Arylations of β-Diketone Dicarbanions with Diaryliodonium Chlorides to Form γ-Derivatives[1a]

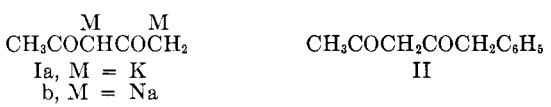
K. GERALD HAMPTON,[1b] THOMAS M. HARRIS, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

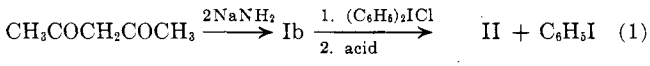
Received July 21, 1964

Disodio β-diketones, prepared from the β-diketones and 2 mole equiv. of sodium amide in liquid ammonia, were arylated with diaryliodonium chlorides to form γ-derivatives. This method of arylation appears superior to the benzyne reaction, and it furnishes a number of β-diketones for which the Claisen type of acylations has not been very satisfactory. Evidence was obtained that the phenylation of disodioacetylacetone with diphenyliodonium chloride involves at least in part the intermediate formations of the phenyl radical and an ion radical, which combine.

Several types of condensations have previously been effected in satisfactory yield at the γ-position of β-diketones through their dipotassio salts, which had been prepared by means of potassium amide in liquid ammonia.[2] For example, alkylation of dipotassioacetylacetone (Ia) with benzyl chloride afforded the terminal benzyl derivative in 60% yield.[2] However, phenylation of dipotassio salt Ia with benzyne gave only 13% of the terminal derivative II.[2a] Even by employing disodio salt Ib, we have been unable to raise this yield above 18%.[3]

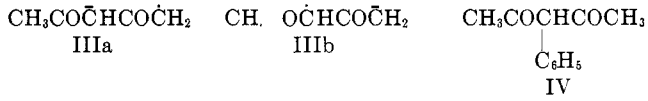


The terminal phenylation of acetylacetone has now been accomplished in excellent yield with diphenyliodonium chloride (eq. 1). This reagent has previously been employed by Beringer and co-workers[4] for phenyl-

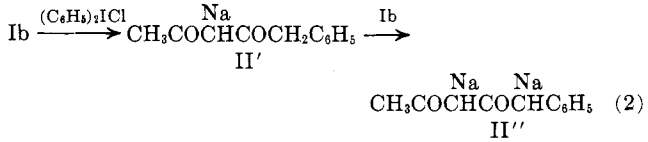


ation of the monoanions of certain β-diketones to form α-derivatives. They proposed a radical mechanism for the reaction.

Similarly, the mechanism of the present reaction appears to involve the intermediate formation of the phenyl radical and an anion radical which combine to give principally the terminal derivative II; two resonance forms of the ion radical would be IIIa and IIIb. Evidence supporting this mechanism is the detection of traces of biphenyl and α-derivative IV in the crude reaction product.[5] In contrast to phenylation, alkylation of Ia with alkyl halides, apparently a simple displacement reaction, affords none of the α-alkylation product.[2] The possibility that, in the present case, direct displacement occurs partly is not ruled out. Direct displacement has been postulated in other arylations employing 1-naphthyl sulfone and 1-fluoronaphthalene.[6]

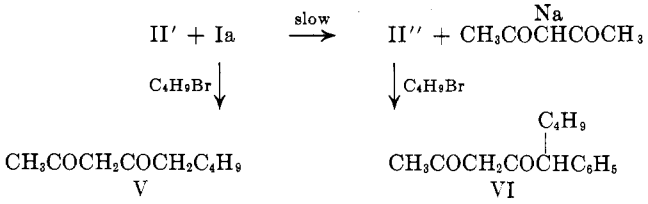


The stoichiometry of phenylation of disodio salt Ib with diphenyliodonium chloride was difficult to determine. Initial experiments showed that the yield of product II, assuming only one phenyl of diphenyliodonium chloride was utilized (see eq. 1), was 92% when a 2:1 ratio of disodioacetylacetone to this reactant was used, but only 47% when the ratio was 1:1. This suggested that the monocarbanion II′ of the product was converted by Ib to dicarbanion II″ (eq. 2).



