[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of N-Benzylthieno[3,2-b]pyrrole[1]

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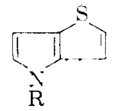
N-Benzylthieno[3,2-b]pyrrole (II) has been synthesized in four steps from N-benzylpyrrole in 19% over-all yield; II and its precursors are shown to be markedly more stable than the des-benzyl analog I and its precursors. An isomer of II, formed as a by-product in the polyphosphoric acid cyclization of 3-(1-benzylpyrrolylthio)-acetic acid, is shown by spectral analysis to be 6-benzyl-2*H*,3*H*-thieno[3,2-b]pyrrol-3-one (VIIa). Similar spectral analyses show that the monobromination product of 2-acetylpyrrole is 2-acetyl-4-bromopyrrole.

A recently described synthesis[3] of thieno[3,2-b]-pyrrole (I) offers a route to a novel series of compounds of potential physiological activity, which are isosteric with derivatives of indole. The preparation of the N-benzyl analog of I has been undertaken in an attempt to improve the stability of I, and to make use of the benzyl residue as a protecting group in reactions of II and its precursors where the acidic pyrrole hydrogen would interfere.



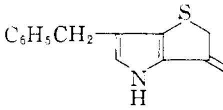
I, R = H
II, R = $CH_2C_6H_5$

The synthesis of II has been accomplished in a series of reactions only slightly different from that described for I. N-Benzylpyrrole (III) was prepared in 64% yield by the reaction of 2,5-diethoxytetrahydrofuran and benzylamine in glacial acetic acid.[4]

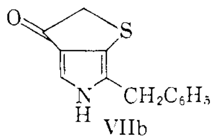
Treatment of III with a freshly prepared solution of thiocyanogen in methanol at −70° afforded 1-benzyl-3-thiocyanopyrrole (IV) in 87% yield. This represents a considerable improvement over the same reaction (56%) in the des-benzyl series. Moreover, the stability of IV is much greater than that of 3-thiocyanopyrrole; the former may be safely stored at room temperature for long periods while the latter is stable only if refrigerated under a nitrogen atmosphere. Alkylation of IV by treatment with bromoacetate ion and potassium hydroxide, followed by acidification, produced 85% of highly stable crystalline acid V. The instability of the des-benzyl analog of V prevented its purification, and it had to be isolated as the ammonium salt.[3]

Polyphosphoric acid cyclization of V provided an amorphous sirup from which VI could be isolated in 30% yield by chromatography on neutral alumina. Elution with chloroform removed VI in the first fractions, and the pure ketone was obtained by crystallization from cyclohexane. The position of attachment of sulfur to the pyrrole ring was established by treatment with Raney nickel and by identification of the product as 2-acetyl-1-benzylpyrrole, identical with an authentic sample.

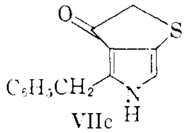
Continued elution with 1–5% methanol in chloroform provided two additional products (7 and 14%, respectively), although separation was not complete even upon rechromatography. Distillation of the first fraction provided an isomer of VI. The infrared and nuclear magnetic resonance spectra of this isomer are consistent with the structures VII. Since the cyclization normally takes place in the α-position, structures VIIb and VIIc are much less probable than VIIa.



VIIa



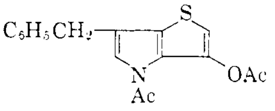
VIIb



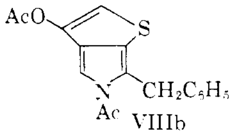
VIIc

The infrared spectrum (Nujol) shows bands at 3120 and 1660 cm.$^{-1}$, indicative of the —NH and C=O groups, respectively, of an acyl pyrrole, and bands at 760 and 688 cm.$^{-1}$, characteristic of a monosubstituted benzene ring.[5] The nuclear magnetic resonance spectrum[6] shows two methylene peaks at +0.78 and +0.95 p.p.m. (relative to pure water) of approximately equal intensity and an unsymmetrical multiplet between −2.50 and −2.30 p.p.m. There is, however, no resonance between −2.30 and 0 p.p.m., indicating that both β-positions in the pyrrole nucleus are substituted.[7]

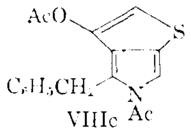
Acetylation of VII affords a diacetyl derivative VIII, whose nuclear magnetic resonance spectrum[6] supports the structural assignment VIIIa. Thus, structure VIIa is indicated for the ketone VII.



