then allowed to stand in the ice-bath for 2 hours. After decanting the toluene–petroleum ether layer, 50 ml. of alcohol was added and the mixture, warmed on the steam-bath, made alkaline with alcoholic potassium hydroxide. The alkaline mixture was poured over crushed ice and water, and allowed to stand for 2 hours. The solid was collected, washed with water, and dried *in vacuo*. Recrystallization of the crude product (11.0 g.) from benzene–petroleum ether yielded 10.6 g. (93%) of colorless crystalline 1-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III), m.p. 160.2–160.6° (reported[6] m.p. 159.5–160°). Further crystallization did not raise the melting point.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.8; H, 5.6; N, 4.1. Found: C, 66.7; H, 5.8; N, 4.1.

In one experiment the yield of product after purification was 97.4%.

2-(3′,4′,5′-Trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV) from 1-(3′,4′,5′-Trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III).—A stirred mixture of 10.23 g. (0.03 mole) of dihydroisoquinoline (III), 24 ml. of methyl sulfate (0.254 mole), 150 ml. of 40% sodium hydroxide solution and 150 ml. of water was heated on the steam-bath under a condenser for 18 hours. The cooled reaction mixture, after acidification with hydrochloric acid, was filtered, and the precipitate washed with water and dried *in vacuo*. Pale yellow crystalline 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV) obtained in this way showed m.p. 139–139.8° and weighed 10.08 g. (98%). A sample prepared for analysis by crystallizing material obtained in an earlier experiment from methanol (90% recovery) showed m.p. 139.2–139.8°. Benzene–petroleum ether was later found to be a more satisfactory solvent mixture for crystallization.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3. Found: C, 66.6; H, 5.3.

2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylic Acid (I).—Five grams of 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (0.0146 mole) was dissolved in 300 ml. of acetone contained in a 1 l. three-necked flask fitted with stirrer and condenser. Solid potassium permanganate (8.84 g. or 0.056 mole) was added portionwise over a period of 1 hour to the stirred and boiling acetone solution. At the disappearance of the permanganate pink color, the condenser was set for distillation, and the acetone removed. Water (150 ml.) was added to the residual solids, and gaseous sulfur dioxide bubbled through the cooled mixture until the brown precipitate disappeared. The cold mixture was filtered and, in order to effect a separation of product and unreacted starting material, the solids were treated with 50 ml. of 2% sodium hydroxide solution. The solid obtained on filtering the alkaline mixture, after washing and drying *in vacuo*, weighed 1.85 g. One crystallization of this material from benzene–petroleum ether furnished 1.75 g. (35% recovery) of 2-(3′,4′,5′-trimethoxybenzoyl)-4,5-methylenedioxystyrene (IV), m.p. 138.5–139.5°.

Acidification of the alkaline filtrate with dilute hydrochloric acid and filtration of the cold mixture afforded crude keto-acid (I) which on drying *in vacuo* weighed 3.05 g. and melted at 211.5–213°.

Purification was effected by decolorizing the crude product in methanol solution followed by crystallization. 2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylic acid (I), m.p. 215.2–215.7° (2.9 g.), was obtained in 85% corrected or 55% uncorrected yield.

Anal. Calcd. for $C_{18}H_{16}O_8$: C, 60.0; H, 4.5. Found: C, 60.0; H, 4.5.

The same material obtained from picropodophyllin (II, m.p. 225–226°) by oxidation according to Späth, *et al.*,[4] melted at 213.4–215.4° and, on admixture with the synthetic material, at 214.4–215.7°. Decarboxylation of the synthetic keto-acid (I) by following essentially the direction of Späth, *et al.*,[4] furnished 3,4,5-trimethoxy-3′,4′-methylenedioxybenzophenone, m.p. 125.3–126.5° (reported[4] m.p. 125–127°).

Ethyl 2-(3′,4′,5′-Trimethoxybenzoyl)-piperonylate.—A solution of 8.0 g. (0.022 mole) of the keto-acid (I) in 350 ml. of absolute ethanol containing 7 ml. of concentrated sulfuric acid was boiled for 3 hours. Most of the solvent was removed under reduced pressure, and the concentrated solution, after dilution with water, was neutralized (cooling) with 10% aqueous sodium bicarbonate solution. Product was isolated by extracting the neutralized solution with ether, and evaporating the ether. The methanol solution of the residual material was first heated with decolorizing carbon, then concentrated, and water added dropwise until a slight turbidity was observed. Addition of a small volume of methanol led to a clear solution which was allowed to stand first at room temperature and then in the refrigerator.

