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Nitroimidazoles: Part XVII—5-Aminoimidazoles†‡

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2-Benzoyl-1-methyl-5-nitroimidazole (**1**) undergoes reduction over Raney nickel catalysed to the amine (**2**), which is transformed into the *p*-chlorobenzamide (**3**), the acylthioureas (**4** and **6**) and the sulphonylthiourea (**5**). Alkaline hydrolysis of **4** affords the thiourea (**7**). Hydrogenation of the *p*-nitrobenzoyl analogue (**10**) of **1** and condensation of the product with dimethylformamide dimethylacetal leads to the bis-amidine (**11**). Catalytic reduction of the nitrosulphone (**12**) affords unstable 2-methanesulphonyl-1-methyl-5-aminoimidazole (**13**) forming stable acyl derivatives (**14a-g**) and thioureas (**15a** and **15b**). Reaction of **13** with *p*-nitrobenzaldehyde furnishes in low yield an anomalous product considered to be **19**, which probably results *via* the benzylidene-bisimidazole (**16**) and the tricyclic condensed pyridines (**17** and **18**). 2-Methanesulphinyl-1-methyl-5-aminoimidazole arising from the nitro derivative (**20a**) is characterised as the acylthioureas (**20b** and **20c**). Likewise the reduction product of 1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**21a**) has been isolated as the acetyl derivative (**21b**).

The literature on aminoimidazoles[1] is relatively scanty for various reasons. The 2-amino compounds, which have recently come into some prominence as precursors for 2-nitroimidazoles related to azomycin[2], are synthesised only with some difficulty, the general method utilised being the condensation of aminoacetals with cyanamide or isothioureas[3]. 2-Amino-5-nitroimidazoles form a special group synthesised from 5-nitroimidazoles with a suitable leaving group at position-2[4]. 4(5)-Aminoimidazoles available by reduction of accessible 4(5)-nitroimidazoles are unstable, presumably because of reversion to labile open-chain products. 4-Aminoimidazole-5-carboxamides are stabler entities and have attracted more chemical effort due to their importance as biosynthetic precursors of purines[1]. 4(5)-Amino-5(4)-nitroimidazoles are again stable derivatives which are prepared from nitrohaloimidazoles. A recent publication reports on an interesting synthesis of 1-aryl-5-morpholino- and 1-aryl-4, 5-dimorphilino-imidazoles and analogues[5].

Our concerted efforts on 5-nitroimidazoles resulted in the synthesis of several potent antiprotozoal preparations among which **21a** (Code No. 10213 Go) is undergoing clinical trials[6]. The biological activity of 5-nitroimidazole derivatives like metronidazole has been attributed to the reduction of the nitro group to unknown products which are lethal to susceptible parasitic or bacterial cells[7]. Hence we felt that the synthesis of 5-aminoimidazoles would be useful both as candidate drugs for antiprotozoal screening and as potential metabolites, when derived from active 5-nitroimidazoles. *A priori* it appeared to us that 5-aminoimidazoles carrying electronegative groups at position-2 had a good chance of survival at least with the amino group protected. Accordingly we concentrated our efforts on the reduction of some 2-acyl- and 2-sulphonyl-5-nitroimidazoles and characterisation of the products. The active antiprotozoal agent, 1-(1-methyl-5-nitroimidazol-2-yl)-3-methyl-2-oxo-sulphonylimidazolidine (**21a**)[6] was also a target of this exercise. We present the results in this paper.

Catalytic reduction of 2-benzoyl-1-methyl-5-nitroimidazole (**1**)[8] in anhydrous ethyl acetate over Raney Nickel catalyst gave the amine (**2**) in good yield. **2** was transformed by standard reactions to the *p*-chlorobenzamide (**3**), and the thioureas (**4-6**). Alkaline hydrolysis of **4** knocked off the carbethoxy group to provide **7**. Condensation of **2** with dimethylacetamide dimethylacetal gave the acetamidine (**8**).