VIIIa



VIIIb



VIIIc

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[1] This investigation was supported in part by a grant [C-3969-(C1)Bio] from the National Cancer Institute, Public Health Service.

[2] National Science Foundation Fellow, 1958–1959.

[3] H. R. Snyder and D. S. Matteson, THIS JOURNAL, **79**, 3610 (1957); *J. Org. Chem.*, **22**, 1500 (1957).

[4] N. Clauson-Kaas and N. Elmling, *Acta Chem. Scand.*, **6**, 867 (1952).

[5] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 76–77.

[6] 20% solution in deuterio-chloroform using a hydrogen precession frequency of 40 Mc. and methylene chloride as an external standard.

[7] R. Abraham and H. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

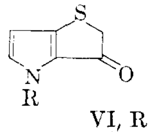
CHART 1

N.M.R. SPECTRUM OF VIIIa

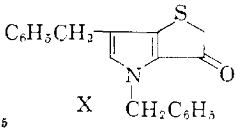
Frequency, p.p.m. relative to H_2O	Multiplicity (and coupling constant)	Assignment
−2.64	Uninterpreted multiplet	Benzene hydrogens
−2.25	Quartet/*ca.* 1.3 c.p.s./ /*ca.* 0.8 c.p.s./	Pyrrole α-hydrogen
−2.05	Doublet (*ca.* 1.3 c.p.s.)	Thiophene α-hydrogen
+0.83	Doublet (*ca.* 0.8 c.p.s.)	Methylene hydrogens
+2.28, +2.38	Singlets	Acetyl methyl hydrogens

Spin–spin coupling, of the magnitude shown in Chart 1, of the α-hydrogen atoms of the pyrrole and thiophene rings has been observed also in 3-acetoxy-4-acetylthieno[3,2-b]pyrrole.[8] The further coupling of the pyrrole hydrogen atom with the methylene protons indicates that they are in close proximity. Although no analogous examples in this series can be presented, splitting of this magnitude is more likely to result from the coupling of a ring proton and an adjacent alkyl group proton, than from a ring proton and a proton of an alkyl group two atoms removed. Therefore, structures VIIIb and VIIIc are considered unlikely.

The final chromatographic fraction was shown to contain the known compound IX,[3] a product of debenzylation. No dibenzyl ketone (X) was observed, although the fractions eluted between those containing VI and VIIa gave dark oils and tars, which could possibly have contained some X.



VI, R = $CH_2C_6H_5$
IX, R = H



X

Infrared spectra of the intermediates III, IV and V show no –NH absorption. Migration of the benzyl group, therefore, must take place in the highly acidic solution used in the ring closure step, a medium suitable for the generation of benzyl carbonium ions.

Electrophilic substitution in the 2-acylpyrroles commonly occurs in the 4-position, *i.e.* the β-position opposite the acyl group. For example, nitration of 2-acetylpyrrole yields principally 2-acetyl-4-nitropyrrole,[9] and sulfonation of 2-acetylpyrrole affords a 75% yield of 2-acetylpyrrole-4-sulfonic acid (isolated as the barium salt).[10] Bromination has been reported to give a heretofore unknown monobromo derivative,[11] but nuclear magnetic resonance analysis now has shown that it also is the 4-isomer, 2-acetyl-4-bromopyrrole. Acetylation of 2-acetylpyrrole gives 2,5-diacetylpyrrole, but this evidently involves an initial acetylation on nitrogen, with subsequent isomerization of the N-acetyl group to the α-position.[12] In the rearrangement of VI, therefore, it is not surprising that the benzyl cation attacks the β-position.

Reduction of VI with sodium borohydride in methanol effects its conversion in a single step to II, m.p. 48–51°, in 84% yield. The ultraviolet spectrum of II (λ_{max}^{EtOH} 267.5, 334 mμ; λ_{min}^{EtOH} 237.5 mμ) is similar to that of I (λ_{max}^{EtOH} 260 mμ; λ_{min}^{EtOH} 233 mμ), but shows a slight bathochromic shift which may be attributed to the effect of the N-alkyl group. Preliminary studies of the behavior of II in the Mannich reaction with formaldehyde and dimethylamine indicate that a condensation occurs, but isolation of the pure Mannich base has not yet been achieved. Attempts to convert the crude base to an analog of 3-indoleacetic acid have been unsuccessful. Results of further studies will be presented at a later date.

