Substituted Derivatives of 3a,4,5,6-Tetrahydrosuccinimido[3,4-b]acenaphthen-10-one.II.[1]

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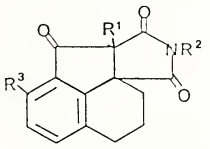
Introduction

The preparation and biological activity of a number of derivatives of 3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (1a) have recently been reported (2). Compound 1a served as a lead compound, since it had interesting biological activity (1). It was therefore interesting to prepare various derivatives for further biological screening. In the first report (2) we described compounds of structure 1, where substitution on nitrogen, R^2, included a variety of pharmacophoric groups, and substitution on the aromatic ring at R^3 included methyl and methoxy groups. We wish to report here compounds of structure 1, where R^3 is H, R^2 is H or CH_3, and R^1 may be methyl, ethyl or allyl.

Figure 1.



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a. R^1= H, R^2= H, R^3= H
b. R^1= CH_3, R^2= H, R^3= H
c. R^1= C_2H_5, R^2= H, R^3= H
d. R^1= H, R^2= CH_3, R^3= H
e. R^1= CH_3, R^2= CH_3, R^3= H
f. R^1= C_2H_5, R^2= CH_3, R^3= H
g. R^1= C_3H_6, R^2= CH_3, R^3= H

We have shown that cyanide ion adds smoothly *via* a Michael reaction to indenone 2 to form the cyanide adduct 3 in high yield (1,2) (Scheme 1). The obvious approach to the synthesis of compounds 1, with substituents at the 10a position (e.g., 1b or 1c) would involve alkylation of the anion derived from 3, which has an acidic α-hydrogen. Indeed, this anion is an intermediate in the Michael addition, and could be alkylated directly, to provide a one-step conversion of 2 to 4 (Scheme 1). However, Koelsch (6) has reported that all attempts to alkylate the cyanide adduct of ethyl 3-phenyl-1-indenone-2-carboxylate were unsuccessful. However, alkylation of intermediate anions derived from Michael addition of cyanide to acyclic unsaturated compounds have been reported (4,7). Koelsch (6) attributed failure of alkylation to the fact that the intermediate anion is a weak base, in which the anion site is flanked by bulky groups. He noted that mono-tertiary alkylated malonic and acetoacetic esters are resistant to alkylation.

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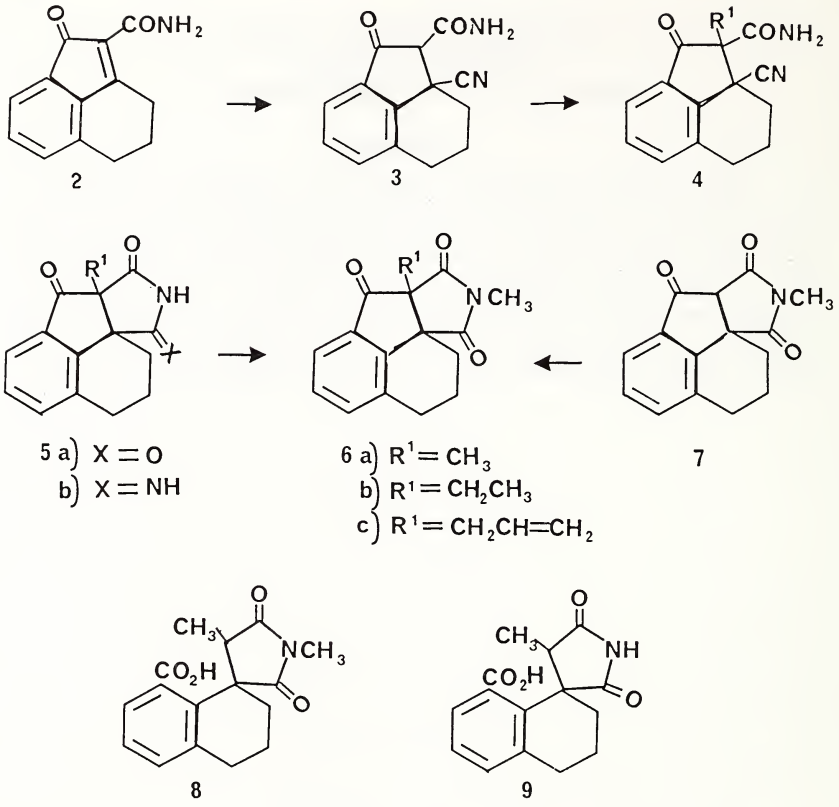
[1] Taken in part from a thesis submitted to Indiana University by D.A.T. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, September, 1968. This work was supported in part by a grant from Bristol Laboratories, Syracuse, NY.

