A MODIFIED BISCHLER SYNTHESIS OF SOME TETRACYCLIC INDOLE DERIVATIVES

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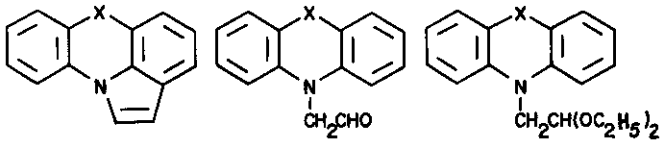
Abstract - The synthesis of 6,7-dihydro-5H-indolo[1,7-ab][1]benzazepine, 5H-indolo-[1,7-ab][1]benzazepine, pyrrolo[3,2,1-kl]phenothiazine and 1-phenylindole was accomplished by cyclization of the corresponding diarylaminoacetaldehydes. Carbazole-9-acetaldehyde gave 2,4-dicarbazol-9-yl-2-butenal. The aldehydes were obtained by acid catalyzed hydrolysis of the corresponding diethyl acetals, which differed considerably in their relative hydrolysis rates.

In connection with work on the synthesis of conformationally restricted tranquilizers and antidepressants, we were interested in developing a convenient synthesis of the tetracyclic indole derivatives 1 (Table 1) as precursers. We planned to prepare 1 via an acid catalyzed cyclization of the diarylamino-acetaldehydes 2 in a modification of the well known Bischler indole synthesis.[1] Most of the reported reactions of this type utilize a one step reaction of an bromo-ketone with an aniline derivative and usually require relatively vigorous conditions. Few examples of successful Bischler reactions using α-bromo-aldehydes (or the equivalent) have been reported presumably owing to the acid instabilities of both the aldehyde and the indole product. Two step versions of such reactions have been studied extensively by Chastrette,[2] who concluded that an α-alkyl group in the aldehyde was required to prevent polymerization and thereby give satisfactory yield of indole. It was anticipated that the vigorous conditions normally required for the classical one step Bischler reaction could be avoided by utilizing a procedure wherein the diethyl (or dimethyl) acetals 3 are first formed, hydrolyzed to 2 and subsequently cyclized to 1.

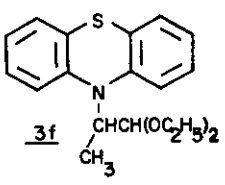
The reported synthesis of pyrrolo[3,2,1-kl]phenothiazine (1_d) by polyphosphoric acid catalyzed cyclization of phenothiazine-10-acetaldehyde (2_d) in chloroform[3] encouraged us to believe that this type of reaction might be more general. However, numerous attempts to repeat this reaction under the literature or other (phosphoric acid, polyphosphoric ester, phosphorous pentoxide, trifluoroacetic acid, boron trifluoride etherate, zinc chloride, p-toluenesulfonic acid) conditions gave, in our hands, only low yields (10-15%) of 1_d and considerable amounts of tar. Since 2_d is apparently relatively stable under acidic conditions,[3] the tars formed must result from acid catalyzed polymerization of 1_d.[4] We, therefore, sought milder and more reliable procedures for the cyclization of the acetaldehyde derivatives (2 a-d) which would

not polymerize the acid sensitive indoles (1 a-d) formed. Recently, we have described the synthesis and spectral properties of indolo[1,7-ab] [1] benzazepine (1c),[5] which was prepared by molecular sieve (5A° Linde) catalyzed cyclization of 5H-dibenz[b,f]azepine-5-acetaldehyde (2c). This report describes the use of molecular sieve for the synthesis of the acid sensitive indoles 1 from the corresponding aldehydes 2 (or acetals, 3). Some observations concerning the relative rates of hydrolysis of the acetals 3 will also be discussed.

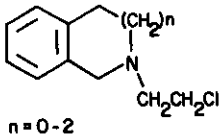
We found that the compounds 1a - 1d (see table 1) could be obtained in high yields via cyclization of the corresponding diarylaminoacetaldehydes 2a - 2d. The cyclization occurred smoothly under acetal hydrolysis conditions from the acetals 3a - 3c. The phenothiazine-10-acetaldehyde 2d was intact under these conditions, but could be cyclized in high yield at room temperature using molecular sieve in toluene. Also the aldehydes 2a and 2c were converted to the indoles (1a and 1c) with molecular sieve at room temperature in high yield while the carbazole-9-acetaldehyde (2e) did not react. Reflux for two days gave the condensation product 4 but no cyclized product 1e was traced.



