of the amine and α-formyl-2-hydroxyacetophenone for 1 hour on a steam-bath.

Reaction of β-Anilino-2-hydroxyacrylophenone with Piperidine.—One gram of β-anilino-2-hydroxyacrylophenone was heated on a steam-bath for 2 hours with 5.2 g. of piperidine. Trituration with water resulted in a quantitative yield of 2-hydroxy-β-piperidinoacrylophenone; m.p. 123–124°. The reaction was reversed by heating 2-hydroxy-β-piperidinoacrylophenone with excess aniline.

LINCOLN 8, NEBRASKA

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Preparation of Substituted 3-Piperidones[1]

BY F. F. BLICKE AND JOHN KRAPCHO[2,3]

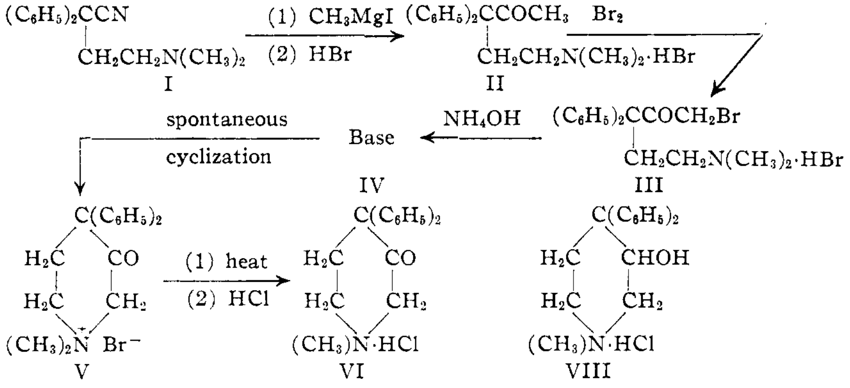
RECEIVED MARCH 27, 1952

The bromination of basic ketone hydrobromides, analogous to Amidone in structure, produced bromo derivatives which, in the form of their free bases, cyclized spontaneously to methobromides of substituted 3-piperidones. The latter compounds when heated, lost methyl bromide with the formation of substituted 3-piperidones which were isolated as hydrochlorides.

Substituted 3-piperidones have been obtained from a diester by a Dieckmann condensation[4] and from a basic γ-bromo ketone by cyclization.[5]

In this paper we have described a synthesis for substituted 1-methyl-3-piperidones which, in the last step, consists of a cyclization of an α-bromo ketone. The procedure is especially adaptable for the preparation of a wide variety of substituted 1-alkyl-3-piperidones.

The synthesis is illustrated below in the case of 1-methyl-4,4-diphenyl-3-piperidone.[6] The yield of each compound (I–VI) was at least 80%. When the free base of VI was treated with methyl bromide, the methobromide V was obtained.[6] This experiment proved that there was no ring contraction during the conversion of V into VI. By the use of the proper disubstituted acetonitrile, basic alkyl chloride and Grignard reagent, various 2-, 4-, 5- and 6-substituted 1-methyl-3-piperidones were obtained.



It was found that the nitrile I could be hydrolyzed to 2,2-diphenyl-4-dimethylaminobutyric acid hydrobromide in 84.5% yield by refluxing it with 48% hydrobromic acid. The corresponding diethylamino nitrile, by the same process, yielded the corresponding diethylaminobutyric acid hydrobromide in 85% yield.[7]

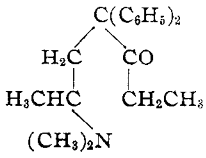
Bromination of II with two molecular equivalents of bromine yielded a dibromo derivative.

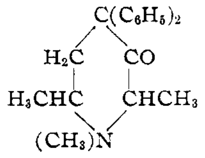
The ketone V was reduced to the corresponding alcohol VII. When the latter was heated under reduced pressure, methyl bromide was evolved with the formation of the same alcohol, VIII, which was obtained by reduction of ketone VI. Alcohol VIII was converted into its acetyl, *p*-nitrobenzoyl and *p*-aminobenzoyl derivative.

1-Methyl-4-phenyl-4-cyclohexyl-, 1,2,5-trimethyl-4,4-diphenyl- and 1,2,6-trimethyl-4,4-diphenyl-3-piperidinol hydrochlorides were obtained by catalytic reduction of the corresponding 3-piperidone hydrochlorides. The first-mentioned piperidinol was converted into its acetyl derivative.

When the ketone V was treated with zinc and hydrochloric acid, compound II, in the form of its hydrochloride, was produced in 79% yield. Compound V probably was first reduced to the corresponding alcohol which underwent a "hydramine fission" similar to that observed in the case of other β-hydroxyamines.[8]

Amidone and isoamidone hydrobromides were


Amidone


"Cyclic Amidone"

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[1] Abstracts of Papers, 113th Meeting of the American Chemical Society, Chicago, Ill., April 19–23, 1948, p. 3K.

