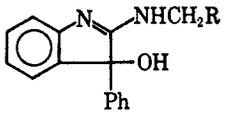
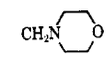
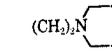
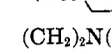
TABLE I

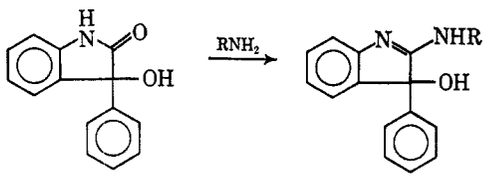


II	R	Mp, °C[a]	Yield, %[b]	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
a	Phenyl	156–157	32	$C_{21}H_{18}N_2O$	80.24	5.77	8.91	80.33	5.74	8.87
b	α-Pyridyl	219–221	71	$C_{20}H_{17}N_3O$	76.16	5.43	13.32	75.95	5.41	13.25
c	CH_2-α-Pyridyl	171–172	39	$C_{21}H_{19}N_3O$	76.58	5.82	12.76	76.45	5.86	12.84
d		187–189	55	$C_{20}H_{23}N_3O_2$	71.20	6.87	12.46	71.04	6.64	12.31
e	$(CH_2)_2N(CH_3)_2$	186–188	80	$C_{19}H_{23}N_3O$	73.74	7.49	13.58	73.55	7.47	13.73
f	$(CH_2)_2N(C_2H_5)_2$	164–165	60	$C_{21}H_{27}N_3O$	74.25	8.07	12.45	74.55	7.96	12.18
g		164–166	65	$C_{22}H_{27}N_3O$	75.45	7.79	12.03	75.15	7.70	12.00
h		157–158	70	$C_{21}H_{25}N_3O_2$	71.78	7.17	11.96	71.51	7.14	11.78
i	$(CH_2)_2N(C_2H_5)(CH)_2OH$	149–150	68	$C_{21}H_{27}N_3O_2$	71.37	7.70	11.90	71.14	7.70	12.01

[a] Melting points were observed on a Fisher-Johns block with a calibrated thermometer. [b] Solvent of recrystallization was 2-propanol.

phosphorus oxychloride is used,[3] and an imino chloride intermediate is first formed.

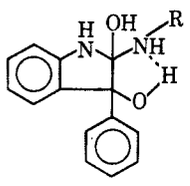
To our surprise, the preparation of the title compounds (II) was accomplished conveniently from 3-hydroxy-3-phenyloxindole (I), and an excess of primary amine in boiling xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid by azeotropic removal of the water formed.



I II

The structure of II was established by infrared data. The oxindole carbonyl band at 1700–1715 cm^{-1} was missing. Instead, three bands at 1620, 1600, and 1580 cm^{-1} appeared, two assignable to phenyl ring vibrations, the remaining one due to C=N stretching vibration. As expected, in KBr the 3200-cm^{-1} region showed intermolecular bonded NH—OH, but in CCl_4 solution the free hydroxyl group was clearly visible at 3600 cm^{-1} and the NH group at 3440 cm^{-1}.

It was found that formation of amidine from I under the conditions used took place only when the 1 position was unsubstituted and free OH in the 3 position was present. It is known that the proton in the 3 position of I is quite readily removed. Hydrogen bridging from the 3-hydroxyl proton to the free electron pair in the addition product (III), necessary for the amidine formation, could block the amine nitrogen effectively, thus allowing protonation merely of the 2-hydroxyl group.



III

(3) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).

Experimental Section

The preparation of the compounds in Table I is demonstrated in the following example.

2-[(3-Morpholinopropyl)amino]-3-phenyl-3H-indol-3-ol.—A mixture of 22.5 g (0.1 mol) of 3-hydroxy-3-phenyloxindole,[4] 28.8 g (0.2 mol) of 4-(3-aminopropyl)morpholine, and a catalytic amount of *p*-toluenesulfonic acid in 400 ml of xylene was boiled with stirring under a Dean–Stark trap for 10–15 hr, after which time 1.8 ml of water was collected. The solvent was evaporated under reduced pressure, and the residue was slurried in isopropyl ether, then recrystallized from 2-propanol to give 24.6 g (70%) of a white crystalline solid.

