Studies Concerning Azabicyclobutanes (1)

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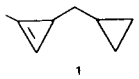
There have been a number of recent publications wherein azabicyclobutanes have been prepared (3) or proposed as unstable reaction intermediates (4). As part of our studies on small ring heterocycles (5-7), we have carried out experiments concerning 1- and 2-azabicyclo[1.1.0]butanes and now report the results of these.

Cyclobutene and 2,3-dichlorocyclobutene react with carboethoxynitrene or *N*-phthalimidonitrene to form the corresponding 5-azabicyclo[2.1.0]pentanes (5,6). In contrast, treatment of 1-methylcyclopropene with these reagents gave no detectable bicyclic product. With carboethoxynitrene (generated *in situ* from ethyl *N*-carboxy-*O*-phenylsulfonylhydroxylamine) a product having spectral characteristics consistent with the dimer (**1**) of 1-methylcyclopropene was found along with diethyl hydrazodicarboxylate and a viscous, nonvolatile material. This result differs also from the formation of an isolable α,β-



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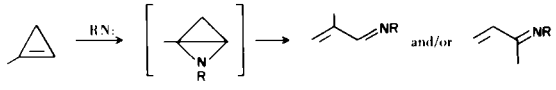
unsaturated imine when the photolytically generated nitrene was employed (4b).

Treatment of 1-methylcyclopropene with *N*-phthalimidonitrene at 0° gave phthalimide (8) and a red, intractable tar. An nmr study of the reaction showed no change at -78° after sixteen hours. At 0° there was slow formation of a singlet at δ 2.27 which was attributed to an α- or β-methyl on an α,β-unsaturated imine (4b). No signals in the expected region (δ 1-2) for a bridgehead methyl on a 2-azabicyclobutane appeared (9). The data may be interpreted to indicate formation of a 2-azabicyclo[1.1.0]butane intermediate (2, R = *N*-phthalimido) which rapidly undergoes a ring opening rearrangement. Attempts to isolate an imine product were unsuccessful.



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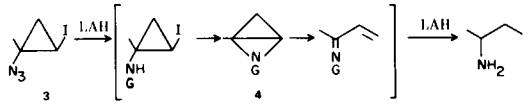
In a different approach, 1-methylcyclopropene was treated with iodine azide. The single addition product obtained showed nmr absorption consistent with the *trans* isomer (**3**) but not with the *cis* isomer or with likely ring-opened products (10). Attempted ring closure of **3** by reaction with lithium aluminum hydride (LAH) yielded *sec*-butylamine as the only organic product formed in significant quantity. Again, this result is reasonably explicable through the intermediacy of an unstable 2-azabicyclobutane species (**4**, G = group derived from LAH), although an alternative path can be written.



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The pyrolysis of **5** could lead to an azetine (11) or, *via* a nitrene, to a 2-azabicyclobutane. The change in ir absorption to 1610 cm^{-1} indicated the formation of an imine group but the product could not be isolated to permit characterization as an azetine or α,β-unsaturated imine.

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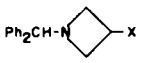
These results are interpreted as analogous to the thermal rearrangement of bicyclo[1.1.0]butane (12) and, even more so, to the formation of α,β-unsaturated aldehydes or ketones on attempted epoxidation of cyclopropenes (13). We attribute the failure to observe the 2-azabicyclo[1.1.0]butane system as a stable molecule to the interaction of the bridging bond orbitals with the nitrogen lone pair. This 4 pi-like interaction (14) destabilizes the structure with respect to rearrangement to an α,β-unsaturated imine. An electronic model of the system can be constructed from the models proposed by Pomerantz and Abrahamson (15) for bicyclo[1.1.0]-butane, using sp or sp^2 ring atoms and pure p orbitals, by replacing a methylene group with an appropriate nitrogen.

A principal route to the bicyclo[1.1.0]butane structure has been 1,3-intramolecular displacement in appropriately substituted cyclobutanes (16). A 1-thiabicyclobutonium ion has been suggested as an intermediate in the hydrolysis of 3-chlorothietane (17) and there is good evidence for the existence of 1-azabicyclobutonium ions arising from 3-substituted azetidines (18). We have carried out some

studies on the formation of 1-azabicyclobutanes from substituted azetidines by two routes: the displacement of a leaving group on the 3-position by the ring nitrogen, and the displacement of a leaving group on the nitrogen by a carbanion generated at the 3-position.