[2] This paper represents part of a dissertation submitted by John Krapcho in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, August, 1949.

[3] Parke, Davis and Company Fellow.

[4] S. M. McElvain, *et al.*, THIS JOURNAL, **55**, 1233 (1933); **71**, 896 (1949); **73**, 448 (1951); A. W. D. Avison and A. L. Morrison, *J. Chem. Soc.*, 1471 (1950).

[5] T. S. Work, *ibid.*, 194 (1946).

[6] In contrast to the smooth conversion of the quaternary compound V into the tertiary amine VI, it is interesting to note that Mannich and Gollasen (*Ber.*, **61**, 263 (1928)) obtained only a tar when they heated 1-methyl-3-pyrrolidone methobromide in an attempt to convert it into 1-methyl-3-pyrrolidone. However, they were successful in the elimination of methyl bromide after the quaternary ketone had been reduced to the secondary alcohol.

[7] D. J. Dupré, *et al.*, (*J. Chem. Soc.*, 500 (1949)) hydrolyzed these two nitriles by heating them with hydrochloric acid in sealed tubes at 150–160°.

[8] Paul Karrer, "Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1950, pp. 839, 867, 869 and 881; P. Rabe and W. Schneider, *Ann.*, **365**, 377 (1909).

TABLE I

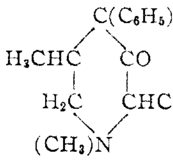
NITRILES, $RR'C(CN)CH_2CH_2N(CH_3)_2$

Hydrochlorides 1, 3 and 4 were recrystallized from isopropyl alcohol, 2 from absolute ethanol.

	R	R′	B.p., °C. (1–2 mm.)	Yield, %	Hydrochloride M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	C_6H_5	C_6H_5	152–155[a]	92	198–199	$C_{18}H_{21}N_2Cl$	9.31	9.27	11.79	11.80
2[b]	C_6H_5	CH_3	100–101	66	225–226	$C_{13}H_{19}N_2Cl$	11.74	11.79	14.85	14.86
3[c]	C_6H_5	$C_6H_{11}CH_2CH_2$	180–182	81	236–237	$C_{20}H_{31}N_2Cl$	8.37	8.37	10.59	10.63
4[d]	C_4H_3S[e]	C_6H_{11}	145–148	90	202–203[d]	$C_{16}H_{25}N_2SCl$	8.95	9.14	11.33	11.50

[a] A. J. Dupré, *et al.*, (ref. 7) obtained this compound in 70% yield; b.p. 150–152° (0.8 mm.). [b] Prepared from phenyl-β-dimethylaminoethylacetonitrile (C. E. Kwartler and P. Lucas, THIS JOURNAL, 68, 2395 (1946)) and methyl iodide by the general method used for compound 1. [c] Obtained by the use of phenyl-β-dimethylaminoethylacetonitrile and β-cyclohexylethyl bromide. [d] Prepared from 2-thienylcyclohexylacetonitrile and β-dimethylaminoethyl chloride in the same general manner as compound 1. Compound 4 has been obtained by A. J. Zambito (ref. 10) from 2-thienyl-β-dimethylaminoethylacetonitrile, cyclohexyl bromide and sodamide; hydrochloride, m.p. 201–203°. [e] 2-Thienyl.

brominated and the bromo derivatives were cyclized. Thermal decomposition of the resulting quaternary bromides yielded the cyclic analogs of Amidone and isoamidone.



"Cyclic Isoamidone"

The piperidones were tested in the Parke, Davis and Company pharmacological laboratories. Most of the products proved to be quite toxic and none of them exhibited promising analgesic activity.

Experimental Part

2-Thienylcyclohexylacetonitrile.—A suspension of 40.0 g. (1.02 moles) of pulverized sodamide in 250 cc. of toluene was prepared in a 2-liter, 3-necked flask equipped with a Hershberg stirrer, a dropping funnel and a condenser fitted with a soda-lime tube. The flask was immersed in an ice–salt-bath and the mixture was stirred during the dropwise addition (45 minutes) of a solution prepared from 123.0 g. (1 mole) of 2-thienylacetonitrile,[9] 163.0 g. (1 mole) of cyclohexyl bromide and 500 cc. of benzene. After 2 hours the nearly black mixture was stirred for 3 hours at room temperature and was then refluxed for 2 hours. Water (250 cc.) was added to the cooled mixture, the aqueous layer was separated and extracted with toluene. The organic layers were combined, washed with water and the solvents were removed under reduced pressure. The yield after two distillations was 97.8 g. (47.7%); b.p. 129–132° (1–2 mm.).