In agreement with eq. 2, treatment of the reaction mixture with *n*-butyl bromide after an appropriate reaction period afforded detectable amounts of VI, which evidently arose by butylation of dicarbanion II″. However, the conversion of II′ to II″ must have been relatively slow since substantially more of V was obtained from butylation of the original dicarbanion I than VI from II″ (Scheme I).

SCHEME I



The following experiments confirmed the slow conversion of II′ to II″. An equimolar mixture of II′ and disodio salt Ib was prepared in liquid ammonia, allowed to equilibrate for a period of time, and treated with *n*-butyl bromide. After 6 min. of equilibration, the ratio of butylation products V and VI was 88:12, and after 120 min. 40:60. This conversion of II′ to II″ appears to be sufficient to have a significant effect upon the stoichiometry of the phenylation reaction.

A further consequence of this proton transfer is that the new dicarbanion II″ might also be expected to undergo phenylation, utilizing some of both the desired product II and the iodonium salt, which was the starting material present in a limiting amount. Although no attempt was made to isolate diphenylated acetyl-

(1) (a) Supported in part by the National Science Foundation; (b) James B. Duke Fellow, 1962–1964.

(2) (a) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); (b) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960).

(3) Disodio salt Ib was recently reported to give better yields than dipotassio salt Ia in alkylation reactions: see K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **28**, 1946 (1963).

(4) See F. M. Beringer and S. A. Galton, *ibid.*, **28**, 3417 (1963), and previous papers.

(5) Presumably α-derivative IV did not arise by reaction of the monoanion[4] since in a blank experiment the monosodio salt of acetylacetone underwent no phenylation with diphenyliodonium chloride under these conditions.

(6) J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.*, **78**, 6265 (1956).

TABLE I

ARYLATION OF DISODIO β-DIKETONES WITH DIARYLIODONIUM CHLORIDES (Ar_2ICl) TO FORM γ-DERIVATIVES

Disodio β-diketones	Ar	Products	Yield, %	B.p., °C. (mm.)	Copper chelate, m.p., °C.
2,4-Pentanedione	C_6H_5	1-Phenyl-2,4-pentanedione (II)	92	139–142 (13)[a]	224–225[b,e]
1-Phenyl-1,3-butanedione	C_6H_5	1,4-Diphenyl-1,3-butanedione (VIIa)	61	165–170 (0.7)[c]	203–205[d,f]
2,4-Heptanedione	C_6H_5	1-Phenyl-2,4-heptanedione (VIIb)	98	145–148 (7)	149–151[e]
2,4-Nonanedione	C_6H_5	1-Phenyl-2,4-nonanedione (VIIc)	78	170–175 (0.7)	138–139.5[e]
2,4-Tridecanedione	C_6H_5	1-Phenyl-2,4-tridecanedione (VIId)	53	121–124 (0.6)	118.5–119.5[e]
2,4-Pentanedione	p-ClC_6H_4	1-(4-Chlorophenyl)-2,4-pentanedione (VIIe)	44	172–175 (0.7)	210–211[f]
1-Phenyl-1,3-butanedione	p-$CH_3C_6H_4$	4-(4-Methylphenyl)-1-phenyl-1,3-butanedione (VIIf)	44	140–145 (0.7)	215.5–216.5[f]
2,4-Nonanedione	p-$CH_3C_6H_4$	1-(4-Methylphenyl)-2,4-nonanedione (VIIg)	21	125–128 (3)	144–145[e]
3,5-Heptanedione	C_6H_5	2-Phenyl-3,5-heptanedione (VIII)	50	125–128 (3)	79–81[e]

[a] Lit.[13] b.p. 150–153° (20 mm.). [b] Lit.[2a] m.p. 227–229°. [c] M.p. 51–52.5°; L. I. Smith and R. E. Kelly [*J. Am. Chem. Soc.*, **74**, 3300 (1952)] give m.p. 52.5°. [d] Lit.[c] m.p. 200–201°. [e] Recrystallized from methanol. [f] Recrystallized from benzene.