The colorless crystals were collected and washed on the funnel with cold aqueous methanol and dried *in vacuo*. Crystallization of the material so obtained (7.5 g., m.p. 95–96°) from aqueous methanol yielded 7.0 g. (81%) of ethyl 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylate, m.p. 96.5–97°.

Anal. Calcd. for $C_{20}H_{20}O_8$: C, 61.9; H, 5.2. Found: C, 61.8; H, 5.1.

BOSTON, MASSACHUSETTS RECEIVED JUNE 4, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Ethanolamides of Some Mono- and Dicarboxylic Acids

BY ARTHUR P. PHILLIPS

A series of ethanolamides has been made from an assorted group of mono- and di-carboxylic acids. A noteworthy difference in chemical properties was observed during attempts to prepare the bis amides and the imides from phthalic acid and succinic acid derivatives. The reaction of ethanolamine with either dimethyl phthalate or phthalic anhydride gave only the cyclic imide, while in contrast diethyl succinate or succinic anhydride gave only the open chain bis-amide. This divergence in behavior is attributed to the steric relationships in the acids concerned.

In connection with earlier investigations of acyl migrations in aminoethanols[1,2] a series of ethanolamides was prepared from a variety of carboxylic acids. Some of these were made for use in rearrangement studies and many have been screened for certain types of pharmacological activity.

Most of these amides were obtained as in the earlier work[1] by a method related to that of D'Alelio and Reid.[3] A mixture of the carboxylic acid methyl or ethyl ester with one to three molecular equivalents of ethanolamine for *each* ester group was refluxed in a metal-bath at or above 160° for varying periods of time.

Compound IX,[4] Table I (B), was best made from *p*-nitrobenzoyl chloride and excess of ethanolamine. Catalytic hydrogenation of IX using Adams catalyst gave X, *p*-amino-N-(β-hydroxyethyl)-benzamide.

N-(β-Hydroxyethyl)-*p*-toluenesulfonamide, XI of Table I (B), was prepared by the interaction of ethanolamine with *p*-toluenesulfonyl chloride in

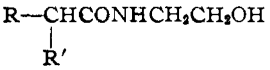
[1] A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).

[2] A. P. Phillips and A. Maggiolo, *ibid.*, **72**, 4920 (1950).

[3] G. F. D'Alelio and E. E. Reid, *ibid.*, **59**, 111 (1937).

[4] H. Brintzinger and H. Koddebusch, *Ber.*, **82**, 201 (1949).

TABLE I

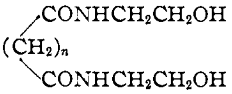
(A) ETHANOLAMIDES OF SUBSTITUTED ACETIC ACIDS 

$$R\!-\!\underset{\displaystyle R'}{\underset{|}{C}}HCONHCH_2CH_2OH$$

Compd. no.	R	R′	Yield, %[a]	M.p., °C.	Crystn. solvent[b]	Reaction conditions, hr.	Reaction conditions, °C.	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
I	Cl	Cl	75	85–86	Ac. Æ. H	2	160	27.9	28.2	4.1	3.9
II	C_6H_5CONH	H	80	125–126	A. Æ	2.5	160	59.4	59.7	6.3	6.3
III	C_6H_5	C_6H_5	60[c]	124–125	Æ. H	2	150	75.2	75.2	6.7	6.8
IV	$(C_6H_5)_2CH$	H	80[c]	95–96	Æ. E. H	5	190	75.8	75.8	7.1	7.1

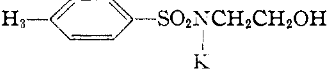
(B) ETHANOLAMIDES OF SUBSTITUTED AROMATIC ACIDS, 

