phenyl group attached to the double bond, the signal of the proton cis to the phenyl would be shifted almost 0.5 ppm downfield from the trans proton. On this basis, 8, having the olefinic proton at τ 4.73, was assigned the *trans* configuration, and 9, with the olefinic proton at τ 4.33, was assigned the *cis* configuration. These assignments are in agreement with those published on the homologous phenylbutene isomers.8

Reaction of Amide Derivatives of α -Methyl- α -butylbenzylamine (2b, 2c, and 2d) with PPA.-Amide 2b (0.20 g) was added to 12 g of PPA and stirred at room temperature for 1 hr. The slurry was then worked up as above. The product mixture (SGN column) had the following composition (wt % as estimated from relative peak areas): 6% 8, 2% 9, 37% benzamide, 52%polymeric olefins, and 3% unreacted 2b. Optically pure 2b was treated with PPA for 15 min, following the above procedure. The product was chromatographed on neutral Woelm alumina and the recovered amide, $[\alpha]^{24}D - 22.9$ (c 2.3, CHCl₃), was racemized to the extent of $9.2 \pm 5.2\%$.

Amide 2c was treated with PPA for 1 hr by the procedure described above and the product mixture had the following composition: 2% 8, 7% 9, 38% polymeric olefins, and 38% unreacted 2d.

Treatment of N-Neopentylpivalamide (4) with PPA.-Compound 4, mp 87-89°, was prepared from neopentylamine²⁵ and pivalyl chloride. This amide had characteristic absorptions in the ir spectrum (CHCl₃) at 3480, 2950, 1650, 1510, 1390, and 1360 cm^{-1}

Anal. Calcd for C10H21NO: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.07; H, 12.24; N, 8.08.

Amide 4 (0.180 g, 0.001 mol) was added to 3.7 g of PPA and stirred for 23 hr at $77-80^{\circ}$. The reaction was then worked up as above. Vpc analysis of the extract indicated that only starting material was present. No pivalamide was evident within the limits of detection (0.3%). Evaporation of the solvent yielded 0.10 g of 4 which was identical with an authentic sample (mixture melting point and ir spectrum).

Treatment of N-Benzoyl- and N-Acetyl-1,1-diphenylmethylamine (5b and 5a) with PPA.—Amide 5b (0.355 g), mp 166-169° (lit.²⁶ 172°, 166-167°), was added to 7.1 g of PPA and this mixture was stirred for 1 hr at room temperature, then treated as in similar experiments described above. Vpc analysis (SGN column) indicated that only unreacted 5b was present. None

(25) D. Y. Curtin and S. M. Gerber, J. Amer. Chem. Soc., 74, 4052 (1952). (26) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953, p 90. of the expected N-alkyl cleavage products were observed within the limits of detection (0.2% total benzamide plus benzylhydrol). Evaporation of the solvent left 0.30 g of 5b which was identical with an authentic sample (mixture melting point and ir spectrum).

A similar result was obtained when 5a, mp 145-148° (lit.27 mp 152°) was treated with PPA for 1 hr at room temperature. However, treatment of 5a for 1 hr at 78° caused considerable N-acyl fission, since large amounts of acetic anhydride were evident in the ir spectrum of the crude reaction mixture.

Treatment of N-Acetyl-1-Cyclohexylethylamine (3) with PPA. -Amide 3 was prepared in quantitative yield by the catalytic hydrogenation of 2e in a Parr apparatus at 48 psig using 15% rhodium on carbon as catalyst. The (+) 3 had mp 96.5-97.5°, and its spectral properties (ir and nmr) were consistent with the expected structure.

Anal. Calcd for C10H19NO: C, 70.96; H, 11.31; N. 8.27.

Found: C, 70.81; H, 11.19; N, 8.11. Optically active 3, mp 101-102.5°, $[\alpha]^{25}$ D 11.7° (c 5.27, DMF), was prepared by hydrogenation of optically active 2c [from (-)-*a*-methylbenzylamine, 98% optically pure]. The optically active **3** (1.15 g, 0.067 mol) was added to 23 g of PPA which was stirring at 80°. The mixture was stirred for 20 hr at 80°, then worked up as above. Vpc of the chloroform extract (DFX column 200°, SGN column 200°) indicated that only 3 was present. Evaporation of the solvent yielded crude 3, which after recrystallization from isopropyl ether showed no significant loss in optical activity.

Registry No.—(+) 2a, 20826-48-6; 2c, 20826-78-2; (\pm) 3, 20826-51-1; 4, 20826-79-3; 8, 20826-49-7; 9, 20826-50-0; 10, 20826-80-6; α-methyl-α-butylbenzylamine $[(\pm)$ -tartrate salt], 20858-73-5.

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(27) A. Kaluszner, S. Blum, and E. Bergmann, J. Org. Chem., 28, 3588 (1963).

