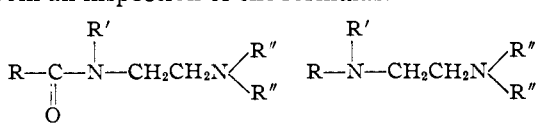
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Amides of Ethylenediamine as Antihistaminic Agents[1]

BY FRANK J. VILLANI, NATHAN SPERBER, JOSEPH LANG AND DOMENICK PAPA

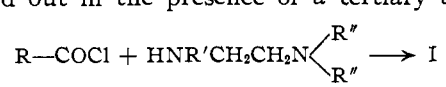
In the course of investigations on the synthesis of new antihistaminic agents, it appeared of interest to study the effect of substituting the quantity R—C(=O)— for the R radical (R is aryl or heterocyclic) into compounds possessing clinical antihistaminic activity. This communication describes the synthesis and preliminary pharmacological data of a series of compounds wherein the R—C(=O)— substitution has been made in the antihistaminics of the ethylenediamine type. The new series of compounds are of general formula I, and the structural similarity of these compounds to the known N′,N′-disubstituted-N,N-dialkylethylenediamines[2] (II) is apparent from an inspection of the formulas.



I II

R and R′ = aryl, aralkyl or heterocyclic; R″ = lower alkyl group

The amides of formula I (Table II) were prepared by the reaction of aryl or heterocyclic acid chlorides with the appropriately substituted ethylenediamines (III) (Table I) as shown in the following equation. The condensations were carried out in the presence of a tertiary amine



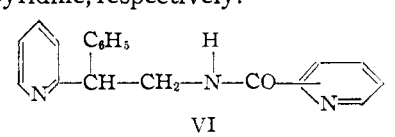
III

such as pyridine, triethylamine and dimethylaniline, with or without an inert diluent. In general, pyridine, diluted with anhydrous benzene, was found to be the solvent of choice for most of the reactions. However, in the case of the picolinoyl amides, pyridine could not be employed as solvent because of the ease with which picolinoyl chloride forms colored complexes with pyridine.[3] For the preparation of the picolinoyl amides, a mixture of triethylamine and anhydrous benzene was used.

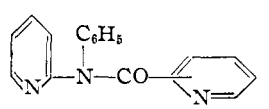
In an attempt to secure the amides I by an alternate synthesis, the ester–amine interchange reaction was studied in the case of N,N-dimethyl-N′-phenyl-N′-picolinoylethylenediamine. When ethyl picolinate was heated with N,N-dimethyl-N′-phenylethylenediamine for sixty hours, the expected product was obtained in only 13% yield. In view of the extended reaction time and poor yields, this procedure was not studied further.

The N′-substituted N,N-dialkylethylenediamines (III) (Table I) were prepared by the alkylation of the aromatic amines with dialkylaminoethyl chloride hydrochloride (IV). The N′-phenyl and substituted phenyl derivatives were conveniently prepared by prolonged reflux of an alcoholic solution of the amine and IV in the presence of anhydrous sodium carbonate. However, benzylamine and IV gave none of the expected N′-benzyl-dimethylethylenediamine (V) by the sodium carbonate procedure. With sodium amide, V was obtained from benzylamine and IV, but only in poor yields.[4] An alternate synthesis of V comprises the reduction of the Schiff base obtained from benzaldehyde and N,N-dimethylaminoethylamine essentially as described for the diethyl compound.[5] The Schiff base forms in 60% yield and the reduction of the benzylidene compound to V proceeds smoothly with Raney nickel catalyst.

Several amides of types VI and VII (Table III) were prepared by the condensation of picolinoyl chloride or nicotinoyl chloride with β-phenyl-β-2-pyridylethylamine, or N-phenyl-2-aminopyridine, respectively.



VI



VII

Pharmacology.—The antihistaminic potency was determined according to the usual technique of protecting guinea pigs against the lethal effects of intravenous histamine. The compound under test was administered either orally or subcutaneously one-half to one hour prior to the intravenous histamine injection. γ-Phenyl-γ-(2-pyridyl)-N,N-dimethylaminopropane (Trimeton) was used as standard and was arbitrarily assigned an activity index of 100.

The four amides listed in Table III had an activity of approximately 0.1 by either route of administration, whereas the amides listed in Table II had an activity of 1 orally and 1–2 subcutaneously, except as follows: Compounds 2, 3, 9, 12 and 23 had an activity index of 20

(1) Presented in abstract before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City Meeting, September 20, 1949.

