A Study of the Synthesis of Barbiturates in Dimethyl Sulfoxide Solvent

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Dimethyl sulfoxide (DMSO) has been found to enhance greatly the rates of barbiturate formation from substituted malonic esters, urea, and a strong base. Various parameters were studied in this solvent to delineate best conditions for the condensation, culminating in the selection of reagent ratios of 1 part ester, 2 parts base, and 5–10 parts urea in DMSO at room temperature. The efficacy of this system was demonstrated by the preparation of 5-*t*-butyl-5-ethylbarbituric acid (*t*-butethal) for the first time. The latter compound was about 50% less active and slightly less toxic than amobarbital, and comparable (if not superior) to phenobarbital in duration of anesthesia.

The enhanced rates of anionic reactions in dimethyl sulfoxide (DMSO)[2,3] suggested application of this solvent to the synthesis of barbiturates. We were rewarded in our initial trials by observation of a spectacular increase in the rate of formation of barbital (5,5-diethylbarbituric acid) in the presence of DMSO (time required for 30% yield of barbital with sodium ethoxide in refluxing ethanol, 770 min; with potassium ethoxide in DMSO at 25°, 1.3 min). It would seem from these data that the DMSO method of preparation of barbiturates would be widely applicable and possibly capable of producing certain derivatives more efficiently than previous methods. For this reason, a thorough study was undertaken to ascertain the best conditions for preparing barbiturates and to clarify the effect of various factors which affect the synthesis. We hoped that the new method would make it possible to prepare certain 5-*t*-butyl derivatives, hitherto inaccessible.

Side Reactions.—The principle reactions observed were barbiturate formation, decarbethoxylation, ester interchange, and degradation of urea. Decarbethoxylation of the malonic ester was shown by Cope and McElvain[4] to be the reason that diethyl diphenylmalonate failed to give diphenylbarbituric acid and instead gave diphenylacetic acid in 80% yield. The same decarbethoxylation reaction was found to be very important in the DMSO system at 25°. When diethyl diethylmalonate was exposed to 1.5 equiv of urea and 4 equiv of potassium ethoxide in DMSO, 55% of diethylbarbituric acid and 45% of ethyl diethylacetate were found after 3 hr. Decarbethoxylation definitely must be contended with in seeking any improvement of yields of barbiturates in DMSO.

Ester interchange was found to be important. When equivalent amounts of diethyl diethylmalonate and potassium *t*-butoxide were allowed to react at 25° for 3 hr in DMSO, only 34% of the total esters recovered remained as the diethyl ester. About 43% had been converted to the mixed ethyl *t*-butyl ester and 23% to the di-*t*-butyl ester.

The base-induced degradation of urea was shown to be unimportant at 25° by negative tests for ammonia. However, at steam-bath temperatures ammonia could be detected. Surprisingly, ethyl carbamate was not the product of ammonia loss but, rather, potassium cyanate as previously demonstrated.[5]

Thus, if condensation was carried out at room temperature, the only important competing reactions were decarbethoxylation and ester interchange, the latter having no bearing on barbiturate formation other than retardation of rates when *t*-butyl esters were formed.

Effect of Water.—Most texts stress that the absence of water in the ethoxide–ethanol is a prime requisite for good yields.[6] We were surprised at the tolerance of the DMSO system to water, the yields decreasing in a simple linear relationship as shown. The per cent yields of barbital are given wherein 0.2 mmole of ester, 0.3 mmole of urea, and 0.4 mmole of potassium ethoxide reacted in 5 ml of DMSO containing various amounts of water (equivalents of water, per cent yield of barbital: 0, 80; 1.4, 70; 2.8, 67; 4.2, 62; 7.0, 47). It is concluded that water must be removed for maximum yields but that no drastic drop in yields can be attributed to "traces" of water. Indeed, it appears that even NaOH catalyst, which must be the predominant species present when 4 equiv or more of water were present, gave barbiturate yields as high as 62%. The tolerance of the DMSO system to water may be attributed to associated species of water which do not solvate the anions efficiently.[7]

Mechanism.—Since the mechanism of barbiturate formation has never been precisely defined, we propose the following series of steps which best explain our data and those of earlier workers.[4,8–11]

The condensation can be visualized to proceed through a small equilibrium concentration of urea anion, very roughly calculated as 10^{-5} mole in a molar solution of urea and ethoxide anion in ethanol (pK (ethanol) = 19; pK (urea) = 29 ± 4).[12] The urea anion concentration can be increased by four factors: (a) increasing the alkoxide concentration, (b) shifting to DMSO solvent which increases the base strength of the alkoxide anion by a considerable factor,[13] (c) lowering the reaction temperature,[13] and (d)

