3-Methylthieno[3,2-c]thiapyrylium Perchlorate (3b).—Carbinol **6b** (1.00 g, 0.0054 mol) dissolved in 16 ml of acetic acid reacted analogously with 1.85 g (0.0054 mol) of trityl perchlorate in 16 ml of nitromethane to yield (after a similar work-up) 1.75 g of crude product, mp 135–140°, which, after two recrystallizations from glacial acetic acid (Norite), afforded 0.15 g (11%) of pure 3-methylthieno[3,2-c]thiapyrylium perchlorate (**3b**) as slightly colored (blue-green) plates: mp 156–158°, uv max (1% perchloric acid in acetonitrile) 229 mμ (log ε 4.32), 264 (4.61), 306 (4.60), and 366 (3.52); nmr (CF_3COOD) δ 10.33 (s, 1, H-1), 9.17 (s, 1, H-4), 8.33 (d, 1, J = 5.5 Hz, H-6), 8.07 (d, 1, J = 5.5 Hz, H-7), and 3.23 ppm (s, 3, CH_3).

Anal. Calcd for $C_8H_7ClO_4S_2$: C, 36.02; H, 2.65; Cl, 13.29; S, 24.04. Found: C, 36.16; H, 2.87; Cl, 13.33; S, 23.93.

Thieno[2,3-c]thiapyrylium Perchlorate (4).—By a procedure similar to that for **3a**, 2.45 g (0.014 mol) of carbinol **8** in 50 ml of glacial acetic acid and 4.88 g (0.014 mol) of trityl perchlorate in 50 ml of nitromethane reacted to give 3.30 g (92%) of crude thiapyrylium salt (**4**), mp 175–182°. Three recrystallizations from glacial acetic acid (Norit) afforded 0.80 g (22%) of pure thieno[2,3-c]thiapyrylium perchlorate (**4**): mp 192–194°; uv max (1% perchloric acid in acetonitrile) 225 mμ (log ε 4.25), 262 (4.29), 304 (3.78), and 381 (4.01); nmr (CF_3COOD) δ 10.67 (br, s, 1, H-1), 9.28 (m, 2, H-3 and H-4), 9.13 (d, 1, J = 5.5 Hz, H-6), and 8.22 ppm (d, 1, J = 5.5 Hz, H-5).

Anal. Calcd for $C_7H_5ClO_4S_2$: C, 33.27; H, 1.99; Cl, 14.03; S, 25.38. Found: C, 33.30; H, 2.06; Cl, 14.09; S, 25.11.

Registry No.—**3a**, 22431-16-9; **3b**, 22431-17-0; **4**, 22482-98-0; **6a**, 22431-18-1; *cis*-**6b**, 22433-06-3; *trans*-**6b**, 22433-03-0; **8**, 22431-19-2.

A Novel Synthesis of Dihydro-*p*-dithiins and Dihydro-1,4-dithiepins[1a,b] Involving an Amide Leaving Group

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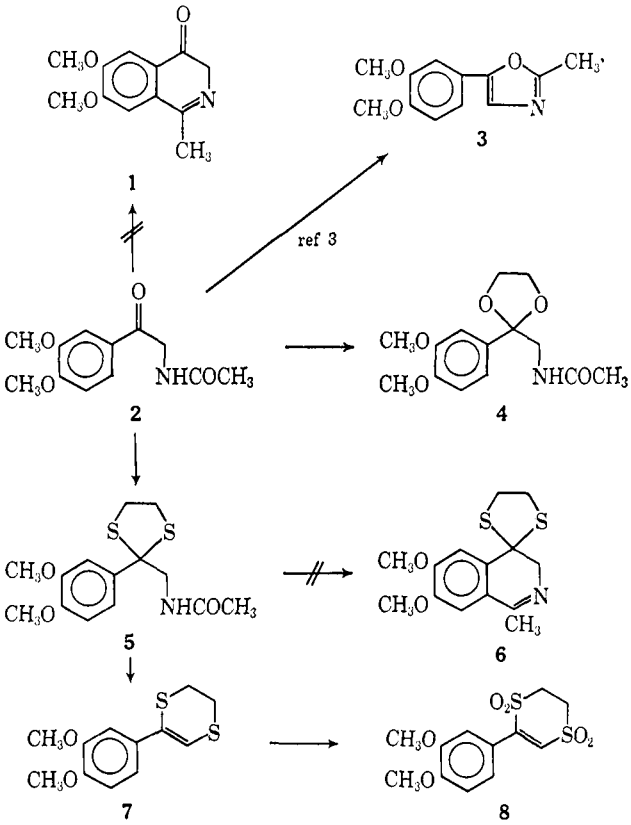
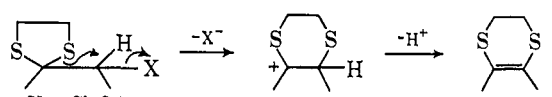
During an investigation of the structures of certain cactus alkaloids,[2] the synthesis of the 4-oxoisoquinoline derivative **1** from the corresponding ring-opened acetamido ketone **2** was contemplated. Since direct cyclization would be expected[3] to lead to the oxazole **3**, a modified Bischler–Napieralski[4] reaction *via* the ethylene ketal **4** was attempted. The oxazole **3** was the only product isolated, perhaps owing to hydrolysis of **4** to the ketone **2** under the reaction conditions. Cyclization of the hydrolytically more stable thioketal **5** therefore was attempted.