(2) Huttrer, "Chemistry of Antihistaminic Substances," *Enzymologia Acta Biocatalytica*, **2**, 286 (1948).

(3) Wolffenstein and Hartwick, *Ber.*, **48**, 2045 (1915).

(4) Compare Whitmore, *et al.*, THIS JOURNAL, **67**, 393, 735 (1945).

(5) German Patent 559,500, *C. A.*, **27**, 819 (1943).

TABLE I

AMINES OF THE FORMULA $H-N(R)-CH_2-CH_2-N(R')_2$

No.	R	R′	Method	B. p. °C.	Mm.	Yield,[a] %	n_D	°C.	Formula	N Analyses, % Calcd.	Found
1	C_6H_5	CH_3	1	90–98[b]	1	52	1.535[c]				
2	p-$CH_3C_6H_4$[e]	CH_3	1	100–103	1	45	1.530[c]		$C_{11}H_{18}N_2$	15.71	15.90
3	m-ClC_6H_4[f]	CH_3	1	105–110	1	39	1.551[c]		$C_{10}H_{15}N_2Cl$	14.10	15.02[d]
4	p-ClC_6H_4	CH_3	1	115–117	1.5	53	1.5519	25	$C_{10}H_{15}N_2Cl$	14.10	14.14
5	o-$CH_3OC_6H_4$	CH_3	1	100–105	0.5	40	1.5420	20	$C_{11}H_{18}ON_2$	14.42	14.77
6	$C_6H_5CH_2$	CH_3	2	104–110	1	22	1.5129	25	$C_{11}H_{18}N_2$	15.73	15.35
7	$C_6H_5CH_2$[g]	C_2H_5	1	115–119	0.5	57	1.499[c]		$C_{13}H_{22}N_2$	13.58	14.68[d]
8	2-C_5H_4N[h]	CH_3	2	103–110	1	34	1.5420	27			
9	C_6H_5[i]	C_2H_5	1	110–118	1	59					
10	2-C_3H_3NS[j]	CH_3	2	105–112	2	7	1.5562	25			

[a] The yields reported do not represent the maximum obtainable since they are based on single experiments. [b] Huttrer, *et al.* (THIS JOURNAL, 68, 1999 (1946)) report b. p. 103–107° at 0.2 mm., $n^{25}D$ 1.5380; Leonard and Solmssen (THIS JOURNAL, 70, 2066 (1948)) report b. p. 100–104° at 6 mm., $n^{25}D$ 1.5395. [c] These measurements were made with a Fischer refractometer. [d] Redistillation of these compounds gave similar analytical results. [e] M. p. picrate, 172.8–173.8°. [f] M. p. picrate, 146.5–150°. [g] Toluene was substituted for ethanol in Method 2 and the mixture was refluxed for twenty-four hours. [h] B. p. 100–106° at 1 mm. Ref. 4. [i] B. p. 154–158° at 17 mm. Ref. *b*. [j] This compound appeared to be unstable and was used immediately for the preparation of the amide (Table II, compound 23).