Compd. no.	R	R′	Yield, %[a]	M.p., °C.	Crystn. solvent[b]	Reaction conditions, hr.	Reaction conditions, °C.	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
V	p-CH_3O		70	101–102	M. Æ	19	160	61.6	61.3	6.7	6.6
VI	m-CH_3		85	63–64		3	160	67.0	66.5	7.3	7.5
			B.p. 208–209 (2 mm.)								
VII	p-Cl		70	118–119	Æ	3	160	54.1	53.8	5.1	5.0
VIII	m-Br		100	106–107	Æ	22	160	44.2	44.5	4.1	4.1
								N, 5.7	N, 5.6		
IX	p-NO_2		100[d]	130–131	Æ			51.4	51.4	4.8	4.7
X	p-NH_2		90[e]	119–120	M. Æ. H			60.0	60.0	6.7	6.6
XI[f]	p-CH_3[e]		80	282–283	M			42.6	42.6	4.8	4.7
								N.E. 253	N.E. 253		

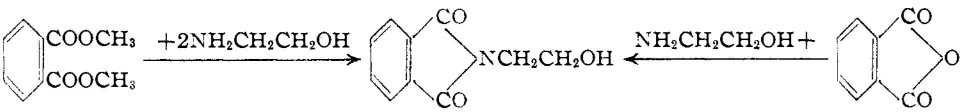
(C) ETHANOLAMIDES OF DICARBOXYLIC ACIDS, 

$$(CH_2)_n\begin{matrix}\diagup CONHCH_2CH_2OH\\ \diagdown CONHCH_2CH_2OH\end{matrix}$$

Compd. no.	n		Yield, %[a]	M.p., °C.	Crystn. solvent[b]	Reaction conditions, hr.	Reaction conditions, °C.	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
XII	0		100	170–171	M	1	100	40.9	41.1	6.9	6.7
XIII	1		100	127–128	A	1	100	44.2	44.2	7.4	7.4
XIV	2		100	156–157	A	2	160	47.0	47.1	7.9	7.9
XIV	2		60[g] 85[h]	156–157	A	1	200	47.0	47.3	7.9	7.7
XV	3		100	119–120	A. Æ	1	200	49.5	49.7	8.3	8.0
XVI	4		100	135–136	A. Æ	2	160	51.7	51.4	8.7	8.7
XVII	C_6H_4[i]		100	130–131	A	2	140	62.8	62.9	4.7	4.6
XVII	C_6H_4[j]		100	130–131	M	0.5	200	62.8	63.0	4.7	4.8

[a] All products were obtained by interaction of the corresponding carboxylic acid methyl or ethyl ester and ethanolamine unless otherwise noted. [b] A = ethanol; Ac = acetone; Æ = ethyl acetate; H = Skellysolve B; M = methanol. [c] Product obtained by heating the free carboxylic acid with ethanolamine. [d] Known compound, see reference (4) of text. This was made from the corresponding acid chloride and excess amine. [e] Compound X was obtained from IX by catalytic hydrogenation in methanol using Adams catalyst. [f] Compound XI is  CH_3—C_6H_4—$SO_2N(K)CH_2CH_2OH$ and was made from p-toluenesulfonyl chloride and ethanolamine. It was purified and analyzed as the potassium salt. [g] This sample of XIV was made by the reaction of ethanolamine (1 mol) with succinic anhydride (1 mol). In attempting to obtain the cyclic imide equimolar amounts of reactants were employed. The yield of product, the diamide, thus is calculated on the basis of ethanolamine used as the limiting factor. [h] This yield of XIV is from the reaction of ethanolamine (2 mol) with succinic anhydride (1 mol). [i] Compound XVII is the known, cyclic hydroxyethyl phthalimide (see references (5) and (6)), obtained from dimethyl phthalate and ethanolamine. [j] This sample of XVII was made from phthalic anhydride and ethanolamine.

benzene solution. This amide was an oil insoluble in water or benzene and was purified by recrystallization from methanol as its potassium salt.



XVII

Fig. 1.

An interesting result was observed in the preparation of the ethanolamides of the dicarboxylic acids. While all of the alphatic dicarboxylic esters gave smoothly the corresponding open chain amides, phthalic acid esters have so far yielded only the cyclic imide (XVII) under a variety of conditions. This same imide[5] was also obtained readily by the reaction of phthalic anhydride and ethanolamine.[6] Thus as shown in Fig. 1 either dimethyl phthalate or phthalic anhydride with ethanolamine gave the same product, XVII.

In the initial attempt to obtain the bis-ethanolamide from dimethyl phthalate, refluxing the ester with 3 molecular equivalents of ethanolamine for *three hours* at 160° gave no crystalline product on cooling. Vacuum distillation of the oily reaction mixture gave an 80%

---

[5] S. Gabriel, *Ber.*, **21**, 566 (1888).

