that obtained by the method of Dreiding and Voltman.[15] The perchloric acid catalyzed reaction was complete in 45 min. as contrasted to the 24 hr. required by the Dreiding and Voltman procedure.

Experimental Section[16]

Reagent A (10^{-3} *M* $HClO_4$).—To 50 ml. of absolute ethyl acetate was added 0.05 ml. of 72% perchloric acid (0.575 mmole). Ten milliliters of this solution was then added to 30 ml. of absolute ethyl acetate and 4.8 ml. (51 mmoles) of acetic anhydride, and the solution was made up to 50 ml. with ethyl acetate to give a reagent 1 *M* in acetic anhydride and 10^{-3} *M* in perchloric acid.

Reagent B (10^{-2} *M* $HClO_4$).—To 40 ml. of absolute ethyl acetate was added 0.05 ml. (0.58 mmole) of 72% perchloric acid and 4.8 ml. (5.1 mmoles) of acetic anhydride, and the solution was made up to 50 ml. with ethyl acetate.

General Procedure.—The keto acid or ketone was dissolved using 1 ml. of reagent for each 10 mg. of compound (reagent A for keto acids and Δ^4-3-ketones and reagent B for saturated 3-ketones), and the solution was let stand for 5 min. at room temperature. Compounds bearing hindered hydroxyl groups (11β or 17α) were allowed 15 min. to ensure complete acetylation. The solution was then washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. Residual acetic anhydride, if any, could be removed by adding a few milliliters of methanol containing a trace of pyridine and again evaporating to dryness. Analytical samples were prepared by recrystallization from methanol containing a trace of pyridine, hexane–ether or acetone, or aqueous acetone. The melting points, yields, and analyses of the products are shown in Tables I and II. For large-scale reactions it was found best to prepare a double-strength reagent which was added to an equal volume of ethyl acetate in which the starting material was previously dissolved.

The reagent can be stored in the refrigerator for several weeks without any noticeable loss of activity, though it slowly acquires a yellow to brown color. It tends to darken more rapidly as the acid concentration is increased and the darkening becomes more pronounced in the reaction mixture. Although good yields may still be obtained at acid concentration up to 0.15 *M* and as low as 10^{-4} *M*, the concentration for optimum yield of lactones and enol acetates of α,β-unsaturated ketones with minimum coloration of the product is 10^{-3} *M* (reagent A).

Dienone–Phenol Rearrangement.—1,4-Androstadiene-3,17-dione (55 mg.) was dissolved in 5 ml. of reagent B. Small samples were removed after 5, 30, and 45 min. and spotted on silica gel t.l.c. microplates, and the plates were developed with benzene–ethyl acetate 19:1. The spot corresponding to the product increased in intensity, and at 45 min. the starting material spot was no longer detected. The reaction mixture was washed with saturated sodium carbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness under nitrogen. The residue (51 mg., 92%) was saponified by refluxing in aqueous methanolic potassium hydroxide for 1 hr. The solution was acidified with dilute hydrochloric acid, and the resulting solid was collected, washed with water, and crystallized from methanol to give 1-hydroxy-3-methyl-1,3,5(10)-estratrien-17-one. The melting point and mixture melting point of a sample prepared by the method of Dreiding and Voltman[15] was 246–249°. The reaction carried out by the method of Dreiding and Voltman (zinc chloride in acetic anhydride) was also monitored by t.l.c. No appreciable reaction had occurred at 45 min., but the reaction appeared to be essentially complete at 20 hr.

Acknowledgments.—The authors are grateful to Dr. Leonard R. Axelrod for his interest and encouragement during the course of this investigation. This work was supported by Grant AM 03270-06 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

[15] A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954).

