SELENIUM DIOXIDE OXIDATIONS IN THE β-CARBOLINE AREA

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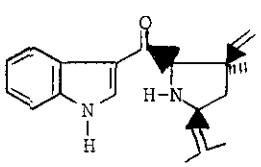
Abstract ----- The reaction of 1-ethyl-3-methoxycarbonyl-1, 2,3,4-tetrahydro-β-carboline 11 with selenium dioxide has resulted in the synthesis of the β-carboline alkaloids, 1-acetyl-3-methoxycarbonyl - β-carboline 14 and 1-acetyl-β-carboline 15. Application of this technology in a different series has resulted in a two step synthesis of canthin-6-one. The scope and/or limitations of the reaction of tetrahydro-β-carbolines with selenium dioxide are discussed.

Although there are relatively few methods available for the preparation of 3-acylindoles, most notable for the present discussion are the thioketal approach of Stadler,[1] the DDQ method developed by Yonemitsu[2] and the work with selenium dioxide,[3] the recent isolation of several natural products which contain the 3-acylindole moiety has stimulated additional interest in this area. Alkaloids of particular importance are borrecapine 1,[4] aristotelinone 2,[5] crenatine 3,[6] 1-methoxy-canthin-6-one[7] and pimprinine.[8] The latter base was synthesized by Joshi,[9] and more recently by Yonemitsu (DDQ technology).[10]



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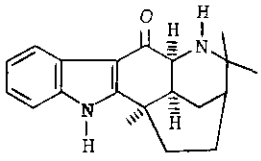

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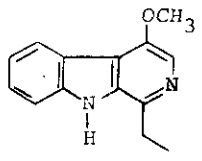

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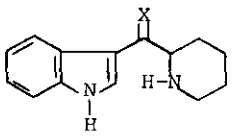
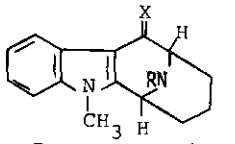
Recently we have shown[3] that the indole piperido base 4 could be converted to the 3-acylindole 5 or to the 3-acylpyridoindole 6 in good to excellent yields

on treatment with selenium dioxide, as illustrated in Scheme I. Moreover, this technology was employed to transform the tetracyclic indole derivative 7 into the desired 3-acylindole 8 in better than 50% yield; however, all attempts to convert 7 to 8 in high yield were unsuccessful. Two experimental parameters, in particular, may be employed to shed some light on the failure to convert 7 to 8 in high yield. After the oxidation (SeO_2, dioxane, Δ) of 7 has been completed, benzaldehyde has been isolated from the reaction mixture. This may result from the oxidation of the N_b-benzyl function to an imine followed by hydrolysis, or might arise from direct oxidation of the N_b-benzyl group to a carbinolamine followed by cleavage of the N_b-C bond. Furthermore, during this oxidation selenious acid is produced[11] which may form a salt either with 7 or 8 resulting in a loss of material and yield. To test this hypothesis the N_b-benzyl compound 7 was subjected to catalytic debenzylation [H_2, Pd/C(10%), 50psi, 7 days] and the product transformed to the N_b-benzamide derivative 9

Scheme I



4, X=H_2
5, X=O
6, X=O, 3-pyrido derivative.



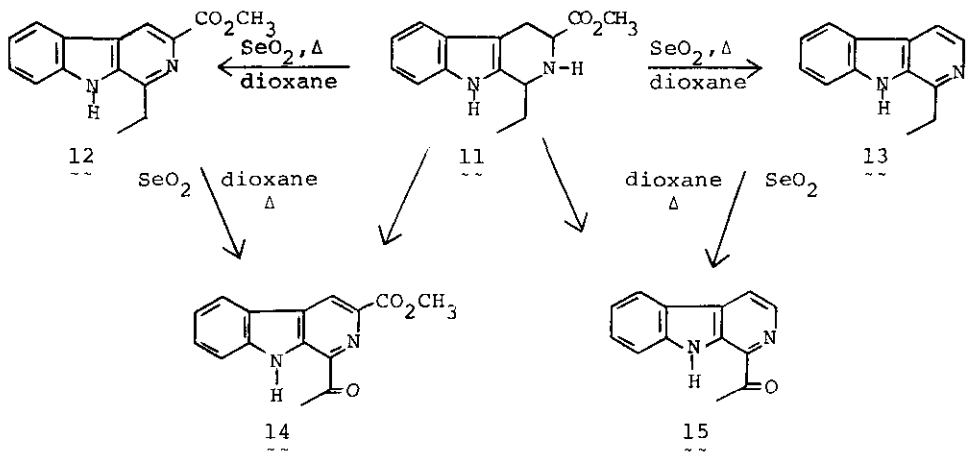
7, X=H_2, R=CH_2Ph
8, X=O, R=CH_2Ph
9, X=H_2, R=$\overset{O}{\overset{\|}{C}}Ph$
10, X=O, R=$\overset{O}{\overset{\|}{C}}Ph$

