Intramolecular N- and C-Arylation of *N*-Phenylpropylenaminones via Benzyne Intermediates Leading to Heterocyclic Systems

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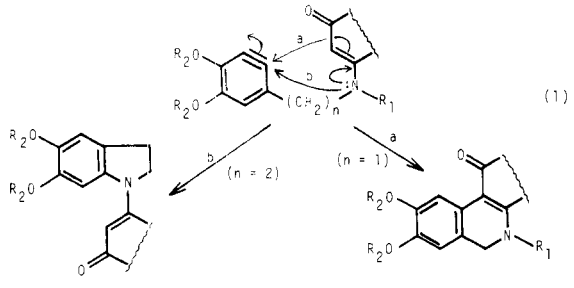
In the enaminone system, N—C=C—C=O, electrophilic attack can occur at the nitrogen, α-carbon, and oxygen atoms and nucleophilic attack at the β- and carbonyl carbon atoms. The chemical versatility of enaminones and their synthetic applicability which are of current interest[1] are based mainly on such multidentate character and have prompted us to utilize enaminones as synthons in the preparation of condensed heterocyclic systems. We previously reported that benzyne cyclization of enaminones proceeds regioselectively via pathway a or b to yield the isoquinoline or indoline nucleus, respectively, depending on the chain lengths of methylenes (n = 1 or 2) as depicted in eq 1.[2] We now report the extension of



(1)

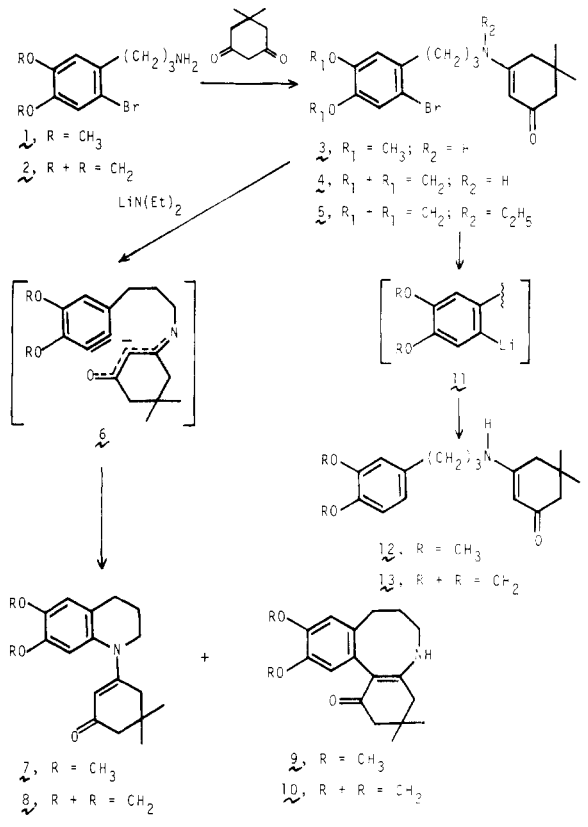
this reaction to *N*-phenylpropyl analogues, in which C_α and N arylations occurred competitively or simultaneously in the molecule.

Results and Discussion

The starting enaminones **3** and **4** were conveniently obtained by condensation of the corresponding phenylpropylamines **1** and **2** with dimedone according to our procedure[3] previously reported. The latter was subsequently subject to N-alkylation by treatment with ethyl iodide and sodium hydride in boiling toluene to give the tertiary enaminone **5** in 90% yield. The enaminone **3** was treated with lithium diethylamide (LDEA) in ether–tetrahydrofuran (THF) at reflux for 30 min. After workup, separation by column chromatography afforded three products. Two of the products were identified as the tetrahydroquinoline **7** and benzazocine **9** in 37 and 11% yield, respectively. In addition, the debrominated product **12** was isolated in 27% yield. The first two products result from competing intramolecular C–N vs. C–C coupling via a benzyne–enaminone anion intermediate **6**; the latter product is generated via halogen–metal exchange with a lithium reagent followed by quenching with diethylamine or water as shown in Scheme I. Similar treatment of **4** with LDEA yielded **8** (33% yield), **10** (10%), and **13** (23%).

