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)

TABLE I

Isomer	$(CH_3)_2NCH(CH_3)\cdot CH_3C(C_6H_5)_2R$ R	M. p.,[a] °C.	Yield, %	$[\alpha]^{25}D$ in water	c	Molecular formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Rat tail burn test Threshold dose, mg./kg.[b]	Rat tail burn test Activity, metadon,[c] %
d	$-COC_2H_5$	239–241 dec.	75	+126°	1.0	$C_{21}H_{27}NO\cdot HCl$	4.05	4.30	10.25	10.03	24	8
l	$-COC_2H_5$	239–241 dec.	71	−127°	1.0	$C_{21}H_{27}NO\cdot HCl$	4.05	3.96	10.25	10.23	1.25	160
α-dl	$-CH(OH)C_2H_5$	192–193	86			$C_{21}H_{29}NO\cdot HCl$	4.03	3.98	10.19	10.13	10	20
α-d	$-CH(OH)C_2H_5$	169–171	93	+ 34°	0.26	$C_{21}H_{29}NO\cdot HCl$	4.03	3.81	10.19	10.10	80	3
α-l	$-CH(OH)C_2H_5$	169–171	90	− 34°	.30	$C_{21}H_{29}NO\cdot HCl$	4.03	3.95	10.19	10.11	5	40
α-dl	$-CH(O_2CCH_3)C_2H_5$	211–213	80			$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.60	9.09	9.22	1.5	133
α-d	$-CH(O_2CCH_3)C_2H_5$	200–203	84	+ 57°	.26	$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.58	9.09	9.05	1	200
α-l	$-CH(O_2CCH_3)C_2H_5$	201–202.5	89	− 59°	.23	$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.58	9.09	8.92	5.5	37
dl	$-CO_2C_2H_5$	178.5–180 dec.	32			$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.85	9.80	9.82	10	20
d	$-CO_2C_2H_5$	171–173 dec.		+ 39°	.26	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.84	9.80	9.62	10	20
l	$-CO_2C_2H_5$	172–173 dec.		− 38°	.20	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.78	9.80	9.73	60	3

[a] Melting points are uncorrected. [b] Subcutaneous. [c] Compared with *dl*-Methadon at 2 mg./kg.

Catalytic reduction of *dl*-Methadon has been reported to give only one of the two possible pairs of diastereoisomeric carbinols.[5,6] *d*- and *l*-Methadon were reduced catalytically to yield only two of the four possible optical isomers. These are designated as the α-isomers. The direction of optical rotation changed. *d*-Methadon hydrochloride was reduced to *α-l*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride, $[\alpha]^{25}D$ −34° (*c* = 0.30 in water). *l*-Methadon hydrochloride was reduced to *α-d*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride, $[\alpha]^{25}D$ +34° (*c* = 0.26 in water).

The *α-d*- and *α-l*-carbinol hydrochlorides were acetylated in pyridine solution by means of acetic anhydride. The observed rotations for *α-d*- and *α-l*-5-acetoxy-2-dimethylamino-4,4-diphenylheptane hydrochlorides were $[\alpha]^{25}D$ +57° and −59° (*c* = 0.2 in water).

The *d*- and *l*-nitriles were hydrolyzed by means of 70% sulfuric acid to the acids and, without isolation, converted to the ethyl esters. The observed rotations of the *d*- and *l*-ethyl 4-dimethylamino-2,2-diphenylvalerate hydrochlorides were $[\alpha]^{25}D$ +39° and −38° (*c* = 0.2 in water).

A preliminary evaluation of the analgesic activity of these compounds was made by means of the rat tail burn method. The subcutaneous threshold dosages and activities as compared with *dl*-Methadon are shown in Table I. Detailed results will be reported elsewhere.

We are indebted to Dr. K. K. Chen, Dr. C. C. Scott and Mr. E. B. Robbins for the pharmacological data reported.

