D-Gala-L-gulo-octitol.—A solution of 2.0 g. of D-gala-L-gulo-octose in 50 cc. of water was agitated at 80° with Raney nickel and hydrogen under a pressure of 100 atmospheres for four hours; the catalyst was removed by filtration and the filtrate, which did not reduce Fehling solution, was concentrated *in vacuo* to dryness. The crystalline residue was dissolved in 3 cc. of warm water and the solution was diluted with 10 cc. of alcohol; upon cooling, clusters of elongated glistening prisms were deposited in the solution. The yield of product, which rotated $[\alpha]^{20}D$ +2.4° in aqueous solution (c, 1.6) was nearly quantitative; it melted at 153–154° and a mixed melting point with D-gluco-L-gala-octitol showed the same melting point; an optical examination of the two compounds by Mr. George L. Keenan disclosed no difference. The identity of this octitol from the two sources constitutes definitive proof by one of Fischer's classical methods of the configurations of D-gluco-L-gala-octose and D-gala-L-gulo-octose and by the epimeric relationship it proves the configurations of D-gluco-L-talo-octose and D-gala-L-ido-octonic acid.

Octaacetyl-D-gala-L-gulo-octitol.—This compound was prepared by the acetylation of 0.5 g. of the alcohol with acetic anhydride and fused sodium acetate. The yield was 0.8 g. (67%). It was recrystallized from 3 parts of alcohol with a recovery of 0.7 g. (88%). The compound melted at 88–89° and this melting point was not depressed upon admixture of octaacetyl-D-gluco-L-gala-octitol; it showed a specific rotation $[\alpha]^{20}D$ +20.5° in chloroform (c, 1.5). A microanalytical optical examination by Mr. Keenan proved it to be identical microscopically with octaacetyl-D-gluco-L-gala-octitol. This proof of identity confirms the conclusions previously stated regarding the configurations of the octose sugars in the glucose and galactose series.

Summary

A new crystalline gala-octose, which was obtained by application of the Fischer cyanohydrin synthesis to D-gala-L-gluco-heptose, has been reduced to an octitol, which proves to be identical with the octitol obtained by reduction of Fischer's α-gluco-octose. The identity of the alcohols constitutes a definitive proof that (1) Fischer's long known α-gluco-octose is D-gluco-L-gala-octose and its recently described epimer is D-gluco-L-talo-octose, and (2) that the new crystalline gala-octose is D-gala-L-gulo-octose. Extensive data on the comparison of similar sugars and derivatives are presented. The usefulness of several empirical rules in aiding the planning of the synthesis of higher carbon sugars is illustrated. The present data in the octose series lead to a very simple additional proof of the configurations of glucose and galactose.

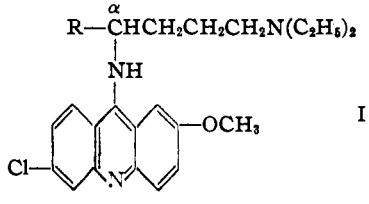
BETHESDA, MARYLAND RECEIVED SEPTEMBER 11, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Atabrine Analogs Having Various Aliphatic α-Substituents in the Side Chain[1]

BY DAVID S. BRESLOW, ROBERT S. YOST, HOWARD G. WALKER AND CHARLES R. HAUSER

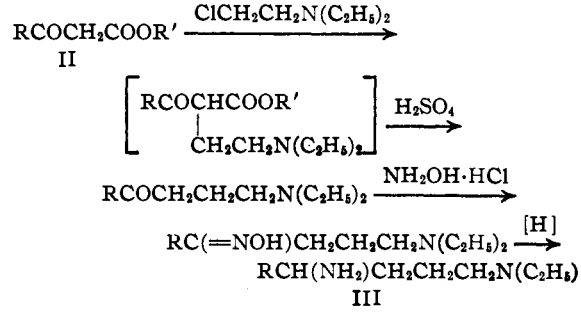
Although many analogs of atabrine (I, R = CH_3) have been synthesized relatively few have



I

been described which have the same length of carbon side chain as atabrine but with a different α-substituent, R.[2] The present paper describes the synthesis of various atabrine analogs in which the α-substituents are alkyl groups higher than methyl.