TABLE II

ANALYSES FOR ARYLATION PRODUCTS AND THEIR COPPER CHELATES

β-Diketones						Copper chelates						
		Calcd., %		Found, %			Calcd., %			Found, %		
Diketone	Formula	C	H	C	H	Formula	C	H	Cu	C	H	Cu
VIIb	$C_{13}H_{16}O_2$	76.44	7.90	76.15	7.87	$C_{26}H_{30}O_4Cu$	66.38	6.43	13.52	66.17	6.48	13.64
VIIc	$C_{15}H_{20}O_2$	77.55	8.68	77.32	8.64	$C_{30}H_{38}O_4Cu$	68.49	7.23	12.10	68.61	7.31	12.01
VIId	$C_{20}H_{28}O_2$	79.12	9.79	78.97	9.65	$C_{40}H_{54}O_4Cu$	71.49	8.53	9.95	71.22	8.43	9.80
VIIe	$C_{11}H_{11}ClO_2$					$C_{22}H_{20}Cl_2O_4Cu$[a]	54.73	4.18	13.16	54.94	4.10	13.22
VIIf	$C_{17}H_{16}O_2$	80.92	6.39	80.84	6.41	$C_{34}H_{30}O_4Cu$	72.14	5.34	11.23	72.01	5.30	11.28
VIIg	$C_{16}H_{22}O_2$					$C_{32}H_{42}O_4Cu$	69.31	7.64	11.47	69.07	7.38	11.66
VIII	$C_{13}H_{16}O_2$					$C_{26}H_{30}O_4Cu$	66.38	6.43	13.52	66.61	6.38	13.47

[a] *Anal.* Calcd. for Cl: 14.69. Found: 14.55.

acetone, Kornblum has observed the occurrence of diphenylation in other systems.[7]

Another factor which complicated the stoichiometry of the phenylation of disodio β-diketones with diphenyliodonium chloride was the observation that the byproduct, iodobenzene (see eq. 1), effected a portion of the reaction. Thus, although iodobenzene by itself failed to phenylate dicarbanion Ib, the yield of II was increased by 17% from 92 to 109% (calculated on the basis of eq. 1), when the 2:1 reaction was conducted in the presence of 1 equiv. of iodobenzene. Moreover, 0.035 mole of γ-derivative IV was obtained from a reaction mixture containing 0.1 mole each of I and iodobenzene along with only 0.01 mole of diphenyliodonium salt. Therefore, the effect of the iodonium salt on the reaction of iodobenzene with Ib must have been catalytic. However, in the reaction involving 2:1 mole ratios of dianion and iodonium salt much of the iodobenzene, which theoretically should have been produced, could be observed by gas chromatography. This, coupled with the observation that the increase in yield was only 17% on addition of 1 equiv. of iodobenzene to the reaction mixture, suggested that the principal reaction had been between dicarbanion Ib and iodonium salt and that the reaction with iodobenzene had in most cases probably not contributed more than about one tenth of the total product. We believe that the yields calculated on the assumption that diphenyliodonium chloride is the only phenylating agent present in the 2:1 reaction, although not rigorously correct, nevertheless provide a basis for the evaluation of the synthetic utility of this method.

(7) N. Kornblum and H. J. Taylor, *J. Org. Chem.*, **28**, 1424 (1963).

A number of other β-diketones were similarly phenylated through their dicarbanions, and certain other arylations were also accomplished. The general procedure involved addition of solid diaryliodonium chloride to 2 mole equiv. of the β-diketone disodio salt in liquid ammonia, the reaction generally being completed in ether. In one case, the phenylation of dipropionylmethane, better yields were obtained when the reaction was completed in liquid ammonia than in ether. The phenylation of acetylacetone did not show this solvent difference. The results are summarized in Tables I and II. Table I shows that the yields of the phenylation products II, VIIa–d, and VIII were good to excellent (50–98%), and those of the substituted phenylation products VIIe–g were fair (21–44%). The distilled products were indicated to be essentially pure by gas chromatography.

