white crystals, m.p. 140–142°. Recrystallization from toluene afforded 0.77 g. (83%) of white needles, m.p. 146–148°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.59; N, 7.09.

Infrared spectrum (Nujol mull): 3.10bm; 3.42i; 3.49i; 5.86sm; 5.98bi; 6.68m; 6.80m; 6.85i; 7.02w; 7.18i; 7.27m; 7.38i; 7.70bm; 8.00i; 8.30w; 8.60w; 9.16bi; 9.32w; 9.70w; 9.98w.

Formaldehyde Condensation Product Vb.—The enol of 1-cyclohexyl-4-bromo-2,3-dioxopyrrolidine, m.p. 150–151° (26.0 g., 0.1 mole), was suspended in a mixture of 2.25 kg. of 37% formalin solution, 450 ml. of methanol, and 300 ml. of concentrated hydrochloric acid. The reaction mixture was refluxed for 3 hr. During the first hour of the heating period the compound completely dissolved. The solution was allowed to cool to room temperature and stand overnight, then was extracted repeatedly with benzene. The benzene extract was dried over sodium sulfate, filtered, and evaporated under reduced pressure to yield a solid residue. The residue was dissolved in 100 ml. of hot ethanol. The hot solution was treated with Norit-A, filtered, and diluted with 100 ml. of hot distilled water. When the solution was cooled white platelets appeared. The product was collected by filtration, washed with 50% aqueous ethanol, and dried. The yield was 16 g. (58%) of a product melting at 155–156°. The melting point did not change on further recrystallization from aqueous ethanol. The product gave no ferric chloride test.

Anal. Calcd. for $C_{12}H_{18}NO_4Cl$: C, 52.27; H, 6.58; N, 5.09; Cl, 12.84. Found: C, 52.27; H, 6.62; N, 4.73; Cl, 12.41.

Infrared spectrum (Nujol mull): 3.18bi; 3.42i; 3.49i; 5.92bi; 6.76m; 6.90m; 7.27m; 8.00bi; 8.22i; 8.54i; 8.76i; 9.10i; 9.50bi; 9.88i; 9.98bi.

1-Cyclohexyl-4-chloro-4-hydroxymethyl-2,3-dioxopyrrolidine (VIIb).—The formaldehyde condensation product Vb, m.p. 155–156° (0.45 g., 0.0016 mole), was dissolved in 20 ml. of hot 95% ethanol. To the solution was added 0.2 ml., (0.002 mole) of aniline and the reaction mixture was refluxed for 3 hr. The solution was cooled to room temperature. The solvent was evaporated under reduced pressure to leave a yellow oil. The oil was dissolved in 50 ml. of hot benzene, treated with Norit-A, filtered, and concentrated to a volume of 20 ml. On cooling, white crystals separated. After the mixture had been allowed to stand for 48 hr. at room temperature, the product was collected by filtration and washed with absolute ether. The yield was 0.13 g. (32%) of material melting at 149–153°. Recrystallization from toluene gave a compound of m.p. 152–154° which contained chlorine and gave a negative ferric chloride test.

Anal. Calcd. for $C_{11}H_{16}NO_3Cl$: C, 53.80; H, 6.58. Found: C, 54.03; H, 6.78.

Infrared spectrum (Nujol mull; bands below 7.5 μ given): 3.04m; 3.42i; 3.49i; 5.62i; 5.86i; 6.85i; 7.27m.

From the mother liquor an oil was obtained after evaporation under reduced pressure. The oil solidified on treatment with absolute ether. It weighed 0.15 g. (37%) and melted at 80–130°. It had the same infrared spectrum as the first crop of the product.

Acknowledgment.—The authors are indebted to George E. Milliman and Dr. Robert J. Kurland for the n.m.r. measurements and to Dr. Nazih Latif for other assistance.