Formation and Reactions of Dianions Derived from 4-Methylcarbostyril and trans- β -Methylcinnamanilide¹

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Treatment of 4-methylcarbostyril (1) with 2 mol equiv of n-butyllithium in tetrahydrofuran-hexane effected ionization of the NH proton and one of the methyl protons to form resonance-stabilized dianion 2. Reaction of dianion 2 with carbonyl compounds, alkyl halides, and carbon dioxide afforded products arising from condensa-tion of the electrophilic reagent at the exocyclic carbanion site. These reactions represent the first examples of successful carbon-carbon condensations at the methyl group of 1, a position which has previously been considered to be unreactive. $trans-\beta$ -Methylcinnamanilide (12) also underwent similar twofold ionization with n-butyllithium to afford dianion 13. Protonation and alkylations of dianion 13 took place predominately at the α -carbanion site, while condensations with benzophenone and 9-fluorenone occurred preferentially at the terminal carbanion position.

Although 4-methylcarbostyril (1) has structural features which might be expected to impart some measure of acidity to the hydrogens of its methyl group, there appear to be no examples in the literature of reactions involving even transient carbanion formation at this

(1) (a) Supported by Grant 14340 from the National Institute of General Medical Sciences. (b) Presented before the Organic Division of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) (a) Taken in part from the Ph.D. thesis of G. B. T., Virginia Polytechnic Institute, Aug 1968.
 (b) National Science Foundation Undergraduate Research Participant, summer 1966.

position. Indeed, failure of 1 to undergo typical carbon-carbon condensation at its methyl group has been cited as evidence that the methyl protons do not possess any appreciable active hydrogen character.³

We now wish to report that treatment of 1 with 2 mol equiv of n-butyllithium in tetrahydrofuran-hexane for

(3) (a) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, p 150; (b) N. K. Khromor-Barisov, R. S. Karlinskaya, and L. N. Aggeva, Zh. Obshch. Khim., 25, 2294 (1955) [Chem. Abstr., 50, 9429g (1956)].

approximately 15 min at room temperature results in a twofold acid-base reaction in which the alkyllithium reagent abstracts the NH proton as well as a methyl proton to produce resonance-stabilized dianion 2.4 In-



itial evidence for formation of dianion 2 was obtained by quenching the reaction mixture with deuterium oxide followed by nmr analysis of the resulting deuterated product. The results of the deuteration experiment were further confirmed by trapping dianion 2 with various electrophilic reagents. These reactions, which are described below, represent the first examples of active hydrogen type condensations at the methyl group of 1, and serve to demonstrate the potential synthetic utility of dianion 2.

Treatment of dianion 2 with cyclohexanone and benzophenone produced tertiary alcohols 3a and 3b, respectively. Similarly, reaction of dianion 2 with anisaldehyde and isobutyraldehyde afforded secondary alcohols 3c and 3d. Alkylations of dianion 2 were effected with benzyl chloride, *n*-butyl bromide, and isopropyl bromide to produce 4-alkylcarbostyril derivatives 4a-c. Carboxylation of dianion 2 with excess solid carbon dioxide gave acid 5. Structural assignments 3a-d, 4a-c, and 5



were based on analyses and spectral characteristics (see Experimental Section). In particular, the nmr spectra were consistent with products arising from condensation at the exocyclic carbanion site of dianion 2. Thus, the methyl resonance, which had appeared at 2.54 ppm in the spectrum of 1, was replaced by absorption for two side-chain methylene protons with the appropriate multiplicity in the spectra of these derivatives. Further support for the structure of acid 5 was obtained by its decarboxylation to regenerate 1. Interestingly, treatment of dianion 2 with ethyl acetate or acetyl chloride afforded tertiary alcohol 6, rather than the expected acetyl derivative 7. That 6 was the



proposed dicondensation product was verified by its mass spectrum, which had a molecular ion peak at m/e 360 (2% of the base peak) along with peaks at m/e 202 (28%) and 159 (base peak). The peak at m/e 202 is presumably due to fragment 8, which results from cleavage at the α (carbinol) carbon of the molecular ion of 6, a process which is characteristic of tertiary alcohols.⁵ The fragment appearing at m/e 159 is assigned structure 9, and apparently arises from a Mc-



Lafferty-type rearrangement of the molecular ion of $\mathbf{6}$ in which α cleavage is accompanied by concomitant transfer of the OH hydrogen of the alcohol function to the 3 position of the carbostyril nucleus.⁶

Formation of carbinol 6 undoubtedly occurs via initial reaction of the acylating agent with dianion 2 to produce monoanion 10. This intermediate then undergoes a rapid carbonyl addition⁷ reaction with a second equivalent of dianion 2 to form trianion intermediate 11, which is converted into 6 on neutralization of the reaction mixture.



The above results with cyclic anilide 1 prompted us to investigate the possibility of effecting similar twofold ionization of trans- β -methylcinnamanilide (12), which may be regarded as an open-chain analog of 1. Treat-

⁽⁴⁾ For analogous examples of dianion formation by means of *n*-butyllithium, which appeared while this work was in progress, see (a) E. J. Corey and T. Durst, J. Amer. Chem. Soc., **38**, 5656 (1966); (b) R. L. Gay and C. R. Hauser, *ibid.*, **39**, 1647 (1967); and (o) R. E. Smith, S. Boatman, and C. R. Hauser, J. Org. Chem., **33**, 2083 (1968).