Anal. Calcd. for $C_{12}H_{15}NS$: N, 6.82. Found: N, 6.76.

Diphenyl-β-dimethylaminoethylacetonitrile (Compound 1, Table I).—A suspension of 43.0 g. (1.1 moles) of pulverized sodamide in 300 cc. of toluene was cooled in an ice–salt-bath and stirred during the dropwise addition (1 hour) of 193.0 g. (1 mole) of diphenylacetonitrile, dissolved in 300 cc. of toluene. The mixture was stirred for 1.5 hours and then a toluene solution of β-dimethylaminoethyl chloride (obtained from 1.1 moles of the hydrochloride) was added during a 15-minute period. The mixture was stirred for 4 hours, cooled, treated with 300 cc. of water and the product was isolated in the usual manner.

4-Dimethylamino- and 4-Diethylamino-2,2-diphenylbutyric Acid Hydrobromide.—A mixture of 13.2 g. of II and 100 cc. of 48% hydrobromic acid was refluxed for 17 hours. After removal of about one-half of the hydrobromic acid under reduced pressure, the product was allowed to separate from the residue. The salt was washed with hydrobromic acid and then with acetone; yield 15.4 g. (84.5%); m.p. 237–239° (dec.); recrystallization from absolute ethanol did not change the melting point.

Anal. Calcd. for $C_{18}H_{22}O_2NBr$: Br, 21.94. Found: Br, 21.95.

The diethylamino nitrile (9.5 g.) was hydrolyzed in the same manner, and then all of the hydrobromic acid was removed under reduced pressure. The residue was dried in a desiccator over solid sodium hydroxide and was then heated with 80 cc. of absolute ethanol. The undissolved ammonium bromide was removed by filtration, and dry ether was added to the filtrate. After several days the precipitated hydrobromide weighed 10.8 g. (85%); m.p. 185–186° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{26}O_2NBr$: Br, 20.37. Found: Br, 20.26.

3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide (Compound 1, Table II).—To methylmagnesium iodide, prepared from 28.0 g. of magnesium, 75 cc. (1.20 moles) of methyl iodide and 300 cc. of ether, there was added 96.0 g. (0.36 mole) of diphenyl-β-dimethylaminoethylacetonitrile dissolved in 500 cc. of benzene. The mixture was refluxed for 48 hours; a precipitate began to form after the first hour. The cold mixture was poured cautiously into 700 cc. of ice-cold, concentrated hydrochloric acid, the organic solvents were distilled from the mixture and the residue was refluxed for 12 hours. The mixture was cooled and the aqueous layer was decanted from the red oil. The latter was refluxed with 300 cc. of concentrated hydrochloric acid for 9 hours; an additional 200 cc. of hydrochloric acid was added and the mixture was refluxed for another 9 hours. The cooled mixture was made alkaline with concentrated sodium hydroxide solution and then extracted thoroughly with ether. The dried ether solution was treated with hydrogen bromide. The precipitated hydrobromide, after it had been triturated with ether and then with isopropyl alcohol, weighed 118.3 g. (89.5%).

The other ketones listed in Table II were prepared from the following compounds: 2, from phenylmethyl-β-dimethylaminoethylacetonitrile and methylmagnesium iodide; 3, from phenylhexyl-β-dimethylaminoethylacetonitrile[10] and methylmagnesium iodide; 4, from phenyl-β-cyclohexylethyl - β - dimethylaminoethylacetonitrile and methylmagnesium iodide; 5, from phenylcyclohexyl-β-dimethylaminoethylacetonitrile[10] and methylmagnesium iodide; 6, from 2-thienylcyclohexyl-β-dimethylaminoethylacetonitrile and ethylmagnesium bromide; 7, from diphenyl-β-dimethylaminoethylacetonitrile and ethylmagnesium bromide; 8, from diphenyl-β-dimethylaminoethylacetonitrile and β-phenylethylmagnesium bromide.

1-Bromo-3,3-diphenyl-5-dimethylamino-2-pentanone Hydrobromide (Compound 1, Table III).—A mixture of 25.0 g. (0.069 mole) of 3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide and 70 cc. of acetic acid was refluxed and a solution of 11.0 g. (0.069 mole) of bromine in 30 cc. of acetic acid was added, dropwise, during a 15-minute period. The mixture was refluxed for 15 minutes, about one-half of the acetic acid was distilled and 200 cc. of ether was added to the cooled residue; yield 27 g. (89%) after recrystallization from 30 cc. of isopropyl alcohol.