The Preparation of 2-Imidazolones. A Novel Ring Closure of Propynylureas with Phosphorus Pentachloride

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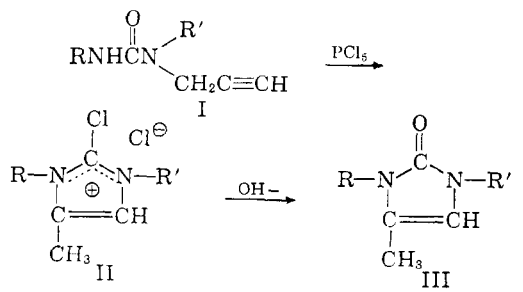
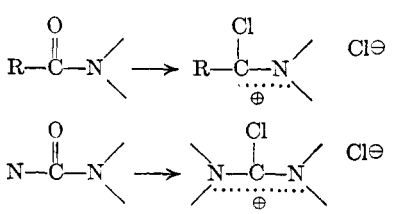
The facile preparation of otherwise inaccessible 1,3-disubstituted 2-imidazolones is reported. The action of phosphorus pentachloride on propynylureas I gave the imidazolium salts II. These on treatment with base were converted to the imidazolones III. A short discussion of the proposed mechanism is included.

We wish to report a novel ring closure effected by treating a suitable propynylurea I with phosphorus pentachloride. A 2-imidazolone III is obtained *via* a stable isolable imidazolium chloride II.



The formation of imidoyl chlorides $\left[\begin{matrix}Cl\\|\\-C=NR\end{matrix}\right]$ on treatment of amides and ureas is well known. Recent reports show the formation of stable acylic amido chlorides and carbamido chlorides from the corresponding amides[1-3] and ureas.[2,4]



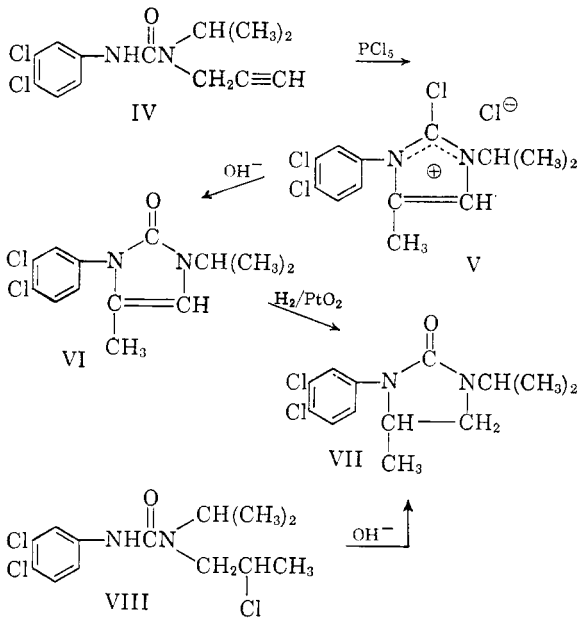
(1) I. Ugi and C. Steinbrückner, *Angew. Chem.*, **72**, 267 (1960).

(2) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *ibid.*, **72**, 836 (1960).

(3) F. Klages and W. Grill, *Ann.*, **594**, 21 (1955).

(4) A. Steindorff, *Ber.*, **37**, 964 (1904).

The carbamido chlorides are less reactive than amido chlorides, because of greater resonance stabilization. Although such chlorinating agents as phosphorus pentachloride, phosgene, thionyl chloride, and oxalyl chloride have been used successfully in amido chloride preparations, only phosgene has proved useful in carbamido chloride syntheses.[2]



Treatment of 3-(3,4-dichlorophenyl)-1-isopropyl-1-(2-propynyl)urea (IV) with phosphorus pentachloride in refluxing benzene gave the crystalline imidazolium chloride V rather than the expected acyclic chloroformamidine or carbamido chloride. Thus, V is the first cyclic carbamido chloride reported. The 2-imidazolone VI is precipitated immediately in good yield when an aqueous solution of V is made slightly alkaline with sodium hydroxide. The conversion of IV to V involves the transformation of the urea to a carbamido chloride accompanied by a rather unique rearrangement and cyclization of the propynyl group.

Identification and structural proof of V and VI were established by two syntheses, IV to VII and VIII to VII.

Evidence that IV cyclized to V was obtained as follows. Titration for ionic chloride gave one readily hydrolyzable chloride ion. Potentiometric titration of V after treatment with alkali gave two equivalents of chloride ion with simultaneous separation of VI. The infrared spectrum of V gave the expected bands at 6.15 μ (C=C) and 6.0 μ (C=N)[5] but lacked the band at 4.5 μ (C≡C) present in IV. The ultraviolet spectrum of IV shows λ_{max} (H_2O), 222 μ (log ϵ 4.21).

The infrared spectrum of VI showed strong absorption at 5.90 μ (C=O), the band at 6.15 μ (C=C), but lacked the band at 6.0 μ (C=N) which was characteristic of V.

