diphenylacetoacetate, m.p. 77–79°, was not depressed.[16] Gas chromatography of the liquid showed that it was still impure.

(16) J. C. Shivers, M. L. Dillon, and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 119 (1947).

Similarly, from acetophenone, ethyl phenylacetate, and sodium amide in ether was formed 16.4 g. (35%) of VIIa, m.p. 51–52.5° after recrystallization from ethanol.[17]

(17) A. Becker, *Helv. Chim. Acta*, **32**, 1114 (1949).

Metalation of N-Methyl-*o*-toluamide with Excess *n*-Butyllithium. Condensations with Ketones and Aldehydes. Cyclizations[1a]

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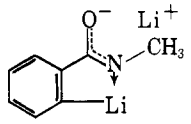
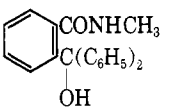
N-Methyl-*o*-toluamide was metalated at the 2-methyl group as well as the nitrogen atom with excess *n*-butyllithium in tetrahydrofuran–hexane. The resulting dilithioamide was condensed with ketones and aldehydes to form δ-hydroxyamides. These products were cyclized thermally to afford δ-lactones.

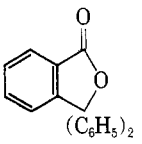
It has recently been shown[2] that N-methylbenzamide reacts with excess *n*-butyllithium in tetrahydrofuran–hexane to form dilithioamide I, which condenses with electrophilic compounds to give *ortho* derivatives. For example, I was condensed with benzophenone to afford γ-hydroxyamide II, which was cyclized thermally to yield γ-lactone III.



I



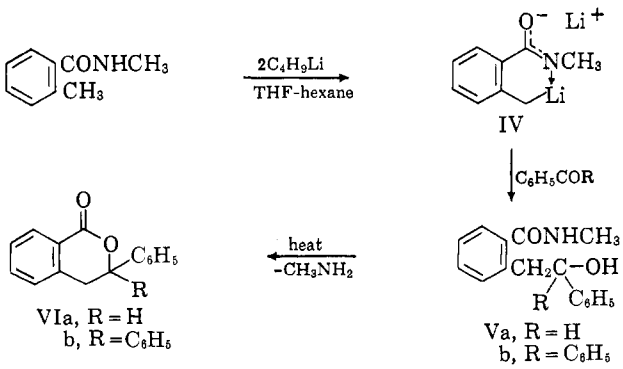
II



III

It has now been found that N-methyl-*o*-toluamide similarly undergoes dimetalation with excess *n*-butyllithium but, instead of the ring being metalated, the 2-methyl group is metalated to afford dilithioamide IV.[3] The formation of IV was indicated by condensations with electrophilic compounds. Thus IV was condensed with benzaldehyde and benzophenone to form δ-hydroxyamides Va and b, which were cyclized thermally to δ-lactones VIa and b, respectively (Scheme I).

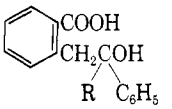
SCHEME I



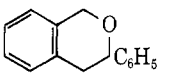
VIa, R = H
b, R = C_6H_5

Va, R = H
b, R = C_6H_5

The structures of alcohol amides Va and Vb were supported by hydrolysis to alcohol acids VIIa and VIIb, which were converted to the known isochroman VIII[4] and to lactone VIb, respectively. Also, VIIb was oxidized to phthalic acid. The melting point of lactone VIa agreed with that reported for this compound prepared by two earlier methods.[5,6]

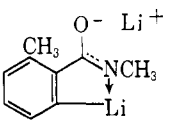


VIIa, R = H
b, R = C_6H_5

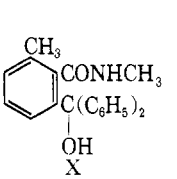


VIII

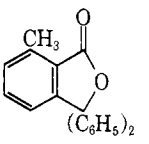
That the intermediate dilithioamide was IV (see Scheme I), not the possible IX, was established not only by the above data but also by the n.m.r. spectra of the benzophenone adduct and its lactone. Thus, the area ratios from these spectra were compatible with δ-hydroxyamide Vb and δ-lactone VIb but not with γ-hydroxyamide X and its lactone XI, which would have been the products had the intermediate dilithioamide been IX (see Experimental).



