Major bands in the infrared spectrum were found at 3.00, 5.92, 7.85, 12.20, and 13.20 μ, and the compound gave a violet color with aqueous, alcoholic ferric chloride.

C. **Anhydro-8-hydroxymercuri-1-naphthoic Acid.**—A solution of 0.0402 g. of III and excess mercuric chloride in aqueous methanol was warmed on a steam bath, until the organomercurial began to precipitate. Filtration and drying afforded the anhydro-8-hydroxymercuri-1-naphthoic acid (0.0266 g., 35%), characterized by the identity of the infrared spectrum with that of an authentic sample.

Heterocyclic Compounds. III. Substituted Barbituric Acids *via* Enamines[1]

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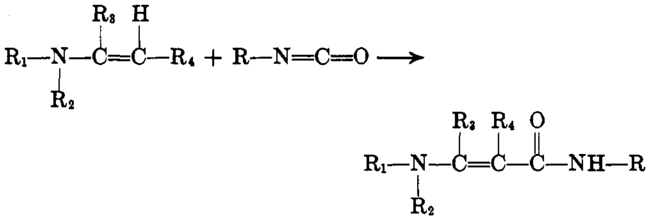
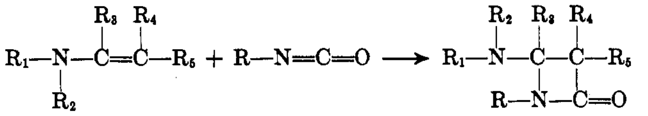
Amino hydrouracils were obtained in good yield from 2 moles of isocyanate and 1 mole of enamine. A new syntheses of substituted barbituric acids was achieved by the acid hydrolysis of this product and subsequent oxidation with chromic acid.

The reaction between enamines and isocyanates has received considerable attention recently. Enamines containing a β-hydrogen add directly to an isocyanate at room temperature to form unsaturated amides.[2,3]

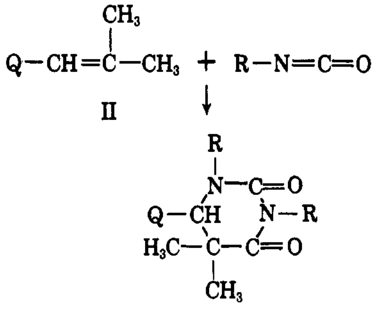


If there is no β-hydrogen on the enamine, a 1:1 addition still occurs at room temperature, and the adduct is a β-lactam[4,5] (I).



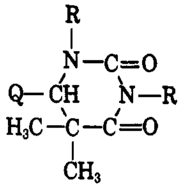
I

We have studied the reaction between β-disubstituted enamines (II) and aryl isocyanates at 120–140°. Under these conditions products were obtained which on the basis of elemental analysis and molecular weight determination were shown to be derived from 2 moles of the aryl isocyanate and 1 mole of the enamine.

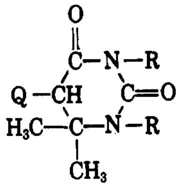


III, Q = $(CH_3)_2N$; R = C_6H_5
IV, Q = piperidino; R = C_6H_5
V, Q = piperidino; R = *p*-tolyl
VI, Q = $(CH_3)_2N$; R = α-naphthyl

The spectral data indicated that a cyclic structure was probable for the adducts. The infrared spectrum showed the absence of an N–H group; the carbonyl absorption ruled out a noncyclic amide and suggested a six-membered system. The n.m.r. spectrum was in agreement with either of the possible structures A and B. Specifically, the chemical shift for the singlet proton (*e.g.*, at τ 6.52 for VI) could be accounted for by either structure. The structure A would appear more probable, however, on the basis of the strongly nucleophilic character of the β-position of the enamine.



A



B

It seemed possible to distinguish between the two structures by attempting an acid hydrolysis. Structure A contains a nitrogen analog of an acetal and thus should be vulnerable to acid hydrolysis and produce an aldehyde. Structure B, which has the amino function as part of an α-amino acid system, is incapable of leading to an aldehyde by hydrolysis. The acid hydrolysis product of A will no longer be basic and will, therefore, precipitate out of the aqueous acid solution, thus preventing further attack on the amide function. This is precisely what occurred when the hydrolysis was carried out. Compounds III and IV, as expected, gave the same compound VIII when heated under reflux with hydrochloric acid.