[16] Melting points were taken in a Thomas–Hoover melting point apparatus and are uncorrected. Optical rotations were determined using a Zeiss-Winkel optical polarimeter. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Reactions of Phenyl Isocyanate with Some Metal Derivatives of Pyrrole

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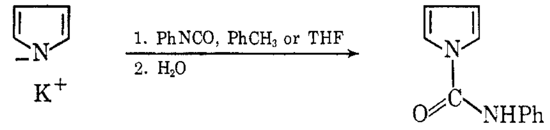
The reactions of phenyl isocyanate with Grignard reagents,[2a] 1,3-dicarbonyl compounds,[2b] and aromatic compounds under Friedel–Crafts conditions[3] to give the corresponding anilides are well known. Among heterocyclic compounds, pyrroles and Grignard reagents of substituted pyrroles react with phenyl isocyanate to form 2-pyrrolecarboxanilides.[4,5] Imidazole yields 1-imidazolecarboxanilide,[6,7] whereas 4,5-diphenylimidazole forms the 1-carboxanilide, the 2-carboxanilide, or a mixture of the latter compound and 2,5,6-triphenylimidazo[1,2-*c*]hydantoin, depending on the experimental conditions.[8]

In the course of a study on acyl derivatives of pyrrole, we found that the reaction of pyrrolylpotassium with phenyl isocyanate in toluene or tetrahydrofuran gives 1-pyrrolecarboxanilide (**1**) in very good yield. The product of this reaction is formulated as **1** because it contains only one active hydrogen atom, and its infrared spectrum shows a carbonyl absorption at 1720 cm.$^{-1}$[9] but no characteristic absorption in the 3400–3500-cm.$^{-1}$ region (pyrrole N–H stretching[10]). In contrast, the spectrum of the known 2-pyrrolecarboxanilide (**2**)[4] has bands at 1660[9] and 3450 cm.$^{-1}$



1

Like 1-imidazolecarboxanilide,[7] the pyrrole derivative **1** undergoes transamination. As expected,[11] however, 1-pyrrolecarboxanilide is more sluggish than its imidazole analog. Thus, reaction of **1** with aniline or piperidine in refluxing tetrahydrofuran proceeded very slowly, and the substitution products, N,N′-diphenylurea (**3**) and N-phenyl-N′,N′-pentamethyleneurea (**4**), could be obtained in satisfactory yields only at higher temperatures in the absence of the solvent.

Refluxing with ethanolic potassium hydroxide for 4 hr. hydrolyzed **1** to pyrrole and aniline. This behavior

[1] To whom correspondence should be addressed: Converse Memorial Laboratory, Harvard University, Cambridge, Mass.

[2] (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1199; (b) W. J. Hickinbottom, "Chemistry of Carbon Compounds," Vol. III, part A, E. H. Rodd, Ed., Elsevier Publishing Co., Inc., New York, N. Y., 1954, p. 202.

[3] F. Effenberger and R. Gleiter, *Ber.*, **97**, 472 (1964), and references therein.

[4] A. Treibs and W. Ott, *Ann.*, **577**, 119 (1952).

[5] A. Treibs and A. Dietl, *ibid.*, **619**, 80 (1958).

[6] R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949).

[7] H. A. Staab, *Ann.*, **609**, 83 (1957).

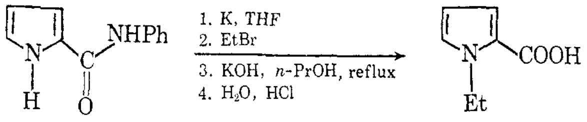
[8] R. Gompper, E. Hoyer, and H. Herlinger, *Ber.*, **92**, 550 (1959).

[9] Carbonyl stretching frequencies are above 1700 cm.$^{-1}$ for N-acylimidazoles and below 1700 cm.$^{-1}$ for C-acylimidazoles.[8]

[10] C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p. 318.

[11] H. A. Staab, *Angew. Chem. Intern. Ed. Engl.*, **1**, 351 (1962).

