VIII crystallized, mp 99° (lit.[7] mp 99°), yield 200 mg (24%, based on VIb). *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

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(7) R. Wolffenstein and F. Hartureh, *Ber.*, **48**, 2043 (1915).

Malonamic Esters. A New Class of Sedative–Tranquilizers

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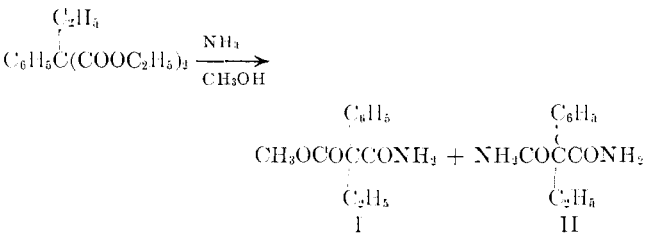
Certain alkylarylmalonamates were found to possess sedative and tranquilizing activity in animals. Methods of synthesis, some chemical transformations, and structure–activity relationships of these compounds are described. The pharmacology and metabolic fate of the most interesting compound, diethyl ethylphenylmalonamate (I), is discussed. This compound shares many of the pharmacological properties of phenobarbital, meprobamate, and glutethimide, but does not possess barbiturate-like physiological dependence capacity in barbital-dependent dogs.

When diethyl ethylphenylmalonate was left in contact with methanolic NH_3 for an extended period of time, in addition to the anticipated diamide II, a small quantity of the transesterified monoamide, methyl ethylphenylmalonamate (I), was obtained and found to



have an interesting profile of CNS depressant activity in animals. A more convenient synthesis was then developed, and a number of related compounds were prepared and tested in order to study the effect of structural changes on the CNS activity.

Most of the compounds (Table I) were prepared *via* the acylal intermediates III, employing the route shown in Scheme I. The acylals were generally crystalline solids, prepared in good yield by condensation of the appropriately substituted malonic acid with acetone in the presence of acetic anhydride and sulfuric acid.[1] Reaction of the acylals with alkoxides gave the malonic monoesters IV; tertiary alkoxides did not react with the acylals.

The half-esters IV were converted to the acid chlorides with $SOCl_2$ and then to the amide by reaction with aqueous NH_3 or amine.

Attempts to prepare ethyl phenylmalonamate by this route failed. Evidently the acylal formed a salt of the enol form, for the acylal was recovered unchanged after aqueous hydrolysis of the reaction mixture.

Another route to I consisted of converting the acylal III to the malonamic acid V by reaction with aqueous NH_3; no reaction occurred when ethereal or methanolic NH_3 was used. Esterification of V with CH_2N_2 proceeded smoothly to give I.

Reaction of the malonamic acid V with acetone under the conditions used for the preparation of the acylals gave a nitrogen analog VI. This is the first example of a 4,6-oxazinedione.

Another synthesis of malonamates, particularly convenient for large-scale preparations, utilizes carbonation of an appropriately substituted acetonitrile (Scheme II). Methyl diphenylmalonamate was prepared by a similar procedure except that the anion prepared from diphenylacetonitrile was directly converted to the ester (VIII, R = C_6H_5) with methyl chloroformate.

The enantiomers of I were obtained as follows. The nitrile acid VII was resolved using quinine to give the levo rotating acid. Esterification gave the levo rotating ester VIII, and hydrolysis gave the dextro rotating product I. From the enriched filtrates, the dextro rotating acid was isolated using *l*-3-phenyl-2-propylamine and converted to I by the same route. (The relationship between the sign of rotation of the optically active isomers and the structures are indicated by the + and − symbols in Scheme II.)

Some chemical reactions of I are illustrated in Scheme III. Methyl ethylphenylmalonamate reacts with chloral to give a hemiacetal-type condensation product IX. Heating I with $Pb(OAc)_4$ in MeOH gives a Hofmann-type rearrangement[2] with formation of the carbamate X. If the lead tetraacetate reaction is carried out in AcOH,[3] the N-acetyl derivative XI of the rearranged product is obtained.

Attempts to convert I to the N-acetyl derivative by refluxing with Ac_2O, or to the thioamide by reaction with P_2S_5, led, in both cases, to the dehydration product methyl 2-phenyl-2-cyanobutyrate (VIII).

Structure–Activity Discussion.—In general, the malonamates have a profile of sedative and/or tranquilizing activity as determined by gross observations in the rat. Some of the data on biological activity of these compounds are summarized in Table I. A more detailed description of the activity of one of these compounds (I) is given further on in this paper.

Examination of the data reveals that relatively minor changes in the structure of the parent compound I sig-

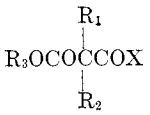
(1) P. J. Schnur and S. G. Cohen, *J. Am. Chem. Soc.*, **80**, 4933 (1958).

(2) Procedure of B. Acott, A. L. J. Beckwith, A. Hassanali, and J. W. Redmond, *Tetrahedron Letters*, 4039 (1965).

(3) Procedure of B. Acott and A. L. J. Beckwith, *Chem. Commun.*, 161 (1965).

