reflecting their different relative acidities. The proton and carbon chemical shifts (Tables II and III) suggest that structure **4b** makes a major contribution to the structure of the diethylamine complex, which is best considered as an ion pair, while the triethylamine complex is essentially un-ionized and is best represented by structure **4a**.

The resonance of the protons in acetyl methyl groups of the diethylamine complex appears at δ 1.92, shifted upfield from that in the enol form of acetylacetone, as is the signal at δ 5.28 arising from the methine proton. The ethyl protons in the amine moiety exhibit downfield shifts comparable to those observed for both amines in methanol solution. These shifts are in accord with the behavior expected for ionic structure **4b**.

The shifts observed for triethylamine are quite different. The resonances from both the amine and acetylacetone moieties suffer very small downfield shifts. The small shifts observed suggest that the structures are not changed very much from the separate neutral compounds and that the complex is best represented by the un-ionized structure **4a**. Apparently, in this solvent the greater acidity of the conjugate acid of triethylamine (over that of diethylamine) is sufficient to suppress proton transfer, and the complex is one in which the triethylamine is only hydrogen bonded to the enolic proton of acetylacetone.

Carbon chemical shifts are also sensitive to amine protonation. Protonation is accompanied by characteristic upfield shifts of several ppm for the β carbons and smaller variable shifts for the α carbons.[8] Table III gives carbon chemical shifts for the two complexes and those in the free amines and the benzoate salts for comparison. Both amines exhibit upfield shifts for the β carbons (methyl carbons) upon conversion to the benzoates in accord with previous observations. The chemical shifts of both methyl and methylene carbon atoms in the triethylamine complex are essentially unchanged from those in the free amine, while those in the diethylamine complex experience upfield shifts which are about 25% of those in the benzoate. While these data may not quantitatively reflect the contributions of the two structures **4a** and **4b**, they do indicate that the contribution of **4b** is much greater for diethylamine.[9]

Experimental Section

Acetylacetone, diethylamine, triethylamine, and benzoic acid were obtained from commercial sources. The complexes were prepared in situ by mixing weighed amounts of the appropriate compounds.

^{1}H NMR spectra were measured on a Varian A60-A spectrometer (60 MHz). Chemical shifts are given in δ units relative to internal tetramethylsilane. Temperatures were controlled with a V-6040 variable-temperature controller and determined by measurement of methanol spectra as outlined in the Varian users manual. Carbon spectra were measured at ambient temperature on a JEOL FX-60 spectrometer (15.04 MHz) and are expressed in δ units relative to internal Me_4Si.

Registry No.—Et_2NH·Hacac, 62154-14-7; Et_3N·Hacac, 62154-15-8; $Et_2NH_2^+C_6H_5CO_2$, 940-90-9; $Et_3NH^+C_6H_5CO_2^-$, 941-02-6.

References and Notes

(1) (a) This work was supported by the National Science Foundation and the National Institute of General Medical Sciences. We also thank the National Science Foundation for an equipment grant used for the purchase of the FX-60 FT-NMR spectrometer used to obtained ^{13}C spectra for this study. (b) Alfred P. Sloan Foundation Fellow, 1972–1976. (c) On leave from the University of Tokyo.
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(9) The changes in the chemical shifts of the acetylacetone moiety are also greater when diethylamine is added. The chemical shifts for the carbonyl, methine, and methyl groups were: Hacac, 191.2, 100.3, 24.7; Hacac·$NHEt_2$, 190.5, 99.4, 26.0; Hacac·NEt_3, 191.2, 100.1, 25.0.

Alkylation and Ring Contraction Reactions of 1,3,4-Benzotriazepine-2,5-dione Systems

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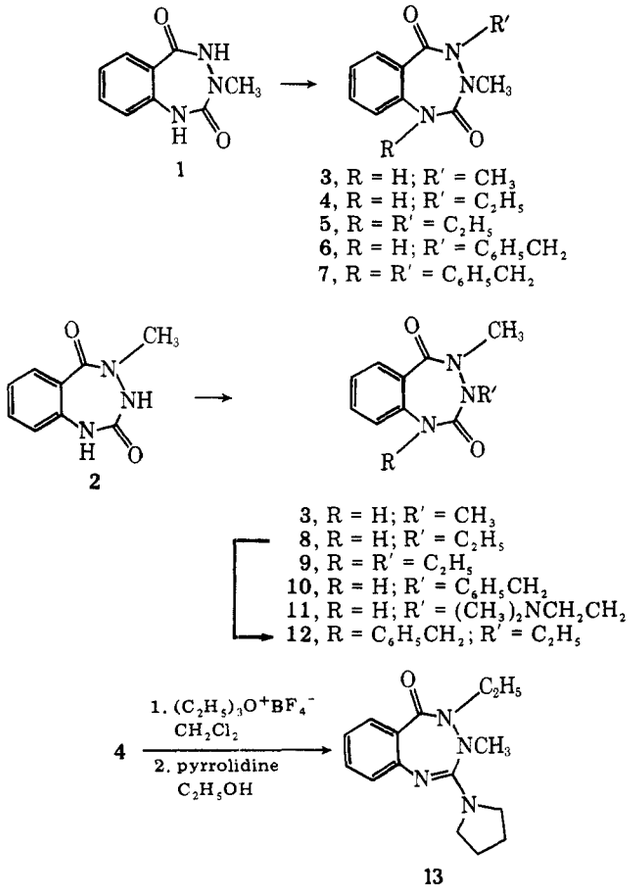
Received December 23, 1976

Alkylation studies on 3,4-dihydro-3-methyl-1*H*-1,3,4-benzotrazepine-2,5-dione (**1**) and its 4-methyl isomer **2** have led to a method for the regiospecific introduction of one or two (similar or dissimilar) alkyl groups to these systems, which allows the preparation of a wide variety of 1,3,4-trialkyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-diones. When ethyl bromoacetate was employed as the alkylating agent, ring contraction reactions occurred to produce 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**) from both **1** and **2**. Treatment of **2** with aqueous base also resulted in ring contraction to produce 3-(methyl)amino-2,4(1*H*,3*H*)-quinazolinedione (**30**), whereas **1**, under the same conditions, yielded 2-(*o*-aminobenzoyl)-1-methylhydrazine (**25**). Further utility of 1-acetyl-1-methylhydrazine was demonstrated in the preparation of authentic samples of **25** and **30**. Mechanisms of the ring contraction reactions are discussed.

