TABLE II

ANALYTICAL DATA ON NEW COMPOUNDS

Compound	%C	%H	Saponification value	Compound	%C	%H	Saponification value
Calcd.	74.93	12.59	256.3	Calcd.	74.93	12.59	256.3
3–13	74.81	12.66	259.3	10–6	74.85	12.43	258.1
5–11	74.94	12.46	256.7	11–5	74.92	12.69	258.2
6–10	74.88	12.59	256.3	13–3	74.94	12.51	258.8
9–7	74.91	12.61	258.0	15–1	75.10	12.65	259.5

Acknowledgment.—The authors wish to express their thanks to Messrs. Deitz and Boone for the determination of the freezing points, and to Messrs. Wenzel, Cox and Leikensohn for certain intermediates.

Summary

Fifteen isomeric esters have been prepared and their more common physical constants have been determined.

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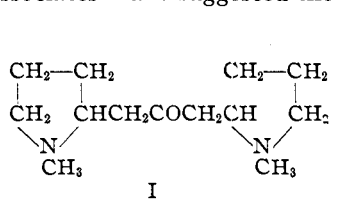
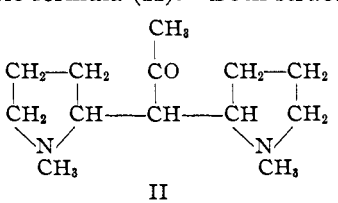
The Structure of Cuscohygrine. Synthesis of Ethyl Homohygrinate

BY W. E. SOHL AND R. L. SHRINER

Two structures have been proposed for cuscohygrine, one of the alkaloids associated with cocaine occurring in "cusco" leaves, a variety of South American coca. The structure (I) was suggested by Liebermann and Cybulski,[1] who were the first to isolate and study the alkaloid. Hess and his associates[2] have suggested the isomeric formula (II). Both structures



I

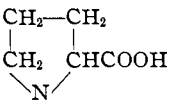


II

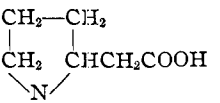
are in agreement with the fact that cuscohygrine gives the typical reactions for a ketone group[2a] and that oxidation with chromic acid yields hygrinic acid (III) whose structure had been established by Willstätter.[3] Although Formula I is the only one which is consistent with the formation of *n*-undecane and *n*-undecanol-6 by an exhaustive methylation and degradation[4] of dihydrocuscohygrine, the structure represented by II has been

(1) Liebermann and Cybulski, *Ber.*, **28**, 578 (1895).
(2) (a) Hess and co-workers, *ibid.*, **53**, 781 (1920); (b) **54**, 2310 (1921); (*c*) **48**, 1986 (1915).
(3) Willstätter, *ibid.*, **33**, 1160 (1900).
(4) Hess and Bappert, *Ann.*, **441**, 137 (1925).

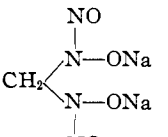
favored chiefly because the degradation of cuscohygrine by Traube's reaction[5] (nitric oxide plus sodium ethoxide) produced homohygrinic acid (IV) and the sodium salt of methylene di-isonitramine[2a] (V) which was supposed to come from the methyl ketone group of Formula (II).



III



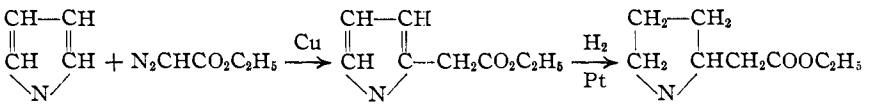
IV



V

Homohygrinic acid was also produced in very small amounts in the chromic acid oxidation of cuscohygrine.[6] Its structure was deduced from analyses and has not previously been confirmed by synthesis. In the present study the structure of homohygrinic acid (IV) has been definitely established by the synthesis of its ethyl ester.

All attempts to rearrange ethyl 1-pyrrylacetate resulted only in the formation of pyridine,[7] but by means of the recently described reaction[8] between 1-methylpyrrole and diazoacetic ester the 1-methyl-2-pyrrylacetic ester (I) was readily obtained. By means of a special reduction procedure this pyrrole compound was reduced catalytically to the 1-methyl-2-pyrrolidine acetic ester (II) with hydrogen and a platinum catalyst.[9]



I II

For purposes of comparison, a sample of cuscohygrine whose composition and molecular weight were checked was subjected to the Traube reaction[5] following exactly the procedure described by Hess[2a] and ethyl homohygrinate isolated. The data in Table I show the comparisons between the synthetic product and that obtained from cuscohygrine.