TABLE II

AMIDES OF THE FORMULA $R-C(=O)-N(R')-CH_2-CH_2-N(R'')_2$

No.	R	R′	R″	Method	B. p. °C.	Mm.	Yield,[a] %	n_D	°C.	Formula	N Analyses, % Calcd.	Found
1	C_6H_5	C_6H_5	CH_3	4	158–159	1	80	1.5654	25	$C_{17}H_{20}ON_2$	10.44	10.31
2	C_6H_5	p-$CH_3C_6H_4$	CH_3	4	159–162	0.5	78	1.5627	25	$C_{18}H_{22}ON_2$	9.92	9.85
3	C_6H_5	2-C_5H_4N	CH_3	4	155–158	1	74	1.5692	25	$C_{16}H_{19}ON_3$	15.60	15.73
4	2-C_5H_4N	H	CH_3[b]	3	113–124	1	29	1.5140	25	$C_{10}H_{15}ON_3$	21.75	20.83[c]
5	2-C_5H_4N	C_6H_5	CH_3	3	177–178	2	27	1.565[d]		$C_{16}H_{19}ON_3$	15.80	15.71
6	2-C_5H_4N	C_6H_5	CH_3	6	177–178	2	13					
7	2-C_5H_4N	p-$CH_3C_6H_4$	CH_3	3	185–190	1	53	1.563[d]		$C_{17}H_{21}ON_3$	14.86	15.20
8	2-C_5H_4N	m-ClC_6H_4	CH_3	3	182–186	2	69	1.571[d]		$C_{16}H_{18}ON_3Cl$	13.82	14.14
9	2-C_5H_4N	p-ClC_6H_4	CH_3	3	185–190	1.5	33	1.5760		$C_{16}H_{18}ON_3Cl$	13.82	13.81
10	2-C_5H_4N	o-$CH_3OC_6H_4$	CH_3	3	183–186	1	28	1.5648	22	$C_{17}H_{21}O_2N_3$	14.04	14.17
11	2-C_5H_4N	$C_6H_5CH_2$	CH_3	3	195–200	2	47	1.5789	25	$C_{17}H_{21}ON_3$	14.83	14.36
12	2-C_5H_4N	2-C_5H_4N	CH_3	3[e]	175–179	1	18	1.5672	25	$C_{15}H_{18}ON_4$	20.73	20.46
13	3-C_5H_4N	H	CH_3[b]	4	140–143	1	32	1.5332	24	$C_{10}H_{15}ON_3$	21.75	20.88[c]
14	3-C_5H_4N	C_6H_5	CH_3	4	187–190	1	51	1.565[d]		$C_{16}H_{19}ON_3$	15.60	15.39
15	3-C_5H_4N	C_6H_5	C_2H_5	5	187–189	0.5	62	1.553[d]		$C_{18}H_{23}ON_3$	14.14	14.68
16	3-C_5H_4N[f]	p-$CH_3C_6H_4$	CH_3	4	180–189	0.5	64			$C_{17}H_{21}ON_3$	14.83	14.40
17	3-C_5H_4N[g]	m-ClC_6H_4	CH_3	4	176–185	2	80			$C_{16}H_{18}ON_3Cl$	13.82	13.83
18	3-C_5H_4N[h]	p-ClC_6H_4	CH_3	4	185–187	1	74			$C_{16}H_{18}ON_3Cl$	13.82	13.57
19	3-C_5H_4N	o-$CH_3OC_6H_4$	CH_3	4	188–192	1	80	1.5670	21	$C_{17}H_{21}O_2N_3$	14.04	13.98
20	3-C_5H_4N	$C_6H_5CH_2$	CH_3	4	193–197	2		1.513[d]		$C_{17}H_{21}ON_3$	14.83	14.63
21	3-C_5H_4N	$C_6H_5CH_2$	C_2H_5	4	193–196	1	81	1.552[d]		$C_{19}H_{25}ON_3$	13.49	13.55
22	2-C_4H_3S	$C_6H_5CH_2$	CH_3	4	187–193	0.5	44	1.5721	27	$C_{16}H_{20}ON_2S$	9.72	9.89
23	3-C_5H_4N	2-C_3H_3NS	CH_3	4	164–169	0.5	52	1.5899	25	$C_{13}H_{16}ON_4S$	20.27	20.17

[a] The yields are based on single experiments and do not necessarily represent the maximum obtainable by the described procedures. [b] N,N-Dimethylethylenediamine was prepared according to Turner, THIS JOURNAL, 68, 1607 (1946). [c] These two substances which were prepared from N,N-dimethylethylenediamine could not be obtained analytically pure, even after repeated distillation. They were submitted for animal tests in this form. [d] These measurements were made with a Fischer Refractometer. [e] Dimethylaniline used instead of triethylamine. [f] Recrystallization from ligroin, m. p. 73–73.5°. [g] Recrystallized from ligroin, m. p. 74–75°. [h] Recrystallized from ligroin, m. p. 73–75°.

orally, subcutaneously 10–30; compound 22 by either route of administration 40–50.

Experimental

The preparation of the following compounds are illustrative of the methods listed in the tables.