We have recently reported[1] syntheses of 3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**1**) and its 4-methyl isomer **2**. It was found that both **1** and **2** undergo selective monomethylations with sodium hydride and methyl iodide in dimethylformamide, to yield the same benzotriazepinedione **3**.[2] In this report we describe additional alkylation studies on **1** and **2**, some of which have led to interesting ring contraction reactions.

Alkylation reactions which were performed with **1** and **2** are described in Scheme I. All of the depicted reactions generally produced a single product in good yield. The selectivity of the monoalkylation reactions which produced 4-alkyl derivatives of **1** and 3-alkyl derivatives of **2** allowed the systematic introduction of a variety of alkyl groups into the benzotriazepinediones. In all cases, sodium hydride was the base employed and the solvent was dimethylformamide. Thus,

Scheme I



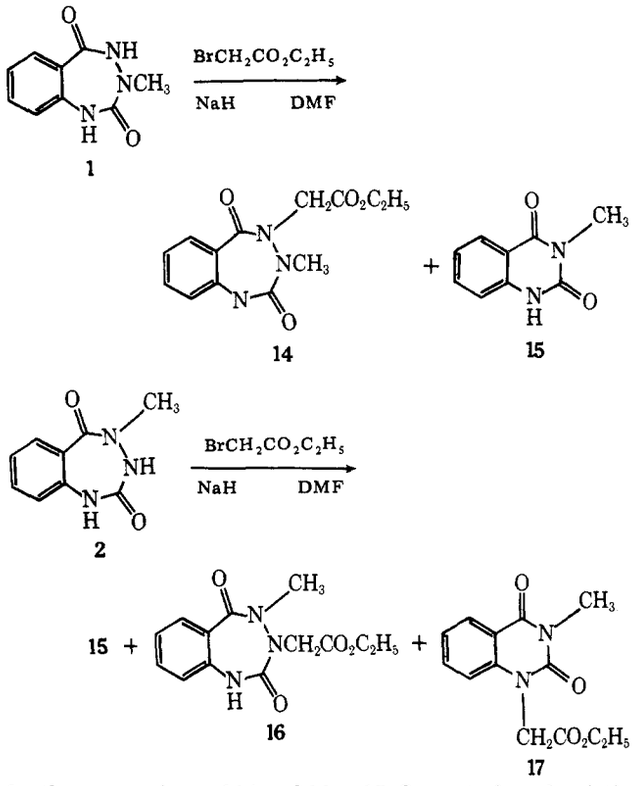
monoalkylation of **1** using equivalent amounts of sodium hydride and ethyl iodide or benzyl bromide yielded the 4-ethyl and 4-benzyl derivatives **4** and **6**, respectively. Dialkylation using 2 equiv each of sodium hydride and the same alkylating agents produced the respective 1,4-diethyl and 1,4-dibenzyl derivatives **5** and **7**.

Similar alkylations of benzotriazepinedione **2** yielded the 3-ethyl (**8**), 1,3-diethyl (**9**), and 3-benzyl (**10**) derivatives of **2**. 2-Dimethylaminoethyl chloride, under conditions of monoalkylation, gave **11**. The preparation of compound **12**, 3-ethyl-3,4-dihydro-4-methyl-1-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione, from **2** via **8** in two successive monoalkylation reactions demonstrates the utility of the alkylation procedure in preparing a 1*H*-1,3,4-benzotriazepine-2,5-dione bearing three different alkyl groups. Treatment of **4** with triethyloxonium tetrafluoroborate followed by quenching with pyrrolidine gave **13**.

Alkylations of **1** and **2** with ethyl bromoacetate led to mixtures resulting from ring contraction reactions of the benzotriazepinediones. The product mixture from **1** gave the expected 4-carbethoxymethyl derivative **14**, and 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**). In the gross transformation of **1** to **15**, an NH group had been removed from the ring and its residue was not to be found on the contracted ring. Even more interesting was the finding that quinazolinedione **15** also resulted from the alkylation of **2** with ethyl bromoacetate. In addition, we isolated the expected 3-carbethoxymethyl derivative **16**, and 1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-quinazolineacetic acid ethyl ester (**17**), which was apparently derived from **15**, after its in situ formation, by alkylation. Thus, the unmethylated nitrogen atom in the 3 and 4 positions of benzotriazepinediones **2** and **1**, respectively, could be completely removed by reaction with ethyl bromoacetate. See Scheme II.