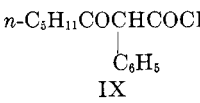
$RCOCH_2COCH_2Ar$

VIIa, R = C_6H_5; Ar = C_6H_5
b, R = n-C_3H_7; Ar = C_6H_5
c, R = n-C_5H_{11}; Ar = C_6H_5
d, R = n-C_9H_{19}; Ar = C_6H_5
e, R = CH_3; Ar = p-ClC_6H_4
f, R = C_6H_5; Ar = p-$CH_3C_6H_4$
g, R = n-C_5H_{11}; Ar = p-$CH_3C_6H_4$

$C_2H_5COCH_2COCHCH_3$
|
C_6H_5
VIII

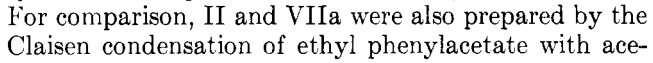
Products II and VIIa are known compounds. The structures of the remaining arylation products were supported not only by analogy with II and VIIa and by analysis but also by alkaline cleavages. Since the arylated β-diketones were apparently pure, the isolation of the respective arylacetic acids from the hydrolysis mixtures represents proof that all of the arylations had occurred at γ-positions to give diketones VIIb–g and VIII. The other arylated diketones that might

have been obtained from these arylations, for example VI and IX from the disodio salt of V, could not have afforded these acids. Samples of the substituted phenylacetic acids resulting from hydrolysis of VIIe–g were collected from the gas chromatograph and found to be identical with authentic samples of the *para*-substituted acids by comparison of the infrared spectra.



IX

The reaction of diaryliodonium chlorides with disodio-β-diketones appears to be a good method for the preparation of γ-arylated β-diketones, such as II, VIIa–g, and VIII. The good yields are to be contrasted with the poor yields obtained with benzyne.[2,3] Moreover, the benzyne reaction would not be applicable to the synthesis of *para*-substituted compounds VIIe–g. For comparison, II and VIIa were also prepared by the Claisen condensation of ethyl phenylacetate with acetone and acetophenone, respectively (eq. 3). Only fair yields were obtained by that method, and distilled II was shown by v.p.c. to be impure.



R = CH_3 and C_6H_5 II and VIIa (3)

Experimental[8]

Iodonium Salts.—Diphenyliodonium chloride was prepared from benzene, potassium iodate, sulfuric acid, and acetic anhydride by the method of Beringer and co-workers.[9] The precipitate was recrystallized from methanol to give colorless crystals of the chloride salt, m.p. 225–226°. 4,4′-Dimethyldiphenyliodonium chloride (m.p. 175–176°) was prepared similarly.[10] 4,4′-Dichlorodiphenyliodonium chloride (m.p. 201–203°) was prepared from chlorobenzene, iodyl sulfate, and sulfuric acid by the method of Beringer and Forgione.[11]

Phenylation of Dicarbanion Ib.—A 1-l. three-necked flask containing a stirred suspension of 0.2 mole of sodium amide, prepared from 4.6 g. (0.2 g.-atom) of sodium, in 600 ml. of liquid ammonia was cooled in a Dry Ice–acetone bath while nitrogen was passed over the reaction mixture. A solution of 10.0 g. (0.1 mole) of acetylacetone in 20 ml. of ether was added in small portions from a pressure-compensating addition funnel. The cooling bath was removed, the temperature of the reaction mixture allowed to return to normal, and the nitrogen flow was stopped. After 0.5 hr., the solution was considered to contain 0.1 mole of Ib. To the solution was added over 5–10 min., 15.8 g. (0.05 mole) of diphenyliodonium chloride through Gooch tubing from an erlenmeyer flask. After 1 hr., 500 ml. of ether was added to the suspension while the ammonia was evaporated cautiously on the steam bath. The ether suspension was refluxed for 1 hr., cooled in an ice bath, and 100 g. of ice and 20 ml. of concentrated hydrochloric acid were added. The ethereal layer was separated and the aqueous layer was extracted several times with ether.[12] The combined ethereal solutions were dried with magnesium sulfate, and filtered; the ether was distilled. The residual liquid was vacuum distilled to give 8.1 g. (92%) of II, b.p. 138–141° at 13 mm. There were small traces of benzene, biphenyl, and 3-phenyl-2,4-pentanedione[13] in the crude mixture as indicated by gas chromatographic comparison with authentic samples.

Four variations of the procedure were investigated. (1) When 0.1 mole each of dicarbanion Ib and diphenyliodonium chloride were employed, 8.2 g. of II (47% based on the iodonium salt and eq. 1) resulted. (2) Treatment of Ib (0.05 mole) with iodobenzene (0.05 mole) afforded no detectable amount of II. (3) However, treatment of Ib (0.1 mole) with a mixture of iodobenzene (0.05 mole) and diphenyliodonium chloride (0.05 mole) afforded 9.6 g. (109%) of II. (4) To demonstrate the catalytic effect of the iodonium salt on the reaction with iodobenzene, 0.10 mole of Ib was treated with 0.10 mole of iodobenzene and 0.01 mole of iodonium salt to yield 6.1 g. (0.035 mole) of II.