Further variants of the ring closure were found in the use of **5** as a substrate with no replaceable hydrogen atom

Scheme I



on the nitrogen atom. Thus **5** was treated in a similar manner as that described for **3** to give the tetrahydroquinoline **15** (25%) and pyridocarbazole **17** (17%) along with the debrominated alcohol **18** (8%) (Scheme II). The formation of **15** and **17** can be rationalized by a pathway (a) involving the zwitterionic intermediate **14** which would be hydrolyzed to give **15** and dimedone. On the other hand, the formation of the pyrido[1,2,3-*jk*]carbazole ring system **14** → **17** is most plausibly accounted for by a mechanism involving an α',β-elimination[4] via intermediate **16** followed by air oxidation. It is of interest to note that the ylide formation in the reaction **14** → **16** arises from "umpolung" of the normal reactivity (nucleophilic) of the α-carbon atom in the enaminone system. Finally **18** may arise via another pathway (b) involving halogen–metal exchange, causing debromination and concomitant base-catalyzed air oxidation at the allylic position.

Experimental Section

Melting points are uncorrected. IR spectra were determined with a Hitachi 215 grating spectrophotometer. NMR spectra were obtained on Varian T-60 or JOEL JNM-PS-100 spectrometers in $CDCl_3$ with $(CH_3)_4Si$ as internal standard. Mass spectra were obtained from a Hitachi KMU-7L double-focusing spectrometer at 70 eV.

3-[3-(2-Bromo-4,5-methylenedioxyphenyl)propylamino]-5,5-dimethylcyclohex-2-en-1-one (4). A mixture of 3-(2-bromo-4,5-methylenedioxyphenyl)propylamine (**2**; 2.3 g, 8.9 mmol) and dimedone (1.25 g, 8.9 mmol) in benzene (40 mL) was heated under reflux with a Dean–Stark trap for azeotropic removal of water for 3 h. The solid product obtained after removal of the solvent was recrystallized from methanol to give **4** as white prisms (2.8 g, 83%): mp 170–171.5 °C; IR ($CHCl_3$) 3400 (NH), 1610 (C=O), 1580 cm^{-1} (C=C); NMR δ 1.07 (s, 6 H, 2 CH_3), 2.17 (s, 4 H, 2 CH_2), 5.07 (s, 1 H, vinylic H), 5.36 (br s, 1 H, NH), 5.92

(1) For a recent review, see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, 6, 277.
(2) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1978**, 100, 3598; *Tetrahedron Lett.* **1978**, 3817.
(3) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, 44, 1236.
(4) Johnson, A. W. "Ylide Chemistry"; Academic Press: New York, 1966; pp 277–281. Hoffmann, P. W. "Dehydrobenzene and Cycloalkynes"; Academic Press: New York, 1967; p 172.

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(s, 2 H, OCH_2O), 6.66 (s, 1 H, C6′ H), 6.95 (s, 1 H, C3′ H); mass spectrum, m/e (rel intensity) 381 (M^+ + 2, 13), 379 (M^+, 11), 376 (13), 374 (11), 300 (41), 213 (23), 153 (100).

Anal. Calcd for $C_{18}H_{22}BrNO_3$: C, 56.85; H, 5.83; N, 3.68. Found: C, 57.18; H, 5.87; N, 3.83.

3-[3-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-ethylpropylamino]-5,5-dimethylcyclohex-2-en-1-one (5). A stirred mixture of NaH (50% dispersion in mineral oil; 120 mg, 2.5 mmol) and **4** (600 mg, 1.58 mmol) in dry toluene (40 mL) was heated under reflux for 1 h, and the resulting slurry was cooled to room temperature. To this was added ethyl iodide (250 mg, 1.60 mmol), and the mixture was heated at 100 °C for 2 h. After being quenched by addition of ice–water, the organic layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The oily residue was chromatographed on a silica gel column with chloroform to give **5** as an oil (580 mg, 90%): IR (neat) 1600 (C=O), 1555 cm^{-1} (C=C); NMR δ 1.08 (s 6 H, 2 CH_3), 1.15 (t, 3 H, J = 7 Hz, CH_2CH_3), 5.14 (s, 1 H, vinylic H), 5.91 (s, 2 H, OCH_2O), 6.66 (s, 1 H, C6′ H), 6.95 (s, 1 H, C3′ H); mass spectrum, m/e (rel intensity) 409 (M^+ + 2, 3), 407 (M^+, 3), 328 (16), 240 (16), 181 (53), 166 (100).