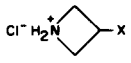
Treatment of **7a**, prepared by the hydrogenolysis of **6a** (22), with potassium *t*-butoxide in glyme or with sodium amide in DMF gave only polymeric material. Heating **7b**, obtained from **6b**, in aqueous sodium hydroxide under vacuum also formed a polymer. The low boiling distillate obtained after neutralization of **7b** with one equivalent of methyllithium in ether followed by shaking with silver oxide in glyme exhibited nmr absorption at δ 2.4 and 2.2 (relative intensities 1:2) and at 0.93 as reported for **8a** (3a) in addition to solvent peaks (17), but the pure azabicyclobutane was not obtained on further fractional distillation. The apparent low yield of **8a** may have been due in part to ring opening catalyzed by Ag (I) as has been observed with bicyclobutanes (20).

From the treatment of **7b** with sodium amide in ammonia was obtained material which showed nmr absorption at δ 2.33 (t), 2.17 (m) and 0.93 (q) indicative of **8a**, plus a broad, low intensity ammonia peak at *ca.* δ 0.6. Attempted isolation of pure **8a** and the formation of a derivative by reaction with tosyl chloride did not succeed.



8a-g

a, X = OMs
b, X = Br
c, X = COOH
d, X = COOPh



7a-g

e, X = COOMe
f, X = COOisoPr
g, X = COOtertBu

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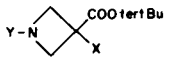
a, R = H
b, R = COOtertBu
c, R = Ph



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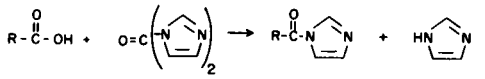
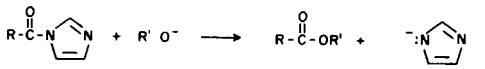
a, X = H, Y = Cl
b, X = Cl, Y = Tosyl

An azabicyclo[3.1.0]hexane compound has been prepared *via* cross ring displacement of a group on nitrogen by a carbanion (21). Following this approach we esterified azetidine-3-carboxylic acid by reaction with phenol and dicyclohexylcarbodiimide. Hydrogenolysis of the hydrochloride of **6d**, however, gave a mixture of the hydrochlorides of the desired ester (**7d**) and the acid (**7c**) from which pure **7d** could not be obtained. Other esters were then investigated. The hydrochlorides of the methyl (**6e**) and isopropyl (**6f**) esters on hydrogenolysis gave semisolids from which **7e** and **7f**, respectively, could not be isolated (23). In contrast, the *t*-butyl ester hydrochloride (**7g**) was crystalline and readily purified.

Esters **6f** and **6g** were prepared by treatment of the acid (**6c**) with carbonyldiimidazole and the corresponding sodium alkoxides. Staab had reported that good yields of esters resulted from the use of alcohol plus a catalytic amount of the alkoxide (23). On a preparative scale we found one equivalent of alkoxide to be necessary. This is reasonable as the imidazole (pK_a = 14.17) anion formed is not basic enough to form a significant amount of alkoxide from the alcohols (pK_a = 18-19).





Treatment of **7g** with sodium hypochlorite formed an unstable, colorless oil which exhibited an nmr spectrum, δ 1.42 (s, 9H), 3.13 (m, 4H), and 3.93 (d, 1H), in agreement with structure **9a**. Heating the oil with sodium hydride gave a brownish liquid. The nmr spectrum of this product consisted of multiplets at δ 1.35 and 2.7 and a sharp singlet at δ 1.45 with the ratio of downfield to upfield hydrogens of 2:11. The large singlet was assigned to the *t*-butyl methyls and, by analogy with the spectra of other azabicyclobutanes, the multiplets at δ 2.7 and 1.35 were assigned to the *exo* (H_X) and *endo* (H_n) hydrogens, respectively, of structure **8b**. The ring hydrogens for **8b** were, as expected, deshielded relative to those of **8a**, and by different amounts (0.53 ppm for H_X and 0.42 ppm for H_n). Corresponding shifts have been observed for **8c** (0.51 ppm for H_X and 0.40 ppm for H_n) relative to **8a** (25). These data are consistent with the H_X hydrogens in a *cis*, and the H_n hydrogens in more of a *trans*, relationship to the substituents in these compounds (26).

