and poured into an aqueous solution of 13.6 g. of sodium acetate trihydrate. The *p*H of the solution was adjusted to 4.5 and the mixture was extracted with chloroform. The chloroform solution was shaken first with 10% sodium hydroxide solution and then with salt water. It was dried, concentrated to 500 ml., and 250 ml. of petroleum ether (60–80) was added. The product was adsorbed by passing the solution through a column of activated alumina and was eluted with a mixture of chloroform and petroleum ether. The eluate, when concentrated under diminished pressure yielded 15 g. of a viscous oil. The oil was dissolved in aqueous hydrochloric acid and, after the *p*H had been adjusted to 5.0 with sodium acetate, a 10% excess of potassium iodide was added. An oil precipitated which, after decantation of the solution, was taken up in hot methanol. Addition of ether precipitated an impure salt which was recrystallized from methanol–ether; 5 g. (11.4%) of monohydriodide which melted at 159.0–160.5° was obtained.

Anal. Calcd. for $C_{25}H_{33}N_3O_3.HI$: C, 54.5; H, 6.17. Found: C, 54.26, 54.11; H, 6.42, 6.12.

Monohydrochlorides and Hydrobromides of 8-Alkylaminoalkylaminoquinolines.—Two general methods for the preparation of these salts were used. The first consisted of dissolving the base in dilute acetic acid and adding and excess of a concentrated aqueous solution of sodium bromide or sodium chloride. The other method consisted of dissolving the base in a slight excess of dilute hydrochloric or hydrobromic acid and adding a concentrated aqueous solution of sodium acetate until the *p*H of the mixture was 5.0. The salts were recrystallized from water, ethanol, or ethanol and ether.

Dihydrobromides and Diphosphates of 8-Alkylaminoalkylaminoquinolines.—These salts were prepared by adding a slight excess of 48% hydrobromic acid or 85% phosphoric acid to a refluxing ethanol solution of the base. The solution was cooled and the crystals removed by filtration. The product was recrystallized from ethanol or ethanol and ether.

Summary

1. Eighteen new relatives, and one nuclear substitution product of pentaquine (SN-13,276), together with the intermediates necessary for their preparation, are described.

2. Short-term chronic toxicities, determined in Rhesus monkeys, are given.

3. None of the drugs is less toxic than pentaquine.

COLLEGE PARK, MD. RECEIVED AUGUST 23, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Alkane-choleic Acids: Compounds of Paraffin Hydrocarbons with Desoxycholic Acid[1]

BY ERNEST H. HUNTRESS AND RALPH F. PHILLIPS[2,3,4]

The number of addition products of desoxycholic acid with organic compounds of widely diverse types is legion, but the only choleic acids from alkanes reported at the time of our work was carried out (February, 1938–June, 1939) were two products incidentally mentioned[5] without details in a report on polycyclic carcinogenic hydrocarbons. Furthermore, Rheinboldt had long been concerned with studies on desoxycholic acid addition products, but none of his work involved alkanes until a paper published[6] after our experiments had been completed. This included certain data on desoxycholic acid compounds of the normal alkanes with 11, 12, 13, 14, 15, 16, 35 and 43 carbon atoms.

Under suitable conditions every one of the thirty-four alkanes which were studied in our work combined with desoxycholic acid in methanol solution to give in good yield a definite compound containing from two to eight moles of desoxycholic acid per mole of hydrocarbon. The composition of this resultant alkane-choleic acid was established by determination of the neutralization equivalent of the complex by titration with standard alkali. In the consolidation of our many experiments to the simple form of Table II, we have taken the mean neutralization equivalent of several runs rarely differing among themselves by more than 3–4 units out of 400–440. Comparison of the values of Table II with the various Kz values for a given composition (Table I) shows that the nearest correspondence is rarely in doubt. Our results show that in general the number of coördinated molecules of desoxycholic acid diminishes with increased forking of the hydrocarbon chain, but that this effect is not sufficiently critical to serve as an infallible means of distinction.