Since 5-diethylamino-2-aminopentane, which yields atabrine when coupled with 2-methoxy-6,9-dichloroacridine, is generally synthesized from ethyl acetoacetate, the appropriate β-keto esters of type (II) were used in the preparation of the desired side chains (III). These β-keto esters were prepared by various methods. The conversion of the β-keto esters to the side chains may be represented by the transformation.



The alkylation of the β-keto esters with β-diethylaminoethyl chloride was carried out in benzene or dioxane and the alkylated product, without isolation, was subjected to ketonic cleavage in the presence of dilute sulfuric acid. The yields of ketones in these two steps (Table I) were in general better than those obtained using alcohol as a solvent for the alkylation. The ketones were converted in excellent yields to the corresponding oximes (Table II), which were reduced in good yields to the corresponding diamines (Table III). The reduction was effected with sodium in butyl alcohol or catalytically in the presence of Raney nickel; the latter method is preferable.

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

(2) Of course it is possible that certain of these compounds were prepared by I. G. Farbenindustrie in their survey of acridine compounds but, if so, the results have not been made available.

TABLE I

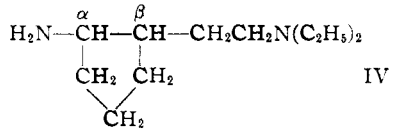
$R—COCH_2CH_2CH_2N(C_2H_5)_2$

R =	Solvent	Yield, %	B. p. °C.	Mm.	Formula	Neutral equivalent[a] Calcd.	Found
Ethyl	Dioxane	44	105–108	20	$C_{10}H_{21}NO$	171	169
n-Propyl	Benzene	65	116–122	20	$C_{11}H_{23}NO$	185	186
Isopropyl	Benzene	59	111–114	20	$C_{11}H_{23}NO$	185	186
Isobutyl	Dioxane	57	123–129	20	$C_{12}H_{25}NO$	199	208
t-Butyl	Benzene	61	117–118	19	$C_{12}H_{25}NO$	199	204
n-Hexyl	Benzene	53	140–150	10	$C_{14}H_{29}NO$	227	233
Cyclohexyl	Benzene	54	135–139	5	$C_{14}H_{27}NO$	225	229
"Cyclo"	Benzene	28	115–118	10	$C_{11}H_{21}NO$	183	185

[a] Samples for analysis were taken from the products whose boiling points are given.

The diamines were coupled with 2-methoxy-6,9-dichloroacridine in the usual manner using phenol as the solvent to form the atabrine analogs, which were isolated as their dihydrochlorides with varying amounts of water of crystallization (Table IV). The yields were quite satisfactory in most cases. However, the diamine having the *t*-butyl group failed to couple under the conditions employed.

In one case the side chain (IV) formed part of the cyclopentyl ring system. It was prepared



IV

from 2-carbethoxycyclopentanone by a series of reactions analogous to those represented above. In the tables the derivatives in this case are designated "Cyclo." The atabrine analog obtained on coupling this diamine with 2-methoxy-6,9-dichloroacridine may be considered as a special case in which there is both an α- and a β-substituent in the side chain.

We wish to thank Drs. H. A. Shonle and Joseph Corse of Eli Lilly and Company for their helpful suggestions for preparing certain of these compounds.

Experimental[3]

Preparation of β-Keto Esters.—Ethyl propionylacetate (b. p. 88–93° at 17 mm.) and ethyl hexahydrobenzoylacetate (b. p. 146–150° at 18 mm.) were prepared from ethyl *t*-butylmalonate and propionyl and hexahydrobenzoyl chlorides, respectively, according to the procedure of Breslow, Baumgarten and Hauser.[4]

Ethyl *n*-butyrylacetate (b. p. 93–95° at 15 mm.) and ethyl isobutyrylacetate (b. p. 90–92° at 15 mm.) were prepared by the acylation of ethyl acetoacetate with *n*- and isobutyryl chlorides, respectively, followed by ammonolysis of the resulting products essentially according to Fischer and Orth.[5]

