Models for the Study of Macrocyclic Ring–Chain Tautomerism

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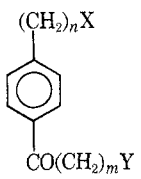
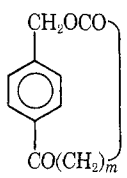
The phenomenon of ring–chain tautomerism[2] is well known in both natural and synthetic organic compounds, where the ring is five or six membered. Yet it has never been observed experimentally in any system involving a large ring (16 membered or higher), in spite of the fact that such large rings, once formed, are stable. The stability of macrocycles is illustrated by the increasingly large number of naturally occurring many-membered ring compounds being investigated. In particular, the macrolides,[3] macrocyclic keto lactones (containing other functional groups as well), bear a structural resemblance to smaller ring tautomers such as phthalaldehydic acid,[4] the alkaloid lycorenine,[5] and the sugars.

As a means of probing for the existence of macrocyclic ring–chain tautomerism, we have synthesized a number of new compounds (**1–12**), which are described in Table I. These were chosen for study because the corresponding ring tautomers would possess the *ansa* structure, which is known to be stable provided the ring is large.[6] It has already been pointed out[7a] that the keto lactone **13a**[7b] is a good model compound for such *ansa* ring tautomers derived from **2–10**.



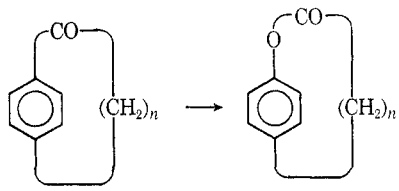
1–10
$n = 0, 1$
$m = 8, 10$



13a, $m = 8$
b, $m = 10$

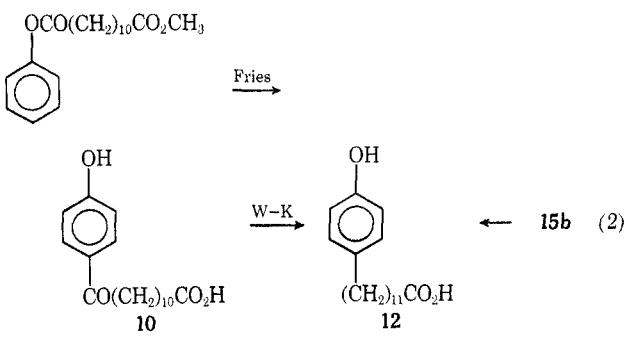
It was expected that cyclization of the bromo acid **2** would afford the homologous, strain-free lactone **13b**, by analogy to the previously reported synthesis of **13a**. Because this ring formation could not be effected cleanly under a variety of conditions, **2** was reduced to **11**, which was subsequently brominated with NBS. The product was a statistical mixture of two monobromo acids which were not amenable to separation, however; so this route to a macrocyclic lactone was not pursued further.

Entrance into a second series of model ring–chain compounds derived from phenolic acids was eventually achieved by a totally different route. Although all attempts to cyclize the phenolic acids **10** and **12** by acid catalysis or by way of the acid chlorides failed, the macrocyclic *ansa* lactone **15b** could be obtained indirectly. The successful route to its synthesis (eq 1) was the Baeyer–Villiger oxidation of the *ansa* ketone **14b**, which could be obtained by Huisgen's intramolecular, high-dilution Friedel–Crafts acylation.[8] It is striking that the ring expansion occurred smoothly with the 16-membered ketone **14b** but failed for the lower homolog **14a**. In the latter case, where the product **15a** would still contain a strained ring, the oxidation led to nonaromatic degradation products.



14a, $n = 9$ **15a**, $n = 9$
b, $n = 11$ **b**, $n = 11$ (1)

The distinctive nmr shielding effect on the bridge methylenes, evident in **14** and **15b**, varied somewhat with ring size. The structure of **15b** was confirmed by saponifying it to the phenolic acid **12** which was synthesized independently, as indicated in eq 2.