by treatment with benzoylchloride in pyridine. When the tetracyclic benzamide 9 was heated with selenium dioxide in dioxane, analogous to the conditions for the conversion of 7 to 8[3] a 90% yield of the 3-acylindole 10[12] was realized. Similar observations (DDQ) have been made by the group in Japan during the synthesis of pimprinine.[10]

In order to examine the scope of the selenium dioxide oxidation, it was decided to synthesize a number of tetrahydro-ß-carbolines, and subject them to treatment with the oxidizing agent in refluxing dioxane. For this purpose, 1-ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-ß-carboline 11 was prepared by a Pictet-Spengler condensation of tryptophan methyl ester with propionaldehyde.[13,14] After the 1-ethyl derivative 11 (see Scheme II) had been heated with selenium dioxide in refluxing dioxane for fourteen hours, four ß-carbolines

were isolated from the mixture. The bases were identified as 1-ethyl-3-methoxycarbonyl-β-carboline 12[15] 1-ethyl-β-carboline 13,[16] 1-acetyl-3-methoxycarbonyl-β-carboline 14[17] and 1-acetyl-β-carboline 15.[18] The structures of these materials were confirmed by spectral data and by comparison of the physical properties of the β-carbolines to those reported in the literature (see References and Notes). The major product (32%) of this sequence was the indole alkaloid, 1-acetyl-3-methoxycarbonyl-β-carboline 14, recently isolated from Vestia lycioides Wild by Faini and Castillo.[17] The base 14 has been prepared by Faini et al., albeit in low yield, and was also synthesized previously in our laboratories, although the route was more complex[19] than the two step process described here. The other β-carbolines 12, 13 and 15, including the alkaloid 1-acetyl-β-carboline 15, recently found in Ailanthus malabarica by

Scheme II



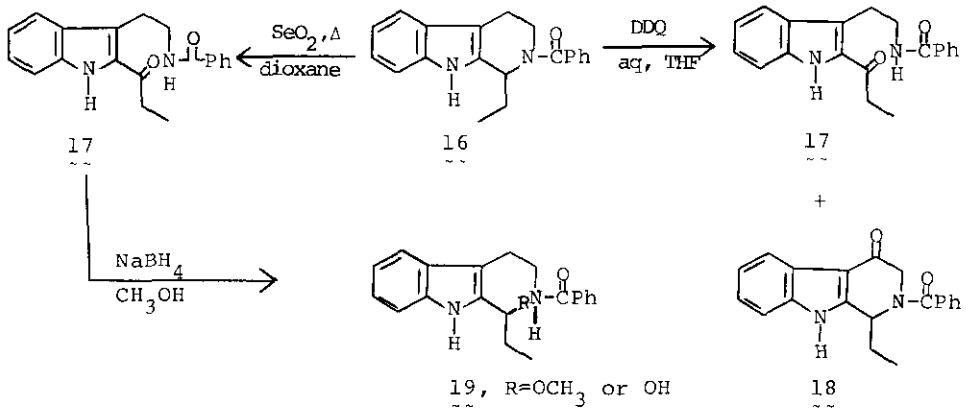
Joshi,[18] were obtained in approximately equal amounts (total, 39%).

Apparently the first step in the oxidation of 11 is the aromatization of ring C to the β-carboline which is not unexpected in view of the 14π electron system which results from such an event. In addition, both 12 and 13 have been shown to be the precursors for 14 and 15 respectively for treatment of 12 with selenium dioxide yielded 14 while heating 13 under the same conditions provided 15 in good yield.