1,1-Dibromo-3,3-diphenyl-5-dimethylamino-2-pentanone Hydrobromide.—3,3-Diphenyl-5-dimethylamino-2-pentanone hydrobromide (14.5 g., 0.04 mole), dissolved in 40 cc. of acetic acid, was brominated in the manner described above with 12.8 g. (0.08 mole) of bromine, dissolved in 25 cc. of the same solvent. The product was recrystallized

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(9) F. F. Blicke and F. Leonard, THIS JOURNAL, **68**, 1934 (1946).

(10) A. J. Zambito, Dissertation, University of Michigan, 1947.

TABLE II

KETONES, RR'C($CH_2CH_2NMe_2$)COR'

All of the hydrobromides except 2 were recrystallized from isopropyl alcohol; 2 was recrystallized from absolute ethanol.

	R	R'	R″	B.p., °C. (1-2 mm.)	Yield, %	Hydrobromide M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
1[a]	C_6H_5	C_6H_5	CH_3	156–158	89	171–173	$C_{19}H_{24}ONBr$	3.87	4.05	22.06	22.17
2	C_6H_5	CH_3	CH_3	95–98	64	163–165	$C_{14}H_{22}ONBr$	4.67	4.67	26.62	26.69
3	C_6H_5	C_6H_{13}	CH_3	140–143	70	129–130	$C_{19}H_{32}ONBr$	3.78	3.83	21.58	21.67
4	C_6H_5	$C_6H_{11}CH_2CH_2$	CH_3	169–172	70	178–179	$C_{21}H_{34}ONBr$	3.53	3.60	20.16	20.14
5	C_6H_5	C_6H_{11}	CH_3	......	69	226–228	$C_{19}H_{30}ONBr$	3.80	3.90	21.70	21.53
6	C_4H_3S[b]	C_6H_{11}	C_2H_5	151–153	89	186–187	$C_{18}H_{30}ONSBr$	3.61	3.64	20.58	20.61
7[a]	C_6H_5	C_6H_5	C_2H_5	......	95	142–143	$C_{20}H_{26}ONBr$	3.72	3.83	21.24	21.32
8	C_6H_5	C_6H_5	$C_6H_5CH_2CH_2$	206–208[c]	70	.....[d]					

[a] Dupré, *et al.*, (ref. 7) obtained the base in 78% yield; the hydrochloride was described. [b] The hydrochloride was described by Zambito (ref. 10). [c] *Anal.* Calcd. for $C_{26}H_{29}ON$: N, 3.77. Found: N, 3.78. [d] The hydrobromide was obtained as an oil. The hydrochloride, after recrystallization from water, was isolated as a monohydrate; m.p. 109–113°. *Anal.* Calcd. for $C_{26}H_{30}ONCl \cdot H_2O$: Cl, 8.32. Found: Cl, 8.34. Methyl iodide (1 g.) was added to an ethereal solution of 1 g. of the base. The precipitated methiodide was recrystallized from water; m.p. 187–188°; since the product softened at 94°, it may have contained water of crystallization.

TABLE III

BROMOKETONE HYDROBROMIDES, RR'C($CH_2CH_2NMe_2$)COR'

Compounds 1, 2, 3, 4, 6 and 7 were recrystallized from isopropyl alcohol, 5 and 9 from acetic acid.

	R	R'	R″	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
1	C_6H_5	C_6H_5	CH_2Br	158–159	89	$C_{19}H_{23}ONBr_2$	3.17	3.13	36.23	36.48
2	C_6H_5	CH_3	CH_2Br	151–152	95	$C_{14}H_{21}ONBr_2$	3.70	3.70	42.15	42.58
3	C_6H_5	C_6H_{13}	CH_2Br	138–139	80	$C_{19}H_{31}ONBr_2$	3.12	3.12	35.57	35.12
4	C_6H_5	$C_6H_{11}CH_2CH_2$	CH_2Br	158–159	84	$C_{21}H_{33}ONBr_2$	2.95	2.92	33.63	33.67
5	C_6H_5	C_6H_{11}	CH_2Br	182–184	86	$C_{19}H_{29}ONBr_2$	3.13	3.15	35.74	35.74
6	C_4H_2BrS[b]	C_6H_{11}	$CHBrCH_3$	179–180	99	$C_{18}H_{28}ONSBr_3$	2.57	2.58	43.89	43.41
7	C_6H_5	C_6H_5	$CHBrCH_3$	173–174	92	$C_{20}H_{25}ONBr_2$	3.08	3.12	35.11	35.18
8	C_6H_5	C_6H_5	$CHBrCH_2C_6H_5$	.....[c]						
9	2-Bromo-4,4-diphenyl-6-dimethylamino-3-heptanone hydrobromide (brominated Amidone)			190	97	$C_{21}H_{27}ONBr_2$	2.99	2.99	34.06	34.13
10	2-Bromo-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone hydrobromide (brominated isoamidone)			195[d]	97	$C_{21}H_{27}ONBr_2$	2.99	2.99	34.06	34.19

[a] All of the salts except 3 melted with decomposition. [b] 5-Bromo-2-thienyl. [c] This salt could not be crystallized. [d] This salt precipitated from an acetic acid solution with solvent of crystallization; m.p. 123–125° (dec.). *Anal.* Calcd. for $C_{21}H_{22}ONBr_2 \cdot CH_3COOH$: N, 2.65; Br, 30.20. Found: N, 2.65; Br, 30.56. The product was obtained solvent-free by solution in chloroform and precipitation with ether.

from 15 cc. of acetic acid; yield 17.4 g. (83%); m.p. 193–194° (dec.).

