Heterohelicenes Containing Seven-Membered Rings. 5,6-Dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepines

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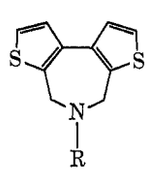
Two new heterohelicenes were prepared containing as central heterounit the 5,6-dihydro-4*H*-dithien-[2,3-*c*:3′,2′-*e*]azepine system. In a one-step reaction 3,3′-bithianaphthenyl-2,2′-dicarboxaldehyde was converted by treatment with benzylamine and sodium dithionite into the condensed azepine. The helical nature of the azepine is revealed by the nonequivalence of geminal protons.

In continuation of our study of the chemical and optical properties[1] of heterohelicenes we are pursuing several goals,[2] of which the following are pertinent to the work reported in this paper: (a) an efficient nonphotochemical helicene synthesis; (b) the use of heterocyclic systems other than thiophene. This article describes the synthesis of a novel ring system, the 5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine system (**1**).[3] The preparation of this class of compounds



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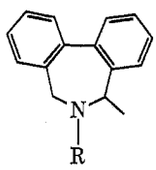


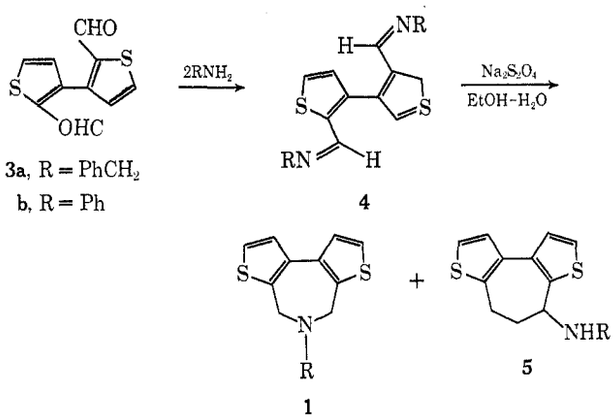
2

represents a preliminary stage in overcoming some of the synthetic obstacles in the preparation of helicenes. Thus, while maintaining an unambiguous helicene synthesis through the use of thiophene or thianaphthene, we found a useful nonphotochemical ring-closure step. The product, an azepine, provides us with an active site—the nitrogen atom—potentially valuable for resolution and for preparation of derivatives.[4]

An added novelty in the synthesis of this new helical ring system is the inclusion of a seven-membered ring. The presence of so large a ring in a helicene may be expected to lower the distortion in the aromatic portion of the molecule, whereas optical stability for the compounds is not unlikely. Even simple biphenyls having 2,2′ three-atom bridges and no 6,6′ substituents have in certain instances been resolved.[5]

Results

Our first attempts at the preparation of compounds **1** were patterned on the successful synthesis of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines (**2**) by Hawthorne and coworkers.[6] This route involved the preparation and isolation of bis Schiff bases derived from biphenyl-2,2′-dicarboxaldehyde, followed by reductive cyclization to azepines **2** using sodium dithionite ($Na_2S_2O_4$). Although these authors report consistent and good yields for virtually all cases studied, the reaction sequence in our hands was of only limited value when 3,3′-bithienyl-2,2′-dicarboxaldehyde (**3**) was used as the starting dialdehyde. Thus attempts to convert bis Schiff bases **4** to the desired appropriate azepines (**1**) at elevated temperatures invariably gave mixture of **1** and the 7-aminobenzo[1,2-*b*:4,3-*b*′]dithiophenes **5**.



3a, R = $PhCH_2$
b, R = Ph

4

1 **5**

When aqueous sodium dithionite was added slowly to a refluxing solution of **4a** in ethanol only a 7% yield of **1a** was collected; the major product, to which we assigned the structure **5a**, was isolated in 74% yield. The two amines could be separated on the basis of their difference in basicity. Similar reduction of **4b** at elevated temperature afforded a mixture of **1b** and **5b** in an approximate ratio of 1:3; the products were both of low basicity and could not be separated.

