β-methyl group would be nearly eclipsed in the bound state. This conclusion appears improbable on the basis of energy considerations. A skewed conformation such as in V is more appealing; a slightly twisted conformation for II is a reasonable approximation of V. If the comparisons are valid, the conclusion emerges that binding on active sites may not necessarily involve the thermodynamically preferred conformation of the ligand, a fact which was recently brought to light in the case of a constrained substrate of chymotrypsin.[11] Results of X-ray studies on crystals,[5,7] as well as theoretical calculations,[13] predict opposite conclusions; the obvious reason for this is that no account is taken of the fact that proteins display conformational specificity.[11] Owing to internal compensation effects,[9] strained conformations of substrates and inhibitors may be readily stabilized through the translocation of conformational energy within the protein. The reduction of the free energy of activation encountered in enzyme-catalyzed reactions has, in fact, been explained by Jencks[26] as resulting from the induction of a strained conformation approaching in structure that of the transition state. Isotope-effect studies on the binding of substrates on enzymes have led us to similar conclusions.[27,28] It does not seem impossible therefore that IV and V may represent the biologically active conformations at the binding site level. Finally, it is of interest to note that the configurational handedness of the AChE binding sites is similar to that of the muscarinic receptor binding sites.

Acknowledgments.—The authors are grateful to the Defence Research Board of Canada and the National Research Council of Canada for the financial support of this work. The 3-quinuclidinol was generously donated by Dr. R. Heggie of the DRB.

(26) W. P. Jencks, in "Current Aspects of Biochemical Energetics," N. Kaplan and E. Kennedy, Ed., Academic Press, New York, N. Y., 1966, p 273.
(27) B. Belleau and J. Moran, *Ann. N. Y. Acad. Sci.*, **107**, 822 (1963).
(28) B. Belleau, *Stud. Biophys.*, **4**, 95 (1967).

2-(N,N-Dialkylamino)ethyl Esters of α-(3-Pyridyl)mandelic Acids. Synthesis and Pharmacological Evaluation

A. NOVELLI, J. R. BARRIO,

Departamento de Química Orgánica

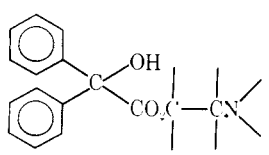
AND H. HUIDOBRO

Departamento de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

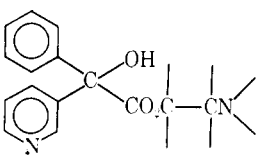
Received April 1, 1969

2-(N,N-Dialkylamino)ethyl esters of α-(3-pyridyl)mandelic acids were prepared and screened for pharmacological activity. Compounds VIIb and e compared favorably with benactyzine hydrochloride as inhibitors of spontaneous motility. Some of them (VIIa, b, d, and e) also show anticholinergic, spasmolytic, antihistaminic, and anti-5-HT effects.

Aminoalkyl benzilate esters (I)[1] possess pharmacological effects that have several clinical applications.[2] The presence of a pyridyl instead of a phenyl radical should change their pharmacological properties. To prove this assumption, synthesis of type II derivatives containing a 3-pyridyl radical was undertaken.



I

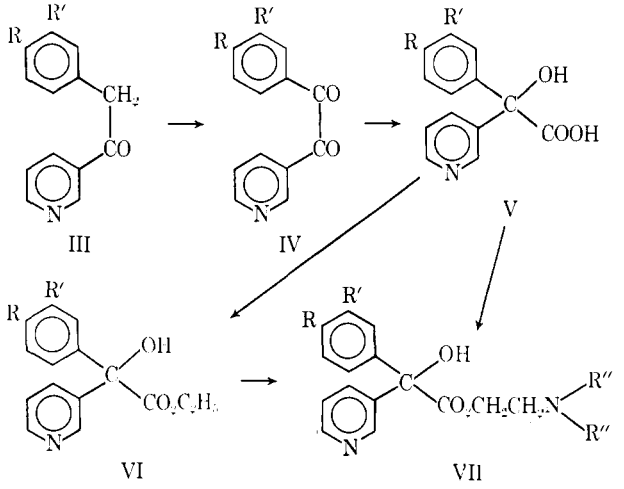


II

The general process of synthesis is shown in Scheme I. IIIa (Table I) was obtained in good yields by condensing ethyl phenylacetate and ethyl nicotinate in NaOEt.

