700 ml of ethanol and 300 ml of methanol yielding 12.2 g (61%) of yellow crystals, mp 183.5–185°.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.32; H, 5.75; N, 3.92.

2-(3,4,5-Trimethoxyphenyl-5,7-dimethyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (25b).—To a suspension of 7 g (0.0195 mol) of the above dione (**24b**) in 105 ml of AcOH was added with stirring 2.6 ml of concd H_2SO_4. After heating on a steam bath for 45 min the solution was cooled, poured into ice water, and neutralized with NaOH. The resulting solid was collected, washed (H_2O), and dried giving 6.73 g (100%) of solid, mp 203–206°. Recrystallization from 175 ml of benzene yielded 4.49 g of light yellow crystals, mp 204–206°.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.47; H, 5.69; N, 3.98.

1-(2-Hydroxy-4,6-dimethyl-3-pyridyl)-3-phenylpropane-1,3-dione[9] (24a).—This was prepared by a process similar to that used for **24b** above. The intermediate 3-acetyl-4,6-dimethyl-2-pyridylbenzoate was distilled, bp 150° (0.05 mm), but was not highly pure. The dione **24a** was obtained in a 62% yield (mp 199–210°) from 3-acetyl-2-hydroxy-4,6-dimethylpyridine on neutralization of the basic solution. After recrystallization of 8.84 g from ethylene glycol monomethyl ether and then from a large volume of methanol 4.6 g of fluffy needles was recovered, mp 220–227° (Bonsall and Hill[9] report mp 220–226°).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.82; N, 5.40.

5,7-Dimethyl-2-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one[9] (25a).—This was prepared by a process similar to that used for **25b** above. A yield of 72.5% of yellow-tan crystals after recrystallization from EtOH, mp 182.5–184.5° (Bonsall and Hill[9] report mp 182–184°).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.58. Found: C, 76.57; H, 5.29; N, 5.88.

Registry No.—1, 25957-01-1; 2, 25957-02-2; 3, 25957-03-3; 4, 25957-04-4; 5, 25957-05-5; 6, 25957-06-6; 7, 25957-07-7; 8, 25957-08-8; 9, 25957-09-9; 10, 25957-10-2; 11, 25957-11-3; 12, 25957-12-4; 13, 25957-13-5; 14, 25957-14-6; 15, 25957-15-7; 16, 25957-16-8; 17, 25957-17-9; 18, 25957-18-0; 19, 25957-19-1; 20, 25957-20-4; 21, 25957-21-5; 23b, 25957-22-6; 24a, 25957-24-8; 24b, 25957-25-9; 25b, 25957-26-0; 3-acetyl-2-hydroxy-6-methylpyridine, 25957-23-7; [(3-hydroxy-2-pyridyl)methylene]malonic acid, 25957-27-1.

Dianions Derived from Glutarimide, 3,5-Morpholinedione, and 3,5-Thiomorpholinedione as Useful New Synthetic Intermediates[1]

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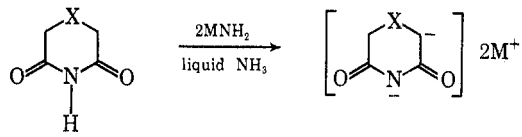
Glutarimide, 3,5-morpholinedione, and 3,5-thiomorpholinedione were converted to their respective dianions by means of slightly more than 2 mol equiv of sodium amide in liquid ammonia. Reactions of the dianions derived from glutarimide and 3,5-morpholinedione with alkyl halides and carbonyl compounds afforded α-substituted derivatives of the parent heterocycles. The dianion of 3,5-thiomorpholinedione gave a similar monosubstituted derivative on treatment with methyl benzoate but underwent a dicondensation reaction with benzophenone and polyalkylation with *n*-butyl bromide. Satisfactory monoalkylation at the α carbon of 3,5-thiomorpholinedione was accomplished when lithium amide was used to generate the dianion. Synthetically useful yields were obtained in a majority of the reactions of these new dianions.

Part A

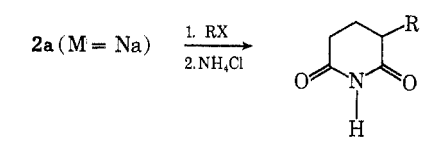
Conventional methods for introduction of substituents at one or both of the α carbons of glutarimide (**1a**), 3,5-morpholinedione (**1b**), and 3,5-thiomorpholinedione (**1c**) involve cyclization of appropriately substituted glutaric, diglycolic, and thiodiglycolic acid derivatives, respectively.[3] Such procedures require the preparation of a number of intermediates, with each member of a series requiring the synthesis of a separate acyclic precursor.

In the present study we have found that dianion **2a–c**,[4] prepared from **1a–c** by means of 2.3–2.4 mol equiv of alkali amide in liquid ammonia, can serve as convenient intermediates for the synthesis of a number of α-substituted derivatives of **1a–c** by virtue of their regiospecific reactions with electrophilic reagents.



1a, X = $-CH_2-$ **2a**, X = $-CH_2-$
b, X = $-O-$ **b**, X = $-O-$
c, X = $-S-$ **c**, X = $-S-$

Results with the Glutarimide Dianion (2a).—Alkylations of dianion **2a** (M = Na) with a series of primary halides produced monlsubstituted glutarimides of type **3** (Table I). Structural assignments for these compounds were based on nmr spectra (see Experimental Section), and acid-catalyzed hydrolysis to the appropriate 2-alkylglutaric acids in 80–90% yield.



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* To whom correspondence should be addressed.

(1) (a) Supported by the Public Health Service, Research Grant No. GM 14340 from the National Institute of General Medical Sciences. (b) For a preliminary account of a porton of this work, see J. F. Wolfe and T. G. Rogers, *Chem. Commun.*, 1040 (1967).

(2) Abstracted from the Ph.D. Thesis of T. G. R., Virginia Polytechnic Institute, Aug 1968.

(3) For examples of such a synthetic procedure as applied to glutarimide derivatives, see (a) T. Kametani, W. Taub, and D. Ginsburg, *Bull. Chem. Soc. Jap.*, **31**, 357 (1958). (b) T. Y. Yu and M. Y. Huang, *Hua Hsueh Hsueh Pao*, **25**, 146 (1959); *Chem. Abstr.*, **54**, 4564*i* (1960). (c) For examples of the synthesis of substituted 3,5-morpholinediones, see F. A. Baron and C. A. Vanderwerf, *J. Med. Chem.*, **10**, 276 (1967). (d) See G. S. Skinner and R. M. MacNair, *J. Org. Chem.*, **25**, 1164 (1960), and references cited therein for examples of the synthesis of substituted 3,5-thiomorpholinediones.

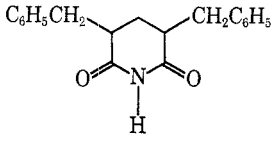
(4) See C. R. Hauser and D. R. Bryant, *J. Amer. Chem. Soc.*, **83**, 3468 (1961), and R. F. C. Brown, *Aust. J. Chem.*, **17**, 154 (1964), for what appear to be the only previous reports of dianions derived from cyclic imides.