Registry No.—IIa, 17510-66-6; IIb, 17510-60-0; IIc, 17510-67-7; IId, 17510-61-1; IIe, 17510-62-2; IIf, 17510-63-3; IIg, 17510-64-4; IIh, 17510-65-5; IIi, 17510-59-7.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and staff for microanalytical data and Dr. J. M. Vandenbelt and Mr. E. J. Schoeb for infrared data.

(4) H. E. Baumgarten and P. L. Creger, *J. Amer. Chem. Soc.*, **82**, 4634 (1960).

Synthesis of β-Hydroxyamides from Phenylacetamides and Ketones or Aldehydes by Means of Alkali Amides and *n*-Butyllithium[1a]

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Until recently,[2] considerable difficulty was encountered in synthesizing β-hydroxyamide **2a** from

(1) (a) Supported at the University of Missouri by the Petroleum Research Fund, administered by the American Chemical Society, on Grant 959-G2, and at Duke University by the National Science Foundation; (b) University of Missouri; (c) Duke University.

(2) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3316 (1966).

TABLE I

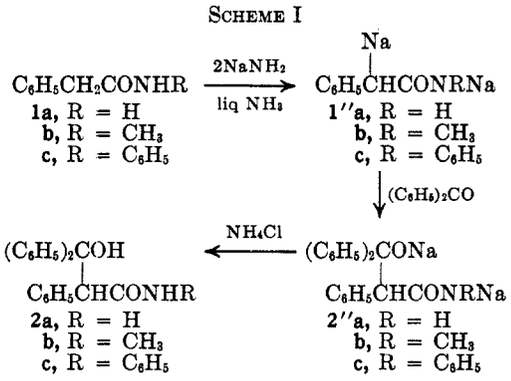
ADDITION REACTIONS OF DIALKALI ARYLACETAMIDES WITH KETONES AND BENZALDEHYDE

R	Carbonyl compound	Adduct	Mp, °C	Yields, %: Method A[a] $NaNH_2$, NH_3	Method A[a] $LiNH_2$, NH_3	Method B[b] n-C_4H_9Li, THF	Method B[b] n-C_4H_9Li, ether
H	Benzophenone	**2a**	202–203[c,d]	86[e]	23	41 (0)	
CH_3	Benzophenone	**2b**	194.5–195.5[e]	59[f]	2	45 (0)	
C_6H_5	Benzophenone	**2c**	202–203[e,g]	85	14	81 (0)	
H	Fluorenone	**3**	161–163[e]	72			
H	Cyclohexanone	**4a**	176.5–178.5[h]	17	39		32
CH_3	Cyclohexanone	**4b**	154–155[i]		33		41
C_6H_5	Cyclohexanone	**4c**	194.5–196[i]		5		80
H	Cyclopentanone	**5a**	123–123.5[e]				35
C_6H_5	Cyclopentanone	**5c**	159–160[h]		13		
H	Benzaldehyde	**6a**	145–146 184–186[j]	54[j]			20[j]
CH_3	Benzaldehyde	**6b**	175–176[j]	25[j]			64[j]
C_6H_5	Benzaldehyde	**6c**	222–224[j]	19[j]			78[j]

[a] At −33°. [b] At 35° or at indicated temperature. [c] See ref 2. [d] Recrystallized from absolute ethanol. [e] Recrystallized from 95% ethanol. [f] Three equivalents of sodium amide and two of benzophenone afforded adduct **2b** in 72% yield. [g] See ref 8. [h] Recrystallized from hexane–ethanol. [i] Recrystallized from hexane–ethyl acetate. [j] In some cases, the adducts consisted of a mixture of diastereoisomers. See D. M. von Schriltz, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **32**, 2610 (1967).

phenylacetamide (**1a**) and benzophenone through the intermediate formation of disodio salts **1''a** and **2''a** (Scheme I). However, with the recognition that the