⁽⁵⁾ R. A. Friedel, J. L. Schultz, and H. G. Sharkey, Anal. Chem., 38, 926 (1956).

⁽⁶⁾ See H. E. Audier, H. Felkin, M. Fetizon, and W. Vetter, Bull. Soc. Chim. Fr., 3236 (1965), for examples of a similar fragmentation pathway in the mass spectra of acyclic unsaturated alcohols.

⁽⁷⁾ Attack of dianion **2** at the carbonyl group of monoanion **10** apparently occurs because the most likely alternate course of reaction, i.e., abstraction of a methylene hydrogen of **10** by dianion **2**, is retarded by the residual negative charge on the heterocyclic ring of **10**.

ment of 12 with 2 mol equiv of *n*-butyllithium in tetrahydrofuran-hexane at room temperature produced dianion 13, as evidenced by its subsequent protonation and condensations with certain electrophiles.



Hydrolysis of dianion 13 with water afforded the less stable, nonconjugated isomer 14⁸ and starting anilide 12 in a ratio of 2.3:1, as determined by nmr analysis of the crude reaction mixture.⁹ Thus, protonation of dianion



14 (70%)

13 follows the Hughes-Ingold rule¹⁰ for proton capture by allylic anions in the respect that the tautomer which is formed more rapidly is the thermodynamically less stable one.

Dianion 13 also underwent alkylation with *n*-butyl bromide and benzyl chloride at its α -carbanion site to afford nonconjugated derivatives 15a and 15b. However, when dianion 13 was allowed to react with benzophenone and 9-fluorenone, only the terminal condensation products 16a and 16b were isolated.¹¹ Examina-



(8) The relative thermodynamic stabilities of 12 and 14 were established by treating each of them with sodium methoxide in methanol to produce the same equilibrium mixture, which consisted of 98% conjugated isomer 12 and 2% nonconjugated isomer 14.

(9) The nmr spectrum of the crude mixture also had absorption characteristic of an *n*-butyl group, indicating that some conjugate addition of *n*butyllithium to the $\alpha_i\beta$ -unsaturated carbonyl system of 12 had occurred. This competitive reaction appears to be responsible for the lower yields obtained from dianion 13 when it and dianion 2 were treated separately with the same electrophilic reagent. (10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry,"

(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 565. For a more recent discussion of allylic anions, including a number of exceptions to the Hughes-Ingold rule, see C. D. Broaddus, *Accounts Chem. Res.*, 1, 231 (1968).

(11) Both **16a** and **16b** had physical properties which were indicative of a single geometric isomer. Although a rigorous proof of their stereochemistry was not attempted, the absence of coupling between the methylene protons and the vinyl proton in the nmr spectra of these compounds indicates that the vinyl hydrogen and the methylene group are *cis* to one another. See J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 99.

tion of the nmr spectra of the unrefined mixtures obtained from these reactions failed to reveal the presence of any significant amounts of the possible isomeric derivatives. Therefore, the isolated products appear to be representative of the major course of reaction of dianion 13 with the respective electrophile.

Discussion

It seems that the rather striking dissimilarities observed in the reactions of dianion 2 and 13 with electrophilic reagents may be best rationalized in terms of different electronic distributions in their respective π systems. The tendency for dianion 2 to undergo reactions exclusively at its exocyclic carbanion site is consistent with a significantly higher degree of negative charge density at that position than at the potentially carbanionic 3 position. In resonance terminology, this would mean that canonical form 17, in which the aromatic character of the heterocyclic ring is maintained and one of the charges resides on electronegative oxygen, contributes more to the hybrid structure of dianion 2 than do other forms having negative charge localized at the 3 position. In contrast to dianion 2, dianion 13



undergoes protonation and alkylation predominately at its α carbanion position because the carbon adjacent to the carbonyl group holds a greater share of the delocalized electron pair than does the terminal carbon. Thus, canonical form 18 may be said to make a greater contribution to the structure of dianion 13 than does canonical form 19. However, the terminal site of dianion 13 still has sufficient charge density to allow reactions to occur there when the steric requirements of the electrophile impede condensation at the α position, as appears to be the case in the reactions of 13 with benzophenone and 9-fluorenone.¹²

The formation of allylic dianion 13 is somewhat surprising in view of a recent report that crotonanilide failed to afford an analogous dianion under similar conditions.^{4b} This failure was attributed to conjugate addition of *n*-butyllithium to the α,β -unsaturated carbonyl system, a process which occurs to some extent in the case of 12. Since the phenyl substituent in 12 would be expected to have little electronic influence on either conjugate addition or proton abstraction, it appears that it exerts primarily a steric effect, thereby re-

⁽¹²⁾ It is possible that the condensations of diamion 18 with benzophenone and 9-fluorenone could involve initial kinetically controlled attack of the ketone at the α position, followed by dissociation and recombination, to form the thermodynamically more stable terminal products. However, we were unable to isolate any α -substituted derivatives, even when shorter reaction periods and lower temperatures were employed.

tarding conjugate addition and allowing proton abstraction to take place.

