2b, **2c**, **2f-2h**, and **2k** were prepared in the same manner. In the other cases, the crude product contained considerable amounts of **3** and **4** (NMR and TLC). On chromatography on silica gel, the amines **4** were eluted first, followed by the lactams **2** and the amides **3**.

Yields, physical data, and anaylses of the products are given in Table II.

Lactams Not Included in Table II. ***cis*-1-Benzyl-3,4-diphenylazetidin-2-one (2k)**: yield 80%; mp 117 °C; IR 1745 cm^{-1} (C=O); NMR (270 MHz) δ 3.93, 5.02 (d, 1 H each, J = 15 Hz, benzylic), 4.836, 4.843 (d, 1 H each, J = 5.72 Hz, H-3 and H-4), and 7.15-7.45 (m, 15 H, aromatic); mass spectrum, m/e (relative intensity) 313 (10, M^+), 195 (100, fragment A), 180 (94, D), 133 (3, C), and 118 (18, B). Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C,84.10; H, 5.72; N, 4.68.

***trans*-3-Acetyl-1,4-diphenylazetidin-2-one (5l)**: eluted with benzene-chloroform (9:1) in 9% yield; mp 98-99 °C; IR 1745 (C=O lactam) and 1710 cm^{-1} (C=O ketone); NMR δ 2.13 (s, 3 H, CH_3), 4.18, 5.55 (d, 1 H each, J = 3 Hz, H-3 and H-4), 7.00-7.45 (m, 10 H, aromatic); mass spectrum, m/e (relative intensity) 265 (39, M^+), 181 (24, fragment A), 119 (30, C), 148 (78, D), and 131(100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.66; H, 6.00; N, 5.21.

The main fraction, eluted with benzene-chloroform (1:1), was identified as *N*-benzylacetoacetanilide (**3l**, 55%, oil): IR 1705 (C=O ketone) and 1660 cm^{-1} (C=O amide); NMR δ 2.13 (s, 3 H, CH_3), 3.35, 4.98 (s, 2 H each, CH_2), and 7.00-7.50 (m, 10 H, aromatic).

Desulfurization of 1m. A solution of **1m**[31] (0.83 g) in ethanol (480 mL) containing 8 g of Raney nickel was stirred at room temperature overnight. Workup as above yielded phenyl-2'-propylacetanilide (**6**), 0.64 g (85%), mp 81 °C (after crystallization from petroleum ether): IR 3280 (NH) and 1653 cm^{-1} (C=O); NMR δ 0.78 (t, 3 H, J = 7 Hz), 1.22-1.32 (m, 2 H), 2.20 (t, 2 H, J = 7 Hz), 3.80 (s, 2 H), and 6.85-7.50 (m, 9 H); mass spectrum, m/e (relative intensity) 329 (100%, M^+), 176 (12), 162 (11), and 120 (83). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.26; H, 7.55; N, 5.84.

Prolonged Desulfurization of 1a. Reaction conditions as above were used and stirring was continued for 5 min after disappearance of color. Workup and chromatography on silica gel (elution with benzene-chloroform 9:1) gave *N*-benzylaniline (**4a**), mp 37-38 °C, and *N*-benzylphenylacetanilide (**3a**): mp 88 °C; NMR δ 3.45, 4.85 (s, 2 H each, benzylic) and 6.90-7.45 (m, 15 H, aromatic). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.72; H, 6.31; N, 4.65. Found: C, 83.90; H, 6.39; N, 4.55.

Registry No. 1a, 18100-80-6; **1b**, 68236-15-7; **1c**, 68236-16-8; **1d**, 73308-31-3; **1e**, 73308-32-4; **1f**, 68236-17-9; **1g**, 73308-33-5; **1h**, 59208-06-9; **1i**, 73308-34-6; **1j**, 73308-35-7; **1k**, 13288-65-8; **1l**, 13288-62-5; **1m**, 43091-21-0; **2a**, 16141-50-7; **2b**, 62500-28-1; **2c**, 68236-19-1; **2d**, 73308-36-8; **2e**, 73308-37-9; **2f**, 37117-44-5; **2g**, 73308-38-0; **2h**, 73308-39-1; **2i**, 73308-40-4; **2j**, 73308-41-5; **2k**, 68236-18-0; **3a**, 73308-42-6; **3l**, 73308-43-7; **4a**, 103-32-2; **5l**, 73308-44-8; **6**, 73308-45-9; *N*-phenylbenzenecarbothioamide, 636-04-4; *N*-phenyl-4-methylbenzenecarbothioamide, 20199-06-8; *N*-(2-methylphenyl)benzenecarbothioamide, 26060-28-6; *N*-(2-chlorophenyl)benzenecarbothioamide, 71651-74-6; *N*-(3-chlorophenyl)benzenecarbothioamide, 10278-49-6; *N*-(4-chlorophenyl)benzenecarbothioamide, 5310-28-1; *N*-(3,4-dichlorophenyl)benzenecarbothioamide, 10278-50-9; *N*-(4-methoxyphenyl)benzenecarbothioamide, 5310-26-9; α-bromobenzeneacetic acid, 4870-65-9; α-bromobenzeneacetyl chloride, 19078-72-9; α-bromo-2-chlorobenzeneacetic acid, 29270-30-2; α-bromo-4-chlorobenzeneacetyl chloride, 52574-79-5; *N*-benzylbenzenecarbothioamide, 14309-89-8.

(31) P. R. Pjelsud and K. Undheim, *Acta Chem. Scand., Ser. A*, **2**, 1763 (1973).

Functionalization of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone and Related Compounds through Carbanion Reactions at the 2-Methyl Group[1]

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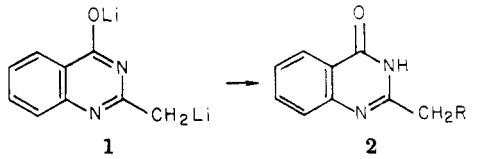
2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone, **3a**), 2,3-dimethyl-4(3*H*)-quinazolinone (**3b**), and 2-methyl-3-phenyl-4(3*H*)-quinazolinone (**3c**) were converted to the 2-lithiomethyl derivatives **4a**, **4b**, and **4c**, respectively, by means of lithium diisopropylamide in THF-hexane at 0 °C. Reactions of **4a-c** with a series of electrophilic reagents led to elaboration at the original 2-methyl group. Thus, **4a** was alkylated with methyl iodide, allyl bromide, and ethyl bromide, sulfenylated with diphenyl disulfide, and condensed with benzaldehyde and cyclohexanone. Although **4a** failed to react with benzophenone and showed a preference for enolization with acetone and butanone, the less hindered salt **4b** added readily to the carbonyl group of benzophenone and acetone. Lithio salt **4c** underwent self-condensation on treatment with cyclohexanone. Photostimulated phenylation of the 2-potassiomethyl derivative of **3a** was effected with iodobenzene. Lateral acylation of **3a** was accomplished with esters of aliphatic and aromatic acids in the presence of excess sodium hydride.

Recently,[2] we reported that 2-methyl-4(3*H*)-quinazolinone underwent twofold metalation with *n*-butyllithium to form dilithio salt **1**, which reacted with alkyl halides and carbonyl compounds exclusively at the exocyclic carbanion site to produce derivatives of type **2**. These results, which represented the first report of synthetically useful lateral metalation of a 2-alkyl-4(3*H*)-quinazolinone, prompted the present investigation of the



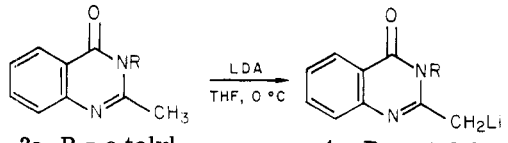
1 **2**

(1) (a) Taken from the Ph.D. dissertation of T.L.R., Virginia Polytechnic Institute and State University, June 1976. (b) Supported in part by Grant No. NS 101 97 from the National Institute of Neurological and Communicative Disorders and Stroke, Grant No. NSG 1524 from the National Aeronautics and Space Administration, and Grant No. CHE 77-13317 from the National Science Foundation.

(2) Murray, T. P.; Hay, J. V.; Portlock, D. E.; Wolfe, J. F. *J. Org. Chem.* **1974**, *39*, 595.