BRIDGING GROUP X			
H, H	1 (a)	2 (a)	3 (a)
CH_2CH_2	(b)	(b)	(b)
CH=CH	(c)	(c)	(c)
S	(d)	(d)	(d)
VALENCE LINE	(e)	(e)	(e)

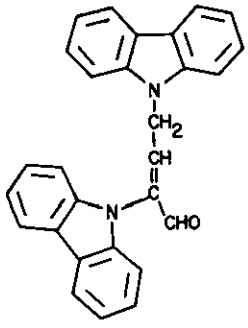


3f



n=0-2

5



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The acetals 3a -3e were obtained in good yields after alkylation with 2-bromoacetaldehyde diethylacetal with the sodium salts of the corresponding amines in refluxing dioxane. Attempted alkylation of the sodium salt of phenothiazine with 2-bromopropionaldehyde diethylacetal gave no alkylated product under these conditions. When the more nonpolar solvent toluene was employed, however 3f could be obtained but in a very low yield (9%).[6]

The hydrolyses of the acetals were performed with p-toluenesulfonic acid in aqueous acetone and the rates of hydrolysis were found to differ considerably depending on the substrate used. Almost all diphenylamine acetaldehyde diethylacetal (3a) was converted to the corresponding aldehyde (2a) after 20 minutes at room temperature, while carbazole-9-acetaldehyde diethylacetal (3e) was not hydrolysed at all after 16 hours. The 10,11-dihydro-5H-dibenz[b,f]azepine derivative 3b hydrolyzed with approximately the same rate as the diphenylamine derivative 3a while the 5H-dibenz[b,f]azepine 3c was hydrolysed slightly slower. After 20 minutes at room temperature, 65% of the acetal 3c still remained unreacted. The phenothiazine derivative (3d) was found to hydrolyze much slower than either 3b or 3c. After 16 hours at room temperature 60% of the starting material 3d remained, but it was hydrolysed considerably faster than the corresponding carbazole derivative (3e).

The hydrolysis of acetals has been studied in detail.[7-10] Kinetic studies reveal, with few exceptions, that the rate determining step is the formation of the oxocarbonium ion intermediate. Speck et al. suggested [11] that the acid catalyzed hydrolysis of methylthioacetaldehyde diethylacetal occurs with neighboring group participation of the methylthio function and that the formation of a cyclic sulfonium ion must be rate-determining. We prefer to explain our differences in hydrolysis rates by the assumption that a "aziridinium ion like" species might lie on the reaction coordinate. The larger the central ring the more stable the ion and the faster rate of hydrolysis. This explanation fits well with our results and is in close analogy to the discussion on the ring size dependence in the cyclization of various α-chloro-ethylamines 5 to ethylenimmonium ions described by Belleau.[12] However, we can not exclude the possibility that a protonated neighboring nitrogen is involved in the rate determining step.

The rate of cyclization of the aldehydes 2a - 2e formed after hydrolysis, differed considerably. The 10,11-dihydro-5H-dibenz[b,f]azepine-5-acetaldehyde cyclized very fast under hydrolysis conditions and was not isolated. Both 2a and 2c were also cyclized at room temperature under acetal hydrolyzing conditions providing prolonged reaction times were used. Cyclization of 2a with molecular sieve gave a high yield of 1-phenylindole after 2 hours, while 16 hours were required to transform 2c to indolo[1,7-ab][1]benzazepine (1c). Pyrrolo[3,2,1-kl]phenothiazine (1d) was isolated in high yield from 2d after reaction with molecular sieve for 4 days. Only a very small amount of tar was formed under these conditions. The mild procedure described above seems to be a valuable alternative when acid sensitive indole derivatives are formed after cyclization of aldehydes.

Some years ago it was reported that carbazole-9-acetaldehyde 2e underwent condensation on alumina to give various products but no cyclized product was reported.[13] It is also known that acid catalyzed condensation of the aldehyde gives polymers.[14] Applying our molecular sieve conditions to the carbazole system gave only starting material 2e after several days at room temperature. Refluxing the mixture for two days gave, in addition to the aldehyde 2e, the aldol condensation product 4 in moderate yield with the same melting point and spectral data as the major product formed in the alumina catalyzed reaction.[13]

EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Varian EM360L spectrometer using tetramethylsilane as an internal standard and the high resolution mass spectra on a Varian MAT 311A double focusing mass spectrometer.