TABLE I
ALKYLATIONS OF DIANION 2a
(M = Na) TO FORM 2-ALKYLGLUTARIMIDES (3)[f]

Alkyl halide	R (no.)	Mp, °C	Yield, %
C_2H_5Br	Ethyl (3a)	101–102[a,b]	66
n-C_4H_9Br	n-Butyl (3b)	97–98[c]	77
n-$C_8H_{17}Br$	n-Octyl (3c)	104–105[a]	59
$C_6H_5CH_2Cl$	Benzyl (3d)	142–144[d,e]	80
p-$ClC_6H_4CH_2Cl$	p-Chlorobenzyl (3e)	158–159.5[d]	56
p-$CH_3OC_6H_4CH_2Cl$	p-Methoxybenzyl (3f)	152–153[d]	83
1-$C_{10}H_7CH_2Cl$	1-Naphthylmethyl (3g)	184–185[d]	65
CH_2=$CHCH_2Br$	Allyl (3h)	107–108[a]	78
$ClCH_2COONa$	Carboxymethyl (3i)	194–196[d]	23

[a] Recrystallized from heptane–acetone. [b] Lit.[3b] mp 103–104°. [c] Recrystallized from heptane. [d] Recrystallized from 95% ethanol. [e] Lit.[3b] mp 143–144.5°. [f] Satisfactory analytical values (±0.3%) were reported for all new compounds: Ed.

In an attempt to apply the present approach to the synthesis of 2,4-dialkylglutarimides, benzyl derivative **3d** was treated with 2.4 mol equiv of sodium amide in liquid ammonia followed by benzyl chloride to give dibenzyl derivatives **4**[5] (37%) and **5** (10%). The structure of **4** was confirmed by its hydrolysis to give the high-melting diastereomer of 2,4-dibenzylglutaric acid.[6]



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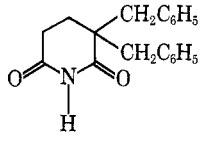

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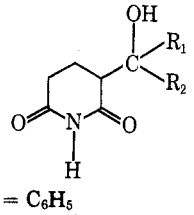
Next, reactions of dianion **2a** (M = Na) with several types of carbonyl compounds were investigated (Table III). This intermediate underwent addition with benzophenone (71%), fluorenone (55%), and cyclohexanone (8%)[7] to produce tertiary alcohols **6**, **7**, and **8**, respectively. Carbinols **6** and **7** were dehydrated



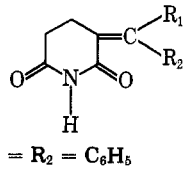
6, $R_1 = R_2 = C_6H_5$

7, R_1 and R_2 =

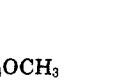
8, R_1 and $R_2 = -(CH_2)_5-$

12a, R_1 = H; $R_2 = p$-$C_6H_4OCH_3$; mp 114–115°

12b, R_1 = H; $R_2 = p$-$C_6H_4OCH_3$; mp 154–155.5°



9, $R_1 = R_2 = C_6H_5$

10, R_1 and R_2 = 

13, R_1 = H; $R_2 = p$-$C_6H_4OCH_3$

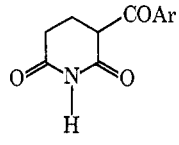
(5) The sharp melting point of this compound was indicative of a single diastereomer.

(6) L. Eberson, *Acta Chem. Scand.*, **12**, 314 (1958).

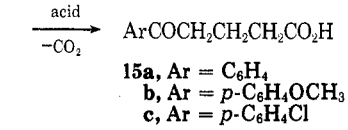
(7) The low yield obtained in this reaction was presumably due to appreciable ionization of an α-hydrogen of the ketone by dianion **2a**; see R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

with p-toluenesulfonic acid in refluxing benzene to yield unsaturated derivative **9** and **10**, the former of which was hydrolyzed to give 2-(diphenylmethylene)-glutaric acid. Dianion **2a** reacted similarly with anisaldehyde to give in low yields the diastereomeric alcohols **12a** and **12b**, each of which was dehydrated to form **13**.

Treatment of dianion **2a** (M = Na) with the appropriate aromatic esters produced 2-aroylglutarimides **14a–c**, which were subsequently hydrolyzed to form 4-aroylbutyric acids **15a–c**.

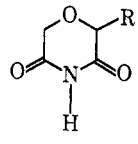


14a, Ar = C_6H_5
b, Ar = p-$C_6H_4OCH_3$
c, Ar = p-C_6H_4Cl



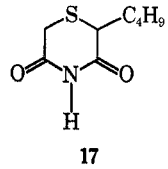
15a, Ar = C_6H_4
b, Ar = p-$C_6H_4OCH_3$
c, Ar = p-C_6H_4Cl

Results with the 3,5-Morpholinedione Dianion (2b).—Reactions of dianion **2b** (M = Na) with a representative series of electrophiles paralleled those of dianion **2a** (Table IV). Thus, treatment of **2b** with benzyl bromide, p-chlorobenzyl chloride, and n-butyl bromide produced C-alkyl derivatives **16a–c**. Dianion **2b** also underwent condensation with benzophenone to afford carbinol **16d** and aroylation with methyl benzoate to give β-keto imide **16e**.



16a, R = $CH_2C_6H_5$
b, R = p-$CH_2C_6H_4Cl$
c, R = n-C_4H_9
d, R = $-C(OH)(C_6H_5)_2$
e, R = COC_6H_5

Results with the 3,5-Thiomorpholinedione Dianion (2c).—In contrast to the clean alkylations of dianions **2a** and **2b**, addition of n-butyl bromide to dianion **2c** (M = Na) afforded an oily mixture consisting of monobutyl derivative **17**, both diastereomers of 2,6-dibutyl derivative **18**, and 2,2,6-tributyl derivative **19** in a relative ratio of 7:6:1,[8] as determined by vapor phase chromatography (vpc). Formation of **18** and **19** was subsequently minimized by slow addition of **2c** (M = Li)



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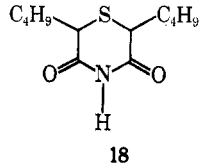

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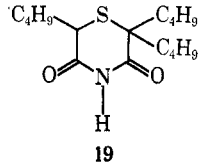


19

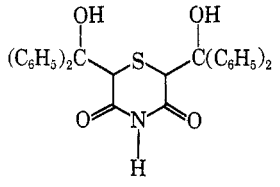
to excess n-butyl bromide in liquid ammonia. This procedure afforded predominately monobutyl derivative **17**, which was isolated in 42% yield by direct crystallization of the crude product mixture.

Dianion **2c** (M = Na) underwent a twofold reaction with benzophenone to form dialcohol **20**; none of the expected monoadduct was isolated. Interestingly, the

(8) The value assigned to dibutyl derivative **18** represents the total concentration of both diastereomers.

yield of **20** was critically dependent on reaction time. For example, a 45% yield of **20** was obtained when the reaction was neutralized after 3–5 min, whereas neutralization after 10 min lead to nearly quantitative recovery of benzophenone.

Finally, reaction of dianion **2c** (M = Na) with methyl benzoate afforded monobenzoyl derivative **21**, uncontaminated by higher benzoylation products.



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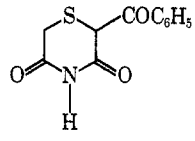

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Part B

Experimental Section[9]

Formation and Deuteration of the Glutarimide Dianion (2a).—To 0.074 mol[10] of sodium amide,[11] prepared from 0.074 g-atom of sodium metal in 400 ml of commercial anhydrous liquid ammonia, contained in a 500-ml, three-necked flask equipped with an air-cooled condenser and a mechanical stirrer, was added 3.39 g (0.03 mol) of finely powdered glutarimide (**1a**).[12] After 30 min, the resulting thick white suspension was assumed to contain 0.03 mol of dianion **2a** (M = Na).

Similarly, addition of 0.03 mol of **1a** to a stirred suspension of 0.07 mol of potassium amide[13] produced a thick white suspension of **2a** (M = K).