Anal. Calcd. for $C_{19}H_{22}ONBr_3$: N, 2.69; Br, 46.10. Found: N, 2.72; Br, 45.89.

1-Bromo-3-phenyl-3-hexyl-5-dimethylamino-2-pentanone Hydrobromide.—During a 30-minute period, a solution of 7.7 g. (0.048 mole) of bromine in 50 cc. of carbon tetrachloride was added to a refluxing solution of 17.8 g. (0.048 mole) of 3-phenyl-3-hexyl-5-dimethylamino-2-pentanone hydrobromide in 100 cc. of carbon tetrachloride. The mixture was refluxed for 15 minutes and then cooled. The product, which crystallized gradually, was recrystallized from isopropyl alcohol; yield 17.2 g. (80%).

2-Bromo-4-(5-bromo-2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone Hydrobromide.—4-(2-Thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide (15.5 g., 0.04 mole), dissolved in 20 cc. of hot acetic acid, was treated with 12.8 g. (0.08 mole) of bromine, dissolved in 25 cc. of acetic acid, during a 20-minute period. The mixture was refluxed for 30 minutes and then cooled. Upon the addition of ether, 21.5 g. (99%) of product precipitated which melted at 179–180° (dec.); recrystallization from isopropyl alcohol did not change the melting point.

All of the other bromo ketones listed in Table III were obtained in the manner described for compound 1.

The bases of Amidone and isoamidone were prepared by the procedure of Schultz, Robb and Sprague.[11] The hydrobromide of Amidone melted at 224°.[12]

1-Methyl-4,4-diphenyl-3-piperidone Methobromide (Methobromide 1, Table IV).—Ammonia water (28%, 9 cc.) was added to a cooled, stirred suspension of 26.4 g. (0.06 mole) of 1-bromo-3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide in 120 cc. of water. A heavy precipitate formed immediately. After 4 hours the product was filtered, washed with a small amount of cold water and recrystallized from absolute ethanol.

In those instances (compounds 2, 3 and 4, Table IV) in which the methobromide did not precipitate from the ammoniacal solution, the solution was evaporated to dryness on a steam-bath. The pulverized residue was refluxed with isopropyl alcohol, the insoluble ammonium bromide was removed by filtration and the filtrate concentrated under reduced pressure. The product precipitated from the cooled filtrate.

1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride (Hydrochloride 1, Table IV).—1-Methyl-4,4-diphenyl-3-piperidone methobromide (6.5 g.) was heated in a 25-cc. distillation flask with a free flame under 0.02 mm. pressure. Methyl bromide was evolved and the distillation product, a light yellow oil which solidified in the receiver, was dissolved in ether and precipitated with hydrogen chloride. After recrystallization from absolute ethanol, the material melted at 235–236° (dec.). The free base, after recrystallization from isopropyl alcohol, melted at 100–102°.

Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Methobromide (V) into 3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide (II).—To a warm mixture of 4.0 g. of V, 100 cc. of concentrated hydrochloric acid and 50 cc. of water, there was added, during the course of an hour, 15.0 g. of zinc dust. The mixture was heated on a steam-bath until all of the zinc had dissolved, cooled, treated with

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[11] E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 2454 (1947).

[12] R. H. Thorp, E. Walton and P. Ofner, *Nature*, **159**, 679 (1947); **160**, 605 (1947).

TABLE IV

SUBSTITUTED 1-METHYL-3-PIPERIDONE METHOBROMIDES AND HYDROCHLORIDES

	Substituents								
	2	3	4	5	6	M.p., °C.^{a}	Yield, %	M.p., °C.	Yield, %
1	H	C_6H_5	C_6H_5	H	H	231–233	82	235–236	80
2	H	C_6H_5	CH_3	H	H	207–208	80	194–195	73
3	H	C_6H_5	C_6H_{13}	H	H	165–167	85	177–178	71
4	H	C_6H_5	$C_6H_{11}CH_2CH_2$	H	H	185–187	80	209–210	65
5	H	C_6H_5	C_6H_{11}	H	H	247–248	95	208–210	74
6	CH_3	$C_4H_2SBr^b$	C_6H_{11}	H	H	235–237	99	216–218	86
7	CH_3	C_6H_5	C_6H_5	H	H	208–210	95	211–213	71
8	$C_6H_5CH_2$	C_6H_5	C_6H_5	H	H	130–131^c	74	202–204^d	90
9	CH_3	C_6H_5	C_6H_5	H	CH_3	228–229	96	219–220	86
10	CH_3	C_6H_5	C_6H_5	CH_3	H	209–210	97	140–142^e	80

