Reaction of 2-methoxytetrahydropyran with di-t-butyl peroxide. A reaction mixture consisting of 46 g. (0.39 mole) of 2-methoxytetrahydropyran and 21.5 g. (0.15 mole) of di-*t*-butyl peroxide was heated at 120–125° for 44 hr. During the course of the heating, material boiling at 83–90° was distilled through an 8-inch Vigreux column as fast as it was formed. At the end of the heating period the reaction mixture was distilled through the same column and material boiling up to 120° was combined with the earlier cut. The combined fractions (21.0 g.) were analyzed by infrared as 0.21 mole of *t*-butyl alcohol and 0.03 mole of unchanged di-*t*-butyl peroxide. The reaction mixture was further distilled until the pot temperature reached 200° yielding 23 g. of material boiling at 120–129°. Analysis of this fraction by gas-liquid partition chromatography showed two peaks, with retention times identical to 2-methoxytetrahydropyran and methyl valerate. Infrared analysis of the mixture showed a very strong ester carbonyl absorption at 5.76 μ. Both infrared analysis and gas-liquid partition chromatography showed the ester content of the mixture to be 40%. The distillation residue amounting to 19.5 g. had a molecular weight of 412. The infrared spectrum of the residue showed it to consist mainly of a product similar to that obtained from the reaction of di-*t*-butyl peroxide and methyl valerate with additional absorption bands at 9.25, 9.45 and 9.68 μ.

p-Toluidide of valeric acid. A portion of the ester-containing mixture was added to the reaction mixture of ethylmagnesium bromide and *p*-toluidine in ether. Hydrolysis yielded the *p*-toluidide of *n*-valeric acid which after recrystallization from dilute alcohol melted at 70°; reported[6] m.p. 70°. A mixed melting point with an authentic sample showed no depression.

n-Butyl valerate. In another reaction 56 g. (0.48 mole) of 2-methoxytetrahydropyran and 17.5 g. (0.12 mole) of di-*t*-butyl peroxide were heated at 125–130° for 23 hr. During the course of the heating, 16.5 g. of material was distilled through an 8-inch Vigreux column at 82–85° which on infrared analysis proved to consist of 13.5 g. (0.18 moles) of *t*-butyl alcohol, a trace amount of acetone, and 2.5 g. of unchanged peroxide (0.017 mole). Further distillation at the end of the heating period yielded 42 g. of material boiling at 126–128° leaving a high boiling residue (pot temperature 210°) amounting to 12.5 g. Infrared analysis of the distillate showed it to consist of 32% methyl valerate (0.13 mole) and the remainder, unchanged 2-methoxytetrahydropyran. This mixture was refluxed for 6 hr. in 100 g. of *n*-butyl alcohol containing 0.025 g. of metallic sodium. During the course of the refluxing, 4.2 g. of methyl alcohol (0.13 mole) were removed by distillation through an 8 inch Vigreux column. The unchanged *n*-butyl alcohol and 2-methoxytetrahydropyran were removed by further distillation. The infrared spectrum of this mixture showed no ester carbonyl present. The remaining material was *n*-butyl valerate which distilled at 119–121° at 104 mm. (n_D^{25} 1.4143) and amounted to 17 g. (0.11 mole). The infrared spectrum of this material was identical with that of an authentic sample of *n*-butyl valerate.

The reaction of 2-methoxytetrahydropyran and 1-octene. Over a period of 24 hr. a solution consisting of 1-octene (33.6 g., 0.30 mole) and di-*t*-butyl peroxide (8.8 g., 0.06 mole) was slowly added to 2-methoxytetrahydropyran (150 g., 1.29 moles) heated to reflux temperature (127°). On distillation through an 8 inch Vigreux column, the reaction mixture yielded about 6 g. of *t*-butyl alcohol and 124 g. of unchanged 2-methoxytetrahydropyran. The residue was distilled through a 12-inch Holzmann column and yielded a fraction amounting to 6.0 g. (b.p. 90–110° at 0.7 mm., n_D^{25} 1.4430) which on infrared examination was found to consist mainly of methyl tridecanoate. Absorptions at 9.25, 9.45, and 9.68 μ in the infrared spectrum of the sample indicate the presence of a pyran ring but are different from those of 2-methoxytetrahydropyran. Reaction of a portion of the 1:1 addition product with the reaction mixture obtained from ethylmagnesium bromide and *p*-toluidine yielded the *p*-toluidide of *n*-tridecanoic acid; m.p. 87–88°, reported[7] m.p. 87°. A high boiling residue amounting to 30 g. remained after distillation of the 1:1 addition product (pot temperature 150°), presumably telomeric products.