Preparation of the arylaminoacetaldehyde diethylacetals 3a - 3f. Purified 10,11-dihydro-5H-dibenz[b,f] azepine, diphenylamine, 5H-dibenz [b,f] azepine, phenothiazine or carbazole (20mmol) was added at room temperature to a solution of sodium hydride (95 mmol) in dry dioxane (50 ml). After reflux for 4 hr 2-bromoacetaldehyde diethylacetal (6.5ml) was added dropwise to the vigourously stirred mixture during a period of 1 hr and under maintained reflux. After reflux over night in argon atmosphere the excess sodium hydride was destroyed by ethanol and the reaction mixture was then poured into toluene and water. The aqueous phase was extracted several times with toluene and the combined organic phases were washed with water, dried ($MgSO_4$) and evaporated to give the crude acetals. After chromatography (silica, toluene) 3a - 3e were obtained as oils. According to NMR analyses the compounds were pure and were used without further purification. Compound 3f was prepared by the same procedure using toluene as the solvent.

10,11-Dihydro-5H-dibenz[b,f]azepine-5-acetaldehyde diethylacetal (3b) yield 4.17g (67%). NMR ($CDCl_3$): δ 7.30-6.80 (m, 8H, aryl), 4.60 (t, 1H, CH), 3.91 (d, 2H, CH_2N),CH_2N = 5.0 Hz, 3.50 (q, 4H, $\underline{CH_2}CH_3$) $^JCH_2$, CH_3 = 7.0 Hz, 3.17 (s, 4H, CH_2CH_2), 1.10(t, 6H, CH_3). ^JCH, $^JCH_2$, CH_3 = 7.0 Hz. Anal molecular weight calcd for $C_{20}H_{25}NO_2$: 311.1885. Found (high resolution mass spectrum): 311.1896.

Diphenylamine acetaldehyde diethylacetal (3a) yield 3.70g (65%). NMR ($CDCl_3$):δ7.30-6.80 (m, 10H, aryl), 4.68 (t, 1H, CH), $^JCH_2$, CH_3 = 7.0 Hz, 3.88 (d, 2H, CH_2N) ^JCH, CH_2N = 5.0 Hz, 3.55 (q, 4H, $\underline{CH_2}CH_3$), 1.12 (t, 6H, CH_3). Anal molecular weight calcd for $C_{18}H_{23}NO_2$: 285.1729. Found (high resolution mass spectrum): 285.1727.

5H-Dibenza b,f azepine-5-acetaldehyde diethylacetal (3c) yield 4.57g (74%). NMR ($CDCl_3$): δ 7.30-6.80 (m, 8H, aryl), 6.70 (s, 2H, CH=CH), 4.61 (t, 1H, CH), 3.89 (d, 2H, CH_2N), ^JCH, CH_2N = 5.0 Hz, 3.48 (q, 4H, CH_2CH_3), $^JCH_2CH_3$ = 7.0 Hz, 1.11 (t, 6H, CH_3). $^JCH_2$,CH_3 = 7.0 Hz. Anal molecular weight calcd for $C_{20}H_{23}NO_2$: 309.1729. Found (high resolution mass spectrum) 309.1713.

Phenothiazine-10-acetaldehyde diethylacetal (3d)[15] yield 4.79g (76%). NMR ($CDCl_3$): δ 7.30-6.80 (m, 8H, aryl), 4.81 (t, 1H, CH), $^JCH_2$, CH_3)= 7.0 Hz, 4.02 (d, 2H, CH_2N), ^JCH, CH_2N= 5.0 Hz, 3.55 (q, 4H, $\underline{CH_2}CH_3$), 1.17 (t, 6H, CH_3, $^JCH_2$, CH_3 = 7.0 Hz. Anal molecular weight calcd for $C_{18}H_{21}NO_2S$: 315.1293. Found (high resolution mass spectrum): 283.1285.

Carbazole-9-acetaldehyde diethylacetal (3e) yield 4.64g (82%). NMR ($CDCl_3$): δ 8.10-6.80 (m, 8H, aryl) 4.73 (t, 1H, CH), 4.34 (d, 2H, CH_2N), J_{CH,CH_2N} = 5.0 Hz, 3.45 (q, 4H, $\underline{CH_2}CH_3$), J_{CH_2,CH_3} = 7.0 Hz, 1.02 (t, 6H, CH_3).

J_{CH_2, CH_3} = 7.0 Hz. Anal molecular weight calcd for $C_{18}H_{21}NO_2$: 283.1573. Found (high resolution mass spectrum): 283.1559.