After considerable experimentation it was discovered that high yields of azepine could be obtained when Schiff base formation was circumvented. Thus when the starting dialdehyde was treated *simultaneously* at room temperature with sodium dithionite and the appropriate amine in aqueous ethanol solution, no Schiff base color was observed and a high yield of the desired azepine crystallized from the reaction mixture within 1 hr; compound **5** was not detected. The white solid (**1**) slowly decomposed and was consequently purified periodically by sublimation. It must be noted that the formation of Schiff base **4b**, using the procedure of Hawthorne, required heating in

(1) J. H. Dopper D. Oudman, and H. Wynberg, *J. Amer. Chem. Soc.*, **95**, 3692 (1973).

(2) (a) M. B. Groen and H. Wynberg, *J. Amer. Chem. Soc.*, **93**, 2968 (1971); (b) H. Wynberg, *Accounts Chem. Res.*, **4**, 65 (1971).

(3) The potent *anti*-epinephrine properties of these compounds stimulated the initial investigations into their synthesis and properties: (a) W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951); (b) W. Wenner, *ibid.*, **17**, 1451 (1952); (c) W. Wenner, U. S. Patent 2,619,484 (Nov 25, 1952); (d) R. A. Schmidt and W. Wenner, U. S. Patent 2,693,465 (Nov 2, 1954).

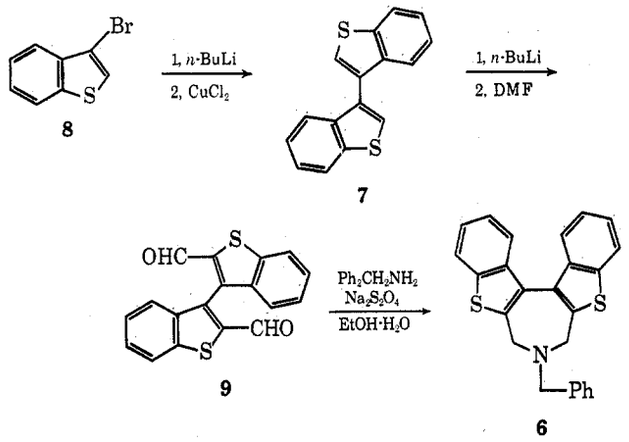
(4) For instance, a number of optically active dibenzazepines having auxiliary ortho substituents have been resolved by conversion to suitable diastereomeric salts; see (a) G. H. Beaven, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952); (b) S. R. Ahmed and D. M. Hall, *ibid.*, 3043 (1958); (c) D. M. Hall and M. Poole, *J. Chem. Soc. B*, 1034 (1966).

(5) (a) W. E. Truce and D. D. Emrick, *J. Amer. Chem. Soc.*, **78**, 6131 (1956); (b) D. C. Iffland and H. Siegel, *ibid.*, **80**, 1947 (1958); (c) D. C. Iffland and H. Siegel, *J. Org. Chem.*, **21**, 1056 (1956).

(6) J. O. Hawthorne, E. L. Mihelic, M. S. Morgan, and M. H. Wilt, *J. Org. Chem.*, **28**, 2831 (1963).

refluxing toluene for several hours, conditions considerably more drastic than needed for the preparation of the azepine **1b** directly from the dialdehyde.

We then turned our attention to the synthesis of the helical structure **6**. The starting material, 3,3′-bithianaphtenyl (**7**), had been prepared previously in 11% yield.[7] We were able to increase the yield to 72% by treating 3-bromobenzo[*b*]thiophene with *n*-butyllithium at −70°[8] and coupling at that temperature in the presence of copper(II) chloride.[9] Compound **7** was obtained as a white solid which slowly decomposes in air. Conversion of **7** to 3,3′-bithianaphthenyl-2,2′-dicarboxaldehyde (**9**) in 66% yield was



achieved *via* lithiathion with *n*-butyllithium and formylation with *N*,*N*-dimethylformamide.