The bis-amidine (**9**) is reported to be a potent antiamoebic agent[9], the activity of similar compounds being ascribed to binding to DNA by electrostatic interaction of the negative phosphate groups of DNA and the positive centres of the bis-amidine[10]. Compound **11** thus became a desirable synthetic objective, and was prepared from 1-methyl-2-(*p*-nitrobenzoyl)-5-nitroimidazole (**10**)[8] by catalytic reduction and subsequent reaction of the diamine with dimethylformamide diacetal.

2-Methanesulphonyl-1-methyl-5-nitroimidazole (**12**)[6] underwent smooth reduction to the amine (**13**), which was found to be unstable. However, in one experiment, when palladium charcoal catalyst was used, it could be isolated as a crystalline solid which decomposed on keeping. Generally it was found to be more advantageous if **12** was reduced over Raney

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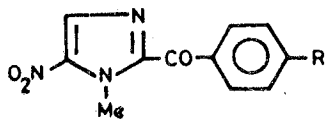
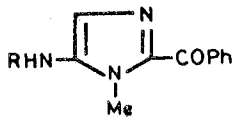


1 R = H

10 R = NO_2



2 R = H

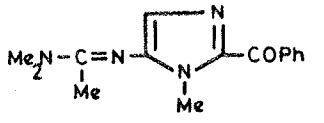
3 R = 4-Cl-C_6H_4CO-

4 R = EtOC(=O)NHCS-

5 R = 4-Me$C_6H_4SO_2$NHCS-

6 R = PhCONHCS-

7 R = H_2NCS-



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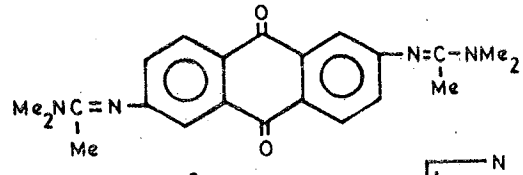

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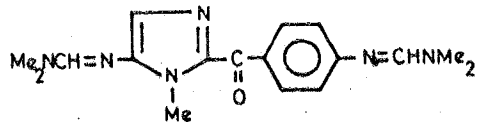

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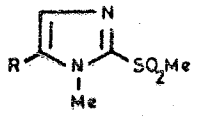
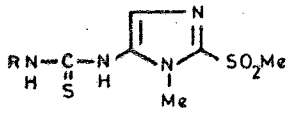