TABLE I

CALCULATED NEUTRALIZATION EQUIVALENTS OF ALKANE-CHOLEIC ACIDS

N = number of molecules of desoxycholic acid (mol. wt., 392) per mole of alkane = Kz (coördination number)

Neutralization Equivalent = (392 N + M.W.)/N = 392 + (M.W./N)

N	1	2	3	4	5	6	7	8
C_8H_{18}	464	428	416	410	406.4	404	402.3	401
C_9H_{14}	478	435	420.7	413.5	409.2	406.3	404.3	402.7
C_7H_{16}	492	442	425.3	417	412	408.6	406.3	404.5
C_9H_{18}	506	449	430	420.5	414.8	411	408.3	406.3
C_9H_{20}	520	456	434.7	424	417.6	413.3	410.3	408
$C_{19}H_{22}$	534	463	439.3	427.5	420.4	415.7	412.3	409.8

Experimental Part

Materials Used.—For many of the samples of highly purified alkanes used in this work the authors are indebted to Messrs. H. Beatty, J. H. Bruun, G. Calingaert, P. L. Cramer, N. L. Drake, G. Egloff, A. V. Grosse, F. D. Rossini and the late F. C. Whitmore as individuals, and

(1) Presented April 23, 1942, at the Memphis Meeting of the American Chemical Society.

(2) This paper has been constructed from a thesis submitted in May, 1939, by Ralph F. Phillips in partial fulfillment of the requirements for the degree of Ph.D. in Organic Chemistry.

(3) A. D. Little Fellow in Chemistry, M. I. T., 1938–1939.

(4) Present address: Sugar Research Foundation, 52 Wall Street, New York 5, N. Y.

(5) Fieser and Newman, THIS JOURNAL, **57**, 1603 (1935).

(6) Rheinboldt, *J. prakt. Chem.*, [2] **153**, 313–326 (1939).

TABLE II

OBSERVED NEUTRALIZATION EQUIVALENTS AND COÖRDINATION NUMBERS FOR DESOXYCHOLIC ACID COMPOUNDS WITH VARIOUS ALKANES

For calculated values see Table I

Hydrocarbon	Dried at 20° Neut. equiv.	Kz	*DT* in °C. uncor.	Dried at 110°[a] Neut. equiv.	Kz
C_5H_{12}[e]					
n-Pentane	409	4	148–150	398	8
2-Methylbutane	415	3	148–149	403	6
2,2-Dimethylpropane	434	2	147–152	...	
C_6H_{14}					
n-Hexane	421	3	148–150	408	6
2-Methylpentane	415[f]	4[f]	147–150	406	6
3-Methylpentane	422	3	149–150	...	
2,2-Dimethylbutane	421	3	149–152	407	6
2,3-Dimethylbutane	421	3	152–154	410	6
C_7H_{16}					
n-Heptane	416	4	147–148	407	6
2-Methylhexane	417	4	148–150	...	
3-Methylhexane	418	4	146–149	406	8
2,2-Dimethylpentane[g]	418	4	147–148	401	8
				409	6
2,4-Dimethylpentane[g]	417	4	147–149	402	8
				408	6
3,3-Dimethylpentane	439	2	148–154	424	3
2,2,3-Trimethylbutane[h]	442	2	166–172	428	3
C_8H_{18}[i]					
n-Octane	423	4	157–160	403	8[b]
2-Methylheptane	...		.....	411	6[c]
2,3-Dimethylhexane	430	3	147–149	...	
2,5-Dimethylhexane	430	3	152–154	...	
3,4-Dimethylhexane	430	3	147–149	...	
2,2,3-Trimethylpentane	430	3	148–151	...	
2,2,4-Trimethylpentane[i]	433	3	149–151	421	4
2,2,3,3-Tetramethylbutane[j]	447	2	169–171	431	3[c]
C_9H_{20}					
2-Methyloctane	434	3	165–166	410	6[c] (or 8)
4-Methyloctane	436	3	161–163	411	6[c] (or 8)
2,6-Dimethylheptane	434	3	159–160	413	6[c]
$C_{10}H_{22}$					
n-Decane	427	4	168–170	407	8[d]
2-Methylnonane	429	4	168–170	413	6[c]
3-Methylnonane	437	3	163–165	416	6[c]
4-Methylnonane	439	3	165	416	6[c]
5-Methylnonane	436	3	169–170	414	6[c]
2,7-Dimethyloctane[l]	430	4	161–163	430	4[d]
3,3,5-Trimethylheptane[k]	440	3	None	430	4
2,2,3,4-Tetramethylhexane[k]	441	3	None	433	4[c]