Experimental[13]

1-Benzylpyrrole (III).—When 149.5 g. (0.935 mole) of 2,5-diethoxytetrahydrofuran[14] and 100 g. (0.935 mole) of benzylamine[14] were dissolved in 185 ml. of glacial acetic acid, a strongly exothermic reaction occurred, and a red color developed. The solution was heated under reflux for 1 hr. and cooled. Acetic acid was removed by distillation under water-pump vacuum, and the dark residue was fractionally distilled through a 10″ Vigreux column. After a small fore-run, 1-benzylpyrrole was collected at 123–125° (12 mm.). The product was a clear, colorless oil and weighed 94 g. (64%).

1-Benzyl-3-thiocyanopyrrole (IV).—A suspension of 33.35 g. (0.344 mole) of potassium thiocyanate in 41 ml. of absolute methanol was cooled to −70° with a Dry Ice–acetone-bath and vigorously stirred while a solution of 27.15 g. (0.17 mole) of bromine in 27 ml. of absolute methanol, also chilled to −70°, was added slowly. It proved essential to add the bromine slowly to allow reaction with the thiocyanate to be complete. An excess of bromine drastically reduced the yield of pyrrole derivative.

To the deep yellow solution of thiocyanogen there was added in one portion a solution of 26.9 g. (0.171 mole) of 1-benzylpyrrole in 41 ml. of absolute methanol. A beautiful magenta color developed, and the temperature of the mixture rose to about −15°. The cooling bath was removed and the mixture allowed to warm while stirring was continued. At a temperature of 15°, the color of the mixture was white, and the contents of the flask were poured onto ice. The crystalline solid which separated was immediately filtered, washed several times with water, pressed dry on the filter, and air-dried for 1.5 hr. The colorless product weighed 31.9 g. (87%). Three crystallizations from cyclohexane afforded colorless needles, m.p. 48.5–50°.

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.25; H, 4.71; N, 13.08. Found: C, 67.45; H, 4.61; N, 13.22.

3-(1-Benzylpyrrolylthio)-acetic Acid (V).—A solution of 44.9 g. (0.21 mole) of IV and 35.1 g. (0.254 mole) of bromoacetic acid in 220 ml. of absolute methanol was chilled to −70° with a Dry Ice–acetone-bath. A solution of 51.9 g. of 85% potassium hydroxide in 220 ml. of 1:1 aqueous methanol was added quickly to the rapidly stirred solution over a period of 10 minutes. After the addition was complete, the cooling bath was removed, and stirring was continued for 3 hr. The pale yellow solution, now at room temperature, was neutralized to about *p*H 8 with solid CO_2, then evaporated to dryness *in vacuo*. The solid salts were washed several times with ether, and after brief drying in air, were then suspended in 250 ml. of methylene chloride. An excess of ice-cold 4 *N* hydrochloric acid was added to the suspension in small portions to minimize foaming. The organic layer was removed, and the aqueous layer was extracted twice with 100-ml. portions of methylene chloride. The organic extracts were combined, dried over magnesium sulfate and

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[8] R. J. Tuite and H. R. Snyder, unpublished observation.

[9] G. Ciamician and P. Silber, *Ber.*, **18**, 1456 (1885); **20**, 2605 (1887); I. J. Rinkes, *Rec. trav. chim.*, **53**, 1167 (1934); **56**, 1142 (1937).

[10] A. P. Terentyev and L. A. Yanovskaya, *J. Gen. Chem. U.S.S.R.*, **19**, a591 (1949).

[11] G. L. Ciamician and M. Dennstedt, *Ber.*, **16**, 2348 (1883); A. P. Terentyev, L. I. Belenky and L. A. Yanovskaya, *J. Gen. Chem. U.S.S.R.*, **24**, 1251 (1954).

[12] A. A. Berlin, *ibid.*, **14**, 438 (1944).

[13] All melting points and boiling points are corrected.

[14] Eastman Kodak Co. Technical grade.

evaporated to yield 47.6 g. (91.5%) of light tan crystalline acid. One crystallization from cyclohexane afforded 44.4 g. (85%) of nearly colorless needles. An analytical sample was prepared by crystallization from ether–pentane and had m.p. 105–107°.

Anal. Calcd. for $C_{13}H_{13}O_2NS$: C, 63.12; H, 5.31; N, 5.66. Found: C, 63.02; H, 5.55; N, 5.54.

The amide, prepared in a conventional way,[15] had m.p. 103–104°.

Anal. Calcd. for $C_{13}H_{14}ON_2S$: C, 63.38; H, 5.74; N, 11.38. Found: C, 63.34; H, 5.65; N, 11.25.