Finally, it should be mentioned that the twofold ionization of 1 to form dianion 2 is of definite synthetic interest in that it transforms what heretofore has been regarded as an inert substituent into a reactive carbanion site. This new reaction center permits facile modification of the original methyl group to produce a variety of 4-substituted carbostyril derivatives from a single, readily available precursor.¹³

Experimental Section¹⁴

Preparation of Starting Materials. A. 4-Methylcarbostyril (1).-This compound was prepared from acetoacetanilide by the method of Lauer and Kaslow¹⁵ and had mp 223-224° (lit.¹⁵ mp 222-224°); nmr & 11.82 (s, 1, NH), 7.60 (m, 4, aromatic), 6.64 (s, 1, vinyl), and 2.54 ppm (s, 3, CH₃).

B. trans- β -Methylcinnamanilide (13).—This compound was prepared in 52% overall yield by allowing dilithioacetanilide^{4b} to condense with acetophenone in tetrahydrofuran (THF)hexane at room temperature. The resulting alcohol, mp 69-71° from carbon tetrachloride, was characterized spectrally and then dehydrated by refluxing it with 10% by weight of *p*-toluene-sulfonic acid in benzene. The resulting solid was recrystallized several times from carbon tetrachloride to afford 13, mp 119-121° (lit.¹⁶ mp 121°); nmr δ 10.0 (s, 1, NH), 7.86 (m, 10, aromatic), 6.76 (q, 1, J = 2 Hz, C=CH), and 2.76 ppm (d, 3, J = 2 Hz, CH₃).

Preparation of 4-Methylcarbostyril Dianion (2).-To a stirred suspension of 3.98 g (0.025 mol) of 1 in 100 ml of anhydrous THF contained in a 250-ml, three-necked, round-bottomed flask at room temperature under nitrogen, was added 38.1 ml (0.056 mol) of a 1.47 \dot{M} solution of *n*-butyllithium in hexane¹⁷ over a period of 3 min to produce a dark red-brown solution. This solution was allowed to stir at room temperature for an additional 10 min before being employed in the reactions described below

Deuteration of Dianion 2.—A solution of dianion 2 (63 mmol) in 20 ml of THF-hexane was prepared as described above. The reaction mixture was then poured into 10 ml of deuterium oxide to produce a heavy white precipitate, which quickly dissolved. The resulting mixture was stirred for 50 min and then concentrated to dryness under reduced pressure. The residual solid was washed with 10 ml of deuterium oxide and dried to afford 0.94 g (94%) of 1-d₂, mp 220-222°, mmp with a sample of 1-d₀, $221-222^\circ$; nmr δ 7.96 (m, 4, aromatic) 6.98 (s, 1, vinyl), and 2.60 ppm (s, 2.1, CH₂D). The integrated intensity of the CH₂D peak compared with that of the aromatic multiplet or the vinyl singlet was consistent with incorporation of 0.9 of one deuterium atom at the methyl position. The spectrum of the deuterated product was devoid of NH resonance. When dianion 2 was quenched with water, a comparable yield of 1 was recovered and no isomeric products were detected.

In order to verify that deuteration at the methyl position of 1

(15) W. M. Lauer and C. E. Kaslow, "Organic Syntheses," Coll. Vol. III,
E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 58. (16) F. Henrich and A. Wirth, Chem. Ber., 37, 732 (1904).

had occurred through dianion 2 and not via exchange catalyzed by the lithium deuteroxide formed in the quenching experiment, a 0.5-g (3-mmol) sample of 1 in 10 ml of THF was treated with 0.14 mol of lithium deuteroxide, prepared from 0.14 g-atom of lithium metal in 5 ml of deuterium oxide, for 1 hr. The reaction mixture was processed as described above to afford a nearly quantitative recovery of $1-d_1$, the nmr spectrum of which showed no NH resonance. The integrated intensity of the methyl protons was undiminished.

Carbonyl Addition Reactions of Dianion 2.-These reactions were carried out using 0.025 mol of dianion 2 in 100 ml of THF. to which was added 0.037 mol of the appropriate aldehyde or ketone in 30 ml of THF over a period of 1-5 min. Additional details are given below.

A. Cyclohexanone.-Addition of the ketone to dianion 2 produced a thick precipitate, which dissolved in a few minutes to produce a light yellow solution. The reaction mixture was allowed to stir for 1 hr, and was then poured into 200 ml of icewater. The two-phase mixture was allowed to warm to room temperature and the THF-hexane was removed on a rotary evaporator. The resulting aqueous solution was allowed to stand overnight in the refrigerator to produce a precipitate, which was collected and recrystallized from aqueous ethanol to afford 6.4 g (87%) of 4-(1-hydroxycyclohexylmethyl)-carbostyril (3a), mp 182–184°; ir 3100–3450 (NH and OH) and 1630 cm⁻¹ (C==O); nmr δ 12.06 (s, 1, NH), 7.76 (m, 4, aromatic), 6.66 (s, 1, vinyl), 4.34 (s, 1, carbinol OH18), 3.00 (s, 2, side-chain CH₂), and 1.52 ppm (broad s, 10, cyclohexyl).

Anal. Calcd for C16H19NO2: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.92; H, 7.51; N, 5.34.

