Investigations in Heterocycles. XVII. An Unusual Transformation of a 4-Phenylthiazole Derivative to a Tetracyclic Heteroaromatic System

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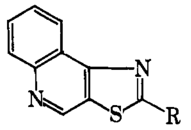
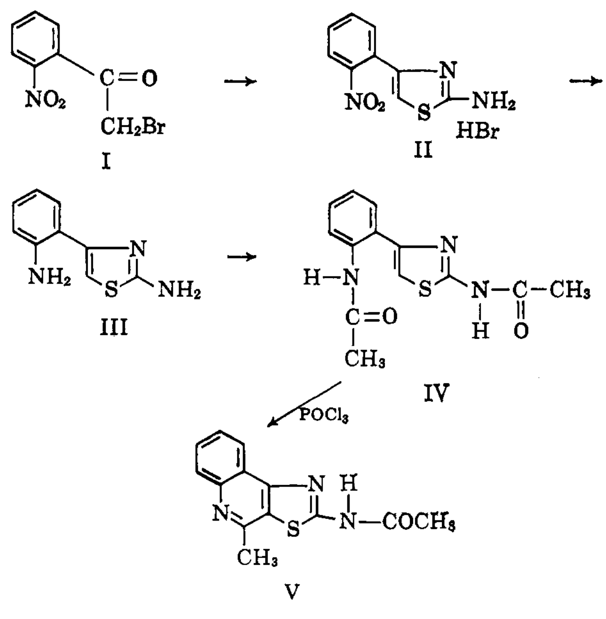
A considerable amount of interest has been deployed of late toward the synthesis of polycyclic heterocycles in which the hetero atoms are present in more than one ring. Some examples of this group of compounds are pyrrolothiophenes,[1] thiazolopyrimidines,[2] pyrazolopyrimidines,[3] and pyrazolo[1,5-*c*]quinazolines.[4] In accordance with similar studies in our laboratory, it was our intention to synthesize some quinolino[4,3-*d*]thiazoles, a heterocyclic system heretofore unreported in the literature.



Quinolino[4,3-*d*]thiazole

It appeared that the most direct route to this system would be through the 4-(2-nitrophenyl)thiazole derivatives. The sequence of reactions which could conceivably lead to a desired quinolino[4,3-*d*]thiazole (V) is shown in Scheme I.

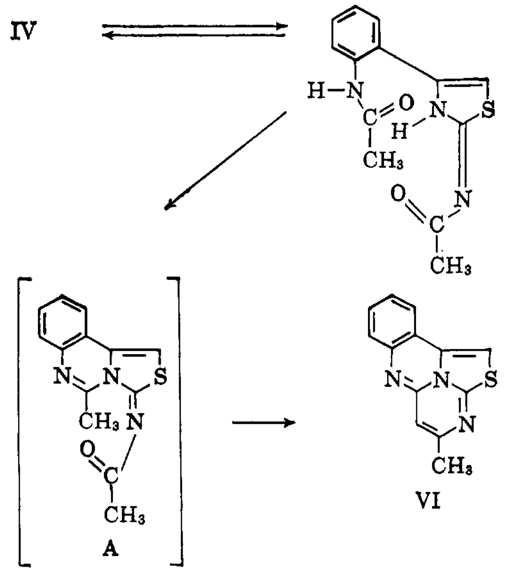
SCHEME I



Thus *o*-nitroacetophenone was brominated to form the α-bromo ketone I which was allowed to react with thiourea in refluxing ethyl alcohol to give 2-amino-4-(2-nitrophenyl)thiazole hydrobromide (II) in excellent yield. Compound II was then reduced catalytically to afford 2-amino-4-(2-aminophenyl)thiazole hydrobromide (III); the conversion in this case was virtually quantitative. Acetylation of compound III with 2 equiv. of acetyl chloride gave a diacetamide whose absorption band in the carbonyl region of the infrared was found at 1687 cm.$^{-1}$. This spectral evidence rules out a 2,2- or 4,4-diacetamide derivative, since it is well known[5] that such imido groups absorb at about 1770 cm.$^{-1}$. Therefore, the acetylation product was assigned structure IV. On treating IV with excess phosphorous oxychloride, a rather vigorous reaction occurred with the liberation of much hydrogen chloride. Work-up of the reaction mixture and fractionation of the main extract by means of thin-layer chromatography resulted in the isolation, in about 15% yield, of bright orange plates whose elemental analysis corresponded to a substance having an empirical formula of $C_{13}H_9N_3S$. Molecular weight determination by osmometry gave a value of 249. These data suggest that intramolecular condensation had occurred through the elimination of 2 equiv. of water.