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(6) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 222.

(7) W. H. Urry and E. S. Huyser, *J. Am. Chem. Soc.*, **75**, 4876 (1953).

Adducts with *N*-Substituted Acrylamides[1]

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Acrylamides, especially the *N*-substituted products, appear as attractive reagents for the synthesis of isomers and analogs of amino acids and peptide-like compounds. The reactions which come under consideration may be summarized as in Fig. 1. Reactions of type (c) are adaptations of the Michael reaction[4] and of type (b) have been employed by Mattocks and Hartung.[5]

EXPERIMENTAL

Acrylamides. By allowing acrylyl chloride[6] to react with an appropriate amine, the following *N*-substituted acrylamides were obtained: Acrylanilide[7] (I), m.p. 105–106°; *p*-acrylotoluidide[8] (II), m.p. 140–141°; diethyl acrylamidomalonate[9] (III), $C_{10}H_{15}NO_5$, yield 56%, m.p. 106–107°; ethyl acrylamidoacetate[10] (IV); diethyl acrylamidobenzylmalonate[11,12] (V), $C_{17}H_{21}NO_5$, yield 62%, m.p. 84–86°.

From cinnamyl chloride[13] and diethyl aminomalonate was

(1) No. 21 in Amino Acid Series. For No. 20 see L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959). Work done at the University of North Carolina.

(2) Supported in part by funds from the Sterling-Winthrop Research Foundation and in part by the American Foundation for Pharmaceutical Education. This assistance is gratefully acknowledged. Present address: Midwest Research Institute, Kansas City, Missouri.

(3) Present address: Medical College of Virginia, Richmond, Virginia.

(4) *Cf.* C. S. Marvel and M. P. Stoddard, *J. Org. Chem.*, **3**, 198 (1938); J. R. Shekelton and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(5) A. M. Mattocks and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 2018 (1946).

(6) Prepared by the procedure of H. C. Brown, *J. Am. Chem. Soc.*, **60**, 1325 (1938), and C. H. Stempel, *et al.*, *J. Am. Chem. Soc.*, **72**, 2299 (1950), in yields of 70–80%.

(7) M. Moureu, *Bull. soc. chim. France* [3] 421 (1893).

(8) M. Moureu, *Bull. soc. chim. France* [3] 422 (1893).

(9) Calcd.: N, 6.11. Found: N, 5.95, 6.13.

(10) See under compound IX below.

(11) Calcd.: N, 4.37. Found: N, 4.24, 4.14.

(12) The intermediate is described by J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc.*, **41**, 578 (1952).

(13) H. Meyer, Sitzber., *Akad. Wiss. Wien, Math. naturiv. Kl. Abt IIB;* **110**, 329 (1901).

