7, since it may also be considered valid for the formation of amides from acids and urea as well as to that of anilides from acids and *s*-diphenylurea.

Experimental[5]

The experimental details described below for the preparation of phenylacetanilide represent a typical case and serve as a model for other cases except for small differences in the maximum temperature employed and the total time allowed for the reaction. The identity of the anilides was confirmed by analysis and mixed melting point determinations with authentic samples prepared from aniline and the respective acid chlorides.

Preparation of Phenylacetanilide.—An intimate mixture of 6.8 g. (0.05 mole) of well dried diphenylacetic acid and an equimolecular quantity (11.4 g.) of *s*-diphenylthiourea was placed in a flask fitted with an air condenser, and was heated gradually in an oil bath. In the course of about 1 hr. the temperature was raised to 180–185° when the actual reaction commenced marked by effervescence and frothing and deposition of some yellow solid (sulfur) in the reflux tube. The reaction was allowed to proceed for another hour, the temperature of bath being maintained between 180–190°. The reaction mixture was cooled and taken up in ether. After extraction with dilute hydrochloric acid, the ethereal solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether and crystallization of the residue from ethanol gave 9.4 g. (90%) of diphenylacetanilide, m.p. and mixed m.p. with an authentic sample[4] of 117–118°. The aqueous hydrochloric acid extract of the ethereal solution of the reaction product gave a positive coupling reaction with β-naphthol.

Preparation of N-Phenylsuccinimide.—A mixture of 5 g. (0.05 mole) of succinic anhydride and an equimolecular quantity (11.4 g.) of *s*-diphenylthiourea was heated at 180–185° for about 2 hr. The cooled reaction mixture was triturated with small portions of ether to remove aniline and the residue was crystallized from ethanol. This gave 6.5 g. (74%) of N-phenylsuccinimide with a m.p. and mixed m.p. with an authentic sample[4] of 155°.

Preparation of Benzanilide from Phenyl Isothiocyanate.—An intimate mixture of 3.66 g. (0.03 mole) of benzoic acid and an equimolecular quantity of phenyl isothiocyanate (4.05 g.) was heated at 180–185° for about 2 hr. A slight deposition of sulfur in the condenser and the evolution of hydrogen sulfide from the out-coming vapors was noted and confirmed. The reaction mixture was allowed to cool and was then taken up in hot alcohol. Treatment of the hot alcoholic solution with active charcoal and evaporation of the solvent from the filtered solution gave 5.2 g. (89%) of benzanilide which on recrystallization from ethanol melted at 162–163° and did not show any depression on admixture with the sample of benzanilide prepared from *s*-diphenylthiourea and an authentic sample prepared from benzoyl chloride and aniline.

TABLE I

Acids	Yields of the Anilides, %	M.p., °C.
Phenylacetic	85	117–118
Diphenylacetic	91	181–182
Benzoic	89	162–163
Succinic	57 (Imide)	154–155
Palmitic	81	86–87
Stearic	84	82–83

The preceeding table summarizes the yields of the anilides obtained from phenyl isothiocyanate and acids other than benzoic acid. The identity of the anilide in each case was confirmed both by mixed melting point determination with samples prepared from *s*-diphenylthiourea and with an authentic sample prepared from the respective acid chloride and aniline and by elemental analysis. It may be noted that the melting point of pure stearic acid anilide prepared by the above two methods and from the acid chloride and aniline, was found to be 82–83° and not 93° as reported in the literature.

Acknowledgment.—The authors wish to express their thanks to "Consejo Nacional de Investigaciones Científicas y Técnicas," Buenos Aires, for a research grant in connection with this work.

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[5] Melting points are uncorrected.

Alternative Approaches to 1-Substituted Thymines

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Received January 19, 1962

Syntheses of the cyclopentane isostere of thymidine and other 1-(hydroxycyclopentyl)thymines[1] required 1-(3-cyclopenten-1-yl)thymine (V) as a key intermediate. For the synthesis of this compound we found that a route to 1-substituted thymines reported by Shaw and Warrener[2] was quite satisfactory, except for the last step, closure of the pyrimidine ring. This note describes an improved ring closure method, as well as an alternative approach to acylurea intermediates.