Because of the propensity with which tetrahydro-β-carbolines undergo aromatization to β-carbolines, it was decided to modify the tetrahydro-β-carboline to prevent this oxidation. Tryptamine was reacted with propionaldehyde

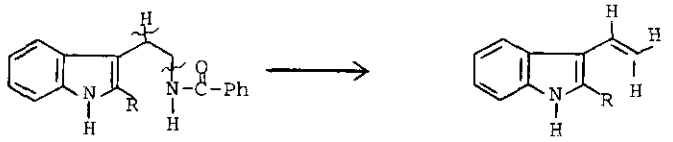
under acidic conditions and the 1-ethyl-1,2,3,4-tetrahydro-β-carboline which formed was converted immediately to the benzamide derivative 16[20] to prevent air oxidation and conversion to 1-ethyl-β-carboline 13. Treatment of 16 with selenium dioxide (6 1/2 hrs) under conditions identical to those discussed above provided a ninety percent yield of the ketoamide 17.[21] The structure of

Scheme III



17 16 17 + 19, R=OCH_3 or OH 18

17 was deduced from spectral data[21] with particular emphasis placed on analogies between the C-13 and mass spectra of 17 with those of N_b-benzoyl tryptamine 20



17, R= 20, R=H 21a, R= (199) 21b, R=H (143)

(mp 138-9°). Loss of the units of PhCONH,H from both 17 and 20 provided the base peak in the spectra of both molecules at 199amu and 143amu, respectively, moreover the ion at 105amu could be assigned to the benzoyl group and was found in the spectrum of 17 and 20. In addition, the benzamide carbonyl which appeared at 167.50 ppm in the carbon spectrum of 20 was also observed at 167.96 ppm in the spectrum of 17. Moreover, reduction of 17 with sodium borohydride, as illustrated in Scheme III, proceeded smoothly to provide a mixture of the methyl ether 19 and the corresponding alcohol (see Reference

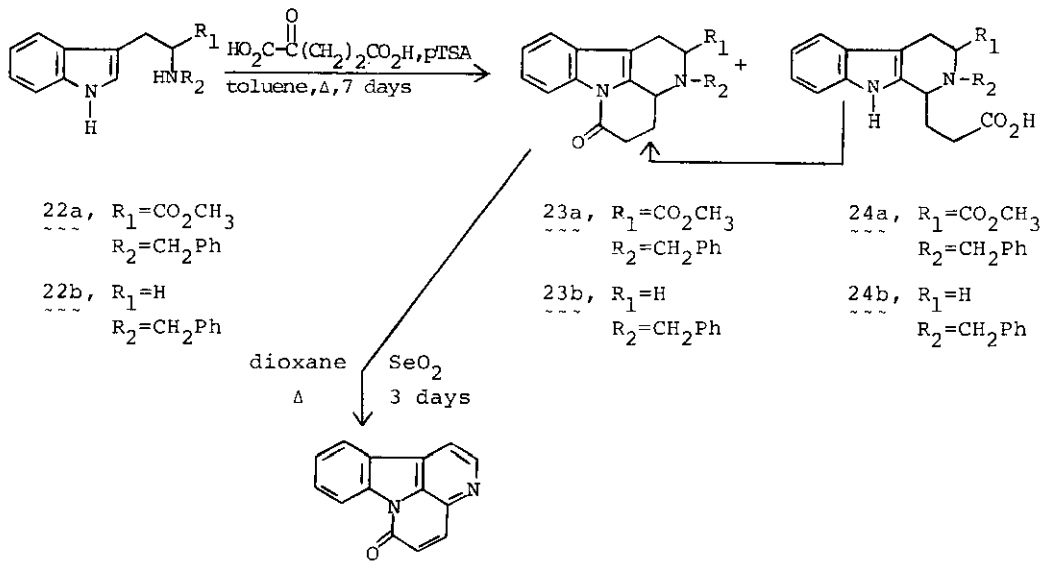
22) with concomitant disappearance of the carbonyl resonance at 194.45 ppm, previously (C-13 nmr) assigned to the keto function of 17.

