulfur into 2-methyl-pentanol-2-one-4 has been completed.

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Ketone Alcohols*[†]

II. Derivatives of the Polymerization of Pentanone-3

By Kathryn C. Odney and Clifton E. Miller[‡]

Certain derivatives of 2-methyl-pentanol-2-one-4 have been prepared (1). The pharmacological action shown by one of these derivatives made it seem worth while to prepare higher homologues, confining our efforts to the even-numbered carbon atom compounds, with the intention of determining the effect of length of carbon chain on the pharmacological action of ketone alcohols. The authors present a report of the work completed thus far on the polymerization of pentanone-3 to form 3-ethyl-octanol-3-one-6.

EXPERIMENTAL

The pentanone-3 employed in this investigation was prepared by the following methods: oxidation of diethyl carbinol by the use of Beckman's oxidizing mixture, employing variable amounts of benzene as a carrying agent; consistently small yields were obtained following this procedure, therefore method two consisting of the dry distillation of calcium propionate was employed with favorable results.

The polymerization of pentanone-3 was accomplished by placing 200 cc. of pure ketone in a 500-cc.

three-neck flask fitted with a Soxhlet extractor containing a thimble of barium hydroxide, a thermometer for recording internal temperature and a device for removal of samples. It was found advantageous to place two long water-cooled condensers above the Soxhlet extractor to minimize the amount of loss by volatilization. Heating, with a flask temperature of 110-115° C., was continued for a period of 100 hrs. during which time the mixture became dark in color and samples were withdrawn at varying intervals for refractive index determinations. The results are summarized in the following table. All readings were made at 20° C.

TABLE I

Hours of Heating	Average Reading	Hours of Heating	Average Reading
0	1.3929	50	1.3947
5	1.3937	60	1.3948
15	1.3937	70	1.3943
20	1.3940	80	1.3951
30	1.3940	90	1.3943
40	1.3940	100	1.3948

It was apparent from the results obtained that a complete polymerization did not occur and this is in accord with the published results of Voitila (2) who found incomplete polymerization of methyl-ethyl ketone under similar conditions. A possible explanation of the oscillation in readings may be that when the samples were withdrawn from time to time the ratio between the polymerized and unpolymerized products was not always the same.

After completing this heating period, the product was allowed to cool to room temperature and filtered.

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