R Benzophenone.-This reaction was carried out as described for the condensation with cyclohexanone, except that, after the organic solvents had been removed, the remaining aqueous solution was made weakly acidic with cold 6 N HCl. The resulting precipitate was recrystallized from a large volume of absolute ethanol to give 6.3 g (74%) of 4-(2,2-diphenyl-2-hydroxyethyl)carbostyril (3b), mp 281–283°; ir 3125–3450 (NH and OH) and 1640 cm⁻¹ (C=O); nmr δ 12.16 (s, 1, NH), 7.88 (m, 14, aromatic), 6.70 (s, 1, vinyl), 6.30 (s, 1, carbinol OH), and 5.2 ppm (s, 2, side-chain CH₂).

Calcd for C23H19NO: C, 80.95; H, 5.57; N, 4.11. Anal. Found: C, 80.77; H, 5.71; N, 4.27.

C. Anisaldehyde.—Dianion 2 was prepared at room tem-perature and then cooled to 0° in an ice-salt bath. A solution of anisaldehyde in THF was added over a period of 1 min and the reaction mixture was allowed to stir for 5 min at 0°19 before being poured into 200 ml of cold 6 N HCl. The layers were separated and the aqueous layer was diluted with 200 ml of cold water and allowed to stir for 30 min. The resulting precipitate was recrystallized from absolute ethanol to give 3.46 g (47%) of (3c), mp 4-[2-hydroxy-2-(p-methoxyphenyl)ethyl]carbostyril 230-231°; ir 3025-3380 (NH and OH) and 1630 cm⁻¹ (C=O); nmr δ 11.92 (s, 1, NH), 7.50 (m, 8, aromatic), 6.50 (s, 1, vinyl), 5.60 (d, 1, carbinol OH), 5.06 (m, 1, carbinol CH), 3.84 (s, 3, OCH₂), and 3.22 ppm (d, 2, side-chain CH₂).

Anal. Calcd for C18H17NO3: C, 73.20; H, 5.80; N, 4.74.

Found: C, 73.46; H, 5.88; N, 4.61. D. Isobutyraldehyde.—This reaction was carried out essentially as described for the anisaldehyde condensation. The crude product was recrystallized from aqueous ethanol to yield 2.58 g (50%) of 4-(2-hydroxy-3-methylbutyl)carbostyril (3d), mp 169–171°; ir 3125–3390 (NH and OH) and 1630 cm⁻¹ (C=O); nmr δ 12.42 (s, 1, NH), 7.86 (m, 4, aromatic), 6.86 (s, 1, vinyl), 4.70 (d, 1, carbinol OH), 3.72 (m, 1, carbinol CH), 3.02 (d, 2, side-chain CH₂), 1.8 (m, 1, isopropyl CH), and 1.02 ppm [d, 6, C(CH₃)₂].

Anal. Calcd for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.10. Found: C, 72.97; H, 7.37; N, 5.89.

Alkylations of Dianion 2.—These reactions were accomplished by adding a solution of 0.037 mol of the appropriate alkyl halide in 25-30 ml of THF to 0.025 mol of dianion 2 in 100 ml of THF at room temperature. Reaction mixtures were processed as in

⁽¹³⁾ For a discussion of a less direct, but widely used procedure for the synthesis of 4-substituted carbostyrils, see B. Staskun, J. Org. Chem., 29, 1153 (1964).

⁽¹⁴⁾ Melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes and are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and in our laboratories by Miss Q. H. Tan using an F & M Model 185 C, H, and N analyzer. Infrared spectra were taken on a Beckman IR-5A spectrophotometer using the potassium bromide pellet method. Nmr spectra were determined with a Varian Associates A-60 spectrometer using DMSO-ds as the solvent for all compounds except 12, 14, and 16a, where acetone-de was employed. Chemical shifts, relative to internal tetramethylsilane, are measured to the center of a singlet or multiplet. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU spectrometer at 50 eV. Gas chromatograms were obtained on a Varian Aerograph Model 1200-1 gas chromatograph using a 5 ft \times 1/s in. 5% SE-30 (Methyl) on 60/80 DMCS Chromosorb W column with nitrogen as the carrier gas. Unless otherwise specified, chemicals were commer-

⁽¹⁷⁾ This reagent was obtained from Foote Mineral Co., Exton, Pa., and was standardized by the procedure of H. Gilman and A. H. Haubein, J. Amer. Chem. Soc., 66, 1515 (1944).

⁽¹⁸⁾ Carbinol OH protons were identified by shaking the nmr samples with a few drops of deuterium oxide and then rescanning the spectrum to ob-serve which of the original peaks had disappeared. This procedure also led to exchange of the NH proton of the carbostyril nucleus.

⁽¹⁹⁾ When the reaction was allowed to proceed for 1 hr at room tempera ture, unchanged 1 was recovered, and none of the desired alcohol could be isolated.

the condensation of dianion 2 with cyclohexanone. Yields, spectral data, and analyses are given below.

A. Benzyl Chloride.-Treatment of dianion 2 with benzyl chloride, followed by recrystallization of the crude product from absolute ethanol, afforded 4.25 g (68%) of 4-(2-phenylethyl)-carbostyril (4a), mp 184–185°; ir 3400, 3100, and 1630 cm⁻¹ (C=O); nmr δ 12.20 (s, 1, NH), 7.68 (m, 9, aromatic), 6.70 (s, 1, vinyl), and 3.16 ppm (m, 4, PhCH₂CH₂).