Phenothiazine-10-(-2-propionaldehyde) diethylacetal (3f) yield 0.59g (9%).NMR ($CDCl_3$): δ 7.30-6.80 (m, 8H, aryl), 4.82 (d, 1H, CH), $J_{CH,CHN}$ = 5.0 Hz, 4.10 (m, 1H, CHN), $J_{CH,CHN}$ = 5.0 Hz, J_{CHN,CH_3} = 7.0 Hz, 3.55(q, 4H, $\underline{CH_2}CH_3$), $J_{CH_2CH_3}$ = 7.0 Hz. 1.60 (d, 3H, $CH\underline{CH_3}$), J_{CHN,CH_3} = 7.0 Hz. 1.20 (t, 3H, $CH_2\underline{CH_3}$). $J_{CH_2CH_3}$ = 7.0 Hz. Anal molecular weight calcd for $C_{19}H_{23}NO_2S$:329.1449. Found (high resolution mass spectrum):329.1448.

Preparation of the arylaminoacetaldehydes 2a, 2c, 2d and 6,7-dihydroindolo[1,7-ab][1]benzazepine (1b)

The acetals 3a - 3e respectively (2.35 mmol) were dissolved in acetone (3.50 ml) and water (0.3 ml) and p-toluene sulfonic acid, (0.235 mmol) were added. NMR and tlc analyses gave the following results:

6,7-Dihydroindolo [1,7-ab][1] benzazepine (1b)

10,11-Dihydro-5H-dibenz[b,f]azepine-5-acetaldehyde diethylacetal (3b) was mainly consumed (15% remained) after 20 min at room temperature and had been converted to 1b. The aldehyde 2b could only be detected by NMR (δ9.57 and 4.50 ppm) and was not isolated. (Using 0.0235 mmol p-toluene sulfonic acid prolonged the reaction time and gave the same 1b/2b ratio). After 16 hr all aldehyde and starting material wereconsumed. The reaction mixture was poured into toluene and aqueous sodium bicarbonate. After extraction, washing and drying ($Mg SO_4$) the combined organic phases were evaporated. Chromatography (silica, toluene) gave 371mg (72%) of 6,7-dihydroindolo[1,7-ab][1]benzazepine (1b); mp 97-99° (ethanol) (lit. 100-102°[16], 99-101°[17]), λmax in accordance with reported data.[16] NMR ($CDCl_3$): δ 7.53 (d, 1H, α-H), 7.50-6.90 (m, 7H, aryl), 6.70 (d, 1H, β-H), 3.20 (s, 4H, CH_2CH_2). $J_{\alpha H, \beta H}$ = 3.5 Hz.

Diphenylamino-N-acetaldehyde (2a)

Diphenylamine-N-acetaldehyde diethyl acetal 3a was mainly consumed (15% remained) after 20 min at room temperature and had been converted to the aldehyde 2a. The reaction mixture also consisted of approximately 20% of 1-phenylindole (1a) according to nmr analyses. A sample was taken out and analysis after 16 hr showed that all starting material and aldehyde were consumed and that 1-phenylindole and a small amount of tar had been formed. The main part of the reaction mixture was, after a total reaction time of 20 min, poured into toluene and water. The aquous phase was extracted several times with toluene and the combined organic phases were washed ($NaHCO_3$ and water), dried ($MgSO_4$) and partly evaporated. The evaporation temperature was kept below 30°. Chromatography (silica, toluene) gave 158mg (32%) of diphenylamino-N-acetaldehyde 2a as on oil as darkened in air. NMR ($CDCl_3$): δ 9.89 (t, 1H, CHO), 7.30-6.80 (m, 10H, aryl), 4.40 (d, 2H, CH_2). J_{CHO, CH_2} = 1.4 Hz. ν CO (film) 1720 cm^{-1}. Anal molecular weight calcd for $C_{14}H_{13}NO$: 211.0997. Found (high resolution mass spectrum): 211.0977.

5-H-Dibenz[b,f]azepine-5-acetaldehyde (2c)

5H-Dibenz [b,f] azepine-5-acetaldehyde diethylacetal 3c was partly converted after 20 min at room temperature to the corresponding aldehyde 2c and the ring closed product 1c could hardly be traced according to tlc. Most of the starting material remained (~65%). After 16 hr the reaction mixture contained at approximately 10% of 3c, 20% of 1c and 70% of the aldehyde 2c. The reaction mixture was worked up as above (evaporation temperature below 30°) and after chromatography (silica, toluene) 265 mg (48%) of 5H-dibenz[b,f]azepine-5-acetaldehyde (2c)[5] was obtained as an oil. NMR ($CDCl_3$): δ 9.58 (t, 1H, CHO), 7.40-6.85 (m, 8H, aryl), 6.77 (s, 2H, CH=CH), 4.40 (d, 2H, CH_2). J_{CHO, CH_2} = 1.4 Hz; ν CO (film) 1725 cm^{-1}.