Vacuum distillation of the brown oil caused decomposition. Reaction with *p*-toluenesulfonyl (tosyl) chloride gave a solid having a composition and nmr spectrum (doublets at δ 3.99 and 4.39, J = 10 Hz, plus absorption from the *t*-butyl and tosyl groups) in accord with structure **9b**. The formation of **9b** is analogous to the reactions of tosyl chloride with 3-alkylazabicyclobutanes (3a).

The evidence for the formation of **8a** and **8b** points to the potential application of this method for the preparation of suitably substituted azabicyclo[1.1.0]butanes (25).

EXPERIMENTAL

Lead tetraacetate (Arapahoe Chemical Co. or Alfa Inorganics) was recrystallized from glacial acetic acid and dried. Melting points are uncorrected. Nuclear magnetic resonance spectra were

recorded on Varian T-60 or HA-100 spectrometers with tetramethylsilane as the internal standard. Infrared spectra were recorded with a Perkin Elmer Model 137 or 225 instrument, and ultraviolet spectra were taken with a Cary Model 14 spectrophotometer. For the reactions to form azabicyclobutanes, all glassware was washed with 1*N* sodium hydroxide and dried in an oven. Vapor phase chromatograms were obtained with a Varian Aerograph. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer. Microanalyses were performed by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany or by Chemalytics, Inc., Tempe, Arizona.

Reaction of 1-Methylcyclopropene with Carboethoxynitrene.

Over a period of several hours a solution of 2.1 g. (8 mmoles) of ethyl *N*-carboxy-*O*-phenylsulfonylhydroxylamine (6) in 15 ml. of dry ether was added to a cooled (Dry Ice), stirred mixture of 5.5 ml. (80 mmoles) of 1-methylcyclopropene (25) and 1.2 ml. (8 mmoles) of triethylamine. After stirring overnight, the precipitated triethylammonium benzenesulfonate (identified by its nmr spectrum in deuterium oxide) was removed by filtration. A sample of the filtrate was subjected to preparative vpc (10% Carbowax, 62°, 3/8" x 12'). The nmr spectrum (carbon tetrachloride) of the third fraction showed absorption at δ 0.08 (m, 2), 0.55 (m, 2), 0.98 (d, 2), 8.95 (s, 1), 1.53 (d of d, J = 1.5 and 2.5 Hz, 1), 2.10 (d, 3) and 6.48 ppm (m, 1), and the ir (neat) spectrum had a peak at 1800 cm^{-1} in agreement with **1**.

From the remainder of the filtrate were obtained diethyl hydrazodicarboxylate (tlc, m/e 176.07972; Calcd. 176.07970) and, after removal of the solvent by distillation, a viscous, nonvolatile, yellow material.

trans-1-Azido-2-iodo-1-methylcyclopropane (**3**).

To a cold (ice-salt bath) solution of 16.89 g. (0.1 mole) of iodine azide in 100 ml. of dry acetonitrile (28) was added 5.4 g. (0.1 mole) of 1-methylcyclopropene in less than 0.5 ml. portions (exothermic reaction) over a period of 3 hours while the temperature was maintained at less than 10°. The mixture was then stirred overnight and worked up in the prescribed manner (28,29). The yellow oil obtained by chromatography of the crude product on a neutral alumina column with 1:1 ether-petroleum ether (30-60°) as the eluent amounted to 18.9 g. (85%). Elution of the oil from a silica gel (200-325 mesh) column gave a colorless product (**3**) containing iodine and nitrogen (sodium fusion) which rapidly discolored in air; nmr (carbon tetrachloride): δ 0.82 (dd, J = 6 Hz, J = 8 Hz, 1), 1.57 (dd, J = 8 Hz, J = 10 Hz, 1), 1.63 (s, 3), and 2.80 ppm (dd, J = 6 Hz, J = 10 Hz, 1); ir (neat) 2050 cm^{-1} (27); m/e 222.9603 (Calcd. for $C_4H_6N_3I$: 222.9608) with base peak at 127 (I^+) and major fragment at 96 ($C_4H_6N_3^+$).