Reaction of **9** at room temperature with a mixture of benzylamine and excess sodium dithionite produced **6** in 65% yield.[10] The white product soon began to turn yellow; it was sublimed whenever pure material was needed. The structure of the azepines **1** and **6** is assigned on the basis of analytical and spectral data. Convincing are the nmr spectra of the two amines, especially with respect to the signals due to the methylene protons. Thus, while **1** exhibits a singlet (4 H) at δ 4.23 due to the four equivalent methylene protons,[11] an AB quartet (J = 13 Hz) at δ 3.66 is clearly discernible for **6**, and is attributed to nonequivalent methylene protons. The nonequivalence of these latter geminal protons on the nmr time scale attests to the increasing optical stability of such compounds as additional ortho-condensed aromatic rings are introduced into the molecular framework. This effect has also been observed in the case of dibenzazepinium salts.[12]

(7) L. J. Pandya, D. S. Rao, and B. D. Tilak, *J. Sci. Ind. Res.*, **18B**, 516 (1959); *Chem. Abstr.*, **54**, 17391*d* (1959). Our melting point for this compound was in close agreement with that reported by these workers (see Experimental Section). The account of a synthesis of **7** of mp 370° by Schuetz and Ciporin is probably not correct: R. D. Schuetz and L. Ciporin, *J. Org. Chem.*, **23**, 206 (1958).

(8) It has been noted that mixtures of products are obtained when the 3-benzo[*b*]thienyllithium is prepared at higher temperatures, or in solvents other than diethyl ether: R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2733 (1968).

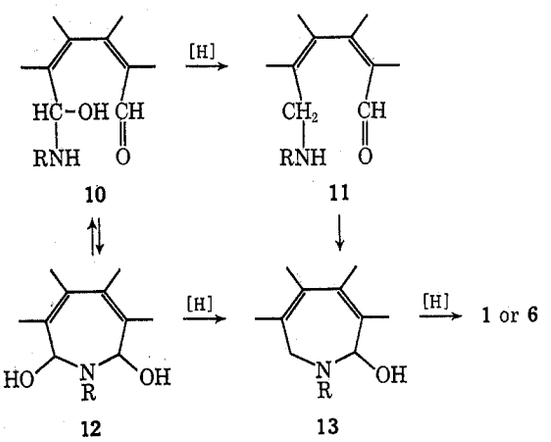
(9) This method is an adaptation of one used by S. Gronowitz and H. O. Karlsson, *Ark. Kemi*, **17**, 89 (1960).

(10) Azepine **6** could also be synthesized from the bis Schiff base **10**, by reduction with $Na_2S_2O_4$. Even when this reaction is carried out in refluxing aqueous ethanol, however, there is no detection of the amine **11**, which in light of previous results might have been an expected product.

(11) The nmr signal remained a singlet even at temperature as low as −40°.

Discussion

Under our conditions bis Schiff bases of **3** and **9** do not seem to serve as intermediates in the direct conversion of dialdehydes **3** and **9** to the appropriate dihydroazepines. This view is supported by the relative mildness of conditions permissible for the direct conversions (*vide supra*), as well as by the color sequence observed for the process (see Experimental Section). Although the nature of the multistep sequence in the direct conversions of **3** to **1** and **9** to **6** at room temperature remains a matter of conjecture, it seems reasonable to propose the following scheme. The dicarbonyl compound is in equilibrium with its carbinolamine adduct. The latter, a benzyl-type alcohol, may be reduced (to **11**), may cyclize (to **12**), and may, in a competing sequence, lose water to form a Schiff base. Both **11** and **12** may form azepine from the cyclic **13** *via* a second reductive step. The scheme



described above allows bis Schiff bases to serve as starting materials if their formation and subsequent hydrolysis to a carbinolamine is rapid.

We have not included the trans rotamer in this scheme. Obviously only the cis rotamer will yield cyclic product.

Experimental Section

All melting points are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 instrument with tetramethylsilane (TMS) as internal standard. The infrared spectra were taken on Perkin-Elmer 125 and Unicam SP-200 instruments. A Zeiss PMQ II spectrophotometer was used for the ultraviolet spectra, while mass spectra were recorded with a AEI MS-9. Microanalyses were carried out in the analytical section of this department, under the direction of Mr. M. W. Hazenberg.

3,3′-Bithienyl-2,2′-dicarboxaldehyde (**3**) was prepared by the method of Wynberg and Sinnige[13] and purified by sublimation at 130° (0.04 mm).