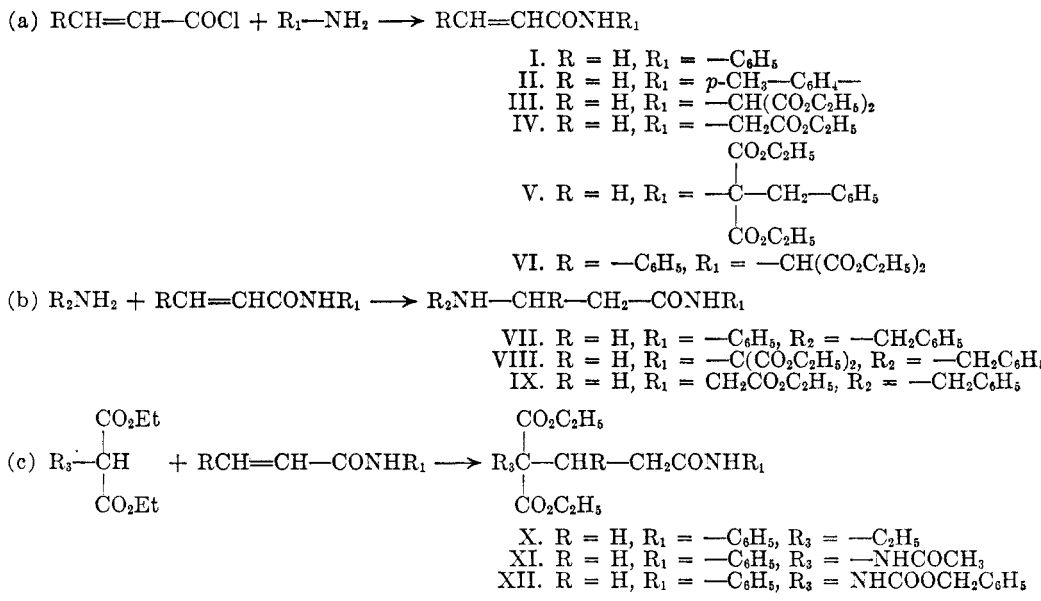


Fig. 1. Synthesis of amino acid isomers and analogs, using *N*-substituted acrylamides

obtained diethyl cinnamamidomalonate[14] (VI), $C_{16}H_{19}NO_5$, yield 91%, m.p. 92–94°.

Amine adducts. β-Benzylaminopropionanilide hydrochloride (VII). A solution of 7.4 g. of I (0.05 mole) and 10.9 g. of benzylamine (0.10 mole) in 25 ml. of anhydrous ethanol was placed in a stoppered flask at room temperature for 2 days with occasional shaking. The solution was then transferred to an evaporating dish and the alcohol evaporated on a hot water bath, the residual red viscous oil was taken up in ether, washed with ten 10-ml. portions of water to remove excess benzylamine, and dried over sodium sulfate. To the dried ethereal solution was added 0.05 mole hydrogen chloride dissolved in 16 ml. of ethanol; the flocculent precipitate which formed was augmented by allowing the solution to stand overnight in the refrigerator. The crude yield of crystals was 13.5 g., 93%. Recrystallized from water, the product melted 260–261°.

Anal. Calcd. for $C_{16}H_{19}N_2OCl\cdot 2H_2O$: N, 8.57. Found: N, 8.55, 8.63.

Diethyl β-benzylaminopropionamidomalonate (VIII). A solution of 2.29 g. of III (0.01 mole), 1.17 g. of benzylamine (0.011 mole) in 10 ml. of absolute ethanol, in a stoppered flask was shaken intermittently; after 5 hr. III had all dissolved; after 48 hr. the ethanol and excess benzylamine were removed under reduced pressure. As the residual product was low melting, it was converted to the hydrochloride; yield, practically quantitative; m.p. 238–239°.

Anal. Calcd. for $C_{17}H_{25}N_2O_5Cl$: N, 7.51. Found: N, 7.46, 7.66.

Ethyl β-benzylaminopropionamidoacetate hydrochloride (IX). A solution of 1.6 g. of IV (0.01 mole) and 1.17 g. of benzylamine (0.001 mole) in 4 ml. of absolute ethanol was allowed to stand at room temperature for 24 hr. To this was added 0.365 g. hydrogen (chloride (0.01 mole) in dry ethanol; on cooling a crystalline precipitate formed; a second crop was obtained by adding ether to the mother liquors; the combined products were recrystallized from ethanol, obtained 2.0 g., yield 66.5%, m.p. 197–198.5°. This product was a hemihydrate.

Anal. Calcd. for $C_{14}H_{21}N_2O_3Cl\cdot 1/2\ H_2O$: N, 9.04. Found: N, 9.04, 9.02.

The melted salt, on cooling solidified without apparent decomposition and remelted at 173–175°, and is very hygroscopic; this is presumably the anhydrous salt.

(14) *Anal.* Calcd.: C, 62.94; H, 6.26; N, 4.58. Found: C, 63.39; H, 6.31; N, 4.76.