The structural assignment for VI and hence V is unambiguous as determined by proton nuclear magnetic resonance. The τ values for all protons are consistent for VI[6]: A doublet at τ = 8.72 (methyl groups of isopropyl), a second doublet at τ = 8.06 (CH_3 attached to C=C), a quartet at τ = 4.00 (single proton attached to C=C), the single proton of the isopropyl group at τ = 5.69 and the aromatic protons at τ = 2.61.

Hydrogenation of VI with platinum oxide gave the 2-imidazolidone VII which was identified by synthesis from the urea VIII. Samples of VII prepared from both VI and VIII gave superimposable infrared spectra, thus confirming the structure of VI unequivocally by synthesis.[6]

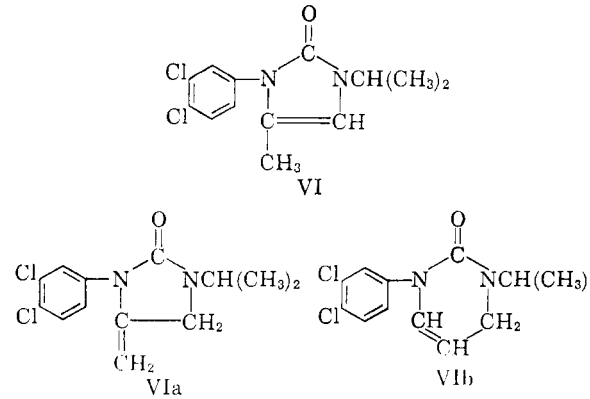
The urea VIII was prepared following conventional procedures: 2-propanolamine → isopropyl-2-hydroxypropylamine → isopropyl-2-chloropropylamine X → VIII.

The imidazolium salts II and imidazolones III are reported in Table I and II. The variety of compounds listed in these tables is indicative of the generality of the reaction for propynyl ureas of the type, When R′ = H, the parent urea is regenerated on treatment of the phosphorus pentachloride–urea product (presumably the carbodiimide) with water or base.

A shift of carbonyl absorption to a higher frequency from six to five-carbon cyclic ketones has been described.[7] It appeared worthwhile to determine the magnitude of the carbonyl shift in some five- and six-membered heterocyclic ureas and carbanilates in the hope that we might be able to differentiate the structure VI from the possible alternates[6] by infrared data alone. Therefore, 1-(3,4-dichlorophenyl)-2-tetrahydropyrimidone

(5) Infrared spectra of caramido chlorides, A. Brügel, ref. 2.

(6) Two alternate paths for ring cyclization can be postulated *a priori*. The n.m.r. data and independent synthesis refute structures VIa and VIb but are consistent for VI.

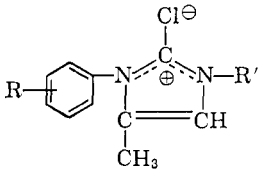


We are indebted to Professor W. H. Urry for the n.m.r. spectrum and its interpretation.

(7) L. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc. New York, 1959.

TABLE I

IMIDAZOLIUM SALTS[a]

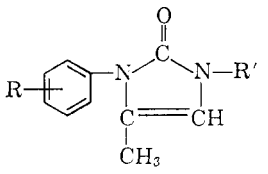


R	R′	Yield, %	M.p., °C.[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3,4-Dichloro	Isopropyl	89.5	275	41.80	41.95	4.15	4.30	46.60	46.40	8.25	8.30
4-Chloro	Isopropyl	74.6	268	51.15	51.03	4.92	4.85	34.94	35.02	9.18	9.10
2-Chloro	Isopropyl	43.6	254	51.15	50.90	4.92	5.20	34.94	34.80	9.18	9.15
4-Nitro	Isopropyl	66.5	...[c]	...	...	...	...	22.44	22.30	13.30	13.10
4-Methyl	Isopropyl	72.4	...[c]	...[d]	...	...[d]	...	...[d]	...	...[d]	...
3,4-Dichloro	Allyl	99.5	200	46.15	46.00	3.55	3.65	42.00	41.80	8.30	8.50
3,4-Dichloro	Propyl	65.4	238	...	...	...	...	46.60	46.35	8.25	8.15
H	Isopropyl	84.5	204	...	...	...	...	26.20	26.10	10.32	9.82
3,4-Dichloro	3,4-Dichlorophenyl	23.7	235	...	...	...	...	48.00	47.90	6.32	6.21
4-Ethoxy	Isopropyl	61.5	...[c]	...	...	..	...	22.50	22.23	8.90	8.95

[a] All compounds show infrared absorption spectra bands at 6.15 μ (C=C) and 6.0 μ (C=N). [b] All melting points are decomposition points. [c] Salts are too hygroscopic to determine decomposition point. [d] The salt is extremely hygrosopic—analyses were not consistent, but the resulting imidazolone (Table II) is correct.