0022-3263/80/1945-2169$01.00/0

metalation of the potent CNS depressant 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone[3] (methaqualone, **3a**) and the



3a, R = *o*-tolyl
b, R = CH_3
c, R = C_6H_5

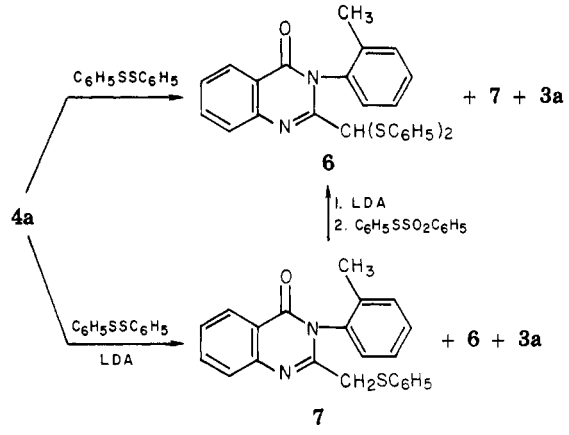
4a, R = *o*-tolyl
b, R = CH_3
c, R = C_6H_5

related 4(3*H*)-quinazolinones **3b** and **3c**. It seemed possible that lithio salts **4a–c** could serve as useful new intermediates for the synthesis of various 2-substituted derivatives of **3a–c** through condensations at the lateral carbanion position. To date, the only active-hydrogen reactions which have been effected at the 2-methyl group of compounds such as **3a–c** involve condensations with aryl aldehydes[4] to form 2-styryl derivatives, reaction with chloral[4d,e,5] to afford 2-(2-hydroxy-3,3,3-trichloropropyl) derivatives, and acylation of **3b** with ethyl oxalate[6] to yield the 2-ethoxalylmethyl derivative. A recent method for functionalization of the 2-methyl group of **3a**[7] and related 2-methyl-3-aryl-4(3*H*)-quinazolinones[4e] involves initial side-chain bromination to form 2-bromomethyl derivatives, followed by nucleophilic displacement of bromide ion. This procedure, in which the 2-(bromomethyl)-quinazolinone serves as the electrophilic component of the reaction, suffers somewhat from the lack of a single, satisfactory method for the preparation of the required 2-bromomethyl derivatives,[7,8] requires isolation and purification of these intermediates, and has not been tested with carbon nucleophiles. Thus, it seemed that substitution at the 2-methyl group of compounds such as **3a–c** might be simplified by a predictable, in situ generation of nucleophilic reagents such as **4a–c** followed by condensations with appropriate electrophiles. The present study provides insight into the scope and limitations of such reactions.

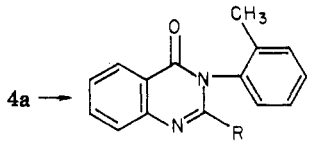
Results and Discussion

Treatment of **3a** with 1 equiv of *n*-butyllithium in THF–hexane at 0 °C, followed by quenching the reaction mixture with water, resulted in recovery of **3a** in only 42% yield. Three other unidentified products were detected in the crude reaction mixture, indicating that attack at the carbonyl group of **3a** by *n*-butyllithium seriously competes with side-chain metalation, perhaps in a fashion analogous to reactions of Grignard reagents with **3c**.[9,10] This problem was circumvented by using lithium diisopropylamide (LDA) as the metalating agent. Treatment of **3a** with LDA in THF–hexane at 0 °C for 1 h, followed by quenching the red-black anion solution with D_2O, afforded a 92% recovery of **3a** containing 0.98 deuterium atoms at the 2-methyl position. The distinct color of lithio salt **4a** allowed qualitative rates of its consumption to be monitored visually.

Scheme I



Alkylations of 4a were effected smoothly with methyl iodide and allyl bromide to afford **5a** and **5b** in yields of



5a, R = CH_2CH_3
b, R = $CH_2CH_2CH{=}CH_2$
c, R = $CH_2CH_2CH_3$
d, R = $CH(CH_2CH_3)_2$
e, R = $CH_2C_6H_5$
f, R = $CH(C_6H_5)_2$

53 and 60%, respectively. Alkylation of **4a** with ethyl iodide proceeded much more slowly than methylation or allylation and resulted in isolation of monoethyl derivative **5c**, diethyl derivative **5d**, and starting material **3a** in yields of 25, 5, and 42%, respectively. Diethylation apparently results from proton–metal exchange[2] between **4a** and monoethyl derivative **5c** to form the side-chain lithio salt of the latter, which then undergoes ethylation to form **5d**. With the more reactive halides the rate of initial alkylation of **4a** appears to be significantly faster than proton–metal exchange and subsequent alkylation of the secondary lithio salts of **5a,b**. Attempts to increase the proportion of monoethylation by raising the temperature to 30 °C, by using hexamethylphosphoramide (HMPA) as the solvent, by employing the potassium salt of **3a** in liquid ammonia, or by adding **4a** to a tenfold excess of ethyl iodide in THF all failed to provide significant increases in the yield of **5c**. Similar problems of dialkylation were encountered in reactions of **4a** with benzyl chloride and of **4b** with ethyl bromide. Previous[2] alkylations of dianion **1** with ethyl bromide and benzyl chloride did not produce isolable amounts of dialkylated products. Presumably the higher reactivity of **1**, as compared to **4a** and **4b**, allows initial alkylation to compete favorably with proton–metal exchange and realkylation.

Phenylation of 3a to give 2-benzyl derivative **5e** was effected in 34% yield through initial formation of the lateral potassium salt by means of potassium amide in liquid ammonia, followed by photostimulated[11] reaction with iodobenzene. A small amount of diphenylated product **5f** was also produced. The phenylation process exhibited mechanistic features characteristic of an $S_{RN}1$[11,12]

(3) (a) Gujral, M. L.; Saxona, P. N.; Tiwari, R. S. *Indian J. Med. Res.* **1955**, *43*, 637. (b) Brown, S. S.; Goenecha, S. *Clin. Pharmacol. Ther.* **1973**, *14*, 314.

(4) (a) Bogert, M. T.; Beal, G. D. *J. Am. Chem. Soc.* **1912**, *34*, 516. (b) Heilbron, I. M.; Kitchen, F. N.; Parkes, E. B.; Sutton, G. D. *J. Chem. Soc.* **1925**, 2167. (c) Bogert, M. T.; Clark, H. *J. Am. Chem. Soc.* **1924**, *46*, 1294. (d) Boltze, K. H.; Dell, H. D.; Lehwald, H.; Lorenz, D.; Rubert-Schwerer, M. *Arzneim.-Forsch.* **1963**, *13*, 688. (e) Singh, B. D.; Chadhury, D. N. *J. Indian Chem. Soc.* **1968**, *45*, 311.

(5) Kulkarni, P. Y. *J. Indian Chem. Soc.* **1942**, *19*, 18.

(6) Cook, A. H.; Naylor, R. F. *J. Chem. Soc.* **1943**, 397.

(7) For a discussion of this synthetic approach, see: Ager, I. R.; Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. *J. Med. Chem.* **1977**, *20*, 379 and references cited therein.

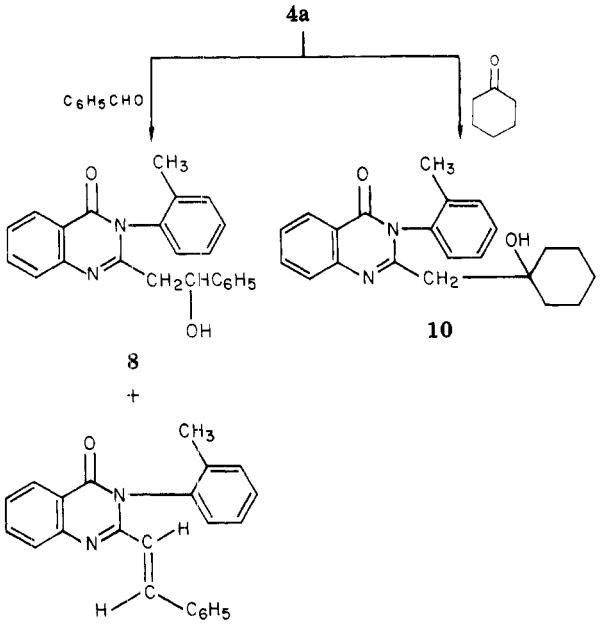
(8) Alla, J. A. *J. Pharm. Sci.* **1974**, *63*, 1627.

(9) Zoheer, S. H.; Kacker, I. K. *Curr. Sci.* **1955**, *24*, 12.