Michael additions. 4,4-Dicarbethoxycaproanilide (X). To a stirred solution of sodium ethoxide, prepared from 0.077 g. of sodium (0.0033 g.-atom) in 30 ml. of anhydrous ethanol was added 3.76 g. of diethyl ethylmalonate (0.02 mole); then was added 2.94 g. of I (0.02 mole). The solution was warmed for 5 hr. to 70–80° and then allowed to stand at room temperature for 4 days; the solution was transferred to an evaporating dish, by addition of acetic acid the *p*H was adjusted to 6, and the ethanol evaporated in a current of air. The crude product crystallized partially, the crystals were removed, weighing 5.2 g., 77.5%; recrystallized from ethanol-water, m.p. 89°.

Anal. Calcd. for $C_{18}H_{25}NO_5$: N, 4.17. Found: N, 3.98, 3.99.

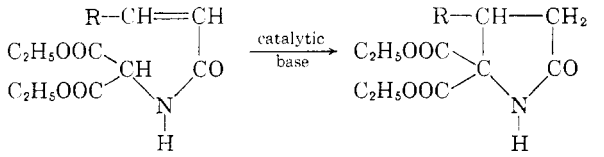
4-Acetamido-4,4-dicarbethoxybutyroanilide (XI). To a stirred solution of 0.080 g. sodium (0.0035 g.-atom) in 40 ml. of ethanol was added 4.5 g. of diethyl acetamidomalonate (0.0275 mole); when solution was complete there was added 3.65 g. of I (0.0275 mole). After 30 min. of intermittent stirring solution was complete. The container was stoppered and sealed with paraffin and allowed to stand for 2 days, at which time there was a solid mass of crystals. The product was transferred to an evaporating dish, neutralized with acetic acid (3 drops), and the ethanol evaporated in stream of air. The resulting solid, crystallized from dilute ethanol, weighed 4.1 g., yield, 40%, and melted 143°.

Anal. Calcd. for $C_{18}H_{24}N_2O_6$: N, 7.69. Found: N, 7.77, 7.42.

4-Carbobenzyloxyamido-4,4-dicarbethoxybutyroanilide (XII). To a solution of 0.80 g. of sodium (0.0035 g.-atom) in 30 ml. anhydrous ethanol was added 6.18 g. diethyl carbobenzyloxyaminomalonate[12] (0.02 mole), followed by 2.94 g. of I (0.02 mole); the container was stoppered, sealed with paraffin, and allowed to stand at room temperature for a week. The reaction mixture developed a red color. The solution was then transferred to an evaporating dish, neutralized with acetic acid (3 drops), and the alcohol removed in a stream of air. The red-brown residue was crystallized several times from dilute ethanol, affording 7.7 g. of colorless crystals, yield 85%, m.p. 99–100°.

Anal. Calcd. for $C_{24}H_{28}N_2O_7$: N, 6.14. Found: N, 5.93, 6.14.

Ethyl cinnamamidoglycine (XIII) *by decarbethoxylation of VI.* Acrylamidomalonic esters, containing within a single molecule all the requisite functional groups to undergo the Michael reaction, were examined for possible pyrrolidone formation,[15] perhaps, according to a scheme that may be indicated as follows:



Accordingly a solution was prepared from 0.023 g. of sodium (0.001 g.-atom) in 250 ml. of anhydrous ethanol, and to this was added 2.73 g. of VI (0.009 mole); the container was fitted with a reflux condenser with calcium chloride tube at the upper opening. The solution was refluxed for 12 hr.; it was then neutralized with acetic acid, the first portion of ethanol was removed by distillation, and the final portion was allowed to evaporate at room temperature. The product, weighing 2.0 g., crystallized first from dilute ethanol and then from benzene–petroleum ether (b.p. 30–60°), melted at 107–108°. The expected pyrrolidinone melts 96–98°.[15] The product still gave a positive test for ethylenic bond; molecular weight determination gave values of 220–230.

Anal. Calcd. for $C_{12}H_{15}NO_3$, m.w., 233: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.98, 66.89; H, 6.35, 6.40; N, 5.86, 5.94.