Reaction of *trans*-1-Azido-2-iodo-1-methylcyclopropane (**3**) with LAH.

In the usual manner, 1.8 g. (8.1 mmoles) of an ethereal solution of **3** was reduced by 1.0 g. (26.3 mmoles) of LAH. After hydrolysis (50% potassium hydroxide) there was obtained (vpc on 3% SE30 at 35°) *sec*-butylamine, identified by its vpc retention time and comparison (nmr in deuterium oxide) of the hydrochloride salt with an authentic sample.

3-Bromoazetidinium Chloride (**7b**).

A solution of 20.34 g. (60 mmoles) of the hydrochloride of 1-benzhydryl-3-bromoazetidine (**6b**) (22) in 225 ml. of methanol was treated wtih hydrogen at 55 psi in the presence of 0.96 g. of palladous hydroxide on C (30) until hydrogen uptake ceased (4 hours). The solid (**7b**) obtained after separation of the catalyst and evaporation of the solvent was washed with anhydrous acetone and dried, m.p. 99-102° (yield 10 g., 99%). The analytical sample was recrystallized from 1-butanol; m.p. 102-104°; nmr (TFA) δ: 4.3 (m, 5, (CH_2CHCH_2) and 7.7 ppm (broad s, 2, $\overset{+}{N}H_2$).

Anal. Calcd. for C_3H_7BrClN: C, 20.85; H, 4.06; Br, 46.40; Cl, 20.61; N, 8.11. Found: C, 21.00; H, 4.22; Br, 46.66; Cl, 20.61; N, 7.97.

Reaction of 3-Bromoazetidinium Chloride (**7b**) with Sodium Amide.

To a mixture of sodium amide, 2 g. (50 mmoles), and 75 ml. of dry liquid ammonia in a 3-neck flask fitted with a Dry Ice-acetone condenser and stirrer was added, with stirring, 1.73 g. (10 mmoles) of **7b** in small portions. Stirring was continued for 3 hours and excess sodium amide was destroyed by the addition of 1.6 g. of ammonium chloride. Ammonia and volatile products were evaporated through two traps in series kept at -18°, with the reaction flask finally warmed to 70°. The material in the traps was taken up in deuterated chloroform. The nmr spectrum (100 M Hz) corresponded to that of **8a**: δ 2.33 (t, J = 1.25 Hz, 1, CH_2CHCH_2, ω (peak width at half height) = 3.75 Hz), 2.17 (m, 2, *H*CNC*H*, ω = 4.5 Hz), and 0.93 ppm, (q, J = 1.25 Hz, 2, *H*CNC*H*, ω = 4.25 Hz); [lit. (3a) δ 2.33 (t, 1, ω = 3.8 Hz), 2.13 (m, 2, ω = 4.6 Hz), and 0.93 (m, 2, ω = 4.4 Hz).]

Phenyl 1-Benzhydrylazetidine-3-carboxylate (**6d**).

To a solution of 33.8 g. (0.126 mole) of 1-benzhydrylazetidine-3-carboxylic acid (**6c**) (22) and 11.8 g. (0.126 mole) of phenol in 570 ml. of dry pyridine at 0° (ice bath) was added 26 g. (0.126 mole) of dicyclohexylcarbodiimide. The mixture was stirred at 0° for 1 hour at room temperature for 2 hours and then placed in a refrigerator overnight. The mixture was filtered, the filtrate poured into 2 l. of water and the milky solution refrigerated overnight. The precipitated solid was collected, dried, and taken up in ether. Filtration separated the remaining, insoluble dicyclohexylurea, and evaporation of the solvent from the filtrate gave 24 g. (56%) of **6d**, m.p. 90-93°. Sublimation at 90° and 10^{-6} torr gave material melting at 93-94°; ir (chloroform): 1740 cm^{-1} (C=O); nmr (carbon tetrachloride) δ: 3.44 (m, 5, CH_2CHCH_2), 4.37 (s, 1, Ph_2CH) and 7.25 ppm (m, 15, Ar*H*).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.5; H, 6.12; N, 4.03. Found: C, 80.38; H, 6.15; N, 4.28.

Hydrogenolysis of **6d** Hydrochloride.