TABLE I

PROPERTIES OF MALONAMIC ESTERS

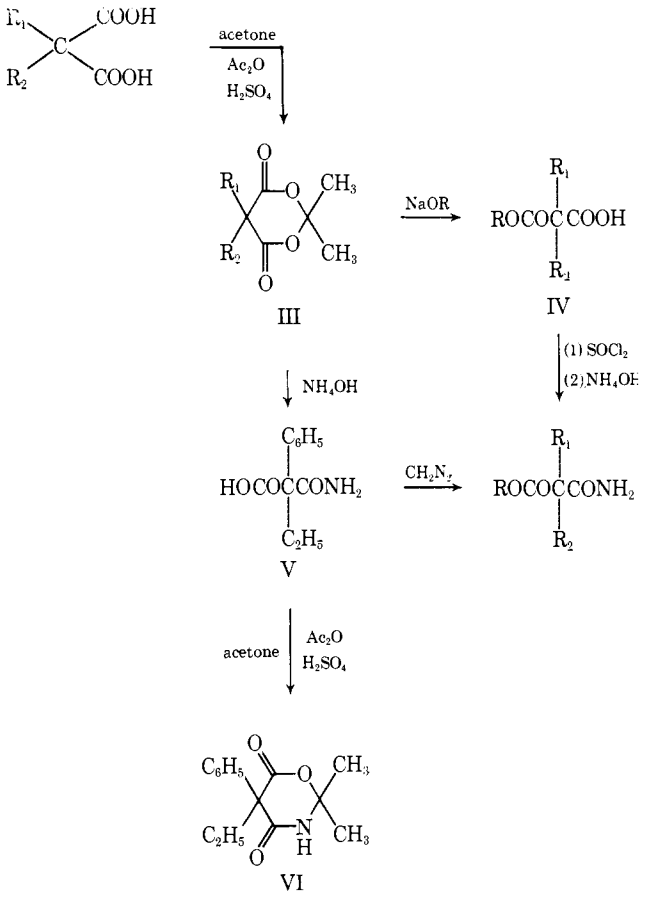


Compd	R_1	R_2	R_3	X	Yield,[a] %	Mp, °C	Overt effects[b] in rat	ED50, mg/kg *po* Anti-met[c]	ED50, mg/kg *po* MES[d]	Formula[i]
1	C_6H_5	Me	Me	NH_2	50	95–96	300	NSA[h]	85	$C_{11}H_{13}NO_3$
2(V)	C_6H_5	Et	H	NH_2	37	118–120[e]	>300	NSA	NSA[h]	
3(I)	C_6H_5	Et	Me	NH_2	91	90–100.5	50	24	76	$C_{12}H_{15}NO_3$
4	C_6H_5	Et	Me	NHMe	60	*f*	300	NSA	NSA	$C_{13}H_{17}NO_3$
5	C_6H_5	Et	Me	NMe_2	70	51–52	300	NSA	NSA	$C_{14}H_{19}NO_3$
6	C_6H_5	Et	Et	NH_2	75	73–74[g]	50	52	35	$C_{13}H_{17}NO_3$
7	C_6H_5	Et	*i*-Pr	NH_2	50	111.5–114	300	NSA	...[j]	$C_{14}H_{19}NO_3$
8(VI)	C_6H_5	Et	$-C(CH_3)_2NH-$		5	153–154	>300	NSA	NSA	$C_{14}H_{17}NO_3$
9	C_6H_5	Bu	Me	NH_2	45	131–132	>300	NSA	NSA	$C_{14}H_{19}NO_3$
10	C_6H_5	C_6H_5	Me	NH_2	50	192–193.5	>300	NSA	NSA	$C_{16}H_{15}NO_3$
11	$(CH_3)_2CHCH_2CH_2$	Et	Me	NH_2	60	96–97	>300	NSA	NSA	$C_{11}H_{21}NO_3$
Meprobamate							125	47	120	
Phenobarbital							50	33	24	

[a] Based on III or immediate precursor. [b] Minimum dose (mg/kg *po*) at which overt effects are produced. [c] Protection against metrazol-induced convulsions in rats. [d] Protection against maximal electroshock seizures in mice. [e] E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani [*Helv. Chim. Acta*, **42**, 2370 (1959)] reported mp 112–113°. [f] Bp 122° (0.025 mm). [g] Lit.[e] mp 78–79°. [h] No significant activity at a dose of 50 mg/kg *po*. [i] All compounds were analyzed for C, H, and N except **2**, a known compound. [j] Active at a dose of 100 mg/kg *po*.

SCHEME I

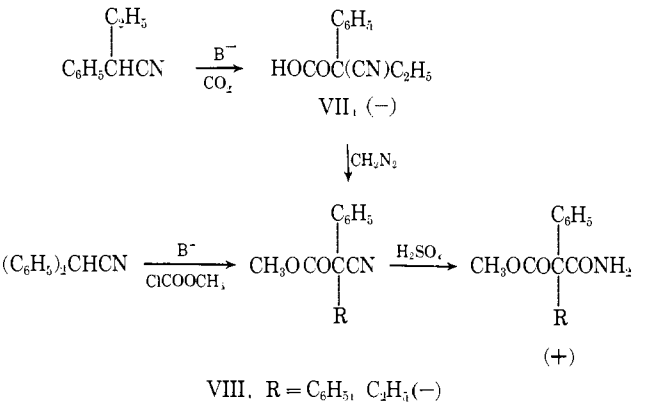
SYNTHESIS OF MALONAMATES *via* THE ACYLAL ROUTE



III IV V VI

SCHEME II

SYNTHESIS OF MALONAMATES *via* THE NITRILE ROUTE



VII, (−) VIII, R = C_6H_5, C_2H_5 (−) (+)

nificantly decreases CNS depressant activity as measured by gross observation in the rodent. Substitution on the amide N (**4** and **5**) was found to eliminate most of the CNS depressant activity. Consequently, subsequent studies were done with unsubstituted amides.