Exact mass calcd for $C_{20}H_{26}{}^{79}BrNO_3$ 407.1096, found 407.1121.

Reaction of 3-[3-(2-Bromo-4,5-dimethoxyphenyl)propylamino]-5,5-dimethylcyclohex-2-en-1-one (3) with LDEA. To a stirred solution of phenyllithium (5.0 mmol in 30 mL of ether) was added diethylamine (120 mg, 1.64 mmol) at 0 °C in a nitrogen atmosphere. After being stirred at 0 °C for 20 min, to the mixture was added dropwise a solution of **3**[3] (630 mg, 1.62 mmol) in anyhydrous THF (40 mL), and it was stirred at 0 °C for 30 min and then at gentle reflux for 2.5 h. After being cooled, the reaction mixture was quenched by addition of ammonium chloride (700 mg), the solvent was evaporated, and chloroform (60 mL) was added to the residue. The resulting solution was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on a silica gel column using chloroform as eluent. The first fractions contained 2,3-dihydro-6,7-dimethoxy-1-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-quinoline (**7**). Recrystallization from acetone–hexane gave colorless prisms [160 mg, 32% (37%, based on the starting material recovered)], mp 119–120 °C (lit.[3] mp 118–120 °C).

The component included in the second fractions was further purified by preparative TLC on Merck precoated silica gel plates [solvent system chloroform–methanol (50:1)] to give 3,4,5,6,-7,8-hexahydro-10,11-dimethoxy-3,3-dimethyldibenz[*b*,*d*]azocin-1(2*H*)-one (**9**). Recrystallization from chloroform gave colorless prisms [50 mg, 10% (11%)], mp 230–232 °C (lit.[3] mp 231–233 °C).

The third fractions afforded a crystalline mixture of unreacted **3** and **12**. NMR analysis indicated that this mixture was composed of 80 mg (13%) of **3** and 120 mg [24% (27%)] of **12**.

Reaction of 3-[3-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-ethylpropylamino]-5,5-dimethylcyclohex-2-en-1-one (4) with LDEA. A mixture of phenyllithium (6.9 mmol in 40 mL of ether) and diethylamine (160 mg, 2.19 mmol) and a solution of **4** (800 mg, 2.11 mmol) in anhydrous THF (40 mL) were treated in the same manner as described above. The first component obtained by chromatography in the same manner stated above was recrystallized from acetone–hexane to give 2,3-dihydro-6,7-methylenedioxy-1-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-quinoline (**8**) as colorless prisms [170 mg, 27% (33%, based on the starting material recovered)]: mp 139–140 °C; IR ($CHCl_3$) 1620 (C=O), 1605 cm^{-1} (C=C); NMR δ 1.07 (s, 6 H, 2 CH_3), 2.21 and 2.37 (each s, 2 H, CH_2 in the cyclohexene ring), 1.90, 2.56, and 3.51 (each t, 2 H, J = 6.5 Hz, C3 H_2, C4 H_2, and C2 H_2, respectively), 5.48 (s, 1 H, vinylic H), 5.92 (s, 2 H, OCH_2O), 6.50 (s, 1 H, C5 H), 6.60 (s, 1 H, C8 H); mass spectrum, m/e (rel intensity) 300 (M^+ + 1, 21), 299 (M^+, 86), 282 (100), 243 (21), 214 (11).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.67. Found: C, 72.20; H, 7.08; N, 4.37.