[a] Heated two hours unless otherwise specified. [b] Heated thirteen hours. [c] Heated three hours. [d] Heated four hours. [e] With these especially volatile alkanes a large excess of hydrocarbon (2 or 3 ml.) gave better yields than the usual 1 ml. [f] Three runs on one sample and two on a different sample all agreed closely. [g] Unlike any of the other heptanes, these isomers required chilling to start precipitation of the alkane-choleic acid. They appear to represent transitional cases from Kz = 4 to Kz = 2 at 20°. [h] The product from this hydrocarbon was the only alkane-choleic acid below $C_{14}H_{30}$ which was not completely soluble in the original boiling methanol solution. [i] Of the isomeric octanes the choleic acid from this isomer ("isoöctane") was slowest in forming and required 1 ml. of alkane instead of usual 0.5 ml. [j] Fieser and Newman[5] were unable to obtain a choleic acid of this isomer. [k] The choleic acids of these isomers were the most difficult to prepare and were the only ones for whose formation heating was essential. [l] This was the only branched chain case observed where the coördination number of the choleic was unchanged by heating.

to the Ethyl Gasoline Corporation, General Motors Corporation, Sun Oil Company and Universal Oil Products Company as companies. The desoxycholic acid (Riedel-de-Haen, Inc.) proved of high purity[7] and was therefore used directly.

Standard Procedure for the Preparation of Alkane-choleic Acids.—Each choleic acid was prepared simply by adding the hydrocarbon (0.5 ml. for those with C_8 or above; 1.0 ml. for those below C_8) to 5 ml. of a filtered solution of desoxycholic acid (10 g.) in acetone-free methanol (50 ml.). The clear solution was then allowed to stand at room temperature for fifteen minutes. If no precipitation had then occurred the solution was chilled in ice water for half an hour, and filtered cold. Blank experiments demonstrated that under these circumstances the original bile acid itself remained completely in solution. If the solid jell produced by chilling was gently warmed in the mother liquor it generally redissolved completely and on cooling would reprecipitate as before. With some hydrocarbons this resolution appeared to effect a slight improvement in yields, which varied from 50–90%. With certain of the higher, less soluble highly branched paraffins the rewarming cycle was essential to choleic acid formation.

The alkane-choleic acid thus precipitated was dried at the pump for half an hour or more to remove excess solvent and/or hydrocarbon. The product may not be dried in the oven since such treatment results in removing sufficient hydrocarbon to mask observation of the decomposition temperature. Although methyl alcohol (contrary to the literature) was found to form a choleic acid itself, the resultant compound is quite soluble in excess methanol as compared to the alkane-choleic acids and does not precipitate under the conditions of our experiments. Other organic solvents may not be employed because of interference from their respective choleic acids, nor may the alkane-choleic acids be recrystallized even from methanol because of their tendency toward dissociation. Attempts to dispense with any solvent and use only the alkane itself with desoxycholic acid were unsuccessful.