***N*-Benzyl-5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine** (**1a**). **A.**—To a vigorously stirred[14] solution of **3** (0.165 g, 0.741 mmol) and 0.161 g (1.50 mmol) of benzylamine in 30 ml of absolute ethanol was added, all at once,[15] a solution of 0.950 g (5.50 mmol)

(12) (a) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1242 (1955); (b) ref 4b.

(13) H. Wynberg and H. J. M. Sinnige, *Recl. Trav. Chim. Pays-Bas*, **88**, 1244 (1969).

(14) Large quantities of dark material are often formed when stirring is inefficient.

(15) It was found that after *gradual* (1 min) addition of the reducing agent no reaction ensued, even upon heating to reflux temperature.

of sodium dithionite[16] in 30 ml of water. The resulting solution was stirred at room temperature in a nitrogen atmosphere. Within several minutes the solution became pink (temporarily) and after 10–15 min white needles began to separate. After 2 hr most of the ethanol was removed on a rotary evaporator. The remaining mixture was filtered and the white crystals were washed with water. Even when dried under vacuum the azepine was found to incorporate much water. The material was thus dissolved in ether and the resulting solution was dried over KOH pellets. Filtration, followed by solvent removal *in vacuo*, afforded 0.207 g (94%) of **1a**. Sublimation at 120° (0.05 mm) gave the pure compound: mp 145–146°; uv max (cyclohexane) 230 mμ (ε 24,100), 282 sh (5540), 291 (6250), 302 sh (4360); nmr (CCl_4) δ 3.63 (s, 2 H), 4.23 (s, 4 H), 6.90–7.35 (AB q, 4 H, $J \approx 5$ Hz), 7.21 (s, 5 H); mass spectrum (70 eV) *m/e* 297 (M^+ – benzyl).

Compound **1a** readily formed an insoluble hydrochloride salt when treated in ether solution with alcoholic HCl. The salt could not be obtained free of contamination by the free amine.

Picric acid and **1a** reacted in ethanol to yield a yellow-orange picrate, which was recrystallized from ethanol, mp 144–145°.

Anal. Calcd for $C_{23}H_{18}N_4O_7S_2$: C, 52.46; H, 3.45; N, 10.64; S, 12.18. Found: C, 52.46; H, 3.58; N, 10.40; S, 12.09.

B.—A solution of 0.250 g (1.12 mmol) of **3** and 0.242 g (2.26 mmol) of benzylamine in 16 ml of absolute ethanol was refluxed for 2 hr. An aliquot of the resulting solution was stripped of solvent under vacuum, yielding an oily yellow solid. Trituration with a small amount of ethanol gave crude di Schiff base **4a** as a pale yellow solid: mp 127–130°; ir (Nujol) 1620 cm^{-1}; nmr ($CDCl_3$) δ 4.71 (broad s, 4 H), 6.99–7.55 (AB q, 4 H, $J \approx 5$ Hz), 7.33 (s, 10 H), 8.32 (broad s, 2 H).

Crude **4a** in 16 ml of ethanol was stirred under reflux. Over a period of 1 min a solution of 1.18 g (6.77 mmol) of sodium dithionite in 8 ml of water was added. The resulting solution was refluxed for 45 min. The mixture was then cooled and most of the ethanol was removed under vacuum. The remaining mixture was extracted with 30 ml of ether in three portions. The combined extracts were washed several times with 30 ml of 5% HCl solution. The remaining ether solution was retained. The acid solution was washed with ether, then neutralized by the addition of ammonium hydroxide. An extraction with 25 ml of ether was carried out; the extracts were washed with water, dried over KOH, and filtered. Ether removal gave 0.024 g (7%) of **1a**. The retained ether solution was likewise washed with water, dried over KOH, and filtered; solvent removal yielded a greenish solid. This was dissolved in 15 ml of ether. Dropwise addition of alcoholic HCl precipitated the hydrochloride salt of **5a**. The solid was filtered, then dissolved in 10 ml of 5% HCl solution. After neutralization with aqueous ammonia, the mixture was extracted with 30 ml of ether in three portions. After being washed with water and dried over KOH, the combined extracts were filtered. Ether removal *in vacuo* gave 0.245 g (74%) of **5a** as a white solid. This could be further purified by sublimation (140°, 0.05 mm): mp 113–114°; uv max (cyclohexane) 238 mμ (ε 20,700), 268 (13,000), 277 (11,900), 292 (13,500), 304 (18,000), 332 (7560); ir (KBr) 3410 cm^{-1}; nmr (CCl_4) δ 3.90 (broad s, 1 H), 4.43 (s, 2 H), 6.94 (s, 1 H), 7.07–7.64 (m, 9 H); mass spectrum (70 eV) *m/e* 295 (M^+), 204 (M^+ – benzyl).