10 **12** (2)

As shown by their infrared, ultraviolet, and nmr spectra, compounds **2–10** and **12** exist at ambient temperatures solely as chain tautomers, within the limits of detection (5–10%). The most important criterion for the presence of ring tautomer was considered to be the appearance in the nmr spectrum of high-field protons caused by aromatic shielding of some of the bridge methylene hydrogens.[7b] Any chemical conversions led to new chain tautomers exclusively. Examples are provided in eq 3 and 4.

(1) (a) Part of this work was initiated during the tenure of a National Science Foundation Science Faculty Fellowship at the Max Planck Institut für experimentelle Medizin, Göttingen, Germany, 1964–1965; (b) taken in part from Ph.D. theses submitted by M. D. S. (1968) and R. J. P. (1967) to the University of New Hampshire; (c) National Science Foundation Summer Fellow, 1967; (d) National Defense Education Act Fellow, 1963–1966.

(2) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(3) (a) M. W. Miller, "The Pfizer Handbook of Microbial Metabolites," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, Chapter 7; (b) M. Berry, *Quart. Rev.*, (London), **17**, 343 (1963); (c) H. Griesbach and W. Hofheinz, *J. Roy. Inst. Chem.*, **88**, 332 (1964).

(4) J. Kagan, *J. Org. Chem.*, **32**, 4060 (1967), and references cited therein.

(5) T. Kitagawa, W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1066 (1955).

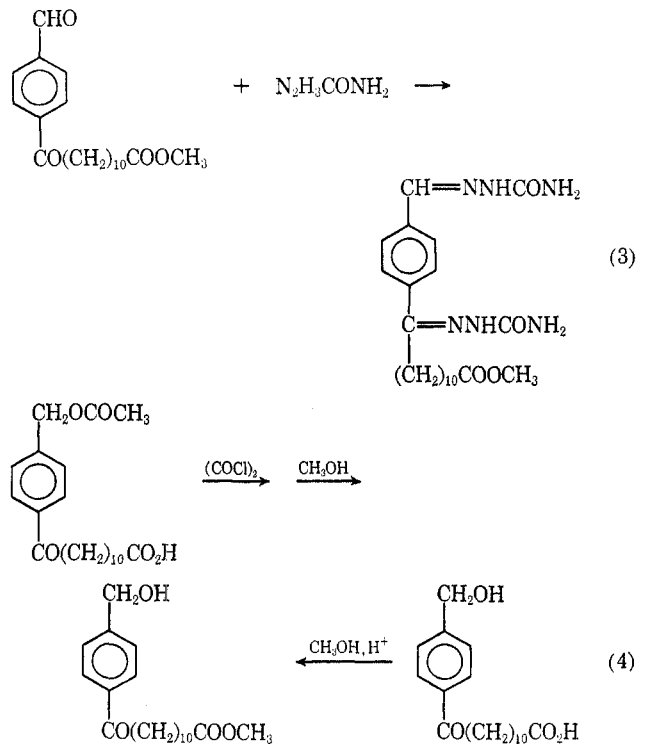
(6) A. Lüttringhaus, *Justus Liebigs Ann. Chem.*, **528**, 181 (1937); D. J. Cram, *Rec. Chem. Progr.*, **20**, 71 (1959).

(7) (a) P. R. Jones, M. D. Saltzman, and R. J. Panicci, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. ORGN 100; (b) P. R. Jones, R. J. Panicci, R. M. Stimson, and L. Port, *J. Org. Chem.*, **31**, 4277 (1966).

(8) R. Huisgen, W. Rapp, I. Ugi, H. Walz, and I. Clogger, *Justus Liebigs Ann. Chem.*, **586**, 52 (1954).