Method of Analysis of Alkane-choleic Acids.—Since because of the molecular magnitudes carbon-hydrogen analyses of these products can have no determinative significance, the various alkane-choleic acids were characterized by their individual neutralization equivalents. Although special manipulative care in weighing and titration were required, experience soon convinced us that consistent values could be reproducibly obtained. Subsequent experiments by entirely different workers on analogous types of compounds have confirmed our procedure. Weighings were made on a long beam balance set to a sensitivity of two divisions per milligram and were by difference to four places. Titrations were made on samples of 50–80 mg. dissolved in neutral methanol (or ethanol) using aqueous 0.01 *N* sodium hydroxide with phenolphthalein as indicator. Frequently better results were obtained by dissolving the sample in excess standard alkali and titrating back with 0.01 *N* hydrochloric acid. The acid and alkali were frequently restandardized to eliminate errors attributable to slight changes of titer. Recognition of the end-point required some experience but was then readily determined. The end-point was delicate but achievable by working in daylight over a white surface particularly by comparison of the titration solution with a water-white blank placed beside it.

Decomposition Temperature of Alkane-choleic Acids.—Although the literature contains many records of melting points observed on other types of choleic acids, it is our observation that alkane-choleic acids do not melt AS SUCH at all. On heating they begin to dissociate at some fairly definite temperature, some of the component hydrocarbon is given off, and the corresponding desoxycholic acid remains, eventually to liquefy at its usual melting point (if pure) or somewhat below it if any hydrocarbon remains. At the temperature of decomposition (*DT*) the initial alkane-choleic acid shrinks sharply with marked softening and coalescence into a small worm-like shape, or some-

(7) Sobotka and Goldberg, *Biochem. J.*, **26**, 555–568 (1932).

times even globules. These always display a *convex* surface, do not form liquids (with concave upper surfaces) in the capillary melting point tube, and hence are not true melting phenomena. Frequently the solid becomes momentarily translucent changing with continued heating to an opaque condition, and finally melting (often quite sharply) at the melting point of the residual desoxycholic acid.

The loss of alkane probably is incomplete at the decomposition temperature, but slowly continues up to and perhaps beyond the melting point of the residual desoxycholic acid. When the temperature is raised at the rate of 4–8° per minute the decomposition temperature is readily reproducible within a degree or two. More rapid rates of heating lead to erratic and erroneous results; slower heating fails to produce deacholation at a rate sufficient to display in the sample the characteristic change of appearance required for easy recognition of the temperature.

Although the decomposition temperatures for the alkane-choleic acids are not in general sufficiently distinctive to warrant their use as a diagnostic tool, they are, at the request of the referees, reported in this paper. While by proper technique the loss of alkane can occur in such fashion as to give easily reproducible DT's, it is also true that the coördination number varies with temperature. Although a given alkane-choleic acid is perfectly stable at a given temperature, if it is maintained at a higher temperature, hydrocarbon is slowly lost without any corresponding change in appearance, DT, or final melting point. The change is evident only from the marked increase in coördination number as detected by diminution of neutralization equivalent. Of the thirty-four alkane-choleic acids here reported, only that from 2,7-dimethyloctane failed to lose achole on heating. This general change of coördination number with temperature emphasizes the necessity for its determination prior to any heating whatever.

The Deacholation of *n*-Heptane-choleic Acid by Heat.—In order to convince ourselves that our products really did obtain hydrocarbon some relatively large-scale experiments were carried out on the choleic acid from *n*-heptane. For example, a 19.3-g. sample of heptane-choleic acid (neut. equiv. 407) prepared from 10 g. of *n*-heptane and 25 g. of desoxycholic acid was placed in a 125-ml. distilling flask with a thermometer dipping into the powdered solid and the whole heated in an oil-bath. No observable effect was noted until after three hours (by which time the inside thermometer had attained 150°) when a visible crack appeared in the powdered solid and the latter began to shrink. During a final hour of heating the inside thermometer rose from 150° to 171°, the flask contents melted to a clear viscous liquid, and about 0.5 ml. of clear distillate weighing 0.2852 g. was collected. This product had a b. p. of 98–99° (recorded for *n*-heptane 98.4°) and had refractive index $n^{23}D$ 1.3842 (original *n*-heptane used 1.3845, recorded $n^{20}D$ 1.3877). This was taken as evidence that it was in fact *n*-heptane. The recovery was 36.5% theoretical.