A solution of 3.8 g. (10 mmoles) of **6d** hydrochloride, prepared by treatment of an ethereal solution of **6d** with dry hydrogen chloride, in 150 ml. of absolute methanol was treated with hydrogen at 50 psi in the presence of 0.3 g. of palladous hydroxide on C (29) until hydrogen uptake ceased (5 hours). The mixture was filtered and the residue remaining after removal of the solvent was washed with dry ether and then taken up in dichloromethane. The insoluble material was separated and evaporation of the solvent from the solution left 0.56 g. of impure **7d** hydrochloride, m.p. 130-135°; ir (potassium bromide): 1740 cm^{-1} (C=O); nmr (deuterium oxide) δ: 4.2 (m, 1, CH_2CHCH_2), 4.47 (d, 4, J = 6 Hz, CH_2NCH_2), 4.7 (s, 2, H_2O), and 7.35 (m, 5, Ar*H*). The dichloromethane insoluble product (1 g.) was acidic to litmus, gave a positive silver nitrate test and showed an nmr (water) spectrum identical to that of **7c** (22).

Methyl 1-Benzhydrylazetidine-3-carboxylate (**6e**).

To a 3% methanolic hydrogen chloride solution, prepared by

mixing 5 ml. of acetyl chloride and 100 ml. of absolute methanol, was added 2.67 g. (10 mmoles) of **6c** and 4.16 g. (40 mmoles) of 2,2-dimethoxypropane and the mixture was stirred at room temperature for 2 days. It was then filtered, the volatile materials were evaporated from the filtrate, and the residue was partitioned between 5% sodium bicarbonate and ether. Removal of the solvent from the dried ether solution gave 2.47 g. (88%) of **6e**, m.p. 65-67°, and 67-68° after recrystallization from ethanol-water; ir (chloroform): 1735 cm^{-1} (C=O); nmr (deuteriochloroform) δ : 3.33 (m, 5, CH_2CHCH_2), 3.63 (s, 3, OCH_3), 4.40 (s, 1, Ph_2CH), and 7.30 ppm (m, 10, ArH).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.7; N, 4.9. Found: C, 76.78; H, 6.60; N, 5.13.

Isopropyl 1-Benzhydrylazetidine-3-carboxylate (**6f**).

To a solution of 2.67 g. (10 mmoles) of **6c** in 20 ml. of dry DMF was added in portions 1.7 g. (10.5 mmoles) of carbonyldiimidazole. After the cessation of carbon dioxide evolution, another 30 ml. of DMF was added, the mixture was stirred for 1 hour, and then a solution of sodium isopropoxide, prepared by dissolving 0.245 g. (11 mmoles) of sodium in 10 ml. of isopropyl alcohol was added. The mixture was stirred overnight and then refluxed for 1 hour before being poured into ice water. The collected, dried precipitate of **6f** amounted to 2.65 g. (86%), m.p. 86-89°, and 89-90.5° after recrystallization from ethanol-water; ir (chloroform): 1735 cm^{-1} (C=O); nmr (carbon tetrachloride) δ: 1.2 (d, 6, J = 6 Hz, CH_3CHCH_3), 3.26 (m, 5, CH_2CHCH_2), 4.33 (s, 1, Ph_2CH), 4.96 (hep, 1, J = 6 Hz, $CHMe_2$), and 7.25 ppm (m, 10 ArH).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.66; H, 7.44; N, 4.53. Found: C, 77.58; H, 7.49; N, 4.33.

t-Butyl 1-Benzhydrylazetidine-3-carboxylate (**6g**).

The procedure for the preparation of **6f** was employed except that 1.2 g. (11 mmoles) of potassium *t*-butoxide in 10 ml. of *t*-butyl alcohol were used. There was obtained 2.2 g. (68%) of **6g**, m.p. 107-110°, and 110-111° after recrystallization from ethanol-water; ir (chloroform): 1735 cm^{-1} (C=O); nmr (deuteriochloroform) δ: 1.42 (s, 9, $C(CH_3)_3$), 3.27 (m, 5, CH_2CHCH_2), 4.37 (s, 1, Ph_2CH) and 7.3 ppm (m, 10, ArH).

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.02; H, 7.74; N, 4.33. Found: C, 77.86; H, 7.72; N, 4.15.

t-Butyl Azetidine-3-carboxylate Hydrochloride (**7g**).