SCHEME I

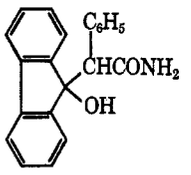


addition reaction of disodio salt **1''a** with the ketone in liquid ammonia is kinetically controlled, the satisfactory synthesis of adduct **2a** was readily achieved. Thus, **2a** was obtained in 86% yield upon inverse neutralization of the reaction mixture[3] after only a few minutes. After a usual reaction period (15 min or longer), the starting materials were recovered since disodio salt **2''a** had then been converted into the sodium amide adduct of benzophenone through a thermodynamically controlled process.[2]

Phenylacetamide (**1a**), N-methylphenylacetamide (**1b**), and phenylacetanilide (**1c**) have now been condensed not only with benzophenone, but also with other ketones and benzaldehyde. Such condensations were effected by means of sodium amide and lithium amide in liquid ammonia (method A) and by n-butyllithium in various inert solvents (method B) to afford β-hydroxyamides **2a–6c**.

In Table I are summarized the results obtained by these two methods. This table shows that for phenylacetamide (**1a**), method A employing sodium amide was more satisfactory than method B for benzophenone and benzaldehyde, and method A was also suitable for fluorenone. However, lithium amide (method A)

(3) This mode of neutralization involves pouring the reaction mixture into excess acid.



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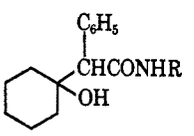
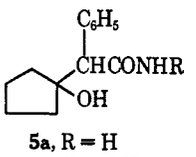
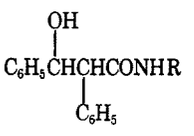


4a, R = H
b, R = CH_3
c, R = C_6H_5



5a, R = H
c, R = C_6H_5



6a, R = H
b, R = CH_3
c, R = C_6H_5

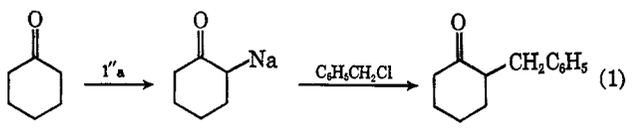
and n-butyllithium (method B) (at 0° but not at 25°) were more satisfactory than sodium amide (method A) for cyclohexanone. In addition, methods A (sodium amide) and B were both suitable for the condensations of N-substituted amides **1b** and **1c** with benzophenone; better yields of **2b**, though, were realized by method A upon using a 100% excess each of sodium amide and the ketone. Method B was more satisfactory than method A in the reactions of amides **1b** and **1c** with benzaldehyde and cyclohexanone.

In general, better yields of the β-hydroxyamides were obtained by the use of 10 mol % excess over the required 2 equiv of alkali amide presumably because of a displacement of the equilibria between the starting dianions **1''a–c** toward the intermediate alkoxides, for example, **2''a–c** (see Scheme I). In the case of **1''b**, though, the best yields of **2b** were obtained by a 100% excess of alkali amide apparently because the inductive effect of the N-methyl group of **1b** causes the amido hydrogen to be less acidic than that of phenylacetamide. Thus, formation of the dianion **1''b** is probably incomplete unless a large excess of base is employed to shift the equilibrium toward this dianion. In the reactions effected by method B, a 10 mol % excess over the necessary 2 equiv of n-butyllithium could be employed only with the N-substituted amides **1b** and **1c** since the parent phenylacetamide (**1a**) is readily con-

verted into trilithio salt 1‴; this salt undergoes a facile elimination of lithium oxide to afford lithiophenylacetonitrile 7′.[4]

1‴ 7′

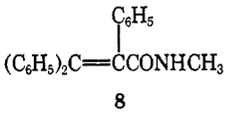
In the condensations of amides **1a–c** with enolizable ketones such as cyclohexanone, dilithio rather than disodio salts are recommended since the sodio salts predominately effect ionization of an α hydrogen of the ketone.[5] This was demonstrated in the current investigation in the reaction of cyclohexanone with disodio salt **1″a** by treatment of the reaction mixture with benzyl chloride to give 2-benzylcyclohexanone (eq 1).