Ultraviolet absorption maxima at 277 mμ (ϵ 32,050) and 347 (10,564) suggested a highly aromatic system. The N–H and OH regions of the infrared were devoid of absorption bands; only one weak absorption band was present at 3080 cm.$^{-1}$, indicative of aromatic CH. Two strong bands were noted at 1630 and 1590 cm.$^{-1}$. These are considered to be characteristic of the quinoline nucleus in polycyclic systems.[6] In the n.m.r. spectrum there is a doublet at δ 2.02 assigned to a group adjacent to a vinyl proton. This vinyl proton in turn gives a quartet at δ 5.58 due to its splitting with the methyl group. A second vinyl proton seen as a sharp singlet was shown at δ 5.90. This is characteristic of a vinyl proton adjacent to sulfur in heterocyclic systems.[7] Finally there was exhibited a complex pattern at δ 6.57 to 7.25. This corresponds to four aro-

SCHEME II



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(1) W. Carpenter and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2592 (1960).

(2) T. Takahashi, T. Maito, and S. Inoue, *Chem. Pharm. Bull.*, **6**, 334 (1958).

(3) P. Schmidt, K. Eichenberger, and M. Wilhelm, *Angew. Chem.*, **73**, No. 1, 15 (1961).

(4) G. deStevens, A. Halamandaris, M. Bernier, and H. M. Blatter, *J. Org. Chem.*, **28**, 1336 (1963).

(5) J. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1958, p. 221.

(6) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 3368 (1958).

(7) "Varian Spectra Catalog," Vol. II, No. 380 and 651.

matic protons, two of which show different chemical shifts.

The above analytical and spectral data have led us to assign structure VI to this substance. The n.m.r. strongly supports this assignment. The formation of VI can be readily explained if one considers firstly that the 2-acetamido group can readily tautomerize, and secondly that the thiazolyl and phenyl groups can and do undergo free rotation readily. Under these conditions, the initial dehydration step can occur to form intermediate A which is then favorably disposed to undergo a second dehydration to form VI. We have named this compound 4-methyl-2-thia-3,6,10c-triazoaceanthrylene. (See Scheme II.)

Experimental

2-Amino-4-(2-nitro phenyl)thiazole Monohydrobromide (II).—A solution of 2-nitro-ω-bromoacetophenone[8] (24.4 g., 0.1 mole) in ethyl alcohol (250 ml.) was treated with 7.6 g. of thiourea and the reaction mixture was heated under reflux for 4 hr. On cooling and addition of ethyl acetate to the concentrated reaction solution crystals appeared which were collected. Three recrystallizations from ethyl alcohol–ethyl acetate gave 20 g. of pure material, m.p. 179–180°.

Anal. Calcd. for $C_9H_8BrN_3O_2S$: C, 35.77; H, 2.66; N, 13.91. Found: C, 35.90, H, 2.91; N, 13.83.

2-Amino-4-(2-aminophenyl)thiazole Monohydrobromide (III).—A solution of 2-amino-4-(2-nitrophenyl)thiazole monohydrobromide (15.1 g., 0.05 mole) in 100 ml. of alcohol was shaken with hydrogen under pressure (45 lb./in.^{2}) at room temperature using 6 g. of 10% palladium–charcoal catalyst. After the theoretical amount of hydrogen was taken up, the catalyst was filtered off and washed with 100 ml. of methanol. The washings were combined with the filtrate; the solution was evaporated to dryness to afford 12 g. of crystalline residue. Recrystallization with methanol–ethyl acetate gave a pure material, m.p. 224–225°.

Anal. Calcd. for $C_9H_{10}BrN_3S$: C, 40.16; H, 3.72; N, 15.50. Found: C, 39.95; H, 3.67; N, 15.46.