(1) (a) A. Aström, *Acta Pharmacol. Toxicol.*, **8**, 363 (1952); (b) E. Jacobsen, *Danish Med. Bull.*, **2**, 159 (1955); (c) E. Jacobsen and Y. Shaarup, *Acta Pharmacol. Toxicol.*, **11**, 117 (1955); (d) E. Jacobsen and E. Sonne, *ibid.*, **11**, 135 (1955); (e) *ibid.*, **12**, 310 (1956); (f) H. Grethe and E. Jacobsen, *ibid.*, **13**, 125 (1957); (g) H. Holten and E. Sonne, *ibid.*, **11**, 148 (1955); (h) M. J. Raymond and C. J. Lucas, *Brit. Med. J.*, **1**, 952 (1956); (i) U. Larsen and C. H. Holten, *Acta Pharmacol. Toxicol.*, **12**, 346 (1956); (j) L. Alexander, *J. Am. Med. Assoc.*, **162**, 966 (1956).
(2) (a) I. Munkvad, *Acta Psychiat. Neurol. Scand.*, **30**, 729 (1955); (b) B. E. Davies, *Brit. Med. J.*, **1**, 480 (1956); (c) C. H. Holten, *Acta Pharmacol. Toxicol.*, **13**, 113 (1957); (d) M. A. Gardes and M. Laulan, *Presse Med.*, **65**, 180 (1957); (e) A. Coady and E. C. O. Jewesbury, *Brit. Med. J.*, **1**, 485 (1956); (f) L. Alexander, *J. Am. Med. Assoc.*, **166**, 1019 (1958).

SCHEME I



Using the same method, mono- (IIIb) and dimethoxy (IIIc) derivatives were obtained from the ethyl esters of homoanisic and homoveratric acids, respectively. Legrand and Lozac'h obtained the β-keto ester by condensing ethyl nicotinate and ethyl phenylacetate in low yields (17%) only.[3] When condensation was carried out with ethyl 3-pyridylacetate and ethyl

(3) L. Legrand and N. Lozac'h, *Bull. Soc. Chim. France*, 79 (1955).

Table I
$RCOCH_2R'$

No.	R	R'	Yield, %	Mp, °C	Cryst. solvent	Formula[c]
IIIa	3-Py	C_6H_5	57	63–64[a]	D	$C_{13}H_{11}NO$
IIIb	3-Py	4-$CH_3OC_6H_4$	50	97–98	H	$C_{14}H_{13}NO_2$
IIIc	3-Py	3,4-$(CH_3O)_2C_6H_3$	41	79–80	D	$C_{15}H_{15}NO_3$
IIId	C_6H_5	3-Py	6	48–49[b]	J	$C_{13}H_{11}NO$
IIIe	3-PyCH_2	3-Py	16	103–104	D	$C_{13}H_{12}N_2O$

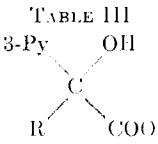
[a] L. Kulczynsky, Z. Machon, and L. Wykret [*Dissertationes Pharm.*, **13**, 299 (1961); *Chem. Abstr.*, **57**, 8540*i* (1962)] reported mp 63–64°. [b] A. D. Miller, C. Osuch, N. N. Goldberg, and L. Levine [*J. Amer. Chem. Soc.*, **78**, 674 (1956)] reported mp 48.6–49.5°. [c] D, ligroin; J, petroleum ether (40–60°). [d] All compounds analyzed satisfactorily for C, H, N.