IX

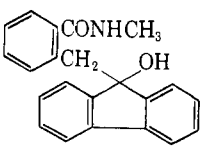


X

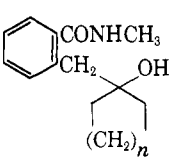


XI

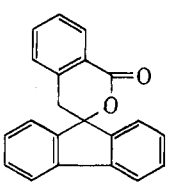
Next the dilithioamide IV (see Scheme I) was condensed with fluorenone, cyclopentanone, and cyclohexanone to form δ-hydroxyamides XII, XIIIa, and XIIIb,



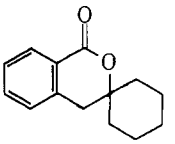
XII



XIIIa, *n* = 2
b, *n* = 3



XIV



XV

(1) (a) Supported in part by the National Science Foundation; (b) Union Carbide Fellow, 1963-1964.

(2) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

(3) The related monometalations of benzyldimethylamine and 2-methylbenzyldimethylamine have similarly been observed to occur at the *ortho* position of the ring and at the 2-methyl group, respectively: F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963), and ref. 4.

(4) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 1387 (1964).

(5) G. Berti, *Gazz. chim. ital.*, **87**, 707 (1957).

(6) G. Berti, *Tetrahedron*, **4**, 393 (1958).

TABLE I

CONDENSATION OF DILITHIOAMIDE IV WITH CARBONYL COMPOUNDS

Aldehyde or ketone	Product	M.p.,[a] °C.	Yield,[b] %	Infrared data,[c] cm.$^{-1}$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Benzaldehyde	2-(β-Phenyl-β-hydroxy)ethyl-N-methylbenzamide (Va)	165–166[d]	51	3279, 1610, 1546, 1316, 1057, 768, 702	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	74.95	6.83	5.47
Benzophenone	2-(β,β-Diphenyl-β-hydroxy)ethyl-N-methylbenzamide (Vb)	176.5–178[d]	93	3448, 1653, 1575, 1325, 1065, 787, 765, 714, 704	$C_{22}H_{21}NO_2$	79.73	6.39	4.23	79.83	6.57	4.30
Fluorenone	α-(9-Hydroxy-9-fluorenyl)-N-methyl-o-toluamide (XII)	233.5–235[e]	50	3356, 1621, 1527, 1299, 769, 737	$C_{22}H_{19}NO_2$	80.22	5.81	4.25	80.23	5.72	4.28
Cyclopentanone	α-(1-Hydroxycyclopentyl)-N-methyl-o-toluamide (XIIIa)	111.5–113.5[f]	41	3333, 1653, 1575, 1340, 1078, 730	$C_{14}H_{19}NO_2$	72.07	8.21	6.00	72.13	8.24	6.14
Cyclohexanone	α-(1-Hydroxycyclohexyl)-N-methyl-o-toluamide (XIIIb)	170–172[f]	65	3226, 1639, 1558, 1330, 1115, 1073, 980, 778, 719	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	72.79	8.56	5.96

[a] Melting points of analytical samples. [b] The melting points of the materials on which these yields are based were slightly lower than those reported here; see Experimental. [c] Spectra were determined by the potassium bromide pellet method. [d] Recrystallized from 95% ethanol. Recrystallized from ethanol–acetone. [f] Recrystallized from hexane containing a few drops of absolute ethanol.