Ethyl isovalerylacetate (b. p. 96–99° at 14 mm.) and ethyl β-ketopelargonate (b. p. 123–128° at 10 mm.) were prepared by the condensation of methyl isobutyl and methyl *n*-hexyl ketones, respectively, with ethyl carbonate[6] in the presence of sodium ethoxide according to the method of Wallingford, Homeyer and Jones.[7]

Methyl trimethylacetoacetate (b. p. 84–86° at 15 mm.) was prepared by the carbonation of pinacolone by means of sodium or potassium amide, followed by esterification of the resulting acid with diazomethane.[8]

2-Carbethoxycyclopentanone (b. p. 88–91° at 5.5 mm.) was prepared from ethyl adipate.[9]

Preparation of β-Diethylaminoethyl Chloride.—In a two-liter three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and reflux condenser (with a drying tube) was placed 205 g. (1.75 moles) of β-diethylaminoethyl alcohol (Eastman Kodak Co.) dissolved in 500 ml. of dry thiophene-free benzene. The flask was chilled in an ice–salt-bath and 230 g. (1.93 moles) of thionyl chloride was added slowly with stirring. The reaction mixture was then allowed to warm up to room temperature and refluxed six hours on a steam-bath. The mixture was cooled, the dark precipitate filtered off and washed with dry benzene, the β-diethylaminoethyl chloride hydrochloride being obtained as a brown solid; yield, 286 g. (95%).

To 300 g. (1.75 moles) of β-diethylaminoethyl chloride hydrochloride was added 100 g. of finely crushed ice and the mixture covered with 400 ml. of ether. Keeping the temperature at 5°, a cold solution of 70 g. of sodium hydroxide in 150 ml. of water was added with stirring. The reaction mixture was allowed to stand for several minutes, the ether layer was separated and dried over Drierite. The ether was removed under reduced pressure, leaving 202 g. (85% based on the hydrochloride) of β-diethylaminoethyl chloride as a red oil; b. p. 69° at 50 mm. The undistilled product is sufficiently pure for the following step. Since it decomposes slowly even at 0°, it was prepared as needed from the stable hydrochloride.

Preparation of Ketones (Table I): **1-Diethylaminoheptanone-4.**—In a one-liter three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and reflux condenser (with a drying tube) was placed 12.7 g. (0.55 mole) of sodium sand suspended in 250 ml. of dry benzene. To this was slowly added 86.9 g. (0.55 mole) of ethyl *n*-butyrylacetate, the reaction mixture being kept at about 50° until practically all the sodium had dissolved. The final solution was clear and yellow. It was cooled to room temperature, the sodium derivative precipitating, and 74.5 g. (0.55 mole) of β-diethylaminoethyl chloride added. The reaction mixture was heated at 50–60° with stirring for three hours (sodium chloride gradually precipitating), allowed to stand overnight at room temperature and then refluxed for three hours. It was cooled, extracted with water to remove sodium chloride and the benzene solution dried over anhydrous potassium carbonate. The benzene was distilled at atmospheric pressure.

The residue left after removing the benzene was heated for twelve hours on a steam-bath with 700 g. of 10% sulfuric acid. The reaction mixture was cooled, excess potas-

(3) Melting points are corrected, boiling points are uncorrected.

(4) Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

(5) Fischer and Orth, "Die Chemie des Pyrrols," Leipzig, 1934, Vol. I, p. 404.

(6) We are indebted to Dr. V. H. Wallingford of the Mallinckrodt Chemical Works for a supply of ethyl carbonate.

(7) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941).

(8) Levine and Hauser, *ibid.*, **66**, 1768 (1944).

(9) Pinkney, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 116.

sium carbonate was added and the oil extracted with ether. The ether solution was dried over potassium carbonate, the ether distilled and the residue fractionated through a 10-cm. Vigreux column.

When dioxane was used as solvent for the alkylation, the reaction was carried out in the same fashion, except that after the completion of the alkylation the dioxane was distilled at slightly reduced pressure, the residue then being decarboxylated as above.