		Methobromides				Hydrochlorides			
	Formula for base	Nitrogen, %		Bromine, %		Nitrogen, %		Chlorine, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{18}H_{19}ON$	3.89	3.83	22.18	21.97	4.64	4.61	11.75	11.64
2	$C_{13}H_{17}ON$	4.70	4.75	26.80	26.82	5.84	5.83	14.79	14.85
3	$C_{18}H_{27}ON$	3.80	3.84	21.70	21.70	4.52	4.57	11.44	11.51
4	$C_{20}H_{29}ON$	3.55	3.52	20.26	20.19	4.17	4.26	10.56	10.63
5	$C_{18}H_{25}ON$	3.82	3.84	21.82	21.83	4.55	4.52	11.52	11.52
6	$C_{17}H_{24}ONSBr$	3.01	3.02	34.35	34.82	3.44	3.44	28.36	28.05^f
7	$C_{19}H_{21}ON$	3.74	3.69	21.35	21.54	4.44	4.44	11.23	11.21
8	$C_{25}H_{25}ON$	2.74	2.81	15.65	15.58^c	3.20	3.19	8.10	8.09^d
9	$C_{20}H_{23}ON$	3.61	3.56	20.58	20.68	4.25	4.01	10.75	10.73
10	$C_{20}H_{23}ON^g$	3.61	3.44	20.58	20.53	3.90	3.86	9.85	9.98^e

[a] At the melting point, which varies somewhat with the rate of heating, these compounds decompose with the liberation of a gas. [b] 5-Bromo-2-thienyl. [c] Contains one molecular equivalent of isopropyl alcohol. [d] Contains one molecular equivalent of ethanol. [e] Contains one-half of a molecular equivalent of isopropyl alcohol. [f] Total halogen. [g] The picrate, obtained by the addition of an alcoholic solution of picric acid to an ethereal solution of the base, melted at 177° (dec.) after recrystallization from acetone. *Anal.* Calcd. for $C_{26}H_{26}O_1N_4$: N, 10.72. Found: N, 10.78. Methobromides: compounds 1, 5 and 9 were recrystallized from absolute ethanol, 2, 3, 4, 8 and 10 from isopropyl alcohol, 6 from acetic acid and 7 from water. Hydrochlorides: compounds 1, 2, 3, 6, 7, 8 and 9 were recrystallized from absolute ethanol, 4 and 10 from isopropyl alcohol and 5 from absolute ethanol–ether.

excess ammonia water, and the base extracted with ether. When hydrogen bromide was passed into the dried ether solution, the hydrobromide precipitated as an oil which became crystalline when it was triturated with ether and then with isopropyl alcohol; yield 3.2 g. (79%); mixed m.p. 171–173°.

Anal. Calcd. for $C_{19}H_{24}ONBr$: Br, 22.06. Found: Br, 22.02.

In another experiment the reaction product was isolated as the hydrochloride; mixed m.p. with 3,3-diphenyl-5-dimethylamino-2-pentanone hydrochloride, 185–186°.

Anal. Calcd. for $C_{19}H_{24}ONCl$: N, 4.41; Cl, 11.16. Found: N, 4.35; Cl, 11.21.

1-Methyl-4,4-diphenylpiperidinol Hydrochloride (VIII) (a).—A suspension of 4.5 g. of V and 0.5 g. of platinum oxide catalyst in 100 cc. of 90% alcohol was hydrogenated for 2 hours under an initial pressure of 45 pounds. After removal of the catalyst and solvent, the product, 1-methyl-4,4-diphenyl-3-piperidinol methobromide (VII), was recrystallized from absolute ethanol; yield 3.9 g. (85%); m.p. 216–217° (dec.).

Anal. Calcd. for $C_{19}H_{24}ONBr$: N, 3.87; Br, 22.06. Found: N, 3.76; Br, 21.73.

Compound VII (1.7 g.) was heated in a small distillation flask under reduced pressure. Methyl bromide was evolved and the 1-methyl-4,4-diphenyl-3-piperidinol sublimed on the walls of the flask. The base was dissolved in dilute hydrochloric acid, precipitated by the addition of excess ammonia water, and recrystallized from isopropyl alcohol; m.p. 158–159°.