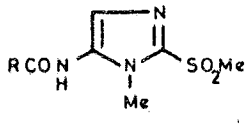
12 R = NO_2

13 R = NH_2



15 a R = EtO_2C-

b R = 4-Me$C_6H_4SO_2$-



14 R

a Me

b $ClCH_2$-

c Cl_2CH-

d 4-$NO_2C_6H_4$-

e 4-ClC_6H_4-

f 3,4,5 tri(OMe)C_6H_2-

g 2-thienyl

nickel catalyst. The solution containing **13** was treated directly with acid chlorides to afford amides (**14**) and with highly reactive isothiocyanates to form thioureas (**15**). In another experiment, the amine solution was left with *p*-nitrobenzaldehyde and trifluoracetic acid for some days to give a low yield of a crystalline product, which was not the expected benzylidene derivative. Analytical and mass spectral data indicated a molecular formula, $C_{16}H_{14}N_6O_5S$ (M^+ 402). The mass spectrum had fragments at *m/z* 386 ($M^+ - O$), 372 ($M^+ - NO$), 354 ($M^+ - SO$), 339 ($M^+ + 1 - SO_2$) and 323 ($M^+ - SO_2Me$), indicating the presence of NO_2 and SO_2Me groups. The PMR spectrum (DMSO-d_6) accounted for the 14 protons as follows: 3.42 (3H, *s*, SO_2Me), 3.49 (3H, *s*, NMe), 4.10 (3H, *s*, NMe), 8.06 (2H, *m*, Ar-H), 8.36 (2H, *m*, Ar-H), 11.60 (1H, *bs*, disappearing with D_2O, NH). In particular it showed the presence of a *p*-nitrophenyl group and the absence of an azomethine proton due to an arylidene function. The IR spectrum displayed $\nu C=O$ at 1700 cm^{-1}, while the UV had λ_{max} at 252, 267 (sh), 308 and 346 nm (sh) ($\log \varepsilon$ 4.03, 3.98, 4.27 and 4.15). These data could be best reconciled with structure (**19**) for the product. The tortuous, but rational pathway for the formation of **19** from **13** envisages condensation of two molecules of **13** with the aromatic aldehyde at the nucleophilic C-4 to form **16**; cyclisation of **16** to the dihydropyridine (**17**) by loss of ammonia; spontaneous oxidation of **17** (well-known for dihydropyridines) to the aromatic tricycle **18** and fortuitous acid-catalysed hydrolysis of *one* of the two methanesulphonyl groups to yield **19** (see Chart 1).

Reduction of 2-methanesulphinyl-1-methyl-5-nitroimidazole (**20a**)[6] afforded the expected amine which was transformed to the thioureas **20b** and **20c**. Finally, the nitroimidazole **21a**[6] was similarly reduced to an unstable amine which, however, formed a crystalline and stable acetyl derivative **21b** in moderate overall yield.

Experimental Procedure

5-Amino-2-benzoyl-1-methylimidazole (**2**)—A solution of 2-benzoyl-1-methyl-5-nitroimidazole (**1**, 10 g) in ethyl acetate (150 ml) was shaken with hydrogen at 40 psi in the presence of Raney Nickel (30 g) and anhydrous sodium sulphate (30 g) until 3 mol of hydrogen were absorbed (6-11 hr). The solution was filtered and concentrated to yield **2**, (4 g), m.p. 197-99°; M^+ 201; PMR (DMSO-d_6 + $CDCl_3$): δ 3.83 (3H, *s*, N

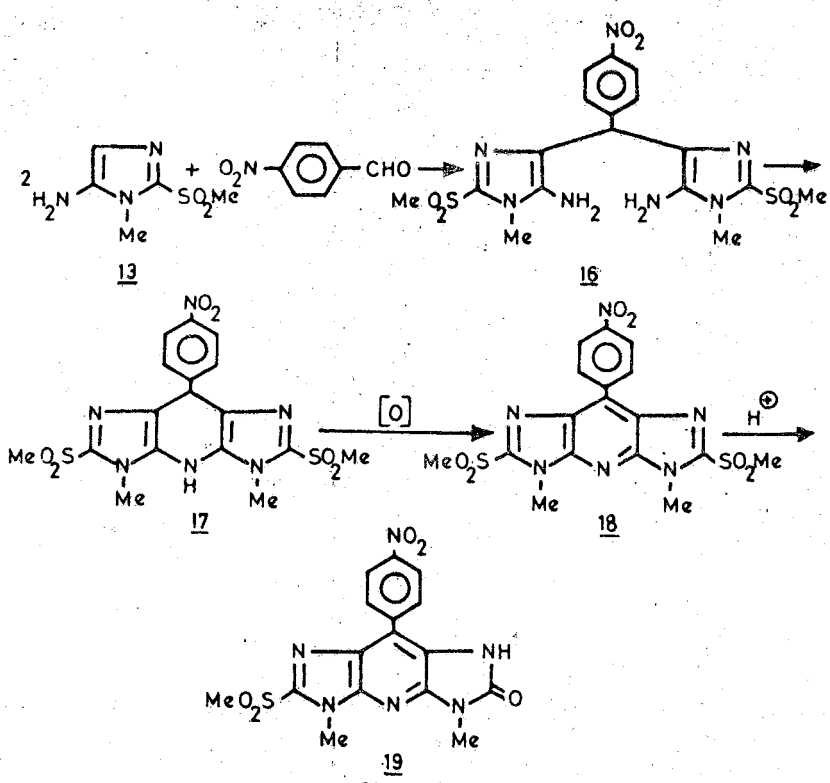
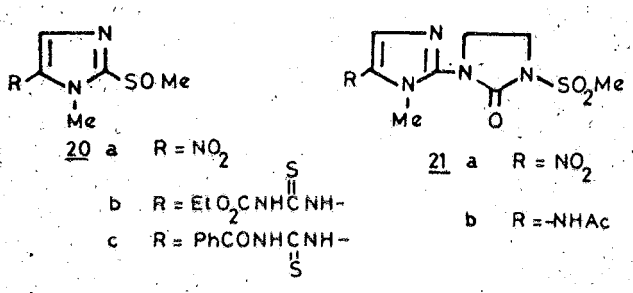