Phenothiazine-10-acetaldehyde (2d)

Phenothiazine-10-acetaldehyde diethyl acetal (3d) was almost intact after 20 min at room temperature. A small amount of the aldehyde 2d had been formed. After 16 hr the reaction mixture consisted of approximately 60% of starting material and 40% of the aldehyde 2d. Warming the reaction mixture at 60° gave after 2 hr complete conversion of the acetal to the aldehyde. No ring closed product 1d was formed. Usual work up and chromatography gave 402 mg (71%) of phenothiazine-10-acetaldehyde (2d); mp 114-116° (ether) (lit. 114-115°[3]); NMR ($CDCl_3$): δ 9.73 (t, 1H, CHO), 7.30-6.30 (m, 8H, aryl), 4.42 (d, 2H, CH_2). J_{CHO, CH_2} = 1.4 Hz; ν CO (KBr) 1720 cm^{-1}.

Carbazole-9-acetaldehyde (2e)

Carbazole-9-acetaldehyde diethylacetal (3e) was not hydrolyzed after 16 hr at room temperature. Warming a reaction mixture, after additional adding of p-toluenesulfonic acid (totally 0.47 mmol) for 1 hr at 60° gave, according to NMR, 10% of carbazole acetaldehyde (2e). Refluxing a reaction mixture of 1.42 g (5.00 mmol) of 3e, acetone (10 ml) water, (0.70ml) and p-toluenesulfonic acid (0.344 g 2.00 mmol) for 4 hr followed by work up and chromatograhy (silica, toluene) gave 609 mg (60%) of carbazole-9-acetaldehyde (2e); mp 140-142°, (carbon tetrachloride) (lit 140.5-141.5°[14]). NMR ($CDCl_3$): δ 9.67 (t, 1H, CHO), 8.20-7.00 (m, 8H, aryl), 4.88 (d, 2H, CH_2). J_{CHO,CH_2} = 1.4 Hz. The value of the coupling constant is reported to be 4 Hz[14] which is not in accordance with our result; ν CO (KBr) 1730 cm^{-1}.

Preparation of 1-Phenylindole(1a), Indolo [1,7-ab] [1] benzazepine(1c), Pyrrolo [3,2,1-kl]phenothiazine (1d) and 2,4-Dicarbazol-9-yl-2-butenal (4) from the Aldehydes, 2a, 2c-2e. The aldehydes, 2a, 2c -2e, (1.00 mmol) respectively were dissolved in toluene (15ml) to which molecular sieve 2.0g (activated Linde type 5Å) was added. Reactions were analyzed by nmr and tlc.

1-Phenylindole (1a)

Diphenylamino-N-acetaldehyde 2a was completely converted to 1-phenylindole 1a after 2 hr at room temperature. Filtration, evaporation and chromatography (silica, toluene) gave 141mg (73%) of 1-phenylindole as an oil (1a). Compound 1a could also be prepared directly under acetal hydrolysis conditions as mentioned above. (λmax in accordance with reported data[18]). NMR ($CDCl_3$):δ7.70-6.50 (m, 10H, arom and α-H), 6.67 (d, 1H, β-H). $J_{\alpha H, \beta H}$ = 3.0 Hz. The assignment of the α-H proton as a doublet at δ 7.32

was confirmed by decoupling by Ganellin and Ridley[18].

Indolo[1,7-ab][1] benzazepine (1c)

Dibenz[b,f]azepine-5-acetaldehyde (2_c) was completely converted to the ring closed system 1_c after 16 hr at room temperature. Filtration, evaporation and chromatography (silica, toluene) gave 145mg (69%) of indolo [1,7-ab] [1]benzazepine (1_c) as yellow crystals; mp 113-114° C, hexane (lit. 113-114°[5]). NMR ($CDCl_3$): δ 7.31 (d, 1H, α-H) 7.20-6.40 (m, 7H, aryl), 6.40 (d, 1H, β-H), 5.80 (d, 1H, CH=), 5.65 (d, 1H, CH=) $J_{\alpha H, \beta H}$ = 3.7 Hz. $J_{CH=,CH=}$ = 12 Hz. The assignment of the α-H and β-H protons was made by decoupling experiments. The compound was also obtained, although in lower yield, directly from the acetal under hydrolysis conditions at room temperature, provided five times the usual amount of p-tolunesulfonic acid was added. Cyclization also occured after warming the aldehyde 2_c at 60° for 7 hrs.