TABLE II

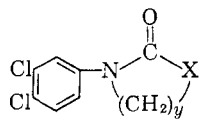
2-IMIDAZOLONES[a]



R	R′	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3,4-Dichloro	Isopropyl	90.5	112.2–112.6	54.60	54.75	3.70	3.72	25.02	24.95	9.60	9.88
4-Chloro	Isopropyl	86.5	137.6–138.5	62.30	62.49	5.98	6.05	14.15	14.30	11.13	11.01
2-Chloro	Isopropyl	83.6	115.5–116.4	62.30	62.22	5.98	6.01	14.15	14.30	11.13	10.90
4-Nitro	Isopropyl	82.5	114.7–115.7	59.80	59.90	5.75	5.78	...	...	16.05	16.15
3-Nitro	Isopropyl	35.0	102.2–103.1	59.80	59.60	5.75	5.55	...	...	16.05	15.95
4-Methyl	Isopropyl	66.5	118.7–119.4	73.00	72.65	7.80	8.00	...	...	12.15	11.85
3,4-Dichloro	Allyl	50.5	62.1–62.7	...	...	...	...	25.02	25.00	9.90	9.85
3,4-Dichloro	Propyl	56.0	62.9–63.4	...	...	...	...	24.95	25.15	9.83	9.75
H	Isopropyl	90.8	53.3–54.1	72.25	71.88	7.40	7.53	...	...	12.93	12.67
3,4-Dichloro	3,4-Dichlorophenyl	25.0	164.7–165.2	...	...	...	...	36.60	36.70	7.22	7.05
4-Ethoxy	Isopropyl	95.6	75.5–76.2	69.25	69.00	7.70	7.85	...	...	10.75	10.90

[a] All compounds show infrared absorption bands at 6.15 μ (C=C) and 5.90–5.95 μ (C=O).

(XI), 1 - (3,4 - dichlorophenyl) - 2 - imidazolidone (XII), 3 - (3,4 - dichlorophenyl)tetrahydro - 1,3-oxazine - 2 - one (XIV), and 3-(3,4-dichlorophenyl)-1,3-oxazolidine-2-one (XV) were prepared as model compounds.



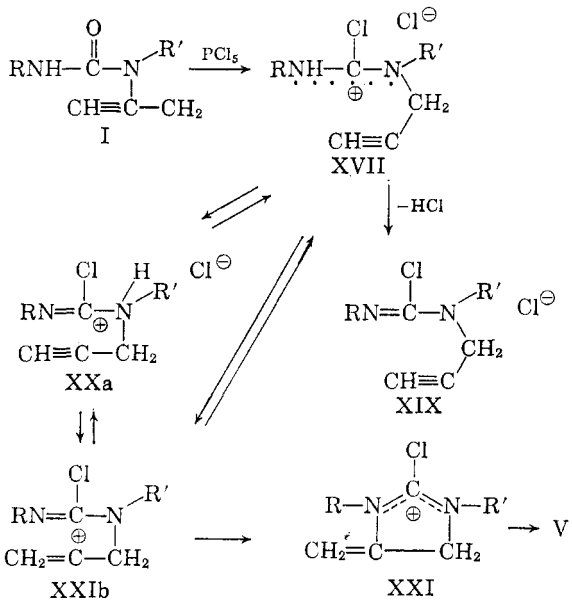
	X	y	$\lambda_{C=O}$ (μ)
XI	NH	3	6.05
XII	NH	2	5.85
XIV	O	3	5.90
XV	O	2	5.70

The cyclic ureas XI, XII, and the cyclic carbanilates XIV, XV exhibited the expected carbonyl shift to a higher frequency (six → five ~ 0.2 μ).

The appearance of the C=O band of VI at 5.95 μ and of VII at 5.90 μ would indicate that determination of ring size by infrared carbonyl shift alone in cyclic ureas would generally differentiate five- and six-membered rings. If the action of phosphorus pentachloride on IV had given the six-membered urea VIb, the carbonyl band should have been observed above 6.0 μ.