The structure A now seemed to be correct and the physical properties of compound VIII further substantiated this conclusion. At room temperature VIII was almost totally in the ring form as evidenced by the spectral data, such as the infrared spectrum, which had a carbonyl pattern very similar to that of III and IV. As the solution was warmed, a small amount of open-chain material was formed as shown by a typical amide absorption at 6.1 μ and an N–H absorption at 2.8 μ. In addition, the warm solution readily reduced Tollens solution, indicating an aldehyde function. When the solution was cooled and allowed to stand for some time, the spectrum slowly returned to that of the

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[1] Part I: A. K. Bose and S. Garratt, *Tetrahedron*, **19**, 85, (1963). Part II: A. K. Bose, S. Garratt, and J. Pelosi, *J. Org. Chem.*, **28**, 730 (1963).

[2] (a) G. Berchtold, *ibid.* **26**, 3043 (1961); (b) S. Hunig, K. Hubner, and E. Benzing, *Ber.*, **95**, 926 (1962).

[3] For a brief review of some of this work, see J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 51 (1963).

[4] M. Perelman and S. Mizsak, *J. Am. Chem. Soc.*, **84**, 4988 (1962).

[5] G. Opitz and J. Koch, *Angew. Chem., Intern. Ed. Engl.*, **2**, 152 (1963).

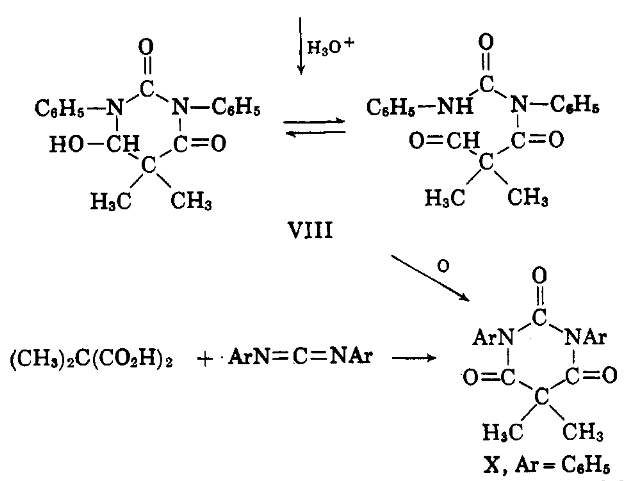
ring form. Only the hydrolysis product derived from A is compatible with these observations.

Compound VIII was not oxidized by neutral permanganate solution at room temperature. Chromic acid oxidation at room temperature in a two phase system readily converted it to the corresponding barbiturate X in good yield. Compound V was also hydrolyzed and oxidized to the corresponding barbiturate XI; however, the intermediate hydroxy compound IX could not be obtained analytically pure. Using a method developed in these laboratories[6] this barbiturate XI was also prepared from dimethyl malonic acid and di-*p*-tolylcarbodiimide.

The barbiturate prepared in this manner was identical with the one prepared from V. The hydrolysis and the subsequent oxidation of the 2:1 adduct from an aryl isocyanate and an appropriate enamine thus constitutes a new synthesis of substituted barbituric acids.

In addition to compound VI, a 1:1 adduct VII between N,N-dimethylisobutenylamine and α-naphthyl isocyanate was obtained. This material, which is not a β-lactam, is being investigated.

III or IV



VIII

X, Ar = C_6H_5
XI, Ar = *p*-tolyl

The mechanism of formation of the six-membered cyclic system has not been elucidated yet. It may involve an attack on the β-lactam system I by an isocyanate and a subsequent four-centered reaction. Further work is in progress on this and related problems.

Experimental

The ultraviolet absorption spectra were recorded on a Beckman DK-2A instrument. A Perkin-Elmer Model 21 spectrophotometer was used for infrared measurements. Only peaks in the 3-μ region and the carbonyl region (5.5–6.5 μ) are reported. The n.m.r. spectra were obtained with a Varian high resolution spectrometer operating at 60 Mc. Tetramethylsilane served as the internal standard. Singlet peaks are unmarked; broad or complex spectra in the aromatic region are reported either as a range or only by the single highest peak: these spectra are designated by c. The approximate peak areas are noted in parenthesis. Melting points, obtained on a Mel-Temp block, are uncorrected. Molecular weight and analytical determinations were made by Schwarzkopf Microanalytical, Woodside, N. Y., or by Alfred Bernhardt Microanaltisches Laboratorium, Max Planck Institute, Mülheim, West Germany.