The ethyl ester **6** at the ED_{50} dose produced only weak protection against the clonic convulsion induced by intravenously administered metrazol. Higher esters are much less active and the free acid is inactive in our test procedures. Activity for CNS depressant action required one aryl and alkyl group, since diaryl (**10**) or dialkyl (**11**) compounds produced little overt CNS depressant activity in the rodent. There was little significant difference in the activity of *d*-, *l*-, or *dl*-I.

Pharmacology of Methyl Ethylphenylmalonamate (I).—In animals methyl ethylphenylmalonamate (I, **3** in Table I) has sedative and tranquilizing activity. It produces overt signs of CNS depression in all species of animals tested, sharing many of the pharmacological properties of phenobarbital, meprobamate, and glutethimide.

Methyl ethylphenylmalonamate, phenobarbital, and glutethimide produce ataxia in the mouse at approximately the same minimal dose levels of 50 mg/kg orally. These studies showed that I differs from phenobarbital in that it exhibits a faster onset of action, a shorter duration of action, and is much less toxic in animals. In addition, this agent does not produce the marked degree of excitement, hypersensitivity, confus-

TABLE II

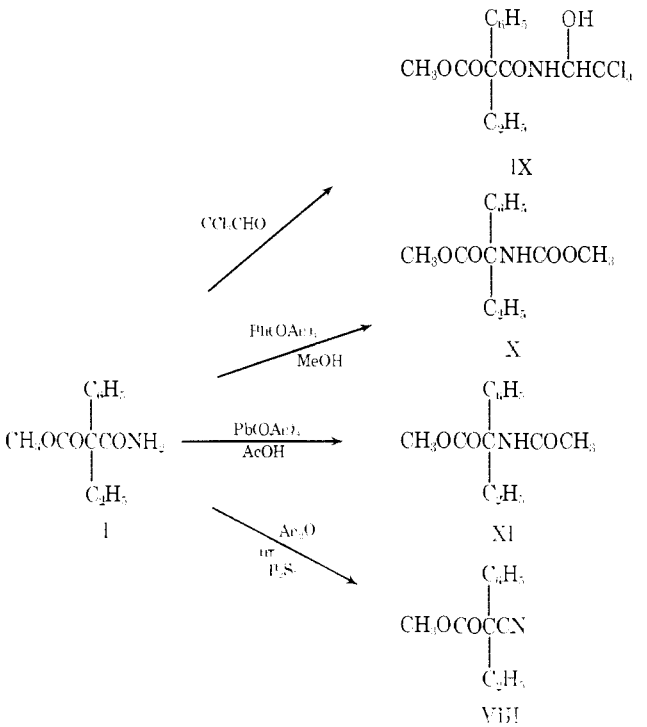
COMPARATIVE EFFECTS ON SPONTANEOUS MOTOR ACTIVITY IN MICE

Drug	Dose, mg/kg *po*	Av % change relative to controls[a] — Pretreatment time, min[b] 0	30	60	120	180	240
Methyl ethylphenylmalonamate (I)	25	7 ↑	19 ↑				
	50	28 ↓	39 ↑	18 ↑	8 ↓		
	100	28 ↓	29 ↑	54 ↑	37 ↑	19 ↑ *	47 ↑ *
	150	20 ↓	55 ↓ *	1 ↓			
	200	38 ↓ *	64 ↓ *	70 ↓ *	NS ↓	NS ↓	NS ↑
Phenobarbital	25	6 ↓	14 ↑	29 ↑	14 ↑		
	50	9 ↑	76 ↑ *	110 ↑	81 ↑ *		
	100	30 ↑	142 ↑ *	106 ↑ *	78 ↑ *	187 ↑ *	145 ↑ *
Glutethimide	25	13 ↑	11 ↓				
	50	27 ↑	77 ↑ *	31 ↑	31 ↑		
	100	97 ↑ *	236 ↑ *	170 ↑ *	74 ↑ *		
	200	105 ↑ *	236 ↑ *	168 ↑ *	144 ↑ *		

[a] NS = not significant. * = significant to P (0.05) or greater, ↑ = increased motor activity, ↓ = decreased motor activity. [b] Different groups of mice per various pretreatment times.

SCHEME III

REACTIONS OF MALONAMATES



ion, or increase in spontaneous motor activity in mice that is produced by phenobarbital or glutethimide.

Experiments were carried out using the measurement of spontaneous motor activity in mice as an indicator of the depressant action of compounds on the CNS.[4] The data in Table II show that I produces only decreased motor activity after administration of 150 or 200 mg/kg *po*. It causes either very slight increases or decreases in spontaneous motor activity, depending on the time of recording after drug treatment, at doses of 25, 50, or 100 mg/kg. The maximum increase in motor activity is only 54% following a dose of 100 mg/kg. On the other hand, phenobarbital causes an increase in motor activity after administration of doses ranging from 25 to 100 mg/kg *po*. It should be further noted that a dose of 100 mg/kg of phenobarbital produces an increase in spontaneous motor activity of 187% over the control values 3 hr after treatment. Glutethimide, a nonbarbiturate sedative, produces, like phenobarbital, a marked increase in spontaneous motor activity. Doses of 100 and 200 mg/kg produce a maximum increase of 236% at a 30-min pretreatment time. Methyl ethylphenylmalonamate has a depressant dose (DD_{50}) of 128 mg/kg (42–392 mg/kg) and a prostrating dose (PD_{50}) of 220 mg/kg (186–260 mg/kg). On the other hand, DD_{50}'s could not be calculated for phenobarbital or glutethimide using the dose regimen shown in Table II since decreases in spontaneous motor activity could be achieved only at dose levels which caused prostration in the mice.