Although the product obtained by degradation distilled within a one-degree range it was not quite pure as evidenced by the differences in density and refractive index. Since the amount of ethyl homohygrinate obtained was about one gram it was impossible to fractionate it further in order to check the physical constants exactly. Hence, three solid derivatives were prepared and recrystallized to constant melting point. The mixed melting point determinations of all three pairs of solid derivatives

(5) Traube, *Ann.*, **300**, 81 (1898).

(6) Trier, Winterstein and Trier, "Die Alkaloide," Berlin, 1927, Vol. I, p. 242.

(7) Sohl and Shriner, THIS JOURNAL, **53**, 4168 (1931).

(8) Nenitzescu and Salomonica, *Ber.*, **64**, 1928 (1931).

(9) Adams, Voorhees and Shriner, "Organic Syntheses," John Wiley and Sons, New York, 1932, Coll. Vol. I, p. 452.

TABLE I

COMPARISON OF THE PROPERTIES OF ETHYL HOMOHYGRINATE FROM DEGRADATION AND SYNTHESIS

Property	From cuscohygrine	From synthesis	Literature
Boiling point	72–73° at 6 mm.	78° at 6 mm.	89–90°[2a] at 15 mm.
M. p. of derivatives, °C.			
(a) Methiodide	120–121	121–122	105–106[2a]
(b) Picrate	112–113	112–113	113°[2a]
(c) Chloroplatinate	Liquid	Liquid	....
(d) Chloraurate	134–135	133–134	134°[6]
Density	0.9900_4^{20}	0.9683_4^{20}	....
Refractive index	1.4501^{20}	1.4490^{20}	....

showed no depression and all analyzed correctly, thus establishing the structure of homohygrinic acid as IV.

Moreover, a study of the conditions under which ketones react with nitric oxide and sodium ethylate according to Traube's procedure demonstrated that the sodium methylene di-isonitramine (V) was produced from the ethyl alcohol used as a solvent[10] and not from cuscohygrine at all. This salt was formed from ethyl alcohol in the absence of cuscohygrine and no such precipitate was obtained when the reaction was carried out in methyl alcohol. In addition, Traube[5] showed that in ketones of the formula CH_3COCH_2R, the nitric oxide and sodium ethylate attacked the methylene group and not the methyl group. The same is true of methyl acetoacetic ester where it is the methine carbon atom which reacts.

Finally, it was established that cuscohygrine does not give the iodoform test which is characteristic of methyl ketones. In order to be certain that the tertiary amino group did not affect adversely the application of this test, the ketone $(C_2H_5)_2NCH_2CH_2COCH_3$ was synthesized and found to give a positive iodoform test. Sodium hypobromite and cuscohygrine gave no bromoform and no acetic acid; the production of which represents one other possible phase of the haloform reaction.[11]

Two remaining objections to Formula I have been cited. It is stated that such a compound should condense with benzaldehyde whereas no such reaction seems to take place. Although diethyl ketone does condense with benzaldehyde[12] the methyl ketones generally react much more readily[13] and hence the non-reactivity of cuscohygrine with benzaldehyde really counts as evidence against formula II.

Treatment of cuscohygrine with bromine yielded a red compound containing three atoms of bromine. This derivative, which may be a mono-

(10) Stechow [*Ber.*, **57**, 1615 (1924)] has also pointed out that ethyl alcohol, nitric oxide and sodium ethylate produce sodium methylene di-isonitramine and that conclusions regarding structure cannot be drawn from this phase of the Traube reaction.

(11) Woodward and Fuson, THIS JOURNAL, **55**, 3472 (1933).

(12) Vorländer, *Ann.*, **294**, 296 (1897).

(13) Claisen, *Ber.*, **14**, 2471 (1881); Harries and Müller, *ibid.*, **35**, 968 (1902); Harries and Bromberger, *ibid.*, **35**, 3089 (1902).

bromo-dihydrobromide or a perbromide, liberated iodine from potassium iodide and on treatment with acetone produced bromoacetone and regenerated cuscohygrine as its dihydrobromide salt.

The last objection cited against formula (I) is that it does not explain the formation of two isomeric hydrazones. It should be pointed out that there are two similar asymmetric carbon atoms and hence the two reported hydrazones may be derived from the meso and racemic forms of (I), respectively.

Experimental

Ethyl 1-Methyl-2-pyrrylacetate.—In a flask equipped with dropping funnel and reflux condenser was placed 70 g. of 1-methylpyrrole with 2 g. of fine copper bronze. The liquid was warmed on the steam cone and 35 g. of ethyl diazoacetate was added during one hour and heated for an additional half hour. The copper was removed by filtration and the liquid fractionated. Fifty grams of 1-methylpyrrole was recovered and 24.7 g. (67.3%) of 1-methyl-2-pyrrylacetic ester was obtained as a light yellow liquid boiling at 115–118° (10 mm.) and 105–110° (6 mm.).

