substituents at the ring carbon C_2 (C_3) and at C_1. This corresponds to the migration of the more electron-rich carbon–carbon bond.[5] (3) The ease of rearrangement (low-energy barrier) depends on a three-center bonding between the atoms C_1, C_2, and C_4 and involves two electrons (of the σ bond C_1–C_2). Hence it can be related to the rearrangement of the cyclopropylcarbinyl cation (unpublished results). The stereochemical integrity of the attacked carbon atom C_2 (or C_3) is conserved, and the neighboring carbon atom C_3 (or C_2, respectively) is not affected by the electrophilic attack.

Finally it must be noted that semiempirical SCF methods such as the MINDO procedure are parametrized to reproduce ground-state properties. Hence the criticism which can be applied to the NDO approximation holds.[20] On this basis one may question the numerical accuracy predicated in our study. Only in one case have rigorous good quality ab initio calculations been reported[21] which confirm the results of the semiempirical quantum mechanical investigations.

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(21) B. Zurawski and W. Kutzelnigg, *J. Am. Chem. Soc.*, **100**, 2654 (1978).

Reductive Ring Contraction of Mesoionic Thiazol-4-ones to Azetidin-2-ones

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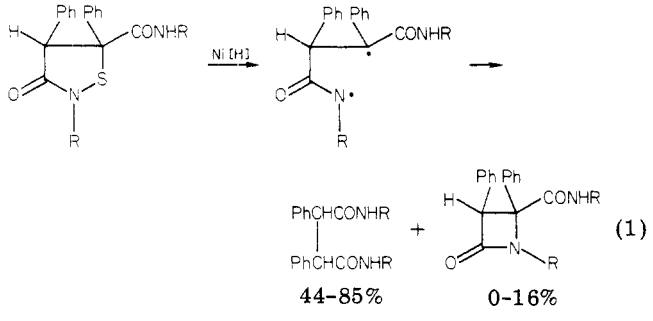
A series of anhydro-2,3,5-triaryl-4-hydroxythiazolium hydroxides was prepared and desulfurized with Raney nickel. The reduction was stereospecific and gave *cis*-1,3,4-triphenylazetidin-2-ones. Desulfurization in the presence of triphenylphosphine gave the corresponding *trans*-azetidinones. Consideration of the possible mechanistic pathways led to the conclusion that the reaction proceeds through formation of a biradical–dipole, hydrogenation to a 1,4-dipole, and ring closure. It was also concluded that in the preparation of β-lactams by the nonconcerted [2 + 2] cycloaddition of imines and ketenes the first step (dipole formation) is the stereochemistry-determining step.

Among the large number of existing synthetic approaches to the β-lactam system[1] only a few are based on ring contractions.[2] The only reported[3] example which involved Raney nickel desulfurization (eq 1) gave β-lactams in low yields, since the initially generated biradical undergoes hydrogenation rather than internal coupling.[4]

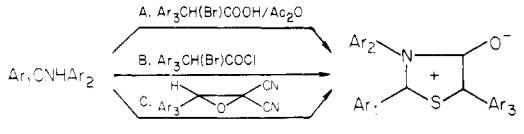


(1)

We expected that the use of mesoionic substrates[5,6] would offer considerable improvement. These compounds, which cannot be formulated by covalent structure, can be expected to furnish dipolar intermediates capable of cyclization even under the reductive desulfurization conditions.

Results[7]

This paper deals mainly with desulfurizations of anhydro-4-hydroxy-2,3,5-triarylthiazolium hydroxides (1). These are prepared by the reaction of thiobenzanilides with either α-bromoarylacetic acids and acetic anhydride[8] (A), α-bromoarylacetyl chlorides[9] (B), or *gem* dicyanoaryl epoxides[10] (C). Compounds 1 prepared for this study and



their physical properties are listed in Table I.