Preparation of Oximes (Table II): **Oxime of 1-Diethylaminoheptanone-4.**—To a chilled solution of 12.5 g. (0.18 mole) of hydroxylamine hydrochloride in 15 ml. of water was added 32.5 g. (0.175 mole) of 1-diethylaminoheptanone-4. The clear reaction mixture was refluxed in an oil-bath for thirty minutes. After standing overnight at room temperature the reaction mixture was diluted with 100 ml. of water, excess potassium carbonate was added and the yellow oil liberated was extracted with ether. The ether solution was dried over potassium carbonate, the ether distilled and the residue fractionated through a 10-cm. Vigreux column, yielding a pale yellow, viscous oil.

TABLE II

R—C(=NOH)$CH_2CH_2CH_2N(C_2H_5)_2$

R =	Yield, %	B. p. °C.	Mm.	Formula	Neutral equivalent[a] Calcd.	Found
Ethyl	90	132–134	5	$C_{10}H_{22}N_2O$	186	189
n-Propyl	91	144–146	5.5	$C_{11}H_{24}N_2O$	200	202
Isopropyl	94	137–138	5	$C_{11}H_{24}N_2O$	200	201
Isobutyl	88	143–146	5	$C_{12}H_{26}N_2O$	214	221
t-Butyl	91	139–141	5	$C_{12}H_{26}N_2O$	214	216
n-Hexyl	81	142–145	1	$C_{14}H_{30}N_2O$	242	247
Cyclohexyl	79	161–164	1.5	$C_{14}H_{28}N_2O$	240	243
"Cyclo"	93	127–137 (m. p., 50–51)	1	$C_{11}H_{22}N_2O$	198	199

[a] Samples for analysis were taken from the products whose boiling points are given.

40 g. of sodium in small pieces was added to the hot solution, the reaction mixture being kept refluxing vigorously, with a free flame if necessary, until all the sodium had dissolved. Toward the end of the reaction a fairly large precipitate of sodium butoxide was present. The reaction mixture was cooled, 300 ml. of water was added and the mixture steam-distilled until no more alkaline material came over. Fifty ml. of concentrated hydrochloric acid was added to the distillate, which was then concentrated to about 200 ml. Excess potassium carbonate was added and the diamine was extracted with ether. The ether solution was dried over potassium carbonate, the ether distilled and the residue fractionated through a 10-cm. Vigreux column.

Preparation of Diamines by Catalytic Reduction (Table III): **1-Diethylamino-6-methyl-4-aminoheptane.**—1-Diethylamino-6-methylheptanone-4 oxime (17.8 g., 0.083 mole) was dissolved in 50 ml. of 95% ethanol, 3 g. of Raney nickel was added and the oxime was reduced at 70° at an initial hydrogen pressure of 1000 lb. The catalyst was filtered off, the alcohol distilled at atmospheric pressure and the residue fractionated through a 10-cm. Vigreux column.

Atabrine Analogs (Table IV).—The diamines were coupled with 2-methoxy-6,9-dichloroacridine using phenol as a solvent in the usual manner.[10] The compounds were purified by pouring the reaction mixture into excess 2 *N* sodium hydroxide, extracting with ether, extracting the ether solution with dilute acetic acid and making the acid solution alkaline with ammonia. The free base was extracted with ether, the ether solution dried and the hydrochloride precipitated with ethereal hydrogen chloride. An alternative procedure was to distill the ether, dissolve the free base in alcohol and make the alcohol solution acid to congo red with concentrated hydrochloric acid. The hydrochlorides were recrystallized from either water, alcohol or alcohol–acetone and were obtained as yellow powders.