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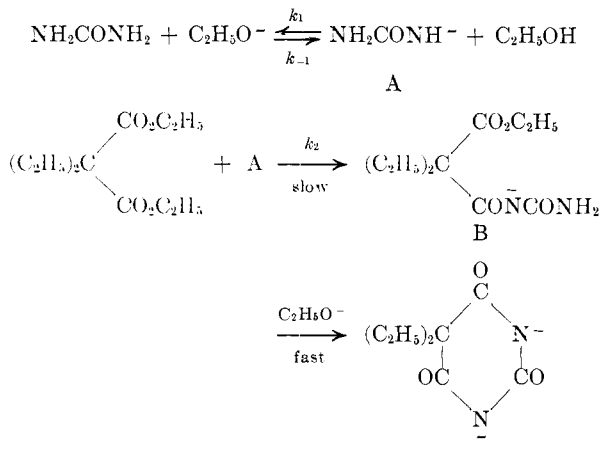

shifting to a stronger base such as *t*-butoxide anion. The use of DMSO therefore has been ideal in bringing factors b and c to bear on increased urea anion formation probably operating by means of dissociation of anionic aggregates.[13] The stronger base, *t*-butoxide, was not utilized in comparative studies because rates of barbiturate formation were too rapid to measure.

There can be no doubt that the reaction of the urea anion with the substituted malonic ester is rate determining. Modifications in the structure of the malonic ester either in the acid or alcohol portion influence the rate of condensation. Following the formation of B, a very rapid ring closure to the barbiturate dianion occurs. Since the rapidity of this step had never been shown, the imide, ethyl diethylmalonurate[14] of the anion, B, was synthesized and its rate of ring closure studied. The rate was too rapid to measure under optimum conditions of barbital synthesis. It was determined, however, that in a 0.1 *M* ethanolamine–phosphoric acid buffer at pH 10, $k_1 = 1.44$ min^{-1}, $t_{1/2} = 0.48$ min at 25°. With such a fast ring closure in mildly alkaline buffer solution, one would expect instantaneous ring closure in sodium ethoxide solution.

Delineation of Best Conditions for Barbiturate Formation in DMSO.—Of all the parameters studied, the effect of base catalyst was the most important in determining yield. The yield rises to a maximum of about 70% with 2 equiv of base catalyst and then decreases with increasing amounts of base catalyst. This is a consequence of the competing decarbethoxylation reaction. At 2 equiv of base, the yield should be 100% as the barbiturate dianion is formed. With increasing base concentration, decarbethoxylation becomes more important, the yield of barbiturate decreasing, more so with *t*-butoxide anion than with ethoxide anion. Moreover, as the malonic ester becomes more branched, as in diethyl ethyl(1-methylbutyl)-malonate, the decarbethoxylation becomes more important, yields reaching a maximum of only 60%. One method has been proposed to minimize decarbethoxylation in which the base is added at a rate paralleling the condensation rate.[15] Fortunately, another parameter could still be varied, the urea concentration. Using 2 equiv of potassium ethoxide in DMSO with diethyl diethylmalonate, the yields were found to vary as shown in Table I. The excellent response of yield to increasing urea concentration suggested an effect more than one of simply increasing urea anion concentration, perhaps some solvation effect on the anion, but, in any event, conditions were now delineated to prepare a novel barbiturate. The conditions were 2 equiv of potassium *t*-butoxide, 5–10 equiv of urea, and DMSO at the lowest temperature feasible. The ester selected for condensation was diethyl ethyl-*t*-butylmalonate. Two previous attempts have been made to prepare the barbiturate from this ester, neither attempt being successful. Dox and Bywater reported an attempt to prepare this compound.[16] Their product, mp 192.5°, undoubtedly was mixed with large amounts of barbital and monoethylbarbituric acid which melt in the same range. Bush and Beauchamp were able to prepare 5-methyl- and 5-allyl-5-*t*-butylbarbituric acids but reported a very low yield (2%) of impure 5-ethyl-5-*t*-butylbarbituric acid.[17] Under our recommended conditions at 25° for 60 hr, we obtained a 20% yield of pure 5-ethyl-5-*t*-butylbarbituric acid (hereafter called *t*-butethal), mp 248–249° dec. Longer exposure times are being studied to increase yields, but the success of this preparation is sufficient to indicate that other very hindered barbiturates can now be made.