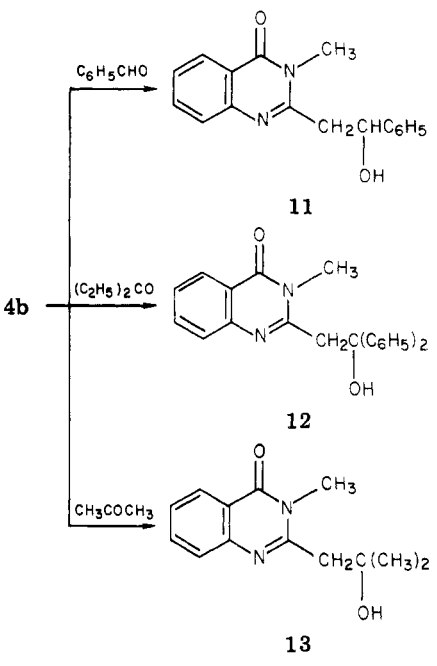
(10) *n*-Butyllithium is satisfactory for formation of dilithio derivative **1** because initial ionization of the amide proton renders the carbonyl group less susceptible to nucleophilic attack by the second equivalent of lithium reagent.

(11) Hoz, S.; Bunnett, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 4690.

Scheme II



Scheme III



reaction in that it proceeded very slowly in the absence of near-ultraviolet irradiation and was inhibited by *p*-dinitrobenzene and di-*tert*-butyl nitroxide.

Sulfenylation of 4a with diphenyl disulfide (1.14 equiv) at 0 °C afforded disulfenylated product **6** (44%), monosulfenylated derivative **7** (8%) and **3a** (48%) (Scheme I). When the reaction was repeated at 0 °C in the presence of an extra 1.1 equiv of LDA,[16] the yield of **7** rose to 53%, while **6** and **3a** were produced in yields of 17 and 29%, respectively. Clean monosulfenylation of **4a** to form **7** (85% by ^{1}H NMR, 65% isolated) was accomplished by addition of 1.5 equiv of diphenyl disulfide to **4a** and 1.4 equiv of LDA at −78 °C.

Attempted disulfenylations of **4a** using excess diphenyl disulfide (2.0–3.4 equiv) and LDA (3.0–4.4 equiv) at −78, −40, and 0 °C were all unsatisfactory. At −78 and −40 °C monosulfenylated derivative **7** was the major product, at 0 °C a mixture of **6**, **7**, and what appeared to be ring-opened products was obtained. Disulfenylated product **6** was, however, obtained in 48% isolated yield by inverse addition of the lateral anion of **7**, prepared from **7** and 1 equiv of LDA, to 1.3 equiv of phenyl benzenethiosulfonate[14] at 0 °C.

Aldol Condensations. Reaction of **4a** with benzaldehyde proceeded rapidly to form crude alcohol **8** (51%) along with traces of styryl derivative **9** (Scheme II). Attempts to purify **8** by recrystallization or column chromatography were hampered by dehydration to form **9** and retro-aldol condensation to regenerate **3a**. Treatment of **8** with dilute lithium hydroxide in THF–water afforded **9** in 84% yield. The tendency for **8** to undergo facile dehydration or retro-aldol condensation appears to arise from severe steric repulsions between the 3-*o*-tolyl group and the bulky 2-(2-hydroxy-2-phenylethyl) substituent. These interactions were evidenced by the ^{1}H NMR spectrum of **8**, which demonstrated that restricted rotation of the *o*-tolyl group about the C–N bond gives rise to atropisomerism[15,16] similar to that recently observed for a series of 2-benzyl-3-aryl-4(3*H*)-quinazolines.[17] This, in conjunction with the presence of a chiral center in the side chain of the quinazolinone nucleus, results in the existence of diastereomeric rotational isomers of **8**. The rate of rotation of the *o*-tolyl group is slow enough on the NMR time scale at 31 °C to cause the appearance of two *o*-tolyl methyl signals at δ 1.87 and 2.11 in Me_2SO-d_6.[18] Attempts to cause coalescence of these signals by raising the temperature in increments to 140 °C were unsuccessful because of extensive retro-aldol condensation and dehydration.

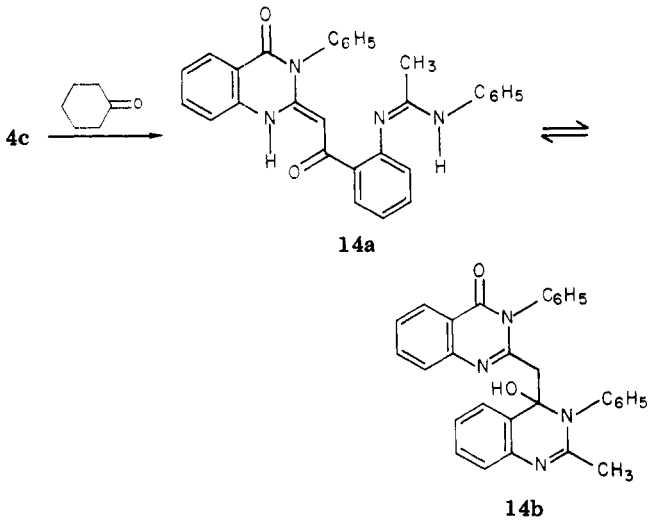
Lithio salt **4a** failed to undergo condensation with benzophenone. Persistence of the intense color of **4a** throughout reaction periods up to 24 h was indicative of steric hindrance to formation of the new carbon–carbon bond rather than a rapid retro-aldol condensation upon quenching of the reaction mixture.

Reaction of **4a** with enolizable ketones resulted in appreciable α-proton abstraction. For example, reaction of **4a** with cyclohexanone afforded 22% of tertiary alcohol **10**. The remainder of the ketone was converted to its lithium enolate as shown by quenching the reaction mixture with trimethylchlorosilane to produce cyclohexanone trimethylsilyl enol ether. Attempted condensation of **4a** with acetone and butanone also resulted mainly in enolization of the ketones. The behavior of **4a** toward aliphatic ketones may result from the tendency of this sterically hindered salt to react preferentially as a base rather than as a nucleophile.[19] This is supported by earlier observations[2] that the less sterically demanding dianion **1**, which should be a stronger base than **4a** because of its higher negative charge density, adds smoothly to the carbonyl group of enolizable ketones.

Aldol product **11** was easily isolated in 73% yield from the reaction of lithio salt **4b** with benzaldehyde (Scheme III). This product did not exhibit the lability associated

(12) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463, 7464. Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. Wolfe, J. F.; Carver, D. R. *Org. Prep. Proced. Int.* **1978**, *10*, 225.
(13) Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587.
(14) Trost, B. M.; Masiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(15) Mislow, K. "Introduction to Stereochemistry"; W. A. Benjamin: New York, 1965; pp 78–81.
(16) Kessler, H. *Angew. Chem., Int. Ed. Eng.* **1970**, *9*, 219.
(17) Colebrook, L. D.; Giles, H. G. *Can. J. Chem.* **1975**, *53*, 3431.
(18) The methylene protons at position 2 are diastereotopic by virtue of the adjacent chiral center and thus cannot be used in this case as a probe for atropisomerism.[17]
(19) Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904.

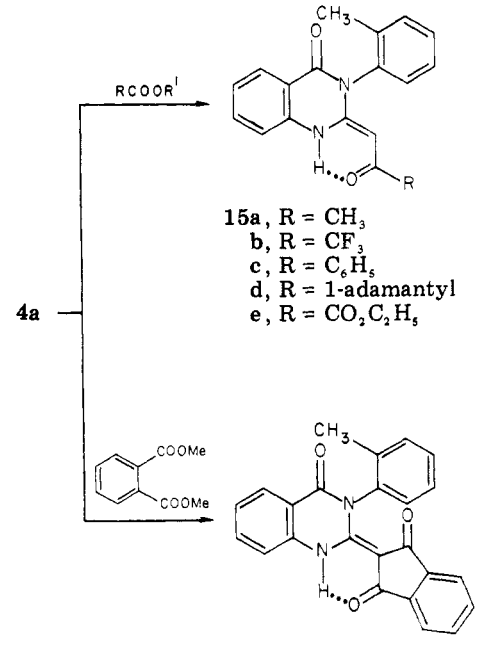
Scheme IV



14a

14b

Scheme V



15a, R = CH_3
b, R = CF_3
c, R = C_6H_5
d, R = 1-adamantyl
e, R = $CO_2C_2H_5$

16

with the more crowded adduct derived from **4a** and benzaldehyde. Moreover, **4b** reacted with benzophenone and acetone to give carbinols **12** and **13** in yields of 69 and 41%, respectively. The less demanding steric requirements of **4b** as compared to **4a** appear to be responsible for the success of these condensations.