(1)

Incidentally, a temperature effect was observed in the condensations of phenylacetanilide (**1c**) with benzophenone effected by *n*-butyllithium (method B). Thus, when the ketone was added to **1″c** at 0°, the resulting solution refluxed for 1 hr, and inverse neutralization then effected at −80 and 64°, the yield of adduct **2c** was 51 and 0%, respectively; inverse neutralization at 25° afforded **2c** in 16% yield. That the lower yields of adduct **2c** at higher temperatures were not due to reaction of starting dilithio salt **1″c** with the THF solvent was demonstrated by a 55% yield of adduct **2c** even when **1″c** was refluxed in THF–hexane for 60 hr prior to addition of benzophenone at 0°. Furthermore, even dilithiophenylacetamide **1″a** was stable to refluxing THF–hexane as evidenced by deuteration after 1–3 hr of reflux to afford recovered phenylacetamide containing 0.43–0.5 α-deuterium atoms per molecule. These results thus imply that alkoxyamides like **2″a–c** are relatively more stable at lower temperatures. Examples are known where the stability of compounds such as amine–borane adducts[6] and sterically hindered hydrocarbons[7] are greater at lower temperatures; perhaps anionic compounds could behave similarly.

The structures of the new compounds were supported by elemental analyses and by infrared (ir) spectroscopy (Table II). In some cases, the β-hydroxyamides were dehydrated. Thus, dehydration of **2b** gave **8** in 65% yield, while dehydration of adduct **3** by hot polyphosphoric acid afforded unsaturated amide **9** in 80% yield. Hydroxyamides **1a** and **1c** have previously been dehydrated.[8]



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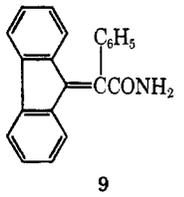

9

(4) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **32**, 3640 (1967).
(5) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 4756 (1953).
(6) H. C. Brown, H. I. Schlesinger, and S. Z. Cardon, *ibid.*, **64**, 325 (1942).
(7) J. B. Conant and N. M. Bigelow, *ibid.*, **50**, 2041 (1928).
(8) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **29**, 722 (1964).

TABLE II

INFRARED AND ANALYTICAL DATA OF NEW β-HYDROXYAMIDES

Adduct	Ir, cm^{-1}	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2b	3350, 3160, 1690, 750, 700	79.73	6.39	4.27	79.81	6.28	4.33
3	3450, 3380, 3180, 1675, 740, 730, 690	79.98	5.43	4.44	79.55	5.51	4.40
4a	3350, 3180, 1630, 730, 700	72.07	8.21	6.00	72.24	8.18	5.91
4b	3480, 3280, 1630, 730, 690	72.84	8.56	5.66	73.01	8.68	5.61
4c	3350, 3190, 1660 750, 690	77.64	7.49	4.53	77.57	7.61	4.69
5a	3440, 3180, 1675 770, 730	71.20	7.82	6.39	70.88	8.02	6.40
5c	3460, 3230, 1660, 740, 690	77.26	7.17	4.74	77.42	7.31	4.71

Experimental Section[9]

Addition Reactions of Arylacetamides with Carbonyl Compounds.—In Table I are summarized the results of the condensation reactions of arylacetamides with various ketones and benzaldehyde. General procedures are described below.

I. Alkali Amides in Liquid Ammonia (Method A).—To a stirred suspension of 0.11 mol of alkali amide in 300 ml of commercial anhydrous liquid ammonia[10] was added 0.05 mol of the solid arylacetamide. After 15 min for sodium amide and 30 min for lithium amide, the reaction mixture was assumed to contain 0.05 mol of the corresponding dialkali arylacetamide. Such salts were then treated during 5 min with a solution of 0.05 mol of the appropriate ketone or benzaldehyde in 50 ml of ether. After 5 min, the resulting suspension was poured into 200 ml of ammonia containing excess ammonium chloride (inverse neutralization), and the ammonia was allowed to evaporate. The solid residue remaining was hydrolyzed by 100 ml of 3 *N* hydrochloric acid, and the products were extracted by three 50-ml portions of ether. Drying ($CaSO_4$ or $MgSO_4$) and concentration afforded the crude product which was recrystallized from a suitable solvent.

II. *n*-Butyllithium in Inert Solvents (Method B).—To 0.05 mol of the arylacetamide in 62.5–69 ml of anhydrous THF or ether at an appropriate temperature under nitrogen was added, during 3–5 min, 62.5–69 ml (0.10–0.11 mol) of 1.6 *M* *n*-butyllithium in hexane.[11] After 5–30 min, the resulting mixture was treated during 5–10 min with a solution of 0.05 mol of the carbonyl compound in 50 ml of THF or ether. After 15 min more, the mixture was poured into ice water–hydrochloric acid. Work-up, isolation, and purification of products were then accomplished as described above.