Desulfurization of 1a–j. Treatment of **1a** with Raney nickel (tenfold excess) in methanol, ethanol, tetrahydrofuran, or acetone caused disappearance of its red color within a few minutes. Workup afforded a single product which was identified[11] as *cis*-1,3,5-triphenylazetidin-2-one (**2a**, 85% yield). **1b–j** reacted similarly, yielding the *cis*-azetidinones **2b–j**, respectively (Table II). The yields listed in Table II were obtained under the standard conditions (see Experimental Section) and were rather low in several cases. This is due mainly to hydrogenolytic

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(4) W. A. Bonner and R. A. Grimm in "The Chemistry of Organic Sulfur Compounds", Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, 1966, pp 35.
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(6) Mesoionic thiazolones were also converted to β-lactams by photolysis: D. H. R. Barton, E. Buschman, J. Hausler, C. W. Holzapfel, T. Sheradsky, and D. A. Taylor, *J. Chem. Soc., Perkin Trans 1*, 1107 (1977).
(7) Partly reported in a preliminary communication: T. Sheradsky and D. Zbaida, *Tetrahedron Lett.*, 2037 (1978).
(8) M. Ohta, H. Chosho, C. G. Shin, and R. Ichimara, *Nippon Kaguku Zasshi*, **85**, 440 (1964); *Chem. Abstr.*, **61**, 14657h, (1964).
(9) K. T. Potts, S. J. Chen, J. Kane, and J. L. Marshall, *J. Org. Chem.*, **42**, 1633 (1977).
(10) M. Baudy, A. Robert, and A. Foucaud, *J. Org. Chem.*, **43**, 3732 (1978).
(11) O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, **90**, 2333 (1968).

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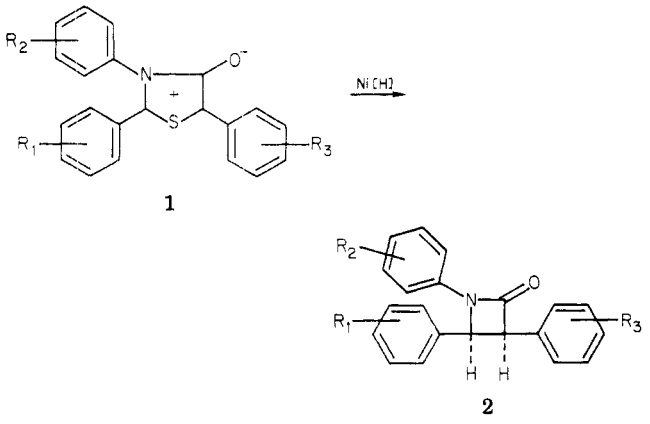
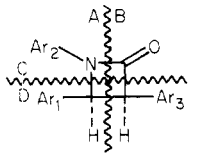


cleavage of the bond between the two benzylic carbons, C-3 and C-4, in the formed β-lactams and also due to some basic hydrolysis. The products in such cases were *N*-benzylphenylacetanilides (**3**) and *N*-benzylanilines (**4**).

		2a	$PhCH_2N(Ph)COCH_2Ph$ 3a	$PhNHCH_2Ph$ 4a
2a	Ni [H], MeOH	10%	39%	28%
1a	Ni [H], MeOH, prolonged stirring	12%	51%	25%

Control experiments confirmed the formation of **3** and **4** from **2** by prolonged desulfurization of **1a** or treatment of **2a** with Raney nickel. It was found that ring cleavage (leading to **3**) was decreased when acetone was the reaction solvent and that hydrolysis (to give **4**) was decreased by careful washing of the Raney nickel.

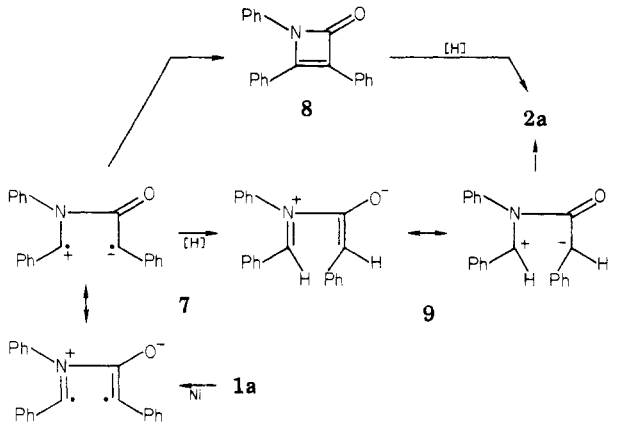
Structural Assignments. The lactams **2** show very distinct spectral features which allow easy identification. The IR carbonyl absorptions appear at 1740–1760 cm^{-1}. The mass spectra are characterized by cleavages across the ring in two directions[12] to imines (fragments A), phenylketenes (B), phenyl isocyanates (C), and stilbenes (D).