TABLE II

CYCLIZATION OF ALCOHOL AMIDES TO LACTONES

Hydroxyamide[a]	Reaction time, hr.	Temp., °C.	Lactone	M.p. or b.p. (mm.), °C.[b]	Yield, %	Infrared data,[c] cm.$^{-1}$	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Va	8	160–170	3-Phenyl-3,4-dihydroisocoumarin (VIa)	88.5–89.5[d]	72[e]	1730, 1276, 1126, 771, 748, 702					
Vb	4	180–190	3,3-Diphenyl-3,4-dihydroisocoumarin (VIb)	144–144.5[f]	82[e]	1712, 1279, 1232, 762, 740, 714, 699	$C_{21}H_{16}O_2$	83.98	5.37	84.06	5.37
XII[g]	1	230–240	Spiro[fluorene-9,3′-isochroman]-1′-one (XIV)	184–185.5[h]	67[e]	1730, 1297, 1261, 777, 745, 737	$C_{21}H_{14}O_2$	84.54	4.73	84.42	4.76
XIII	5	190–200	Spiro[cyclohexane-1,3′-isochroman]-1′-one (XV)	142–144 (0.35)	85	1698, 1282, 1235, 1111, 1075, 1022, 965, 741, 714	$C_{14}H_{16}O_2$	77.75	7.46	77.53	7.56

[a] 0.02 mole of hydroxyamide unless otherwise noted. [b] Physical constants of analytical samples. [c] Spectra of solids were obtained by the potassium bromide pellet method. Spectra of liquids are of the neat liquid between sodium chloride plates. [d] Recrystallized from 95% ethanol. [e] The melting points of the materials on which the yields are based were slightly lower than reported here. [f] Recrystallized from hexane–ethanol. [g] Hydroxyamide, 0.01 mole. [h] Recrystallized from acetone–ethanol.

respectively. Adducts XII and XIIIb were cyclized thermally to give δ-lactones XIV and XV, respectively.

The data for the aldehyde and ketone adducts and for their lactones are summarized in Tables I and II. The yields of these products were fairly good to excellent (41–93%). The infrared spectra of all of the adducts showed peaks in the 3448–3165- and 1653–1610-cm.$^{-1}$ regions for the secondary amide group.[7] The infrared spectra of the lactones prepared from the hydroxyamides showed absorption in the 1730–1720-cm.$^{-1}$ region for a six-membered α,β-unsaturated lactone.[8] The spectra of adducts Va and b and corresponding lactones VIa and b exhibited peaks in the 770–730- and 710–690-cm.$^{-1}$ regions for the five adjacent aromatic hydrogens.[9] Absorption in the 770–735-cm.$^{-1}$ region could also indicate four adjacent aromatic hydrogens although such a distinction is not possible in the presence of five adjacent aromatic hydrogens.[8] Adducts XII, XIIIa, and XIIIb, and lactones XIV and XV showed absorption in the 770–735 cm.$^{-1}$ with no peaks in the 710–690-cm.$^{-1}$ region. This is compatible with their having four adjacent aromatic hydrogens and substantiates the evidence presented above that the dilithioamide intermediate was IV, not IX. Peaks in the 1055–1000- and 1005–952-cm.$^{-1}$ regions in the spectra of adduct XIIIb and lactone XV were attributed to the cyclohexane ring.[10]

Discussion

As in the previous *ortho* metalation of N-methylbenzamide, the success of the present metalation at the 2-methyl group of N-methyl-*o*-toluamide is presumably dependent on an initial deactivation of the carbonyl group through N-metalation.[2]

The present metalation reaction furnishes a convenient route not only to the aldehyde and ketone adducts but also to the δ-lactones. This method for the lactones appears superior to the earlier procedures for lactone VIa[5,6] and to a previous method for lactone XV, which was obtained contaminated with 3-cyclohexylphthalide.[11]

It should be pointed out that the present δ-hydroxyamides undergo thermal cyclization much less readily than the corresponding γ-hydroxyamides such as II,[2] the recrystallizations of which required special conditions to minimize the cyclization.