A solution of 3.28 g. (9.13 mmoles) of the hydrochloride of **6g**, prepared by treatment of an ethereal solution of **6g** with dry hydrogen chloride, in 70 ml. of absolute methanol was treated with hydrogen at 50 psi in the presence of 0.3 g. of palladous hydroxide on C (30) until hydrogen uptake ceased (5 hours). The mixture was filtered and the solvent removed from the filtrate. The residue was washed with THF and dried to give 1.56 g. (88%) of **7g**, m.p. 120-123°; ir (potassium bromide): 2300-2700 cm^{-1} ($\overset{+}{N}H$), 1700 cm^{-1} (C=O); nmr (deuterium oxide) δ: 1.42 (s, 9, $C(CH_3)_3$), 3.7 (m, 1, CH_2CHCH_2), 4.23 (d, 4, J = 7 Hz, CH_2CHCH_2), and 4.53 ppm (s, 2, H_2O).

Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.27; Cl, 18.35; N, 7.24. Found: C, 49.24; H, 8.11; Cl, 18.44; N, 6.81.

Reaction of **7g** with Sodium Hypochlorite.

To 0.968 g. (5 mmoles) of **7g** covered with 20 ml. of pentane and cooled to 0° was added in the dark with stirring 40 ml. of cold (ice bath), freshly prepared 0.02 *M* sodium hypochlorite. Stirring was continued for 2 hours and the separated aqueous phase was extracted twice with 20 ml. portions of pentane. Removal of the solvent from the combined, dried (magnesium sulfate and then calcium sulfate), filtered (glass wool) pentane solution gave 0.9 g. (84%) of colorless oil which, in agreement with the structure of *t*-butyl 3-chloroazetidine-3-carboxylate (**9a**), gave a purple starch-iodide test, was unstable to light, and showed nmr absorption (carbon tetrachloride) at δ 1.42 (s, 9, $C(CH_3)_3$), 3.13 (m, 1, CH_2CHCH_2) and 3.93 ppm (d, 4, J = 7 Hz, CH_2CHCH_2).

t-Butyl 1-Azabicyclo[1.1.0]butane-3-carboxylate (**8b**) and *t*-Butyl 1-Chloro-3-*p*-toluenesulfonylazetidine-3-carboxylate (**9b**).

To 0.26 g. (11 mmoles) of sodium hydride, prepared by washing 0.5 g. of a 53% suspension in mineral oil three times with dry *n*-pentane, covered with 5 ml. of dry THF in a three-neck 25-ml. flask equipped with a gas outlet tube, magnetic stirrer, and pressure-equalizing dropping funnel and protected from the light was added dropwise a solution of 0.9 g. (4.6 mmoles) of the oil assigned structure **9a** in 12 ml. of dry THF. Immediate gas evolution was observed. The mixture was then heated at 50° for 3 hours under a nitrogen atmosphere. Filtration and removal of the THF from the filtrate (reduced pressure) left 0.61 g. (94%) of **8b** as a brownish oil; nmr (carbon tetrachloride) δ: 1.35 (m, 2, *endo* CHNCH), 1.45 (s, 9, $C(CH_3)_3$), and 2.7 ppm (m, 2, *exo* CHNCH).

In a separate, duplicate reaction, a solution of 0.8 g. (4.2 mmoles) of tosyl chloride in 3 ml. of dry THF was added to filtrate containing **8b** and the mixture was stirred for 24 hours. Evaporation of the solvent left 1.32 g. (76%) of **9b**, m.p. 102-106°, and 106-108° after recrystallization from 95% ethanol; nmr (deuteriochloroform) δ: 1.42 (s, 9, $C(CH_3)_3$), 2.47 (s, 3, $ArCH_3$), 3.99 (d, 2, J = 10 Hz, CHNCH), 4.39 (d, 2, J = 10 Hz, CHNCH), 7.4 (d, 2, J = 8 Hz, ArH), and 7.8 (d, 2, J = Hz, ArH).

Anal. Calcd. for $C_{15}H_{20}NClO_4S$: C, 52.09; H, 5.79; Cl, 10.26; N, 4.05; S, 9.26. Found: C, 51.95; H, 5.32; Cl, 10.82; N, 3.75; S, 9.09.

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