Table II
RCOCOR'

No.	R	R'	Yield, %	Mp, °C	Cryst.[b] solvent	Formula[c]
IVa	3-Py	C_6H_5	81	59–60[a]	F	$C_{13}H_9NO_2$
IVb	3-Py	4-$CH_3OC_6H_4$	56	73–74	D	$C_{14}H_{11}NO_3$
IVc	3-Py	3,4-$(CH_3O)_2C_6H_3$	61	124–125	D	$C_{15}H_{13}NO_4$

[a] Bp 168–170° (5 mm), lit.[5] mp 55–57°. [b] D, ligroin; F, petroleum ether (60–80°). [c] See footnote *d*, Table I.

Table III



No.	R	R'	Yield, %	Salt	Mp, °C	Cryst.[a] solvent	Method	Formula	Analyses
Va	C_6H_5	H	88		174–175[a]	C–J		$C_{13}H_{11}NO_3$	C, H, N
Vb	4-$CH_3OC_6H_4$	H	80		175–176	C–J		$C_{14}H_{13}NO_4$	C, H, N
Vc	3,4-$(CH_3O)_2C_6H_3$	H	75		177–178	C–J		$C_{15}H_{15}NO_5$	C, H, N
VIa	C_6H_5	C_2H_5	82		93–94	D		$C_{15}H_{15}NO_3$	C, H, N
VIb	4-$CH_3OC_6H_4$	C_2H_5	68		78–79	E–F		$C_{16}H_{17}NO_4$	C, H, N
VIc	3,4-$(CH_3O)_2C_6H_3$	C_2H_5	67		95–96	C–F		$C_{17}H_{19}NO_5$	C, H, N
VIIa	C_6H_5	$(CH_2)_2N(CH_3)_2$	34	2HCl[b]	161–162	H–E	A	$C_{17}H_{22}Cl_2N_2O_3$	C, Cl; H, N[d]
VIIb	4-$CH_3OC_6H_4$	$(CH_2)_2N(CH_3)_2$	36	2HCl	177–178	H–E	B	$C_{18}H_{24}Cl_2N_2O_4$	C, H, Cl; N[e]
VIIc	3,4-$(CH_3O)_2C_6H_3$	$(CH_2)_2N(CH_3)_2$	41	2HCl	188–190	H–E	B	$C_{19}H_{26}Cl_2N_2O_5$	C, H, N, Cl
VIId	C_6H_5	$(CH_2)_2N(C_2H_5)_2$	35	2HCl	168–169	H–E	A	$C_{19}H_{28}Cl_2N_2O_3$	C, H, N, Cl
VIIe	4-$CH_3OC_6H_4$	$(CH_2)_2N(C_2H_5)_2$	32	2HCl[c]	124–126	H–E	B	$C_{20}H_{28}Cl_2N_2O_4$	N, Cl; C, H[f]
VIIf	3,4-$(CH_3O)_2C_6H_3$	$(CH_2)_2N(C_2H_5)_2$	37	2HCl[c]	103–104	I–E	B	$C_{21}H_{30}Cl_2N_2O_5$	C, H, N, Cl