In a modification of the published route, methyl 3-methoxy-2-methylacrylate was saponified and the resulting sodium salt converted directly to the acid chloride, bypassing an intervening[2] isolation of the free acid. Conversion of the acid chloride to the acyl isocyanate I and then to the ethoxycarbonylamide[2] III proceeded smoothly. In a subsequent reaction of III with an equivalent amount of 3-cyclopenten-1-ylamine[3] in hot aqueous sodium hydroxide, a condensation–cyclization gave the desired 1-(3-cyclopenten-1-yl)thymine (V), but the yield was only 23%. It seems likely that saponification of the starting ethoxycarbonylamide (III) or of a noncyclized intermediate was a competing side reaction. Other workers have found that in an analogous cyclization with benzylamine as the amine component the yield of 1-benzylthymine was 24%,[4] and even with large excesses of ammonia or methylamine the yields of thymine and 1-methylthymine were 42 and 44%,

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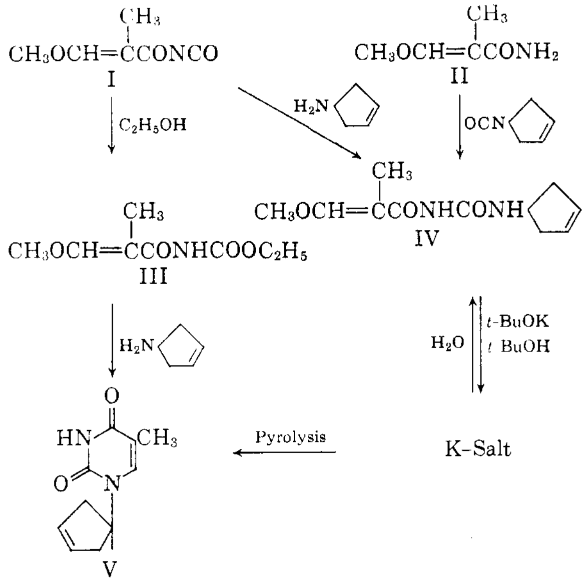
[1] K. C. Murdock and R. B. Angier, Abstracts of Papers, 141st Meeting, American Chemical Society, Washington, D. C., March, 1962, p. 22-N; *Tetrahedron Letters*, 415 (1962); *J. Am. Chem. Soc.*, in press.

[2] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 153, 157 (1958).

[3] K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

[4] M. H. Benn, B. Chatamra, and A. S. Jones, *J. Chem. Soc.*, 1014 (1960).

respectively.[2] Our yield of V was not significantly changed when hot aqueous potassium carbonate was the condensing agent. Experiments using unheated, aqueous potassium carbonate, ethanolic sodium ethoxide, or hot undiluted triethylamine were unsuccessful.



In another approach, the addition of 3-cyclopenten-1-ylamine to the acyl isocyanate (I) gave the cyclopentenylurea (IV). Shaw and Warrener cyclized the corresponding phenylurea to 1-phenylthymine in good yield in aqueous alkali. But an analogous synthesis of 1-methylthymine was not successful in aqueous alkali and the yield was only 26% when an excess of aqueous methylamine was used as the condensing agent.[2] Since our cyclopentenylamine was not plentiful other methods were sought. With a solution of potassium *t*-butoxide in *t*-butyl alcohol at 36°, the cyclopentenylurea (IV) formed an insoluble salt. On contact with water this salt reverted to the cyclopentenylurea. But it was found that pyrolysis of the dry salt *in vacuo* expelled the elements of methanol and gave the required 1-(3-cyclopenten-1-yl)-thymine (V) in 75% yield. This ring closure procedure should also be useful in the synthesis of 1-substituted uracils.[cf. 5]

Since 3-cyclopenten-1-yl isocyanate[3] is a precursor of 3-cyclopenten-1-ylamine a one-step synthesis of the cyclopentenylurea (IV) from this isocyanate was desirable, even though the N-acylation of amides by isocyanates is a reaction that appears to have been used only infrequently and with variable success.[6] With the above acid chloride and anhydrous ammonia in cold ethylene chloride 3-methoxy-2-methylacrylamide (II) was prepared in high yield. (With aqueous ammonia at −10° the yield was just 19%.) Subsequent condensation of this amide with the cyclopentenyl isocyanate gave the cyclopentenylurea (IV) in 59% yield. The generality of this amide–isocyanate approach was established with analogous condensations with butyl isocyanate and phenyl isocyanate. Cyclizations of the resulting ureas gave 1-*n*-butylthymine and 1-phenylthymine, respectively.