Pyrrolo[3,2,1-kl]phenothiazine (1d)

Phenothiazine-10-acetaldehyde 2_d was completely cyclized to 1_d after 4 days at room temperature. Filtration, evaporation and chromatography (silica, hexane) gave 185 mg (83%) of pyrrolo[3,2,1-kl]-phenothiazine (1_d); mp 116-117° (hexane) (lit. 117-118°[3]); NMR ($CDCl_3$):δ7.31 (d, 1H,α-H), 7.15-6.50 (m, 7H, aryl) 6.37 (d, 1H, βH). J αH, βH =3.4 Hz. No cyclization occurred with molecular sieve 3Å (pellet type). Cyclization using PPA according to the literature procedure[3] gave in our hands a low yield of 1_d and a considerable amount of tar.

2,4-Dicarbazole-9-yl-2-butenal (4)

Carbazole-9-acetaldehyde (2_e) was intact after a day at room temperature. No cyclized product could be traced. Refluxing the mixture for 2 days, filtration, evaporation and chromatography (silica, toluene) gave 31mg (15%) of starting material and 110 mg of 2,4-dicarbazol-9-yl-2-butenal 4; mp 172-174°, toluene (lit 172-174°[13]) NMR, IR and mass spectra were identical to literature data.[13] No cyclized product was detected.

Attempted molecular sieve induced cyclization of the acetals (3a - 3e) The acetals 3_a - 3_e (1.0 mmol) respectively were dissolved in toluene (15 ml) to which molecular sieve (2.0g) was added. NMR analyses of the reaction mixtures showed unreacted starting material (90-100%) after reaction at room temperature for 6 days in all cases except one. The acetal 3_b had been transformed to 6,7-dihydroindolo[1,7-ab] [1]benzazepine 1_b in 67% yield as determined by NMR.

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REFERENCES AND NOTES

1. W.A. Remers and R.K. Brown, Heterocyclic Compounds, Part 1, 1972, p 317-385.

2. M. Chastrette, Ann. Chim. (Paris), 1962, 7, 643.

3. R.A. Hollins and A.C. Pinto, J. Heterocyclic Chem., 1978, 15, 711.

4. Indeed treatment of 1d with PPA at 25° in chloroform with stirring for 4 hrs has caused formation of a black tar in the PPA phase and loss of most of the 1d from the chloroform phase.

5. A. Hallberg and A.R. Martin. J. Heterocyclic Chem. (in press).

6. We found the target compound, 1-methylpyrrolo[3,2,1-kl]phenothiazine, presumably formed after hydrolysis and subsequent cyclization of 3f more readily available via alkylation of the 1-lithio derivative of 1d (A. Hallberg and A.R. Martin, unpublished results.)

7. E.H. Cordes, Prog. Phys. Org. Chem., 1967, 4, 1.

8. T.H. Fife, Acc. Chem. Res.,1972, 8, 264.

9. E.H. Cordes and H.G. Bull. Chem. Rev., 1974, 74, 581.

10. R.A. McClelland and M. Ahmad, J. Am. Chem. Soc.,1978, 100, 7027.

11. J.C. Speck, JR, D.J. Rynbrandt and I.H. Kochevar, J. Am. Chem. Soc.,1965, 87, 4979.

12. B. Belleau, J. Med. Pharm. Chem., 1959, 1, 343.

13. B.M. Vittimberga and M.L. Herz, J. Org. Chem., 1970, 35, 3974.

14. B.M. Vittimberga and M.L. Herz, J. Org. Chem., 1970, 35, 3694.

15. R. Madronero, C. Corral and I. Lissavetzky, Eur. J. Med. Chem., 1978, 13, 389.

16. C.J. Cattanach, A. Cohen and B. Heath-Brown J. Chem. Soc., Perkin 1, 1973, 1041.

17. L. Toscano, G. Grisanti, G. Fioriello and E. Seghetti, J. Med. Chem., 1976, 19, 208.

18. C.R. Ganellin and H.F. Ridley, J. Chem. Soc., 1969, 1537.

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