Anal. Calcd for C₁₇H₁₅NO: C, 81.9; H, 6.06; N, 5.62. Found: C, 82.18; H, 5.99; N, 5.69.

B. *n*-Butyl Bromide.—This reaction produced 3.14 g (58%) of 4-*n*-pentylcarbostyril (4b), mp 146–148° from 95% ethanol; ir 3400, 3150, and 1630 cm⁻¹ (C=O); nmr δ 12.14 (s, 1, NH), 7.84 (m, 4, aromatic), 6.76 (s, 1, vinyl), and 1.82 ppm (m, 11, n-C₅H₁₁).

Anal. Calcd for C14H17NO: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.12; H, 8.08; N, 6.22. C. Isopropyl Bromide.—Treatment of dianion 2 with iso-

propyl bromide for 1.5 hr afforded 2.52 g (50%) of 4-isobutyl-carbostyril (4c), mp 167-169° from 95% ethanol; ir 3450, 3110, and 1630 cm⁻¹ (C=O); nmr & 13.42 (s, 1, NH), 7.58 (m, 4, aromatic), 6.70 (s, 1, vinyl), 2.78 (d, 2, CH₂), 2.10 (m, 1, CH), and 1.00 ppm [d, 6, C(CH₃)₂].

Anal. Calcd for $C_{18}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.65; H, 7.50; N, 6.95.

Carboxylation of Dianion 2.- A solution of 0.025 mol of dianion 2 was prepared in the usual manner and then poured onto a large excess of finely powdered Dry Ice contained in a 1-l. roundbottomed flask equipped with a magnetic stirrer. The resulting slurry was stirred for 2.5 hr as more Dry Ice was added periodically. The reaction mixture was then poured into 200 ml of cold water and the organic layer was evaporated under reduced pressure. The remaining aqueous solution was cooled in an ice bath and acidified with cold 6 N HCl. The solid which precipitated was washed with water and recrsystallized from absolute ethanol to afford 2.53 g (50%) of 4-carboxymethylcarbostyril (5), mp $213-214^\circ$; ir 3350-3500 (NH and OH), 1700 (COOH), and 1630 cm⁻¹ (NC=O); nmr δ 7.70 (m, 4, aromatic), 6.82 (s, 1, vinyl), and 4.40 ppm (s, 2, CH₂COOH).

Anal. Caled for C₁₁H₉NO₃: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.09; H, 4.53; N, 6.76.

A 0.3-g sample of acid 5 was heated at 220-230° under nitrogen until gas evolution ceased to afford 4-methylcarbostyril (1), which was identified by mixture melting point and comparison of its ir spectrum with that of an authentic sample.

Reaction of Dianion 2 with Ethyl Acetate and Acetyl Chloride. -To a stirred solution of 0.025 mol of dianion 2 under nitrogen at room temperature was added 3.30 g (0.0375 mol) of ethyl acetate in 30 ml of dry THF. A heavy precipitate formed immediately. After 1 hr, the reaction mixture was poured into 100 ml of cold 6 N HCl. The resulting precipitate was collected by filtration, washed with water, and recrystallized from aqueous dimethylformamide to give 3.56 g (79%) of 1,3-bis(2-hydroxy-4metnyhormanide to give 3.30 g ($19\%_0$) of 1,3-018(2-hydroxy-4-quinolyl)-2-methyl-2-propanol (6), mp 303-304°; ir 3380-3500 (NH and OH) and 1650 cm⁻¹ (C=O); nmr δ 9.00 (m, 8, aro-matic), 7.08 (s, 2, vinyl), 4.90 (s, 1, OH), 3.40 (s, 4, CH₂), and 1.16 ppm (s, 3, CH₃); mass spectrum (50 eV) m/e (rel inten-sity) 360 (2), 202 (28), and 159 (100). Anal. Calcd for C₂₂H₂₀N₂O₃: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.37; H, 5.60; N, 7.68. In a similar avneriment diapion 2 (0.025 mcl) was traated with

In a similar experiment, dianion 2 (0.025 mol) was treated with 0.025 mol of acetyl chloride to produce 2.10 g (46%) of tertiary alcohol 6.

Preparation of trans- β -Methylcinnamanilide Dianion (13). To a stirred solution of 2.97 g (0.0125 mol) of 12 in 60 ml of THF under nitrogen at room temperature, was added 22 ml (0.028 mol) of 1.3 M n-butyllithium in hexane during 3 min. After an additional 10 min, the dark brown solution was used as described below

Hydrolysis of Dianion 13.-A solution of dianion 13 (0.0125 mol), prepared as described above, was poured into 60 ml of cold water and the resulting two-phase system was allowed to stir for 5 min. The layers were separated and the aqueous layer was extracted with ether. The original THF layer and the ether extracts were combined, dried (MgSO4), and evaporated to produce a semisolid. This material was chromatographed on a florisil column using hexane-benzene (3:2) as the eluting solvent. The first fractions yielded 0.68 g of starting anilide 12. Further elution afforded 0.75 g of 3-phenyl-3-butenanilide (14), mp 125.5-126.5° from aqueous ethanol; ir 3380 (NH), 1710 (C=O), and 895 cm⁻¹ (C=CH₂); nmr δ 8.1 (s, 1, NH), 7.56 (m, 10, aromatic), 6.0 (s, 1, C=CH₂), 5.6 (s, 1, C=CH₂), and 3.68 ppm (s, 2, COCH2).