TABLE III

R—CH(NH_2)$CH_2CH_2CH_2N(C_2H_5)_2$

R =	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	N Analyses,[c] % Calcd.	Found
Ethyl	64[a]	105–112	20	Picrolonate	194–195	$C_{20}H_{32}N_8O_5$	19.3	19.7
n-Propyl	84[b]	120–123	20	Picrate	139	$C_{17}H_{29}N_5O_7 \cdot 2H_2O$	15.5	15.7
Isopropyl	45[b]	116–118	20	Picrate	75–76	$C_{17}H_{29}N_5O_7 \cdot 2H_2O$[d]	15.5	15.6
Isobutyl	75[a]	125–129	20	Picrolonate	206–207	$C_{22}H_{36}N_8O_5$	18.1	18.1
t-Butyl	83[a]	121–125	20	Picrolonate	205–206	$C_{22}H_{36}N_8O_5$	18.1	18.4
n-Hexyl	72[a]	142–152	10	Dipicrolonate	217–218	$C_{34}H_{48}N_{10}O_{10}$	18.5	18.5
Cyclohexyl	87[a]	137–140	5	Picrate	151–152	$C_{20}H_{33}N_5O_7$	15.4	15.4
"Cyclo"	52[b]	111–114	10	Picrolonate	230–231	$C_{21}H_{32}N_8O_5$	18.7	18.7

[a] Catalytic reduction. [b] Sodium in alcohol reduction. [c] Microanalyses by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois. [d] Calcd.: H_2O, 7.98. Found: H_2O, 8.17.

TABLE IV

ATABRINE ANALOGS (I)

R =	Yield, %	M. p., °C.	Formula	Cl^- Analyses,[a] % Calcd.	Found
Ethyl	71	165–169	$C_{24}H_{32}ClN_3O \cdot 2HCl \cdot H_2O$	14.04	14.30
n-Propyl	76	152–155	$C_{25}H_{34}ClN_3O \cdot 2HCl \cdot H_2O$	13.66	13.66
Isopropyl	52	171–173	$C_{25}H_{34}ClN_3O \cdot 2HCl \cdot H_2O$	13.66	13.74
Isobutyl	52	160–164	$C_{26}H_{36}ClN_3O \cdot 2HCl \cdot H_2O$	13.31	13.56
n-Hexyl	70	63–65	$C_{28}H_{40}ClN_3O \cdot 2HCl$	13.06	13.08
Cyclohexyl	33	174–176	$C_{28}H_{38}ClN_3O \cdot 2HCl$	13.11	13.37
"Cyclo"	79	219–221	$C_{25}H_{32}ClN_3O \cdot 2HCl \cdot 2H_2O$	13.25	13.20

[a] Macroanalyses by Miss Virginia B. Zerfass and Miss Mary K. Scholl.

Preparation of Diamines by Sodium Reduction (Table III): **1-Diethylamino-4-aminoheptane.**—The oxime of 1-diethylaminoheptanone-4 (31.2 g., 0.156 mole) was dissolved in 400 ml. of dry butanol (distilled from sodium) in a one-liter round-bottom flask equipped with a reflux condenser and the solution was heated to boiling. About

Summary

The syntheses of seven 4-diethylamino-1-alkyl-1-aminobutanes and of 2-(β-diethylaminoethyl)-

(10) Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2012 (1943).

cyclopentylamine from the corresponding β-keto esters are described.

Seven of these have been coupled with 2-methoxy-6,9-dichloroacridine to form analogs of atabrine.

DURHAM, NORTH CAROLINA RECEIVED AUGUST 16, 1944

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Formation of Isomeric Hydroxy Acids by Sulfation of Oleic Acid

BY B. B. SCHAEFFER, E. T. ROE, J. A. DIXON AND W. C. AULT

During sulfation of oleic acid and hydrolysis of the resulting product, formation of monohydroxy acids with the hydroxyl group attached at either the 9- or the 10-carbon position would normally be expected. A study of the sulfation reaction led us to suspect, however, that the mixture of hydroxy acids obtained was considerably more complex than previously indicated.

It has been established[2] that under certain conditions of sulfation the gamma stearolactone is formed. This would seem to be conclusive evidence that during the process the substituent group has migrated to the gamma position with respect to the carboxyl group. Our investigation did not disclose any definite information regarding the mechanism involved in the shift. While this work was in progress, a paper[3] dealing with olefins came to our attention which reports that mixed alcohols are formed by sulfation, indicating probable migration of the hydroxyl group.