(b).—A mixture of 10.8 g. of VI, 0.3 g. of platinum oxide catalyst and 100 cc. of 90% alcohol was hydrogenated in the manner described above. The crude product, VIII, weighed 10.9 g. (100%); m.p. 254–256° (dec.); m.p. 257–258° (dec.) after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{18}H_{22}ONCl$: N, 4.61; Cl, 11.67. Found: N, 4.69; Cl, 11.68.

The liberated base was mixed with the base obtained by method (a); mixed m.p. 158–159°.

1-Methyl-3-acetoxy-4,4-diphenylpiperidine Hydrochloride.—A mixture of 2.0 g. of VIII and 10 cc. of acetic anhydride was refluxed for one minute, cooled and diluted with ether. The product, after recrystallization from absolute ethanol–ether, weighed 1.9 g. (84%); m.p. 226–227° (dec.).

Anal. Calcd. for $C_{20}H_{24}O_2NCl$: N, 4.05; Cl, 10.26. Found: N, 4.05; Cl, 10.21.

1-Methyl-3-(4-nitrobenzoyloxy)-4,4-diphenylpiperidine Hydrochloride.—A mixture of 3.9 g. of VIII, 4.0 g. of 4-nitrobenzoyl chloride and 25 cc. of dry pyridine was heated on a steam-bath for 3.5 hours. After removal of the pyridine, the residue was triturated with ether, suspended in 20 cc. of water, the mixture made alkaline with sodium hydroxide and then extracted with ether. The dried extract was treated with hydrogen chloride, and the product (4.0 g., 67%) was recrystallized from absolute ethanol.

Anal. Calcd. for $C_{25}H_{25}O_4N_2Cl$: Cl, 7.83. Found: Cl, 7.87.

1-Methyl-3-(4-aminobenzoyloxy)-4,4-diphenylpiperidine Hydrochloride.—A mixture of 2.5 g. of the nitrobenzoate hydrochloride, 0.15 g. of platinum oxide catalyst and 40 cc. of 90% alcohol was hydrogenated, under an initial pressure of 45 pounds, for 2 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness in a nitrogen atmosphere. The residue was dissolved in 30 cc. of absolute ethanol, and cooled. The precipitated salt weighed 2.0 g. (76%); the product, which contained alcohol of crystallization, softened at about 200° and melted at 212–215° (dec.).

Anal. Calcd. for $C_{25}H_{27}O_2N_2Cl \cdot C_2H_5OH$: Cl, 7.54. Found: Cl, 7.52.

The hydrochloride was dissolved in hydrochloric acid and the solution was evaporated to dryness in a desiccator. The dihydrochloride obtained was recrystallized from absolute ethanol. It contained alcohol of crystallization, softened at about 200° and melted at 219–222° (dec.).

Anal. Calcd. for $C_{25}H_{28}O_2N_2Cl_2 \cdot C_2H_5OH$: N, 5.54; Cl, 14.03. Found: N, 5.48; Cl, 14.16.

1-Methyl-4-phenyl-4-cyclohexyl-3-piperidinol Hydrochloride.—This compound was obtained in practically quantitative yield by catalytic reduction of the corresponding piperidine hydrochloride by the process which has been described; m.p. 271–272° (dec.) after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{18}H_{28}ONCl$: N, 4.52; Cl, 11.44. Found: N, 4.55; Cl, 11.44.

1-Methyl-3-acetoxy-4-phenyl-4-cyclohexylpiperidine Hydrochloride.—A mixture of 3.2 g. of the piperidinol hydrochloride and 10 cc. of acetic anhydride was refluxed for several minutes, cooled and the product precipitated by the addition of ether; yield 2.7 g. (73%); m.p. 199–201° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{30}O_2NCl$: N, 3.98; Cl, 10.07. Found: N, 3.88; Cl, 9.89.

1,2,5-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride.—This product was prepared by catalytic reduction of the corresponding piperidone hydrochloride. After recrystallization from absolute ethanol, it melted at 284–285° (dec.).

Anal. Calcd. for $C_{20}H_{26}ONCl$: N, 4.22; Cl, 10.68. Found: N, 4.37; Cl, 10.77.

1,2,6-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride.—This substance, obtained by catalytic reduction of the corresponding piperidone hydrochloride, melted at 293° (dec.) after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{20}H_{26}ONCl$: N, 4.22; Cl, 10.68. Found: N, 4.24; Cl, 10.67.