Detection of II″ by Conversion to VI.—To a mixture of Ib (0.10 mole) and diphenyliodonium chloride (0.05 mole), which had stirred for 5 hr. after mixing, was added 0.05 mole of 1-bromobutane. Gas chromatography of the product showed a detectable amount of VI but a much larger amount of V.

Partial Equilibration of Sodio Mono- and Dicarbanions.—To 0.10 mole of sodium amide in 400 ml. of liquid ammonia was added rapidly 8.8 g. (0.05 mole) of 1-phenyl-2,4-pentanedione in 20 ml. of anhydrous ether. After 30 min., 6.1 g. (0.05 mole) of monosodio acetylacetone, prepared by reaction of the diketone with metallic sodium in ether, was added from an erlenmeyer flask through Gooch tubing. After 6 min., 6.85 g. (0.05 mole) of 1-bromobutane in ether was added as rapidly as possible. The products were isolated as before. Gas chromatography indicated the presence of acetylacetone, 1-phenyl-2,4-pentanedione (II), and 5-phenyl-2,4-nonanedione (VI), but no 2,4-nonanedione (V). The yield of 5-phenyl-2,4-nonanedione was 79%.[14] Repeating the procedure, except allowing the mono- and dicarbanions to equilibrate for 2 hr., afforded 82% of 5-phenyl-2,4-nonanedione and a negligible amount of 2,4-nonanedione.

In contrast, when 9.9 g. (0.05 mole) of monosodio 1-phenyl-2,4-pentanedione (II′), prepared from II and sodium amide, was added to 0.05 mole of Ib in 400 ml. of liquid ammonia, and after 6 min. treated with 6.85 g. (0.05 mole) of 1-bromobutane in ether, v.p.c. indicated that 2,4-nonanedione (V) and 5-phenyl-2,4-nonanedione (VI) had been formed in a ratio of 88:12. A ratio of 40:60 was obtained when the procedure was repeated with the anions being allowed to equilibrate for 2 hr.

Other Arylations.—To a stirred suspension of 0.2 mole of sodium amide in 600 ml. of liquid ammonia was added 0.1 mole of β-diketone in 20 ml. of ether.[15] After 0.5 hr., 0.05 mole of diaryliodonium chloride was added over 5–10 min. from an erlenmeyer flask through Gooch tubing. The products VIIa–g and VIII were isolated by the same procedure as that for II (see Table I). The phenylation of 3,5-heptanedione was more satisfactory when the reaction was conducted in liquid ammonia for 6 hr. Phenylation of Ib under these conditions occurred in 89% yield.

Copper Chelates of Arylation Products.—The copper chelates were formed by adding a filtered, aqueous solution of copper acetate to 0.5–1.0 g. of II, VIIa–g, and VIII. The blue-gray chelates were recrystallized from methanol or benzene. The results are summarized in Tables I and II.

Hydrolysis of Arylation Products.—Solutions of 0.7–2.0 g. of β-diketones VIIa–g and VIII in 20 ml. of 10% aqueous potassium hydroxide were refluxed 3–4 hr. The mixtures were cooled and washed with ether. The basic solutions were acidified and extracted with ether. The extracts were concentrated and analyzed by v.p.c. The retention times of the arylacetic acids were compared with those of authentic samples. Also, the *para*-substituted acids were collected from the vapor phase chromatograph and compared with authentic samples by infrared spectra.

Independent Synthesis of II and VIIa.—Acetone and ethyl phenylacetate were condensed by means of sodium amide in ether as described previously.[13] The diketone was isolated through the copper chelate by treatment of the chelate with acid. The liquid was distilled to give 26.2 g. (30%) of II, b.p. 141–143° at 15 mm. The product was impure and crystals, m.p. 77–79°, gradually separated. A mixture melting point of the solid with ethyl α,γ-

(8) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn. and by Dr. Ing. A. Schoeller, Mikro-Labor, Kronach, West Germany. Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids, and the neat liquid between sodium chloride plates for liquids. Vapor phase chromatograms were obtained on an F and M Model 500 gas chromatograph.