Experimental

Resolution of *dl*-4-Dimethylamino-2,2-diphenylvaleronitrile.—A warm solution containing 83 g. (0.3 mole) of *dl*-nitrile[7] and 45 g. (0.3 mole) of *d*-tartaric acid in 500 cc. of acetone and 50 cc. of water was cooled to yield 62 g. of *l*-nitrile *d*-bitartrate, m. p. 110–115°. After one recrystallization from aqueous acetone solution, the *l*-nitrile *d*-bitartrate melted at 114–117°, $[\alpha]^{23}D$ + 14° (*c* = 1.0 in water). The *l*-nitrile was regenerated with dilute sodium hydroxide and recrystallized from aqueous ethanol, m. p. 99–101°, wt. 31 g. (75%), $[\alpha]^{23}D$ −50° (*c* = 1.0 in ethanol).

The acetone mother liquor was concentrated to dryness *in vacuo*, treated with dilute sodium hydroxide, and the *d*-nitrile recrystallized three times from aqueous ethanol solution, m. p. 97–100°, wt. 30 g. (72%), $[\alpha]^{25}D$ + 47° (*c* = 1.0 in ethanol).

***α-dl*-, *α-d*- and *α-l*-6-Dimethylamino-4,4-diphenyl-3-heptanol Hydrochlorides.**—The nitriles were readily converted to the ketones by means of excess ethylmagnesium bromide.[8]

The ketone hydrochlorides in water solution were readily converted to the carbinol hydrochlorides at 3 atmospheres pressure of hydrogen using Adams platinum oxide catalyst. The water was removed *in vacuo* and the product crystallized from ethanol–ether solution. *d*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride was reduced to *α-l*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride. *l*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride was reduced to *α-d*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride.

***α-dl*-, *α-d*- and *α-l*-5-Acetoxy-2-dimethylamino-4,4-diphenylheptane Hydrochloride.**—A reaction mixture containing one part of the alcohol hydrochloride, one part of acetic anhydride, and two parts of pyridine was heated overnight at 50°. The resulting solution was diluted with ether until cloudy and chilled. The product was recrystallized from ethanol–ether solution.

***dl*-, *d*-, and *l*-Ethyl 4-Dimethylamino-2,2-diphenylvalerate Hydrochloride.**—A solution of 100 g. (0.36 mole) of *dl*-2,2-diphenyl-4-dimethylaminovaleronitrile in 300 g. of 70% sulfuric acid was stirred and heated in an oil-bath at 150° for eighteen hours.

The oil-bath was cooled to 120° and the flask fitted with a dropping funnel and distilling condenser. One liter of absolute ethanol was added during ten hours, allowing the alcohol to distill. The reaction mixture was poured onto ice and made basic with 50% sodium hydroxide solution. The oil was extracted with ether, dried over magnesium sulfate, and then distilled *in vacuo*. The fraction boiling at 158–168° (0.70 mm.), wt. 62 g., was collected. The hydrochloride was prepared in ether and recrystallized from ethanol–ether solution, m. p. 178.5–180°,[8] wt. 42 g. (32%).

The *d*- and *l*-isomers were prepared by the same procedure using the resolved nitriles.

Summary

The optical isomers of *α-dl*-6-dimethylamino-4,4-diphenyl-3-heptanol, *α-dl*-5-acetoxy-2-dimeth-

(5) M. E. Speeter, W. M. Byrd and L. C. Cheney, THIS JOURNAL, **71**, 57 (1949).

(6) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(7) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188 (1947); E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

(8) Subsequent to submission of this paper for publication, this compound has been reported by J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2906 (1948), to melt at 151–152°. Following their procedure we have been able to obtain only the crystalline modification melting at 178.5–180°.

ylamino-4,4-diphenylheptane, and *dl*-ethyl 4-dimethylamino-2,2-diphenylvalerate hydrochlorides have been prepared using *d*- and *l*-4-dimethylamino-2,2-diphenylvaleronitrile as the starting materials.