A suspension of 0.03 mol of **2a** (M = Na) was prepared as described above, and the ammonia was than evaporated on a steam bath as an equal volume of anhydrous ether was added. To the resulting ethereal suspension was added 10 ml of 10 *N* deuterioacetic acid in deuterium oxide.[14] The acidified mixture was allowed to stir for 1 hr. The precipitate which formed was separated by filtration and washed with dry ether. The original ethereal solution and washing were combined, dried, and concentrated. The resulting solid was dried under vacuum and then sublimed twice to afford 1.87 g of deuterated **1a**, mp 154–156°. The nmr spectrum ($CDCl_3$) of this material had multiplets at δ 2.68 and 2.10 ppm for the C-2 and C-3 protons, respectively. The ratio of the intergrated intensities of these multiplets was 1.67:1, indicating incorporation of 0.66 of a deuterium atom at C-2 of imide **1a**. The spectrum of the deuterated material was devoid of NH absorption.

Alkylations of Dianion 2a.—To a stirred suspension of 0.03 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.033 mol of the appropriate halide as a solution in 20–30 ml of anhydrous ether. The reaction mixture was stirred for 1 hr, then neutralized with excess solid ammonium chloride. The liquid ammonia was evaporated (steam bath) as an equal volume of ether was added. To the resulting ethereal suspension was added a mixture of 75–100 ml of 6 *N* HCl and 250 g of crushed ice, and the resulting two-phase system was allowed to stir until the ice had melted. In reactions where the product separated between the aqueous and ethereal layers, it was collected by filtration and recrystallized from the appropriate solvent (Table I). The remaining ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal fractions were dried and concentrated; residues were recrystallized to afford additional product. In reactions where no solid appeared, the layers were separated and the aqueous layer was extracted with ether. The ethereal extracts were dried and concentrated to give the appropriate alkyl derivative, which was then recrystallized.

In the reaction of **2a** with sodium chloroacetate, the alkylating agent was added as a finely divided solid and the reaction was allowed to proceed for 3 hr. A reaction time of 3 hr was also required for optimum yields of octyl derivative **3c**. Highest yields of ethyl derivative **3a** were obtained by continuously extracting the aqueous layer with ether for 6 hr.

Yields and analytical data for alkylation products **3a–i** are presented in Table I. The ir spectra of these derivatives were characterized by NH adsorption at 3350–3400 and C=O absorption at 1700 cm^{-1}. All of the nmr spectra[15] had an NH singlet at 9.36–11.56 ppm. The spectra of **3d–g** had adsorption for the appropriate number of aromatic protons, with those of **3d** and **3e** appearing as singlets at 7.35 (5 H) and 7.62 (4 H), those of **3f** as a quartet at 7.50 (4 H), and those of **3g** as a multiplet at 8.20 ppm (7 H). The vinyl protons of **3h** appeared as multiplets at 5.82 (2 H) and at 6.0 ppm (1 H). The complex splitting patterns in the 1–3 ppm region of the spectra of alkyl derivatives **3a–c** and carboxymethyl derivative **3i** made it difficult to determine with certainty which of the signals were due to the hydrogens of the glutarimide ring, and which were attributable to the side-chain protons.

Reaction of 0.03 mol of dianion **2a** (M = Na) with 6.04 g (0.043 mol) of β-phenylethyl chloride afforded a clear oil with an ir spectrum very similar to that of styrene. Treatment of this oil with a solution of bromine in carbon tetrachloride until a color persisted, afforded 1.17 g of α,β-dibromoethylbenzene as white needles from 95% ethanol, mp 72.5–74° (lit.[16] 74–74.5°).

Attempted alkylation of dianion **2a** (M = Na) (0.03 mol) with 6.7 g (0.033 mol) of benzhydryl chloride produced 3.88 g (71%) of tetraphenylethylene, mp 222–224° (lit.[17] mp 222–224°). A mixture melting point with an authentic sample was not depressed.

Treatment of **2a** (M = Na) (0.03 mol) with isopropyl bromide (0.035 mol) as described above afforded only recovered **1a**.

Dipotassio derivative **2a** (M = K) (0.03 mol) was treated with benzyl chloride as described above to afford 4.0 g (65%) of benzyl derivative **3d**, mp 142–144°.

In one experiment imide **1a** (0.03 mol) was treated with 0.072 mol of freshly prepared lithium amide[18] in 400 ml of liquid ammonia for 1 hr to form presumably dilithio salt **2a** (M = Li). Subsequent addition of benzyl chloride (0.03 mol) was accompanied by the bright purple color associated with stilbene formation.[19] The reaction was processed in the usual manner to afford 0.9 g (15%) of **3d** and 1.04 g (35%) of stilbene, mp 121–123°, mmp (with an authentic sample)[19] 122–123°.

Hydrolysis of Alkylation Products 3a–e and 3g.—A 0.9–2.7-g sample of the appropriate alkylation product was refluxed for 24 hr with 100 ml of 6 *N* HCl. The reaction mixture was cooled and the 2-alkylglutaric acids were isolated either by filtration or extraction of the aqueous acid solution with ether. Several of the low-melting acids were slow to crystallize, but, once crystalline, their melting points were in excellent agreement with reported values. The results of these hydrolysis reactions are presented in Table II.

(9) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Ir-5A infrared spectrophotomer; potassium bromide pellets were used for solids, and neat samples between sodium chloride plates were used for liquids. Nmr spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to internal tetramethylsilane, are measured to the center of a singlet or multiplet. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU spectrometer at 50 eV. Vapor phase chromatography (vpc) measurements were carried out on a Varian-Aerograph 90P chromatograph using a 5 ft × 0.25 in. stainless steel column packed with 20% SE-30 on 60–80 A/W DMSC Chromosorb W at 200–250° with helium as the carrier gas. Product ratios were determined by measuring peak areas using the method of triangulation. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and in our laboratories by Dr. C. S. Menon and Miss Q. H. Tan, using an F & M Model 185 C, H, and N analyzer. Unless otherwise specified, all chemicals were commercial reagent grade and were used without further purification. Anhydrous sodium sulfate was employed as a drying agent.

(10) This molar ratio of amide to starting imide **1a** consistently gave reproducible yields, whereas exactly 2 mol equiv of base led to erratic results in several instances.

(11) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(12) G. Paris, L. Berlinguet, and R. Gaudry, *Org. Syn.*, **37**, 47 (1957).

(13) C. R. Hauser, and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

(14) This reagent was prepared by diluting 12.81 g of acetic anhydride to 25 ml with deuterium oxide (99.9% isotropic purity) and allowing the resulting solution to stir for 15 hr.

(15) The spectra of **3a–c** and **3h** were measured using $CDCl_3$ as the solvent The spectra of **3d–g** and **3i** were determined using DMSO-d_6 as the solvent.

(16) I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1938, p 644.

(17) L. J. Durham and H. S. Mosher, *J. Amer. Chem. Soc.*, **84**, 2811 (1962).

(18) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

(19) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Broadhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

TABLE II
HYDROLYSIS OF 2-ALKYLGLUTARIMIDES TO FORM 2-ALKYLGLUTARIC ACIDS ($HO_2CCHRCH_2CH_2CO_2H$)

2-Alkylglutarimide	Acid R	Yield, %	Mp, °C	Lit. mp, °C
3a	C_2H_5	84	59–61	58–60[a]
3b	n-C_4H_9	88	40–42	40[a]
3c	n-C_8H_{17}	73	50–52	50.5[b]
3d	$C_6H_5CH_2$	82	76–78	77–78[a]
3e	p-$ClC_6H_4CH_2$	93	141–142[c]	...[d]
3g	1-$C_{10}H_7CH_2$	91	145–147	144–146[a]

[a] M. F. Ansell and D. H. Hey, *J. Chem. Soc.*, 1683 (1950). [b] L. Dubravkova, I. Jezo, P. Sefcovic, and Z. Voticky, *Chem. Zvesti*, 9, 541 (1955); *Chem. Abstr.*, 50, 16764*h* (1956). [c] Recrystallized from benzene–heptane. [d] *Anal.* Calcd for $C_{12}H_{13}ClNO_4$: C, 56.15; H, 5.10. Found: 56.37; H, 5.27.