(9) F. M. Beringer, E. J. Geering, I. Kuntz, and M. Mausner, *J. Phys. Chem.*, **60**, 141 (1956).

(10) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *J. Am. Chem. Soc.*, **81**, 342 (1959).

(11) F. M. Beringer and P. S. Forgione, *Tetrahedron*, **19**, 739 (1963).

(12) In some cases the ethereal solution was very dark and appeared to contain iodine. These solutions were extracted with dilute aqueous sodium thiosulfate until no further diminution of this color occurred.

(13) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).

(14) The yield of 5-phenyl-2,4-nonanedione was calculated from the ratio of its v.p.c. peak area to that of 1-phenyl-2,4-pentanedione.

(15) The 1-phenyl-1,3-butanedione was added as a solid through a powder funnel.

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]

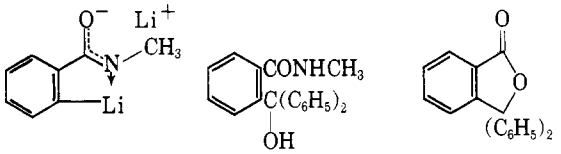
RANN L. VAULX,[1b] WALTER H. PUTERBAUGH, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

Received August 5, 1964

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.

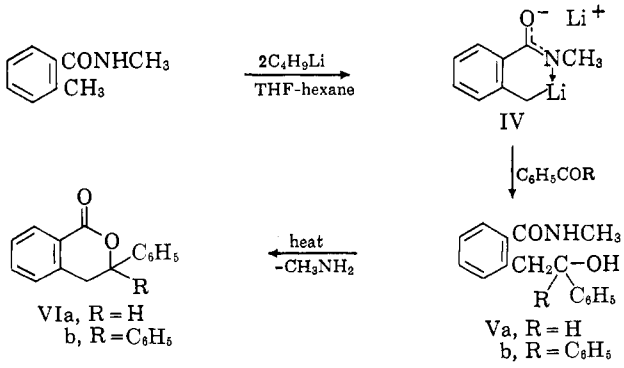
It has recently been shown[2] that N-methylbenzamide reacts with excess *n*-butyllithium in tetrahydrofuran–hexane to form dilithioamide I, which condenses with electrophilic compounds to give *ortho* derivatives. For example, I was condensed with benzophenone to afford γ-hydroxyamide II, which was cyclized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



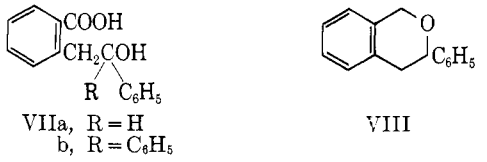
I II III

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).

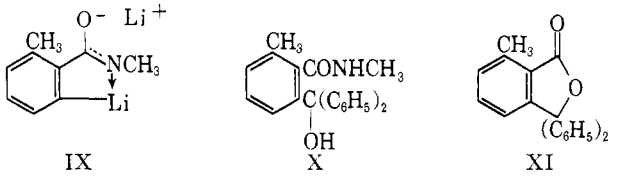
SCHEME I



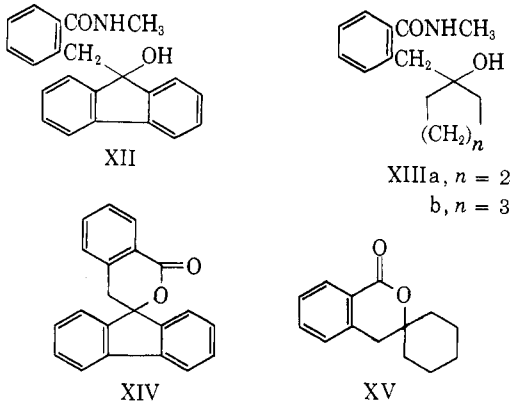
The structures of alcohol amides Va and Vb were supported by hydrolysis to alcohol acids VIIa and VIIb, which were converted to the known isochroman VIII[4] and to lactone VIb, respectively. Also, VIIb was oxidized to phthalic acid. The melting point of lactone VIa agreed with that reported for this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



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).



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



(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).