Scheme III indicates some possible mechanistic pathways

Scheme II



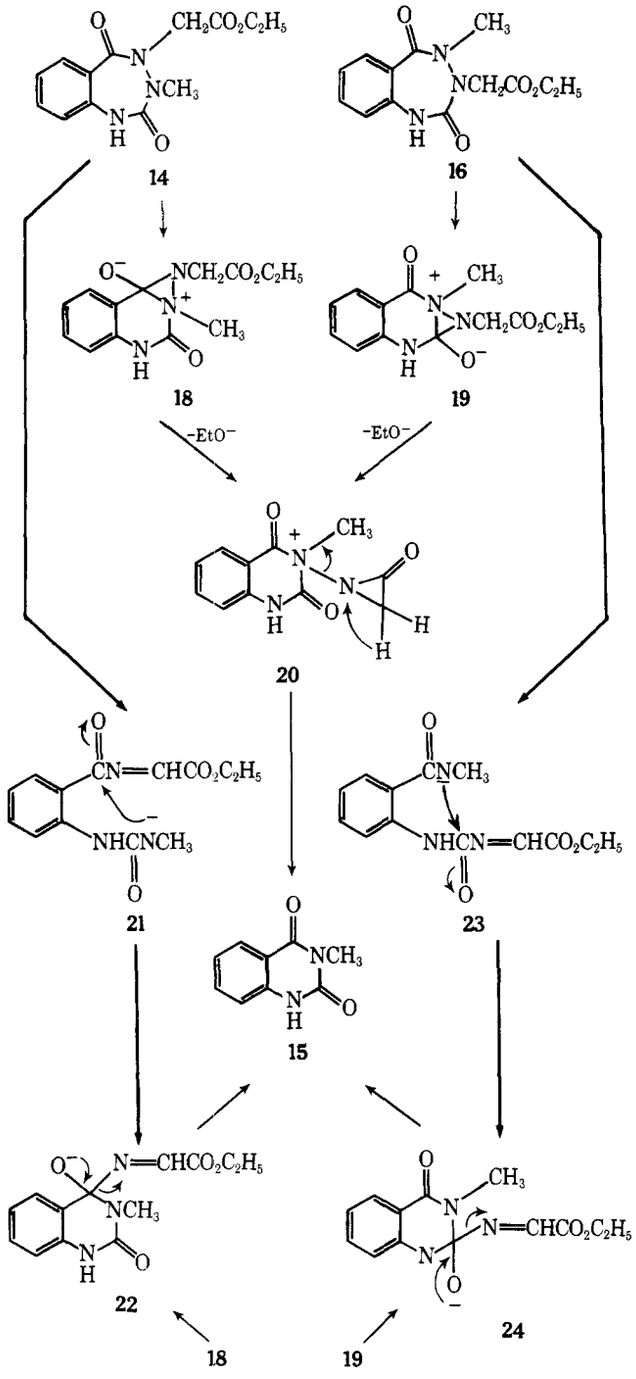
for the conversions of **14** and **16** to **15**. One set of mechanistic pathways avoids the intermediacy of acyclic precursors and invokes the aziridinone **20** as a common intermediate, which could arise from diazirine intermediates **18** and **19**, and which could liberate the constituents of HCN and CO to yield quinazolinedione **15**. Alternatively, methylene proton abstraction could lead to acyclic intermediates **21** and **23**, which then could reclose to the six-membered intermediates **22** and **24**. These latter intermediates could also arise from intermediates **18** and **19**, respectively. Extrusion of the imine salt of ethyl glyoxylate from intermediates **22** and **24** would then yield quinazolinedione **15**. It is clear that the mechanisms for these transformations involve the carbethoxymethyl group in some special manner, as do the mechanisms depicted in Scheme III, since no ring contraction reactions were observed with other monoalkylated derivatives of **1** or **2** under the same reaction conditions.

It was necessary for us to verify that quinazolinedione **15** was being produced in situ from benzotriazepinediones **14** and **16**. Experiments which strongly suggested this were alkylations of **1** and **2** with ethyl bromoacetate at a low, controlled temperature (10 °C). In these reactions, the major products were the unrearranged, alkylated benzotriazepinediones **14** and **16**, which were obtained in 69 and 64% yields, respectively. These reactions supplied sufficient quantities of **14** and **16** for subsequent experiments which established the intermediacy of these compounds in the formation of quinazolinedione **15** in the original alkylations. Treatment of **14** and **16** with equivalent amounts of sodium hydride in dimethylformamide at 90–100 °C for 2 h produced **15** in isolated yields of 82 and 88%, respectively.

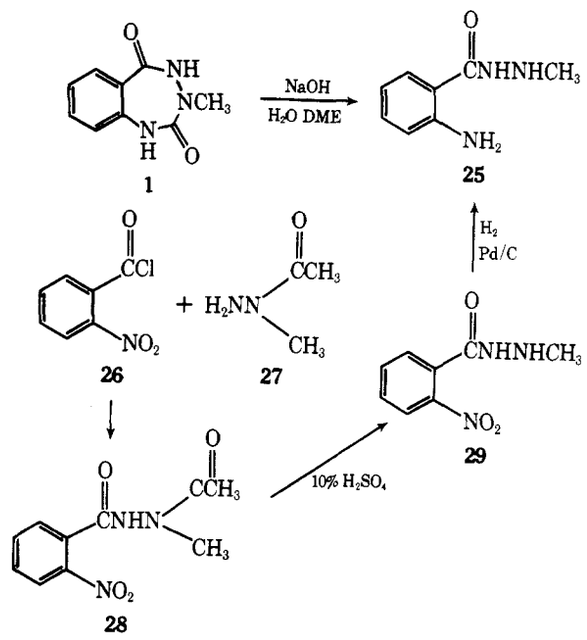
Recently reported dihydro-5*H*-1,3,4-benzotriazepin-5-ones[3,4] have been shown to undergo base-induced rearrangements to quinazolinones.[5] A review of ring contraction reactions of seven-membered ring heterocycles,[6a] including a recent report on the ring contraction of a benzo-1,2,5-triazepin-4-one,[6b] has appeared.