4-Benzyl-2*H*,3*H*-thieno[3,2-b]pyrrol-3-one (VI).—One hundred forty grams of polyphosphoric acid was placed in a 200-ml., 3-necked flask and brought to 120° while it was rapidly stirred. Temperature was determined by a thermometer inserted into the reaction mixture. A solution of 10 g. (0.04 mole) of V in 50 ml. of methylene chloride was added dropwise at such a rate that the temperature of the mixture was maintained at 115–120° throughout the reaction. When the addition of V was complete, the reddish-brown mixture was allowed to cool to about 95° and then poured into a mixture of 480 ml. of water and 300 ml. of ethyl acetate. After stirring for 0.5 hr., the ethyl acetate layer was removed, and the aqueous layer was saturated with sodium chloride and extracted with three 150-ml. portions of ethyl acetate. The combined ethyl acetate solutions were washed with aqueous sodium bicarbonate until the washings were slightly basic, then dried over magnesium sulfate. Evaporation of the solvent provided 8.4 g. of a dark brown oil.

The crude product was dissolved in the minimum amount of chloroform and placed on a column prepared from 150 g. of neutral alumina. During elution with chloroform the presence of three bands on the column was easily discernible. The most rapidly moving band was eluted in the first 125-ml. fraction, and upon concentration and dilution with petroleum ether (30–60°) yielded 2.7 g. (30%) of nearly pure VI. An analytical sample, m.p. 106–107.5°, was prepared by crystallization from cyclohexane; infrared absorption (Nujol): 1640(s), 755(s), 710(s), 693(s); n.m.r.[16] spectrum (20% CCl_4): −2.48(m), −2.18(d), −1.21(d), −0.46(s), +0.98(s) p.p.m.

Anal. Calcd. for $C_{13}H_{11}ONS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.50; H, 4.88; N, 5.85.

6-Benzyl-2*H*,3*H*-thieno[3,2-b]pyrrol-3-one (VIIa).—The middle band was eluted with 250 ml. of 1–2% methanol in chloroform. Concentration of the eluate gave 0.61 g. (6.8%) of a light tan, crystalline material. After two recrystallizations from cyclohexane, followed by distillation in a sublimation apparatus at 150° (0.05 mm.), white crystals were obtained, m.p. 155–158°, softens at 147°.

Anal. Calcd. for $C_{13}H_{11}ONS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.22; H, 4.78; N, 5.94.

Continued elution with 5% methanol in chloroform followed by concentration gave a total of 0.80 g. (14%) of brown material, m.p. 158–190°. After two sublimations, followed by recrystallization from 95% ethanol, pure IX was obtained, m.p. 186–188°, undepressed upon admixture with an authentic sample of IX.[3] The infrared spectra of the two samples were identical.

3-Acetoxy-4-acetyl-6-benzylthieno[3,2-b]pyrrole (VIIIa).—A solution of 100 mg. (0.438 mmole) of VIIa in 5 ml. of acetic anhydride was heated under reflux for 14 hr. The excess solvent was removed under reduced pressure, and the resulting oil transferred to a sublimation tube with acetone. Distillation at 142° (0.05 mm.) afforded a light yellow oil, which crystallized upon vigorous scratching. The yield of slightly yellow crystals, VIIIa, was 72 mg. (52.5%). After treatment with Darco and two recrystallizations from ethanol–water, the melting point was 117–119°; infrared spectrum (Nujol): 1765(s), 1710(s), 742(m), 691(w) cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{15}O_3NS$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.47; H, 4.77; N, 4.50.

2-Acetyl-4-bromopyrrole.—2-Acetylpyrrole[17] was brominated using the method of Ciamician and Dennstedt.[11] The product had m.p. 107–108°. The n.m.r. spectra[18] are: 2-acetylpyrrole (20% CCl_4): −2.39(m), −2.13(m),[19] −1.42(m), +2.39(s) p.p.m.; 2-acetyl-4-bromopyrrole (20% $CDCl_3$): −2.36(q), −2.24(q), +2.27(s) p.p.m.

The Desulfurization of VI.—A solution of 0.35 g. (0.00153 mole) of VI in 25 ml. of 95% ethanol was heated under reflux for 4 hr. with *ca.* 3.5 g. of Raney nickel (W-2). The solution was filtered while hot, and the catalyst was washed several times with small portions of solvent. The filtrate was concentrated *in vacuo* to give a small amount of a clear, colorless oil. The infrared spectrum of the oil was identical in all respects to that of authentic 2-acetyl-1-benzylpyrrole. The 2,4-dinitrophenylhydrazone of the desulfurization product melted at 202–204° and did not depress the melting point of 2-acetyl-1-benzylpyrrole 2,4-dinitrophenylhydrazone.