Method 1.—N,N-Dimethyl-N′-(*p*-chlorophenyl)-ethylenediamine (Table I, compound 4): A mixture of 190 g. (1.5 moles) of freshly distilled *p*-chloroaniline, 144 g. (1.0 mole) of dimethylaminoethyl chloride hydrochloride, 212 g. (2.0 moles) anhydrous sodium carbonate and 1000 cc. of absolute alcohol was refluxed with stirring for eight hours. The inorganic salts were filtered off and the

TABLE III

AMIDES OF FORMULA $R-N(R')-C(=O)-R''$[a]

No.	R	R'	R''	B. p. °C.	Mm.	M. p., °C.	Yield, %	Formula	N Analyses, % Calcd.	Found
1	C_6H_5	2-C_5H_4N	3-C_5H_4N			177–178[b]	51	$C_{17}H_{13}ON_3$	15.26	15.05
2	C_6H_5	2-C_5H_4N	2-C_5H_4N			107–108[c]	18	$C_{17}H_{13}ON_3$	15.26	15.84
3	C_6H_5, 2-C_5H_4N $>CH-CH_2$	H	3-C_5H_4N	184–187[d]	0.5		19	$C_{19}H_{17}ON_3$	13.85	14.09
4	C_6H_5, 2-C_5H_4N $>CH-CH_2$	H	2-C_5H_4N	191–196[e]	2		32	$C_{19}H_{17}ON_3$	13.85	13.73

[a] These compounds were prepared by method 7. [b] Recrystallized from benzene. [c] Recrystallized from hexane. [d] $n^{27}D$ 1.5832. [e] $n^{27}D$ 1.6021.

alcohol was removed under vacuum on the steam-bath. The residue, which partially solidified on cooling, was dissolved in water and made strongly basic with dilute sodium hydroxide. The liberated amine was extracted with ether, the ether extracts dried over anhydrous sodium sulfate and after removal of the solvent, the residue distilled as a colorless oil.

Method 2.—N,N-Dimethyl-N'-benzylethylenediamine (Table I, compound 6): To a mixture of 114.4 g. (0.8 mole) of dimethylaminoethyl chloride hydrochloride and 85.6 g. (0.8 mole) of benzylamine in 500 ml. of dry toluene, a toluene suspension of sodium amide (1.6 moles) was added in the course of one-half to one hour. The mixture was refluxed with stirring for twenty-four hours. Water was carefully added and the organic layer separated from the aqueous layer. After ether extraction of the aqueous layer, the combined ether–toluene solutions were extracted several times with dilute hydrochloric acid. The acid solution was made alkaline with sodium hydroxide and extracted thoroughly with ether. The ether extracts were dried and finally distilled.

Method 2A.—To 26 g. (0.5 mole) of benzaldehyde dissolved in 100 cc. of anhydrous benzene contained in a 200-ml., three-necked flask equipped with a stirrer and a Dean Stark trap, 35 g. (0.4 mole) of N,N-dimethylethylenediamine was added slowly with efficient cooling and stirring. The mixture was heated under reflux for four hours and after removing the benzene *in vacuo*, the residue was distilled, yield 27 g. (61%), b. p. 98–103° (3 mm.). The N'-benzylidene-N,N-dimethylethylenediamine was reduced to the N'-benzyl compound with Raney nickel catalyst in alcohol at room temperature and an initial pressure of 40–50 lb., yield 85%.

Method 3.—N,N-Dimethyl-N'-picolinoyl-N'-(*m*-chlorophenyl)-ethylenediamine (Table II, compound 8): To 18.4 g. (0.15 mole) of picolinic acid in a 1,000 cc., three-necked flask equipped with stirrer, dropping funnel and reflux condenser, there was added with cooling 200 cc. of purified thionyl chloride.[6] The greenish-yellow mixture was stirred for two hours at 0–5°. The excess thionyl chloride was removed *in vacuo;* and, to the residue, 100 cc. of anhydrous benzene was added. The benzene was removed *in vacuo;* and, to the residue, 200 cc. of dry benzene and 40 g. of triethylamine were added. To the dark brown mixture, a solution of 29.7 g. (0.15 mole) of N,N-dimethyl-N'-(m-chlorophenyl)-ethylenediamine in 50 ml. of dry benzene was added dropwise with stirring. After refluxing for eight hours on the steam-bath, the solvents were removed *in vacuo* and the thick brown residue was poured on ice. The substituted ethylenediamine was isolated as described in method 2 and was obtained after distillation as a light yellow oil.