We have also examined the reactions of benzotriazepines **1** and **2** with aqueous base. Simple hydrolytic cleavage appears

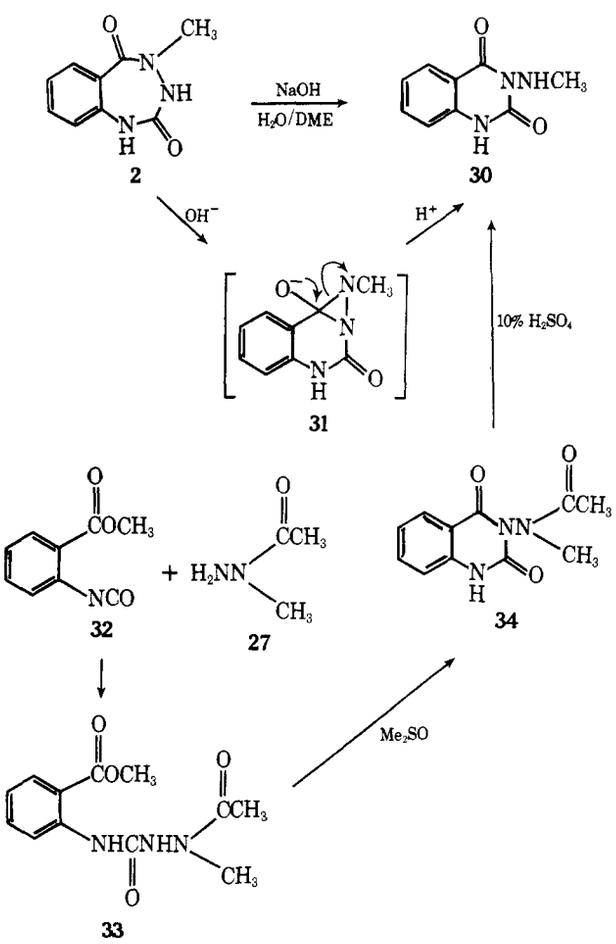
Scheme III



Scheme IV



Scheme V



to account for the formation of 2-(*o*-aminobenzoyl)-1-methylhydrazine (**25**) from **1**. The identity of **25** was established by comparison with an authentic sample, whose synthesis[7] is shown in Scheme IV. Acylation of 1-acetyl-1-methylhydrazine (**27**) with *o*-nitrobenzoyl chloride (**26**) gave hydrazide **28**, which was hydrolyzed with dilute sulfuric acid to produce **29**. Catalytic reduction of **29** gave **25**.

Treatment of **2** with aqueous base resulted in its rearrangement to 3-methylamino-2,4(1*H*,3*H*)-quinazolinedione (**30**). A possible intermediate (**31**) in this transformation is shown in Scheme V, which is reminiscent of intermediates **18** and **19** in the rearrangements of **14** and **16** to **15**.

Our preparation of an authentic sample of quinazolinedione **30** demonstrates once again the utility of 1-acetyl-1-methylhydrazine (**27**) in heterocyclic synthesis.[7] Treatment of 2-carbomethoxyphenyl isocyanate (**32**) with **27** gave semicarbazide **33**. A good method for the quantitative conversion of **33** to quinazolinedione **34** presented itself while we were recording the NMR spectrum of **33** in dimethyl sulfoxide-d_6. The conversion of **33** to **34** in dimethyl sulfoxide at room temperature was easily followed by NMR spectroscopy, and was 60% complete after 30 min, and 90% complete after 2.5 h. The disappearance of the three methyl singlets of **33** was accompanied by the appearance of a methanol signal and two pairs of singlets for the methyl groups of **34**. The pairs of sin-

glets indicated restricted rotation about the acetyl–nitrogen or nitrogen–nitrogen bond in **34**. It was also observed that **33** thermally cyclized to **34** at its melt temperature (180–182 °C). The final step in the preparation of authentic **30** was accomplished by removal of the acetyl group in **34** with 10% sulfuric acid.

The NMR spectra of alkylated 1,3,4-benzotriazepin-5-ones bearing substituted methylene groups, i.e., ethyl, benzyl, carbethoxymethyl, or 2-(dimethylamino)ethyl groups, at positions 1, 3, or 4, showed the methylene protons to be distinctly nonequivalent (see Experimental Section). For example, the chemical shift difference for the methylene protons in **6** is greater than 1 ppm. In contrast to this observation, the methylene group in quinazolinedione **17** appears as a singlet. The NMR spectrum of compound **11** was particularly interesting in that the nonequivalence of the methylene protons attached to the ring caused the methylene group adjacent to the dimethylamino group to appear as a pair of doublets (A_2 of A_2XY pattern where $J_{AY} = 7$ and $J_{Ax} = 6$ Hz).

Experimental Section[8]

4-Ethyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4). To a mixture of 0.960 g (40.0 mmol) of NaH in 25 mL of dimethylformamide (DMF) was added 7.64 g (40.0 mmol) of **1**. After 5 min, 6.24 g (40.0 mmol) of ethyl iodide was added to the clear solution. The addition was exothermic, and the temperature of the reaction solution rose to 80 °C. After 4 h, the solution was poured into water and extracted with several portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), concentrated, and diluted with ether. The resulting solid was collected and air dried to afford 5.76 g (65%) of **4**: mp 128–130 °C; mp 129–130 °C (CH_2Cl_2–hexane); IR (Nujol) 3225 (NH), 1685 (C=O), 1645 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.65 (s, 1, NH), 8.10–7.17 (m, 4, aromatic), 4.70–3.98 (d of q, Y of A_3XY pattern, $J_{XY} = 14.5$, $J_{AY} = 7.5$ Hz, 1, one CH_2 proton), 3.83–3.12 (d of q, X of A_3XY pattern, $J_{XY} = 14.5$, $J_{AX} = 7.5$ Hz, 1, one CH_2 proton), 3.03 (s, 3, NCH_3), 1.17 (t, A_3 of A_3XY pattern, $J_{AX} = J_{AY} = 7.5$ Hz, 3, CH_2CH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.55; H, 6.02; N, 19.23.

1,4-Diethyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (5). To a mixture of 0.300 g (12.5 mmol) of NaH in 20 mL of DMF was added 1.19 g (6.25 mmol) of **1**. After 5 min, 3 mL of ethyl iodide was added (exothermic). After 2 h the solution was diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and concentrated to leave 980 mg of thick oil. Trituration with ether afforded 800 mg (52%) of **5**: mp 98–99 °C; IR (Nujol) 1675 (C=O) and 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.20 (m, 4, aromatic), 4.70–3.18 (m, 4, both CH_2 groups), 2.04 (s, 3, NCH_3), 1.10 (t, $J = 7.5$ Hz, 6, both CH_2CH_3 groups).