Experimental[7]

3-Methoxy-2-methylacrylamide (II).—A solution of 40.3 g. (0.3 mole) of 3-methoxy-2-methylacryloyl chloride[2] in 600 ml. of ethylene chloride[8] was partially frozen, then maintained at or below −25° during the introduction of *ca.* 13.5 g. (0.9 mole) of gaseous ammonia. The resulting slurry was agitated for 5 min., and excess ammonia was removed by evaporation at *ca.* 20°. The slurry was diluted with 200 ml. of chloroform, solids were collected by filtration, then extracted on the filter with three 100-ml. portions of chloroform. Evaporation of the filtrates, crystallization of the residue from benzene, and washing the product with carbon tetrachloride gave 29.1 g. (84%) of needles, m.p. 109–111°. The product gradually decomposed during 4 months at room temperature, but was stable at −5°.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.20; H, 8.01; N, 12.52.

N-(3-Cyclopenten-1-yl)-N′-(3-methoxy-2-methylacryloyl)urea (IV).—(A) A suspension of 35.9 g. (0.3 mole) of 3-cyclopenten-1-ylamine hydrochloride[3] in 70 ml. of toluene was swirled and cooled during the gradual addition of a warm solution of 24 g. (0.6 mole) of sodium hydroxide in 20 ml. of water. The resulting thick slush was warmed until it was more mobile and then was agitated for a few minutes. The organic layer was decanted, and the slush was extracted by warming, agitation, and decantation using four 10-ml. portions of toluene. The combined organic layers were dried for 1 hr. with frequent shaking over pellets of potassium hydroxide. The resulting amine solution was filtered through absorbent cotton and held for later use.

To a well stirred solution of 40.4 g. (0.3 mole) of 3-methoxy-2-methylacryloyl chloride[2] in 300 ml. of dry benzene was added 75.0 g. (0.5 mole) of pulverized dried (4 hr. at 135° and 1 mm. over phosphorus pentoxide) silver cyanate. The mixture was stirred and heated under reflux with exclusion of moisture for 0.5 hr., then chilled with an ice bath during the addition of the above amine solution from a separatory funnel at a rate such that the temperature of the reaction mixture did not exceed 10°. The mixture was warmed to 25° and allowed to stand for 15 min. Silver salts were removed by filtration, the filtrate was treated with decolorizing charcoal, refiltered, and then evaporated to dryness at *ca.* 60°. Crystallization of the residue from ethanol–water gave 55.8 g. (83%) of needles, m.p. 124–126°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.55; H, 7.40; N, 12.47.

(B) A well stirred solution of 1.121 g. (17.2 mmoles) of sodium azide in 5 ml. of water was kept at 0–5° during the dropwise addition of a chilled solution of 1.121 g. (8.58 mmoles) of 3-cyclopentene-1-carbonyl chloride[3] in 5 ml. of acetone. The mixture was stirred at 0° for 0.5 hr., the bottom layer was extracted with two 5-ml. portions of

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(5) J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 583 (1962); T. Naito, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **9**, 249 (1961).

(6) P. F. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949); B. Kuhn, *Ber.*, **17**, 2882 (1884).

(7) We thank Mr. Louis Brancone and Mr. William Fulmor and their groups for microanalyses and spectral determinations and Mr. E. R. Ruckel for large-scale preparations of several intermediates. Melting points are corrected. Evaporations were conducted under reduced pressure. Solids were pressed with potassium bromide for infrared spectral determinations.