Reduction of Ethyl 1-Methyl-2-pyrrylacetate.—The reduction was carried out in a special vessel made by joining the neck of a 200-cc. round-bottomed flask through a 5-mm. Pyrex glass stopcock to the bottom of a second 200-cc. round-bottomed flask. This arrangement permitted the catalyst (0.6 g. platinum oxide) to be reduced separately and the ester (7.5 g.) could be introduced and the apparatus freed from air. Additional catalyst could be added as needed.

After the reduction was completed (twenty-four hours) the catalyst was removed by filtration and 15 cc. of concentrated hydrochloric acid added to the filtrate. The alchol and acetic acid were removed by distillation under vacuum. The residue was then treated with cold saturated potassium carbonate solution, extracted with ether and dried over solid potassium carbonate. The ether was then evaporated and the ester fractionated; b. p. 88–89° (10 mm.), 78° (6 mm.); d_4^{20} 0.96838; n_D^{20} 1.4465; M_D calcd., 47.35; found, 47.30.

Anal. Calcd. for $C_9H_{17}O_2N$: N, 8.18. Found: N, 8.33.

Cuscohygrine.—Thirty-five grams of cuscohygrine dinitrate was dissolved in 25 cc. of water and an excess of saturated sodium hydroxide solution added. The free base separated as a clear oil. The aqueous lower layer was extracted five times with ether. The extracts were combined and dried over anhydrous magnesium sulfate for several days. The ether solution was then filtered and the ether distilled.

The cuscohygrine was distilled at 2 mm. pressure and boiled at 118–125° (corr.); d_4^{20} 0.9733; n_D^{20} 1.4832; M_D calcd., 66.02; found, 65.75. *Mol. wt.* (cryoscopic in benzene). Calcd. for $C_{13}H_{24}ON_2$: 224. Found: 223.

Anal. Calcd.: N, 12.50. Found: N, 12.27.

Cuscohygrine gave no iodoform when treated with sodium hypoiodite and no bromoform with sodium hypobromite as the reagent. A careful examination of the products of the latter reaction showed that no acetic acid was produced.[11]

No condensation products with benzaldehyde could be obtained in the presence of either alkali or acid using the customary procedures.[12,13]

Preparation of Ethyl Ester of Homohygric Acid from Cuscohygrine.—A three-necked, one-liter flask equipped with a mercury-sealed stirrer, a dropping funnel and a tube for entrance of nitric oxide gas was swept free of air with nitric oxide which was generated in a Kipp apparatus by the action of dilute (1:1) nitric acid on copper. The nitric oxide was washed with water to remove higher oxides of nitrogen and then dried

in a tube filled with soda lime. When the brown color due to the presence of higher oxides of nitrogen disappeared the flask was considered to contain no air.

Six-tenths mole of sodium was dissolved in 250 cc. of absolute alcohol and then run into the nitric oxide filled flask. The cuscohygrine was added and stirring started. The nitric oxide was absorbed very rapidly at first and then at about 15 cc. per minute. After eighteen hours the absorption had ceased. About 30 cc. of water was added to the cherry-red solution which caused a slimy solid to precipitate. This solid was filtered, dissolved in 100 cc. of water and the solution acidified with acetic acid. Addition of lead acetate gave a precipitate which on decomposition with sulfuric acid gave lead sulfate. No pure organic compound could be isolated from this solution.

The alcoholic filtrate from which the slimy precipitate was removed was next acidified with hydrochloric acid and filtered. The alcohol was evaporated and the residual solution was made alkaline with sodium hydroxide and extracted six times with ether to remove unchanged cuscohygrine which amounted to 5 g.

The alkaline residue was acidified with hydrochloric acid and evaporated to dryness over water-bath, then dried completely in a vacuum over phosphorus pentoxide. The brown hard residue was broken up and placed in a 500-cc. round-bottomed flask with 250 cc. of absolute alcohol and the mixture saturated with dry hydrogen chloride. This mixture was refluxed for one day, then cooled to below 0° in an ice–salt-bath and made alkaline with saturated solution of potassium carbonate. The alcohol ester layer was separated and dried with magnesium sulfate. The alcohol was distilled and a high boiling fraction collected. This high boiling material was next refractionated and the portion boiling at 72–73° (6–7 mm.) collected. This amounted to about 1 g., n_D^{20} 1.4501; d_4^{20} 0.9900.