2-Acetamido-4-(2-acetamidophenyl)thiazole (IV).—The base from above salt (5.7 g.) was dissolved in tetrahydrofuran (80 ml.) and treated with pyridine (4.7 ml.). This solution was warmed to 40° and treated with 4.5 g. of acetyl chloride and boiled under reflux for 2 hr. The solvent was removed under reduced pressure; the residue was suspended in water. The suspension was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate and evaporated to dryness. This gave 5.0 g. of diacetamide which was recrystallized from methanol–ethyl acetate to yield pure white crystals, 242–243°.

Anal. Calcd. for $C_{13}H_{13}O_2N_3S$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.48; H, 4.85; N, 15.34.

4-Methyl-2-thia-3,6,10c-triazoaceanthrylene (VI).—2-Acetamido-4-(2-acetamido phenyl)thiazole (2.0 g.) was treated with 6 ml. of phosphorus oxychloride. The reaction mixture was warmed on the steam bath for 12 min. and later boiled under reflux for 1.5 hr. The excess of phosphorus oxychloride was distilled under reduced pressure on the steam bath and the residue was carefully diluted with water (125 ml.). The gummy suspension was washed with ethyl acetate. The aqueous extract was made basic with 2 *N* sodium hydroxide solution (50 ml.) and the suspension was extracted with ethyl acetate (500 ml.). This extract was dried over anhydrous sodium sulfate and evaporated to dryness (0.8 g.). On chromatography on chromatoplates, the following fractions were obtained: fraction A, 5-cm. movement, 250 mg., highly crystalline, m.p. 208–209°; fraction B, 8-cm. movement, 140 mg., residue not crystalline; fraction C, 9-cm. movement, 140 mg., residue amorphous. Recrystallization of fraction A from ethyl alcohol gave pure material, m.p. 214–215°, which remained unchanged on repeated recrystallizations.

Anal. Calcd. for $C_{13}H_9N_3S$: C, 65.26; H, 3.79; N, 17.57; S, 13.38; mol. wt., 239.23. Found: C, 65.07; H, 3.76; N, 17.35; S, 13.55; mol. wt., 249.

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[8] H. Gevekoht, *Ann.*, **221**, 327 (1883).

Mass Spectrometry for Structure Determination. Simple Nitrogen Heterocycles

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A number of recent studies[1–6] have demonstrated the utility of mass spectrometry in organic structure determinations. The method basically consists of the identification of modes of fragmentation which are characteristic of certain structural features. A careful study of the fragmentation patterns of related known compounds and application of the information so obtained to the spectrum of the unknown sample reveals structural information concerning the unknown.

As a basis for extension of the technique, we have examined the mass spectra of twenty simple nitrogen heterocyclic compounds, fourteen of which have not previously been reported. The instrument used in this work was a Consolidated Engineering Corp. mass spectrometer Model 21-102, modified to perform as the Model 21-103C, with the exception that the original four-coil magnet has been retained. Additionally, the instrument has been modified for high temperature sample introduction and automatic mass to charge ratio (m/e) marking.

The complete spectra obtained are too lengthy for reproduction here, but they have been submitted for distribution through Committee E-14 of the American Society for Testing Materials.[7] The purpose of this note is to point out certain features which are thought to have general structural significance. The structures of the fragments discussed are postulated from the standpoint of the driving force for their formation. This driving force is usually the formation of a very stable molecule or ion.[1] Rearrangement processes were in evidence and were particularly common when migration of hydrogen atoms was involved.[2] Since there are frequently several different fragments formed by different modes of fragmentation or rearrangement that can appear at the same m/e ratio, the absence of a peak may be of more conclusive diagnostic significance than the appearance of a peak.

As shown in Table I, a significant (greater than 5%) m/e of 28 was present in the spectra of all compounds investigated except 2-methylcarbazole. Owing to the

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[1] K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, and references therein.

[2] J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960.

[3] J. L. Courtney and J. A. Shannon, *Tetrahedron Letters*, **1**, 13 (1963), and references therein.

[4] F. W. McLafferty, "Determination of Organic Structures by Physical Methods," Vol. 2, F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1961.

[5] T. Nakano and C. Djerassi, *J. Org. Chem.*, **26**, 167 (1961).

[6] J. H. Beynon and A. E. Williams, *Appl. Spectry.*, **13**, 101 (1959); **14**, 27 (1960).

[7] These spectra have also been deposited as Document number 7914 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $6.25 for photoprints or $2.50 for 35-mm. microfilm. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.