Benzylation of 3d to Form Dibenzyl Derivatives 4 and 5.—To a stirred suspension of 0.048 mol of sodium amide in 400 ml of liquid ammonia was added 4.06 g (0.02 mol) of 2-benzylglutarimide (**3d**). After 1 hr, 2.53 g (0.02 mol) of benzyl chloride in 30 ml of anhydrous ether was added and the reaction mixture was allowed to stir for 1 hr before being processed as described for the alkylations of dianion **2a**. The ethereal extracts were concentrated to give a solid residue, which was recrystallized from 95% ethanol to produce 2.14 g (37%) of 2,4-dibenzylglutarimide (**4**): mp 138.5–140°; ir 3400 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.56 (s, 1, NH), 7.58 (m, 10 aromatic), 3.30 (m, 6, overlapping ring methine and CH_2Ph), and 1.71 ppm (t, 2, $-CH_2-$); mass spectrum, molecular ion peak at m/e 293 with abundant fragment peaks at m/e 174, 131, and 91.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.86; H, 6.39; N, 4.76.

The mother liquor from the above recrystallization was concentrated to afford a second crop of impure solid, which was recrystallized from heptane–chloroform to afford 0.56 g (10%) of 2,2-dibenzylglutarimide (**5**): mp 140–141.5°; ir 3400 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.04 (s, 1, NH), 7.60 (s, 10, aromatic), 3.19 (ABq, 4, CH_2Ph), 2.54 (m, 2, $-CH_2C=O$), and 1.90 ppm (m, 2, $-CH_2-$); mass spectrum, molecular ion peak at m/e 293 with abundant fragment peaks at m/e 202 and 91.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.51; H, 6.47; N, 4.60.

A 2.27-g sample of **4** was refluxed for 36 hr with 150 ml of 6 *N* HCl. The precipitate which formed on cooling was recrystallized from 80% aqueous acetic acid to give 0.66 g of recovered **4** and three crops, totaling 1.40 g, of impure diacid, which was dissolved in chloroform and then extracted into aqueous $NaHCO_3$. The $NaHCO_3$ solution was acidified with concd HCl to precipitate 1.02 g (42%) of the pure, high-melting diastereomer of 2,4-dibenzylglutaric acid, mp 150–151.5° (lit.[6] mp 149–151°). The ir spectrum of this acid was identical with that of an authentic sample prepared by the method of Eberson;[6] a mixture melting point determination showed no depression.

Condensation of Dianion 2a with Ketones.—To a stirred suspension of 0.03 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.033–0.042 mol of the respective ketone in 30 ml of dry ether. After an appropriate time[20] the reaction mixture was neutralized by rapidly pouring it into a solution of excess ammonium chloride in 100 ml of liquid ammonia (inverse neutralization).[21] The ammonia was removed on the steam bath and replaced by 300–400 ml of ether. The resulting ethereal suspension was treated with 50 ml of 6 *N* HCl and 200 g of crushed ice. In the reactions with benzophenone and fluorenone, most of the product separated between the layers and was collected by filtration. The ethereal layers were also dried and concentrated to afford additional material. In the condensation with cyclohexanone the product was isolated entirely from the etheral layer. Yields and analytical data for products obtained in these reactions are given in Table III. The spectral characteristics of the products derived from these reactions were consistent with their assigned structures. Thus, **6**, **7**, and **8** had principal ir bands at 3250–3500 (NH and OH) and 1680–1700 cm^{-1} (C=O). The nmr spectrum of **6** had peaks (DMSO-d_6) at δ 11.20 (s, 1, NH), 7.94 (m, 10, aromatic), 5.80 (s, 1, OH),[22] 4.30 (t, 1, ring methine), 2.66 (m, 2, $-CH_2C=O$), and 1.80 ppm (m, 2, $-CH_2-$). The spectrum of **7** had peaks (DMSO-d_6) at δ 11.42 (s, 1, NH), 7.94 (m, 8, aromatic), 6.50 (s, 1, OH), 3.72 (m, 1, ring methine), 2.34 (m, 2, $-CH_2C=O$), and 1.38 ppm (m, 2, $-CH_2-$). The spectrum of **8** had peaks (DMSO-d_6) at δ 10.04 (s, 1, NH), 4.64 (s, 1, OH), 2.64 (m, 3, overlapping ring methine and $-CH_2C=O$), 2.10 (m, 2, $-CH_2-$), and 1.60 ppm (broad s, 10, cyclohexyl).

Condensation of Dianion 2a with Anisaldehyde.—To 0.05 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 9.53 g (0.07 mol) of anisaldehyde in 30 ml of dry ether. After 10 min the reaction mixture was neutralized inversely and processed as described for the condensation with ketones. The ethereal layer afforded a semicrystalline residue which was washed with petroleum ether (bp 40–60°) and recrystallized from heptane–acetone to give 1.36 g (11%) of high-melting diastereomer **12b**: ir 3200–3450 (NH and OH) and 1680 cm^{-1} (C=O; nmr (DMSO-d_6) δ 11.20 (s, 1, NH), 7.50 (q, 4, aromatic), 5.70 (s, 2, OH and side-chain CH), 3.90 (s, 3, OCH_3), 2.64 (m, 3, $-CH_2C=O$ and ring methine), and 1.76 ppm (m, 2, $-CH_2-$).

The mother liquor remaining from the recrystallization of **12b** was concentrated to dryness and the residue was recrystallized from benzene to give 0.97 g (8%) of low-melting diastereomer **12a**: ir 3200–3500 (NH and OH) and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 10.94 (s, 1, NH), 7.32 (q, 4, aromatic), 5.60 (d, 1, OH), 5.36 (t, 1, side-chain CH), 3.90 (s, 3, OCH_3), 2.96 (m, 1 ring methine), 2.48 (m, 2, $-CH_2C=O$), and 1.56 ppm (m, 2, $-CH_2-$).

Dehydration of Carbonyl Addition Products 6, 7, 12a, and 12b.—A 0.75-g sample of **6** was refluxed for 20 hr with 0.1 g of *p*-toluenesulfonic acid in 25 ml of benzene. The reaction mixture was cooled to afford a white solid, which was recrystallized from 95% ethanol to give 0.59 g (85%) of 2-diphenylmethyleneglutarimide (**9**): mp 197–198°; ir 3400 (NH), 1650, 1700, and 1710 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.02 (s, 1, NH), 7.54 (m, 10, aromatic), and 2.67 ppm (m, 4, $-CH_2C=O$ and $-CH_2-$).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.06; H, 5.34; N, 5.03.

Similarly, a 1.06-g sample of **7** afforded 0.58 g (58%) of 2-fluorenylideneglutarimide (**10**) as yellow plates from 95% ethanol: mp 201–202°; ir 3450 (NH), 1650 and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.96 (s, 1, NH), 8.20 (m, 8, aromatic), 3.64 (t, 2, $-CH_2C=O$), and 2.86 ppm (t, 2, $-CH_2-$).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.73; N, 5.09. Found: C, 78.42; H, 4.99; N, 5.01.

Dehydration of 250 mg of **12a** with a few crystals of *p*-toluenesulfonic acid in 10 ml of refluxing benzene afforded 180 mg (78%) of 2-(*p*-methoxybenzylidene)glutarimide (**13**), as colorless needles from 95% ethanol: mp 171–172.5°; ir 3450 (NH), 1600 and 1670 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.40 (s, 1, NH), 8.18 (s, 1, vinyl), 7.72 (q, 4, aromatic), 4.04 (s, 3, OCH_3), 3.10 (m, 2, $-CH_2C=O$), and 2.74 ppm (m, 2, $-CH_2-$).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.55; H, 5.63; N, 6.06. Found: 67.80; H, 5.80; N, 6.04.