The NMR spectra exhibit two 1 H doublets at the δ 5–6 region, and the coupling constant (ca. 7 Hz) indicates a cis configuration. In this series the *trans*-lactams show a coupling constant of 2–3 Hz.[13] The general rule that $J_{cis} > J_{trans}$ for vicinal protons has been verified for a large series of monocyclic and bicyclic β-lactams.[13,14]

Stereospecifity. Careful examination of the reaction mixtures revealed no *trans*-lactams in most cases (within the analytical limits of NMR spectroscopy). The exceptions were early experiments with the *N*-chlorophenyl derivatives **1d** and **1f**, in which varying amounts (5–10%) of *trans*-lactams (**5d** and **5f**) were obtained. We found, however, that these *trans*-lactams were formed by cis–trans isomerization, catalyzed by the base (NaOH) present in the commercial aqueous suspension of Raney nickel used[15] (see Experimental Section). Indeed, use of nickel which

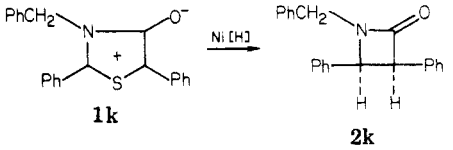
Scheme I



has been well washed prevented this isomerization and the reaction was cis stereospecific in all cases. Control experiments showed that **2a** and **2f** isomerize in dilute ethanolic sodium hydroxide solution and that **2f** isomerizes much faster. The significant effects of the 1-(*p*-chlorophenyl) group in β-lactams have been demonstrated before in isomerization experiments and X-ray studies on 1,4-diphenyl-3-isopropylazetidin-2-one.[16,17]

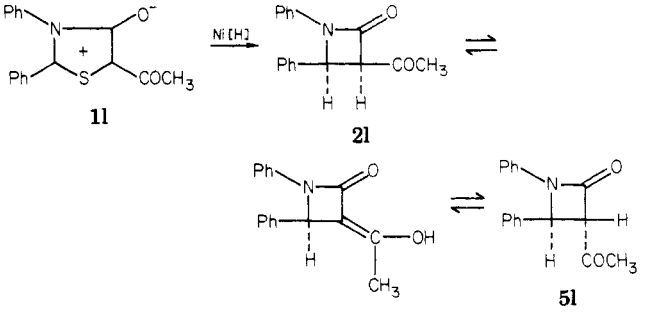
The ring contraction described here is the first direct stereospecific preparation of *cis*-3,4-disubstituted lactams. Another published method, which employed nitrones and copper acetylide,[18] had been shown later[19] to be only stereoselective. An indirect method, which involves desulfurization of alkylthiolactams, has been reported by Bose and co-workers.[20]

Some preliminary work was also carried out on mesoions **1** carrying nonaromatic substituents. The *N*-benzyl derivative **1k** gave the lactam **2k** in 80% yield. The NMR



spectrum of **2k** indicated, as expected,[13] a nonequivalence of the benzylic protons (J = 15 Hz). The two vicinal protons at C-3 and C-4, however, appeared as a singlet at 60 and 100 MHz. Separation to a pair of doublets was observed only at 270 MHz ($\Delta\delta$ = 0.007 ppm) and the cis geometry was confirmed.