Reaction of lithio salt **4c** with cyclohexanone led to an unexpected result in that dimer **14a** was isolated in 36% yield (Scheme IV). The ^1H NMR spectrum of this product in $CDCl_3$ indicated the occurrence of ring–chain tautomerism[20] in which chain tautomer **14a** was preferred by a factor of ca. 9:1, while in Me_2SO-d_6, **14a** was apparently the only tautomer present. It seems likely that **14a,b** are produced by α-proton abstraction from cyclohexanone to generate neutral **3c** in the presence of anion **4c**. The latter then adds to the lactam carbonyl of **3c**. This mechanism is supported by the observation that addition of **3c** to a THF solution of **4c** resulted in formation of **14a,b** in 47% yield. The absence of isolable quantities of a self-condensation product corresponding to **14a,b** in the reaction of **4a** with cyclohexanone may be due to the fact that the carbonyl group of neutral **3a** is sufficiently hindered by the 3-*o*-tolyl group to prevent attack by **4a** at a rate competitive with the sum of its rates of neutralization and addition to cyclohexanone.

Acylations. Reaction of **4a** with ethyl acetate afforded a low (8%) yield of ketone **15a**, even when anion **4a** was added to the ester (Scheme V). This undoubtedly results from the inherently unfavorable stoichiometry of Claisen condensations of this type[21] and from α-ionization of the ester of **4a**. Recently,[22] we reported that lateral acylation of various methylated heteroaromatic azines and diazines could be accomplished with nonenolizable esters by using sodium hydride as the condensing agent. However, it was observed that attempted acylation of quinaldine with ethyl acetate failed because of competing self-condensation of the ester to form ethyl acetoacetate. Even though the 2-methyl protons of **3a** should be more acidic than the lateral protons of quinaldine, it was still somewhat surprising to discover that **3a** underwent sodium hydride promoted acylation with ethyl acetate to form **15a** in 61% yield. Similarly, **3a** was acylated with ethyl trifluoroacetate, methyl benzoate, ethyl 1-adamantylcarboxylate, and ethyl oxalate to form **15a–e**[23] and with dimethyl phthalate to afford **16**. The general procedure for preparing **15a–e** involved addition of **3a** and the appropriate ester (10% molar excess) to a slurry of excess sodium hydride in refluxing 1,2-dimethoxyethane (DME). The reaction was terminated after evolution of 2 molar equiv of hydrogen (based on **3a**). Reaction periods of 1–5 h produced the acylated derivatives **15a–e** in yields of 80–90%. The yields of 2-ethoxalylmethyl derivative **15e** and 1,3-indandione **16** were highest when **3a** was added slowly to a mixture of excess sodium hydride and the acylating ester; in this way, intermolecular condensation was minimized.

As had been observed[22] with other methylated azines, **3a** was not significantly metalated by excess sodium hydride in DME after 20 h at reflux. However, when **3a** was allowed to react with excess sodium hydride in the presence of ethyl acetate, hydrogen evolution was complete in 3.5 h. It should be noted that formation of ethyl acetoacetate from ethyl acetate by means of sodium hydride in refluxing DME was found to be essentially complete after 1.5 h in the absence of **3a**.

Although the present results are consistent with our earlier proposal[22] concerning the mechanism of sodium hydride promoted acylation of methylated heteroaromatics, we have found that metalation of **3a** by sodium hydride is markedly accelerated by molar quantities of 15-crown-5. These results indicate that the slow reaction of compounds such as **3a** with sodium hydride may result, at least in part, from coating of the hydride surface by small amounts of the insoluble sodium salt of the lateral anion of the methylated heterocycle.[24] The crown ether

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(22) Wolfe, J. F.; Portlock, D. E.; Feuerbach, D. J. *J. Org. Chem.* **1974**, *39*, 2006.

(23) Compounds **15a–e** and **16** are totally enolic in solution as shown by ^1H NMR. The tautomers represented above are assigned as the preferred structures on the basis of studies of related heterocyclic systems containing exocyclic β-carbonyl substituents. See: Mondelli, K.; Merlini, L. *Tetrahedron* **1966**, *22*, 3253. Bass, R. G.; Crichton, D. D.; Meetz, H. K.; Johnson, A. F., Jr. *Tetrahedron Lett.* **1975**, 2073.
(24) Calculations based on the assumptions that the sodium hydride dispersion is composed of spheres with an average diameter of 2.5×10^{-3} cm and a density of 1.396 gm/cm^3 and that the longest interatomic distance in **3a** is 1.12×10^{-7} cm reveal that only 0.0035% of **3a** need be converted to the insoluble sodium salt in order to completely cover the surface of the sodium hydride used in a typical reaction.

may serve to solubilize the monoanion by complexation with sodium ion, thereby cleansing the hydride surface and allowing continuous ionization to occur. We are currently investigating this premise in more detail.

Experimental Section

Melting points were taken on either a Thomas-Hoover or a Mel-Temp apparatus in open capillaries and are uncorrected. Boiling points were also uncorrected. Elemental analyses were performed in this laboratory under the direction of Thomas E. Glass, using a Perkin-Elmer 240 C, H, and N analyzer. IR measurements were made with potassium bromide pellets or dilute solutions in CCl_4 on a Beckman IR-20 AX spectrometer. ^1H NMR spectra were recorded on a JEOL JMN-PS-100 instrument. Chemical shifts are reported in δ units (parts per million downfield from tetramethylsilane as internal standard). The splitting patterns are reported as follows: m = multiplet, q = quartet, t = triplet, d = doublet, and s = singlet. ^{19}F NMR spectra were recorded on the same instrument with the proper probe at 94 MHz. Chemical shifts for fluorine are reported in parts per million downfield from hexafluorobenzene (HFB). Mass spectra were taken with a Varian MAT 112 double-focusing-version mass spectrometer with a pressure of less than 10^{-6} mm maintained in the analyzer tube.

Analytical thin-layer chromatography (TLC) was carried out by using Eastman Chromagram sheets, type 6060 (silica gel), or EM Merck sheets (silica gel) both of which contained fluorescent indicator. Developing solvents are designated below, and spots were detected with ultraviolet light or iodine. Silica gel was employed in all column chromatography by using a ratio of 1 g of sample to 50 g of adsorbent. Vapor-phase chromatography (VPC) was conducted by using a Varian Aerograph Model 90-P instrument. Tetrahydrofuran (THF) was distilled immediately before use from lithium aluminum hydride. Diisopropylamine was distilled from barium oxide and stored over 3A molecular seives in a desiccator charged with Drierite. 1,2-Dimethoxyethane (DME) was refluxed first over sodium metal and then over oil-free sodium hydride, from which it was distilled immediately prior to use. Unless otherwise specified, all other chemicals were commercial reagent grade and were used without further purification. Sodium hydride, as a 50 or 57% mineral oil dispersion, and *n*-butyllithium as 1.6, 1.9, and 2.4 M solutions in hexane were obtained from Ventron Corp., Inc. A 1.6 M solution of *n*-butyllithium in hexane was also obtained from Aldrich Chemical Co. Photostimulated reactions were conducted in a Rayonet RPR-208 photochemical reactor equipped with four 24-W 350-nm lamps.

Preparation of Starting Materials. The procedure of Grimmel, Guenther, and Morgan[25] was used to prepare **3a**, mp 114–115 °C (lit.[26] 115–116 °C), and **3c**, mp 143–144 °C (lit.[26] mp 145–147 °C). 2,3-Dimethyl-4(3*H*)-quinazolinone (**3b**) was prepared by alkylating 2-methyl-4(3*H*)-quinazolinone (6.36 g, 40 mmol) with 5.6 g (45 mmol) of dimethyl sulfate in 140 mL of THF–water containing 3.2 g (56 mmol) of potassium hydroxide. The reaction mixture was maintained at 50–60 °C for 18 h. The resulting brown solution was cooled to room temperature, poured into 100 mL of water, and extracted three times with 100-mL portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and concentrated to give a yellow oil, which solidified on standing. The crude product was recrystallized twice from isopropyl alcohol–hexane to give 4.4 g (63%) of **3b** as light yellow needles: mp 108–110 °C (lit.[27] mp 108–109 °C); ^1H NMR ($CDCl_3$) δ 8.18 (d, J = 8 Hz, 1 H, 5-H), 7.76–7.18 (m, 3 H, aromatic), 3.69 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3); IR (KBr) 1660 cm^{-1} (C=O).

Metalation of 3a–c by Means of LDA To Form Lithio Salts 4a–c. To 0.7 g (5 mmol) of diisopropylamine in 40 mL of dry THF was added 3.1 mL (5 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After 15 min, LDA formation was assumed to be complete, and a solution of 5 mmol of **3a–c** in 10 mL of dry THF was added dropwise to the LDA solution. The dark red anion color appeared immediately, and the reaction mixture was allowed to stir for 20 min before addition of the appropriate electrophile.