TABLE I

Urea, equiv	% yield	Temp, °C
1.5	71	25
5	90.5	25
10	98	Steam bath

Pharmacology.—The median anesthetic dose and median fatal dose for *t*-butethal in mice was found to be approximately 50% higher than for amobarbital. *t*-Butethal showed a lag in onset of anesthesia comparable to phenobarbital, and duration of anesthesia was similar to that for this well-known drug. Some mice were anesthetized for as long as 48 hr.

Experimental Section

General Procedure for the Rate and Product Studies.—The malonic ester and urea were each weighed into a flask equipped with a side-arm removal port and drying tube. Then, the appropriate amount of dry DMSO was added, and the contents were mixed. At complete solution, the flask was immersed in a thermostated, circulating water bath, set at 25.0 ± 0.1° and brought to temperature equilibrium. The appropriate amount of KOR–DMSO solution was added quickly at time zero. Elapsed time was recorded using a stopwatch, and 1.00-ml samples were removed at predetermined times, taking the time of quenching in ice water as the time of removal of that particular sample.

General Analysis Technique.—Samples were removed from the reaction mixture with an automatic-filling syringe calibrated to deliver 1.00 ± 0.05 ml. These 1-ml aliquots were quenched by immediate discharge into the appropriate amount of chilled distilled H_2O in a volumetric flask (usual dilutions were either 1:10 or 1:25 depending on the concentration of barbiturate present). The contents of the flask were made to volume with H_2O and stored in the refrigerator until used for the ultraviolet analysis. The analyses were carried out according to the method of Bush;[18] the buffers were 0.1 *M* (pH 6.0 and 10.0) ethanolamine phosphate solutions.

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TABLE II[a]

SYNTHESIS OF BARBITAL

Solvent	Base	Equiv of base	Yield, %
EtOH[b]	NaOEt	2[c]	2.5
		2[d]	14
		4[d]	21
		8[d]	37
DMSO	KOEt	0.5	25
		1	47
		2	71
		2[e]	90
		2.5	70
		3	68
		4	61
		4[e]	87
DMSO	KO-*t*-Bu	0.5	26
		1	48
		2	61.5
		2[f]	98
		3	48.5
		4	38

[a] All reactions were carried out with 1 mmole of malonic ester and 1.5 equiv of urea in 25 ml of solvent for 3 hr at 25°, except as noted (per cent yield based on the malonic ester). [b] Reflux temperature. [c] 1440 min. [d] 10 equiv of urea, 1200 min. [e] 5 equiv of urea. [f] 10 equiv of urea.

TABLE III[a]

SYNTHESIS OF PENTOBARBITAL

Solvent	Base	Equiv of base	Yield, %
DMSO	KOEt	1[b]	31
		2	60
		2[c]	73
		3	58.5

[a] All reactions were carried out using 1 mmole of malonic ester and 1.5 equiv of urea in 25 ml of solvent for 6 hr at 25°, except as noted (per cent yield based on the malonic ester). [b] 1 hr. [c] 5 equiv of urea.

Effect of Reagent Concentrations on Yields and Rates.—The results on yields are given in Tables II and III. Some of the rates are given in the discussion. Kinetic results were quite complex because of the numerous equilibria and side reactions involved. Therefore, most comparisons of times were made at 30% product formation (more detail is available in thesis of J. A. B.[1]) when 1 mmole of ester, 1.5 mmoles of urea, and 2 mmoles of base were dissolved in 25 ml of DMSO (time in minutes for 30% reaction: KOC_2H_5 and diethyl diethylmalonate at 25°, 1.3 min; potassium *t*-butoxide, too fast to measure; diethyl ethyl(1-methylbutyl)malonate and KOC_2H_5, 45 min; time in minutes for 30% reaction of various esters of diethylmalonic acid using 1 mmole of KOC_2H_5: dimethyl ester, 0.5 min; diethyl ester, 1.3 min; diisopropyl ester, 18 min; diallyl ester, 20 min.

The Synthesis and Cyclization of Ethyl Diethylmalonurate.—To a slurry of 3.0 g (0.020 mole) of silver cyanate[19] in 20 ml of hexane was added 4.1 g (0.020 mole) of diethylmalonyl chloride monoethyl ester.[20] The mixture was heated gently under reflux for 20 hr. Then, 1.85 ml (0.020 mole) of concentrated NH_4OH was added, and reflux was continued for 0.5 hr. The AgCl was removed, and the ether was partially removed by evaporation to give 1.25 g of colorless crystals, a mixture of ethyl diethylmalonamate and ethyl diethylmalonurate. Upon recrystallization from petroleum ether (bp 60–70°), two crystal forms were noted, needles and prisms. These were mechanically separated, whereupon 330 mg of needles, mp 77–81°, and 65 mg of prisms, mp 83–85°, were obtained. The needles were identified as ethyl diethylmalonamate [lit.[21] mp 79°] and the prisms as ethyl diethylmalonurate [lit.[19] mp 85°] by ir spectrum and by quantitative conversion to barbital when treated with 0.10 *M* (pH 10.0) ethanolamine–phosphate buffer.