TABLE I
MODEL CHAIN COMPOUNDS

Compd	X	n	m	Y	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
A. $X(CH_2)_nC_6H_4CO(CH_2)_mY$												
1	H	1	10	CO_2H	86–88	$C_{19}H_{28}O_3$	74.96	9.27	...	75.11	9.45	...
1 semicarbazone	H	1	10	CO_2H	156–158	$C_{20}H_{31}N_3O_3$	66.45	8.64	11.62 (N)	66.32	8.59	11.60 (N)
2	Br	1	10	CO_2H	113–115	$C_{19}H_{27}BrO_3$	59.51	7.11	20.85 (Br)	59.27	7.06	20.86 (Br)
3	AcO	1	10	CO_2H	94–96	$C_{21}H_{30}O_5$	65.59	8.34	...	65.51	8.20	..
4	TsO	1	10	CO_2H	108–110	$C_{26}H_{34}O_6S$	65.80	7.22	...	65.96	7.22	...
5	HO	1	10	CO_2H	83–84	$C_{19}H_{28}O_4$	71.22	8.81	...	70.99	8.61	...
6	HO	1	8	CO_2CH_3	70–70.5	$C_{18}H_{26}O_4$	70.56	8.55	...	70.38	8.43	...
7	HO	1	10	CO_2CH_3	76–78	$C_{20}H_{30}O_4$	71.82	9.04	...	71.73	9.02	...
8	AcO	1	8	CHO	110–112	$C_{19}H_{26}O_4$	71.67	8.23	...	71.46	8.05	...
9	CHO	0	10	CO_2CH_3	161 dec	$C_{20}H_{28}O_4$	72.26	8.49	...	71.80	8.45	...
9 bissemicarbazone	CHO	0	10	CO_2CH_3	208–210	$C_{22}H_{34}N_6O_4$	59.17	7.67	18.82 (N)	59.45	7.76	18.54 (N)
10	HO	0	10	CO_2H	92–94	$C_{18}H_{26}O_4$	70.56	8.55	...	70.39	8.85	...
B. $X(CH_2)_nC_6H_4(CH_2)_mY$												
11	H	1	11	CO_2H	57–59	$C_{19}H_{30}O_2$	78.57	10.41	...	78.44	10.09	...
12	HO	0	11	CO_2H	103–105	$C_{18}H_{28}O_3$	73.93	9.65	...	73.74	9.77	...



Failure of any of the acyclic *p*-phenylene bridged compounds **2**–**12** to undergo spontaneous ring tautomerization may reflect the high entropy requirement for such a process. The unfavorable geometry of X and Y in **1**–**12**, where these groups are part of flexible chains emerging from diametrically opposing points on the aromatic ring, probably mitigates against bridging to an *ansa* structure.

Experimental Section[9]

11-(*p*-Toluyl)undecanoic Acid (1).—To a stirred solution of 48.8 g (0.2 mol) of 11-carbomethoxyundecanoic acid,[10] bp 170° (10 mm), in 200 ml of dry ether was added batchwise 60 g (0.4 mol) of thionyl chloride. The mixture was stirred at room temperature for 8 hr and then the solvent and excess thionyl chloride were removed *in vacuo*. The residual yellow oil (52.6 g, 0.2 mol), ν_{CO} 1800 cm^{-1}, was used without further purification. To a solution of the crude acid chloride in 250 ml of dry toluene was added 54 g (0.4 mol) of anhydrous aluminum chloride portionwise so as to maintain the temperature below 10°. Heated overnight on the steam bath, the mixture was decomposed in ice–6 *N* HCl; the organic layer, combined with ether washings of the aqueous phase, was washed repeatedly with saturated solutions of $NaHCO_3$ and NaCl, dried, and freed of solvent by rotary evaporation. Vacuum distillation effected removal of dimethyl dodecanedioate and then of the methyl ester of **1**. The latter was saponified in refluxing methanolic KOH for 3 hr. The alkaline solution was acidified with 6 *N* HCl and the product **1** was collected, dried, and recrystallized from ether–ligroin (bp 30–60°): yield 30 g (50%); ir (CCl_4) 1720 (acid) and 1690 cm^{-1} (ketone); nmr (acetone) 7.5 (q), 2.8 (t), 2.3 (t), and 1–1.8 ppm (m).