The general profile of overt effects such as ataxia, decreased motor activity, hypotonia, and prostration seen after treatment by I in animals resembles those seen with clinically useful CNS depressants such as phenobarbital, glutethimide, or meprobamate. As shown in Table II, methyl ethylphenylmalonamate produces a diphasic effect on motor activity, with relatively little excitatory action in animals at dose levels causing CNS depression or ataxia. In this respect, I resembles the minor tranquilizer, meprobamate. In contrast, phenobarbital or glutethimide cause excitement, restlessness, hypersensitivity, and irritability prior to and in conjunction with depression in animals.

A good correlation has been demonstrated between pentylenetetrazole antagonist activity in rats and minor tranquilizing activity.[5] In this test procedure in which pentylenetetrazole is rapidly administered intravenously to rats, I has an ED_{50} of 24 mg/kg (17–34 mg/kg) orally in preventing 5 sec or more of uninterrupted clonic seizure activity. For comparison, meprobamate has an ED_{50} of 47 mg/kg (36–61 mg/kg) in protecting against intravenous pentylenetetrazole-induced convulsions. Thus, in this experimental procedure, I appears to be approximately twice as potent as meprobamate as a minor tranquilizer.

Many psychotherapeutic drugs such as chlorpromazine, meprobamate, and phenobarbital have broad spectrums of neurological activity (Table III). Methyl ethylphenylmalonamate is similar to phenobarbital or meprobamate in its neurological profile, and these activities may indeed be important in the management of the less severe behavioral disorders. I inhibits the con-

(4) L. Cook, E. F. Weidley, R. W. Morris, and P. A. Marris, *J. Pharmacol. Exptl. Therap.*, **113**, 11 (1955).

(5) F. A. Parish, C. A. Vandenwerf, and D. H. Tedeschi, *J. Med. Chem.*, **10**, 276 (1967).

TABLE III
ORAL ED_{50} VALUES IN SEVERAL PHARMACOLOGICAL TESTS

Test	ED_{50}, mg/kg: Methyl ethylphenylmalonamate (I)	Sodium phenobarbital	Meprobamate
Pentylenetetrazole antag (rat)	24 (17–34)	26 (18–38)	47 (36–61)
CAR[a] (rat)	66	70	340
Fighting behavior (mouse)	50 (25–75)	44 (34–56)	84 (56–126)
Max electroshock (mouse)	76 (65–89)	24 (18–25)	132 (122–143)
Strychnine antag (mouse)	135 (82–223)	111 (79–157)	300 (99–906)

[a] Estimated values.

ditioned avoidance response (CAR) in rats.[4] The inhibition of the CAR appears to be nonselective since blockade of the conditioned response is accompanied by a block of the unconditioned response. In mice this compound also prevents the foot shock induced fighting behavior,[6] prevents the convulsions produced after maximal electroshock[7] and subcutaneously adminstered strychnine,[8] and potentiates hexobarbital sleeping time.

Methyl ethylphenylmalonamate is well tolerated by the animals. Daily oral administration of 100 mg/kg of the drug fails to produce cumulative toxic effects; repeated daily administration does not produce appreciable tolerance as determined by using the incidence and duration of ataxia.

I does not influence autonomic standard test agents when tested intravenously in the anesthetized dog (1–20 mg/kg). It has no effect on mean arterial blood pressure in the anesthetized dog in doses up to 10 mg/kg iv. A dose of 20 mg/kg iv causes only a transient depressor response, slight respiratory depression, and a slight decrease in the heart rate. In the unanesthetized dog, this compound fails to show any electrocardiographic evidence of toxicity after acute doses of 100 mg/kg orally.

The ED_{50} values for I, meprobamate, and phenobarbital in a number of pharmacological tests are presented in Table III.

Since it is well known that phenobarbital is capable of stimulating microsomal enzyme activity, I was evaluated for possible similar action. Groups of rats were treated orally with doses of 100 mg/kg of phenobarbital, 100 mg/kg of barbital, or 150 mg/kg of I daily for 4 consecutive days. On day 4, hexobarbital was administered. Sleeping time was markedly reduced in those rats which received phenobarbital or barbital. On the other hand, sleeping times of the I-treated rats were essentially the same as those of the control rats which received hexobarbital alone. Thus I does not resemble phenobarbital in its ability to stimulate microsomal metabolism of hexabarbitol, as indicated by its lack of effect on hexobarbital sleeping time.

Deneau and coworkers[9] tested I in beagle dogs made physically dependent on a dose of 100 mg/kg of sodium barbital, orally, once daily. Dogs on this dose of sodium barbital will show convulsions and delirium during withdrawal. Substitution of I for sodium barbital in the above protocol resulted in delirium and severe tremors at 30 hr. It was concluded that I does *not* possess any barbiturate-like physiological dependence capacity.