The oxidation of 16 at position -1 of the tetrahydro-β-carboline is in sharp contrast to the formation of the 3-acylindoles 5, 6, 8, and 10 depicted in Scheme I. The differences in reactivity, however, are not difficult to rationalize for the bases 4, 5 and 6 have no alkyl substituent at position -2 of the indole. Moreover the strain (geometry) inherent in the bicyclononane skeleton of 7 and the tetracyclic bases 7 and 9 prohibits planarity at the indole-2-alkyl position, therefore, precluding this oxidation in favor of the formation of 3-acylindoles 8 and 10.

At this juncture, it was decided to treat 16 with dichlorodicyanobenzoquinone in aqueous tetrahydrofuran, according to the method developed by Oikawa and Yonemitsu,[2] a technology previously employed in our laboratory to prepare the β-carboline antibiotic, pyridindolol.[19] Treatment of 16 with DDQ under a variety of conditions always furnished a mixture of the ketoamide 17 and the desired 3-acylindole 18.[23] Generally, the ratio of 17 to 18 increased with increasing temperature (room temperature, 41% 17, 47% 18, overall yield-94%) while the best yield of 18 was obtained when the oxidation was carried out at 0°C (33% 17, 66% 18, overall yield 75%). The structure of the 3-acylindole[18] was determined from ir, proton nmr, and mass spectrometry and corroborated by CMR spectroscopy (see reference 23 for details).

Finally, we would like to describe a two step synthesis of the alkaloid canthin-6-one 25 which has been isolated from several species of plants.[24] The preparation of this material was based upon observations made in our laboratory on the Pictet-Spengler reaction (aprotic media) in 1976.[25] It was found that when 22a was refluxed with α-ketoglutaric acid for several days both the lactam 23a and the monoacid 24a were formed;[25] moreover, on heating 24a under analogous conditions more of the lactam 23a was formed. Simple extrapolation of this technology, to the case of N_b-benzyl tryptamine 22b provided the desired lactam 23b[26] in 82% yield when the reaction mixture was heated for seven days. A mixture of 23b and 24b[27] was obtained when the time of reaction was held to six days or less; however, 24b, in this case, was converted to 23b by heating the reactants for seven days in the same medium (yield 79%). Since benzaldehyde had been recovered from the selenium

Scheme IV



25

dioxide oxidation of 7, it was decided to omit the previously planned conversion of 23b to the N_b-H derivative (R_1=R_2=H) and to subject the lactam 23b directly to this oxidation thereby sacrificing yield but eliminating a synthetic step. Treatment of 23b with selenium dioxide in refluxing dioxane for three days did indeed provide a 30 to 40% yield of canthin-6-one 25[28] accompanied also by benzaldehyde, as predicted. There have been several syntheses of 25 reported in the literature (see reference 29); however, to this authors knowledge the two step process outlined in Scheme IV is the shortest to date. Although red selenium is difficult to remove from the reaction medium, it can be converted to black selenium and filtered from the reaction mixture by following procedures previously reported (see Citation 15, Reference 3 for Details).

The use of selenium dioxide and dichlorodicyanoquinone for construction of alkaloids derived from, or related to 3-acylindoles is underway in our laboratory and will be reported on in due course.

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12. 10: mp 171-3°; ir (KBr) 1660 and 1635 cm^{-1}; nmr ($CDCl_3$) δ 1.50-2.00 (m, 6H), 3.56, 3.66 (two singlets, 3H, rotomers), 4.35 (s, broad, 1H), 6.15 (s, broad, 1H), 7.30 (m, 8H), 8.10 (M, 1H). Mass spectrum (C.I., NH_3) 345 (M + 1, 100). The structure of this material was confirmed by comparison of the spectral data for 10 with those of 8, including carbon spectroscopy.

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15. 12: mp 209-211°C; ir (KBr) 3340, 3050 and 1705 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (t, 3H, J=7Hz) 3.07 (q, 2H, J=7Hz), 3.98 (s, 3H), 7.10-7.60 (m, 3H), 8.13 (d, 1H, J=7Hz), 8.68 (s, 1H), 9.83 (s, 1H); mass spectrum (70 eV) 254 (M^+, 100). Treatment of 11 with Pd/C, cumene, Δ also provided 12.