The second component was recrystallized from chloroform to give 3,4,5,6,7,8-hexahydro-10,11-methylenedioxy-3,3-dimethyldibenz[*b*,*d*]azocin-1(2*H*)-one (**10**) as colorless needles [50 mg, 8% (10%)]: mp 248–249 °C; IR ($CHCl_3$) 3410 (NH), 1605 (C=O), 1570 cm^{-1} (C=C); NMR δ 1.11 (s, 6 H, 2 CH_3), 2.29 (s, 4 H, C2 H_2 and C4 H_2), 5.88 (s, 2 H, OCH_2O), 6.49 (s, 1 H, C12 H), 6.68 (s, 1 H, C9 H); mass spectrum, m/e (rel intensity) 300 (M^+ + 1, 35), 299 (M^+, 100), 270 (26), 243 (18), 214 (27), 135 (46).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.67. Found: C, 72.12; H, 7.23; N, 4.61.

The third fraction provided a mixture constituting of unreacted **4** (150 mg, 19%) and the debrominated product **13** [120 mg, 19% (23%)].

Reaction of 3-[3-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-ethylpropylamino]-5,5-dimethylcyclohex-2-en-1-one (5) with LDEA. A mixture of phenyllithium (5.0 mmol in 30 mL of ether) and diethylamine (110 mg, 1.51 mmol) and a solution of **5** (600 mg, 1.47 mmol) in anhydrous THF (30 mL) were treated according to the same procedure above for **3** except that it was carried out at room temperature for 1 h. The crude product obtained by standard workup was chromatographed on a silica gel column using benzene as eluent. The oily product obtained as the first component was further purified by preparative TLC on Merck precoated silica gel plates (chloroform) to give an oil which was identified as 1-ethyl-1,2,3,4-tetrahydro-6,7-methylenedioxyquinoline (**15**; 75 mg, 25%): NMR δ 1.12 (t, 3 H, J = 7 Hz, CH_2CH_3), 5.76 (s, 2 H, OCH_2O), 6.25 and 6.48 (each s, 1 H, Ar H); mass spectrum, m/e (rel intensity) 205 (M^+, 53), 174 (13), 146 (13), 196 (100), 160 (13), 132 (28).

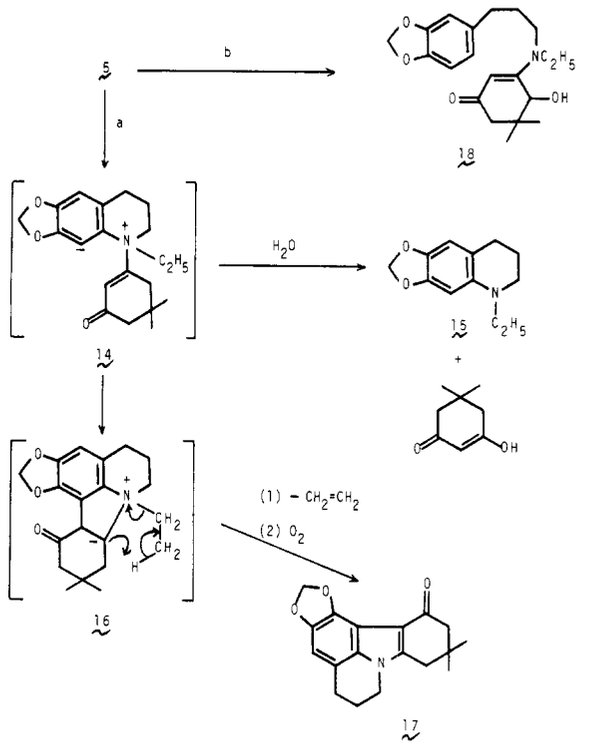
The product contained in the second elution was recrystallized from benzene–hexane to give 1*H*-2,3,7,8,9,10-hexahydro-9,9-dimethyl-5,6-methylenedioxypyrido[1,2,3-*jk*]carbazol-7-one (**17**; 75 mg, 17%) as colorless prisms: mp 248–249 °C; IR ($CHCl_3$) 1625 cm^{-1} (C=O); NMR δ 1.17 (s, 6 H, 2 CH_3), 2.40 (s, 2 H, C10 H_2), 2.69 (s, 2 H, C8 H_2), 3.98 (t, 2 H, J = 6 Hz, NCH_2), 6.04 (s, 2 H, OCH_2O), 6.54 (s, 1 H, C4 H); mass spectrum, m/e (rel intensity) 298 (M^+ + 1, 21), 297 (M^+, 100), 243 (54), 213 (16), 185 (17).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.43; H, 6.70; N, 4.52.