An authentic sample of ethyl cinnamamidoacetate was prepared from cinnamyl chloride and ethyl glycinate, m.p. 109°; the melting point when mixed with product obtained was not depressed.

Such decarbethoxylation probably proceeds by the same mechanism by which diethyl diphenylmalonate and diethyl phenylethylmalonate form ethyl diphenylacetate and ethyl α-phenylbutyrate, respectively, when heated in an alcoholic solution containing an equivalent of sodium ethoxide.[16]

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(16) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4319 (1932).

1-Alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas

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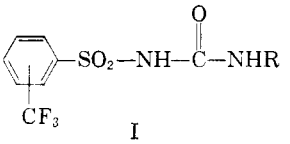
We are reporting the preparation of a group of 1-alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas(I). These compounds are now being evaluated for hypoglycemic activity.[1]



I

The literature on the procedures which may be employed for the synthesis of compounds like I has been reviewed recently.[2a,b] In our approach, the α,α,α-trifluoro-o- and -m-tolyl derivatives were prepared as shown in Chart I. The synthesis of the *p*-derivative differed only in the procedures used for the preparation of the intermediate (α,α,α - trifluoro - *p* - tolyl)sulfonamide (Chart II A,B)

Chart I

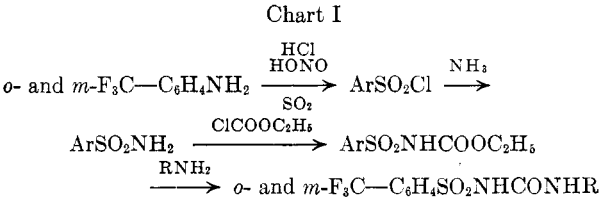
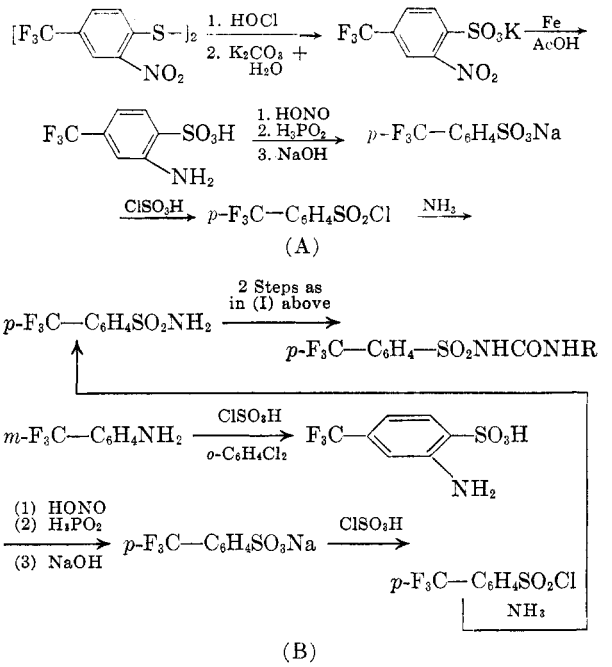


Chart II



Kracker and Herrlein[3a] have reported that one mole each of α,α,α-trifluoro-*m*-toluidine and chlorosulfonic acid in *o*-dichlorobenzene at 180° gave 4 - amino - α,α,α - trifluoro - *o* - toluenesulfonic acid. Similarly, Zitscher and Kehlen[3b] stated that α,α,α-trifluoro-*m*-acetotoluidide and an excess of fuming sulfuric acid in tetrachloroethane at 145° gave 4-acetamido-α,α,α-trifluoro-*o*-toluenesulfonic acid. Neither group of workers provided proof for their structural assignments. We have repeated[4] the procedure described by Kracker and Herrlein and obtained an amino-α,α,α-trifluorotoluenesulfonic acid whose infrared spectrum was identical with that obtained from the 2-amino-α,α,α-

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(3a) H. Kracker and F. Herrlein, U.S. Patent **2,119,882**, June 7, 1938; (b) A. Zitscher and H. Kehlen, U. S. Patent **2,141,893**, Dec. 27, 1938.

(4) This experiment was carried out by Dr. W. B. McDowell of the Chemical Development Section, Squibb Institute for Medical Research.