(8) This procedure for the synthesis of amides is adapted from W. E. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, **69**, 516 (1947).

toluene, then discarded. The upper layer and the toluene extracts were dried over magnesium sulfate, filtered, then washed with two 1-ml. portions of dry toluene. The combined filtrates were heated under reflux with exclusion of moisture for 0.5 hr., when the evolution of nitrogen was virtually complete. To half of the resulting isocyanate solution was added 0.576 g. (5 mmoles) of dried (3 hr. at 1 mm. over phosphorus pentoxide) 3-methoxy-2-methylacrylamide (II). The resulting solution was protected from atmospheric moisture with a calcium chloride tube, then heated under reflux for 12 hr.; when a droplet from the reaction mixture was then allowed to dry on filter paper it no longer emitted the sharp odor of the isocyanate. The solution was evaporated to dryness, the solid residue washed with petroleum ether (b.p. 30–60°) then extracted on a filter with a total of 11 ml. of carbon tetrachloride, leaving 0.223 g. of a white solid. Evaporation of the carbon tetrachloride filtrates and crystallization of the residue from ethanol-water gave 0.564 g. (59%) of needles, m.p. 121–124°, or m.p. 122–124° after admixture with the product of method A (above).

In a comparable experiment, starting with 22.4 g. of the acid chloride and 23.0 g. of the amide, refluxing was continued for 6 days; the yield of product was 20.9 g. (54%), m.p. 125–127°. The extraction step with carbon tetrachloride left 12.2 g. of insoluble, crystalline material. Extraction of this with one 20-ml., then two 10-ml. portions of water left 4.5 g. (27%) of N,N'-di(3-cyclopenten-1-yl)-urea, m.p. 214–216°. Crystallization from butanone gave rods, m.p. 217–218°, identical with material prepared by the reaction of 3-cyclopenten-1-yl isocyanate with aqueous alkali (below).

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.81; H, 8.65; N, 14.45.

Evaporation of the aqueous extracts and crystallization of the residue from benzene gave 6.8 g. (30% recovery) of rods, m.p. 113°; the mixture m.p. with starting amide II was 110–112°.

N,N'-Di(3-cyclopenten-1-yl)urea.—From 34.4 g. of 3-cyclopenten-1-carbonyl chloride there was prepared[3] 200 ml. of a solution of 3-cyclopenten-1-yl isocyanate in benzene. When a 2-ml. aliquot of this solution was heated on the steam bath with 0.10 ml. of water a homogeneous solution resulted, but almost no solid separated. So a second, 2-ml. aliquot was stirred and heated under reflux for 0.5 hr. with 2 ml. of 2 *M* aqueous potassium carbonate. Surprisingly,[cf. 9] even then only a modest amount of solid had separated, and the sharp odor of the isocyanate was still present. The benzene was boiled out and the mixture heated over the steam bath without a condenser for 0.5 hr., the mixture was cooled, the solid removed by filtration, and washed with water: 0.156 g. (62%), leaflets, m.p. 215–216°. After crystallization from butanone, the m.p. and mixture m.p. with the by-product of the preceding experiment were 217–218°. The infrared spectra of the two samples were identical.

N-*n*-Butyl-N'-(3-methoxy-2-methylacryloyl)urea.—A solution of 4.44 ml. (3.96 g., 0.04 mole) of *n*-butyl isocyanate and 4.60 g. (0.04 mole) of dry 3-methoxy-2-methylacrylamide (II) in 50 ml. of dry toluene was heated under reflux for 20 hr., cooled, filtered, and evaporated to dryness. The residue was extracted with three 50-ml. portions of boiling petroleum ether (b.p. 30–60°). The combined extracts were cooled, decanted from the gum which had separated, clarified with 1 g. of decolorizing charcoal, then filtered. At −5° the concentrated filtrate deposited 2.71 g. (32%) of needles, m.p. 75–77°. A portion (0.053 g.) was sublimed at 100° (0.3 mm.) to give 0.050 g. of purified product, m.p. 79°.

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.13; H, 8.55; N, 12.83.

N-(3-Methoxy-2-methylacryloyl)-N'-phenylurea.—A solution of 2.38 g. (0.02 mole) of phenyl isocyanate and 2.30 g. (0.02 mole) of vacuum-dried 3-methoxy-2-methylacrylamide (II) in 25 ml. of dry toluene was protected from atmospheric moisture, heated under reflux for 20 hr., then evaporated. The residual solid was washed with ethanol: 3.21 g. (69%), m.p. 140–143° or m.p. 142–144° after crystallization from ethanol (lit.,[2] m.p. 144°). The structure of the product was confirmed by cyclization[2] to form 1-phenylthymine, m.p. 205° after crystallization from butanone (lit.,[2] m.p. 199°).