16. 13: mp 192-194°, lit mp 192-194°C; ir (KBr)3440, 3120 and 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (t, 3H, J=7.5Hz), 3.20 (q, 2H, J=7.5 Hz), 7.20 - 7.70 (m, 3H), 7.83 (d, 1H, J=6.0 Hz), 8.18 (d, 1H, J=8.0 Hz) 8.42 (d, 1H, J=

6.0 Hz), 8.93 (s, broad, 1H); mass spectrum (70 ev) 196 (M^+, 80). Literature reference - W. H. Müller, R. Preub, and E. Winterfeldt, Chem. Ber., 1977, 110, 2424; S. Bamgbose, K. Drmane and J. Okogun, Planta Medica, 1977, 31, 193.

17. 14: mp 228-230°, lit. mp 234-236°, ir (KBr) 3400, 3180, 1710, 1670 and 1625 cm^{-1}; nmr ($CDCl_3$) δ 2.90 (s, 3H), 4.05 (s, 3H) 7.20-7.70 (m, 3H), 8.15 (d, 1H, J=8.0 Hz); 10.50 (s, 1H); mass spectrum (70 ev) 268 (M^+, 100). Literature reference - F. Faini, M. Castillo, and R. Torres, Phytochem, 1978, 17, 175.

18. 15: mp 216-217°, lit. mp 203-5°; ir (KBr) 3340 and 1640 cm^{-1}; nmr ($CDCl_3$) δ 2.90 (S, 3H), 7.30-7.60 (m, 4H), 8.20 (d, 1H, J=5.0 Hz),8.60 (d, 1H, J=5.0 Hz), 10.60 (s, broad, 1H); mass spectrum (70 eV) 210 (M^+, 92), 168 (100). Literature reference - B. S. Joshi, V. N. Kamat, and D. H. Gawad, Heterocycles, 1977, 7, 193.

19. G. Wu, E. Yamanaka, and J. M. Cook, Heterocycles, 1978, 9, 175.

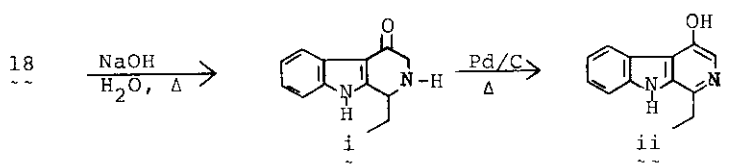
20. 16: mp 166-168°; yield 85.3%; ir (KBr) 3265 and 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (t, 3H, J=7Hz), 2.00 (m, 2H), 2.78 (m, 2H), 3.00-4.10 (m, 2H), 5.90 (m, 1H), 6.80-7.80 (m, 9H), 8.60 (m, 1H). Mass spectrum (C.I., NH_3) 305 (M + 1, 100).

21. 17: mp 191-192°, ir (KBr) 3395, 3310, 1640, 1615 (shoulder) and 1580 cm^{-1}; nmr (pyridine-d_5) δ 1.20 (t, 3H, J=6Hz), 3.10 (q, 2H, J=6Hz), 3.85 (m, 4.5 H), 4.85 (s, 0.5H), 7.00-8.65 (m, 9H), 9.15 (s, broad, 0.5H), 12.35 (s, broad, 0.5H). The signals at 4.85, 9.15 and 12.35 δ dissappeared on addition of D_2O to the sample, moreover, a portion (0.5H) of the signal at 3.85 δ also vanished. Mass spectrum (70 ev), 320 (M^+, 10) 199 (100), 158 (44), 105 (72) and 77 (61); nmr (C-13 , pyridine-d_5), 8.30 (34), 26.10 (30), 33.93 (49), 41.75 (37), 112.80 (33), 120.37 (56), 121.58 (57), 126.04 (30), 127.93 (109), 128.66 (105), 127.50 (below threshold), 129.14 (25), 131.34 (43), 133.26 (15), 136.10 (below threshold), 137.48 (12), 167.96 (27, N-C(=O)-) and 194.45 (30, ketone).