Benzylation of Disodiophenylacetamide–Cyclohexanone Reaction Mixture.—Cyclohexanone (4.9 g, 0.05 mol) was condensed with disodio salt **1″a** as described in I, except that after 5 min, the reaction mixture was treated with 6.33 g (0.05 mol) of benzyl chloride instead of effecting the inverse neutralization. After 45 min, the resulting solution was poured into ammonia containing excess ammonium chloride, and the ammonia was allowed to evaporate as it was replaced by ether. The ethereal solution was concentrated, and the crude product was analyzed by vpc; the major product exhibited the same retention time as an authentic sample of 2-benzylcyclohexanone. Distillation of a portion of the crude product afforded pure 2-benzylcyclohexanone, bp 164–166° (17 mm) [lit.[12] bp 162–165° (17 mm)].

Dehydration of β-Hydroxyamide 2b.—Solid adduct **2b** (1.0 g) was added in small portions to 20 ml of magnetically stirred concentrated sulfuric acid maintained at 0°. After most of the solid had dissolved, the reaction mixture was poured into 60 g of ice water, and the resulting yellow solid was extracted into 200 ml of ether. The combined extracts were washed with water, then

(9) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer as potassium bromide disks. Vapor phase chromatograms were obtained on a F & M Model 500 Chromatograph using a 5-ft silicon oil column. Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and Triangle Chemical Laboratories, Chapel Hill, N. C.
(10) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).
(11) Supplied by the Foote Mineral Co., Exton, Pa.
(12) A. Tiffeneau and M. Porcher, *Bull. Soc. Chim. Fr.*, **31**, 329 (1922).

with saturated aqueous sodium bicarbonate. After drying ($CaSO_4$) and concentrating, the resulting crude product was recrystallized from 95% ethanol to afford 0.6 g (65%) of N-methyl-2,3,3-triphenylpropenamide hemihydrate (**8**): mp 172.5-174°; ir 3250 (NH), 1620 (C=O), 770 (C=C), and 685 (ArH).

Anal. Calcd for $C_{44}H_{40}N_2O_3$: C, 81.96; H, 6.25; N, 4.34. Found: C, 82.32; H, 6.55; N, 4.27.

Dehydration of β-Hydroxyamide 3.—Solid adduct **3** (2.0 g) was added in small portions to 45.6 g of polyphosphoric acid maintained at a sufficiently high temperature to allow magnetic stirring. After 5 min, the brown-green solution was treated with 50 g of ice, and the cold solution was extracted several times with a total of 400 ml of ether. After work-up as in the dehydration of adduct **2b**, the resulting residue was recrystallized from benzene to give 1.47 g (80%) of 2-(9-fluorenyl)-2-phenylacetamide (**9**), mp 229-231°.

Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.09; N, 4.71. Found: C, 84.52; H, 5.25; N, 4.48.

Registry No.—*n*-Butyllithium, 109-72-8; **2b**, 2683-62-7; **3**, 17510-68-8; **4a**, 17510-69-9; **4b**, 17510-70-2; **4c**, 17510-71-3; **5a**, 17510-72-4; **5c**, 17510-73-5; N-methyl-2,3,3-triphenylpropenamide, 2683-63-8; **9**, 17510-75-7.

Metalation at Methyl Group of N-Substituted *o*-Toluenesulfonamides by Excess *n*-Butyllithium. Condensation with Benzophenone[1]

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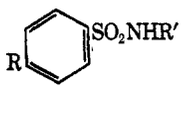
Received May 20, 1968

N-Substituted benzenesulfonamides **1** (R = H; R′ = CH_3 or C_6H_5) and also *p*-toluenesulfonanilide (**1**, R = CH_3; R′ = C_6H_5) have previously[2] been shown to undergo *ortho* metalation, as well as N metalation, with excess *n*-butyllithium, as evidenced by condensations of the resulting dilithiosulfonamides with benzophenone to form *ortho* derivatives **2**; these products underwent thermal cyclodehydration to give the sultams **3**.