SCHEME 1.



Discussion

We have found that the anion of 3, formed by addition of cyanide to 2, may be alkylated in good yield in several polar solvents. Thus a mixture of 2 and sodium cyanide in DMSO (dimethylsulfoxide), DMF (dimethylformamide) or *t*-butyl alcohol/water mixture, treated with methyl iodide produced 4a ($R^1 = CH_3$) in yields ranging from 53% to 85%. However, attempts to methylate the anion of 3 with dimethyl sulfate in DMSO or DMF were unsuccessful.

On melting at 214-217°, compound 4a was found to resolidify and melt again at 251-254°. This product was shown to be isomeric with 4a, and was assigned the iminopyrrolidine structure 5b ($R^1 = CH_3$) on the basis of its spectral characteristics and ready hydroylsis to 5a ($R^1 = CH_3$). The propensity for cyclization of 4a to 5b on heating, coupled with the pmr spectrum of 4a which showed only one methyl singlet, indicate that the addition of cyanide and alkylation proceed in a nearly exclusive *trans* manner to give an adduct in which cyanide and carbamoyl functions are *cis*-oriented. It should be noted that this ready cyclization exhibited by 4a on heating was not observed with other Michael adducts.

The desired 10a-alkylated derivatives of 1 were prepared by the acid-catalyzed cyclization of compounds 4 (1). Since compound 1a has an active hydrogen at the 10a position, it should also be possible to alkylate the parent 1a. However, it would be necessary to

block the acidic imide hydrogen, which is readily methylated (3) to produce compound 7. Treatment of 7 with sodium hydride and an alkylating agent gave the 10a-alkylated 2-methyl derivatives 6. Compounds 5a could also be methylated on nitrogen to produce 6.

An attempt was made to prepare 6a directly by dimethylation of compound 1a, using a three-fold excess of sodium hydride, followed by excess methyl iodide. When the reaction mixture was hydrolyzed, the dimethyl derivative 6a did not precipitate, but acidification of the hydrolysate led to the isolation of a crystalline acid, 8, as evidenced by elemental analysis and spectral properties. This same acid was produced when 6a was treated with sodium hydroxide in aqueous tetrahydrofuran, the result of characteristic acid cleavage of β-ketoacid derivatives (5). The isolation of 8 from 1a indicates that dimethylation had occurred before acid cleavage by excess base present. Solution of 5a ($R^1 = CH_3$) in aqueous potassium hydroxide, followed by acidification, produced the spiro acid derivative 9. This fascile acid cleavage of these fused-ring β-ketoamides may be facilitated by relief of strain in these systems, as well as the known ease of cleavage of α, α-disubstituted β-ketoacid derivatives (5).

Pharmacological Results

Compounds 4a-g, 5a ($R^1 = CH_3$ and $R^1 = C_2H_5$), 6a-c, 7 and 8 were submitted to Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, NY, for pharmacological evaluation.[2]

Although none of the compounds exhibited anticonvulsant activity, other activities were observed. Compounds 4c (R = allyl), 5a ($R^1 = C_2H_5$), 6a and 8 were found to inhibit gastric secretion in rats when administered intraperitoneally, and compound 6b demonstrated smooth muscle relaxant activity *in vitro*.

The modifications of structure 1 described here and earlier (2), in which different substituents have been placed at R^1, R^2 and R^3 have all led to compounds inactive as anticonvulsants. Lack of activity of these derivatives indicates that a high degree of specificity is inherent in the activity of 1a. Lack of activity in the N-alkylated derivatives clearly indicates need for a free imide hydrogen. However, the lack of activity in derivatives of 5a is surprising, since the imide ring projects approximately 70° out of the plane of the nearly planar acenaphthenone ring system and the newly introduced alkyl groups are projecting in the opposite direction.

Experimental

All melting points were determined in open capillary tubes with a Mel-Temp heating block and are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, IN. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 137 Infracord, and were calibrated with polystyrene. Ultraviolet spectra were determined in 95% ethanol with a Bausch and Lomb Spectronic 505 Recording Spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer in indicated solvents using tetramethylsilane as an internal standard, except when hexadeuteriodimethyl-sulfoxide was the solvent, sodium 2,2-dimethyl-2-silapentane 5-sulfonate (DDS) was used as the standard.

2-Carbamoyl-2-methyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4a, $R^1 = CH_3$).