In a second experiment entirely similar except that the *n*-heptane-choleic acid had previously been washed with ether (to see if exchange of ether for hydrocarbon would occur) 16.05 g. gave 0.4431 (67.6%) of *n*-heptane, b. p. 97–98.5°, $n^{23}D$ 1.3848. (Note the value for ether is much lower, *viz.*, 1.3526.) Furthermore, the loss in weight of the charge was 0.653 g. representing 4.07%; the per cent. of *n*-heptane in *n*-heptane-hexacholeic acid is 4.08%. During neither of these two distillations was any trace of carbon dioxide detectable in an attached barium hydroxide bubbler.

The Action of Aqueous Alkali on Alkane-choleic Acids.—Two samples of *n*-heptane-hexacholeic acid were dissolved, one in excess aqueous sodium hydroxide, the other in excess aqueous ammonium hydroxide. Both solutions were completely clear and showed no sign of any hydrocarbon. Upon acidification of these solutions and vacuum drying of the products, the latter shrank around 100–120°, gave a *DT* of 148° and finally melted at 168–169°. Further drying of the product from ammonium hydroxide in the oven at 85° for eighteen hours, then at 110° for seven hours gave material which still showed a *DT* of 147–150° with no sign of softening or shrinking. This is definite evidence for the survival of the original *n*-heptane-choleic acid.

Summary

1. Thirty-four paraffin hydrocarbons have been shown to form with desoxycholic acid (in methyl alcohol) easily reproducible definite molecular compounds in which one mole of hydrocarbon is combined with from two to eight molecules of the bile acid.

2. Although the characteristics of these alkane-choleic acids proved inadequate to constitute a general means of identification, their ability to retain the hydrocarbon in alkaline solutions may be found useful in other fields of interest.

CAMBRIDGE, MASS. RECEIVED AUGUST 11, 1948

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Optically Active Compounds Related to Methadon

BY ALBERT POHLAND, FREDERICK J. MARSHALL AND THOMAS P. CARNEY

l-Methadon,[1] *l*-6-dimethylamino-4,4-diphenyl-3-heptanone, has been reported to have twice the analgesic activity of *dl*-Methadon.[2,3] The greatly increased activity of the levo isomer as compared with the racemic mixture led to the preparation of the optical isomers of compounds related to Methadon for pharmacological examination.

dl-4-Dimethylamino-2,2-diphenylvaleronitrile was resolved through the *d*-bitartrate salt by essentially the procedure of Thorpe, Walton, and Ofner.[3] The yield of both isomers was over 70% of the theoretical amount. The *d*- and *l*-nitriles were readily converted to the ketones by means of ethylmagnesium bromide. The observed rotations for *d*- and *l*-Methadon hydrochlorides were $[\alpha]^{25}D$ +126° and −127° (c = 1.0 in water). The calculated specific rotations for the cations in water are +141° and −142°. Thorpe, Walton, and Ofner[3] reported $[\alpha]D$ +143° and −145° for the cations of *d*- and *l*-Methadon in water. Brode and Hill[4] resolved Methadon through the *d*-bitartrate and obtained $[\alpha]^{23}D$ +127.5° and −127.8° (c = 2.96 in water) for *d*- and *l*-Methadon hydrochlorides.

(1) Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **134**, 1483 (1947). The Council recognized the term Methadon in place of the term Amidone.

(2) R. H. Thorpe, E. Walton and P. Ofner, *Nature*, **159**, 679 (1947).

(3) R. H. Thorpe, E. Walton and P. Ofner, *ibid.*, **160**, 605 (1947).

(4) W. R. Brode and M. W. Hill, *J. Org. Chem.*, **13**, 191 (1948)