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.00; H, 6.98; N, 17.05.

3,4-Dihydro-3-methyl-4-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (6) and 3,4-Dihydro-3-methyl-1,4-bis(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (7). To a mixture of 0.384 g (16.0 mmol) of NaH in 25 mL of DMF was added 2.87 g (16.0 mmol) of **1**. After 5 min, 2.57 g (15.0 mmol) of benzyl bromide was added (exothermic). After 15 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to a thick oil which crystallized upon standing to yield 2.80 g (66%) of **6**: mp 147–148 °C; mp 150–151 °C (ethanol); IR (Nujol) 3240 (NH), 1690 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.05–7.87 (d of d, $J_{ortho} = 7$, $J_{meta} = 2$ Hz, 1, H ortho to C=O), 7.78 (s, 1, NH, D_2O exchangeable), 7.50–7.03 (m, 7, aromatic), 6.90–6.74 (d of d, $J_{ortho} = 7$, $J_{meta} = 1.5$ Hz, 1 aromatic), 5.50 (d, $J = 16$ Hz, 1, one CH_2 proton), 4.42 (d, $J = 16$ Hz, 1, one CH_2 proton), 2.97 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.00; H, 5.49; N, 15.04.

When the above experiment was performed with a 25% excess of NaH,[9] workup afforded an oil from which preferentially crystallized, in 24% yield, compound **7**: mp 173–174 °C; IR (Nujol) 1670 (C=O), 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.03–6.85 (m, 14, aromatic), 5.48 (d, $J = 16$ Hz, 1, one 1-benzyl CH_2 proton), 4.79 (s, 2, 4-benzyl CH_2 group), 4.69 (d, $J = 16$ Hz, 1, one 1-benzyl CH_2 proton), 3.07 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.70; H, 5.89; N, 11.24.

3-Ethyl-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (8). To a mixture of 0.960 g (40.0 mmol) of NaH in 15 mL of DMF was added 7.60 g (39.8 mmol) of **2**. To the slurry, after 5 min of stirring, was added 6.24 g (40.0 mmol) of ethyl iodide (exothermic). After 3 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to a small volume. The white, crystalline product which formed was collected to yield 6.65 g (76%) of **8**: mp 186–188 °C; IR (Nujol) 3270 (NH), 1700 cm^{-1} (C=O); NMR ($Me_2SO$$d_6$) δ 9.72 (s, 1, NH), 8.08–7.13 (m, 4, aromatic), 3.90–2.94 (m, 5, NCH_3 and NCH_2CH_3, with NCH_3 s at 3.16), 0.94 (t, $J = 7.2$ Hz, 3, NCH_2CH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.50; H, 5.91; N, 19.01.

1,3-Diethyl-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (9). To a mixture of 0.349 g (14.2 mmol) of NaH in 20 mL of DMF was added 1.20 g (6.28 mmol) of **2**. To the slurry, after 5 min of stirring, was added an excess (3.2 mL) of ethyl iodide (exothermic). After 3 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to an oil which crystallized upon trituration with ether to yield 1.14 g (73%) of **9**: mp 77–79 °C; IR (Nujol) 1680 (C=O) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.17–7.23 (m, 4, aromatic), 4.30–3.00 (m, 7, both CH_2 groups and NCH_3 group, with NCH_3 s at 3.17), 1.14 (t, $J = 7.2$ Hz, 3, NCH_2CH_3), 0.87 (t, $J = 7.2$ Hz, 3, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.00; H, 6.85; N, 17.11.

3,4-Dihydro-4-methyl-3-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (10). To a mixture of 0.900 g (37.5 mmol) of NaH in 15 mL of DMF was added 5.74 g (30.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 5.13 g (30.0 mmol) of benzyl bromide (exothermic). After 3 h the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to yield a white solid which was recrystallized from CH_2Cl_2–hexane to yield 5.70 g (68%) of **10**: mp 183–184 °C; IR (Nujol) 3240 (NH), 1695 (C=O), 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.87 (s, 1, NH), 7.98–7.05 (m, 9, aromatic), 4.95 (d, $J = 15$ Hz, 1, one CH_2 proton), 4.46 (d, $J = 15$ Hz, 1, one CH_2 proton), 3.23 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.50; H, 5.34; N, 14.85.

3-[2-(Dimethylamino)ethyl]-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (11). To a mixture of 2.00 g (83.3 mmol) of NaH in 25 mL of DMF was added 5.74 g (30.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 4.32 g (30.0 mmol) of 2-dimethylaminoethyl chloride hydrochloride (Aldrich) in portions. The addition was exothermic and the temperature was controlled below 35 °C. After stirring overnight, the solution was diluted with water and extracted with CH_2Cl_2. The combined extracts were concentrated to a light oil which was taken up in ether and treated with HCl gas. The resulting white, hygroscopic material was partitioned between CH_2Cl_2 and 20% NaOH. The organic layer was dried (Na_2SO_4) and concentrated to yield ca. 2 g of light oil from which crystallized, upon trituration with ether, compound **11** (mp 154–156 °C): mp 158–159°C (CH_2Cl_2–hexane); IR (Nujol) 3250 (NH), 1690 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.03–7.87 (m, 1, H ortho to C=O, 7.56–7.07 (m, 3, NH and 2 aromatic protons), 7.04–6.87 (m, 1, H ortho to NH), 4.17–3.79 (d of t, Y of A_2XY pattern, $J_{AY} = 7$, $J_{XY} = 14.5$ Hz, 1, one ring-adjacent CH_2proton), 3.49–3.12 (d of t, X of A_2XY pattern, $J_{AX} = 6$, $J_{XY} = 14.5$ Hz, 1, one ring-adjacent CH_2 proton), 3.33 (s, 3, NCH_3), 2.50–2.20 [d of d, A_2 of A_2XY pattern, $J_{AX} = 6$, $J_{AY} = 7$ Hz, 2, $CH_2N(CH_3)_2$], 2.07 [s, 6, $N(CH_3)_2$]; mass spectrum (70 eV, chemical ionization, methane) m/e 263 ($M^+ + 1$), 291 ($M^+ + 29$).