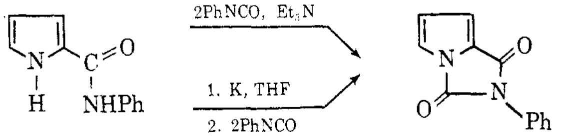
of 1-pyrrolecarboxanilide contrasts with the resistance to hydrolysis of 2-pyrrolecarboxanilides. 2,4-Dimethyl-5-pyrrolecarboxanilide is reported to remain unaltered after prolonged boiling with concentrated alcoholic or aqueous sodium hydroxide,[4] and 2-pyrrolecarboxanilide was obtained as the hydrolysis product of other compounds in the present work (*cf.* hydrolysis of compound 6). Introduction of an alkyl group at the 1-position of the pyrrole ring enhances the tendency of 2-pyrrolecarboxanilides to undergo hydrolysis, as evidenced by the conversion of 2-pyrrolecarboxanilide (2) to 1-ethyl-2-pyrrolecarboxylic acid (5) by ethylation and subsequent treatment with potassium hydroxide in refluxing *n*-propyl alcohol.



2 5

Unlike pyrrolylpotassium, which gives one product upon treatment with phenyl isocyanate, pyrrolylmagnesium bromide reacts with this reagent in tetrahydrofuran to give, after hydrolysis, a mixture of 1-pyrrolecarboxanilide (80%) and 2-pyrrolecarboxanilide (20%).

When 2-pyrrolecarboxanilide (2)[4] is treated with 2 equiv. of phenyl isocyanate in the presence of triethylamine, N,N′-diphenylurea and 2-phenylpyrrolo[1,2-*c*]hydantoin (6) are formed in very good yield. The latter product is also obtained by the action of 2 equiv. of the isocyanate on the potassium salt of 2. The hydantoin structure for compound 6 is supported by the high carbonyl absorptions in its infrared spectrum (1800 and 1750 cm.$^{-1}$), which correspond well with the reported carbonyl bands[8] in the spectrum of 2,5,6-triphenylimidazo[1,2-*c*]hydantoin (1813, 1760, and 1709 cm.$^{-1}$). Further support for the proposed structure is furnished by an independent synthesis of compound 6 from phosgene and the mono- or dipotassium salt of 2-pyrrolecarboxanilide.



2 6

+

PhNHCONHPh

3

Compound 6 is hydrolyzed by alkali to the expected 2-pyrrolecarboxanilide. The latter product is also formed, together with N,N′-diphenylurea, by the action of aniline on 6.

Experimental Section

1-Pyrrolecarboxanilide (1).—Pyrrolylpotassium was prepared in a nitrogen atmosphere from 33.5 g. (0.50 mole) of pyrrole and 15.6 g. (0.40 g.-atom) of potassium in 200 ml. of toluene by stirring the mixture at reflux until all of the metal had reacted and the blue color of the slurry had disappeared. After addition of a further 200 ml. of toluene, the temperature was brought down to 30°, and 38.1 g. (0.32 mole) of phenyl isocyanate in 100 ml. of toluene was added dropwise over a period of 1 hr. The resulting mixture was stirred at 40–50° for 9 hr. and at 65–70° for an additional 13 hr. and was filtered. The precipitate was washed with dry ether, air dried, mixed thoroughly with water, and allowed to stand for 4 hr. Filtration and drying yielded 58.0 g. of a solid which on crystallization from toluene gave 49.9 g. (84%) of 1-pyrrolecarboxanilide, m.p. 154–155°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04; active H, 0.541. Found: C, 70.74; H, 5.47; N, 14.98; active H, 0.561.

The same reaction, run in tetrahydrofuran, yielded 56.6 g. of crude 1-pyrrolecarboxanilide.

Reaction of 1-Pyrrolecarboxanilide (1) with Piperidine.—A mixture of 2.0 g. of 1 with 20 ml. of piperidine was refluxed for 22 hr. Cooling and filtration yielded 1.7 g. of a solid, m.p. 169–170°, identified as N-phenyl-N′,N′-pentamethyleneurea (4) (lit.[12] m.p. 168°, 170–171°, 171–172°) by mixture melting point and by comparison of its infrared spectrum with that of an authentic sample.