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[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

Thiolesters of Perfluorocarboxylic Acids

BY MURRAY HAUPTSCHEIN, CHARLES S. STOKES AND EDWARD A. NODIFF

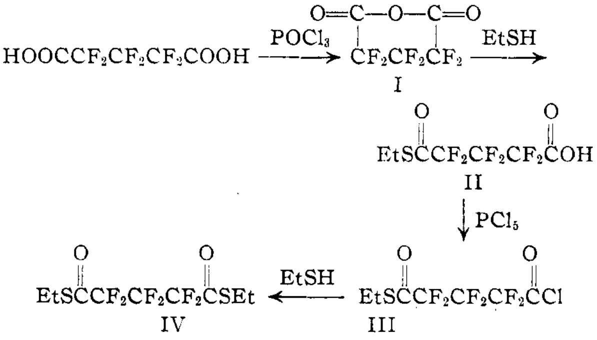
RECEIVED FEBRUARY 27, 1952

A series of thiolesters and dithiolesters of perfluoro-fatty acids has been prepared by the reaction of perfluoro-fatty acid chlorides and anhydrides with thiols and dithiols. Perfluoroglutaric anhydride has been prepared and converted to its dithiolester by a three step synthesis and to a polythiolester by a condensation polymerization reaction. Infrared absorption and molecular refractivity data of fluorinated thiolesters and oxygen esters are compared with their non-fluorinated analogs, and various correlations are noted and interpreted. New light is shed on the influence of perfluoroalkyl groups on adjacent carbonyl groups. Certain "characteristic" wave length bands for fluorocarbon derivatives have been empirically assigned.

The main purpose of this study was to prepare thiolesters of perfluoro-fatty acids, a class of compounds which has not been reported hitherto.[1] It was found that perfluoro-fatty acid chlorides and anhydrides react readily with thiols and dithiols, in the absence of any solvents, to form high yields of the corresponding thiolesters and dithiolesters.[2] In one case, an attempt to prepare a thiolester by the direct esterification of the free acid and mercaptan resulted in only a very small yield of thiolester.

Trifluoroacetic anhydride or acid chloride, pentafluoropropionyl chloride and *n*-heptafluorobutyryl chloride have been allowed to react with ethyl mercaptan and pentamethylene dimercaptan to form ethyl thioltrifluoroacetate, thiolpentafluoropropionate, thiolheptafluorobutyrate, as well as pentamethylene dithiol bis-(trifluoroacetate), bis-(pentafluoropropionate) and bis-(heptafluorobutyrate).

It was found necessary to go through the following sequence in order to prepare diethyl dithiolhexafluoroglutarate.



$$HOOCCF_2CF_2CF_2COOH \xrightarrow{POCl_3} \underset{\text{I}}{CF_2CF_2CF_2(C{=}O)_2O} \xrightarrow{EtSH} \underset{\text{II}}{EtSCOCF_2CF_2CF_2COOH} \xrightarrow{PCl_5} \underset{\text{III}}{EtSCOCF_2CF_2CF_2COCl} \xrightarrow{EtSH} \underset{\text{IV}}{EtSCOCF_2CF_2CF_2COSEt}$$

It was necessary to employ the anhydride (I) as the acylating agent since perfluoroglutaryl chloride, which should give IV directly, could be prepared only in extremely small yield by the action of phosphorus pentachloride or thionyl chloride on hexafluoroglutaric acid, the reaction resulting primarily in cleavage products due to loss of carbon dioxide.

Perfluoroglutaric anhydride (I) was prepared for the first time by the reaction of perfluoroglutaric acid with phosphorus oxychloride at 150°.[3] It is interesting to note that the boiling point of I (72°) is approximately *208° lower* than that of its "hydrocarbon" analog, glutaric anhydride. This is an even greater reduction than in the case of γ-perfluorobutyrolactone,[1] the empirical formula of which differs from I by one less C=O group. The perfluoro lactone boils at 18°[1] or *188° below* its hydrocarbon analog, γ-butyrolactone. These novel type perfluoro compounds are built up entirely of carbon and the two most *electronegative* elements, fluorine and oxygen. The repulsive forces between these molecules must be exceptionally large, and since there is absolutely no possibility of hydrogen-type bonding, the intermolecular forces of attraction are unusually weak.

In agreement with the poor reactivity of perfluorinated acids with thiols, none of the dithiolester (IV) was isolated in the reaction of I with ethyl mercaptan even though the molar ratio of mercaptan to I was 2:1. Instead, the acid-thiol-

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(1) Diethyl dithioltetrafluorosuccinate, $C_2H_5SCOCF_2CF_2COSC_2H_5$, has been prepared by the reaction of ethyl mercaptan with perfluorobutyrolactone (M. Hauptschein, C. S. Stokes and A. V. Grosse, THIS JOURNAL, **74**, 1974 (1952)).

(2) This procedure is an extension to "fluorocarbon" derivatives of the well-known method for preparing "hydrocarbon" thiolesters. For literature review see H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., Second Edition, 1943, p. 932.

(3) J. J. Padbury and E. L. Kropa, U. S. Patent 2,502,478 (April 4, 1950).