Similar treatment of a 1-g sample of **12b** produced 0.66 g (71%) of **13**, which had identical physical and spectral properties with those of a sample of **13** obtained by dehydration of **12a**.

Hydrolysis of Unsaturated Derivative 9.—A 1.0-g sample of unsaturated imide **9** was refluxed with 50 ml of a 1:1 v/v solution of 50% H_2SO_4–glacial acetic acid for 24 hr. The reaction mixture was cooled and extracted with ether. The ethereal extracts were dried and concentrated. Residual acetic acid was removed by vacuum distillation on a steam bath. The resulting red oil was triturated with a mixture of ether–petroleum ether (bp 40–60°) until crystallization occurred. The solid residue was then recrystallized from benzene–petroleum ether (bp 40–60°) to give 0.32 g (33%) of 2-diphenylmethyleneglutaric acid (**10**): mp 177–178°; ir 3100–3450 (COOH) and 1650 cm^{-1} (C=O); nmr (DMSO-d_6) δ 12.84 (s, 2, COOH), 7.40 (m, 10, aromatic), and 2.52 ppm (broad s, 4, $-CH_2CH_2-$).

(20) Reaction periods of 10 min, 0.5 hr, and 1 hr were employed with each ketone. Best yields were obtained with benzophenone, fluorenone, and cyclohexanone after 0.5 hr, 1 hr, and 10 min, respectively.

(21) This inverse neutralization procedure was employed to minimize possible reversion of the carbonyl addition; see ref 31.

(22) Signals arising from OH protons were assigned by adding several drops of deuterium oxide to the nmr sample and then rescanning the spectrum.

TABLE III

REACTIONS OF DIANION 2a (M = Na) WITH CARBONYL COMPOUNDS[d]

Carbonyl compound	Product	Mp, °C	Yield, %
Benzophenone	2-(α-Hydroxy-α,α-diphenylmethyl)-glutarimide (6)	184–187[a]	71
Fluorenone	2-(9-Hydroxy-9-flourenyl)-glutarimide (7)	210–211 dec[a]	55
Cyclohexanone	2-(1-Hydroxycyclohexyl) glutarimide (8)	158–159[b]	8
Anisaldehyde	2-(α-Hydroxy-p-methoxybenzyl)-glutarimide (12a)	114–115	8
Anisaldehyde	2-(α-Hydroxy-p-methoxybenzyl)-glutarimide (12b)	154–155.5	11
Methyl benzoate	2-Benzoylglutarimide (14a)	120.5–121.5[a]	72[c]
Methyl anisate	2-Anisoylglutarimide (14b)	169.5–170.5[a]	76[c]
Methyl p-chlorobenzoate	2-(p-Chlorobenzoyl)glutarimide (14c)	177–178[a]	67[c]

[a] Recrystallized from 95% ethanol. [b] Purified by sublimation at 130–150° (0.5–1.0 mm). [c] Yield based on ester. [d] Satisfactory analytical data (±0.3% in C, H, N) were submitted for all compounds: Ed.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.18; H, 5.27.

Reaction of Dianion 2a with Aromatic Esters.—To a stirred suspension of 0.06 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.03 mol of the appropriate ester in 20–30 ml of dry ether. The reaction mixture was stirred for 4–5 hr and then processed as in the alkylations of dianion **2a**. Yields and analytical data for the products from these reactions are given in Table III. The ir spectra of **14a–c** had NH absorption at 3450 and broad carbonyl absorption at 1610–1725 cm^{-1}. The nmr spectrum of **14a** had peaks (DMSO-d_6) at δ 11.46 (s, 1, NH), 8.20 (m, 5, aromatic), 5.14 (t, 1, ring methine), 2.64 (broad s, $-CH_2C{=}O$), and 2.32 ppm (m, 2, $-CH_2-$). The spectrum of **14b** had peaks (DMSO-d_6) at δ 11.38 (s, 1, NH), 7.84 (q, 4, aromatic), 5.04 (t, 1, ring methine), 4.0 (s, 3, OCH_3), 2.58 (broad s, $-CH_2C{=}O$), and 2.30 ppm (m, 2, $-CH_2-$). The spectrum of **14c** had peaks (DMSO-d_6) at δ 11.40 (s, 1, NH), 8.18 (q, 4, aromatic), 5.12 (t, 1, ring methine), 2.60 (broad s, 2, $-CH_2C{=}O$), and 2.30 ppm (m, 2, $-CH_2-$).

Hydrolysis of 2-Aroylglutarimides 14a–c.—A 1.0-g sample of **14a** was refluxed for 24 hr with 25 ml of 6 *N* HCl. The resulting solid was dissolved in ether, the ethereal layer was extracted with aqueous $NaHCO_3$, and the basic extracts were acidified with concd HCl to afford 0.84 g (87%) of 4-benzoylbutyric acid (**15a**), mp 128–130°. A mixture melting point determination with an authentic sample of this acid obtained from Aldrich Chemical Co. was undepressed; the ir spectra were identical. Similar hydrolysis of **14b** (0.5 g) gave 0.41 g (87%) of 4-anisoylbutyric acid, **15b**, mp 139.5–141° (lit.[23] 138–140°). Hydrolysis of **14c** (0.51 g) produced 0.46 g (99%) of 4-(p-chlorobenzoyl)butyric acid (**15c**), mp 125–126° (lit.[24] mp 123–125°).

Independent Synthesis of 2-Benzoylglutarimide (14a).—To a suspension of 20 g of a 60% mineral oil dispersion of sodium hydride[25] in 350 ml of 1,2-dimethoxyethane[26] (DME) contained in a 1-l. three-necked flask equipped with a condenser, mechanical stirrer, and pressure-equilizing addition funnel was added a solution of 11.3 g (0.10 mol) of 4-cyanobutyric acid[12] and 13.6 g (0.10 mol) of methyl benzoate in 75 ml of DME. The reactions mixture was refluxed under nitrogen for 70 hr. The DME was removed under vacuum to leave a pasty residue to which was added 150 ml of ether. The ethereal suspension was cooled in an ice bath and the excess sodium hydride was destroyed by cautious addition of 250 ml of cold water. The ethereal layer was separated and discarded. The aqueous layer was poured into a mixture of 100 ml of concd HCl and 600 g of crushed ice. The acidic solution was extracted with three 100-ml portions of ether. The extracts were dried and concentrated to give a red oil, which solidified after 2 days. The resulting crude solid was recrystallized from benzene to yield 12.2 g (56%) of 4-benzoyl-4-cyanobutyric acid (**27**): mp 98–99.5°; ir 3400 (COOH), 2500 (CN), and 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 12.60 (s, 1, COOH), 8.18 (m, 5, aromatic), 5.46 (t, 1, $PhCOCHCN$), and 2.40 ppm (m, 4, $-CH_2-CH_2-$).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 4.10; N, 6.45. Found: C, 66.07; H, 5.12; N, 6.40.

A 1.0-g sample of **16** was heated with 5 ml of concd H_2SO_4 on a steam bath for 30 min. The resulting purple solution was poured cautiously onto crushed ice to precipitate 30 mg (4%) of 2-benzoylglutarimide (**14a**), mp 119–121°. A mixture melting point with a sample of **14a** prepared from dianion **2a** was not depressed.

Formation of the 3,5-Morpholinedione Dianion (2b).—To 0.07 mol of sodium amide in 400 ml of liquid ammonia was added 3.45 g (0.03 mol) of finely powdered 3,5-morpholinedione.[27] The resulting grey-green solution of dianion **2b** (M = Na) was allowed to stir for 30 min before being employed in the reactions described below.