To determine whether hydroxy acids other than those formed by substitution in the 9- and 10-carbon positions are obtained by the sulfation and hydrolysis of purified oleic acid, the oxidation products of the mixed hydroxy acids were investigated.

It is difficult to separate monohydroxy acids from unreacted oleic acid by crystallization without removing isomeric hydroxy acids during purification. To avoid these losses, the acids in the crude reaction product were converted to methyl esters, and the mixed methyl hydroxystearates thus obtained were fractionally distilled under high vacuum. The esters were oxidized with nitric acid and steam distilled yielding volatile and non-volatile fractions.

Obviously, if only 9- and 10-monohydroxystearic acids were present in the hydrolysis product, oxidation would produce 8-, 9- and 10-carbon monobasic acids and the 8-, 9- and 10-carbon dibasic acids. If the hydroxyl group were closer to the carboxyl group, longer-chain monobasic acids and shorter-chain dibasic acids would result. On the other hand, if the hydroxyl group were located farther away from the carboxyl group than the 10-carbon position, oxidation would produce shorter-chain monobasic acids and longer-chain dibasic acids.

Fractionation of the methyl esters prepared from the non-volatile, water-insoluble portion of the oxidation products showed that this portion had contained 14-, 15- and 16-carbon dibasic acids, the chain lengths of which were estimated from refractive index data, saponification equivalents and cryoscopic molecular weights given in Table I. The dimethyl ester of 1,14-tetradecanedicarboxylic acid was isolated from one of these fractions. This compound could have been formed only as the result of a shift away from the carboxyl group. The possibility of its formation from a saturated acid need not be considered because such acids were removed by fractional distillation before the material was oxidized. Cleavage of a hydroxy acid at the 16-carbon position without shifting would have given a hydroxy dibasic acid instead of the unsubstituted compound.

TABLE I

DISTILLATION OF METHYL ESTERS OF STEAM-NONVOLATILE WATER-INSOLUBLE FATTY ACIDS

Fraction No.	Range b. p., °C. at 1.5–2 mm.	Distilland 35.6 g. Recovery, g.	$n^{30}D$	Sapn. equiv.	Mol. wt., cryoscopic	No. C atoms in acid calcd. from Sapn. equiv.	No. C atoms in acid calcd. from Mol. wt.
I	58–80	2.0	1.4147	181.8	183.0	9.7	9.8
II	80–105	4.1	1.4190	177.7	196.0	..	..
III	105–120	6.4	1.4255	140.7	223.0	..	..
IV	120–140	9.2	1.4317	133.6	244.5	..	..
						twice the sapn. equiv.	
V	140–159	5.1	1.4352	145.7	281.0	14.4	13.7
VI	159–171	6.5	1.4377	153.4	297.0	15.5	14.7
Residue	.....	2.1	1.4462	146.7	322.0	..	..

Experimental

Oleic Acid.—A purified oleic acid was prepared by fractional distillation and crystallization of commercial oleic acid.[4] The iodine value (Wijs, one-half hr.) of this material was 88.2. Its melting point was 11.9–12.4°. Spectrophotometric examination showed 0.2% linoleic acid, 0.1% linolenic acid, 0.005% arachidonic acid, 0.3% diene conjugated acids and 0.006% triene conjugated acids. Calculations based on these data indicate the product to be approximately 97% oleic acid.

Methyl Monohydroxystearate—The oleic acid was sulfated at 10° with a three-to-one molar ratio of sulfuric

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) A. A. Shukoff and P. I. Schestakoff, *J. Russ. Phys.-Chem. Soc.*, **35**, 1 (1903); *ibid.*, **40**, 830–839 (1908); P. W. Clutterbuck, *J. Chem. Soc.*, **125**, 2330–2333 (1924).

(3) P. Baumgarten, *Ber.*, **76B**, 213–218 (1943); **75B**, 977–983 (1942).

(4) J. B. Brown and G. Y. Shinowara, THIS JOURNAL, **59**, 6 (1937).