11-(*p*-Bromomethylbenzoyl)undecanoic Acid (2).—The bromination of 15.2 g (0.05 mol) of **1** with NBS was carried out as described previously for a lower homolog.[7] After crystallization from THF–ligroin, there was obtained 11 g (57%) of the acid. The nmr spectrum (dioxane) contained a characteristic singlet at 4.5 ppm (CH_2Br).

11-(*p*-Acetoxymethylbenzoyl)undecanoic Acid (3).—A mixture of 5.8 g (0.015 mol) of **2**, 1.6 g (0.02 mol) of sodium acetate, and 100 ml of glacial acetic acid was heated at reflux for 10 hr. The mixture was decomposed in ice–water and the solid was collected by filtration, washed repeatedly with water, dried, and recrystallized from chloroform–hexane: yield 2.3 g (44%); ir ($CHCl_3$) 1750 (ester), 1720 (acid), and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 5.17 ppm (s, CH_2OAc).

11-[*p*(*p*-Toluenesulfonylmethyl)benzoyl]undecanoic Acid (4).—A mixture of 5.7 g (0.015 mol) of bromo acid **2**, 4.5 g (0.015 mol) of silver *p*-toluenesulfonate,[11] and 100 ml of acetonitrile was stirred in the dark for a period of 48 hr. The reaction mixture was added to water and the product was extracted with two 100-ml portions of ethyl ether. The ethereal extract was washed several times with saturated NaCl and dried, and the solvent was removed *in vacuo*. The residual solid, a mixture of bromo acid and tosylate, was subjected to the above treatment again. The tosylate was finally obtained in 10% yield after recrystallization from ether–hexane, nmr ($CDCl_3$) 5.08 ppm (s, CH_2OTs).

11-(*p*-Hydroxymethylbenzoyl)undecanoic Acid (5). A.—A mixture of 1.5 g of the bromo acid **2**, 5.6 g of KOH, and 100 ml of THF was heated at reflux ovenight. It was acidified, concentrated, and extracted with ether several times. The ether solution was washed repeatedly with saturated NaCl, dried ($MgSO_4$), and freed of solvent by rotary evaporation. The solid was re-

(9) Nmr chemical shifts are given in parts per million downfield from TMS.

(10) L. J. Durham, D. J. McLeod, and J. Cason, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 635.

(11) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959).

crystallized repeatedly from benzene–pentane: ir ($CHCl_3$) 3500 cm^{-1} (broad) (OH); nmr ($CHCl_3$) 4.78 ppm (s, CH_2OH). The hydroxy acid reacted instantaneously with chromic acid.[12]

B.—Saponification of 10.8 g (0.03 mol) of **3** with methanolic KOH led to a solid, which was identical in every way with that from A, yield 7.5 g (79%).

Methyl 9-(*p*-Hydroxymethylbenzoyl)nonanoate (6).—The following is typical of the Fischer esterifications carried out with several acids. A solution of 2.6 g (0.01 mol) of 9-(*p*-hydroxymethylbenzoyl)*nonanoic acid in saturated methanolic hydrogen* chloride was heated at reflux for 2–14 hr. The mixture was poured into ice–water; the ether layer, combined with ether washings of the water layer, was extracted with $NaHCO_3$ and water, dried ($MgSO_4$), and then concentrated. The ester was separated from the residual oil by thick layer chromatography on silica gel (5% MeOH in $CHCl_3$): uv max (methanol) 250 mμ (ε 54,000); ir (double mull) 3400 (OH), 1750 (ester), and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 4.76 (s, CH_2OH), 3.57 (s, CO_2CH_3), 2.3 (t, $COCH_2$), 2.9 (t, $CH_2CO_2CH_3$), and 1–2 ppm (*m*, CH_2). The same ester was obtained by Fischer esterification of 9-(*p*-acetoxymethylbenzoyl)nonanoic acid.