Compound **5a** formed a dark brown picrate derivative upon treatment with picric acid in ethanol, mp 155–156°.

Anal. Calcd for $C_{23}H_{18}N_4O_7S_2$: C, 52.67; H, 3.07; N, 10.68; S, 12.23. Found: C, 52.81; H, 3.20; N, 10.58; S, 12.21.

***N*-Phenyl-5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine (1b)** was prepared in 86% yield at room temperature according to method A for the synthesis of **1a**. The white needles were purified by sublimation (120°, 0.05 mm): mp 142–143°; uv max (cyclohexane) 233 mμ (ε 26,600), 246 sh (22,300), 283 (7730), 305 sh (3610); nmr (CCl_4) δ 4.90 (s, 4 H), 6.55–7.27 (m, 9 H); mass spectrum (70 eV) *m/e* 283 (M^+).

Azepine **1b** failed to form a picrate. It readily gave a 2:1 complex with trinitrobenzene, however; recrystallization from benzene–ethanol gave maroon needles, mp 139–140°.

Anal. Calcd for $C_{38}H_{29}N_6O_6S_4$: C, 58.52; H, 3.75; N, 8.98; S, 16.44. Found: C, 58.38; H, 3.79; N, 8.80; S, 16.39.

3-Bromobenzo[*b*]thiophene (8) was prepared by the method of Szmuszkovicz and Modest.[17] The fraction of viscous yellow liquid distilling at 85–95° (1.5 mm) was collected.

3,3′-Bithianaphthenyl (7).—Into a three-necked flask under an atmosphere of dry nitrogen was placed 12.0 ml of 2.30 *M* *n*-butyllithium solution (27.5 mmol) in hexane, followed by 15 ml of dry ether. The resulting solution was stirred and cooled to −70°. Over a period of 10 min a solution of 5.32 g (25.0 mmol) of **8** in 9 ml of anhydrous ether was added dropwise to the cold solution. The mixture was stirred for an additional 30 min at −70°, giving a suspension of 3-thianaphthenyllithium. Then anhydrous copper(II) chloride (3.92 g, 29.1 mmol) was added and the resulting mixture was stirred vigorously at −70° for 3.5 hr. Afterwards the reaction mixture was allowed to warm up slowly. When the temperature reached 0° about 30 ml of 2 *M* HCl was added and the mixture was allowed to stand overnight. The copper salt was filtered off and washed with ether and dilute HCl solution. The resulting filtrate was separated and the ether layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. Solvent removal *in vacuo* afforded 2.40 g (72%) of **8** as a pink solid. The color could be removed by elution of the material with hexane on a column of silica gel. Recrystallization from petroleum ether (bp 40–60°) gave pure **7** as white plates: mp 82.7–83.0° (lit.[7] mp 85°); nmr ($CDCl_3$) δ 7.18–7.47 (m, 4 H), 7.54 (s, 2 H), 7.63–8.06 (m, 4 H); mass spectrum (70 eV) *m/e* 266 (M^+).