Anal. Calcd for $C_9H_{18}N_2O_4$ (ethyl diethylmalonurate): N, 12.17. Found: N, 11.92.

Kinetics of Cyclization.—Crystalline ethyl diethylmalonurate (17.8 mg) was dissolved in 25.00 ml of 20% EtOH. This was diluted 1:50 with the 0.10 *M* pH 6 and pH 10 buffers preequilibrated at 25°. The buffered solutions were quickly transferred to the Beckman cuvettes, and the optical density at 239 mμ was monitored with time using a Beckman DB recording spectrophotometer. The results are given in the discussion.

Diethyl Ethyl-*t*-butylmalonate.—To a stirred suspension of 3.31 g (0.066 mole) of a 50% mineral oil dispersion of NaH in 25 ml of DMF at room temperature was added 14.4 g (0.066 mole) of diethyl *t*-butylmalonate.[22] The mixture was stirred until H_2 evolution ceased. Then, 15.0 ml (0.20 mole) of EtBr was introduced slowly, and the mixture was stirred for 1 additional hr. It was then poured into an equal volume of H_2O and extracted with 2 vol. of ether. The ether extract was dried ($MgSO_4$) and stripped of solvent, and the residue was fractionally distilled. Diethyl ethyl-*t*-butylmalonate, 11.5 g (70%), was obtained as a colorless liquid, bp 101–105° (6.5 mm), $n^{25}D$ 1.4370.[17]

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.80. Found: C, 64.30; H, 9.97.

5-Ethyl-5-*t*-butylbarbituric Acid.—Diethyl ethyl-*t*-butylmalonate (2.0 g, 8 mmoles) and 2.4 g of urea (40 mmoles) were dissolved in 25 ml of DMSO. To this solution was added dropwise with stirring a solution of 1.8 g (16 mmoles) of KO-*t*-Bu in 20 ml of DMSO. After the addition was complete, the reaction mixture was stirred at room temperature for about 60 hr. The reaction was terminated by pouring the mixture into 2 vol. of ice–H_2O, extracting the basic solution with ether to remove unreacted ester, and then acidifying with HCl. The acid solution was extracted again three times with ether to remove the barbiturate. The extracts were dried ($MgSO_4$), and the ether was removed under vacuum, leaving a crystalline residue which, recrystallized from methanol, gave 350 mg (20%) of colorless crystals, mp 247–248° dec, $\lambda_{max}^{pH\ 10}$ 245 mμ (ε 8100) (0.10 *M* ethanolamine–phosphate buffer). The ir spectrum (KBr) showed characteristic bands at 3440, 3250, 1760–1690 (broad), 1430, and 830 cm^{-1}. The nmr spectrum (NaOD in D_2O) consisted of a quartet at τ 8.00 (area 2), a triplet at 9.24 (area 3, ethyl group), and a singlet at 8.95 (area 9, *t*-butyl). The p*K'* (first ionization constant) is 8.1. The partition coefficient between 1-chlorobutane and aqueous buffer (pH 6.8, 0.1 *M* phosphate) is 0.20, about one-tenth that of amobarbital.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.58; H, 7.60; N, 13.20; neut equiv, 212. Found: C, 56.23; H, 7.44; N, 13.37; neut equiv, 207.

Pharmacology.—The technique used was essentially that of Butler.[23] The pure acid forms of amobarbital and *t*-butethal were weighed and dissolved in 2 equiv of 0.03 *N* NaOH and enough NaCl to make the solutions isotonic. The final concentrations of drugs were 3–4 mg/l. (pH 11.5); both drugs were stable in these solutions for at least 12 hr at room temperature as judged from no changes in optical density. Intravenous injections of 0.3–0.5 ml were made during 25–35 sec into male, albino mice (Dublin, ICR) of 20–25 g. Doses larger than 125 mg/kg were injected intraperitoneally in solutions containing 5–6 mg/ml. Ten mice were used at each of six doses for each drug. The median anesthetic and median fatal doses were estimated by interpolation from these results (Table IV). A mouse was considered "anesthetized" if he was unable to right himself when stimulated by pinching his tail.

TABLE IV

Compd	AD_{50}, mg/kg	LD_{50}, mg/kg
Amobarbital	60	175
Amobarbital[25]	54	
t-Butethal	100	225

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