To 5 mmol of **4a**, prepared as described above, was added 3 drops of deuterium oxide via syringe, and the reaction mixture was stirred until the color of **4a** disappeared (10 s). The reaction solution was immediately concentrated and the concentrate dried in a vacuum oven at 50 °C for 12 h. The ^1H NMR spectrum ($CDCl_3$) of the resulting solid revealed that 98% of one deuteron was incorporated at the 2-methyl position. TLC analysis (benzene–ether, 3:1) showed only **3a**.

Alkylations of Lithio Salt 4a. A. With Methyl Iodide. To a solution of 5 mmol of **4a** in 75 mL of THF–hexane was added 0.71 g (5 mmol) of methyl iodide via syringe. The anion color was discharged within 2 min. After 30 min, the reaction mixture was poured into 50 mL of cold water containing 10 mL of 1 N HCl. The resulting two-phase mixture was extracted twice with 100-mL portions of ether. The ethereal layers were combined, dried ($MgSO_4$), and concentrated. The resulting light yellow solid was recrystallized from isopropyl alcohol–hexane to afford 0.69 g (53%) of **5a**: mp 93–94 °C (lit.[4d] mp 91–92 °C); ^1H NMR ($CDCl_3$) δ 8.33 (d, J = 8 Hz, 1 H, H_5), 7.89–7.09 (m, 7 H, aromatic), 2.39 (q, J = 7 Hz, 2 H, CH_2), 2.14 (s, 3 H, CH_3), 1.23 (t, J = 7 Hz, 3 H, CH_3); IR (KBr) 1670 cm^{-1} (C=O).

B. With Allyl Bromide. To a solution of 5 mmol of **4a** in 75 mL of THF–hexane was added 0.72 g (6 mmol) of allyl bromide via syringe. After 30 min, the solution was poured into 100 mL of cold water containing 10 mL of 1 N HCl. The resulting solution was extracted twice with 150-mL portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and concentrated. The light orange oil yielded a yellow solid on trituration with hexane. The crude product was recrystallized from isopropyl alcohol to afford 0.87 g (60%) of 2-(3-butenyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**5b**) as white rhombic crystals: mp 269–270 °C; ^1H NMR ($CDCl_3$) δ 8.28 (d, J = 8 Hz, 1 H, H_5), 7.78–7.08 (m, 7 H, aromatic), 6.00–5.54 (m, 1 H, vinyl), 5.03–4.85 (m, 2 H, vinyl), 2.62–2.16 (m, 4 H, CH_2CH_2), 2.07 (s, 3 H, CH_3); IR (KBr) 1675 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.83; H, 6.63; N, 9.56.

C. With Ethyl Iodide. To a solution of 5 mmol of **4a** in 60 mL of THF–hexane–diisopropylamine was added 0.78 g (5 mmol) of ethyl iodide via syringe. After 1 h the reaction mixture was processed as in B. TLC (benzene–ether, 98:2) analysis of the crude product revealed the presence of three spots. The component having the lowest R_f value was identified as unreacted **3a**. Column chromatography was then carried out. Elution with hexane–ether (95:5) afforded 0.08 g (5%) of 2-(3-pentyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**5d**) as white crystals: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 8.47 (d, J = 8 Hz, 1 H, H5), 7.95–7.27 (m, 7 H, aromatic), 2.59–2.13 (m, 1 H, CH), 2.27 (s, 3 H, CH_3), 2.13–1.55 (m, 4 H, CH_2), 1.11–0.89 (dt, 6 H, CH_3). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.44; H, 6.60; N, 10.06.

Elution with hexane–ether (75:25) yielded 0.53 g (42%) of recovered **3a**, mp 110–113 °C. Separation of **5c** and **5d** was hampered by considerable overlap of these two compounds during development of the column.

The above reaction was repeated by adding 0.91 g (5 mmol) of HMPA to the THF–hexane solution of anion **4a**. TLC analysis (benzene–ether, 98:2) revealed the presence of three spots with R_f values corresponding to **3a**, **5c**, and **5d**. Similar results were obtained when the reaction was conducted in HMPA alone, in liquid ammonia with potassium amide as the ionizing base, or by dropwise addition of a THF solution of **4a** to a tenfold excess of ethyl iodide in dry THF at 0 °C.

Photostimulated Phenylation of the Potassium Salt of 3a. The reaction was performed in a cylindrical Pyrex vessel, having an inside diameter of 4.2 cm and a height of 43 cm. This flask was equipped with a magnetic stirrer and a three-necked adapter to which a solid carbon dioxide–isopropyl alcohol condenser fitted with a nitrogen inlet was attached. To a stirred suspension of 10 mmol of potassium amide, prepared from 0.40 g (10 mmol) of potassium in 300 mL of anhydrous liquid ammonia and a catalytic amount of ferric nitrate, was added 2.50 g (10 mmol) of **3a** as a solid through a long-stemmed funnel. The deep red anion color appeared immediately. After 1 h, 3.06 g (15 mmol) of iodobenzene in 30 mL of dry ether was added, and the reaction

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flask was lowered into the photoreactor and irradiated for 1 h. The red solution was quenched by carefully adding 1 g of solid ammonium chloride. The condenser was removed and the ammonia evaporated while 150 mL of ether was added. Water (150 mL) was added to the resulting suspension. The organic phase was separated and the aqueous phase extracted twice with 100-mL portions of chloroform. The organic phases were combined, dried ($MgSO_4$), and concentrated to afford a yellow oil. TLC analysis (chloroform) of the crude product showed the presence of four components. By comparison of R_f values, the broad leading spot and slowest moving spot were identified as iodobenzene and **3a**, respectively. The crude product was chromatographed. After the residual iodobenzene had been eluted with hexane, elution with hexane–ether (9:1) afforded ca. 15 mg of 2-(diphenylmethyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**5f**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.28 (d, J = 8, 1 H, H_5), 7.73–6.83 (m, 17 H, aromatic), 5.08 (s, 1 H, CH), 2.93 (s, 3 H, CH_3). Elution with hexane–ether (80:20) yielded 0.55 g (34%) of 2-benzyl-3-*o*-tolyl-4(3*H*)-quinazolinone (**5e**) as white plates: mp 113–114 °C (lit.[17] mp 113 °C); ^1H NMR ($CDCl_3$) δ 8.27 (d, J = 8 Hz, 1 H, H_5), 7.80–6.77 (m, 12 H, aromatic), 3.84 (s, 2 H, CH_2), 1.67 (s, 3 H, CH_3); IR (KBr) 1660 cm^{-1} (C=O). Continued elution with hexane–ether (80:20) afforded 0.51 g (41%) of recovered **3a**.

The above reaction procedure was repeated except that the reaction vessel was enclosed in aluminum foil prior to addition of iodobenzene, and the reaction was allowed to proceed without external illumination. After 1 h, an aliquot was removed by means of a dip tube and quenched with solid ammonium chloride. To the resulting mixture was added 5 mL of water. The resulting solution was extracted with 5 mL of chloroform. TLC analysis (chloroform) of the organic phase revealed that no **5e** was present. After 4 h an aliquot treated as described above revealed only unreacted **3a** and iodobenzene. The aluminum foil was then removed, and the reaction solution was irradiated. After 5 min of irradiation, TLC analysis of an aliquot revealed that formation of **5e** was complete.

To 10 mmol of the potassium salt of **3a** prepared as before in 300 mL of anhydrous ammonia was added 0.084 g (0.5 mmol) of solid *p*-dinitrobenzene, which caused the dark red solution to become dark green. Iodobenzene (3.06 g, 15 mmol) in 30 mL of dry ether was added, and the resulting solution was irradiated for 1 h. TLC analysis (chloroform) of an aliquot after 5 min revealed no detectable amounts of **5e** or **5f**, while after 15 min both products had begun to form. When the above experiment was repeated with 0.072 g (0.5 mmol) of di-*tert*-butyl nitroxide as an inhibitor, similar results were obtained.