3,3′-Bithianaphthenyl-2,2′-dicarboxaldehyde (9).—To a stirred solution of 0.821 g (3.08 mmol) of **7** in 60 ml of dry ether, under a nitrogen atmosphere, was added 6.5 ml of a 2.30 *M* solution of *n*-butyllithium (14.9 mmol) in hexane. The mixture was refluxed for 90 min. A solution of *N*,*N*′-dimethylformamide (4.15 g, 56.7 mmol) in 6 ml of anhydrous ether was then added dropwise over a period of 5 min and the resulting mixture was refluxed for 30 min. It was then poured into a mixture of 17.8 ml of 2 *M* HCl and 60 g of ice. The ether was removed *in vacuo* and the remaining mixture was extracted with 100 ml of methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and filtered. Solvent removal yielded a yellow oil, most of which soon solidified. Recrystallization from petroleum ether–methylene chloride afforded 0.655 g (66%) of **9**. The analytical sample was obtained by two recrystallizations from benzene, followed by vacuum drying at 55°: mp 171–172°; uv max (EtOH) 232 mμ (ε 29,500), 250 sh (19,600), 303 (24,600), 345 sh (7280); ir (KBr) 1660 cm^{-1}; nmr ($CDCl_3$) δ 7.20–8.22 (m, 8 H), 9.88 (s, 2 H); mass spectrum (70 eV) *m/e* 322 (M^+), 293 (M^+ – CHO), 264 (M^+ – 2 CHO).

***N*-Benzyl-7,8-dihydro-6*H*-bis[1]benzothien[2,3-*c*:3′,2′-*e*]azepine (6).** **A.**—The desired compound was prepared in 65% yield at room temperature from **9**, 2 equiv of benzylamine, and excess $Na_2S_2O_4$ in 40 ml of 1:1 ethanol–water according to method A for the synthesis of **1a**. The white needles were purified by sublimation (160°, 0,01 mm): mp 175–176°; uv max (EtOH) 222 mμ (ε 51,200), 244 (37,800), 271 sh (9720), 289 (8020), 299 (9500), 308 (10,500); nmr ($CDCl_3$) δ 3.36–3.98 (AB q, 4 H, J = 13 Hz), 3.77 (s, 2 H), 7.08–7.61 (m, 9 H), 7.71–8.13 (m, 4 H); mass spectrum (70 eV) *m/e* 397 (M^+), 306 (M^+ – benzyl).

4 failed to form stable complexes with picric acid or trinitrobenzene.

B.—A solution of 0.0750 g (0.232 mmol) of **9** and 0.0498 g (0.464 mmol) of benzylamine in 5 ml of absolute ethanol was refluxed for 1 hr. An aliquot of the resulting solution was stripped of solvent, giving crude di Schiff base **10** as a pale yellow solid: mp 144–148°; ir (Nujol) 1625 cm^{-1}; nmr ($CDCl_3$) δ 4.69 (s, 4 H), 7.07–7.64 (m, 16 H), 7.80–8.05 (m, 2 H), 8.22–8.36 (m, 2 H); mass spectrum (70 eV) *m/e* 500 (M^+). Crude **10** in 5 ml of ethanol was stirred at reflux temperature. A solution of 0.340 g (1.95 mmol) of sodium hydrosulfite in 2 ml of water was added, and the mixture was refluxed for 2 hr. The mixture was diluted with 5 ml of water and most of the ethanol was removed *in vacuo*. The remaining mixture was extracted with 20 ml of ether. The combined extracts were washed with

(16) Available in 83% purity from Baker Chemical Co. Aqueous solutions should not be prepared until immediately before use, since the material undergoes facile hydrolysis.

(17) J. Szmuszkovicz and E. J. Modest, *J. Amer. Chem. Soc.*, **72**, 571 (1950). The purification problems noted by other authors were not encountered.

water, dried over KOH, and filtered. Solvent removal on the rotary evaporator gave an oily yellow solid. This was sublimed to give 64.8 mg (70%) of **6**.

Registry No.—**1a**, 40386-84-3; **1a** picrate, 40306-86-3; **1b**, 40306-87-4; **1b**-trinitrobenzene, 40306-88-5; **3**, 40306-89-6; **4a**, 40306-90-9; **5a**, 40306-91-0; **5a** picrate, 40531-26-8; **6**, 40306-92-1; **7**, 40306-93-2; **8**, 7342-82-7; **9**, 40306-95-4; **10**, 40306-96-5; benzylamine, 100-46-9; sodium dithionite, 7775-14-6; *n*-butyllithium, 109-72-8; copper(II) chloride, 7447-39-4; *N*,*N*'-dimethylformamide, 68-12-2.