Reaction of 1-Pyrrolecarboxanilide (1) with Aniline.—A mixture of 2.0 g. of 1 with 20 ml. of aniline was heated at 130–140° for 24 hr. Cooling, filtration, and washing of the precipitate with chloroform yielded 1.8 g. of a solid, m.p. 238–239°, identified as N,N′-diphenylurea (3) by mixture melting point and by comparison of its infrared spectrum with that of an authentic sample.

Hydrolysis of 1-Pyrrolecarboxanilide (1).—A solution of 7.0 g. of 1 and 4.2 g. of potassium hydroxide in 25 ml. of ethyl alcohol was refluxed for 4 hr. Gas–liquid partition chromatography showed that the alcoholic solution contained equimolar quantities of pyrrole and aniline.

Reaction of Pyrrolylmagnesium Bromide with Phenyl Isocyanate.—To a solution of ethylmagnesium bromide, prepared from 12.2 g. (0.50 g.-atom) of magnesium and 60 g. (0.55 mole) of ethyl bromide in 180 ml. of tetrahydrofuran under a nitrogen atmosphere, was added dropwise over a period of 45 min. 33.5 g. (0.50 mole) of pyrrole in 100 ml. of tetrahydrofuran. To the resulting solution of pyrrolylmagnesium bromide, cooled to room temperature, 54 g. (0.45 mole) of phenyl isocyanate in 80 ml. of tetrahydrofuran was added dropwise in the course of 45 min. Stirring was continued for 22 hr., and then the solution was hydrolyzed by the addition of 250 ml. of a saturated aqueous solution of ammonium chloride. An ether extract of the aqueous layer was combined with the organic layer and the solvents were removed under reduced pressure. Crystallization of the crude product from toluene yielded 70.3 g. of a solid (m.p. 147–150°), the infrared spectrum of which showed that it was a mixture of 1- (1) (80%) and 2-pyrrolecarboxanilide (2) (20%).

1-Ethyl-2-pyrrolecarboxylic Acid (5).—To a solution of 5.6 g. (0.03 mole) of 2-pyrrolecarboxanilide (2)[4] in 50 ml. of tetrahydrofuran, kept in a nitrogen atmosphere, was added 1.17 g. (0.03 g.-atom) of potassium. The mixture was stirred at reflux until all of the metal had reacted, cooled to room temperature, and treated with 3.3 g. (0.03 mole) of ethyl bromide. After the mixture had been stirred for 14 hr., a further 3.3 g. of ethyl bromide was added to ensure completion of the reaction, and stirring was resumed for an additional 6 hr. at 45–50°. Dilution with ether and filtration yielded a precipitate which was dissolved in a small amount of water. An ether extract of this solution was combined with the filtrate, and the solvents were removed under reduced pressure. The residue was stirred with 10 g. of potassium hydroxide and 30 ml. of *n*-propyl alcohol at reflux for 24 hr. The material obtained by concentration of this solution under reduced pressure was diluted with water and washed with ether. After treatment with animal charcoal, the aqueous solution was cooled to 0° and acidified with cold, dilute hydrochloric acid. The precipitate was collected by filtration, washed with cold water, and air dried. Extraction with ether of the filtrate and evaporation of the extract to dryness yielded a residue which was added to the precipitate. The combined products were stirred with an excess of chloroform, and the resulting solution was treated with animal charcoal and filtered. Evaporation of the filtrate to dryness under reduced pressure (40–50°) yielded 2.1 g. (50%) of 1-ethyl-2-pyrrolecarboxylic acid, m.p. 80–81° (lit.[13] m.p. 78°). Recrystal-

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(12) F. K. Beilstein, "Handbuch der Organischen Chemie," Vol. XX, Verlag von Julius Springer, Berlin, 1935, p. 54.