Methyl 11-*p*-(Hydroxymethylbenzoyl)undecanoate (7). **A.**—Fischer esterification of either the hydroxy acid **5** or acetoxy acid **3** led to the methyl ester, which was recrystallized from chloroform–hexane: ir ($CHCl_3$) 1735 (ester) and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 4.75 (s) and 3.67 (s).

B.—A mixture of 2 g (0.0055 mol) of 11-(*p*-acetoxymethylbenzoyl)*undecanoic acid* (**3**), 1.3 g (0.01 mol) of oxalyl chloride, and 50 ml of anhydrous ethyl ether was stirred at room temperature for 12 hr. After the solvent and excess oxalyl chloride had been removed *in vacuo*, excess methanol was added and the mixture was stirred for 2 hr and decomposed with water. The organic product was taken up in ether, washed with saturated NaCl, $NaHCO_3$, and again with NaCl, and dried ($MgSO_4$). The product obtained by removal of the solvent and recrystallization as above was identical with the ester from A.

9-(*p*-Acetoxymethylbenzoyl)nonanal (8).—A solution of acid chloride, prepared from 10 g (0.03 mol) of *p*-(acetoxymethylbenzoyl)nonanoic acid and oxalyl chloride, in 50 ml of dry diglyme was cooled to Dry Ice–acetone temperature. To this was added 7.6 g (0.03 mol) of lithium aluminum tri-*t*-butoxyhydride in 50 ml of dry diglyme over a period of 1 hr, with stirring. After removal of the bath, the solution was stirred for an additional 2 hr and then decomposed in ice–dilute HCl. The combined ether extracts were washed with dilute NaOH and water, dried ($MgSO_4$), and concentrated. The residual yellow, waxy solid was recrystallized six times from ether–hexane: ir (double mull) 1760 (ester), 1720 sh (aldehyde), and 1690 cm^{-1} (ketone); nmr ($CHCl_3$) 2.13 (s, $OCOCH_3$), 5.18 (s, CH_2OCO–), and 9.88 ppm (s, CHO).

The yield of aldehyde was greatly increased by use of THF instead of diglyme as solvent.

10-(*p*-Hydroxymethylphenyl)-1,10-decanediol.—To a magnetically stirred suspension of 1.6 g of lithium aluminum hydride in 70 ml of anhydrous ether was added, over a 2-hr period, 2 g of 9-(*p*-acetoxymethylbenzoyl)nonanoic acid. Then refluxing was maintained for 4 hr and the mixture was decomposed by dropwise addition first of water and then of dilute HCl. The ether layer and ether extracts of the aqueous layer were combined, washed with $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The triol, after recrystallization from ether–hexane, amounted to 1.67 g (98%): mp 88–90°; ir (double mull) 3200 cm^{-1} (broad, OH); mass spectrum *m/e* 280 (molecular ion).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.8; H, 10.3.

All attempts to oxidize the triol selectively with MnO_2 or $KMnO_4$ failed.

Methyl 11-(*p*-Formylbenzoyl)undecanoate (9).—To a solution of 0.01 mol of **1** in 50 ml each of glacial acetic acid and acetic anhydride, cooled in an ice–salt bath, was added first 3 ml of concentrated H_2SO_4 and then 0.04 mol of chromium trioxide such that the temperature never exceeded 5°. Stirring was continued for 10 min, and then the solution was poured into ice–water. The crude *gem*-diacetate was collected, washed with water repeatedly to remove chromium salts, and air-dried. It was heated at reflux with 10 ml of ethanol, 10 ml of water, and 1 ml of concentrated H_2SO_4 for 30–40 min. The hot mixture was filtered and the filtrate was cooled to give solid, which was recrystallized from ether–ligroin: nmr ($CDCl_3$) 2.91 and 2.33 (t, $-CH_2CO$), 8.05 (d, ArH), 3.63 (s, $COOCH_3$), 10.01 (s, CHO), and 1–1.8 ppm (m, $-CH_2-$).