Experimental[12]

N-Methyl-*o*-toluamide.—*o*-Toluic acid (136.15 g., 1.0 mole) was refluxed for 2 hr. with 200 g. (1.68 moles) of thionyl chloride. After removal of the excess thionyl chloride, the *o*-toluyl chloride was dissolved in 200 ml. of anhydrous ether. The solution was added to excess 40% aqueous methylamine to give, after recrystallization from aqueous ethanol, 107.67 g. (72%) of N-methyl-*o*-toluamide, m.p. 78–79°, lit.[13] m.p. 75°.

Metalation of N-Methyl-*o*-toluamide with *n*-Butyllithium to form Dilithioamide IV.—To a stirred solution of 7.46 g. (0.05 mole) of N-methyl-*o*-toluamide in 80 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) in a dry flask under nitrogen was added, during 10 min., 80 ml. (0.125 mole) of 1.55 *M* *n*-butyllithium in hexane as described recently for N-methylbenzamide.[2] During the addition the mixture refluxed spontaneously and deposited a white precipitate which dissolved to give a red solution as the last of the *n*-butyllithium was added. After refluxing 15 min., the dark red solution of dilithioamide IV was cooled to room temperature and employed as described below.

Condensations of Dilithioamide IV with Aldehydes and Ketones (Table I).—Solutions of 0.08 mole of the appropriate aldehyde or ketone in 80 ml. of anhydrous ether were added to the stirred solution of IV under nitrogen as described below.

A. With Benzaldehyde.—The solution of the aldehyde was added during 30 min. to the solution of IV cooled in an ice bath. A white solid formed. The mixture was stirred 20 min., then the cooling bath was removed and the stirring continued for 45 min. After cooling again, the reaction mixture was poured into 70 ml. of 2 *M* hydrochloric acid and 30 g. of ice. The resulting white solid was collected and washed with ether to give 9.09 g. of crude hydroxyamide Va, m.p. 142–150°. Recrystallization from 95% ethanol afforded 6.46 g. (51%) of Va, m.p. 162–165°. Only a few more crystals could be obtained from the original filtrate.

B. With Benzophenone.—The solution of the ketone was added to the solution of IV during 15 min. The mixture was refluxed 0.5 hr., then cooled in an ice bath and 100 ml. of water added. The resulting white precipitate was collected and dried to give 15.4 g. (93%) of hydroxyamide Vb, m.p. 174–176°.

The n.m.r. spectrum of Vb (m.p. 176.5–178°) showed a doublet centered at −170 ± 1 c.p.s. attributed to the N-methyl group, a singlet at −222 ± 1 c.p.s for the methylene, and an aromatic multiplet between −410 and −450 c.p.s. The area ratios were as follows: CH_3–CH_2, 1.35 (calcd. 1.50), and aromatic hydrogens–CH_2, 7.06 (calcd. 7.00). This spectrum was taken in deuteriochloroform.

C. With Fluorenone.—The solution of the ketone in 120 ml. of ether was added (15 min.) to the cooled solution of IV. After removing the ice bath and stirring for 0.5 hr., the black mixture was cooled again and poured into 70 ml. of 2 *M* hydrochloric acid and 30 g. of ice. The resulting yellow solid was collected and dried to give 9.16 g. of hydroxyamide XII, m.p. 221–224°. Recrystallization from ethanol–acetone afforded 7.67 g. of XII, m.p. 228–229.5°. More (0.5 g.) of XII, m.p. 229–231°, was isolated from the original filtrate; total was 8.17 g. (50%).

D. With Cyclopentanone.—To the solution of IV cooled in a Dry Ice–acetone bath was added dropwise during 0.5 hr. the solution of the ketone. After stirring for 1 hr. with a cooling bath and 1 hr. without a cooling bath, the mixture was poured with stirring into 90 ml. of 2 *M* hydrochloric acid and 50 g. of ice. The two layers were separated. The organic layer (combined with an ethereal extract of the aqueous layer) was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solution was concentrated (rotary evaporator, room temperature) to approximately 30 ml. and cooled and scratched to give 4.70 g. (41%) of hydroxyamide XIIIa, m.p. 111.5–113.5°.