1-(Cyclopenten-4-yl)thymine (V).—(A) A mixture of 0.299 g. (2.5 mmoles) of 3-cyclopenten-1-ylamine hydrochloride,[3] 2.5 ml. of 2 *N* sodium hydroxide, and 0.468 g. (2.5 mmoles) of N-ethoxycarbonyl-3-methoxy-2-methylacrylamide (III) was stirred and heated on the steam bath for 3 hr., when almost all of the solid had dissolved. The solution was cooled, filtered, and then neutralized with concentrated hydrochloric acid. The resulting solid was collected and washed with water: 0.111 g. (23%), m.p. 165–167°; or m.p. 168° after crystallization from benzene; $\lambda_{max}^{CH_3OH}$ 272 mμ (ϵ 9900), $\lambda_{max}^{0.1N\ HCl}$ 273 mμ (ϵ 10,100), $\lambda_{max}^{0.1N\ NaOH}$ 271 mμ (ϵ 7900); λ_{max}^{KBr} 3.16 (enolic OH), 5.95 (broad, cyclic amide), 6.06, 6.80, 7.02, 7.17, and 14.33 μ (*cis* olefin).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.59; H, 6.41; N, 14.38.

(B) Reaction was as above except that the hydrochloride was neutralized with 1.25 ml. of 2 *N* sodium hydroxide, made basic with 2.5 ml. of 2 *M* potassium carbonate, then heated for 1.5 hr. After crystallization from benzene the yield of product was 0.123 g. (26%), m.p. 167–168°.

(C) To a hot solution of 20.9 g. (0.0932 mole) of N-(3-methoxy-2-methylacryloyl)-N'-(3-cyclopenten-1-yl)urea(IV) in 94 ml. of dry *t*-butyl alcohol in a 1-l., round-bottomed flask was added 94 ml. of a 1 *N* solution of potassium *t*-butoxide in *t*-butyl alcohol. The solution was heated under gentle reflux for 15 min., when much solid had separated.[10] (A portion was washed with *t*-butyl alcohol: m.p. 170–185° with gassing until 230°. Treatment with water regenerated the starting urea (IV), m.p. and mixture m.p. 121–122°.) Rotary evaporation at aspirator pressure gave a solid residue spread out in a thin layer on the inside of the flask. The flask was evacuated to a pressure of 0.5 mm., then lowered up to the neck into an oil bath maintained at 210–215°. Fusion of the solid was complete after 10 min., the evolution of gas (presumably methanol) had ceased and the oil pump had lowered the pressure of the system back to 1 mm. The cooled, dark red melt was dissolved in a total of 31 ml. of water. The solution was filtered, then neutralized to pH 5–6 by the dropwise addition with swirling and cooling of 8.2 ml. of concentrated hydrochloric acid. The mixture was chilled with an ice bath, the solid collected, and washed with water to give 14.4 g., m.p. 162–167°. Recrystallization from benzene returned 12.6 g. of product, m.p. 168–169°, undepressed after admixture with the product of method A. Treatment of the unheated mother liquor with decolorizing charcoal followed by filtration and concentration gave another 0.76 g. of crystals (total yield, 75%), m.p. 166–168°.

1-(*n*-Butyl)thymine.—The conversion of 1.714 g. of N-*n*-butyl-N'-(3-methoxy-2-methylacryloyl)urea to a potassium salt followed by pyrolysis and acidification as in method C of the preceding experiment gave 0.901 g. (62%) of a granular product, m.p. 135–138°. Crystallization from water gave plates, m.p. 140°, $\lambda_{max}^{CH_3OH}$ 272 mμ (ϵ 8900).

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.33; H, 7.97; N, 15.53.

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(9) T. Curtius and W. Ulmer, *J. prakt. Chem.*, **125**, 60, 167 (1930).

(10) In some runs no solid separated. Final yields were not significantly different.