Instead of the desired isoquinoline derivative **6**, however, a sulfur-containing, nitrogen-free product was isolated whose infrared and nmr spectra suggested the structure **7**, 2,3-dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin. This hypothesis was supported by the elemental analyses of both the compound and its tetroxide derivative **8**.



Several other syntheses of dihydro-*p*-dithiins are known in which an ethylene thioketal is either the starting material or a possible intermediate.[5–8] The common feature of each of these reactions is that the position α to the original carbonyl carbon atom may develop electrophilic character by loss of acetate ion[5] or chloride ion[6,8] or by opening of an epoxide ring.[7] This process in turn could initiate (or occur simultaneously with) the 1,2 migration of sulfur to give a



carbonium ion (**9**), which on loss of a proton would lead to the dihydro *p*-dithiin **10**. An analogous mechanism for the formation of **7** from **5** would require loss of the elements of acetamide. Under the conditions of the reaction (P_2O_5 in pyridine), this might occur by elimination of acetonitrile from an intermediate Vilsmeier–Haack adduct (**11**).[9] This hypothesis is supported by

(1) (a) Reported in part at the 23rd Southwest Regional Meeting of the American Chemical Socieity, Little Rock, Ark., Dec 1967. (b) Taken in part from the Ph.D. Dissertation of J. L. Massingill, Jr., Texas Christian University, 1968. (c) To whom inquiries should be addressed.

(2) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, Jr., *Tetrahedron Lett.*, 1321 (1967).

(3) (a) R. Robinson, *J. Chem. Soc.*, 275 (1933); (b) J. S. Buck, *ibid.*, 740 (1933). (c) E. Zalay, *Vegyip. Kut. Intez. Kozlem.*, **4**, 101 (1954); *Chem. Abstr.*, **52**, 16273*b* (1958).

(4) N. Itoh and S. Sugasawa, *Tetrahedron*, **6**, 16 (1959).

(5) L. F. Fieser, C. Yuan, and T. Goto, *J. Amer. Chem. Soc.*, **82**, 1996 (1960).

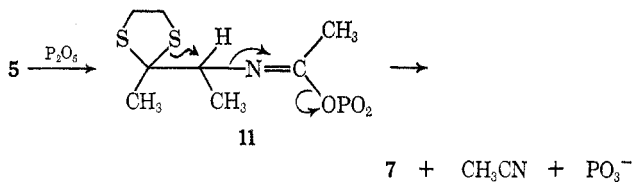
(6) G. Karmas, *J. Org. Chem.*, **32**, 3147 (1967).

(7) M. Tomoeda, M. Ishizaki, H. Kayashi, S. Kantomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, **21**, 733 (1965).

(8) (a) L. Levine, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 24. (b) After this paper was accepted for publication another example of this type of synthesis of dihydro-*p*-dithiins was reported utilizing α-bromo ketones as starting materials: H. Rubenstein and M. Weurthele, *J. Org. Chem.*, **34**, 2762 (1969).