1,3-Diphenyl-5,5-dimethyl-6-(dimethylamino)hydrouracil (III).—A mixture of 27.0 g. (0.273 mole) of N,N-dimethylisobutenylamine and 28.5 g. (0.24 mole) of phenyl isocyanate was placed in a thick-walled tube about 60-cm. long. The tube was flushed with nitrogen and sealed. The sealed tube was immersed to about one-third of its length in an oil bath and heated at 120–140° for 5 hr. After cooling, the contents were transferred to a round-bottom flask and the unreacted enamine was removed on a rotary evaporator. The residual oil was taken up in ether and the hydrochloride was precipitated by passing anhydrous hydrogen chloride gas through the ether. The material, m.p. 179–180°, so obtained was analytically pure and amounted to 40 g. (90%): λ_{max}^{Nujol} 5.72 (m), 5.87 (s), and 6.22 (w) μ.

Anal. Calcd. for $C_{20}H_{23}N_3O_2 \cdot HCl$: C, 64.25; H, 6.47; N, 11.24; Cl, 9.48. Found: C, 64.10; H, 6.68; N, 10.99; Cl, 9.22.

This hydrochloride was sparingly soluble in water; an alternate method of preparation was to shake the ether extract with 2 *N* hydrochloric acid, and then filter under suction.

The free base was obtained as follows: the dry hydrochloride (1.15 g., 0.00308 mole) was taken up in 20 ml. of methanol, a mixture of 2 g. of sodium hydroxide in 10 ml. of methanol was added, and the solution was poured into 100 ml. of water and extracted with ether. A brownish solid amounting to 0.65 g. was obtained. This material was recrystallized from ethyl acetate–hexane, yielding a tan solid: m.p. 103–104°; λ_{max}^{EtOH} 240 mμ (ϵ 7800); and τ (CCl_4) 2.73 c (1H), 5.57 (1H), 7.75 (6H), 8.48 (3H), and 8.77 (3H).

1,3-Diphenyl-5,5-dimethyl-6-piperidinohydrouracil (IV).—When 4.17 g. (0.030 mole) of 1-piperidinoisobutene and 8.45 g. (0.071 mole) of phenyl isocyanate were mixed together in a thick-walled tube, an exothermic reaction occurred (this is the β-lactam formation). A white material precipitated which redissolved as the temperature rose. After 20 min., the tube, now at room temperature, was flushed with nitrogen, then sealed and heated in an oil bath at 125–140° for 2.5 hr. After standing for several days, the clear, solid mass in the tube was triturated with ether and filtered, yielding 8.4 g. of a white solid, m.p. 142–145°. Another 0.6 g. was recovered from the wash ether by extraction with hydrochloric acid and regeneration of the free base. The total yield was 80%. After recrystallization from aqueous acetone, IV had m.p. 149.5–150.5°; $\lambda_{max}^{CHCl_3}$ no peaks in 3.0-μ region, 5.77 (s), 5.94 (s), and 6.21 (m) μ; and $\lambda_{max}^{C_2H_5OH}$ 240 mμ (ϵ 7700).

Anal. Calcd. for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13; mol. wt., 377.5. Found: C, 73.39; H, 7.09; N, 11.03; mol. wt., 383.

Reaction between 1-Naphthyl Isocyanate and N,N-Dimethylisobutenylamine. A. 1:1 Adduct (VII).—A mixture of 1-naphthyl isocyanate (8.44 g., 0.05 mole) and N,N-dimethylisobutenylamine (15.0 g., 0.150 mole) was heated in a nitrogen-flushed sealed tubed at 120–130° for 4 hr. The excess enamine was stripped off on a rotary evaporator, leaving a gummy, yellow mass. This material was recrystallized from aqueous acetone, yielding 6.2 g. (45%) of material: m.p. 160.5–161°; $\lambda_{max}^{CHCl_3}$ 3.02 (m), 5.92 (s), 6.20 (w), and 6.28 (m) μ; $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ϵ 52,000) and 303 mμ (ϵ 8800); and τ (CCl_4) −0.46 (1H), 2.14–2.96 (6H), 6.57 (1H), 7.87 (6H), 8.52 (3H), and 8.82 (3H).

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44; mol. wt., 268.4. Found: C, 76.20; H, 7.34; N, 10.26; mol. wt., 263.

B. 1,3-Di(1-naphthyl)-5,5-dimethyl-6-(dimethylamino)hydrouracil (VI).—A mixture of 1-naphthyl isocyanate (8.44 g., 0.05 mole) and N,N-dimethylisobutenylamine (5.0 g., 0.05 mole) was heated in a nitrogen-flushed sealed tube at 120° for 4 hr. Upon cooling, a hard, glassy solid was formed in the tube. This material was crystallized from acetone to give 3.9 g. (35%) of a solid: m.p. 263–264° (several recrystallizations from acetone raised this to 270–271° dec.); λ_{max}^{Nujol} no peaks in 3-μ region, 5.76 (m), 5.92 (s), and 6.19 (w) μ; $\lambda_{max}^{HCCl_3}$ 282 mμ (ϵ 14,000); τ ($DCCl_3$) 1.94–2.86 (14H), 6.52 (1H), 7.87 (6H), 8.48 (3H), and 8.84 (3H).