INDIANAPOLIS, INDIANA RECEIVED JULY 21, 1948

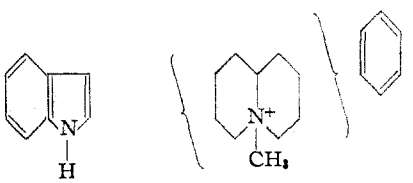
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Curariform Activity and Chemical Structure. III. Syntheses in the 3-Indolylmethylamine Series[1]

BY L. E. CRAIG[2] AND D. S. TARBELL

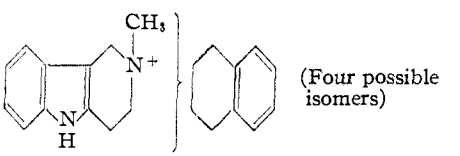
The most physiologically effective of the curare alkaloids belong to the calabash curare group. Of the eighteen alkaloids which have been isolated from calabash curare, the most active is C-toxiferine-I, which paralyzes frogs in doses of 0.005–0.009 mg./kg.[3]

Karrer and Schmid[4] showed that C-curarine-I chloride ($C_{20}H_{21}ClN_2$) contains a secondary, non-basic nitrogen, which is the nitrogen of an indole ring-system, and a quaternary nitrogen present in a tetrahydroisoquinoline ring system, common to two rings, and containing a methyl group. On the basis of this, the following structure can be drawn



Since the benzene ring must be attached in a position to give a tetrahydroisoquinoline, fourteen isomeric hexahydrobenzoindoloquinolizines are possible.

The most probable structures are those in which the quaternary nitrogen is separated from the indole ring by one carbon. On the basis of similarity of color reactions, Schmid and Karrer[3] postulated that C-toxiferine-I might be related to tetrahydro-9-pyrido(3,4-b)indoles, which would mean that the above proposed structure would have the β-carboline arrangement of the nitrogen atoms. Wieland, Witkop and Bähr[5] isolated isoquinoline, skatole and impure 3-ethylindole from a zinc dust distillation of another of the calabash curare alkaloids, C-dihydrotoxiferine-I chloride ($C_{20}H_{23}ClN_2$). The isolation of the 3-ethylindole supports the β-carboline structure proposed by Schmid and Karrer; however, the isolation of skatole suggests the γ-carboline structure, as follows:



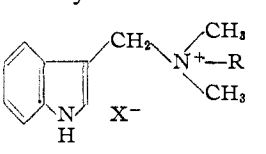
The present papers reports the synthesis of, and the preliminary pharmacological tests on, compounds containing a quaternary nitrogen in the γ-carboline structure, that is, 3-indolylmethylammonium salts.

The 3-indolylmethylamines were prepared conveniently by the Mannich reaction, essentially by the method of Kühn and Stein.[6]

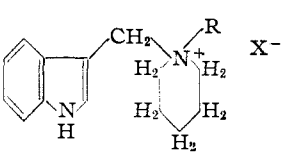
When the Mannich reaction was attempted with indole, formaldehyde and 1,2,3,4-tetrahydroisoquinoline hydrochloride, methylene-bis-(N,N′-1,2,3,4-tetrahydroisoquinoline) and a polymeric material[7] were obtained. The methylene-bis-compound was obtained in good yield when the amine hydrochloride and aqueous formaldehyde were heated together. Attempts to prepare derivatives of this previously unreported compound led to some anomalous results.

On treatment of the methylene-bis-compound with ethanolic picric acid, the picrate of 1,2,3,4-tetrahydroisoquinoline was obtained. Treatment of the bis-compound with methyl iodide yielded N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide. The cleavage of the methylenediamine linkage with ethanolic picric acid is not without precedent, as Elderfield and Kreysa[8] reported a similar reaction.

The tertiary 3-indolylmethylamines were converted by conventional methods into various quaternary salts.



I, R = $-CH_3$
II, R = $-CH_2C_6H_5$
III, R = $-CH_2CH_2C_6H_5$



IV, R = $-CH_3$
V, R = $-CH_2C_6H_5$

(1) For the second paper of this series, see Craig and Tarbell, THIS JOURNAL, **70**, 2783 (1948).

(2) Aided by a Grant from the National Foundation for Infantile Paralysis. Present address, General Aniline and Film Corporation, Easton, Pennsylvania.

(3) Schmid and Karrer, *Helv. chim. acta*, **30**, 1162 (1947).

(4) Karrer and Schmid, *ibid.*, **29**, 1853 (1946).

(5) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

(6) Kühn and Stein, *Ber.*, **70**, 567 (1937).

(7) Indole has been reported to polymerize in the presence of acids; see Schmitz-Dumont, Hamann and Diebold, *ibid.*, **71**, 205 (1938).

(8) Elderfield and Kreysa, THIS JOURNAL, **70**, 44 (1948).