[a] Lit.[5] mp 165–166°. [b] Free base (VIIa$_1$) [*Anal.* ($C_{17}H_{20}N_2O_3$) C, H, N]: nmr peaks (in $CDCl_3$), δ 8.6 (1 H, quadruplet), 8.3 (1 H, quadruplet), 7.8 (1 H, complex), 7.4 (5 H, s), 7.3 (1 H, complex), 4.8 (1 H, wide), 4.3 (2 H, triplet), 2.6 (2 H, triplet), 2.1 (6 H, s); hydrate (VIIa$_2$) [*Anal.* ($C_{17}H_{22}N_2O_4$) C, H, N]: nmr peaks (in $CDCl_3$), δ 8.6 (1 H, quadruplet), 8.3 (1 H, quadruplet), 7.8 (1 H, complex), 7.4 (5 H, s), 7.3 (1 H, complex), 4.3 (2 H, triplet), 3.8 (3 H, wide), 2.6 (2 H, triplet), 2.1 (6 H, s). [c] Very hygroscopic. [d] H: calcd, 5.89; found, 6.31. N: calcd, 7.50; found, 7.05. [e] N: calcd, 6.94; found, 7.40. [f] C: calcd, 55.68; found, 55.1. H: calcd, 6.49; found, 7.04. [g] C, AcOH; D, ligroin; E, Et_2O; F, petroleum ether (60–80°); G, C_6H_6; H, EtOH; I, MeCN; J, H_2O.

benzoate, the expected 3-phenacylpyridine (IIId) was obtained in poor yields (6%); 1,3-bis(3-pyridyl)-propanone (IIIe) resulting from self-condensation of ethyl 3-pyridylacetate was the main product; this ketone was the only condensation product obtained from ethyl nicotinate and ethyl 3-pyridylacetate.

Oxidation of the benzyl 3-pyridyl ketones (IIIa–c) was carried out with SeO_2. The oxidation of IIIa with $KMnO_4$ in neutral solution at room temperature gave nicotinic and benzoic acids identified by paper chromatography under the usual conditions.[4]

Under the conditions described in the Experimental Section, which differ from those mentioned by Stempel,[5] the diketones IVa–c (Table II) were subjected to the benzilic acid type rearrangement, giving the corresponding acids V (Table III).

The 2-(N,N-dialkylamino)alkyl esters were prepared by transesterification of the ethyl esters of the α-(3-pyridyl)mandelic acids with 2-N,N-dialkylamino alcohols with yields between 30 and 40% (method B). It was also possible to prepare VIIa and VIId with like yields by heating a 2-N,N-dialkylamino alcohol with α-(3-pyridyl)mandelic acid, using excess H_2SO_4 (method A). It was not possible to obtain the 2-(N,N-dialkylamino)alkyl esters of the methoxy acids by this method.

If the equilibrium of the reaction is not displaced by distillation of the EtOH produced during its course, the yields of transesterification become considerably lower. This was found in the preparation of VIIa and VIIc, but when an attempt was made to prepare VIIb by the same technique, the main product isolated was 3-pyridyl *p*-methoxyphenyl ketone (VIII).

Pharmacological Evaluation.—The 2-(N,N-dialkylamino)ethyl esters were screened for pharmacological activity and the results of the observations are summarized in Table IV.

Compounds VIIb and VIIe (monomethoxylated) showed significant inhibition of spontaneous motility,

(4) E. Lederer and M. Lederer, "Cromatografía," El Ateneo, Buenos Aires, 1960, p 210.

(5) A. Stempel, *Chem. Abstr.*, **61**, P10661 (1964).

TABLE IV

	Guinea pig ileum[a]					Spontaneous motility[b]		
Compd	Dose, mg/ml	Anticholinergic effect	Spasmolytic effect	Antihistaminic effect	Anti-5-HT effect	Dose, mg/kg	Activity cage	Duration, min
VIIa	0.01	45	40	50	30	0.1	0	
	1	70	60	70	55	10	19	20
VIIb	0.01	0	0	0	0	0.1	18	17
	0.1	10	8	10	5	10	75	30
	1	100	85	90	85			
VIIc	1	0	0	0	0	0.1	0	
						10	17	55
VIId	0.1	70	50	65	65	0.1	0	
	1	100	100	100	100	10	23	36
VIIe	0.01	10	10	16	10	0.1	19	38
	0.1	60	45	60	60	10	70	65
VIIf	1	0	0	0	0	0.1	0	
						10	12	20
Benactyzine HCl						10	27	40
Chlordiazepoxide						10	0	
						50	30	30