E. With Cyclohexanone.—The condensation was effected as described for cyclopentanone. Decomposition of the reaction mixture with hydrochloric acid afforded a white precipitate, which was collected and dried to give 5.7 g. of crude hydroxyamide XIIIb, m.p. 160–165°, and 4.24 g., m.p. 170–172°, after recrystallization from hexane containing a few drops of absolute ethanol.

The two layers of the original filtrate of the acidified reaction product were separated. The organic layer (combined with an ethereal extract of the aqueous layer) was dried over anhydrous magnesium sulfate and concentrated to about 30 ml. (rotary evaporator, room temperature). The resulting crystals were collected and dried to give 3.8 g. of XIIIb, m.p. 169–171°; total was 8.04 g. (65%).

Thermal Cyclization of Hydroxyamides.—The hydroxyamide (0.01 and 0.02 mole, Table II) was placed in a 50-ml. round-bottom flask fitted with a two-necked adaptor for gas inlet and exit. The system was evacuated to 1 mm. and refilled with dry nitrogen three times. After flushing the system for 0.5 hr. with a slow stream of dry nitrogen (which was continued during the

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 205.

(8) See ref. 7, pp. 185-186.

(9) See ref. 7, pp. 76–78.

(10) See ref. 7, p. 31.

(11) G. Berti, A. Marsili, and V. Mini, *Ann. chim.* (Rome), **50**, 669 (1960).

(12) Analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected. Infrared spectra were produced on a Perkin-Elmer Infracord 137. N.m.r. spectra were produced on a Varian A-60 n.m.r. spectrometer using solutions with a tetramethylsilane internal standard.

(13) P. Van Romburgh, *Rec. trav. chim.*, **4**, 388 (1885).

reaction), the flask was immersed in a Woods' metal bath, which had been preheated to the appropriate temperature (see Table II). When a basic gas (presumably methylamine) was no longer being released, as indicated by litmus paper, the system was allowed to come to room temperature. Lactones VIa, VIb, and XIV crystallized and were recrystallized from appropriate solvents (see footnotes to Table II). Lactone XV was distilled.

The n.m.r. spectrum of lactone VIb showed a singlet at -222 ± 1 c.p.s. attributed to the methylene hydrogens and an aromatic multiplet between -420 and -450 c.p.s. The area ratio was 7.21 for aromatic hydrogens–CH_2 (calcd. 7.00). This spectrum was taken in carbon tetrachloride.

Hydrolysis of Hydroxyamide Va to Hydroxy Acid VIIa.—A sample of Va (5.1 g., 0.02 mole) in 50 ml. of 95% ethanol and 50 ml. of 6 *M* sodium hydroxide was refluxed until the evolution of methylamine ceased (10 hr.). After cooling, the reaction mixture was acidified with 12 *M* hydrochloric acid to give 4.65 g. (96%) of *o*-(2-phenyl-2-hydroxyethyl)benzoic acid, m.p. 115–118° and 123–124° after two recrystallizations from aqueous ethanol and drying *in vacuo*.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.37; H, 5.70.

A sample of VIIIa was reduced to the corresponding diol, which was cyclized to isochroman VIII as described recently.[4]

Hydrolysis of Hydroxyamide Vb to Hydroxy Acid VIIb.—A solution of 6.63 g. (0.02 mole) of Vb and 11.2 g. (0.20 mole) of potassium hydroxide in 30 ml. of ethanol and 40 ml. of water was refluxed for 10 hr. The ethanol was removed (rotary evaporator) and the residual aqueous mixture was washed with several portions of ether. Acidification of the aqueous solution afforded a gum, which was scratched to give 5.8 g. (91%) of *o*-(2,2-diphenyl-2-hydroxyethyl)benzoic acid (VIIb), m.p. 123.5–124.5° and 125.5–126° dec. after recrystallization from hexane–benzene–ethanol.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.08; H, 5.73.