Anal. Calcd for $C_{13}H_{18}N_4O_3$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.30; H, 6.97; N, 21.41.

3-Ethyl-3,4-dihydro-4-methyl-1-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (12). To a mixture of 0.619 g (25.8 mmol) of NaH in 25 mL of DMF was added 5.65 g (25.8 mmol) of **8**. To the slurry, after 5 min of stirring, was added 4.41 g (25.8 mmol) of benzyl bromide (exothermic). After 15 h, the solution was concentrated and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated to leave 7.98 g (100%) of **12** as a colorless oil: IR (Nujol) 1660 cm^{-1} (broad C=O); NMR ($CDCl_3$) δ 8.03–7.75 (m, 1, H ortho to C=O), 7.60–7.00 (m, 8, remaining aromatic), 5.23 (d, $J = 7.5$ Hz, 1, one benzyl CH_2 proton), 4.75 (d, $J = 7.5$ Hz, 1, one benzyl CH_2 proton), 3.87–3.08 (m, 5, NCH_2CH_3 and NCH_3 s at 3.30), 1.03 (t, $J = 7$ Hz, 3, NCH_2CH_3); mass spectrum (70 eV) m/e 309 (molecular ion).

4-Ethyl-3-methyl-2-(1-pyrrolidinyl)-3*H*-1,3,4-benzotriaze-

pin-5(4*H*)-one (13). To a solution of 4.38 g (20.0 mmol) of **4** in 50 mL of CH_2Cl_2 under a nitrogen atmosphere was added 20 mL (0.200 mol) of 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2 (Aldrich). After 24 h at room temperature, the solution was concentrated and the residual oil was reconstituted in 200 mL of absolute ethanol. Excess (20 g) pyrrolidine was added and the solution was heated at reflux for 15 h. The solution was concentrated and a CH_2Cl_2 solution of the residue was washed with water and then extracted with aqueous hydrochloric acid. The aqueous layer was neutralized with sodium hydroxide and extracted with CH_2Cl_2 to leave, after drying (Na_2SO_4) and concentration, 2.34 g of oil. GLC (5% SE-30, 5 ft × 0.125 in., 250 °C, 30 mL/min of He) indicated two well-separated components (1.4 and 3.7 min) as did TLC. A 2.07-g quantity of the oil was applied to 120 g of alumina (Fisher A-540) and eluted with 1 L of ether to cleanly remove the component which eluted at 3.7 min by GLC. Concentration of the ether solution afforded 0.820 g of oil which crystallized upon trituration with ether–hexane to yield **13** as a white solid: mp 71–72 °C; IR (Nujol) 1655 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.08–7.80 (m, 1, H ortho to C=O), 7.57–6.87 (m, 3, remaining aromatic), 4.18–3.27 (m, 6, CH_2NCH_2 and NCH_2CH_3), 2.70 (s, 3, NCH_3), 2.31–1.83 (m, 4, $NCH_2CH_2CH_2$), 1.32 (t, J = 7.2 Hz, 3, NCH_2CH_3); mass spectrum (70 eV) m/e 272 (molecular ion).

Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 65.90; H, 7.45; N, 20.26.

The remaining component was cleanly removed from the column by elution with ethyl acetate, but it was not identified.

Alkylation of 1 with Ethyl Bromoacetate. To a mixture of 0.960 g (40.0 mmol) of NaH in 25 mL of DMF was added 7.64 g (40.0 mmol) of **1**. To the slurry, after 5 min of stirring, was added 6.68 g (40.0 mmol) of ethyl bromoacetate, dropwise. The temperature of the reaction mixture during the exothermic addition was kept at 50–55 °C. After 2.5 h, the red solution was poured into water. A 500-mg quantity of **1**, which was soluble in neither phase, was recovered by filtration. (Concentration of the aqueous phase afforded an additional 295 mg of **1**.) The organic phase was dried (Na_2SO_4) and concentrated to leave 11.9 g of semisolid from which was removed, by filtration, 1.19 g of 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**): mp 233–235 °C (CH_2Cl_2) (lit. mp 236[10] and 236–238 °C[11]); IR (Nujol) 1715 (C=O), 1665 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.85 (m, 1, H ortho to C=O), 7.85–7.52 (m, 1, aromatic), 7.38–7.05 (m, 2, aromatic), 3.30 (s, 3, CH_3); mass spectrum (70 eV) m/e 176 (molecular ion).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.50; H, 4.51; N, 16.04.

From an ether solution of the filtrate was obtained, by crystallization, 2.07 g of 1,2,3,5-tetrahydro-3-methyl-2,5-dioxo-4*H*-1,3,4-benzotriazepine-4-acetic acid ethyl ester (**14**, mp 137–139 °C): mp 138–140 °C (ethanol–hexane); IR (Nujol) 3300 (NH), 1730 (ester C=O), 1705 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.10–7.84 (m, 2, NH and H ortho to C=O), 7.63–6.90 (m, 3, aromatic), 4.80 (d, J = 18 Hz, 1, one NCH_2 proton), 4.28 (d, J = 18 Hz, 1, one NCH_2 proton), 4.27 (q, J = 7.2 Hz, 2, OCH_2), 1.30 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 277 (molecular ion).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.10; H, 5.41; N, 14.96.

When the alkylation was performed with 4.59 g (24.0 mmol) of **1**, 0.660 g (27.5 mmol) of NaH, and 4.59 g (27.5 mmol) of ethyl bromoacetate, and the reaction temperature was controlled at 10–13 °C, workup as above afforded 3.72 g (69%) of **14**.