Metabolism.—Analysis of the urine of rats dosed acutely with 100 mg/kg of I orally, showed the presence of some unchanged drug and some ethylphenylmalonamic acid (V). No decarboxylated material, α-phenylbutyramide, could be detected in the urine.

Because of certain structural similarities to phenobarbital, the urine of these animals was also analyzed for the presence of phenobarbital and its metabolites, but none were found. For the same reason, the urine of rats dosed with phenobarbital was analyzed for the presence of I or its metabolite, ethylphenylmalonamic acid, but no traces of either were found.[10]

Summary.—Methyl ethylphenylmalonamate (I) may be characterized as a sedative with a component of tranquilizing properties; it shares properties with both phenobarbital and meprobamate. In addition, preliminary studies indicate that I differs from the barbiturates in that it does not appear to stimulate microsomal activity in the liver and does not possess any barbiturate-like physiological dependence capacity.

Experimental Section[11]

Substituted Malonic Acids. General Procedure.—A solution of 1.5 moles of NaOH dissolved in 100 ml of H_2O was added slowly to a stirred solution containing 0.2 mole of the malonic ester in 40 ml of MeOH. The reaction was usually exothermic; a white precipitate soon formed. The stirred suspension was heated for 2–4 hr, then put under vacuum to remove most of the MeOH. The solution was cooled and extracted once with Et_2O, then the aqueous layer was cooled and acidified with dilute HCl, and the malonic acid separated as a solid and was filtered or as an oil which was isolated by extraction with Et_2O. The acids can be used in the following steps without purification. All of the acids were known compounds.

2,2-Dimethyl-5-phenyl-5-alkyl-4,6-dioxo-1,3-dioxane (Acetonides, III). General Procedure.[1]—A suspension of 0.033 mole of the malonic acid in 10 ml of Ac_2O was cooled to 15°, then 0.5 ml of concentrated H_2SO_4 was added. To the resulting solution was then added 10 ml of dry Me_2CO dropwise over 5 min while maintaining the temperature at 15°. The solution was stirred 1 hr then kept at 0° overnight. In most cases the solid acetonide separated in pure form and was filtered and rinsed with ice water. An additional quantity of product was obtained by pouring the organic filtrate into ice water. An oil separated and then crystallized on stirring. The acetonides can be recrystallized from i-Pr_2O or used without further purification. The acetonides show a characteristic doublet at 5.63 (m) and 5.78 μ (s) in the ir; they also show strong absorptions at 8.2–8.3 and 9.3–9.4 μ (mulls). The following new acetonides were prepared: 5-phenyl-5-methyl-, mp 144–146° (70% yield); 5-phenyl-5-butyl-, mp 77–79° (84% yield); 5-ethyl-5-isoamyl-, bp 94–102° (0.2 mm) (85% yield). *Anal.* ($C_{22}H_{13}O_4$) C, H. For 5-phenylacetonide

(6) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **125**, 28 (1959).

(7) J. E. P. Toman and L. S. Goodman, *Proc. Assoc. Res. Nervous Mental Disease*, **26**, 141 (1947).

(8) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exptl. Biol. Med.*, **70**, 254 (1949).

(9) G. A. Deneau and M. Wilson, Addendum to Annual Report, Problems of Drug Dependence, 31st Meeting of Committee on Problems of Drug Dependence, National Academy of Sciences, National Research Council, Feb 24–26, 1969, Indianapolis, Ind. Compound 1 is referred to as SKF 24298 and NIH No. 8248.

(10) We are indebted to E. L. Haines, A. Post, and M. Eisele of our laboratories for these chromatographic studies.

(11) All melting points (Thomas–Hoover apparatus) are corrected; analyses were performed by the Analytical Department of these laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

we obtained mp 147–47.5° (95% yield); the literature[1] reports mp 133–134°. *Anal.* ($C_{12}H_{12}O_4$) C, H.

Alkyl Hydrogen Malonates (IV). General Procedure.— A suspension of the acetonide in MeOH was added to a solution of an equimolar quantity of NaOMe in MeOH, and the resulting clear solution was stirred at room temperature for 15 min. The yellow solution was concentrated to dryness, *in vacuo*, maintaining the temperature below 40°. The residue was treated with H_2O and extracted with Et_2O to remove unreacted acetonide, then the aqueous layer was cooled and acidified. The monoester separated as a solid or an oil and was extracted with Et_2O; the solution dried, and the solvent was removed to give the monoester as a pale yellow oil or solid. The crude materials may be used without further purification; they can be recrystallized from Et_2O–hexane.

When the acetonide of phenylmalonic acid was similarly treated, the acetonide was removed unchanged after acidification of the aqueous solution.

The following new monomethyl esters were prepared of methylphenylmalonic acid, mp 74–76° (70% yield); of butylphenylmalonic acid, oil (70% yield); and of *i*-amylethylmalonic acid, oil (85% yield).

Ethyl Phenylmalonamic Acid (V). (**a**) The acetonide of ethylphenylmalonic acid (15.0 g, 0.06 mole) was added with stirring to 375 ml of concentrated NH_4OH and the mixture was stirred at room temperature for 3.5 hr. A small amount of insoluble material was filtered, and the filtrate was concentrated to remove most of the NH_3. The aqueous solution was then chilled to 10°, and made strongly acid with concentrated HCl. A greenish yellow oil separated and was extracted with Et_2O; the Et_2O solution was dried and concentrated to give 17.9 g of a semisolid. On stirring with C_6H_6 a crystalline solid separated and was filtered: 6.4 g, mp 116–119°.