A mixture of indenone 2 (5 g, 23.5 mmoles) prepared as previously reported (1), and sodium cyanide (1.5 g, 30.8 mmoles) in DMSO (35 mL) was warmed on a steam bath

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[2] We are indebted to Dr. M.H. Pindell of Bristol Laboratories for supplying selected preliminary test data.

to give a deep red solution. The solution was cooled and treated with methyl iodide (10 g). After 48 hr the reaction mixture was diluted with 250 mL of water and the excess methyl iodide was removed on a steam bath. The solution was cooled and the resulting precipitate was collected by filtration to give 4a (5.05 g, 85%). An analytical sample of 4a (white plates) was obtained by recrystallization from 95% ethanol: mp 214-217°, solidified and remelted 251-254°; ir 2.95 and 3.19 (NH_2), 3.39 (CH), 4.47 (CN), 5.83 (CO), 5.94 ($CONH_2$), and 6.29 μ (aromatic); uv (λ max) 211 (ϵ 22,800), 261 (ϵ 13,500), and 300 mμ (ϵ 3,160); pmr (DMSO-d_6) δ 7.66 (5H, multiplet, aromatic and amide), 3.15-2.05 (methylene multiplet obscured by DMSO), and 1.30 (3H, singlet, methyl).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.77; H, 5.77; N, 11.25.

Compound 4a was also prepared in 66% yield in DMF following the procedure described above.

A mixture of indenone 2 (4.8 g, 22.5 mmoles) and sodium cyanide (1.5 g, 30.8 mmoles) in a solution of t-butanol (50 mL) and water (50 mL) was warmed on a steam bath to effect solution (yellow). The solution was cooled, treated with methyl iodide (20 g), the two phase system stirred for 72 hr and the resulting precipitate collected to give 4a (3.0 g, 53%).

3-Imino-10a-methyl-1-oxo-3a,4,5,6-tetrahydropyrrolidino[3,4-b]acenaphthen-10-one (5b, $R^1 = CH_3$).

A flask containing 4a (1.5 g, 5.9 mmoles) was heated in an oil bath to 235° (the compound melted). The flask was cooled and the resulting solid recrystallized from 95% ethanol to yield 5b (0.9 g, 60%) as white plates; mp 258-261°; ir 2.81 and 2.95 (NH), 3.35 (CH), 5.76 (imide carbonyl), 5.85 (ketone carbonyl), 6.00 (C = N), and 6.27 μ (aromatic).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.86; H, 5.51; N, 11.02. Found: C, 70.85; H, 5.75; N, 10.64.

2-Carbamoyl-2-ethyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4b, $R^1 = C_2H_5$).

Following the procedure described above for 4a in DMSO, the cyanide adduct of 5 g (23.5 mmoles) of 2 was treated with excess ethyl bromide, to give 3.65 g (58%) of 4b, white crystals melting at 214-215° after recrystallization from ethanol; ir 2.92 (NH_2), 4.45 (CN), 5.84 (CO) and 5.94 μ ($CONH_2$).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.66; H, 6.38; N, 10.44. Found: C, 71.90; H, 6.11; N, 10.35.

2-Carbamoyl-2-allyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4c, $R^1 = CH_2CH=CH_2$).

As above, treatment of the solution with allyl bromide gave 4c in 81% yield, melting at 200-201°; ir 2.92 (NH_2), 4.44 (CN), 5.84 (CO). 5.90 ($CONH_2$), 10.03 and 10.95 μ (allyl C = C).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.49; H, 5.78; N, 10.00.

2-Carbamoyl-2-carbethoxymethyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4d, $R^1 = CH_2COOC_2H_5$).

Following the above procedure, 5 g (23.5 mmoles) of 2 was treated with cyanide followed by 4.1 g (24.5 mmoles) of ethyl bromoacetate. The product, worked up in the usual manner and recrystallized from ethanol, gave 4.82 g (63%) of white crystals of 4d, melting at 205-207°; ir 2.91 (NH_2), 4.48 (CN), 5.74 (COOR), 5.84 (CO) and 5.93 μ ($CONH_2$).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.59. Found: C, 66.39; H, 5.65; N, 8.43.

2-Carbamoyl-2-butyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4e, $R^1 = C_4H_9$-n).

Following the procedure for the preparation of 4a, and using excess 1-bromobutane (Aldrich), compound 4e was obtained in 91% yield as white crystals melting at 138-140° after recrystallization from benzene: ir 2.95 (NH_2), 4.47 (CN), 5.85 (CO) and 5.95 μ ($CONH_2$).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.46. Found: C, 73.11; H, 7.06; N, 9.72.

2-Carbamoyl-2-hexyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4f, $R^1 = C_6H_{13}$-n).