Alkylation of 2 with Ethyl Bromoacetate. To a mixture of 0.700 g (29.2 mmol) of NaH in 20 mL of DMF was added 4.59 g (24.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 4.80 g (28.7 mmol) of ethyl bromoacetate. The addition was exothermic and the reaction temperature was not controlled. The red solution was stirred at room temperature for 2.5 h, diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to a small volume. Filtration afforded 815 mg of **17**. An ether solution of the filtrate yielded 950 mg of 2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1*H*-1,3,4-benzotriazepine-3-acetic acid ethyl ester (**16**): mp 146–148 °C (ethanol–hexane); IR (Nujol) 3250 (NH), 1750 (ester C=O), 1690 (C=O), 1630 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.77 (s, 1, NH), 8.17–7.17 (m, 4, aromatic), 4.67 (d, J = 18 Hz, 1, one NCH_2 proton), 4.42 (d, J = 18 Hz, 1, one NCH_2 proton), 4.12 (q, J = 7.2 Hz, 2, OCH_2), 3.30 (s, 3, NCH_3), 1.08 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 277 (molecular ion).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.50; H, 5.49; N, 15.13.

The ether filtrate subsequently yielded 200 mg of 1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-quinazolineacetic acid ethyl ester (**17**, mp 128–130 °C); mp 132–133 °C (ethanol–hexane); IR (Nujol) 1740 (ester C=O), 1705 (C=O), 1670 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.43–8.15 (m, 1, H ortho to C=O), 8.15–7.78 (m, 1, aromatic), 7.72–7.34 (m, 2, aromatic), 5.09 (s, 2, NCH_2), 4.32 (q, J = 7.2 Hz, 2, OCH_2), 3.42 (s, 3, NCH_3), 1.27 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 262 (molecular ion).

When the alkylation was repeated with 4.59 g (24.0 mmol) of **2**, 0.900 mol (37.5 mmol) of NaH, and 4.95 g (29.6 mmol) of ethyl bromoacetate, and the reaction temperature was controlled at 10–13 °C, workup as above afforded 3.52 g (64%) of **18** and 0.800 g (13%) of **17**.

Preparation of 15 from 14 and 16. To a solution of 0.500 g (1.80 mmol) of **14** in 25 mL of DMF was added 0.480 g (2.00 mmol) of NaH and the mixture was heated in an oil bath at 90–100 °C for 2 h. The solution was cooled, diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was washed with ether to afford 0.260 g (82%) of **15**, mp 235–239 °C. On the same scale was prepared **15** (mp 238–240 °C) from **16** in 88% yield.

Treatment of 1 with Aqueous Base. A 1.00-g (5.23 mmol) quantity of **1** was dissolved in a mixture of 10 mL of 2 N NaOH solution and 10 mL of dimethoxyethane and heated at reflux for 2 h. The solution was diluted with 125 mL of water and acidified with concentrated HCl. A crop of white crystals afforded, after filtration and drying, 0.26 g of **1**. The filtrate was made basic with $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to yield 0.38 g of material which was slurried with ether and filtered to remove an additional 40 mg of **1** (20% total yield). The filtrate, by evaporative crystallization from ether–hexane, afforded 150 mg (17%) of 2-aminobenzoic acid 2-methylhydrazide (**25**), mp 70–77 °C (lit.[7] mp 90–91 °C), whose IR (Nujol) and NMR ($CDCl_3$) spectra were identical with those of authentic **25**.[7] A mass spectrum (70 eV) of **25** displayed a molecular ion at m/e 165.

Treatment of 2 with Aqueous Base. A 1.00-g (5.23 mmol) quantity of **2** was dissolved in 10 mL of 2 N NaOH solution and 10 mL of dimethoxyethane and heated at reflux for 2 h. The solution was cooled, acidified with concentrated HCl, and basified with $NaHCO_3$ solution. Extraction with CH_2Cl_2 removed, after drying (Na_2SO_4) and concentrating the combined extracts, 0.45 g of oil which, when triturated with ether–ethanol, afforded 100 mg (10%) of 3-(methyl)-amino-2,4(1*H*,3*H*)-quinazolinedione (**30**), mp 186–188 °C, which was spectrally identical with an authentic sample whose preparation follows.

2-{[(2-Acetyl-2-methylhydrazino)carbonyl]amino}benzoic Acid Methyl Ester (33). To a stirring solution of 8.86 g (0.500 mol) of 2-carbomethoxyphenyl isocyanate[12] in 50 mL of CH_2Cl_2 with ice-bath cooling was added 4.41 g (0.500 mol) of 1-acetyl-1-methylhydrazine.[7] After 30 min at room temperature, the solution was concentrated to a small volume and the resulting solid was collected and air dried to yield 12.9 g (97%) of **33**: mp 180–182 °C, followed by resolidification and remelt at 291–293 °C (2-propanol); IR (Nujol) 3270 and 3230 (NH), 1715 (ester C=O), 1695 (amide C=O), 1640 cm^{-1} (semicarbazide C=O); NMR ($CDCl_3$) δ 10.90 (s, 1, NH), 8.60–8.43 (m, 1, aromatic), 8.08–7.80 (m, 1, aromatic), 7.80 (s, 1, NH), 7.64–7.30 (m, 1, aromatic), 7.16–6.84 (m, 1, aromatic), 3.87 (s, 3, OCH_3), 3.29 (s, 3, NCH_3), 2.20 (s, 3, $COCH_3$).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.60; H, 5.65; N, 15.55.