[6] H. Wenker, THIS JOURNAL, **59**, 422 (1937).

yield of the cyclic imide XVII. In order to determine whether the strenuous conditions of the vacuum distillation (b.p. 205–206° at 12 mm.) were responsible for this unexpected result (the cyclic product) the reaction was repeated with refluxing extended to *24 hours* and subsequent careful removal of excess ethanolamine *in vacuo* maintaining the bath temperature always below *180°*. From this procedure 100% of pure XVII was obtained. Finally the reaction was carried out by refluxing *two hours* at *140°*. After careful evaporation of unreacted amine and methanol *in vacuo* below *140°*, 100% of XVII again was the sole product.

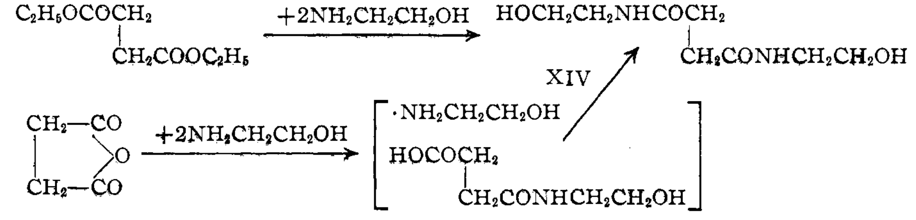


Fig. 2.

Succinic acid bis-ethanolamide (XIV) was obtained in nearly the theoretical amount either by the reaction of ethyl succinate with 2 mol of ethanolamine or by the reaction of succinic anhydride with ethanolamine as outlined in Fig. 2. In contrast with the phthalic acid derivatives no isolable amount of the cyclic imide was found in this case under any of the conditions employed. When 2 mol of ethanolamine were used per mol of succinic anhydride 85% of XIV (based on the anhydride) resulted while with 1 mol of amine only a 50–60% yield (based on ethanolamine) of XIV was obtained. The poorer yield in the latter case may be explained by the difficulties involved in separating the nearly equimolar mixture of bis amide and free succinic acid which should be the principal products.

This marked difference in chemical behavior and stabilities of products may reasonably be attributed to the difference in spatial configurations of the two acids concerned. While the phthalic derivatives, either open chain or cyclic, are held more or less rigidly in a *cis* configuration favorable to easy ring closure under slight provocation, the open chain succinic derivatives are probably more stable in the *trans* arrangement. Since even the anhydride reaction (see Fig. 2) undoubtedly involves an open chain intermediate, this probably would tend to assume the *trans* relationship of the reacting groups to yield the open chain product. Only by the application of very much larger amounts of energy might the cyclic succinimide types of product result. Results attributable, at least in part, to similar steric relationships have been reported earlier.[2]

No useful pharmacological activity has been found so far for these compounds although in general they have low toxicities.

The succinic acid bis-ethanolamide (XIV) is related structurally to the bis-β-tertiaryaminoethyl amides of dicarboxylic acids reported recently.[7] Unlike the aminoamides the bis-ethanolamides showed no ability to prolong the duration of neuromuscular block produced by diacetylcholine in the cat.

Experimental

Preparation of the Ethanolamides.—A mixture of from one to three mol of ethanolamine for each ester group and the methyl or ethyl ester of the carboxylic acid was refluxed, in a metal-bath, at or near 160°. Usually the reaction was complete within a few minutes, but in some cases longer reflux intervals, from two to 20 hours, were used either arbitrarily or as a matter of convenience (overnight heating). Excess ethanolamine and by-product alcohol were removed *in vacuo* at 100°, and the product was purified by vacuum distillation or by recrystallization. Yields approached the theoretical. Details for all compounds are shown in Table I.

Two compounds, III and IV of Table I (A), were obtained by heating the free acids, diphenylacetic acid and β,β-diphenylpropionic acid, respectively, with ethanolamine.

Many of the derivatives from aromatic acids seemed very difficult to purify by crystallization. In contrast most of the derivatives of substituted acetic acids and of the dicarboxylic acids appeared to have much stronger crystallization tendencies.

Acknowledgment.—The author is indebted to Mr. Samuel W. Blackman for the microanalytical results included in this paper.

TUCKAHOE 7, NEW YORK RECEIVED JUNE 4, 1951

---

[7] A. P. Phillips, *Science*, **112**, 536 (1950).