(9) (a) Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.*, **27**, 2886 (1962). (b) A related, acid-catalyzed, N-alkyl cleavage of amides is the subject of a recent paper by A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969).

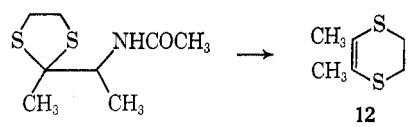
the identification of acetonitrile in the cyclization reaction (**5** → **7**).



11

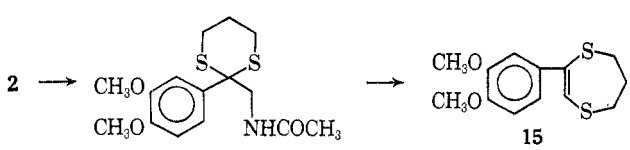
$$7 + CH_3CN + PO_3^-$$

The potential scope of this synthesis[10] is illustrated by the following reactions. The presence of an aromatic ring, perhaps expected to help stabilize the carbonium ion **9**, is not required since the dimethyldihydro-*p*-dithiin **12** can be prepared by this reaction.



13 **12**

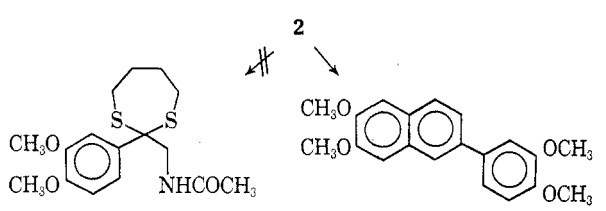
Nor is this synthesis restricted to the formation of six-membered rings; the propylene thioketal **14** leads to a dihydrodithiepin **15** under the usual reaction conditions. Even without an attempt having been made to



14 **15**

optimize the reaction conditions, this method appears competitive with other entries into the 1,4-dithiepane ring system.[11-13]

Preliminary efforts to utilize this synthetic method for the preparation of the 1,4-dithiocane ring system were unsuccessful. Attempts to prepare the required intermediate butylene thioketal **16** led to the napthalene derivative **17** previously obtained from acid-catalyzed reactions of compounds closely related to **2**.[14,15]



16 **17**

(10) Preparations of dihydro *p*-dithiins are summarized by D. S. Breslow and H. Skolnik in "The Chemistry of Heterocyclic Compounds," part II, Vol. 21, Interscience Publishers, Inc., New York, N. Y., 1966, p 1123.

(11) A. T. Bottini and E. F. Böttner, *J. Org. Chem.*, **31**, 586 (1966).

(12) E. G. Howard and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **82**, 158 (1960).

(13) (a) R. C. Fuson and A. J. Speziale, *ibid.*, **71**, 823 (1949). (b) After this paper was accepted for publication the preparation of a 1,4-dithiepane by a related rearrangement of a propylene thioketal was reported: J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).

(14) K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and K. K. Purushothaman, *J. Chem. Soc.*, 1144 (1957).

(15) M. Kawazu, *Yakugaku Zasshi*, **78**, 975 (1958); *Chem. Abstr.*, **53**, 4295c (1959).

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer and the ultraviolet spectra on a Cary 15 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 or A-60A instrument using $CHCl_3$ or $CDCl_3$ as solvent and tetramethylsilane as internal standard. Gas chromatography data was obtained using a Barber–Coleman 5000 gas chromatograph and a 6 ft × 0.125 in., 1% JXR silicone column. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2-Acetamido-3′,4′-dimethoxyacetophenone (2).—To a stirred solution of 36 g of α-ketohomoveratrylamine hydrochloride[16] in 80 ml of water at 5° was added 20 ml of acetic anhydride. Solid sodium carbonate was added until a heavy white precipitate formed, and the resultant mixture was allowed to stir for about 30 min. The slurry was diluted with 100 ml of water, and extracted with three 75-ml portions of chloroform. The combined extracts were washed with three 100-ml portions of water, dried first with saturated salt solution and then with anhydrous sodium sulfate, and the chloroform was removed on a rotary evaporator. Crystallization of the residue from benzene gave 28 g (85%) of **2**: mp 137–138°; ir ($CHCl_3$) 3310 (NH), 1680 (ArC=O), and 1640 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.3–3.2 (m, 4, ArH and NH), 5.25 (d, 2, J = 4 Hz, CH_2), 6.04 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), and 7.88 (s, 3, CH_3CO).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.9. Found: C, 60.9; H, 6.5; N, 6.0.