The 5-acetyl derivative **1l** gave only the corresponding *trans*-lactam **5l**. We assume that the initially formed cis



isomer **2l** epimerized very rapidly as C-3 is a part of the

(12) P. G. Bird and W. J. Irwin, *J. Chem. Soc., Perkin Trans 1*, 2664 (1973).
(13) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3325 (1965).
(14) H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Lett.*, 941 (1964).
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(16) J. L. Luche, H. B. Kagan, R. Parthagarathy, G. Tsoucaris, C. De Rango, and C. Zeliver, *Tetrahedron*, **24**, 1275 (1968).
(17) R. Parthasarathy, *Acta Crystallogr., Sect. B*, **26**, 1283 (1970).
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(20) A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Lett.*, 2823 (1972).

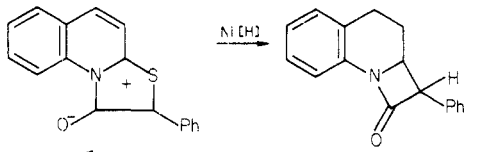
Table I. Anhydro-4-hydroxy-2,3,5-triphenylthiazolium Hydroxides (1)[c]

compd no.	substituents R_1	R_2	R_3	preparation method	yield, %	mp, °C	IR (C=O), cm^{-1}	UV, nm (log ε)
1a	H	H	H	A	50	270[a]		
1b	4-Me	H	H	A	40	157	1630	265 (3.85) 450 (3.83)
1c	H	2-Me	H	A	39	175-176	1630	262 (3.92) 450 (3.81)
1d	H	2-Cl	H	B	86	145-147	1625	263 (3.92) 455 (3.85)
1e	H	3-Cl	H	B	92	193-194	1620	262 (3.40) 450 (3.23)
1f	H	4-Cl	H	B	85	280	1630	268 (3.89) 452 (3.83)
1g	H	H	2-Cl	A	72	222-223	1610	285 (sh, 3.77) 445 (3.97)
1h	H	H	4-Cl	B	86	300[b]		
1i	H	3,4-diCl	H	B	84	256-260	1630	268 (3.78) 455 (3.67)
1j	H	4-OMe	H	B	83	255-256	1620	271 (4.50) 450 (4.45)

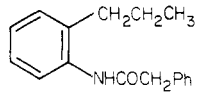
[a] Lit. mp 270,[7,9] 253-256[8] °C. [b] Lit.[9] mp 300 °C. [c] Satisfactory analyses (±0.4% for C, H, N, S, and Cl (when present) were reported for all compounds in Tables I and II.

easily enolizable β-keto amide moiety.

We have also carried out desulfurizations of several bicyclic mesoionic 4-thiazolones, but in no case were β-lactam products isolated. **1m** gave the hydrogenolysis product **6** in 85% yield, possibly via the lactam **2m**.



1m **2m**



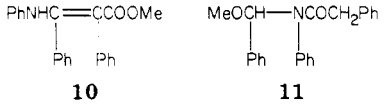
6

Discussion

Mechanism. It has been well-established[4] that Raney nickel desulfurizations of bivalent sulfur compounds proceed through a free-radical mechanism. The sulfur coordinates to the catalyst surface through its unshared 3p electrons, and the C–S bonds are then cleaved to give a radical pair. The final step is hydrogenation of the biradicals; however, some radical coupling may also occur.

On applying this general mechanism to the present case, the initial intermediate formed would be the biradical–dipole **7** (see Scheme I). It can then either cyclize to the unsaturated lactam **8** and subsequently be hydrogenated to **2** or first be hydrogenated and then cyclize via the dipole **9**.

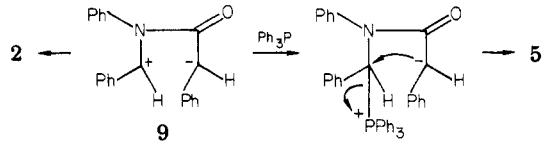
The obvious way to determine the right pathway is the interception of the intermediates by trapping. Although alcohols are considered as good trapping agents for dipoles,[21] we detected from the reaction in methanol neither the aminoacrylate **10** (expected from **8**)[6,22] nor the methoxy amide **11** (from **9**).[23]



10 **11**

The only nucleophile which we found to affect the product composition was triphenylphosphine, and its effect supports the intermediacy of **9**. When triphenylphosphine was present in an equimolar amount to **1**, the desulfurization product was pure *trans*-lactam (**5**). With smaller amounts of phosphine, mixtures were obtained in which the trans/cis ratios corresponded to the molar amounts of added phosphine. (This was verified by the reaction of **1a** and **1f** with different amount of phosphine, covering the whole range.)