Preparation of 2-[Bis(phenylthio)methyl]-3-*o*-tolyl-4-(3*H*)-quinazolinone (6). To a solution of 5 mmol of **4a** in 40 mL of THF at 0 °C under nitrogen was added a solution of 1.24 g (5.7 mmol) of diphenyl disulfide in 15 mL of THF. After 1.5 h at 0 °C the reaction mixture was poured into 100 mL of 10% Na_2CO_3, and the resulting mixture was extracted with two 100-mL portions of ether. The ethereal extracts were washed with water and 0.1 N HCl (100 mL), dried ($MgSO_4$), and concentrated. The percentages of disulfenylated product **6**, monosulfenylated derivative **7**, and starting material (**3a**) were determined to be 44, 8, and 48%, respectively, by integration of the ^1H NMR signals from the lateral methine proton of **6** and the lateral methylene protons of **7** vs. the signal for the C-5 proton of the quinazolinone ring, which had the same chemical shift in the case of all three derivatives. Column chromatography of the crude reaction mixture afforded, on elution with ether–hexane (3:20), 0.57 g (25%) of 2-[bis(phenylthio)methyl]-3-*o*-tolyl-4(3*H*)-quinazolinone (**6**) as a white solid, mp 139–142 °C. After recrystallization from ether–hexane the sample had the following: mp 142–143 °C; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 7, 1 H, H_5), 7.80–6.74 (m, 17 H, aromatic), 4.90 (s, 1 H, CH), 2.04 (s, 3 H, CH_3); mass spectrum, m/e 467 (m^+); IR (KBr) 1670 cm^{-1} (C=O). Anal. Calcd for $C_{28}H_{22}N_2OS_2$: C, 72.07; H, 4.75; N, 6.00. Found: C, 72.35; H, 5.08; N, 6.28. Further elution with the same solvent mixture afforded 0.11 g of a mixture of **6** and **7**. Final elution with ether–hexane (1:3) gave 0.38 g (30%) of **3a**, mp 112–114 °C.

Alternatively, **6** was prepared by inverse addition of the anion of **7** to the sulfenylating agent. Thus, 0.4 g (1.1 mmol) of **7** in 2 mL of THF was added via syringe to 1.1 mmol of LDA in 30 mL of THF at 0 °C under nitrogen. After 5 min, the solution was slowly transferred by nitrogen pressure through a thin metal tube into a solution of 0.36 g (1.43 mmol) of phenyl benzenethiosulfonate. Addition of the anion of **7** took 45 min, after which 20 mL of water and 50 mL of ether were added. The aqueous layer was washed with two 50-mL portions of ether, which were then combined with the original organic extract, dried ($MgSO_4$), and concentrated. The percentages of **6** and **7** as determined from the ^1H NMR spectrum were 90 and 10%, respectively. Chromatography with ether–hexanes (1:5) initially afforded excess phenyl benzenethiosulfonate. Further elution with ether–hexanes (2:5) gave 0.45 g (85%) of **6** as a yellow oil. Crystallization from ether–hexanes gave 0.25 g (48%) of **6**, mp 141–142 °C.

Preparation of 2-[(Phenylthio)methyl]-3-*o*-tolyl-4(3*H*)-quinazolinone (7). Diphenyl disulfide (1.09 g, 5 mmol) was added to a solution of 5 mmol of **4a** and 5 mmol of extra LDA in 40 mL of THF at 0 °C. After 1.5 h the reaction mixture was processed as described above for the initial preparation of **6**. The ^1H NMR spectrum indicated that the percentages of **6**, **7**, and **3a** were 17, 53, and 29%, respectively. Chromatography of the crude reaction mixture with ether–hexane (1:33) afforded 0.06 g (5.5%) of recovered diphenyl disulfide. Continued elution with ether–hexane (3:17) afforded 0.06 g (2.6%) of **6**, mp 137–140 °C. Further elution with the same solvent mixture afforded 0.52 g (29%) of **7**: mp 102–104 °C; ^1H NMR ($CDCl_3$) δ 88.23 (d, J = 8 Hz, 1 H, H_5), 7.82–7.00 (m, 12 H, aromatic), 3.91 (d, J = 14 Hz, 1 H, CHS), 3.76 (d, J = 14 Hz, 1 H, CHS), 2.16 (s, 1 H, CH_3). Anal. Calcd for $C_{22}H_{18}N_2OS$: C, 73.72; H, 5.06; N, 7.81. Found: C, 73.58; H, 5.05; N, 7.78. This compound was identical with an authentic sample of **7** prepared from the reaction of 2-(bromomethyl)-3-*o*-tolyl-4-(3*H*)-quinazolinone with sodium thiophenoxide in refluxing ethanol.

In another experiment, 0.5 g (2 mmol) of **3a** was added to a solution of 4.8 mmol of LDA in 50 mL of THF at −78 °C under nitrogen. After 10 min, 0.65 g (3 mmol) of diphenyl disulfide was added rapidly from a pressure-equalizing addition funnel. The reaction was quenched after 2 min with 10 mL of 95% ethanol. After warming to room temperature, the reaction mixture was poured into a mixture of 20 mL of ether and 30 mL of water. The organic layer was washed with two 30-mL portions of 1.0 N NaOH, which were then extracted with two 50-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The ^1H NMR spectrum indicated that the percentages of **6**, **7**, and **3a** were 9, 85, and 6%, respectively. Chromatography with hexanes afforded diphenyl disulfide. Continued elution with ether–hexanes (1:5) afforded 0.05 g (5%) of **6**. Continued elution with the same solvent afforded 0.47 g (65%) of **7** as a white solid. Further elution afforded 0.02 g of a mixture of **7** and **3a**.

Aldol Condensations of 4a. A. With Benzaldehyde. To a solution of 5 mmol of **4a** was added 0.53 g (5 mmol) of freshly distilled benzaldehyde via syringe. After 3 min, the resulting clear yellow solution was poured into 100 mL of cold water containing 10 mL of 1 N HCl. The aqueous THF solution was extracted three times with 100-mL portions of ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated at room temperature. TLC analysis (hexane–ether–acetone, 70:25:5) of the yellow oil revealed a three-component mixture. The major component, **8**, was located between the two minor components corresponding to **9** (greatest R_f) and **3a** (smallest R_f). Trituration of the oil with hexane afforded 0.91 g (51%) of crude **8** as a yellow amorphous solid, mp 119–128 °C. Attempted purification of **8** by recrystallization was unsuccessful. TLC analysis revealed that attempted recrystallization caused decomposition of **8** to **9** and **3a**.

The reaction was repeated, and the crude product was chromatographed. Elution with hexane–ether (95:5) afforded 0.25 g of 2-styryl-3-*o*-tolyl-4(3*H*)-quinazolinone (**9**): mp 160–161 °C (lit.[4d] mp 162–163 °C); ^1H NMR ($CDCl_3$) δ 8.44 (d, J = 8 Hz, 1 H, H_5), 8.12 (d, J = 16 Hz, 1 H, vinyl), 2.16 (s, 3 H, CH_3). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.29. Found: C, 81.32; H, 5.18; N, 8.24. Elution with hexane–ether (90:10) gave 0.030 g of 2-(2-hydroxy-2-phenylethyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**8**) as a white solid: mp 136–141 °C; ^1H NMR ($CDCl_3$) δ 8.43 (d, J = 8 Hz, 1 H, H_5), 8.00–7.00 (m, 12 H, aromatic), 5.82 and 5.68 (s, 1 H, OH), 5.36 and 5.26 (m, 1 H, CH), 2.96–2.32 (m, 2 H, CH_2), 2.74 and 2.06 (s, 3 H, CH_3); ^1H NMR (Me_2SO-d_6) δ 8.18–7.05 (m, 12 H, aromatic), 5.50 and 5.54 (s, 1 H, OH), 5.40–5.03 (m, 1 H, CH), 2.77–2.59 (m, 2 H, CH_2), 2.09 and 1.85 (s, 3 H, CH_3); IR (KBr)

1670 cm^{-1} (C=O). An analytical sample of **8** was obtained from a fraction with a melting point of 137–138 °C. Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.61; N, 7.86. Found: C, 77.31; H, 5.54; N, 7.90. Continued elution with hexane–ether (80:20) afforded 0.1 g (8%) of recovered **3a**.

In a third experiment the reaction mixture was quenched with 10 mL of water and allowed to stir for 2 h before being processed as described above to afford 1.4 g (84%) of **9**.

High-pressure LC analysis of **8** employing a Zorbax-SIL column, chloroform–methanol–cyclohexane (19.5:0.5:80) as the eluting solvent, and a flow rate of 0.5 mL/min at 1800 psi failed to effect separation of the possible diastereomers of **8**.

B. With Cyclohexanone. To a stirred solution of 5 mmol of **4a** was added 0.49 g (5 mmol) of cyclohexanone via syringe. After 2 h the reaction mixture was processed as in the reaction with benzaldehyde. Column chromatography and elution with hexane–ether (85:15) yielded 0.38 g (22%) of 2-[(1-hydroxy-1-cyclohexyl)methyl]-3-o-tolyl-4(3H)-quinazolinone (**10**) as a viscous syrup: ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 8 Hz, 1 H, H_5), 8.04–7.17 (m, 7 H, aromatic), 6.48 (s, 1 H, OH), 2.43 (d, J = 16 Hz, 2 H, CH_2), 2.18 (s, 3 H, CH_3), 2.01–1.05 (br m, 10 H, cyclohexyl); mass spectrum, m/e 348 (m$^+$); IR (CCl_4) 3375 (OH), 1690 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.89; H, 7.25; N, 7.94. Elution with hexane–ether (60:40) afforded 0.7 g (56%) of recovered **3a**.