2-Acetamido-3′,4′-dimethoxyacetophenone Ethylene Ketal (4).—A solution of 6 g of **2**, 2.4 g of ethylene glycol, and 0.89 g of *p*-toluenesulfonic acid in 250 ml of benzene was heated under reflux for 18 hr while water was removed with a Dean–Stark tube. The cooled solution was washed with 100 ml of 2% NaOH, 100 ml of H_2O, and 50 ml of saturated salt solution and then dried over anhydrous Na_2SO_4. Evaporation of the benzene at reduced pressure gave a partially solidified oil, which on recrystallization from benzene gave 5 g (70%) of **4**: mp 137–138°; ir (KBr), 3290 (NH) and 1640 cm^{-1} (amide C=O); nmr ($CHCl_3$) τ 2.7–2.9 (m, 3, ArH), 3.35 (br, 1, NH), 6.03 (s, 6, OCH_3) 5.8–6.3 (m, 6, CH_2O and CH_2N), and 7.98 (s, 3, CH_3C=O).

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.8; N, 4.98. Found: C, 59.55; H, 6.72; N, 5.24.

2-Methyl-5-(3′,4′-dimethoxyphenyl)oxazole (3).—To a gently refluxing solution of 8.7 g of **4** in 300 ml of anhydrous pyridine was added four 25-g portions of P_2O_5 at 30-min intervals. After an additional 6 hr of heating under reflux, the reaction mixture was cooled, the dark brown pyridine layer was decanted, and the residue was washed with four 50-ml portions of hot pyridine. The combined pyridine layers were evaporated under reduced pressure and the residue was extracted with three 50-ml portions of hot benzene. The benzene-soluble portion contained 0.3 g (4%) of the previously reported[2c] but uncharacterized oxazole **3**: mp 102–103°; nmr ($CDCl_3$) τ 2.58–3.20 (m, 4, ArH), 6.04 (s, 3, OCH_3), 6.09 (s, 3, OCH_3), and 7.48 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.5; H, 6.0; N, 6.2.

2-Acetamido-3′,4′-dimethoxyacetopheneone Ethylene Thioketal (5).—A solution of 3.5 g of **2**, 0.5 g of *p*-toluenesulfonic acid, and 4 ml of 1,2-ethanedithiol in 125 ml of benzene was heated under reflux for 20 hr while water was removed with a Dean–Stark tube. The reaction mixture was worked up as described for **4** to give 3 g (65%) of **5**: mp 142–144°; ir ($CHCl_3$) 3380 (NH) and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.3–3.05 (m, 3, ArH), 3.62 (br, 1, NH), 5.85 (d, 2, $J \cong 6$ Hz, CH_2N), 5.95 (s, 3, OCH_3), 6.02 (s, 3, OCH_3), 6.49 (s, 4, SCH_2),[6] and 8.02 (s, 3, CH_3C=O).

Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47; S, 20.46. Found: C, 53.58; H, 6.12; N, 4.51; S, 20.60.

2,3-Dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin (7).—To a refluxing solution of 4 g of **5** in 200 ml of anhydrous pyridine were added four portions of 10 g of P_2O_5 and 50 g of sand, each at intervals of 30 min. The solution was decanted and the sand was washed with three 100-ml portions of pyridine. The combined pyridine layers were evaporated at reduced pressure and that portion of the residue soluble in 200 ml of hot benzene was

(16) H. D. Moed, M. Asscher, P. J. A. Van Draanen, and H. Niewind, *Rec. Trav. Chim. Pays-Bas*, **71**, 933 (1952).

filtered through a column of 30 g of Alcoa F-20 alumina to give 1.1 g (34%) of **7**: mp 85.2–86.2° after recrystallization from ether–hexane; ir no NH or C=O; nmr (CCl_4) τ 2.7–3.5 (m, 3, ArH), 3.53 (s, 1, C=CH), 6.03 (s, 3, OCH_3), 6.06 (s, 3, OCH_3), and 6.66 (s, 4, SCH_2);[6,7] uv max (95% EtOH) 308 mμ (ϵ 11,000) and 245 (sh, 8400).[17]

Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.54; S, 25.21. Found: C, 56.69; H, 5.78; S, 25.49.