The mechanism for cyclization of I → II → III can be postulated as proceeding through an intermediate carbamido chloride XVII which is stabilized by resonance. Since the chloroform–amidine XIX was not isolated,[4] and only a trace of hydrogen chloride was evolved at the very beginning of the reaction, the transformation XVII→ XIX can be excluded. However, since the reaction mixture is highly acidic, a series of equilibria XVII ⇌ XXa ⇌ XXb are visualized in which

protonation can occur at the N-1, N-3 or at the terminal carbon atom of the propynyl group. Although the C≡C group is less basic than either of the two nitrogen atoms, its protonation would lead irreversibly to ring closure and product. In acidic media, an allylic shift of the exocyclic double bond in XXI leads to the stable imidazolium salt (V).[8]



Experimental

2-Chloro-3-(3,4-dichlorophenyl)-1-isopropyl-4-methylimidazolium Chloride (V).—A solution of 1-(3,4-dichlorophenyl)-3-isopropyl-3-(2-propynyl)urea 67.0 g. (0.24 mole) and phosphorus pentachloride 50.0 g. (0.24 mole) in 150 ml. of benzene was refluxed for 4 hr. A trace of hydrogen chloride was evolved and a white granular product gradually separated. The product was filtered and washed with two 50-ml. portions of ether, 69.0 g. (95%). Two recrystallizations from chloroform gave fine colorless needles, m.p. 275° dec.; yield 60.5 g. (76.8%).

Infrared spectrum showed absorptions at 6.15 μ (C=C) and at 6.0 μ (C=N).

3-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-2-imidazolone (VI).—The salt V 17.0 g. (0.05 mole) was dissolved in 50 ml. of water and made slightly alkaline with 20% sodium hydroxide. A white granular product separated and was filtered. Two recrystallizations from ethyl acetate gave small stout prisms, m.p. 112.1–112.6°; yield 13.1 g. (91.0%).

Infrared spectrum shows absorption at 6.15 μ (C=C) and at 5.90 μ (C=O).

3-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-2-imidazolidone (VII).—3-(3,4-Dichlorophenyl)-1-isopropyl-4-methylimidazolone 42.7 g., (0.15 mole) and 10.0 g. of platinum oxide in 50 ml. of glacial acetic acid were charged into a Parr hydrogenator. The reduction was completed in 6 hr. at 30° and 50 p.s.i. The solution was filtered and distilled free of acetic acid. Fractionation gave cut A, b.p. 155–160° (8.0 mm.); m.p. 111.1–112.0°, wt. 10.1 g. A second fraction was obtained at 225–235° (8.0 mm.), m.p. 67.8–68.2° (white granules from hexane) wt. 23.6 (55%). This product gave an infrared spectrum identical with VII obtained *via* ring closure of the urea VIII.

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O$: C, 54.40; H, 5.58; Cl, 24.75; N, 9.7. Found: C, 54.15; H, 5.62; Cl, 24.80; N, 9.45.

Cut A has not been identified as yet.

3-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-2-imidazolidone (VI) *via* Ring Closure of Chlorourea. (a) Isopropyl-2-hydroxypropylamine (IX).—Better yields were realized using excess amine rather than caustic to remove the hydrogen bromide. Isopropyl bromide [102.0 g. (0.82 mole)] was added dropwise at 50° to 1-amino-2-propanol 125.1 g. (1.64 moles) and held at 65–70° for 6 hr. The yellow sirup was distilled directly until the amine salt caked in the still pot. Redistillation of the product gave a colorless liquid; b.p. 60–62° (13.0 mm.); $n^{25}D$ 1.4405; wt. 66.0 g. (69.0%).

Anal. Calcd. for $C_6H_{15}NO$: N, 11.95. Found: N, 12.20.

(b) Isopropyl-2-chloropropylamine Hydrochloride (X).—Isopropyl-2-hydroxypropylamine [66.0 g. (0.565 mole)] was dissolved in 150 ml. of chloroform and excess anhydrous hydrogen chloride was passed through, using an ice bath to control temperature at 50–55°. Thionyl chloride [71.0 g. (0.6 mole)] was added dropwise at 50–55° and refluxed for 3 hr. Excess thionyl chloride and chloroform were removed *in vacuo*, and 100 ml. of benzene was added. After removal of trace moisture by azeotropic distillation, a buff granular mass remained.

Anal. Calcd. for $C_6H_{15}Cl_2N$: Cl, 41.20. Found: Cl, 38.60.