Anal. Calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.02; H, 6.14; N, 6.04.

In a second experiment, dianion 13 was hydrolyzed as described above, and the crude semisolid product mixture was analyzed directly by nmr using acetone- d_6 as the solvent. The integrated intensity of the peaks for each isomer as compared to the intensity of the phenyl absorption showed the presence of nonconjugated isomer 14 and conjugated isomer 12 in a ratio of 2.3:1. The spectrum also had complex absorption centered at 1.2 ppm characteristic of an n-butyl group. Analysis of the mixture by vapor phase chromatography (vpc) at 200° revealed the same ratio of 12 and 14 along with a less volatile product, which may have arisen from addition of n-butyllithium to 12.

Equilibration of 12 and 14.-A 0.5-g sample of 12 was dissolved in a sodium methoxide solution prepared from 0.97 g of sodium and 50 ml of methanol. The mixture was stirred at room temperature and aliquots were taken at appropriate intervals for 48 hr. The aliquots were acidified with 6 N HCl and extracted with ether, and the extracts analyzed by vpc at 200°. After 48 hr, the mixture had come to equilibrium with 98% 12 and 2%14.

A 77-mg sample of 14 was dissolved in a sodium methoxide solution prepared from 0.15 g of sodium and 30 ml of methanol. Aliquots were taken as above and analyzed over a period of 36 hr. After 12 hr, the conjugated isomer 12 represented 82% of the mixture, and, after 36 hr, the mixture had reached equilibrium with 98% 12 and 2% nonconjugated isomer 14. Alkylations of Dianion 13.—To a solution of dianion 13

(0.0125-0.025 mol) was added 0.019-0.03 mol of the appropriate halide in 30 ml of THF over a period of 1-5 min. The reaction mixture was allowed to stir at room temperature for 1.25 hr and was then hydrolyzed with 100 ml of cold 6 N HCl. The resulting two-phase system was stirred for 15 min and the layers were separated. The original THF layer and the ethereal extracts of the aqueous layer were combined, dried $(MgSO_4)$, and concentrated to afford an oil, which soon solidified. Further details are given below.

A. n-Butyl Bromide.--Reaction of 0.0125 mol of dianion 13 with 0.019 mol of this halide afforded, after several recrystallizations of the crude product from aqueous ethanol, 1.45 g (39%)of 2-n-butyl-3-phenyl-3-butenanilide (15a), mp 99-101°; ir 3360 (NH), 1650 (C=O), and 897 cm⁻¹ (C=CH₂); nmr δ 10.54 (s, 1, NH), 7.76 (m, 10, aromatic), 5.66 (broad s, 2, C=CH₂), 3.9 (m, 1, methine), and 1.34 ppm (m, 9, n-C₄H₉).

Anal. Calcd for C20H23NO: C, 81.87; H, 7.90; N, 4.77. Found: C, 82.01; H, 8.04; N, 4.70.

B. Benzyl Chloride.-Treatment of dianion 13 (0.025 mol) with 0.03 mol of this halide yielded, after recrystallization of the crude product from carbon tetrachloride, 3.85 g (47%) of 2benzyl-3-phenyl-3-butenanilide (15b), mp 152-154°; ir 3400 (NH), 1650 (C=O), and 910 cm⁻¹ (C=CH₂); nmr δ 10.44 (s, 1, (111), 7.66 (m, 15, aromatic), 5.66 (d, 2, C=CH₂), 4.26 (m, 1, methine), and 3.26 ppm (m, 2, PhCH₂).

Anal. Calcd for C23H21NO: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.41; H, 6.63; N, 4.07.

Carbonyl Additional Reactions of Dianion 13.-These condensations were accomplished by adding 0.019 mol of the appropriate ketone in 30 ml of THF to 0.0125 mol of dianion 13. The reaction mixture was allowed to stir for 1 hr and was then processed as in the alkylations of dianion 13.

A. Benzophenone.-The crude solid obtained from this reaction was recrystallized from carbon tetrachloride to give 2.7 g (51%) of 3-(2,2-diphenyl-2-hydroxyethyl)cinnamanilide (16a), mp 176-177°; ir 3400-3480 (NH and OH) and 1640 cm⁻¹ (C=O); nmr δ 10.08 (s, 1, NH), 7.74 (m, 20, aromatic), 6.64 (s, 1, C=CH), 4.40 (s, 2, CH₂), and 3.17 ppm (s, 1, OH).