Cyclization of 4.2 g. of VIIb by heating it above its melting point *in vacuo* for several minutes afforded 3.7 g. (88%) of lactone VIb, m.p. 143.5–144° and 144–144.5° after recrystallization from hexane–ethanol.

Oxidation of 3.2 g. of VIIb with excess alkaline potassium permanganate afforded 0.7 g. (42%) of phthalic acid, m.p. 208–209°, undepressed on admixture with an authentic sample. The infrared spectra of the two samples were identical.

The Synthesis of Royal Jelly Acid and Its Homologs from Cycloalkanones[1]

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Received July 6, 1964

Two methods for the synthesis of royal jelly acid, *trans*-10-hydroxy-2-decenoic acid (Ia), from cyclooctanone are reported. Homologs of Ia were prepared utilizing one of the methods which involved an initial oxidation of a cycloalkanone to an ω-lactone (II). The resulting lactone was treated with sodioacetonitrile to produce a 3-keto-ω-hydroxynitrile (IX), which was reduced and hydrolyzed to afford the corresponding 3,ω-dihydroxycarboxylic acid (VIII). The latter was then dehydrated to give the desired ω-hydroxy-α,β-unsaturated carboxylic acid I.

Royal jelly is the remarkable substance, secreted by the common honey bee *Apis mellifira*, which is responsible for the ultimate differentiation of bee larva into queen bees.[2] One of the major components of royal jelly has been isolated[3] and identified[4] as *trans*-10-hydroxy-2-decenoic acid (Ia). This acid, commonly referred to as royal jelly acid, has been found to possess antibiotic[5] and antitumor activities.[6] In order to obtain homologs and analogs for the purpose of biological testing, a synthetic program was initiated for the synthesis of royal jelly acid utilizing a scheme which could be readily extended to similar compounds. The synthesis of the parent compound has been reported by a number of different groups.[7]

The methods for the preparation of royal jelly acid utilized in these laboratories involved the use of cyclooctanone as the starting material. This cyclic ketone was oxidized to the lactone IIa employing peroxytrifluoroacetic acid.[8] Two routes *via* the dihydroxy acid VIII were developed (Scheme I).

In the first method the lactone IIa was hydrolyzed and the resulting 8-hydroxyoctanoic acid (III) was converted to 8-acetoxyoctanoyl chloride (V). This acid chloride was allowed to react with ethyl sodioacetoacetate to give ethyl 3-keto-10-acetoxydecanoate (VI) after deacylation with ammonia.[9] Conversion of the keto ester VI to ethyl 3-hydroxy-10-acetoxydecanoate (VII) was accomplished by ruthenium-catalyzed hydrogenation.[10] Hydrolysis of VII followed by dehydration of the resulting 3,10-dihydroxydecanoic acid (VIIIa) utilizing acetic anhydride gave the unsaturated acid Ia which was identical with the naturally occurring acid[11] with respect to mixture melting point and infrared spectrum.

A shorter alternate method for the synthesis of the dihydroxy acid VIIIa from the lactone IIa was achieved by extending Hauser's method for the acylation of nitriles with esters.[12] The procedure used involved the treatment of the lactone IIa with 2 equiv. of sodioacetonitile to produce 3-keto-10-hydroxydecanitrile (IXa). This intermediate was converted to the acid

(1) Taken in part from the dissertation presented by J. F. Muren, Jan., 1961, to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the Ph.D. degree.

(2) I. Johansson, *Bee World*, **36**, 3, 21 (1955).

(3) A. Butenandt and H. Rembold, *Z. Physiol. Chem.*, **308**, 284 (1957).

(4) S. A. Barker, A. B. Foster, D. C. Lamb, and N. Hodgson, *Nature*, **183**, 996 (1959); S. A. Barker, A. B. Foster, D. C. Lamb, and L. J. Jackman, *ibid.*, **184**, 634 (1959).

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