[a] Reduction of spontaneous contractions (%) against acetylcholine chloride, 0.1 μg/ml; $BaCl_2$, 100 μg/ml; histamine dihydrochloride, 0.01 μg/ml; and 5-HT, 0.1 μg/ml, respectively. These pharmacological assays were performed on isolated organs (R. A. Turner, "Screening Methods in Pharmacology," Academic Press, New York, N. Y., 1965, p 43). The test compounds were added to the bath 30–60 sec before the agonists. [b] Reduction of spontaneous motility of mice in jiggle cages (J. R. Boissier, *Therapie*, **13**, 1074 (1958)). Ten mice were used for each dose level and the animals were injected intraperitoneally. Controls were injected with saline. When the compound was active, the effect appeared 4–7 min after injection.

with a prolonged effect. Compounds VIIa, c, d, and f were moderately effective. All the compounds tested were nontoxic at 0.1 mg/kg; however, at higher doses (10 mg/kg), the decreased spontaneous motor activity was usually accompanied by respiratory depression and/or tremors or convulsions. None of the compounds was lethal at 10 mg/kg.

VIIa, b, d, and e also showed anticholinergic, spasmolytic, antihistaminic, and anti-5-HT effects, while VIIc and VIIf (dimethoxylated) were ineffective.

Experimental Section[6]

Benzyl 3-Pyridyl Ketone (IIIa).—A mixture of 37.7 g (0.25 mole) of ethyl nicotinate and 44.0 g (0.26 mole) of ethyl phenylacetate was added, over a period of 45 min, to 27 g (0.39 mole) of NaOEt, with vigorous stirring. The mixture was kept at 20–25° for 0.5 hr and then heated for 12 hr at 60–70° with constant stirring. After cooling, 78 ml of concentrated HCl were added, and the mixture was heated under reflux for 3 hr. On cooling, benzyl 3-pyridyl ketone hydrochloride crystallized and was collected and washed with $CHCl_3$. The crude product was dissolved in H_2O, and the ketone was separated with 10% NaOH, filtered, washed, dried, and recrystallized.

4-Methoxybenzyl 3-Pyridyl Ketone (IIIb).—The technique used was the same as for IIIa but the hydrochloride did not crystallize. H_2O (100 ml) was added and the aqueous layer was extracted twice with $CHCl_3$. The ketone was precipitated by adding 10% NaOH, filtered, washed, and recrystallized. Similarly, **3,4-dimethoxybenzyl 3-pyridyl ketone (IIIc)** was prepared.

Condensation of Ethyl Benzoate and Ethyl 3-Pyridylacetate.—The general procedure described for IIIb was employed. When the aqueous extract was made alkaline, the oil that separated was extracted with $CHCl_3$ and dried ($MgSO_4$). The solvent was removed and the residue was distilled, bp 175–190° (5 mm). On cooling, the distillate solidified and was extracted with cold Et_2O. The recrystallized residue gave **1,3-bis(3-pyridyl)propanone (IIIe)**. The ethereal extract was dried ($MgSO_4$), and the solvent evaporated. The recrystallized residue gave IIId.

(6) All melting points were taken in capillaries and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 137 B Infracord. Satisfactory ir spectra were recorded for all compounds listed in the tables. Nmr spectra were determined on a Varian A-60 (TMS). Microanalyses were performed at this laboratory. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Substituted 1-Phenyl-2-(3-pyridyl)glyoxals. General Procedure.—To a solution of 0.10 mole of the appropriate benzyl ketone in 200 ml of AcOH, 11.1 g (0.10 mole) of sublimed SeO_2 was added and the mixture was heated at 120° for 4 hr. After cooling, Se was filtered off and the filtrate was poured into 500 ml of H_2O and neutralized with concentrated NH_4OH. If the product crystallized, it was filtered, washed, and purified. If it was an oil it was extracted with $CHCl_3$ and dried ($MgSO_4$), and the solvent evaporated. The residue was distilled under reduced pressure and then recrystallized.