Method 4.—N,N-Dimethyl-N'-nicotinoyl-N'-phenylethylenediamine (Table II, compound 14): Fifteen grams of nicotinic acid was converted into the chloride hydrochloride by refluxing with 100 cc. of thionyl chloride for one-half hour. The thionyl chloride was removed *in vacuo*, 100 cc. anhydrous benzene added and the solvent removed *in vacuo*. About 200 cc. of dry pyridine and 16.4 g. (0.1 mole) of N,N-dimethyl-N'-phenylethylenediamine was added slowly with stirring. The mixture was warmed on the steam-bath for eight hours. The pyridine was removed by vacuum distillation and the residue poured onto ice. The reaction mixture was worked up as described in method 2.

Method 5.—N,N-Diethyl-N'-nicotinoyl-N'-phenylethylenediamine (Table II, compound 15): To a solution of 36 g. of nicotinoyl chloride[7] in 200 ml. of anhydrous benzene, 48 g. of N,N-diethyl-N'-phenylethylenediamine dissolved in 100 ml. of benzene was added slowly with stirring. The mixture was then heated for eighteen hours on the steam-bath. The benzene was removed and the residue was poured onto ice. The ethylenediamine derivative was isolated as described under method 2.

Method 6.—N,N-Dimethyl-N'-picolinoyl-N'-phenylethylenediamine (Table II, compound 6): In a three-necked flask equipped with thermometer, stirrer and fractionating column attached to a condenser for downward distillation, there was placed 15.1 g. (0.1 mole) of ethyl picolinate and 32.8 g. (0.2 mole) N,N-dimethyl-N'-phenylethylenediamine. The mixture was heated to 170–190° and the reaction maintained at this temperature for sixty hours. The mixture was fractionally distilled.

Method 7.—N-Nicotinoyl-β-(2-pyridyl)-β-phenethylamine (Table III, compound 3): thirty-six and nine-tenths grams (0.3 mole) of nicotinic acid was converted into the chloride hydrochloride by method 4. Pyridine (200 ml.) and 39.6 g. (0.2 mole) β-phenyl-β-(2-pyridyl)-ethylamine were added slowly with cooling and stirring and the mixture refluxed for six hours. The reaction mixture was then worked up as described in method 2.

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Summary

A series of N',N'-disubstituted N,N-dialkylethylenediamines have been prepared in which one of the N'-substituents of the known ethylenediamine antihistaminics has been replaced by a benzoyl, picolinyl, nicotinoyl and isonicotinoyl radical. Methods for the synthesis of these

(6) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 381.

(7) Chiang and Hartung, *J. Org. Chem.*, **10**, 27 (1945).

compounds and intermediates are described. Preliminary pharmacological data for the new tetra-substituted ethylenediamines is reported.

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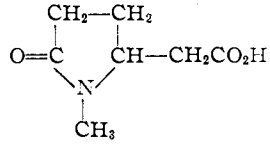
Synthesis of Ecgoninic Acid and Related Pyrrolidones

BY G. L. EVANS, H. W. GRAY AND H. W. JACOBSON

Ecgoninic acid, the end-product of the controlled oxidation of the alkaloids tropine and ecgonine, was shown to be 1-methyl-5-oxo-2-pyrrolidineacetic acid by Willstätter and Hollander[1] who synthesized it by the action of methylamine on β-bromoadipic acid.

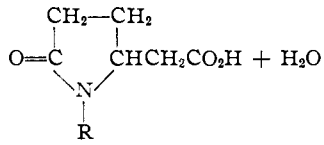
$$CH_3NH_2 + HO_2CCH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CO_2H \longrightarrow$$



Compounds containing the ring system of ecgoninic acid have been prepared in a variety of ways, for example by heating the methyl ester of the lactone of γ-hydroxyadipic acid with ammonia,[2] by heating lactones with amines,[3,4,5] or by catalytic reduction of γ-nitrocarboxylic acids.[6]

A convenient and general reaction for the synthesis in good yield of ecgoninic acid and related acids and their derivatives has been found in heating ammonium or amine salts of β-hydromuconic acid at elevated temperatures.