Alkylations of Dianion 2b.—To 0.03 mol of dianion **2b** (M = Na), prepared as described above, was added 0.033 mol of the appropriate halide in 30 ml of dry ether. The reaction was allowed to proceed for 1 hr and was then processed as in the alkylations of dianion **2a**. Additional details are given in Table IV. Addition of benzyl bromide to **2b** produced none of the purple color characteristic of stilbene formation. Vpc analysis of crude butyl derivative **16c** showed <10% of polyalkylation products. The ir spectra of **16a–c** had principal bands at 3400 (NH) and 1700 cm^{-1} (C=O). The nmr spectrum of **16a** had peaks (DMSO-d_6) at δ 11.82 (s, 1, NH), 7.52 (s, 5, aromatic), 4.66 (q, 1, ring methine), 4.44 (s, 2, $-OCH_2C{=}O$), and 3.20 ppm (m, 2, $PhCH_2$). The spectrum of **16b** had peaks (DMSO-d_6) at δ 12.01 (s, 1, NH), 7.68 (s, 4, aromatic), 4.78 (q, 1, ring methine), 4.56 (s, 2, $-OCH_2-C{=}O$), and 3.30 ppm (m, 2, $PhCH_2$). The spectrum of **16c** had peaks (Cl_3CCN) at δ 10.20 (s, 1, NH), 4.49 (ABq, 2, $-OCH_2-C{=}O$), 4.21 (t, 1, ring methine), and 1.51 ppm (m, 9, n-C_4H_9).

Condensation of Dianion 2b with Benzophenone.—To 0.03 mol of dianion **2b** (M = Na) in 400 ml of liquid ammonia was added 6.20 g (0.034 mol) of benzophenone in 20 ml of dry ether over a period of 5 min. The reaction mixture was allowed to stir for 10 min, neutralized inversely, and then processed in the usual manner. The ir spectrum of **16d** had bands at 3450 (NH and OH) and 1690 cm^{-1} (C=O). The nmr spectrum had peaks (DMSO-d_6) at δ 11.98 (s, 1, NH), 7.76 (m, 10, aromatic), 6.42 (s, 1, OH), 5.72 (s, 1, $-OCHC{=}O$), and 4.58 ppm (AB q, 2, $OCH_2C{=}O$).

Reaction of Dianion 2b with Methyl Benzoate.—To 0.06 mol of dianion **2b** (M = Na) in 400 ml of liquid ammonia was added 4.08 g (0.03 mol) of methyl benzoate in 20 ml of anhydrous ether. The resulting olive-green suspension was stirred for 3 hr, neutralized directly with excess solid ammonium chloride, and worked up as in the aroylations of dianion **2a**. The ir spectrum of **16e** had peaks at 3450 (NH), 1640 and 1700 cm^{-1} (C=O). The nmr spectrum had peaks (DMSO-d_6) at δ 12.56 (s, 1, NH), 8.24 (m, 5, aromatic), 6.38 (s, 1, $-OCHC{=}O$), and 4.82 ppm (ABq, 2, $-OCH_2C{=}O$).

(23) M. G. Pratt, J. O. Hoppe, and S. Archer, *J. Org. Chem.*, **13**, 576 (1948).

(24) Dr. Ernst Berliner, Bryn Mawr College, personal communication, 1967.

(25) Obtained from Metal Hydrides Inc., Beverly, Mass.

(26) The DME was distilled from sodium ribbon immediately before use.

(27) This compound, mp 143–145°, was prepared by the method of W. Heintz, *Justus Liebigs Ann. Chem.*, **128**, 134 (1863): nmr (DMSO-d_6) δ 11.60 (s, 1, NH) and 4.37 ppm (s, 4, $-CH_2OCH_2-$).

TABLE IV

REACTIONS OF DIANION 2b (M = Na) WITH ALKYL HALIDES AND CARBONYL COMPOUNDS

Halide or carbonyl compound	Product	Mp, °C	Yield, %	Formula	Calcd, %			Found, %		
					C	H	N	C	H	H
Benzyl bromide	2-Benzyl-3,5-morpholinedione (16a)	92–93[a]	46	$C_{11}H_{11}NO_3$	64.38	5.40	6.83	64.08	5.50	6.62
p-Chlorobenzyl chloride	2-(*p*-Chlorobenzyl)-3,5-morpholinedione (16b)	135–136.5[a]	54	$C_{11}H_{10}ClNO_3$[d]	55.13	4.21	5.84	55.16	4.35	5.76
n-Butyl bromide	2-*n*-Butyl-3,5-morpholinedione (16c)	60–61.5[b]	67	$C_8H_{13}NO_3$	56.13	7.65	8.18	56.37	7.85	7.92
Benzophenone	2-(α-Hydroxy-α,α-diphenylmethyl)-3,5-morpholinedione (16d)	160–161.5[a]	45	$C_{17}H_{15}NO_4$	68.68	5.09	4.71	68.50	5.15	4.45
Methyl benzoate	2-Benzoyl-3,5-morpholinedione (16e)	135–136.5[c]	23[c]	$C_{11}H_9NO_4$	60.27	4.14	6.39	60.38	4.24	6.14

[a] Recrystallized from 95% ethanol. [b] Recrystallized from heptane. [c] Yield based on ester. [d] Calcd: Cl, 14.79. Found: Cl, 14.95.

Benzylation of 1b by Means of Sodium Hydride.—A mixture of 11.51 g (0.1 mol) of **1b**, 0.13 mol of methyl benzoate, and 20 g of sodium hydride dispersion in 450 ml of DME was refluxed under nitrogen for 115 hr. The DME was removed under vacuum and 150 ml of ether was added to the resulting red paste. To the ethereal suspension was cautiously added 150 ml of glacial acetic acid. The acidified mixture was filtered and the filtrate was dried and concentrated. The residue was washed with sufficient petroleum ether (bp 30–60°) to remove the mineral oil. The remaining yellow semisolid was dissolved in ether and the ethereal solution was washed with aqueous $NaHCO_3$, dried, and concentrated to afford, after initial recrystallization from benzene and then from 95% ethanol, 4.47 g (34%) of **16e**. The ir spectrum of this material was identical with that of a sample of **16e** prepared from dianion **2b**; a mixture melting point showed no depression.

Formation of the 3,5-Thiomorpholinedione Dianion (2c).—To 0.048 mol of sodium amide in 400 ml of liquid ammonia was added 2.62 g (0.02 mol) of finely powdered 3,5-thiomorpholinedione (**1c**).[28] After 30 min, the resulting dark green solution was presumed to contain 0.02 mol of dianion **2c** (M = Na).

Similarly, addition of 0.02 mol of **1c** to 0.048 mol of lithium amide in 400 ml of liquid ammonia afforded, after 30 min, a green solution of dilithio derivative **2c** (M = Li).

Alkylations of Dianion 2c. A. Benzyl chloride.—To 0.03 mol of dianion **2c** (M = Na), prepared as described above, was added 4.60 g (0.036 mol) of benzyl chloride in 30 ml of dry ether. No stilbene formation was evident. The reaction mixture was stirred for 1 hr and worked up as described for the alkylations of dianion **2a**. The resulting oil was shown by vpc to contain unreacted halide, starting imide **1c**, and at least three other components, which were assumed to be mono- and polyalkylation products.