Benzilic Acid Type Rearrangement. General Procedure.—The appropriate glyoxal (20 g) suspended in a solution of 20 g of KOH in 100 ml of H_2O was heated on a water bath at 80° for 10 min. The solution was cooled and acidified with concentrated HCl to pH 4. The acid was filtered off, washed ($CHCl_3$), and recrystallized.

Ethyl Esters. General Procedure.—The appropriate acid (11.0 g) was added to a cold mixture of 17.5 ml of concentrated H_2SO_4 and 200 ml of absolute EtOH, with stirring and heating under reflux for 4 hr. Most of the alcohol was evaporated under reduced pressure. Then 200 ml of H_2O was added and the ester was precipitated by adding 10% NaOH. The solid was filtered, washed, and recrystallized.

2-(N,N-Dialkylamino)ethyl Esters. Method A.—α-(3-Pyridyl)-mandelic acid (1.0 g) was added to a cold mixture of 3.3 ml of concentrated H_2SO_4 and 3.0 ml of 2-(N,N-dialkylamino)ethanol; the mixture was heated at 100° for 4 hr, then cooled and poured into 10 ml of H_2O. The 2-(N,N-dialkylamino)alkyl ester was separated by adding concentrated NH_4OH, extracted ($CHCl_3$), and dried ($MgSO_4$), the solvent was evaporated, and the hydrochloride was prepared.

Method B.—Na (50 mg) was added to a mixture of anhydrous 2-(N,N-dialkylamino)ethanol (5 ml, excess) and dry C_6H_6 (40 ml), in a flask fitted with a short fractionating column and a still head. The solution was heated until it refluxed (bp 80°). The appropriate ethyl ester (2 g) in C_6H_6 (30 ml) was then added slowly, the vapor temperature falling to 60–65°. C_6H_6–EtOH was then distilled off until all the ester had been added and the vapor temperature had risen to 80°. The PhH solution was washed three times (H_2O) and dried ($MgSO_4$), the solvent was evaporated *in vacuo*, and the hydrochloride was prepared.

3-Pyridyl *p*-Methoxyphenyl Ketone (VIII).—2-(N,N-Dimethylamino)ethanol (2 ml) was added to 20 mg of Na in 10 ml of PhMe. The mixture was heated until it refluxed; then 1.0 g of VIb in 20 ml of PhMe was added dropwise and the mixture was heated for 5 hr. The PhMe solution was washed three times with H_2O and the solvent was distilled *in vacuo*. The residue was extracted with hot petroleum ether (bp 40–60°) and after 24 hr

VIII crystallized, mp 99° (lit.[5] mp 99°), yield 200 mg (24%, based on VIb). *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

Acknowledgment.—This work was supported by a grant to one of us (A. N.) from the Consejo Nacional de Investigaciones Científicas y Técnicas. The authors are indebted to the Departamento de Química Orgánica of the Facultad de Ciencias Exactas y Naturales (Buenos Aires) for nmr spectra.

(5) R. Wolffenstein and F. Harturch, *Ber.*, **48**, 2043 (1915).

Malonamic Esters. A New Class of Sedative–Tranquilizers

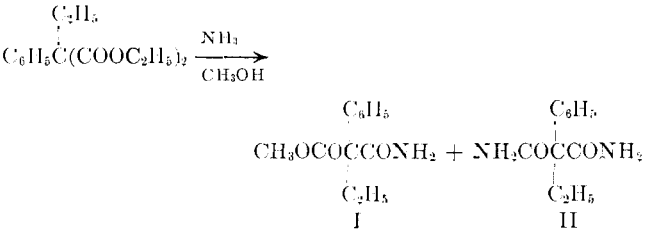
BERNARD LOEV, EDWARD MACKO, AND IRVING M. FRIED

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania

Received January 28, 1969

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, methyl 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. Scheuer 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).