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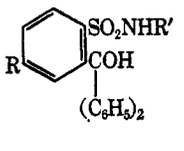

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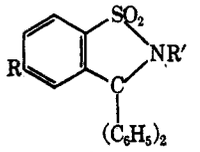
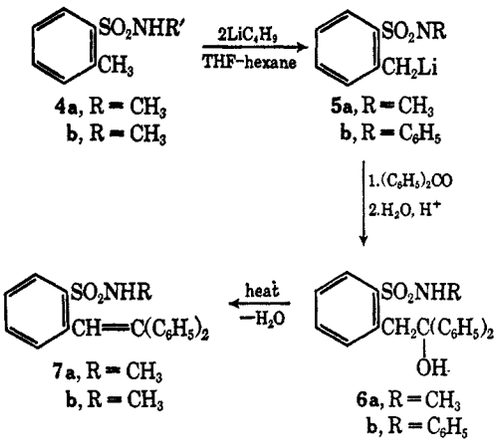


3

N-Substituted *o*-toluenesulfonamides **4a, b** have now been found to undergo metalation at the methyl group, as well as N metalation, with excess *n*-butyllithium to form dilithiosulfonamides **5a, b**, as evidenced by condensation with benzophenone to give carbinol sulfonamides **6a, b**; these products underwent thermal dehydration to afford unsaturated sulfonamides **7a** and **b**, respectively (Scheme I).

The carbinol sulfonamides **6a, b** and their dehydration products **7a, b** were obtained in high yields (73–96%). Their structures were supported by analyses and absorption spectra. Surprisingly, carbinol sulfonamide **6b** appeared to undergo a change in structure on standing at room temperature, especially in the presence of polyphosphoric acid, as evidenced by a change in the nmr spectrum. That the second structure was still essentially carbinol sulfonamide **6b** was supported, not only by analysis and absorption spectra, but also by dehydration to form the unsaturated sulfonamide **7b** (see Experimental Section).

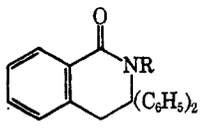
SCHEME I



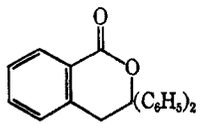
The difference in the courses of metalation of the *o*- and *p*-toluenesulfonamides appears to be due to initial coordination of the lithium of the *n*-butyllithium with the nitrogen of the monolithio intermediate to form a complex in which the potential *n*-butyl carbanion is directed to a methyl hydrogen in the 2-methyl compounds **4a, b** but to an *ortho* hydrogen in the 4-methyl compound **1** (R = CH_3; R′ = C_6H_5). Thus, although a nucleophilic mechanism probably operates to form a weaker base in both cases, the lithium cation also plays an important role especially in the latter case where an *ortho* hydrogen rather than the probably more acidic 4-methyl hydrogen is ionized.[3]

The difference in the courses of thermal dehydration of the benzophenone adducts of the *o*- and *p*-toluenesulfonamides is evidently due to the presence of methylene hydrogen β to the hydroxyl group in the former compounds, but not in the latter. Thus, whereas the carbinol sulfonamides **2** can undergo only cyclodehydration, the carbinol sulfonamides **6a, b** can, and do, exhibit linear dehydration involving their methylene hydrogen. Although **6a, b** also underwent linear dehydration with acid catalysts in refluxing acetic acid or benzene, they might possibly exhibit cyclodehydration with acids at lower temperatures since the corresponding carbinol carboxamides **8**, which have methylene hydrogen, have recently been observed to undergo cyclodehydration with cold sulfuric acid to form **9**.[4] Unfortunately, cold sulfuric acid has now been found

8



9



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(1) Supported by Army Research Office (Durham).

(2) H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).

(3) See K. P. Klein and C. R. Hauser, *ibid.*, **32**, 1479 (1967); also see A. A. Morton, "Solid Organoalkali Reagents," Gordon and Breach, Inc., New York, N. Y., 1964.

(4) I. T. Barnish, C. L. Mao, and C. R. Hauser, *Chem. Commun.*, 564 (1968).