All attempts at purification led to decomposition. The crude material was used in the next step.

(c) 1-(2-Chloropropyl)-3-(3,4-dichlorophenyl)-1-isopropylurea (VIII).—A solution of the crude salt X (34.4 g., 0.2 mole) in 100 ml. of water was neutralized with 20% sodium hydroxide at 0–5° and rapidly extracted with three 100-ml. portions of ether. The ethereal layer was separated, filtered through calcium chloride, and added to a solution of 3,4-dichlorophenyl isocyanate (37.6 g., 0.2 mole) in 100 ml. of ether giving the theoretical yield of a viscous brown sirup. The sirup was treated directly with acetone and excess 10% caustic giving 28.2 g. of a dark brown sirup. The sirup was chromatographed on alumina, eluting and discarding four 100-ml. portions of hexane and five 100-ml. portions of 4:1 hexane–benzene mixture. Six 100-ml. portions of benzene and a last containing 10% methanol gave 13.0 g. of a white solid which was recrystallized from hexane as colorless granules, m.p. 67.6–68.2°. The mixed melting point with VII was not depressed and infrared spectra were identical.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: C, 54.40; H, 5.58; Cl, 24.75; N, 9.77. Found: C, 54.30; H, 5.53, Cl, 24.65; N, 9.90.

1-(3,4-Dichlorophenyl)-2-tetrahydropyrimidone (XI).—A solution of 3-chloropropylamine hydrochloride 19.5 g. (0.15 mole) in 100 ml. of water was neutralized with 20% sodium hydroxide at 0–5°, and rapidly extracted with three 100-ml. portions of ether. The ethereal layer was separated, filtered through calcium chloride, and added to a solution of 3,4-dichlorophenyl isocyanate 18.8 g. (0.1 mole). The product, 1-(3-chloropropyl)-3-(3,4-dichlorophenyl)urea separated as white fluffs, m.p. 133.8–134.6°; wt. 10.5 g. (37.6%).

The product was immediately dissolved in 20 ml. of acetone and refluxed with 50 ml. of 10% sodium hydroxide for 1 hr. The product XI separated on cooling as long slender needles, m.p. 192.3–192.8°, wt. 9.2 g. (99.1%).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.08; Cl, 28.95; N, 11.42. Found: C, 48.82; H, 4.20; Cl, 28.82; N, 11.15.

1(2-Bromoethyl)-3-(3,4-dichlorophenyl)urea (XIII).—2-Bromoethylamine hydrobromide [40.9 g. (0.2 mole)] was dissolved in 50 ml. of water and made slightly alkaline with 50% sodium hydroxide at 0–5°. The solution was extracted with two 100-ml. portions of ether, separated and the ether

(8) Several alternate reaction paths can be written depending on which of the protonated forms of XVII, XXa, and XIX are used. These, however, offer no advantage over those which are here proposed. We are also considering the possibility that the propynyl group is converted to an allene system prior to cyclization.

solution stirred directly into a solution of 3,4-dichlorophenyl isocyanate [38.2 g. (0.15 mole)] in 50 ml. of ether. The product was filtered and recrystallized from ethanol as small white rosettes, m.p. 119.1–119.6°, wt. 31.0 g. (66.2%).

Anal. Calcd. for $C_9H_9Cl_2BrN_2O$: Cl, 22.75; Br, 25.60; N, 8.95. Found: Cl, 22.80; Br, 25.35; N, 8.80.

1-(3,4-Dichlorophenyl)-2-imidazolidone (XII).—A solution of 1-(2-bromoethyl)-3-(3,4-dichlorophenyl)urea 15.6 g. (0.05 mole) in 80 ml. of acetone and a slight excess of 10% aqueous sodium hydroxide was refluxed 3 hr. The acetone layer was separated and evaporated to *ca.* 25 ml. from which the product separated. Recrystallization from acetone gave small glistening plates, m.p. 184.1–185.0°, wt. 10.1 g. (88.0%).

Anal. Calcd. for $C_9H_8Cl_2N_2O$: Cl, 30.70; N, 12.10. Found: Cl, 30.60; N, 11.97.

3-(3,4-Dichlorophenyl)tetrahydro-1,3-oxazine-2-one (XIV).—A solution of 1-(3-bromopropyl)-3,4-dichlorocarbanilate 25.0 g. (0.076 mole) in 250 ml. of 5% sodium hydroxide was refluxed for 1 hr. An oil separated and solidified on cooling. Recrystallization of the solid from 95% ethanol gave small white granules, m.p. 136.2–137.0 (63.8%).