(13) C. A. Bell, *Ber.*, **10**, 1861 (1877).

lization from petroleum ether (b.p. 38–56°) gave colorless needles, m.p. 81–82°. The infrared spectrum showed peaks at 2500–3000 (broad), 1680, 1430, 1250, and 930 cm.$^{-1}$.

2-Phenylpyrrolo[1,2-*c*]hydantoin (6).—A mixture of 5.60 g. (0.03 mole) of 2-pyrrolecarboxanilide (2),[4] 7.14 g. (0.06 mole) of phenyl isocyanate, and 1.50 g. of triethylamine (distilled from lithium aluminum hydride) was heated at 60–70° for 22 hr. The resulting solid was ground into a powder which was washed with petroleum ether, dried, and stirred thoroughly with 800 ml. of chloroform. The insoluble material (6.1 g., 95%) was shown to be N,N′-diphenylurea (3) by comparison of its infrared spectrum with that of an authentic sample. Crystallization from ethyl alcohol gave colorless needles, m.p. 238–240°. A mixture melting point with an authentic sample showed no depression. Evaporation of the filtrate to dryness under reduced pressure yielded 5.9 g. (92%) of 2-phenylpyrrolo[1,2-*c*]hydantoin (6). Crystallization from ethyl alcohol gave colorless crystals, m.p. 226–227°.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20; mol. wt., 212. Found: C, 68.09; H, 3.89; N, 13.38; mol. wt., 208.

2-Phenylpyrrolo[1,2-*c*]hydantoin (6) from the Potassium Salt of 2-Pyrrolecarboxanilide (2) and Phosgene.—A solution of 9.30 g. (0.05 mole) of 2[4] in 70 ml. of tetrahydrofuran was stirred at reflux with 1.95 g. (0.05 g.-atom) of potassium until all of the metal had reacted. After dilution with 100 ml. of tetrahydrofuran, the temperature was brought down to 0° and 7 g. of phosgene dissolved in 100 ml. of tetrahydrofuran at 0° was added in the course of 15 min. The cooling bath was then removed, and the mixture was stirred overnight. After removal of the solvent under reduced pressure, the residue was treated with 250 ml. of ethyl alcohol, and the mixture was filtered. Crystallization of the precipitate from ethyl alcohol yielded 2.7 g. of 6, melting at 225–226°.

Similar treatment of the dipotassium salt of 2 (from 9.30 g. of 2 and 3.90 g. of potassium) afforded 3.75 g. of 6, m.p. 225–226°.

2-Phenylpyrrolo[1,2-*c*]hydantoin (6) from the Potassium Salt of 2-Pyrrolecarboxanilide (2) and Phenyl Isocyanate.—To a solution of the potassium salt of 2, made from 4.65 g. (0.025 mole) of 2, 0.97 g. (0.025 g.-atom) of potassium, and 20 ml. of tetrahydrofuran, was added 5.95 g. (0.050 mole) of phenyl isocyanate in one portion. The mixture was stirred for a few minutes, mixed with petroleum ether, and filtered. The precipitate was treated with water and the resulting solid was dried and stirred with an excess of chloroform. Filtration and evaporation of the filtrate to dryness yielded a solid which, on recrystallization from ethyl alcohol, gave 1.6 g. of 6, m.p. 225–227°.

Hydrolysis of 2-Phenylpyrrolo[1,2-*c*]hydantoin (6).—A mixture of 1 g. of 6, 2 g. of potassium hydroxide, and 20 ml. of ethyl alcohol was heated until a clear solution had been obtained. Cooling, dilution with cold water, and filtration gave 0.75 g. of a solid, m.p. 153–154°. This product was identified as 2-pyrrolecarboxanilide (2) by mixture melting point and comparison of the infrared spectra.