Following the procedure described for 4d, 3.96 g (24 mmoles) of 1-bromohexane (Aldrich) was added to the mixture, to give on work-up 6.24 g (82%) of 4f, melting at 158-159° after recrystallization from benzene: ir 2.88 (NH_2), 4.47 (CN), 5.79 (CO) and 6.09 μ ($CONH_2$?).

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found, C, 73.91; H, 7.62; N, 8.83.

2-Carbamoyl-2-benzyl-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (4g, $R^1 = CH_2C_6H_5$).

Following the procedure for 4d, 3.0 g (23.7 mmoles) of benzyl chloride was added, and the usual work-up gave 7.60 g (98%) of white crystals melting at 238-240° after recrystallization from ethanol; ir 2.92 (NH_2), 4.48 (CN), 5.85 (CO) and 5.96 μ ($CONH_2$).

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.21; H, 5.65; N, 8.70.

10a-Methyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (5a, $R^1 = CH_3$).

Polyphosphoric acid (100 g) was added to a flask containing 4a (3.6 g, 14.2 mmoles). The mixture was stirred w ith a mechanical stirrer at 105° for 7 hr, and then hydrolyzed by pouring onto 750 mL of cracked ice. After 24 hr, the resulting solid was collected by filtration to give 5a (2.3 g, 63%), mp 238-241°. Recrystallization from 95% ethanol afforded an analytical sample of white crystals: mp 249-251°; ir 3.12 (NH), 3.38 (CH), 5.60 and 5.89 (imide carbonyls), 5.78 (ketone carbonyl), and 6.29 μ (aromatic).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.49. Found: C, 70.66; H, 5.24; N, 5.42.

10a-Ethyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (5a, $R^1 = C_2H_5$).

Following the procedure described above, 5a, $R^1 = C_2H_5$ was prepared in 79.2% yield from 4b. An analytical sample was prepared by recrystallization from 95% ethanol: mp 247-248°; ir 3.14 (NH), 5.64 and 5.92 (imide carbonyls), and 5.80 μ (ketone carbonyl).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.10; H, 5.59; N, 5.46.

2-Methyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (7).

This compound was prepared as previously reported (3), by methylation of 2.4 g (0.1 mole) of 1a (1) with methyl iodide in DMF. The resulting solid recrystallized from ethanol to give 2.5 (88%) of 7 as white crystals melting at 142.5-144°; *ir 3.38 (CH), 5.61* and 5.92 (imide (CO), 5.80 (CO) and 6.29 μ (aromatic).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.54; H, 5.09; N, 5.49. Found: C, 70.25; H, 5.34; N, 5.47.

2,10a-Dimethyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (6a, $R^1 = CH_3$).

Sodium hydride (0.55 g of 50% NaH in mineral oil, 11.4 mmoles) was added to a mixture of 7 (2.55 g, 10 mmoles) in 30 mL of dry THF in an Erlenmeyer flask fitted with a drying tube (Drierite). After the evolution of hydrogen, methyl iodide (5 mL) was added

and the mixture stirred at room temperature for 24 hr, then poured into 250 mL of water and the excess methyl iodide removed on a steam bath. The resulting solid was collected by filtration to give 6a (2.22 g, 83%, mp 137-138°). When the reaction was run in DMSO, 6a was isolated in 74% yield. An analytical sampe of 6a was prepared by recrystallization from 95% ethanol as white crystals: mp 143-144°; ir 3.40 (CH), 5.61 and 5.90 (imide carbonyl), 5.79 (ketone carbonyl), and 6.29 μ (aromatic); pmr ($CDCl_3$) δ 7.52 (3H, multiplet, aromatic), 2.95 (3H, singlet, NCH_3), 2.6-1.7 (multiplet, methylene), and 1.47 (3H, singlet, CH_3).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.57; N, 5.20. Found: C, 71.66; H, 5.85; N, 5.06.

A mixture of 5a ($R' = CH_3$) (0.47 g, 1.84 mmoles), potassium carbonate (0.27 g, 1.95 mmoles) and methyl iodide (2mL) in 6mL of DMF was stirred at room temperature for 20 hr. The reaction was poured into 100 mL of water and the resulting solid was collected to give 0.41 g (83%) of white crystals melting at 138.5-140°. A sample was recrystallized from 50% ethanol, and melted at 143-144°. This compound was identical to 6a prepared by methylation of 7 as evidenced by identical infrared spectrum and undepressed mixture melting point.

10a-Ethyl-2-methyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (6b, $R' = C_2H_5$).