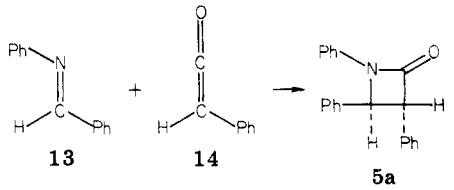
Since triphenylphosphine does not react with either the starting material **1** or the product **2**, this "steric steering" must result from its reaction with the intermediate. The only plausible position for such interaction is with the electrophilic center of **9** to give a new intermediate (**12**).



9 **12**

The reaction **9** → **12** is faster than the ring closure **9** → **2**, while the cyclization **12** → **5** is slower. The intermediate **12** is thus formed only in equivalent amount to the phosphine present, while the remaining part cyclizes directly to **2**.

Stereospecifity. The dipole **9** is also the acknowledged intermediate in the nonconcerted [2 + 2] cycloaddition of imines and ketenes.[23,24] However, the addition of benzilidene aniline (**13**) to phenylketene (**14**)[25] gives stereospecifically the *trans*-lactam **5a**.[26,27] Thus the two prep-



13 **14** **5a**

(21) R. Huisgen, *Acc. Chem. Res.*, **10**, 117, 199 (1977).
(22) G. Kretschmer and R. N. Warrener, *Tetrahedron Lett.*, 1335 (1975).
(23) H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1968).
(24) H. W. Moore, L. Hernandez, and R. Chambers, *J. Am. Chem. Soc.*, **100**, 2245 (1978), and references cited herein.
(25) Although the preformation of the ketene **14** in the reaction of **13** with phenylacetyl chloride–triethylamine is questionable,[26] the *trans*-lactam **5a** was also obtained when the ketene was generated by the Wolf rearrangement.[27]

Table II. *cis*-1,3,5-Triarylazetidin-2-ones (2)

compd no.	yield, %	mp, °C	IR (C=O), cm^{-1}	NMR, δ			mass spectra, *m/e* (relative intensity)				
				H-3[a]	H-4[a]	Me[b]	M$^+$	A	B	C	D
2a	85	182–183[c]									
2b	80	156–157	1750	5.10	5.75	2.20	313 (18)	195 (93)	118 (19)	119 (3)	194 (100)
2c	18	143–144	1740	4.99	5.77	2.20	313 (20)	195 (90)	118 (16)	133 (17)	180 (100)
2d	30	96–97	1740	5.40	6.13		333[d] (8)	215 (37)	118 (24)	153 (3)	180 (68)
2e	42	157–158	1745	5.09	5.50		333 (6)	215 (36)	118 (23)	153 (2)	180 (100)
2f	78	160–161	1740	5.05	5.45		333 (7)	215 (100)	118 (17)	153 (2)	180 (64)
2g	61	166–167	1740	5.00	5.49		333 (3)	181 (100)	152 (10)	119 (2)	219 (29)
2h	48	214–215	1740	5.00	5.49		333 (3)	181 (100)	152 (9)	119 (2)	214 (28)
2i	42	140–141	1750	5.09	5.50		368 (8)	250 (100)	118 (19)	188 (9)	180 (63)
2j	25	139–140	1732	4.92	5.38	3.74	329 (40)	211 (100)	118 (22)	133 (21)	180 (50)

[a] Doublet, 1 H, J = 7 Hz. [b] Singlet, 3 H. [c] Lit.[11] mp 182–183 °C. [d] *m/e* 181 (100%).