***N*-(1,4-Dihydro-2,4-dioxo-3(2*H*)-quinazolinyl)-*N*-methylacetamide (34).** A 3.75-g (14.1 mmol) quantity of **33** was dissolved in 20 mL of dimethyl sulfoxide, warmed at 60 °C for 30 min, and allowed to stand at room temperature for 15 h. With the addition of a small volume of water, crystallization commenced to yield, after collection, washing with water, and air drying, 3.30 g (100%) of **34**: mp 291–293 °C (ethanol); IR (Nujol) 3270 and 3220 (NH), 1730 (C=O), 1685 (C=O), 1665 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.44 (m, 1, aromatic), 7.74–7.50 (m, 1, aromatic), 7.40–7.04 (m, 2, aromatic), 3.24 and 3.10 (2 singlets, in a ratio of ca. 1:2.5, respectively, 3, NCH_3), 2.18 and 1.80 (2 singlets, in a ratio of ca. 1:2.5, respectively, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.70; H, 4.79; N, 18.17.

Preparation of 30 from 34. A 3.30-g (12.4 mmol) quantity of **34** in 60 mL of 10% H_2SO_4 was heated at reflux for 15 h. The clear solution was cooled and neutralized with cold, dilute NaOH solution. The precipitate which resulted was collected and air dried to yield 2.10 g (89%) of **30** (mp 194–196 °C): mp 195–196 °C (ethanol); IR (Nujol) 3400–3000 (broad NH), 1720 (C=O), 1670 cm^{-1} (C=O); NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.20–7.97 (m, 1, H ortho to C=O), 7.78–7.00 (m, 3, remaining aromatic), 5.63 (broad signal, 1, NH, D_2O exchangeable), 2.84 (broad s, 3, CH_3).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C,

56.31; H, 4.60; N, 21.70.

Registry No.—**1**, 55043-79-3; **2**, 55043-81-7; **4**, 62493-12-3; **5**, 62493-13-4; **6**, 62493-14-5; **7**, 62493-15-6; **8**, 62493-16-7; **9**, 62493-17-8; **10**, 62493-18-9; **11**, 62493-19-0; **12**, 62493-20-3; **13**, 62493-21-4; **14**, 62493-22-5; **15**, 607-19-2; **16**, 62493-23-6; **17**, 62493-24-7; **25**, 59169-47-0; **27**, 3530-13-0; **30**, 62493-25-8; **32**, 1793-07-3; **33**, 62493-26-9; **34**, 62493-27-0; ethyl iodide, 75-03-6; benzyl bromide, 100-39-0; 2-dimethylaminoethyl chloride HCl, 4584-46-7; pyrrolidine, 123-75-1; ethyl bromoacetate, 105-36-2.

References and Notes

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Cycliacylation Studies on 3,5-Disubstituted Phenylalkanoic Acids[1]

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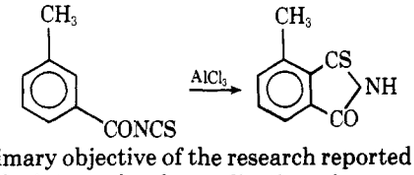
Received December 21, 1976

The syntheses of 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**) are described. The ring closure of these acids to mixtures of 6,8-disubstituted tetralones and 5,7-disubstituted indanones by five reagents (anhydrous HF, polyphosphoric acid, $AlCl_3$ on RCOCl in benzene and in nitroethane, and $SnCl_4$ on RCOCl in benzene) were studied. For acids **1** and **7**, ring closure took place predominantly (2:1) at the position para to the chlorine. For acids **4** and **10**, ring closure took place predominantly (66–91%) para to the methoxy group.

Relatively little systematic study has been made on preferential intramolecular Friedel–Crafts-type acylation reactions. The cases studied include mainly the cyclization of dibasic acids which gave six-membered ring compounds in preference to five- and seven-membered rings,[3] and monobasic acids which can react with either of two different rings or with one ring in two different locations.[3] One interesting such reaction involves the cyclization of *m*-tolyl isothiocyanate exclusively to 2a-thio-3-methylphthalimide[4] although the para position is available.



The primary objective of the research reported herein was to study the intramolecular cyclization of unsymmetrical 4-(3,5-disubstituted phenyl)butanoic acids to isomeric 6,8-disubstituted tetralones. We hoped to learn something about the relative directive influence of substituents on the aromatic ring in cyclization experiments and about the effect of cyclizing reagent on the proportions of isomers found. The products obtained might provide new intermediates for the synthesis of trisubstituted naphthalenes desired as starting materials in certain projected syntheses. As the work progressed, we included studies on the cyclization of unsymmetrical 3-(3,5-disubstituted phenyl)propanoic acids to yield isomeric 5,7-disubstituted indanones because, by so doing, the effects in ring closures to five-membered rings might be compared to the effects in six-membered rings. The substituents chosen for study involved methyl vs. chlorine and methyl vs. methoxy.

To fulfill the above objectives, we synthesized 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**). All were cyclized to the tetralones and indanones shown in Scheme I.

The cyclizations of the acids were accomplished by means of the following reagents: (A) hydrogen fluoride, (B) polyphosphoric acid (PPA), (C) aluminum chloride in benzene using acid chloride, (D) aluminum chloride in nitroethane using acid chloride, and (E) stannic chloride in benzene using acid chloride. The results are summarized in Table I.

The results listed in Table I show that the proportions of isomers formed are essentially the same in comparable cases when a five- or six-membered ring ketone was formed. Furthermore, there is very little effect on the proportions of isomers formed when the cyclization conditions were changed. In the cases of both the chloro- and methoxy-substituted compounds, the reagent which gave the least selectivity was the action of aluminum chloride on the acid chloride in benzene. This lack of selectivity was more pronounced in the methoxy compounds than in the chloro compounds. The best selectivity was obtained with the methoxy compounds using aluminum chloride in nitroethane to give products in which the ketone function was produced by cyclization para to the methoxy group.

The proportions of isomeric ketones formed in each case represents the resultant of a number of parameters which must relate to the tendencies to react para to one function and ortho to the other. Since no quantitative data relating to ortho substitution in Friedel–Crafts acylations are at hand, no attempt to calculate the expected ratios was made.