B. *n*-Butyl Bromide.—Addition of an ethereal solution of 0.02 mol of this halide to 0.02 mol of dianion **2c** (M = Na) in 400 ml of liquid ammonia gave, after a reaction period of 1 hr, 2.38 g of red oil, which failed to crystallize. Vpc analysis revealed the presence of (in order of elution) 2-*n*-butyl-3,5-thiomorpholinedione (**17**), the two diasteromers of 2,6-di-*n*-butyl-3,5-thiomorpholinedione (**18**), and 2,2,6-tri-*n*-butyl-3,5-thiomorpholinedione (**19**) in a relative ratio of 7:6:1. A sample of monobutyl derivative **17**, collected from the chromatograph column at 200°, had mp 61–62.5°; ir 3450 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.20 (s, 1, NH), 3.76 (sharp s superimposed on broad m, 3, $-SCH_2C{=}O$ and ring methine), and 1.64 ppm (m, 9, *n*-C_4H_9).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48; S, 17.12. Found: C, 51.19; H, 6.97; N, 7.48; S, 17.03.

A sample of tributyl derivative **19** collected at 200° for spectral analysis, had nmr peaks ($CDCl_3$) at δ 8.48 (s, 1, NH), 3.90 (m, 1, ring methine), and 1.50 ppm (m, 27, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 299 with abundant fragment peaks at *m/e* 243 and 242. The two diastereomers of dibutyl derivative **18** were separated and collected from the chromatography column at 175°. The more volatile diastereomer had nmr peaks ($CDCl_3$) at δ 9.14 (s, 1, NH), 3.76 (m, 2, –CHSCH–), and 1.64 ppm (m, 18, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 243 with abundant fragment peaks at *m/e* 187 and 55. The less volatile diastereomer had nmr peaks ($CDCl_3$) at δ 9.00 (s, 1, NH), 4.00 (m, 2, –CHSCH–), and 1.82 (m, 18, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 243 with abundant fragment peaks at *m/e* 187 and 55.

A solution of 0.02 mol of **2c** (M = Li) in 300 ml of liquid ammonia was prepared in a 500-ml three-necked flask, equipped with a mechanical stirrer, air-cooled condenser, and an outlet tube at the bottom, which was connected *via* a ball and socket stopcock adapter to the center neck of a second 500-ml three-necked flask. The lower flask, which was equipped with an air-cooled condenser and magnetic stirrer, was charged with 0.06 mol of *n*-butyl bromide in 100 ml of liquid ammonia. The contents of the upper flask were added to the solution of halide in the lower flask over a period of 1 hr. The resulting mixture was stirred for an additional 30 min, neutralized with excess solid ammonium chloride, and processed in the usual fashion to give 3.07 g of a yellow oil. Analysis of the oil by vpc revealed the presence of **17**, **18**, and **19** in a ratio of 100:20:1. Dissolution of

(28) This compound, mp 129–131°, was prepared according to the method of C. Barkenbus and P. S. Landis, *J. Amer. Chem. Soc.*, **70**, 684 (1948): nmr (acetone-d_6) δ 3.96 ppm (s, $-CH_2SCH_2-$).

the oil in heptane, followed by cooling and seeding with a sample of **17** collected by vpc, produced 1.55 g (42%) of monobutyl derivative **17**, mp and mmp 59–61°.

Condensation of Dianion 2c with Benzophenone.—To a stirred solution of 0.02 mol of dianion **2c** (M = Na) in 400 ml of liquid ammonia was added 4.0 g (0.022 mol) of benzophenone in 30 ml of anhydrous ether. The resulting navy-blue solution was stirred for 4–5 min then poured rapidly into a solution of excess ammonium chloride in 100 ml of liquid ammonia. The ammonia was replaced by ether and the ethereal suspension was treated with enough cold dilute HCl to acidify the mixture. The resulting thick organic precipitate was collected by suction filtration and recrystallized from heptane–acetone to give 1.74 g (45% based on dianion **2c**) of 2,6-bis(α-hydroxy-α,α-diphenylmethyl)-3,5-thiomorpholinedione (**20**): mp 150–151°; ir 3400 (NH and OH) and 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.24 (s, 1, NH), 7.68 (m, 20, phenyl), and 6.0 ppm (broad s, 4, OH and -CHSCH-).

Anal. Calcd for $C_{30}H_{25}NO_4S$: C, 72.71; H, 5.08; N, 2.83; S, 6.47. Found: C, 72.60; H, 4.82; N, 2.73; S, 6.54.

In another experiment, the reaction mixture was neutralized inversely after 10 min to afford a quantitative recovery of benzophenone, which was isolated as its 2,4-dinitrophenylhydrazone, mp 239°.

Reaction of Dianion 2c with Methyl Benzoate.—To a solution of 0.02 mol of dianion **2c** (M = Na), prepared as described above, was added 1.36 g (0.01 mol) of methyl benzoate in 30 ml of dry ether. The reaction mixture was allowed to stir for 4 hr and was then processed in the usual manner to give a crude yellow solid, which was recrystallized from benzene to furnish 1.51 g (45% based on ester) of 2-benzoyl-3,5-thiomorpholinedione (**21**) as yellow platelets: mp 134–136°; ir 3450 (NH), 1625 and 1680 cm^{-1} (C=O). The nmr spectrum of **21** was obtained in two solvents of different polarity. In DMSO-d_6, peaks were observed at δ 12.50 (s, 1, NH), 8.50 (m, 5, aromatic), 6.42 (s, 1, ring methine), and 3.84 ppm (ABq, 2, $-SCH_2C=O$). In $CDCl_3$ peaks were observed at δ 15.70 [s, $-SC=C(OH)Ph$], 9.26 (s, 1, NH), 8.06 (m, 5, aromatic), 5.44 (s, ring methine), and 3.62 ppm (ABq, 2, $-SCH_2C=O$).

Benzoylation of 1c by Means of Sodium Hydride.—A mixture of 2.62 g (0.02 mol) of **1c**, 2.73 g (0.02 mol) of methyl benzoate, and 8.0 g of sodium hydride dispersion in 350 ml of DME was refluxed under nitrogen for 22 hr. The reaction was processed as in the sodium hydride benzoylation of **1b** to produce 3.81 g (81%) of **21**: mp 127–129°, and 134–136° after two recrystallizations from benzene. The infrared spectrum of this material was identical with that of a sample prepared by benzoylation of dianion **2c**.

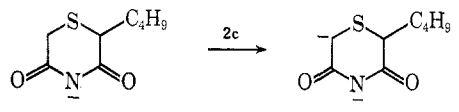
Discussion

Certain additional comments concerning the chemistry of dianions **2a–c** are now presented in this section.

As mentioned above, alkylations of dianion **2a** (M = Na) with the primary halides listed in Table I proceeded smoothly. However, attempted alkylations with β-phenylethyl chloride and benzhydryl chloride afforded styrene and tetraphenylethylene, respectively. Apparently dianion **2a** served as a base rather than a nucleophile in these two instances to effect elimination in the case of the former halide and dimerization of the latter.[29] Competitive elimination may also have been responsible for the failure of dianion **2a** to undergo satisfactory alkylation with isopropyl bromide. When dianion **2a** (M = K) was prepared by means of potassium amide and alkylated with benzyl chloride, the yield (65%) of benzyl derivative **3d** was comparable to that (80%) obtained with sodium amide. In a similar experiment employing lithium amide, **3d** was obtained in only 15% yield and stilbene (35%) was isolated, indicating that the twofold ionization of **1a** to form **2a** (M = Li) was incomplete.[30]

(29) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960), have observed similar elimination and dimerization reactions on treatment of acetylacetone dianion with these halides.