The reaction was also carried out by adding NH_4OH to a solution of acetonide in an EtOH–dioxane mixture and then saturating with NH_3. The yield was about the same. No reaction occurred using ethereal NH_3. A sample of the malonamic acid was recrystallized from cyclohexane–*i*-Pr_2O, mp 119–120° (lit.[12] mp 112–113°).

(**b**) Ethylphenylmalonic acid (38.5 g, 0.18 mole) was suspended in 200 ml of dry Et_2O and 25.7 g (0.216 mole) of $SOCl_2$ was added. The mixture was refluxed with stirring for 18 hr and then concentrated at 30°, *in vacuo*. The resulting semisolid was stirred with hexane and the insoluble solid was filtered. The filtrate was concentrated at 35°, *in vacuo*, giving the acid chloride (22 g) as a pale yellow oil. A solution of 22 g (0.097 mole) of this acid chloride in 150 ml of $CHCl_3$ was cooled and saturated with NH_3. The mixture was stirred for 3 hr, and the resulting precipitate was filtered and dissolved in H_2O. On acidification of the aqueous solution a gum separated and was extracted with CH_2Cl_2. After removing the organic solvent, a solid was obtained which was stirred with hexane and filtered, giving 6.5 g of product identical with the material described above.

2-Phenyl-2-cyanobutyric Acid (VII).— 2-Phenylbutyronitrile (Aldrich Chemical Co.) (100 g, 0.7 mole) in dry THF was added over 1 hr to a suspension of KH (70 g of a 40% dispersion in oil) in THF. The temperature gradually rose to 40° and the suspension turned yellow. The mixture was heated at gentle reflux for 1.5 hr, then was cooled to 20° and dry CO_2 was bubbled into the suspension for 20 min. Cooling was required to maintain the temperature below 25°. The viscous suspension was stirred an additional 1 hr, then most of the solvent was removed by warming, *in vacuo*. Water (500 ml) was added, then the mixture was extracted with Et_2O. The aqueous layer was then made strongly acid with HCl and a pale yellow oil separated, which was extracted with CH_2Cl_2; on concentration the extract gave 114.4 g (86% yield) of VII as a yellow oil, $n^{25}D$ 1.5021 (lit.[13] $n^{25}D$ 1.5170). The structure of this material was confirmed by the ir spectrum and formation of salts as described under the resolution experiments (see later).

This procedure was found to be far more convenient, and to give better yields than the use of $NaNH_2$ in liquid NH_3,[13] which in our hands gave a 62% yield. NaH in THF gave a 74% yield.

Methyl 2-Phenyl-2-cyanobutyrate (VIII, R = Et). (**a**) An Et_2O solution of CH_2N_2 was added to an Et_2O solution of ethylphenylcyanoacetic acid (17 g, 0.09 mole) at 5–10°, until a permanent yellow color persisted. The slight excess of CH_2N_2 was destroyed by the addition of a little AcOH, then the Et_2O solution was washed with 5% $NaHCO_3$ solution, dried, and concentrated to give 14 g of methyl 2-phenyl-2-cyanobutyrate, $n^{24}D$ 1.5022. A portion of this material (5.6 g) was distilled, bp 90–96° (0.3 mm), 3 g, $n^{24}D$ 1.5040.

(**b**) A solution of 2 g of I in 30 ml of Ac_2O was heated at reflux for 3 hr, the volatile materials were removed *in vacuo* and the residual oil was distilled at 70–95° (0.1 mm) to give 0.9 g of VIII (R = Et), $n^{25}D$ 1.5042, identical with that described above.

(**c**) A mixture of 5.0 g (0.023 mole) of I, 2.5 g (0.011 mole) of P_2S_5, and 34 ml of dry dioxane was heated at reflux for 45 min. The solution was poured into H_2O, and the resulting oil was extracted with Et_2O. The Et_2O solution was dried, and the solvent was removed leaving 4.2 g of a yellow oil which was distilled, bp 82–100° (0.3 mm), giving 3.1 g of pale yellow oil, $n^{23}D$ 1.5050, identical with the materials obtained above. *Anal.* ($C_{13}H_{15}NO_2$) C, H, N.

Alkyl Alkylphenylmalonamates. (**a**) **From the Alkyl Hydrogen Malonates (IV). General Procedure.**— A solution of the alkyl hydrogen malonates in excess $SOCl_2$ was heated at reflux for 1.5 hr, then the excess $SOCl_2$ was removed by heating *in vacuo*. The resulting crude acid chloride was dissolved in Et_2O and chilled in an ice bath, and NH_3 or amine was bubbled in until the solution was saturated. The mixture was kept at room temperature for 15 hr, then the volatile materials were removed by heating *in vacuo*. The residue was stirred with H_2O, and the H_2O-insoluble product was filtered or extracted with Et_2O. The Et_2O solution was then dried, the solvent was removed *in vacuo*, and the residue crystallized and was recrystallized.

(**b**) Methyl 2-phenyl-2-cyanobutyrate (VIII) (5 g) was hydrolyzed with H_2SO_4 by the procedure of Testa, *et al.*,[12] to give 5 g of crude product. Recrystallization from *i*-Pr_2O gave 3.5 g of methyl ethylphenylmalonamate, mp 98–100°, identical with that prepared by the other routes.

(**c**) Ethylphenylmalonamic acid was converted to the methyl ester with CH_2N_2 as described for methyl 2-phenyl-2-cyanobutyrate. A 90% yield of I was obtained.