Anal. Caled for C29H25NO2: C, 83.03; H, 6.01; N, 3.34. C, 83.09; H, 6.10; N, 3.33. Found:

B. 9-Fluorenone.—This reaction produced 2.97 g (57%) of 3-(9-hydroxy-9-fluorenylmethyl)cinnamanilide (16b), mp 203-205° from absolute ethanol; ir 3330-3400 (NH and OH) and 1630 cm⁻¹ (C=O); nmr δ 10.54 (s, 1, NH), 7.72 (m, 18, aromatic), 6.52 (s, 1, C=CH) 6.37 (s, 1, OH), and 4.80 ppm (s, 2, CH₂).

Calcd for C₂₉H₂₃NO₂: C, 83.43; H, 5.55; N, 3.36. Anal. Found: C, 83.51; H, 5.66; N, 3.07.

Registry No.—1, 607-66-9; **3a**, 21298-73-7; **3b**, 21298-74-8; **3c**, 21298-75-9; **3d**, 21298-76-0; **4a**, 21298-77-1; **4b**, 21298-78-2; **4c**, 21298-79-3; **5**, 21298-80-6; **6**, 21298-81-7; **12**, 21298-82-8; **13**, 12370-05-7; **14**, 21298-87-3; **15a**, 21298-83-9; **15b**, 21298-84-0; **16a**, 21298-86-2; **16b**, 21298-85-1.

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Reinvestigation of the Action of N-Halosuccinimides on Bis(8-quinolinolato)copper(II)¹

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Halogenation of bis(8-quinolinolato)copper(II) with N-halosuccinimides revealed that on monochlorination a mixture of 5- and 7-chloro chelates was obtained, whereas, on monobromination, only the 5-bromo chelate and on monoidination the 7-iodo chelate formed. Convenient syntheses of 7-chloro-, 7-bromo-, and 7-iodo-8-quino-linols from 8-quinolinol derivatives were also achieved.

As part of our studies on the mechanisms of antifungal action of 8-quinolinol and derivatives,²⁻⁵ it was desired to prepare the copper(II) complex of tritiated 5-iodo-8-quinolinol. The method of Prasad, et al.,6 appeared to offer a good approach to this compound. It was reported that on treatment of cobalt(III), aluminum(III), cobalt(II), and copper(II), chelates of 8-quinolinol with either N-chloro-, N-bromo-, or N-iodosuccinimide (1 mol/mol of 8-quinolinol in the chelate) in chloroform solution, monhalogenation took place, and that the halogen was found exclusively in the 5 position of the quinoline. This was reported to have been determined by comparison of the infrared and proton magnetic resonance spectra of the ligands prepared in this manner with the spectra obtained of authentic samples of the 5-halogeno-8-quinolinols.

Preliminary trials with the iodination of nontritiated 8-quinolinol copper(II) chelate by means of N-iodosuccinimide in chloroform⁶ were carried out at 40-60° in order to reduce the volume of solvent employed. After completing several iodination reactions, the complex obtained always melted between five and ten degrees lower than authentic bis(5-iodo-8-quinolinolato)copper(II). Thin layer chromatography on silica gel revealed that the product obtained via N-iodosuccinimide had an R_f value different from those of authentic samples of bis(5-iodo-8-quinolinolato)copper(II). Differences in the infrared spectra of the respective ligands and copper(II) chelates also were found.

As a result of our inability to obtain the desired product by the method described⁶ together with the incorrect characterization of the product reported,⁶ it was deemed desirable to reinvestigate the halogenation of bis(8-quinolinolato)copper(II) with N-halosuccinimides. Several variations of the conditions of halogenation were carried out. All reactions were conducted in chloroform, and the molar ratios of N-halosuccinimide to chelate were 2:1, 4:1, and 6:1. Reaction temperatures were either ambient or in the range of 40–60°, and the reaction time was 3 hr in all cases. The different ratios of halogenating agent to chelate were employed to determine whether only monohalogenation could take place and, if not, what the orientation of second and possibly third substituents would be. Since it was reported that the rates of halogenation were too rapid for classical kinetic studies,⁶ it was felt that kinetic effects might still be detected, on a gross scale, by identifying the formed products and determining their ratios. For this reason, two reaction temperatures were employed.

Upon completion of each halogenation, the reaction mixture was freed of solvent by evaporation, and the residue was dissolved in acid and treated with hydrogen sulfide to eliminate the copper(II). The filtrate was brought to pH 5 and extracted with chloroform in order to obtain all of the 8-quinolinols present. They were then converted into the trimethylsilyl derivatives and subjected to gas chromatography. The products were identified by retention times and infrared spectra. Quantitation was achieved by determining the area under the peaks in the gas chromatograms. Where only one product was detected or an overwhelming proportion of one component was present, infrared spectra of the chelates were taken and compared with spectra of authentic samples.

Retention data are listed in Table I, and the results of the halogenation reactions are compiled in Table II. Infrared spectra of the copper(II) chelates and their respective ligands have been obtained.⁷

The data of Table II indicate that chlorination of bis(8-quinolinolato)copper(II) with N-chlorosuccinimide yielded three halogenated derivatives, 5-chloro-, 7-chloro-, and 5,7-dichloro-8-quinolinol. It appears that the two monohalogeno quinolinols formed simultaneously, and that raising the temperature somewhat favored the formation of 5-chloro-8-quinolinol over the

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