Pteridines. XXXII. 2-Amino-3-cyano-5-chloromethylpyrazine 1-Oxide and Its Conversion to 6-Alkenyl-Substituted Pteridines[1,2]

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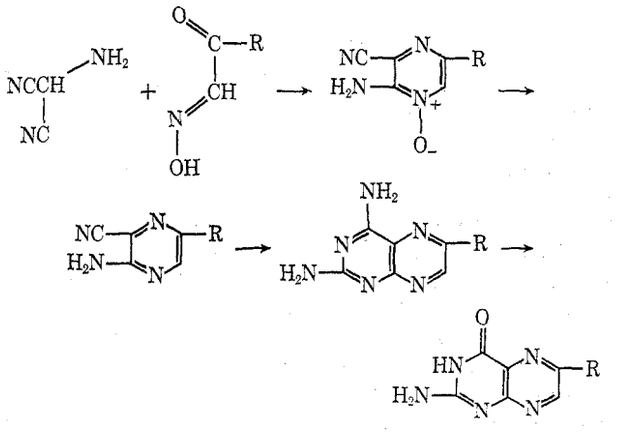
2-Amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**), prepared by the condensation of β-chloropyruvaldoxime with aminomalononitrile tosylate, was deoxygenated with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**4**). Both **2** and **4** were converted by conventional procedures to triphenylphosphonium ylides (Wittig reagents) and, hence, by condensation with aldehydes to parallel series of 5-alkenylpyrazines (**9** and **10**). Cyclization of **10a–e** with guanidine gave 2,4-diamino-6-alkenylpteridines (**11a–e**), of interest as intermediates for the synthesis of biopterin and biopterin analogs. Some additional reactions of the above pyrazine intermediates are also described.

We have described in recent articles[1,3] a new, general, and versatile synthetic route to pteridines and pterins which involves, as its initial key step, the condensation of α-aminonitriles with α-oximino carbonyl compounds. For example, aminomalononitrile and α-ketoaldoximes give 2-amino-3-cyano-5-substituted pyrazine 1-oxides; deoxygenation and subsequent condensation with guanidine lead to 2,4-diamino-6-substituted pteridines, which upon acid or base hydrolysis yield pterins. One of the major advantages of this simple procedure over the classical Isay synthesis[4] is the unambiguous positioning of the side chain in the pyrazine ring.



Although this new procedure could, in principle, be adapted to the direct synthesis of pteridine natural products possessing multifunctional C-6 substituents (*i.e.*, biopterin, folic acid, methotrexate), complex, fragile, and difficultly accessible α-ketoaldoxime intermediates would be normally required. We describe in the present and subsequent papers a simple modification of this pteridine synthesis which permits deferral of the elaboration of the requisite C-6 side chains until *after* the initial construction of the pyrazine ring. The key intermediate, from which pteridines of both the biopterin and folic acid classes of natural products can be prepared, is 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**). This paper describes the preparation of **2** and its use for the preparation of pyrazines and pteridines suitable for final elaboration into the biopterin series.[5] A following paper will describe the elaboration of **2** to pteridines and pterins related to folic acid.

β-Chloropyruvaldoxime (**1**), readily prepared from diketene,[6] and less conveniently (and unreliably) by chlorination of α-oximinoacetone in chloroform solution,[7] was smoothly converted by reaction with aminomalononitrile tosylate in 2-propanol to **2**. Since **2** could be converted to 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide (**3**) upon refluxing in methanol solution, it appeared that the chloromethyl group of **2** might well be used for the introduction of diverse side chains at position 5 (pteridine position 6) by nucleophilic displacement reactions with suitable nucleophiles. Vindication of this prediction will be given in future papers in this series.

Treatment of **2** and **3** with phosphorus trichloride at room temperature in tetrahydrofuran solution resulted in smooth deoxygenation to give 2-amino-3-cyano-5-chloromethylpyrazine (**4**) and 2-amino-3-cyano-5-methoxymethylpyrazine (**5**), respectively. The ease with which these deoxygenations proceed contrasts with the vigorous conditions required for deoxygenation of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide[8] and may be a reflection of decreased steric hindrance at the *N*-oxide grouping. Deoxygenation

(1) Part XXXI: E. C. Taylor and R. F. Abdulla, *Tetrahedron Lett.*, 2093 (1973).

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