(**d**) Diethyl ethylphenylmalonate (50 g) was added to 500 ml of saturated NH_3–MeOH, then 1 g of NaOMe was added. After 4 months at room temperature the solvent was removed *in vacuo*, and the residual oil was stirred with H_2O, and a solid separated, 38 g. This solid was recrystallized from EtOAc to give 10.2 g of a solid, mp 112–120°. Recrystallization from $MeNO_2$ gave 6 g of ethylphenylmalondiamide, mp 118–121° (lit.[14] mp 124°). *Anal.* ($C_{11}H_{14}N_2O_2$) C, H, N.

The EtOAc filtrate from the above recrystallization was concentrated to a small volume and cooled, depositing 14.7 g of a solid, mp 89–96°. This was recrystallized from *i*-Pr_2O to give 10 g of methyl ethylphenylmalonamate, mp 99–100°, identical in all respects with the materials prepared by the other routes.

Methyl Diphenylcyanoacetate (VIII, R = C_6H_5). One-half of a solution containing 21 g (0.19 mole) of PhCl, 29.0 g (0.15 mole) of diphenylacetonitrile, and 50 ml of dry C_6H_6 was added slowly to a stirred suspension of 9.5 g (0.41 g-atom) of Na in 70 ml of dry C_6H_6 maintained at 37°. A slight exothermic reaction was observed. The mixture was stirred at room temperature for 18 hr, then the mixture, which now contained a yellow solid, was heated to 40°, and the balance of the original solution was added. After stirring for an additional 1 hr, the mixture was heated at 60° for 1 hr then cooled to 10° and a solution of 18.4 g (0.19 mole) of methyl chloroformate was added dropwise. After the addition was complete, the suspension was heated to 80° for 1 hr and filtered, and the filtrate was concentrated *in vacuo*. The residual oil (33 g) crystallized on stirring with hexane, giving 21 g of solid, mp 60–75°, which was recrystallized from hexane, 13.5 g, mp 72–79°. A sample was again recrystallized from *i*-Pr_2O, mp 81–85°. *Anal.* ($C_{16}H_{13}NO_2$) C, H, N.

Methyl Diphenylmalonamate.— Methyl diphenylcyanoacetate (VIII, 4.0 g, 0.016 mole) was added rapidly to 35 ml of concentrated H_2SO_4 preheated to 90°. The dark brown solution was kept at 95–100° for 5 min then poured onto ice. The resulting solid was filtered and dissolved in CH_2Cl_2, and the organic solution was then washed with dilute aqueous $NaHCO_3$. The organic layer was dried and the solvent was removed, giving 3.7 g of solid which was recrystallized from *i*-PrOH to give 1.9 g of product, mp 190–193.5°.

(−)-2-Cyano-2-phenylbutyric Acid. A modification of the procedure of Cram and Haberfield[15] was used. *dl*-2-Cyano-2-

(12) See footnote *r*, Table I.

(13) D. J. Cram and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 2354 (1961).

(14) V. Heyden, German Patent 310,426 (1919).

phenylbutyric acid (VII, 100 g) was added to a solution of 100 g of quinine in 200 ml of MeOH. The solution was cooled in an ice bath and stirred vigorously until a precipitate formed. The suspension was then further cooled in a Dry Ice–Me_2CO bath and then filtered. The solid was stirred with *i*-PrOH and filtered, then stirred with Et_2O and filtered again, yielding 87 g of salt, partially melting at 125–135°, with the balance melting at 145–147°, $[\alpha]^{25}D$ −119° (in MeOH; all rotations are of 1% concentration solution). A 2-g sample was converted to the free acid by dissolving in dilute HCl, extracting the aqueous mixture and Et_2O, and concentrating the Et_2O layer to give 0.8 g of the acid as a colorless oil, $n^{25}D$ 1.4998, $[\alpha]^{26}D$ −13° (in $CHCl_3$). The quinine salt was recrystallized three times by rapidly dissolving in $CHCl_3$ and precipitating with *i*-Pr_2O, to give 60 g of salt. Samples from the three recrystallizations gave the following rotations: $[\alpha]^{25}D$ −120, −121, and −121° (in MeOH). Recrystallization from MeOH did not change the rotation. Hydrolysis gave the acid $[\alpha]^{25}D$ −19° (in $CHCl_3$), $n^{25}D$ 1.5139.

Methyl (−)-2-Cyanophenylbutyrate.—(−)-2-Cyano-2-phenylbutyric acid (17 g) was converted to the methyl ester (14 g) with CH_2N_2, by the procedure described earlier, $[\alpha]^{25}D$ −39.2° (in $CHCl_3$). *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

Methyl (+)-Ethylphenylmalonamate.—Methyl (−)-2-cyano-2-phenylbutyrate (14 g) was hydrolyzed with H_2SO_4 by the procedure described previously, to give 5 g of product, $[\alpha]^{25}D$ +39.3° (in $CHCl_3$), mp 98–99°. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N.