The bissemicarbazone was recrystallized twice from ethanol–water.

11-(*p*-Hydroxybenzoyl)undecanoic Acid (10).—A solution of 78 g of polyphosphate ester,[13] 12.2 g (0.13 mol) of phenol, and 31.7 g (0.13 mol) of 11-carbomethoxyundecanoic acid[10] was heated at reflux for 1 hr and then added to ice–water. The organic phase, combined with chloroform washings of the aqueous layer, was washed with 7.5% KOH and saturated NaCl and dried ($MgSO_4$). After removal of the solvent, there remained 35.5 g (83%) of pale yellow, liquid phenyl methyl dodecanedioate, ir (neat) 1765 and 1750 cm^{-1} (ester CO). The Fries rearrangement was carried out by mixing, in the cold, 16 g (0.05 mol) of ester, 26.8 g (0.20 mol) of anhydrous aluminum chloride, and 100 ml of nitrobenzene and allowing the mixture to stand at room temperature for 2 days. It was decomposed in ice–water and extracted twice with ether. The ether solution was extracted with 10% NaOH and the basic solution was acidified with 6 *N* HCl. The solid product was taken up in ether and washed with saturated NaCl, and the solution was dried ($MgSO_4$) and concentrated. After recrystallization of the residue from benzene–hexane, it amounted to 3.8 g (25%): ir (double mull) 3300–3500 (ArOH), 1720 (COOH), and 1690 cm^{-1} (ketone).

12-(*p*-Tolyl)dodecanoic Acid (11).—Wolff–Kishner reduction of 30.4 g of methyl 11-(*p*-toluyl)undecanoate in 300 ml of diethylene glycol with 25 ml of 85% hydrazine hydrate gave, after recrystallization from ligroin, 17 g (61%) of acid: nmr ($CDCl_3$) 2.30 (s, $ArCH_3$) and 7.08 (s, ArH).

12-(*p*-Hydroxyphenyl)dodecanoic Acid (12).—Wolff–Kishner reduction in diethylene glycol of 3.5 g (0.012 mol) of **10** furnished 1.1 g (31%) of **12** after two recrystallizations from ether–ligroin: ir ($CHCl_3$) 3350 (broad, ArOH) and 1715 cm^{-1} (COOH); nmr ($CDCl_3$) 6.87 ppm (q, ArH).

Intramolecular, High-Dilution, Friedel–Crafts Acylations.—The *ansa* ketones **14a** and **14b** were prepared according to Huisgen, *et al.*,[8] from the corresponding ω-phenylalkanoic acids. Data for **14a** follow: mp 87–89° (aqueous ethanol) (lit.[8] mp 92–93°); nmr ($CDCl_3$) 7.4 (q, 4, ArH), 2.75 (q, 4, $ArCH_2$, $-CH_2CO$), 1–1.8 [m, 6, $-(CH_2)_n-$], and 0.5–1.0 ppm [m, 8, $-(CH_2)_n-$]. The semicarbazone of **14a** was prepared, mp 200–202° (methanol) (lit.[8] mp 207–208°). Data for **14b** follow: mp 74–76° (methanol) (lit.[8] mp 78–78.5°); nmr (CS_2) 7.4 (q, 4, ArH), 2.75 (m, 4, $ArCH_2$, $-CH_2CO$), 1–2 (m, 6, $-(CH_2)_n-$), and 0.5–1.0 ppm [m, 12, $-(CH_2)_n-$]. The 2,4-dinitrophenylhydrazone of **14b** was prepared, mp 150–152° (lit.[8] mp 154°).