The third component isolated as an oil was identified as 3-[3-(4,5-methylenedioxyphenyl)-*N*-ethylamino]-6-hydroxy-5,5-dimethylcyclohex-2-en-1-one (**18**; 40 mg, 8%): IR ($CHCl_3$) 3390 (OH), 1600 (C=O), 1545 cm^{-1} (C=C); NMR δ 1.17 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.19 (s, 6 H, 2 CH_3), 1.83–2.68 (m, 4 H, $PhCH_2CH_2$), 2.27 (s, 2 H, $CH_2C{=}O$), 3.08–3.33 (m, 4 H, 2 NCH_2), 3.79 (s, 1 H, >CHOH), 5.12 (s, 1 H, vinylic H), 5.91 (s, 2 H, OCH_2O), 6.64 (s, 3 H, Ar H); mass spectrum, m/e (rel intensity) 345 (M^+, 43), 330 ($M^+ - CH_3$, 8), 316 ($M^+ - C_2H_5$, 13), 17 (42), 182 (31), 162 (93), 125 (100).

Exact mass calcd for $C_{20}H_{27}NO_4$ 345.2123, found 345.2154.

Scheme II



Registry No. 2, 71382-80-4; 3, 69089-11-8; 4, 71382-81-5; 5, 71382-82-6; 7, 69089-17-4; 8, 71382-83-7; 9, 69120-33-8; 10, 71382-84-8; 12, 71382-85-9; 13, 71382-86-0; 15, 71382-87-1; 17, 71382-88-2; 18, 71382-89-3; dimedone, 126-81-8; ethyl iodide, 75-03-6; LDEA, 816-43-3.

Modified Retro-Ritter Reaction of 2-Acrylamido-2-methylpropanesulfonic Acid

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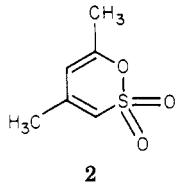
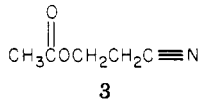
We wish to report an unusual fragmentation reaction observed with 2-acrylamido-2-methylpropanesulfonic acid (1). Warming a suspension of 1 and excess acetic anhydride on a steam bath resulted in gradual dissolution of 1 and formation of a black reaction solution. GLPC analysis indicated the presence of two major and three minor components in addition to acetic acid and acetic anhydride. 4,6-Dimethyl-1,2-oxathiin 2,2-dioxide (2) (>95%) was isolated from the reaction mixture by fractional distillation, while 3-acetoxypropionitrile (3) (41%) and 2,4-dimethylbenzonitrile (4) (4%) were isolated by preparative GLPC.[1]

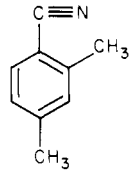
$CH_2{=}CHCONHC(CH_3)_2CH_2SO_3H$
1



2



3



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Compound 2 was initially identified by examination of its mass and NMR spectra. The mass spectrum indicated that the molecular formula was $C_6H_8O_3S$. The proton spectrum showed two olefinic protons and two methyl groups with no vicinal coupling. A $C(CH_3){=}CHC(CH_3){=}CH$ arrangement was deduced from the undecoupled ^{13}C spectrum. The methyl resonance at 19.9 ppm was a quartet of doublets, indicating coupling to only one olefinic proton, while the methyl resonance at 21.2 ppm was a quartet of doublets of doublets which indicated coupling to both olefinic protons. This coupling constant pattern provided definitive assignment of the methyl groups and proved that the assignment suggested by Kausch et al.[2] for 2 was correct.

Corroboration of the structure of compound 2 and unambiguous identification of compound 3 were accomplished by comparison with authentic samples, while compound 4 was identified by comparison of its infrared and ^1H NMR with published spectra.[3]

The nature of the major products indicated that compound 1 had been cleaved under the reaction conditions. A possible reaction mechanism accounting for products 2 and 3 involving a modified retro-Ritter reaction as the key step is outlined in Scheme I.