An experiment similar to that described above was repeated to the point of allowing cyclohexanone to react with **4a** for 1 h. A solution of 0.87 g (8 mmol) of trimethylchlorosilane and 0.81 g (8 mmol) of triethylamine in 30 mL of THF was the added rapidly via a pressure-equalizing addition funnel. After addition was complete the ice–bath was removed and the solution concentrated. Analysis of the residual oil by VPC (6-ft column, 6.3% Carbowax on Chromosorb Z, 60/80 mesh, at 120 °C) revealed the presence of the trimethylsilyl enol ether of cyclohexanone as determined by comparison of its retention time and ^{1}H NMR spectrum with an authentic sample;[28] no cyclohexanone could be detected.

In a blank experiment it was found that cyclohexanone trimethylsilyl enol ether was not produced from equimolar amounts of cyclohexanone, trimethylchlorosilane, triethylamine, and diisopropylamine in THF for 5 h at 25 °C.

Aldol Condensation of 4b. A. With Benzaldehyde. To a solution of 5 mmol of lithium salt **4b** in 60 mL of THF was added a solution of 0.53 g (5 mmol) of benzaldehyde in 5 mL of THF. The dark red anion solution immediately turned clear yellow, and the reaction was allowed to continue until all visible traces of anion **4b** had reacted. The clear yellow solution was processed as described in the aldol condensations of **4a** to give a light yellow solid upon concentration of the ethereal extract. The crude product was recrystallized from isopropyl alcohol–ether to yield 1.0 g (73%) of 2-(2-hydroxy-2-phenylethyl)-3-methyl-4(3H)-quinazolinone (**11**) as white crystals: mp 132–133 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8 Hz, 1 H, H_5), 7.80–7.12 (m, 8 H, aromatic), 5.50 (d, J = 2 Hz, 1 H, OH), 5.38 (overlapping triplets, J = 6 Hz, 1 H, CH), 3.50 (s, 3 H, CH_3), 3.05 (d, J = 6 Hz, 2 H, CH_2); IR (KBr) 3460 (OH), 1650 cm^{-1} (C=O). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.08; H, 5.46; N, 10.33.

B. With Benzophenone. To a solution of 5 mmol of **4b** was added 0.91 g (5 mmol) of solid benzophenone. After 3 min, the original dark red solution became light orange, and the reaction was continued for 0.5 h. The resulting light orange solution was processed in the usual manner to give a light yellow solid, which was recrystallized from isopropyl alcohol–acetone to yield 1.23 g (69%) of 2-(2-hydroxy-2,2-diphenylethyl)-3-methyl-4(3H)-quinazolinone (**12**), mp 159–161 °C. A second recrystallization produced an analytical sample as white crystals: mp 161–162 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 1 H, H_5), 7.70–7.04 (m, 14 H, 13 aromatics and one OH), 3.66 (s, 2 H, CH_2), 3.60 (s, 3 H, CH_3); IR (KBr) 3330 (OH), 1660 cm^{-1} (C=O). Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.36; H, 5.39; N, 7.53.

C. With Acetone. Reaction of 5 mmol of **4b** with 0.29 g (5 mmol) of acetone afforded a yellow oil which was chromatographed by using hexane–ether–chloroform (80:10:10) to afford 0.45 g (41%) of 2-(2-hydroxy-2,2-dimethylethyl)-3-methyl-4(3H)-quinazolinone (**13**): mp 123–124 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J = 8 Hz, 1 H, H_5), 7.84–7.40 (m, 3 H, aromatic), 6.15 (s, 1 H, OH), 3.62 (s, 3 H, CH_3), 2.92 (s, 2 H, CH_2), 1.42 (s, 6 H, CH_3); IR (KBr) 3480 (OH), 1640 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.92; H, 6.99; N, 11.91.

Attempted Condensation of Lithium Salt 4c with Cyclohexanone. To a solution of 10 mmol of **4c** in 70 mL of dry THF at 0 °C under nitrogen was added 0.98 g (10 mmol) of cyclohexanone. The anion color disappeared slowly, and after 1 h the clear orange-yellow reaction mixture was processed in the usual fashion to give a yellow oil. TLC analysis (chloroform) of the concentrate revealed two major components. The less mobile component had an R_f value identical with **3c**. Trituration with hexane–ether afforded 0.81 g (36%) of **14a,b** as a white solid, mp 176–180 °C. Recrystallization from isopropyl alcohol–chloroform raised the melting point to 193–194 °C; ^{1}H NMR ($CDCl_3$) δ 13.08 (s, 0.9 H, enol), 8.37 (s, 0.9 H, NH), 8.28–7.01 (m, 18 H, aromatic), 4.52 (s, 0.9 H, vinyl), 3.83 (s, <1 H, OH), 1.90 (s, 2.7 H, CH_3–chain), 1.74 (s, CH_2), 1.64 (s, 0.3 H, CH_3–ring); ^{1}H NMR (Me_2SO-d_6) δ 13.00 (s, 1 H, enol), 10.63 (s, 1 H, NH), 8.20–7.00 (m, 18 H, aromatic), 4.32 (s, 1 H, vinyl), 1.98 (s, 3 H, CH_3) (the signals at δ 13.00 and 10.63 exchanged with deuterium oxide); mass spectrum, m/e 472 (m$^+$); IR (KBr) 3380 (NH), 1670 cm^{-1} (C=O). Anal. Calcd for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.85. Found: C, 76.34; H, 5.08; N, 12.01.

Preparation of **14a,b** was also achieved by reacting 0.69 g (2.9 mmol) of **3c** with 1.5 mmol of LDA in THF for a period of 1.5 h. Processing of the reaction solution afforded three crops of solid. The second of these crops yielded 0.32 g (47%) of **14a,b**, mp 190–192 °C. The ^{1}H NMR and IR spectra were identical with **14a,b** obtained from the reaction of the lithium salt **3c** with cyclohexanone. The first and third crops of crystals (total 0.3 g) were subsequently identified as **3c** by ^{1}H NMR.

Condensation of 4a with Ethyl Acetate. To a magnetically stirred solution of 5 mmol of LDA in 25 mL of dry THF at 0 °C under nitrogen was added 1.25 g (5 mmol) of **3a**. After 30 min the resulting solution of lithium salt **4a** was transferred via syringe (50 mL) to an addition funnel which was attached to a three-necked 100-mL flask. The bottom half of the addition funnel was loosely enclosed in aluminum foil which formed a cup that held several small pieces of dry ice. The solution of **4a** was then added over a 65-min period to a solution of 4.40 g (50 mmol) of ethyl acetate in 60 mL of THF at 0 °C. After addition was complete, the clear yellow solution was poured into 100 mL of water containing 10 mL of 1 N HCl. The resulting solution was extracted twice with 200-mL portions of ether, which were combined, dried, and concentrated. TLC analysis (ether–acetone, 98:2) revealed two spots, with **3a** as the major component. Column chromatography afforded, on elution with hexane–ether (9:1), 0.14 g (8%) of 2-acetonyl-3-o-tolyl-4(3H)-quinazolinone (**15a**) as white crystals, mp 164–165.5 °C. The ^{1}H NMR spectrum was identical with that of a sample of **15a** prepared by the general sodium hydride acylation procedure described below.

Sodium Hydride Promoted Acylations of 3a. The apparatus used in these reactions consisted of a 250-mL three-necked flask equipped with a heating mantle, a magnetic stirring bar, a 60-mL pressure-equalizing addition funnel, and an efficient condenser. The condenser was connected at its upper end to a U-shaped drying tube charged with Drierite and moisture indicator. The drying tube was in turn connected to a Precision Scientific wet-test meter or a 1000-mL gas buret. Both measurement devices were filled with water. A 2.50-g (52 mmol) sample of 50% sodium hydride–mineral oil dispersion was washed with 30 mL of hexane and filtered, and the oil-free sodium hydride was quickly added to the reaction flask along with 150 mL of dry DME. The resulting gray slurry was brought to reflux, and a solution of 10 mmol of **3a** and 11–13 mmol of the appropriate ester in DME was added dropwise over a period of 15 min. When addition was completed, the stirred reaction mixture was allowed to reflux until the theoretical amount of hydrogen had evolved. The heating mantle was removed, and the flask was allowed to cool to room temperature. To the thick reaction mixture was added dropwise 3.12 g (52 mmol) of acetic acid (**Caution**!), followed by 50 mL of cold water. The resulting mixture was transferred to a 500-mL sep-

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aratory funnel, and an additional 100 mL of water was added. The resulting aqueous solution or suspension was made basic with 5% sodium bicarbonate solution. Chloroform (100 mL) was added to the basic solution. The organic phase was separated, and the remaining aqueous phase was extracted twice with 100-mL portions of chloroform. The organic extracts were combined, dried, ($MgSO_4$), filtered, and concentrated, and the crude products were recrystallized from appropriate solvents.