Baeyer–Villiger Oxidation of 14b.—To a mechanically stirred mixture of 2 g (0.008 mol) of **14b** in 75 ml of methylene chloride containing 6.2 g (0.04 mol) of disodium hydrogen phosphate was added, at room temperature over a period of 30 min, a solution containing 0.016 mol of freshly prepared trifluoroperoxyacetic acid dissolved in 25 ml of methylene chloride. Refluxing was maintained for 18 hr; the mixture was filtered and the filtrate was washed successively with water, 10% $NaHCO_3$, and water and dried ($MgSO_4$). An infrared spectrum of the crude product remaining after removal of solvent indicated both ketone and lactone. After the entire oxidation process had been repeated and the product had been purified by thick layer chromatography on silica gel (75% chloroform, 25% benzene), **15b** was in the form of an oil: nmr ($CDCl_3$) 7.08 (q, 4, ArH), 2.4 (broad m, 4, $ArCH_2$, $-CH_2COO-$), 1–1.9 [m, 7, $-(CH_2)_n-$], and 0.5–1.0 ppm [m, 11, $-(CH_2)_n-$].

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.79; H, 9.55. Found: C, 78.58; H, 9.45.

Saponification of 15b.—A solution of 0.2 g of KOH and 0.1 g of **15b** in 25 ml of methanol was heated at reflux for 2 hr. It was added to dilute HCl and the mixture was extracted twice with ether. The ether solution was washed several times with saturated NaCl and dried ($MgSO_4$), and the solvent was removed to give, after recrystallization from chloroform–ligroin (bp 40–60°), 0.07 g (68%) of **12**, mp 104–106°. A mixture melting point with **12** prepared above was undepressed, and their ir spectra were identical.

Registry No.—**1**, 23334-73-8; **1** semicarbazone, 23293-58-5; **2**, 23293-59-6; **3**, 23293-60-9; **4**, 23293-

(12) F. G. Bordwell and K. M. Wellman, *J. Chem. Educ.*, **39**, 308 (1962).

(13) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, K. Matsuzaki, and Y. Ban, *Chem. Ind.* (London), 2102 (1964).

61-0; **5**, 23293-62-1; **6**, 23293-63-2; **7**, 23293-64-3; **8**, 23293-65-4; **9**, 2334-74-9; **9** bissemicarbazone, 23293-66-5; **10**, 23293-67-6; **11**, 23293-68-7; **12**, 23293-69-8; **15b**, 23293-71-2; 10-(*p*-hydroxymethylphenyl)-1,10-decanediol, 23293-70-1.

Substituent Constants of Difluoraminoalkyl and *gem*-Bis(difluoramino)alkyl Groups[1]

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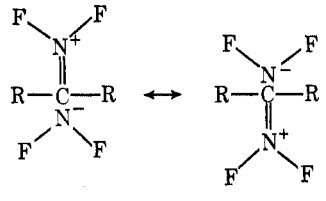
Although the difluoramino group of simple difluoramino alkanes has an electron-withdrawing inductive effect,[2] the difluoramino group is also capable of supplying electrons mesomerically to support simple cations such as NF_2O^+ and $NF_2{=}NF^+$,[3,4] as well as difluoraminocarbonium ions.[5,6] The operation of this effect in *gem*-bisdifluoramino compounds could reduce the additive inductive effects by resonance structures such as the following. The aliphatic substituent constant,



σ^*, would therefore show a "saturation" effect[7] relative to that of compounds with single difluoramino groups.

3-Difluoraminopropionic acid,[5] 4,4-bis(difluoramino)-pentanoic acid,[8] and 5,5-bis(difluoramino)hexanoic acid[8] were prepared as described previously. 4-Difluoramino-4-methylpentanoic acid was obtained by the alkaline hydrolysis of methyl 4-difluoramino-4-methylpentanoate, which in turn was obtained by the reaction of methyl 4-methyl-4-nitropentanoate[9] with difluoramine in the presence of fuming sulfuric acid. Although replacement of nitro groups by difluoramine under these conditions has been used extensively with α-halo derivatives,[10] the synthesis of a tertiary alkyl difluoramino compound in this way has not been reported previously.

$$(CH_3)_2C(NO_2)CH_2CH_2CO_2CH_3 \xrightarrow[H_2SO_4,\ SO_3]{HNF_2} (CH_3)_2C(NF_2)CH_2CH_2CO_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOH,\ H_2O} (CH_3)_2C(NF_2)CH_2CH_2COOH$$

(1) This work was supported by the Office of Naval Research.