2-Acetyl-1-benzylpyrrole.—To a solution of 10 g. (0.063 mole) of N-benzylpyrrole and 35 ml. of acetic anhydride was added with swirling 0.6 ml. of 47% aqueous hydriodic acid containing a trace of free iodine. The reaction mixture was refluxed for 1.5 hr., cooled, and treated with an excess of 10% sodium hydroxide. The mixture was then allowed to stand at room temperature for 1 hr. with occasional vigorous shaking in order to hydrolyze the excess acetic anhydride. The black organic material was extracted with ether, dried over magnesium sulfate, and the ether distilled. Fractional distillation of the black oily residue yielded a major fraction of yellow oil, b.p. 131–131.5° (1.5 mm.), yield 4.27 g. (34%). An analytical sample was prepared by redistillation to a colorless liquid, $n^{24}\text{D}$ 1.5851.

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.17; H, 6.30; N, 7.02.

The product formed a 2,4-dinitrophenylhydrazone, which was purified by two recrystallizations from ethyl acetate, m.p. 204–206°.

Anal. Calcd. for $C_{19}H_{17}O_4N_5$: C, 60.01; H, 4.52; N, 18.41. Found: C, 59.78; H, 4.46; N, 18.76.

N-Benzylthieno[3,2-b]pyrrole (II).—A solution of 1.55 g. (0.0068 mole) of VI in 50 ml. of absolute methanol was swirled gently while 0.85 g. (0.0225 mole) of sodium borohydride was added in portions. An exothermic reaction occurred. The flask was allowed to stand until evolution of gas had ceased, then filled with nitrogen and tightly stoppered. Previous experiments disclosed that standing under the atmosphere produced a red coloration.

The clear solution was kept at 25° for about 16 hr., then about 0.1 g. of sodium borohydride was added and the mixture was gently warmed for 15 min. On cooling, it was poured into 210 ml. of water containing 3.9 ml. of acetic acid. The product was extracted with three 75-ml. portions of methylene chloride, and the methylene chloride solution was washed once with water before drying over magnesium sulfate. Before concentration, the solution was filtered onto potassium carbonate and allowed to stand 2 hr. Evaporation of the solvent *in vacuo* yielded 1.2 g. (84%) of a light-colored oil which crystallized on cooling and scratching. Purification was effected by sublimation at an oil-bath temperature of 110° at 0.1 mm. in an apparatus which enabled collection of the oily sublimate on a condenser chilled by Dry Ice–acetone. Scratching caused the colorless oil to crystallize to a white solid, m.p. 45–48°. An analytical sample, m.p. 48–51°, was prepared by a second sublimation.

The ultraviolet spectrum shows $\lambda_{\max}^{\text{EtOH}}$ 267.5 mμ (ϵ 12,000), 334, mμ (ϵ 1320); $\lambda_{\min}^{\text{EtOH}}$ 237.5 mμ (ϵ 5625). In comparison, I shows $\lambda_{\max}^{\text{EtOH}}$ 260 mμ (ϵ 11,800); $\lambda_{\min}^{\text{EtOH}}$ 233 mμ (ϵ 4900).

Anal. Calcd. for $C_{13}H_{11}NS$: C, 73.19; H, 5.28; N, 6.56. Found: C, 73.05; H, 5.26; N, 6.62.

URBANA, ILL.

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[15] R. Shriner, R. Fuson and D. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 200.

[16] Frequencies in p.p.m. relative to water. Letters in parentheses refer to the multiplicity of the bands; *e.g.*, (s) = singlet, (d) = doublet, (t) = triplet, (q) = quartet, (m) = uninterpreted multiplet. A hydrogen precession frequency of 40 Mc. was used, and methylene chloride served as an external standard.

[17] H. Adkins, I. Wolff, A. Pavlic and E. Hutchinson, THIS JOURNAL, **66**, 1293 (1944).

[18] These spectra were also run using a hydrogen precession frequency of 60 Mc., thereby affording greater separation of the two lower frequency bands.

[19] This band is assigned to the proton in the 3-position. Lowering of the frequency results from the electron-withdrawing effect of the adjacent acetyl group.