Initial formation of the mixed-anhydride 5 is reasonable under the reaction conditions and has precedent.[4] The subsequent steps involved in the ultimate formation of 3, however, are somewhat less clear. It is tempting to propose nitrilium ion formation via dehydration of 5, followed by a retro-Ritter reaction forming acrylonitrile and cation 11. Conjugate addition of acetic acid to acrylonitrile would then afford 3. This is especially attractive since compound 1 is prepared by a Ritter reaction of acrylonitrile, isobutene, and chlorosulfonic acid.[5]

This sequence of events, however, is apparently not operative since repeated efforts on our part to prepare 3 from acrylonitrile under seemingly equivalent conditions, i.e., acetic anhydride with methanesulfonic acid, have failed. Thus, since acrylonitrile is apparently not a reaction intermediate, cleavage is proposed to occur subsequent to formation of isoimide 6.

The actual cleavage product, then, is isoimide 7 or its N-acetylated derivative 8. Formation of 3 from either 7 or 8 could then take place by a stepwise conjugate addition of acetic acid (path a) followed by elimination of acetic acid or acetic anhydride or, perhaps, via an intramolecular acetyl migration (path b) in which the ketenimine 10 is an intermediate.

Concerning the other major product, compound 2, Scheme I depicts a reasonably straightforward route from cation 11 involving a Prins-type ring-closure step.

The formation of 2,4-dimethylbenzonitrile (4) in the reaction could possibly be explained by a Diels–Alder reaction between 2 and some dienophile such as 7 or 8. Subsequent extrusion of sulfur trioxide, oxidation, and loss of either acetic anhydride or acetic acid could then afford 4. We have, however, been unable to obtain 4 via a Diels–Alder reaction of 2 with acrylonitrile.

Experimental Section

Reaction of 2-Acrylamido-2-methylpropanesulfonic Acid with Acetic Anhydride. 2-Acrylamido-2-methylpropanesulfonic acid[6] (41.1 g, 0.200 mol) was suspended in 300 mL of acetic anhydride and heated on a steam bath. The initially colorless supernatant gradually became black as the white solid dissolved. After 100 min the heating was discontinued. Some unreacted starting material (4.2 g) was recovered from the reaction mixture by filtration.

The filtrate was evaporated in vacuo to remove acetic acid and acetic anhydride. The black oily residue that remained was examined by GLPC with *m*-tolunitrile as an internal standard. GLPC analysis (6 ft × $^1/_8$ in. column, 10% UC W-98 on 80–100 mesh Chromosorb W, 100–250 °C at 10 °C/min; injection port 270 °C; detector 320 °C) showed that five components were present other than residual acetic acid and acetic anhydride.

component	t_r, min	wt %
1	2.78	21
2	5.68	2
3	6.79	5
4	8.41	71
5	11.47	1

The reaction mixture was fractionally distilled at reduced pressure. A water-white fraction distilling at 79–112 °C (1 torr) was obtained before a white solid collected in the distilling head and condenser. The white solid, component 4 of the mixture, was identified as 4,6-dimethyl-1,2-oxathiin 2,2-dioxide (2) from its spectral properties compared with those of an authentic sample prepared according to literature procedures.[7] Components 1 and 2 were

(1) Yields were determined by an internal standard GLPC technique.
(2) M. Kausch, H. Durr, and S. H. Doss, *Org. Magn. Reson.*, **10**, 208 (1977).
(3) Infrared spectrum No. 33634 and proton NMR spectrum No. 5797, Sadtler Research Laboratories, Inc., Philadelphia, Pa.
(4) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).
(5) D. Arlt, Netherlands Appl. 6611091 (1967); *Chem. Abstr.*, **67**, 11213 (1967).
(6) (a) H. S. Killam, U.S. Patent 3544597; *Chem. Abstr.*, **74**, 141314 (1971). (b) Available from the Lubrizol Corp., Cleveland, Ohio, under the tradename AMPS.

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