Anal. Calcd. for $C_9H_{17}O_2N$: N, 8.18; C, 63.10; H, 10.02. Found: N, 10.27, 10.24; C, 62.75; H, 10.24.

These analyses show that the degradation product was not pure but the amount available was insufficient for further fractionation.

Preparation of Derivatives.—Three solid derivatives of the synthetic ester and of the ethyl homohygrinate from cuscohygrine were prepared. Their properties and analyses are summarized in Table II.

TABLE II

DERIVATIVES OF ETHYL 1-METHYL-2-PYRROLIDINEACETATE

		Synthetic			From cusocohygrine		
	Formula	M. p., °C.	Analysis, % Calcd.	Found	M. p., °C.	Analysis, % Calcd.	Found
Picrate	$C_{15}H_{20}O_9N_4$	112–113	N, 14.00	14.58	112–113	N, 14.00	14.27
Methiodide	$C_{10}H_{20}O_2NI$	121–122	I, 40.54	40.46	120–121	I, 40.54	40.89
Chloraurate	$C_9H_{17}O_2N \cdot AuCl_3 \cdot 2H_2O$	133–134	Au, 38.61	38.40	134–135	Au, 38.61	38.90

The chloroplatinate and methyl *p*-toluene sulfonate were liquids and the flavianic acid salts were too soluble.

Action of Bromine on Cuscohygrine.—The free base was dissolved in 90 g. of glacial acetic acid and 10 g. of acetic anhydride and treated with 6.4 g. of bromine whereupon an oily red precipitate formed which later solidified. This was removed by filtration. The product could not be recrystallized and hence the analysis for bromine was high.

Anal. Calcd. for $C_{13}H_{25}N_2OBr_3$: Br, 51.56. Found: Br, 53.37.

The red substance on treatment with acetone precipitated a white powder melting at 236° with decomposition at 240°.

Anal. Calcd. for $C_{13}H_{26}N_2OBr_2$: Br, 41.40. Found: Br, 40.70.

A sample of cuscohygrine dihydrobromide was prepared from cuscohygrine and hydrobromic acid. It melted at 239° and was identical with the above product.

1-Diethylaminobutanone-3.[14]—In a 500-cc. flask fitted with a reflux condenser was placed 43 g. of formalin solution, 54.7 g. of diethylamine hydrochloride and 145 g. of acetone. The mixture was refluxed for twelve hours and the acetone and some water removed by distillation. The residue was treated with potassium carbonate solution and extracted with ether. The ether extract was dried over potassium carbonate and then fractionated. The amino ketone boiled at 84° (30 mm.) and 53° (4 mm.); yield, 31 g. or 42%.

Anal. Calcd. for $C_8H_{17}ON$: N, 9.79. Found: N, 9.80.

Treatment of this amino ketone with sodium hypoiodite yielded yellow crystals of iodoform melting at 118–119°.

Summary

1. Ethyl 1-methyl-2-pyrrolidineacetate has been synthesized by the catalytic reduction of the ethyl 1-methyl-2-pyrrylacetate which was prepared from 1-methylpyrrole and ethyl diazoacetate.

2. This synthetic ester was identical with ethyl homohygrinate obtained as a degradation product of cuscohygrine by the action of nitric oxide and sodium ethylate.

3. Cuscohygrine did not react with benzaldehyde and failed to give an iodoform test.

4. These data together with previous investigations indicate that cuscohygrine is probably a *sym-bis*-(1-methylpyrrolidyl)-acetone.

(14) Mannich, *Arch. Pharm.*, **255**, 261 (1917).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CINCINNATI]

Synthesis and Resolution of Phenyl-α-(β-methoxynaphthyl)-aminomethane

BY FRANCIS EARL RAY AND WILLIAM A. MOOMAW

In a previous paper[1] the authors described the effect of negative substituents in the benzene ring on the amines resulting from the condensation of aromatic aldehydes with β-naphthol and ammonia. It was found that the presence of negative substituents decreased the stability of the amines.

As it was thought that the tautomerism of the β-naphthol contributed to the instability of the amine we sought to replace the ionizable hydrogen with a methyl group.

When, however, β-methoxynaphthalene was mixed with benzaldehyde and ammonia no reaction took place. It was necessary, therefore, to use other means to synthesize the desired amine. Attempts to methylate or acetylate the hydroxy group, I, were unsuccessful as the amino group reacted first.[2] If the amino group was first blocked the hydroxyl group

(1) Ray and Moomaw, THIS JOURNAL, **55**, 749 (1933).

(2) Nzeer Ahmed, Master's Thesis, University of Cincinnati, 1933.