arations of the lactam, which proceed via the same intermediate, gave products of reverse stereochemistry. This discrepency leads to the conclusion that the different steric relationships of the hydrogens already exist in the dipole **9** which collapses before internal rotation can take place. In our case, the two hydrogens come from the same source, which is the nickel surface, and thus approach **7** from the same side to form a cis dipole, while in the cycloaddition the two components **13** and **14** approach each other in the less-hindered manner to give a trans dipole. Ring closure is faster than rotation[21] and thus the two stereoisomeric dipoles give rise to the corresponding stereoisomeric lactams. Another important conclusion concerns the controversial point of the stereochemistry-determining step in the cycloaddition. It is evident now that the stereochemistry is determined in the first step (the dipole formation). The stereochemistry in the addition **13** + **14** is directed by steric effects,[28] but our conclusion is probably valid also for cases in which it is directed by electronic effects,[29] since Huisgen has shown[21] that cyclization is faster than rotation in 1,4-dipoles which carry very polar substituents.

Recently Moore and co-workers[24] reported another independent generation of a similar 1,4-dipole and observed that it gives a β-lactam of the same stereochemistry as the one obtained in the corresponding [2 + 2] cycloaddition. This result does not contradict our conclusion, as it is possible that in certain cases the same electronic effects would operate in intermediate formation by the two different routes, resulting in the same lactams.

Experimental Section

Physical data were obtained on the following instruments: melting points on a Thomas-Hoover capillary apparatus, IR spectra (Nujol mulls) on a Perkin-Elmer 157 spectrometer, UV (ethanolic solutions) on a Unicam SP-800 spectrometer, NMR (in $CDCl_3$) on a Varian T-60, EM-360, or Brucker WH-270 spectrometer, and mass spectra on a Varian MAT-311 spectrometer.

Thiobenzanilides. The preparation from benzanilide and P_4S_{10} described[30] for the unsubstituted material was followed, employing dioxane as a solvent instead of pyridine.

Anhydro-2,3,5-trisubstituted-4-hydroxythiazolium Hydroxides (1). The procedures described in ref 3 (method A) and 4 (method B) were employed for the preparation of **1a–l**. Details, properties, and analyses are given in Table I.

Raney Nickel. The reagent used in most experiments was no. 28 Raney active nickel catalyst in water, made by W. R. Grace & Co. This suspension was found to be highly basic (pH 9.5–10) and in later reactions was used after several washings with water (pH 7.5–8). In some cases freshly prepared W-2 catalyst was employed with the same results.

Desulfurization of Compounds 1. Typical Procedure. To a solution of **1a** (0.658 g, 0.02 mol) in ethanol (850 mL) was added Raney nickel in water (7 g), and the mixture was stirred. After 2–5 min, the red solution became colorless, and stirring was immediately stopped. The catalyst was allowed to settle at the bottom of the flask and the solution was removed by decantation. After three washings with 50-mL portions of ethanol (stirring and decantation), the combined ethanolic solution was filtered and evaporated. The residue was dissolved in chloroform (10 mL), dried, and evaporated. Crystallization from ethanol afforded 0.51 g (85%) of **2a**, mp 182–183 °C.

(26) A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Lett.*, 4091 (1972).
(27) (a) W. Kirmse and L. Horner, *Chem. Ber.*, **89**, 2759 (1956); (b) R. Pfleger and A. Jager, *Chem. Ber.*, **90**, 2460 (1957); (c) J. M. Decazes, J. L. Luche, and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 2450 (1968).
(28) J. M. Decazes, J. L. Luche, and H. B. Kagan, *Tetrahedron Lett.*, 3661, 3665 (1970).
(29) R. Chambers, D. Kunert, L. Hernandez, F. Mercer, and W. H. Moore, *Tetrahedron Lett.*, 933 (1978).
(30) E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951).

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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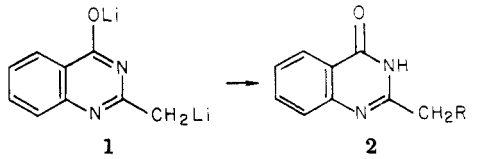
2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone, **3a**), 2,3-dimethyl-4(3*H*)-quinazolinone (**3b**), and 2-methyl-3-phenyl-4(3*H*)-quinazolinone (**3c**) were converted to the 2-lithiomethyl derivatives **4a**, **4b**, and **4c**, respectively, by means of lithium diisopropylamide in THF-hexane 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



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(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.

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