The apparatus and general procedure described above were used in obtaining the hydrogen-evolution data given in the Results and Discussion section. Hydrogen volumes were corrected to STP conditions.

A. With Ethyl Acetate. A reaction time of 3.5 h followed by recrystallization from isopropyl alcohol yielded 1.78 g (61%) of 2-acetonyl-3-*o*-tolyl-4(3*H*)-quinazolinone (**15a**) as light yellow crystals: mp 163–164 °C; ^1H NMR ($CDCl_3$) δ 14.98 (br s, 1 H, enol), 8.11 (d, J = 8 Hz, 1 H, H_5), 7.76–7.06 (m, 7 H, aromatic), 4.39 (s, 1 H, vinyl), 2.18 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3); IR (KBr) 1680 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.13; H, 5.60; N, 9.48.

B. With Ethyl Trifluoroacetate. A reaction period of 1.5 h was followed by recrystallization of the crude product from isopropyl alcohol–chloroform to afford 3.02 g (87%) of 2-(3,3,3-trifluoroacetonyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**15b**) as white crystals: mp 194–195 °C; ^1H NMR ($CDCl_3$) δ 14.987 (br s, 1 H, enol), 8.41 (d, J = 8 Hz, 1 H, H_5), 8.07–7.26 (m, 7 H, aromatic), 4.92 (s, 1 H, vinyl), 2.23 (s, 3 H, CH_3); ^{19}F NMR ($CDCl_3$) δ 94.3 (s); IR (KBr) 1690 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.50; H, 3.81; N, 7.98.

C. With Methyl Benzoate. Following a reaction period of 5 h, recrystallization of the crude product from isopropyl alcohol afforded 2.84 g (80%) of 2-phenacyl-3-*o*-tolyl-4(3*H*)-quinazolinone (**15c**) as light yellow flakes: mp 216–217 °C; ^1H NMR (Me_2SO-d_6) δ 15.50 (br s, 1 H, enol), 8.18 (d, J = 1 Hz, 1 H, H_5), 7.98–7.32 (m, 12 H, aromatic), 5.07 (s, 1 H, vinyl), 2.19 (s, 3 H, CH_3); IR (KBr) 1680 cm^{-1} (C=O). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.13; H, 5.12; N, 8.17. Found: C, 77.41; H, 5.04; N, 8.27.

D. With Ethyl 1-Adamantylcarboxylate. A reaction period of 3.5 h followed by recrystallization from isopropyl alcohol–chloroform–hexane afforded 3.3 g (81%) of 2-[2-oxo-2-(1-adamantyl)ethyl]-3-*o*-tolyl-4(3*H*)-quinazolinone (**15d**): mp 221–222 °C; ^1H NMR ($CDCl_3$) δ 15.82 (br s, 1 H, enol), 8.20 (d, J = 8 Hz, 1 H, H_5), 7.72–7.16 (m, 7 H, aromatic), 4.56 (s, 1 H, vinyl), 2.18 (s, 3 H, CH_3), 2.06–1.48 (m, 15 H, CH and CH_2); IR (KBr) 1680 cm^{-1} (C=O). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.23; H, 6.69; N, 6.64.

E. With Ethyl Oxalate. To a refluxing slurry of 1.05 g (25 mmol) of sodium hydride (57% dispersion) and 3.2 g (22 mmol) of diethyl oxalate in 140 mL of DME was added dropwise 1.25 g (5 mmol) of **3a** in 40 mL of DME over a period of 4.5 h. When addition was complete, the reaction was allowed to continue at reflux for an additional 45 min. The resulting yellow reaction mixture was processed as described above. The resulting concentrate was triturated with hexane–ether to afford a yellow solid that was recrystallized from isopropyl alcohol to give 1.08 g (62%) of 2-(ethoxalylmethyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**15e**): mp 191–191.5 °C; ^1H NMR ($CDCl_3$) δ 15.51 (br s, 1 H, enol), 8.35 (d, J = 8 Hz, 1 H, H_5), 8.00–7.24 (m, 7 H, aromatic), 5.47 (s, 1 H, vinyl), 4.30 (q, J = 7 Hz, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 1.35 (5, J = 7 Hz, 3 H, CH_3); IR (KBr) 1710, 1680 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.03; N, 7.88.

F. With Dimethyl Phthalate. This reaction was accomplished by dropwise addition of 1.25 g (5 mmol) of **3a** in 40 mL of DME to a refluxing slurry of 1.05 g (25 mmol) of sodium hydride (57% dispersion) and 3.88 g (20 mmol) of dimethyl phthalate in 140 mL of DME, over a period of 6 h. After addition was complete, the reaction was allowed to continue for an additional 1 h. The orange reaction mixture was processed as usual, and the crude product was chromatographed. Elution with ether–chloroform (98:2) gave 0.43 g (22%) of 2-(1,3-dioxo-2-indanyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**16**) as yellow crystals: mp 268–270 °C; ^1H NMR ($CDCl_3$) δ 14.66 (br s, 1 H, enol), 8.22 (d, J = 8 Hz, 1 H, H_5), 7.90–7.07 (m, 11 H, aromatic), 2.39 (s, 3 H, CH_3); IR (KBr) 1710, 1690 cm^{-1} (C=O). Anal. Calcd for $C_{24}H_{16}N_2O_3$: C, 75.78; H, 4.24; N, 7.36. Found: C, 75.71; H, 4.33; N, 7.00.

Registry No. 3a, 72-44-6; **3a** potassium salt, 73308-58-4; **3b**, 1769-25-1; **3c**, 2385-23-1; **4a**, 73308-59-5; **4b**, 73308-60-8; **4c**, 73308-61-9; **5a**, 1898-07-3; **5b**, 73308-62-0; **5c**, 30006-43-0; **5d**, 73323-95-2; **5e**, 19857-39-7; **5f**, 73308-63-1; **6**, 73283-05-3; **7**, 73308-64-2; **8**, 73283-06-4; **9**, 2004-80-0; **10**, 73308-65-3; **11**, 73308-66-4; **12**, 73308-67-5; **13**, 73308-68-6; **14a**, 73308-69-7; **14b**, 73308-70-0; **15a**, 73308-71-1; **15b**, 73308-72-2; **15c**, 73308-73-3; **15d**, 73308-74-4; **15e**, 73308-75-5; **16**, 73308-76-6; 2-methyl-4(3*H*)-quinazolinone, 1769-24-0; methyl iodide, 74-88-4; allyl bromide, 106-95-6; ethyl iodide, 75-03-6; diphenyl disulfide, 882-33-7; phenyl benzenethiosulfonate, 1212-08-4; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; benzophenone, 119-61-9; acetone, 67-64-1; ethyl acetate, 141-78-6; ethyl trifluoroacetate, 383-63-1; methyl benzoate, 93-58-3; ethyl oxalate, 95-92-1; dimethyl phthalate, 131-11-3.

Photocyclization of 1-(1-Chloroisoquinolin-6-yl)-1*H*-*v*-triazolo[4,5-*c*]pyridines to 10-Chloro-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinolines (Azaellipticines)[1]

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Whereas thermal cyclization of 1-(5,8-dimethyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-1*H*-*v*-triazolo[4,5-*c*]pyridine affords 6,11-dimethyl-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinolin-10(9*H*)-one which cannot be chlorinated to the corresponding chloro derivative, photocyclization of the 1-(5,8-dimethyl-1-chloroisoquinolin-6-yl)-1*H*-*v*-triazolo[4,5-*c*]pyridine allows for the synthesis of the expected 6,11-dimethyl-10-chloropyrido[3′,4′:4,5]pyrrolo-[2,3-*g*]isoquinoline. Subsequent conversions of this last compound yield 10-((dialkylamino)alkyl)amino-substituted derivatives, which are dimethylated analogues of a previously described potent antitumor azaellipticine derivative. potent antitumor azaellipticine derivative.

In a recent paper the synthesis of an aza analogue of ellipticine 1[2] which has antitumor activity on L1210 leukemia in mice[3] has been described. However, 10-(((γ-dialkyamino)propyl)amino)-6-methyl-5*H*-pyrido-

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