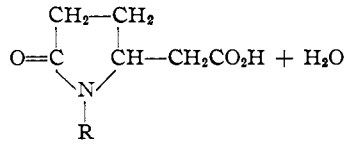
$$RNH_3{}^+[{}^-O_2CCH_2CH{=}CHCH_2CO_2H] \longrightarrow$$



If two moles of organic base for each mole of acid is employed, the corresponding amide is obtained. A plausible mechanism for this reaction involves a shift of the double bond of the β-hydromuconic acid to an α,β-position followed by addition of ammonia or amine to the unsaturated system and ring closure as indicated in the following scheme.

$$RNH_3{}^+[{}^-O_2CCH_2CH{=}CHCH_2CO_2H] \longrightarrow$$
$$RNH_3{}^+[HO_2CCH_2CH{=}CH{-}CHCO_2H] \rightleftharpoons$$
$$RNH_3{}^+[HO_2CCH_2{-}CHCH{=}CHCO_2H] \longrightarrow$$
$$RNH_2 + HO_2CCH_2CH_2CH{=}CHCO_2H \longrightarrow$$

$$HO_2CCH_2CH_2\underset{\displaystyle NHR}{\underset{|}{C}}HCH_2CO_2H \longrightarrow$$



Experimental

β-Hydromuconic Acid.—Three hundred sixty-six grams of 1,4-dicyano-2-butene, prepared by the action of sodium cyanide on 1,4-dichloro-2-butene in acetonitrile solution with cuprous bromide catalyst,[7] was hydrolyzed by dissolving in a mixture of 1 l. of concentrated hydrochloric acid and 1 l. of water and refluxing the solution for five hours. The reaction mixture was cooled to 10°, filtered and the crude product was crystallized from 4 l. of water. There was obtained 418 g. of β-hydromuconic acid (84% yield), m. p. 196–197° (uncor.).

Ecgoninic Acid.—A mixture of 12 g. of methylamine (0.388 mole) and 55.8 g. of β-hydromuconic acid (0.388 mole) was heated in a sealed glass tube at 210° for two hours. After cooling to room temperature, the tube was opened and the pale yellow, viscous product was dissolved in 100 ml. of acetone. After drying the solution over anhydrous magnesium sulfate, it was concentrated to approximately one-half the original volume and cooled to induce crystallization. There was obtained 43 g. (71% yield) of ecgoninic acid which was recrystallized from acetone, m. p. 94–95°. *Anal.* Calcd. for $C_7H_{11}NO_3$: C, 53.50; H, 7.06; N, 8.92; neut. eq., 157.2. Found: C, 53.72; H, 7.17; N, 8.86; neut. eq., 158.0.

5-Oxo-2-pyrrolidineacetic Acid.—Fifty grams of ammonium acid β-hydromuconate, prepared by adding one mole of ammonia to one mole of β-hydromuconic acid in absolute methanol, was heated for three hours at 200–210° in a sealed tube. The viscous product was dissolved in 50 ml. of absolute ethanol. One hundred twenty-five ml. of benzene was added, and the solution dried by azeotropic distillation. After removal of water, the benzene was poured off the lower layer of viscous product (benzene insoluble) from which crystals weighing 20.9 g. (47% yield) were deposited. This crude product was purified by precipitation with ether from chloroform solution, and recrystallization from butanol, to give white, water-soluble crystals, m. p. 120.5–122.2°. *Anal.* Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.30; N, 9.79; neut. eq., 143. Found: C, 50.84; H, 6.49; N, 9.84; neut. eq., 142.8.

1-Butyl-5-oxo-2-pyrrolidineacetic Acid.—A mixture of 14.6 g. of butylamine (0.2 mole) and 28.8 g. of β-hydromuconic acid (0.2 mole) was heated as described for ecgoninic acid. There was obtained 30 g. (65% yield) of acid, b. p. 188–190° (5 mm.), m. p. 70–71°. *Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.55; N, 7.04; neut. eq., 199.2. Found: C, 60.30; H, 8.78; N, 7.04; neut. eq., 199.9.

The methyl ester was prepared in 55% yield by the method of Newman,[8] b. p. 142–144° (2 mm.); $n^{25}D$

(1) Willstätter and Hollander, *Ber.*, **34**, 1818 (1901).
(2) Leuchs and Möbis, *ibid.*, **42**, 1234 (1909).
(3) Zienty and Steahly, THIS JOURNAL, **69**, 715 (1947).
(4) Schuster and Seib, U. S. Patent 2,267,757 (Dec. 30, 1941).
(5) Meyer and Kissin, *Ber.*, **42**, 2837 (1909).
(6) French Patent 880,400 (Dec. 27, 1942).
(7) Hager, U. S. Patent 2,462,388 (Feb. 22, 1949).
(8) Newman, THIS JOURNAL, **63**, 2431 (1941).