Anal. Calcd. for $C_{10}H_9Cl_2NO_2$: Cl, 28.82; N, 5.69. Found: Cl, 28.87; N, 5.55.

3-(3,4-Dichlorophenyl)-1,3-oxazolidine-2-one (XV).—The same procedure using 1-(2-chloroethyl)-3,4-dichlorocarbanilate 42.0 g. (0.146 mole) gave fine, colorless needles on recrystallization from ethanol; m.p. 126.3–127.0°, wt. 26.0 g. (73.0%).

Anal. Calcd. for $C_9H_7Cl_2NO_2$: Cl, 30.60; N, 6.03. Found: Cl, 30.68; N, 6.10.

1-(3,4-Dichlorophenyl)-3-(2-propynyl)urea (XVI).—Maximum yields were obtained by dissolving propargylamine hydrochloride 27.5 g. (0.3 mole) in 100 ml. of water, made strongly alkaline with 20% sodium hydroxide at 0–5°, and immediately extracted with three 100-ml. portions of ether. The ether was filtered through calcium chloride and added to a solution of 3,4-dichlorophenyl isocyanate 38.0 g. (0.2 mole) in 100 ml. of ether. After evaporation to 75 ml. the product precipitated. Two recrystallizations from ethyl acetate gave small white plates, m.p. 178.7–179.3°, wt. 35.0 g. (72.1%, based on isocyanate).

Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: Cl, 29.22; N, 11.52. Found: Cl, 29.40; N, 11.35.

New Syntheses in the Coumarin Series

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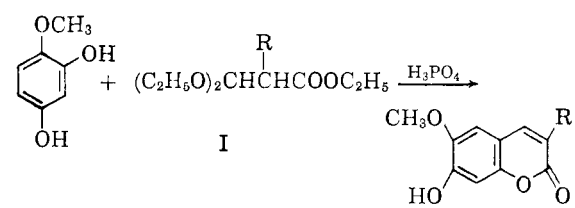
Reaction of the appropriate substituted phenols with ethyl 3,3-diethoxypropionate (I) in the presence of mineral acid provided good yields of the coumarins scopoletin, isoscopoletin, and scoparone. Substitution of ethyl 3,3-diethoxy-2-methylpropionate gave the corresponding 3-methylcoumarins. Two moles of 3,4-methylenedioxyphenol reacted with I to form a 3,4-dihydro-4-substituted coumarin which decomposed to ayapin upon heating. The coumarins, including ayapin, also could be obtained by the replacement of the diethoxy ester with 3-ethoxyacrylyl chloride.

Coumarins are becoming recognized as common minor constituents of plants. Among the naturally occurring compounds, those with oxygen attached at the 6- and 7-positions appear to be of special interest; scopoletin (6-methoxy-7-hydroxycoumarin), in particular, has been widely implicated in plant functions.

The glycoside esculin (6-β-D-glucosyloxy-7-hydroxycoumarin) has been the most usual starting point for synthetic work in this series. For instance, it may be methylated and then hydrolyzed to isoscopoletin (6-hydroxy-7-methoxycoumarin),[2] hydrolyzed directly to provide esculetin (6,7-dihydroxycoumarin),[3] or carried through a series of reactions to give scopoletin.[4] Esculetin has served as precursor for scoparone (6,7-dimethoxycoumarin)[5] and ayapin (6,7-methylenedioxycoumarin)[6]; it has been prepared synthetically in low yield from 1,2,4-triacetoxybenzene,[7] but the synthesis of its derivatives such as scopoletin has been much more elaborate. The Pechmann synthesis and related methods are unsatisfactory in these instances.

We have found that reaction of the appropriate phenol with ethyl 3,3-diethoxypropionate (I. R = H) in the presence of mineral acid provides good yields of these substituted coumarins. For example:



The reaction was conducted at steam bath temperatures in the presence of an excess of acid condensing agent which also acted as solvent. Although concentrated sulfuric acid, polyphosphoric acid, and, in some cases, even aqueous hydrochloric acid were effective, optimum results were obtained with 85% sirupy phosphoric acid. Organic acids and acidic ion exchange resins were unsatisfactory. The coumarins were formed rapidly, and heating periods longer than one or two hours did not afford increased yields.

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