Reaction of 2-Phenylpyrrolo[1,2-*c*]hydantoin (6) with Aniline.—A mixture of 2 g. of 6 with 20 ml. of aniline was refluxed for 14 hr., cooled, and diluted with an excess of chloroform. Filtration afforded 1.65 g. of a solid, the infrared spectrum of which was identical with that of an authentic sample of N,N′-diphenylurea (3). Crystallization from ethyl alcohol gave colorless crystals, m.p. 238–239°, not depressed by an authentic sample of 3. The chloroform filtrate was washed with cold, dilute hydrochloric acid, then with water, and was evaporated to dryness under reduced pressure. Washing of the residue with petroleum ether yielded 1.30 g. of a solid, the infrared spectrum of which was identical with that of an authentic sample of 2. Crystallization from benzene–methanol (85:15) gave pure 2-pyrrolecarboxanilide, m.p. 153–154°.

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Cleavage of α,β-Unsaturated Ethers by Diisobutylaluminum Hydride

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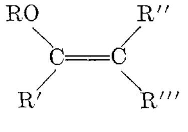
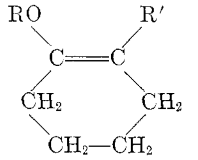
Only a few reports have appeared in the literature on the reaction of α,β-unsaturated ethers with organometallic compounds.

The alkyl vinyl ethers are cleaved[1] by lithium alkyls, yielding acetylene and aliphatic alcohols; α-ethoxystyrene and some related compounds are cleaved[2] by Grignard reagents, yielding olefins. Diisobutylaluminum hydride, at 30–35°, cleaves[3] vinyl *n*-butyl ether, forming ethylene.

In connection with some investigations on the stereospecific polymerization of vinyl ethers,[4] we have examined the reaction between diisobutylaluminum hydride and α,β-unsaturated ethers of the types I, II, and III.



Ia, R = alkyl; R′, R″, R‴ = H
b, R, R″ (or R‴) = alkyl; R′, R‴ (or R″) = H
c, R, R″, R‴ = alkyl; R′ = H



II, R = alkyl; R′ = H

$RO{-}C{\equiv}C{-}R'$

III, R, R′ = alkyl

In agreement with the results obtained by Zakharkin and Savina in the case of *n*-butyl vinyl ether,[3] by mixing at 25° isobutyl vinyl ether or 2-ethylhexyl vinyl ether with diisobutylaluminum hydride, a remarkable temperature increase and a rapid gas evolution took place, the gas evolved being practically pure ethylene. At the same time, diisobutylaluminum isobutoxide, or diisobutylaluminum 2-ethylhexyloxide, was formed. However, the reaction did not occur when the temperature of the reagents was kept below 20°.

A smooth cleavage of isobutyl vinyl ether by diisobutylaluminum hydride occurred also in the presence of an excess of triisobutylaluminum, but temperatures higher than 50° were required.

1-Methyl-2-ethoxyethylene and 1-propyl-2-ethoxyethylene (Ib) (both mixtures of *cis* and *trans* isomers), when treated in isooctane solution at 50–100° with diisobutylaluminum hydride, yielded propylene or 1-

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[1] K. E. Piotrovskiĭ and M. P. Stotskaya, *Dokl. Akad. Nauk SSSR*, **135**, 868 (1960).

[2] C. M. Hill, R. A. Walker, and M. E. Hill, *J. Am. Chem. Soc.*, **73**, 1663 (1951).

[3] L. I. Zakharkin and L. A. Savina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 444 (1959).

[4] In a series of polymerization experiments of some vinyl ethers, carried out in the presence of $TiCl_3$ and an excess of $Al(i\text{-}C_4H_9)_3$ at 100°, small quantities of polyethylene were obtained. On the basis of previous[3] and present findings, the above result can be accounted for admitting that, because of the presence of $Al(i\text{-}C_4H_9)_2H$ deriving from $Al(i\text{-}C_4H_9)_3$ by thermal decomposition, the monomer decomposed giving rise to ethylene which then polymerized.