Anal. Calcd. for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.61; mol. wt., 437.5. Found: C, 76.77; H, 6.06; N, 9.50; mol. wt., 428.

C. Preparation of VI and VII.—A mixture of 1-naphthyl isocyanate (8.44 g., 0.05 mole) and N,N-dimethylisobutenylamine (10.0 g., 0.10 mole) was heated in a nitrogen-flushed sealed tube at 125° for 4 hr. The solid in the tube was triturated with ether and filtered, yielding 3.5 g. of VI (30%). Upon recrystallization from acetone, VI had m.p. 270° dec. The ether solution was washed with 10% hydrochloric acid. The acid was neutralized

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(6) A. K. Bose and S. Garratt, *J. Am. Chem. Soc.* **84**, 1310 (1962).

with sodium bicarbonate and the solution was extracted with ether. When the ether was dried and evaporated, 4.0 g. of white solid, VII, was obtained, (29%). Upon recrystallization from acetone–water, this material melted at 160–160.5°.

1,3-Di-*p*-tolyl-5,5-dimethyl-6-piperidinohydrouracil (V).—A mixture of *p*-tolyl isocyanate (13.30 g., 0.10 mole) and 1-piperidinoisobutene (6.95 g., 0.05 mole) was sealed in a thick-walled tube and heated at 110–120° for 20 hr, then at 150° for 3 hr. The glassy solid was taken up in hot acetone to remove it from the tube. Upon evaporation of the acetone, an oil was obtained which did not solidify. The oil was taken up in dry ether and hydrogen chloride gas was passed into it. The hydrochloride precipitated as a white hygroscopic solid. This hydrochloride was then dissolved in a mixture of 3 g. of sodium hydroxide in 15 ml. of methanol and 100 ml. of water. This solution was then stirred with ether for 1.5 hr. After separation, the ether was washed with water, then dried over magnesium sulfate, and evaporated. The residual oil (20 g., 98%) solidified after standing for a week. After several recrystallizations from aqueous acetone, the resulting white solid had m.p. 157–158°; $\lambda_{\max}^{\text{Nujol}}$ no peaks in 3-μ region, 5.81 (s), 5.94 (s), and 6.18 (w) μ. Elemental analysis was performed on the picrate. To a solution of 0.526 g. of V in 3.0 ml. of methanol was added 3.0 ml. of a saturated (at 24°) picric acid solution. The mixture was warmed for 5 min. on a steam bath, then allowed to stand at room temperature overnight. The solid obtained on filtration was washed with ethanol, then recrystallized from ethanol, yielding material with m.p. 170–171°.

Anal. Calcd. for $C_{31}H_{34}N_6O_9$: C, 58.67; H, 5.40; N, 13.24. Found: C, 58.96; H, 5.54; N, 13.27.

1,3-Dimethyl-5,5-dimethyl-6-hydroxyhydrouracil (VIII). **A. Preparation from IV.**—To a solution of 40 ml. of hydrochloric acid and 10 ml. of water was added 7.6 g. (0.0201 mole) of IV. The solution was then refluxed for 17 hr. After the reaction mixture had cooled, it was filtered and 6.1 g. (97%) of material with m.p. 216–220° was obtained: several recrystallizations from aqueous acetone raised this to 228–231°; $\lambda_{\max}^{\text{Nujol}}$ 2.85 (m), 5.75 (s), 5.97 (s), and 6.24 (w) μ; $\lambda_{\max}^{\text{CH}_3\text{CN}}$ 2.87 (m), 5.75 (s), and 5.91 (s) μ; and τ (CH_3CN) 2.65 c (10 H), 5.20 (1H), 7.78 (1H, hydroxy), 8.48 (3H), and 8.68 (3H). Upon warming, new peaks appeared in the infrared at 2.85 and 6.12 μ.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.57; H, 5.89; N, 9.29.

B. Preparation of III (Hydrochloride).—To a solution of 10 ml. of hydrochloric acid and 15 ml. of water was added 1.7 g. of the hydrochloride of III. The solution was refluxed for 42 hr., then cooled and filtered. The solid obtained after being washed with ether had m.p. 223–225°. The weight obtained was 1.15 g. (82%). The infrared spectrum was identical with that of VIII prepared from IV. After recrystallization from dimethylformamide it melted at 228–230°. The mixture melting point with material VIII derived from IV was unchanged.