22. 19: nmr ($CDCl_3$) δ, 0.85 (t, 3H, J=7.5 Hz), 1.80 (m, 2H), 3.00 (m, 2H), 3.14 (s, OCH_3), 3.67 (m, 2H), 4.40 (t, 1H, J=7.5Hz), 6.50 (m, 1H), 7.00-7.80 (m, 8H) and 8.60 (s, 1H); C-13 nmr ($CDCl_3$). In comparison with the spectrum of 17, new signals at 56.34 (24, OCH_3) and 67.87 (9,-CHOR)

appeared in the spectrum of 19 while the carbonyl signal at 194.45 ppm, was absent, moreover, the amide carbonyl resonance line remained (167.71, N-C(=O)-). This material was obtained as the methoxy derivative 19 contaminated somewhat with the corresponding alcohol 19 (R=H).

23. 18: mp 130°, ir (KBr) 3200, 1640 and 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (t), 2.10 (m), 4.30 (s, broad), 6.40 (t), 7.00-7.60 (m, 8H), 8.10 (m, 1H), 11.25 (s, 1H, D_2O exchangeable); mass spectrum (70 ev), 318 (M^+, 71.8), 289 (44), 213 (60) and 105 (100); C-13 nmr ($CDCl_3$) 10.77 (21, q), 26.54 (23, t), 50.14 (23, d), 52.39 (17, t), 109.99 (23, s), 111.58 (49, d), 121.09 (52, d), 122.72 (43, d), 123.78 (95, d), 126.66 (69, d), 128.06 (12, s), 128.78 (119, d), 130.34 (35, d), 134.76 (42, s), 136.16 (19, s) 151.86 (22, s), 171.63 (30, s, N-C(=O)-), 186.14 (20, s, ketone at C-4). The structure of the 4-Oxo-tetrahydro-β-carboline 18 has been further substantiated by its conversion to desmethoxycrenatine ii as illustrated below:



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26. 23b: mp 170-173°C; ir (KBr) 1685 cm^{-1}; nmr δ ($CDCl_3$) 1.60-2.20 (m, 1H), 2.20-2.95 (m, 6H), 3.28 (d overlapping m, 3H, J_d=14 Hz), 4.10 (d, 1H, J=14 Hz), 7.15-7.40 (m, 8H), 8.30 (m, 1H). Mass spectrum (70 ev), 316 (M^+, 15), 315 (12), 259 (10), 196 (100), 167 (30), 153 (10), 91 (55).

27. 24b: mp 140-144°C; ir (KBr) 3600-2700 (broad envelope), 1700 shoulder, and 1600 cm^{-1}, nmr (DMSO) δ 1.80-2.80 (m, 8H), 3.70 (s, broad, 3H), 6.80-7.40 (m, 10H); mass spectrum (CI, NH_3) 335 (M + 1, 100). The monoacid was converted to the lactam 23b in 79% yield when the acid was heated for seven days in refluxing toluene/dioxane in the presence of p-toluenesulfonic acid. For a similar sequence in the case of N_b-benzyltryptophan methyl ester see J. Sandrin et al., Heterocycles, 1976, 4, 1101.

23. 25: Canthin-6-one; mp 152°, lit,[24] 160-1°; ir (KBr) 1670 cm^{-1}; nmr ($CDCl_3$) 6.78 (1H, d, J=9Hz), 7.20-8.10 (5H, m), 8.40 (1H, dd, J_1=9Hz, J_2=2Hz) 8.50 (1H, m). Mass spectrum (C.I., NH_3) 221 (M + 1, 100); C-13 nmr ($CDCl_3$) 116.02 (d), 117.08 (d), 122.37 (d), 124.20 (s), 125.39 (d), 128.13 (s), 128.75 (d), 192.81 (s), 130.06 (s), 130.63 (d), 136.06 (s), 139.28 (d), 145.50 (d), 159.18 (s).

29. For other syntheses of 25 see H. J. Rosenkranz, G. Batyos, and H. Schmid, Liebigs Ann. Chem., 1966, 691, 159; L. A. Mitscher, M. Shipchandler, H. D. H. Showalter and M. S. Bathala, Heterocycles, 1975, 3, 1; R. Oehl G. Lenzer and P. Rosemund, Chem. Ber., 1976, 109, 705.

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