(2) The electronegativity of the difluoramino group has been reported to be 3.25: R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).

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TABLE I
IONIZATION CONSTANTS

Compd	pK at 25°	σ^*	$\sigma^*_{NF_2}$
$NF_2CH_2CH_2COOH$	3.74	0.528	4.13
$(CH_3)_2C(NF_2)CH_2CH_2COOH$	4.35	0.174	4.84
$CH_3C(NF_2)_2CH_2CH_2COOH$	4.01	0.372	4.33
$CH_3C(NF_2)_2CH_2CH_2CH_2COOH$	4.62	...	...
$CH_3C(NF_2)_2CH_2CH_2C(NO_2)_2H$	3.87	0.381	4.42

The ionization constants of the carboxylic acids, determined by potentiometric titration,[11] and the corresponding σ^* values of R in RCOOH are shown in Table I. The ionization constant of 5,5-bis(difluoramino)hexanoic acid was within experimental error of that of the reference, acetic acid[7]; it was not informative as to the effect of the difluoramino groups because of the distance between functional centers.

The ionization constant of 5,5-dinitro-2,2-bis(difluoramino)pentane[8] was obtained by the spectroscopic method. The σ^* value of 0.381 was calculated using the ρ^* for 1,1-dinitro alkane ionization reported by Sitzmann, Adolph, and Kamlet.[12] The σ^* values for $CH_3C(NF_2)_2CH_2CH_2-$ derived from the dinitro alkane and the carboxylic acid ionization constants are within experimental error.

The σ^* value of the difluoramino group was calculated using the normal quenching factor of 2.8 for intervening methylene groups and the value of σ^* for hydrogen, 0.49, to convert methyl groups into hydrogens.[7] The value of $\sigma^*_{NF_2}$ derived from 3-difluoraminopropionic acid is considered the most reliable because only two correction factors were required.

Within the combined calculation uncertainties, the σ^* values for two difluoramino groups are additive and therefore do not present evidence for unusual resonance effects. The difluoramino group is seen to be strongly electron-withdrawing, comparable with the nitro group. The reported pK for 4,4-dinitropentanoic acid[13] is, in fact, almost identical with that of the corresponding difluoramino acid.

Experimental Section

Because difluoramine and many difluoramino compounds are sensitive explosives, the safety precautions described previously[5] were followed. Ionization constants of the carboxylic acids were determined with a Metrohm E336 potentiograph at expanded scale by standard methods.[11]

The reduction of 5,5,5-trinitro-2,2-bis(difluoramino)pentane with alkaline hydrogen peroxide was carried out using $^1/_{20}$ of the previously described quantities.[8] The salt solution was diluted to 10 ml with water, and 1-ml aliquots were diluted with base, acid, and buffers as described by Sitzmann, Adolph, and Kamlet.[12] The log ϵ value of the 0.1 N sodium hydroxide solution was 4.11 at λ_{max} 375 mμ.

Methyl 4-Difluoramino-4-methylpentanoate.—The previously described[5] difluoramine generation procedure was followed. Methyl 4-methyl-4-nitropentanoate[9] (5.0 g, 0.0286 mol) was added dropwise with stirring to 9 g of refluxing difluoramine and 8 ml of 20% fuming sulfuric acid. The mixture was quenched with 100 ml of ice 15 min after the addition was completed. The product was extracted with three 10-ml portions of methylene chloride, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 1.30 g (25.1% conversion, 40.5%

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