(+)-2-Cyano-2-phenylbutyric Acid.—The combined filtrates from the recrystallization of the quinine salt prepared from *dl*-2-cyano-2-phenylbutyric acid (above) were concentrated and hydrolyzed to the acid. (−)-3-Phenyl-2-aminopropane (14.5 g) was added to 29 g of this acid dissolved in 200 ml of Et_2O. A solid soon separated, 12.5 g, mp 91.5–92.5°. After three recrystallizations from $CHCl_3$–Et_2O, 7.8 g of salt was obtained, mp 95–95.5°, with the following rotations: $[\alpha]^{25}D$ −40.75, −43.3, −43.7° (in $CHCl_3$). Hydrolysis of 5.5 g of the salt gave 3.3 g of the acid, $[\alpha]^{25}D$ +18.5° (in $CHCl_3$).

Methyl (−)-Ethylphenylmalonamate.—(+)-2-Cyano-2-phenylbutyric acid was converted to methyl (−)-ethylphenylmalonamate, $[\alpha]^{25}D$ −40.9° (in $CHCl_3$), mp 98–100°, by the same procedure as described above for the dextro rotating isomer. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N.

2,2-Dimethyl-4,6-dioxo-5-ethyl-5-phenyltetrahydro-1,3-oxazine (VI).—Concentrated H_2SO_4 (0.5 ml) was added to a suspension of 6.5 g (0.03 mole) of ethylphenylmalonamic acid in 19 ml of Ac_2O, and a clear solution resulted. The solution was cooled to 5° and 7.3 ml of Me_2CO was added over 5 min, then the solution was allowed to warm to room temperature and was stirred for an additional 2 hr. The resulting orange-brown solution was diluted with H_2O, the oil that separated was extracted with Et_2O, and the organic layer was washed with dilute $NaHCO_3$. After drying and concentrating the organic solution, 1.8 g of an orange oil was obtained. On addition of *i*-Pr_2O, a solid separated, 0.5 g, mp 147–149°. Recrystallization from C_6H_6 gave 0.4 g of product: mp 153–154°; ir (mull) 3.1 (w), 5.74 (s), 5.98 (s), 7.9 (s), 8.7 (s), 8.8 (s), 13.2 (s), and 14.4 (s) μ.

Methyl N-(1-Hydroxy-2,2,2-trichloroethyl)ethylphenylmalonamate (IX).—A solution of 3.6 g (0.016 mole) of I and 2.69 g (0.016 mole) of chloral hydrate in 30 ml of C_6H_6 was refluxed for 1.5 hr. The solution was diluted with CH_2Cl_2 and extracted with H_2O. The organic layer was dried ($MgSO_4$) and concentrated to dryness, *in vacuo*, to give 5.3 g of a yellow oil. The oil, when triturated with hexane, crystallized to give a white solid, mp 89–115°, 4.6 g. The solid was recrystallized from *i*-Pr_2O and then from CCl_4 and $CHCl_3$ to give 0.6 g of product, mp 141–143.5°. *Anal.* ($C_{14}H_{16}Cl_3NO_4$) C, H, N.

Methyl α-Phenyl-α-(N-carbomethoxyamino)butyrate (X).—$Pb(OAc)_4$ (2.2 g, 0.05 mole) was added to a solution of I in MeOH. The system was flushed with N_2, and the solution was then heated at reflux for 1 hr while N_2 was bubbled through the system. The color first became bright yellow, then later disappeared. Dilute aqueous Na_2CO_3 was added, the mixture was extracted with Et_2O, and the Et_2O extracted was dried and concentrated to give 10.5 g of an oil that crystallized on stirring with a little *i*-Pr_2O, mp 60–62°. The material was purified by "dry column" chromatography[15] on an alumina column, 58.6 × 3.8 cm, using CH_2Cl_2 as solvent. By this means 5 g of an oil that crystallized, mp 72–74°, was obtained. Recrystallization from hexane gave 3.9 g of product, mp 73–75°. *Anal.* ($C_{13}H_{17}NO_4$) C, H, N.

Methyl 2-Phenyl-2-acetamidobutyrate (XI).—$Pb(OAc)_4$ (40 g, 0.09 mole) was added to a solution of 20 g of I in 400 ml of AcOH. The solution was heated at reflux for 4 hr, then diluted with H_2O and extracted with CH_2Cl_2. Concentration of the organic layer gave 18 g of a dark oil. Five grams of this oil was chromatographed by the "dry column" procedure[15] on a column 73.8 × 3.8 cm using CH_2Cl_2 as solvent, to give 0.9 g of solid, mp 150–152°. This was then vacuum sublimed to give the product, mp 153–154°. *Anal.* ($C_{13}H_{17}NO_3$) C, H, N.

Metabolic Studies.—The urine of rats dosed with 100 mg/kg *po* of methyl ethylphenylmalonamate was collected for 5 hr following administration. The urine was chromatographed[10] on silica gel G plates using a C_6H_6–dioxane–AcOH system (90:25:4), and spots were located using a $Hg(OAc)_2$–diphenylcarbazone spray reagent. In this system, the following R_f's and colors are obtained: ethylphenylmalonamic acid (V, R_f 0.45, purple color), methyl ethylphenylmalonamate (I, R_f 0.74, purple), and phenobarbital (R_f 0.8, blue). The urine of control rats was chromatographed and showed no interfering substances. The urine of the rats which had been dosed with methyl ethylphenylmalonamate showed only a single spot at R_f 0.45 (purple) corresponding to ethylphenylmalonamic acid. The urine of the rats treated with phenobarbital showed a major spot (R_f 0.80, blue) corresponding to unchanged phenobarbital and a minor spot (R_f 0.55, blue) unidentified.

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(15) B. Loev and M. M. Goodman, *Chem. Ind.* (London), 2026 (1967).