1,3-Di-*p*-tolyl-5,5-dimethyl-6-hydroxyhydrouracil (IX).—To a solution of 50 ml. of hydrochloric acid and 20 ml. of water was added 12.0 g. (0.0296 mole) of V. The reaction mixture was refluxed for 12 hr. The solid obtained after cooling and filtering weighed 7.6 g. (0.0225 mole, 76%). This material was pure enough to be used directly in the next step.

1,3-Diphenyl-5,5-dimethylbarbituric Acid (X).—To a solution of VIII (1.0 g., 3.18 mmoles) in 40 ml. of methylene chloride was added a solution of 3.3 g. (0.011 mole) of sodium dichromate dihydrate and 3.6 g. of sulfuric acid, diluted to 10 ml. with water. After addition, the two-phase system was stirred for 20 hr. The methylene chloride layer was washed with water, dried over magnesium sulfate, and evaporated. A white solid was obtained (86%) which, after recrystallization from aqueous acetone, had m.p. 230–232°; $\lambda_{\max}^{\text{Nujol}}$ no peaks in 3-μ region, 5.64 (w), 5.80 (s), 5.85 (s), and 6.24 (w) μ; and τ (CCl_4) 2.57 c (10H), 8.25 (6H).

1,3-Di-*p*-tolyl-5,5-dimethylbarbituric Acid (XI). **A.**—To a solution of 3.0 g. (.87 mmoles) of IX in 40 ml. of methylene chloride was added slowly with stirring and cooling a solution of 6.6 g. (0.022 mole) of sodium dichromate dihydrate and 8.0 g. of sulfuric acid, diluted to 20 ml. with water. After addition, the two-phase system was stirred for 24 hr. Using the isolation procedure described for compound X, 2.1 g. (70%) of the desired product XI was obtained. After recrystallization from ethanol–water, it had m.p. 164–165°; $\lambda_{\max}^{\text{Nujol}}$ no peaks in 3-μ region, 5.64 (w), and 5.83 (s) μ; and n.m.r. (CCl_4) typical AB pattern from *p*-tolyl peaks at τ 2.78, 2.91, 3.02, and 3.15 (8H), 7.64 (6H), and 8.37 (6H).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.26; H, 5.92; N, 8.11.

B.—A solution of 1.32 g. of dimethylmalonic acid (0.010 mole) in 20 ml. of dry tetrahydrofuran was mixed at room temperature with a solution of 4.44 g. of N,N′-di-*p*-tolylcarbodiimide (0.020 mole) in 25 ml. of dry tetrahydrofuran. No precipitate came out of solution after 30 min. at room temperature, so the reaction mixture was warmed for 10 min. on a steam bath and a white solid began to come out of solution. The reaction mixture was allowed to stand at room temperature for 6 hr., with warming on a steam bath for 5 min. after 2 hr. and after 4 hr. At the end of 6 hr., the reaction mixture was chilled briefly, then filtered. The solid residue was washed several times with cold tetrahydrofuran, then dried, yielding 1.3 g. of di-*p*-tolylurea with m.p. 268–269°. The reaction mixture was evaporated and the solid obtained was recrystallized from ethanol-water. Insoluble material and the first two crops of crystals were all di-*p*-tolylurea. In all, 2.3 g. (95%) of this material was obtained. The third crop of crystals weighed 1.3 g. (38%) and, after a recrystallization from ethanol–water, had m.p. 164–165°. The melting point and infrared and n.m.r. spectra of this material XI (B) were identical with those for XI (A) and for a mixture of XI (A) and XI (B).

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Lithiated Diamines as Metalating Agents

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Lithium metal reacts with diamines to give lithiated derivatives. Such lithiated diamines can be used to metalate a variety of weakly acidic compounds. In general, the metalation products form 1:1 complexes with the diamines. The corresponding sodium series has also been studied.

In a previous publication[1] we reported the ready preparation and isolation of N-lithioethylenediamine by the reaction of lithium metal powder with ethylenediamine in an organic solvent. We further showed that, once formed, N-lithioethylenediamine could be used as a metalating agent in its reaction with acetylene to produce a stable lithium acetylide–ethylenediamine complex.

We now wish to report that both of the above reactions are general. Lithium metal powder reacts with a variety of diamines to give lithiated derivatives which can be used to metalate a variety of weakly acidic compounds.

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(1) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).