Another reaction was carried out in essentially the same way as above, except that after separation of the sand and pyridine by decantation, the pyridine was distilled at atmospheric pressure and the distillates were analyzed by gas chromatography and infrared spectroscopy. A compound with a retention time corresponding with that of authentic acetonitrile on three different gas chromatography columns (15 ft × 0.125 in., 7% Apiezon L; 6 ft × 0.125 in., 1% JXR methyl silicone; and 6 ft × 0.125 in., 2% Epon 1001) was detected. The infrared spectrum of the first pyridine distillate, with a pyridine reference, contained absorptions at 2260 (C≡N) and 920 cm^{-1}, present in the spectrum of authentic acetonitrile.

2,3-Dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin-1,1,4,4-tetroxide (8).—A mixture of 1 g of **7**, 2 ml of 30% H_2O_2, and 5 ml of glacial acetic acid was heated at 30° for 48 hr. The crystals of **8** which formed melted at 253–254° after recrystallization from glacial acetic acid.

Anal. Calcd for $C_{12}H_{14}O_6S_2$: C, 45.3; H, 4.41. Found: C, 45.23; H, 4.42.

3-Acetamido-2-butanone Ethylene Thioketal (13).—With the procedure previously described for the preparation of **5**, compound **13** was obtained from 1,2-ethanedithiol and 3-acetamido-2-butanone[18] as crystals: mp 106–107° from ether–hexane; ir ($CHCl_3$) 3400 (NH) and 1640 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 3.8–4.2 (br, 1, NH), 5.55 (d of q, 1, J_d = 9.5 Hz, J_q = 6.3 Hz, CH), 6.65 (s, 4, CH_2S),[6] 7.98 (s, 3, CH_3C=O), 8.20 [s, 3, $CH_3C(S)S$], 8.70 (d, 3, J = 6.3 Hz, CH_3C).

Anal. Calcd for $C_8H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.83; S, 31.2. Found: C, 46.7; H, 7.5; N, 6.6; S, 31.5.

2,3-Dihydro-5,6-dimethyl-*p*-dithiin (12).—With the procedure described for the preparation of **7**, compound **12** was obtained in 42% yield as a clear liquid: bp 113–114° (25 mm); ir (film) no NH or carbonyl; nmr ($CDCl_3$) τ 6.85 (s, 4, CH_2S)[6] and 8.12 (s, 6, CH_3).

Anal. Calcd for $C_6H_{10}S_2$: C, 49.3; H, 6.9; S, 43.9. Found: C, 49.1; H, 7.2; S, 43.6.

2-Acetamido-3′,4′-dimethoxyacetophenone Propylene Thioketal (14).—With the procedure described for the preparation of **5**, compound **14** was obtained in *ca.* 65% yield from **2** and 1,3-propanedithiol as crystals: mp 109–111° from ether–hexane; ir ($CHCl_3$) 3350 (NH) and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.55–3.20 (m, 3, ArH), 4.1 (br, 1, NH), *ca.* 6.0 (partially obscured d, 2, CH_2N), 6.10 (s, 6, OCH_3), 6.5–7.8 (m, 4, SCH_2), 8.0 (m, 2, CCH_2C), and 8.06 (s, 3, CH_3C=O).

Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.1; H, 6.46; S, 19.58. Found: C, 55.25; H, 6.41; S, 19.67.

2-(3′,4′-Dimethoxyphenyl)-6,7-dihydro-5H-1,4-dithiepin (15).—From 4 g of **14** treated as described for the preparation of **7** was obtained, after chromatography through alumina, 2.07 g of recovered **14** and 0.54 g (34%) of compound **15**: mp 101–103°; ir no NH or carbonyl; nmr ($CDCl_3$) τ 2.8–3.3 (m, 3, ArH), 3.91 (s, 1, C=CH), 6.10 (s, OCH_3), 6.38 (t, 4, J = 6 Hz, CH_2S), and 7.81 (quintuplet, 2, J = 6 Hz, CCH_2C).

Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.17; H, 6.01; S, 23.89. Found: C, 58.28; H, 6.07; S, 23.90.

6-(3′,4′-Dimethoxyphenyl)-2,3-dimethoxynaphthalene (17).—A solution of 6 g of **2**, 6 ml of 1,4-butanedithiol, and 1 g of *p*-toluenesulfonic acid in 250 ml of dry benzene was heated under reflux for 10 hr while water was removed with a Dean–Stark tube. The reaction mixture was washed with successive 100-ml portions of 1 *M* NaOH, H_2O, and saturated NaCl solutions and dried over anhydrous Na_2SO_4, and the solvent was removed at reduced pressure. The residue was chromatographed through 60 g of Alcoa F-20 alumina to give 4 g (96%) of **17** as white flakes: mp 179–180° (lit.[19] mp 179–180°); ir no NH or carbonyl; nmr ($CDCl_3$) τ 2.1–3.3 (m, 8, ArH), 6.08 (s, 3, OCH_3), and 6.18 (s, 9, OCH_3); mass spectrum parent peak 324 (calcd mol wt, 324).

(17) For 2,5-diphenyl-*p*-dithiin, uv max 309 mμ (ϵ 8900) and 259 (22,100): W. E. Parham and V. J. Traynelis, *J. Amer. Chem. Soc.*, **76**, 4960 (1954).

(18) R. H. Wiley and O. H. Borum, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 5.

Registry No.—**2**, 5190-84-1; **3**, 22796-22-1; **4**, 22796-21-0; **5**, 22796-23-2; **7**, 22796-24-3; **8**, 22796-25-4; **12**, 22796-26-5; **13**, 22796-27-6; **14**, 22796-28-7; **15**, 22796-29-8.

Acknowledgment.—This investigation was supported by the Texas Christian University Research Foundation. The authors wish to thank George Grins for helpful discussions.

(19) J. Cunningham, E. Hoslum, and R. D. Haworth, *J. Chem. Soc.*, 2875 (1963).

Synthesis of Substituted 1-Styryl-3,4-dihydroisoquinolines

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Received June 20, 1966

The conventional methods for the synthesis of 1-styrylisoquinoline or its derivatives center around two main approaches, the cyclization of the Schiff bases derived from cinnamaldehyde[1] or the condensation of 1-methylisoquinoline with aromatic aldehydes.[2] However, both of these syntheses leave the isoquinoline nucleus either completely saturated or unsaturated in the heterocyclic ring. Because of the possible usefulness of substituted 1-styryl-3,4-dihydroisoquinolines as intermediates in organic syntheses, we have developed a rather convenient method for the preparation of these compounds. The procedure involves the cyclodehydration of substituted β-phenethylamides to 3,4-dihydroisoquinolines through the Bischler–Napieralski reaction.[3]

The substituted β,β-diarylacryl chlorides **1a–1e** were prepared by the reaction of 1,1-diarylethylenes and oxalyl chloride.[4] The acid chlorides **1f–h** were prepared by treating the corresponding carboxylic acids (the *trans* acid **1f** was prepared by the procedure of Lipkin and Stewart,[5] whereas the acids **1g** and **1h** were commercially available) with thionyl chloride. The acid chloride **1b** was a mixture of *cis* and *trans* isomers, whereas **1g** and **1f** were *trans* isomers. Treatment of **1** with β-(3,4-dimethoxyphenyl)ethylamine (**2**) in the presence of sodium hydroxide afforded the amides **3**. The cyclodehydration of **3** to the corresponding substituted 1-styryl-3,4-dihydroisoquinolines **4** was achieved by using phosphorus oxychloride. It was possible to isolate the compounds **4** as such, but for the sake of identification they were converted into crystal-

(1) E. C. Weinbach and W. H. Hartung, *J. Org. Chem.*, **15**, 676 (1950); W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1962).

(2) W. H. Mills and J. L. B. Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(3) T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *J. Chem. Soc., C*, 874 (1969).

(4) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowicz, *J. Amer. Chem. Soc.*, **70**, 1612 (1948).

(5) D. Lipkin and T. D. Stewart, *ibid.*, **61**, 3295 (1939).