Following the procedure outlined for the preparation of 6a, 6b was obtained in 72% yield from 7 and ethyl iodide. An analytical sample was prepared by recrystallization from aqueous ethanol: mp 103.5-104.5°; ir 3.41 (CH), 5.63 and 5.91 (imide carbonyls), 5.80 (ketone carbonyl) and 6.29 μ (aromatic).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.00; N, 4.94. Found: C, 71.99; H, 6.12; N, 4.90.

10a-Allyl-2-methyl-3a,4,5,6-succinimido[3,4-b]acenaphthen-10-one (6c, $R' = C_3H_6$).

Following the procedure outlined for the preparation 6a, 6c was obtained in 46% yield from 7 and allyl bromide. An analytical sample was prepared by recrystallization from 95% ethanol: mp 83-84°; ir 3.4 (CH), 5.62 and 5.92 (imide carbonyls), 5.80 (ketone carbonyl), 6.1 (C=C), 6.29 (aromatic), and 10.05 and 10.78 μ (allyl).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.75. Found: C, 72.94; H, 5.72; N, 4.73.

Spiro[8'-carboxy-1',2',3',4'-tetrahydronaphthene-1',3-1,4-dimethylsuccinimide] (8).

Sodium hydride (1.5 g of 50% NaH in mineral oil, 31.2 mmoles) was added to a mixture of 1a (1) (2.41 g, 10 mmoles) in 75 mL of dry THF in an Erlenmeyer flask fitted with a drying tube (Drierite). After the evolution of hydrogen, excess methyl iodide (10 mL) was added, the solution was stirred at room temperature for 24 hr, poured into 300 mL of water and the excess methyl iodide was removed on a steam bath. After cooling in an ice-water slurry, the solution was acidified with 20% sulfuric acid to pH 1. The resulting precipitate was collected to give 2.88 g (100%) of 8 melting at 210-212°. Compound 8 was purified for analysis by recrystallization from benzene: mp 215-218°; ir 3.0-3.2 and 3.7-3.9 (H-bonding), 3.36 (CH), 5.61 and 5.90 (imide carbonyls), 5.78 (acid carbonyl), and 6.28μ (aromatic); pmr ($CDCl_3$) δ 8.95 (1H, singlet, acid), 7.77 (1H, multiplet, aromatic), 7.29 (2H, multiplet, aromatic), 3.10 (3H, singlet, NCH_3), 2.85 (3H, multiplet, methylene), 2.00 (4H, multiplet, methylene), and 1.04 (3H, doublet, J = 8 cps, CCH_3); the compound is soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.92; N, 4.88. Found: C, 66.68; H, 5.98; N, 4.77.

The dimethylated imide 6a (1.3 g, 5 mmoles) was added to a solution of 2.1 mL of

10% sodium hydroxide (5.1 mmoles) in 10 mL of water and 10 mL of THF, and the mixture was stirred at room temperature for 4 hr to produce a clear solution. The solution was acidified to pH 1 with 20% sulfuric acid and extracted with chloroform. The chloroform phase was dried with magnesium sulfate and concentrated to dryness at reduced pressure to give 8 (1.4 g, 98%) as evidenced by congruent infrared spectrum and melting point.

Spiro[8′-carboxy-1′,2′,3′,4′-tetrahydronaphthalene-1′,3-4-methylsuccinimide] (9).

Imide 5a ($R^1 = CH_3$) (0.5 g, 1.96 mmoles) was dissolved in 10 mL of 1% potassium hydroxide. The solution was extracted with chloroform, the aqueous phase was acidified to pH 1 with 20% sulfuric acid and the resulting solid was collected to give 9 (0.39 g, 73%). Compound 9 was purified for analysis by recrystallization from aqueous ethanol: mp 259-262° (dec) (the 3° melting range observed for this acid and acid 8 is attributed to a diastereoisomeric mixture); ir 2.85-2.95, 3.05, 3.3-3.6, 3.7-3.9 (H-bonding and CH), 5.68 and 5.90 (imide carbonyls), 5.80 (acid carbonyl), and 6.29 μ (aromatic); pmr (DMSO-d_6) δ 9.14 (1H, singlet, acid proton), 7.44 (3H, multiplet, aromatic), 2.93 (3H, multiplet, methylene), 1.90 (4H, multiplet, methylene), and 0.88 (3H, doublet, J = 7.5 cps, methyl).

Anal. Calcd. for $C_{15}H_{14}NO_4$: C, 65.94; H, 5.49; N, 5.13. Found: C, 66.12; H, 5.58; N, 5.06.

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