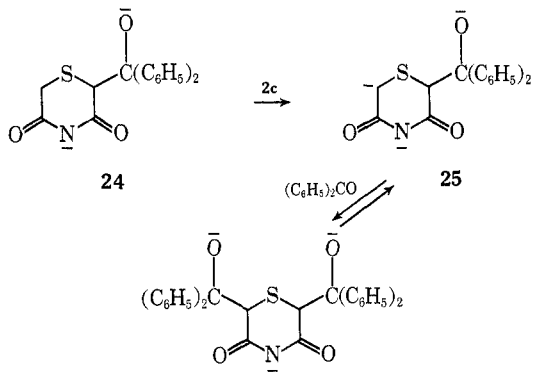
The tendency for dianion **2c** (M = Na) to yield appreciable amounts of polyalkylation products is undoubtedly caused by rapid proton–metal exchange between this intermediate and alkylated monoanion **22** to produce dianion **23**, which then undergoes further alkylation. When the more covalent dilithio derivative of **2c** is employed, the exchange reaction is inhibited and monoalkylation predominates. In addition, inverse mixing of the reactants serves to suppress the formation of alkylated dianion **23** by keeping the concentration of original dianion **2c** low throughout the reaction.



22 **23**

Formation of dialcohol **20** in the reaction of **2c** (M = Na) with benzophenone evidently involves a similar proton–metal exchange in which the initially formed intermediate **24** loses a methylene proton to dianion **2c** to form trianion **25**. Reaction of **25** with a second molecule of benzophenone then produces trianion **26**, which affords dicondensation product **20** on neutralization (Scheme I). The fact that the yield of **20** decreased dramatically, while the recovery of benzophenone increased, when neutralization was delayed, implies that this reaction represents an example of kinetic *vs.* thermodynamic control in which the kinetically favored intermediate **26** is eventually converted to the thermodynamically more stable monanion of **1c** and the sodium amide adduct of benzophenone.[31]

SCHEME I



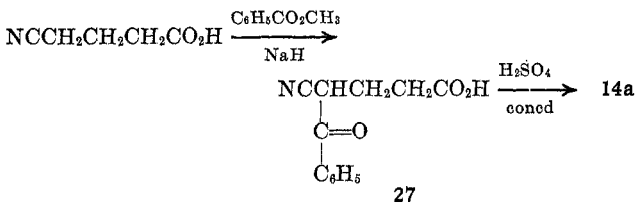
24 **25** **26**

During the course of the present work, several alternative methods for the preparation of α-benzoyl derivatives **14a**, **16e**, and **21** were investigated. Thus, **14a** was synthesized through cyano keto acid **27** as shown in Scheme II, but the overall yield was quite low. Direct introduction of a benzoyl group at the α position of **1b** and **1c** was accomplished satisfactorily on treatment of these compounds with methyl benzoate and excess sodium hydride in refluxing 1,2-dimethoxyethane (DME). However, sodium hydride was not suitable

(30) See R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967), and references cited therein.

(31) For a discussion of kinetic *vs.* thermodynamic control in the addition of benzophenone to 1,3-dialkali salts of phenylacetamide in liquid ammonia, see E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966).

SCHEME II



for alkylations and carbonyl addition condensations involving **1a–c**, presumably because dianion formation was incomplete with this reagent.[32]

The present dianion route to α-substituted derivatives of **1a–c** permits the synthesis of a variety of such compounds in a single operation under mild conditions. Condensation at the carbanion site of dianions **2a–c** followed by hydrolysis of the imide function also offers a facile two-step method for the preparation of certain acyclic compounds, *e.g.*, the synthesis of 2-alkylglutaric and 4-aroylbutyric acids *via* dianion **2a**. Even in reactions where yields were low the dianion method may still be perferred over more circuitous procedures because of its greater convenience and the ease with which the water soluble heterocyclic precursors to dianions **2a–c** can be separated from the desired products.

(32) See J. F. Wolfe, G. B. Trimitsis, and C. R. Hauser, *Can. J. Chem.*, **43**, 2561 (1968).

Registry No.—**3b**, 19450-21-6; **3c**, 24866-78-2; **3e**, 24866-79-3; **3f**, 24866-80-6; **3g**, 24866-81-7; **3h**, 24866-82-8; **3i**, 24866-83-9; **4**, 24866-84-0; **5**, 24866-85-1; **6**, 19450-22-7; **7**, 24929-21-3; **8**, 24866-87-3; **9**, 24866-88-4; **10**, 24866-89-5; **12**, 24866-90-8; **13**, 24866-91-9; **14a**, 24866-92-0; **14b**, 19450-23-8; **14c**, 24866-94-2; **16a**, 24866-95-3; **16b**, 24866-96-4; **16c**, 24866-97-5; **16d**, 24866-98-6; **16e**, 24866-99-7; **17**, 24867-00-3; **18**, 24929-22-4; **20**, 24867-01-4; **21**, 24867-02-5; **27**, 24867-03-6; 2-(*p*-chlorobenzyl)glutaric acid, 24867-04-7.

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Optically Active Adamantanes *via* Microbiological Hydroxylation. Absolute Configuration and the "Anti-octant" Effect of the Axial 3-Methyl Group of Cyclohexanone[1]

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Oxygenation of *N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine (**3**) with *Sporotrichum sulfurescens* (ATCC 7159) gave *N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,7-diol (**5**) and (1*S*)-*N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,6α-diol (**6**). Oxygenation of the epimeric substrate, *N*-benzoyl-4α,*N*-dimethyl-1-adamantanamine (**4**), gave (1*R*)-*N*-benzoyl-6α,*N*-dimethyl-1-adamantanamine-4α-ol (**11**). Diol **6** readily formed a cyclic sulfite ester (**7**), proving the 1,3 diaxial relationship of the two hydroxyl groups and also establishing the relative configuration of the methyl substituent in all compounds. Nmr established that diol **6** was substituted at the 4,6 positions. Optical activity was demonstrated by circular dichroism (CD) spectra of ketones **8** and **12**, derived from **6** and **11**, respectively. The absolute configuration of the optically active molecules was assigned on the basis of the CD curve of (1*R*)-*N*-benzoyl-*N*-methyl-6-methylene-1-adamantanamine-4-one (**9**), derived from **8**. The two series of products were correlated by reduction of **9** to a mixture of **12** and its epimer, **10**. Ketone **12**, which contains an axial 3-methyl cyclohexanone system, demonstrates a weak "anti-octant" effect for this system in its CD spectrum.

Part A

Optically active adamantanones have been prepared[2] in order to test the effects of certain substituents on the octant rule.[3] Other optically active adamantanes have been prepared[4] in order to assess the effect of distance upon the optical rotatory power of various functional groups in chiral molecules.[5] In every case, resolution was achieved by the classical method of fractional crystallization of the appropriate carboxylic acid salt. We have recently found that optically active products may be obtained from the microbiological oxygenation of either achiral molecules[6] or racemic mixtures of chiral molecules[7] by the mold *Sporotrichum sulfurescens* (ATCC 7159). We have also found that the same microorganism gives good yields of hydroxylated products when *N*-acyl-1-adamantanamines are used as substrates.[8] The possibility of preparing an optically active adamantane by a microbial reaction therefore was of interest, since this would provide an alternate route to such molecules and would also further test the ability of the microbial reagent to achieve stereoselective reactions. The hydroxylation of the

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(1) Stereochemistry of Microbiological Hydroxylation. Part V.

(2) (a) W. S. Briggs, M. Suchý, and C. Djerassi, *Tetrahedron Lett.*, 1097 (1968); (b) G. Snatzke and G. Eckhardt, *Chem. Ber.*, **101**, 2010 (1968); (c) G. Snatzke and G. Eckhardt, *Tetrahedron*, **24**, 4543 (1968).

(3) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(4) (a) H. Hamil and M. A. McKervey, *Chem. Commun.*, 864 (1969); (b) J. Applequist, P. Rivers, and D. E. Applequist, *J. Amer. Chem. Soc.*, **91**, 5705 (1969).

(5) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).

(6) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(7) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **34**, 2279 (1969), and references cited therein.

(8) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3201 (1968).