Chart 1



$-CH_3$), 5.4 (2H, broad signal $-NH_2$), 6.52 (1H, *s*, C-4H), 7.4 (3H, *m*, C-3, C-4, C-5H in the phenyl ring), 8.1 (2H, *m*, C-2 and C-6H in the phenyl ring) (Found: C, 65.5; H, 5.8; N, 20.8. $C_{11}H_{11}N_3O$ requires C, 65.7; H, 5.5; N, 20.9%).

5-(4-Chlorobenzamido)-2-benzoyl-1-methylimidazole (**3**)—**1** (6 g) in ethyl acetate (150 ml) was catalytically hydrogenated over Raney Nickel as usual and the filtered solution treated with *p*-chlorobenzoyl chloride at room temperature and left for 48 hr. The solvent was removed under reduced pressure, the residue treated with ice and aq potassium bicarbonate and the solid filtered off. The solid was chromatographed over silica gel in chloroform and the product crystallised from methylene chloride-ether to yield **3** (2.5 g), m.p. 208-10°; M^+ 339 (Found: C, 63.4; H, 4.4; N, 12.5. $C_{18}H_{14}ClN_3O_2$ requires C, 63.6; H, 4.2; N, 12.4%).

N-Carbethoxy-N'-(2-benzoyl-1-methylimidazolyl-5)thiourea (**4**)—**1** (4 g) was reduced as usual. The solution was treated with carbethoxy isothiocyanate (3 g) and left at room temperature for 24 hr. The product was filtered off and crystallised from methylene chloride-ether to yield **4** (2 g), m.p. 190° (d); M^+ 332 (Found: C, 54.3; H, 5.2; N, 16.9. $C_{15}H_{16}N_4O_3S$ requires C, 54.2; H, 4.9; N, 16.9%).

Similar reactions with *p*-toluenesulphonyl isothiocyanate and crystallisation of the product from methylene chloride-ether gave **5**, m.p. 219-21°; M^+ 414. (Found: C, 55.2; H, 4.7; N, 13.2. $C_{19}H_{18}N_4O_3S_2$ requires C, 55.1; H, 4.4; N, 13.5%); and with benzoyl isothiocyanate, **6** (from methylene chloride-ether) (2 g), m.p. 190-92°. (Found: C, 62.6; H, 4.6; N, 15.5. $C_{19}H_{16}N_4O_2S$ requires C, 62.6; H, 4.4; N, 15.4%).

N-(2-Benzoyl-1-methylimidazolyl-5)thiourea (**7**)—A mixture of **4** (2.2 g) and sodium hydroxide (1.4 g) in water (35 ml) was stirred at room temperature for 19 hr, cooled and neutralised with acetic acid. The solid was filtered off, washed with water and crystallised from ethyl acetate to yield **7** (1 g), m.p. 207-9°(d) (Found: C, 55.7; H, 4.9; N, 21.9. $C_{12}H_{12}N_4OS$ requires C, 55.4; H, 4.7; N, 21.5%).

N, N-Dimethyl-N'-(2-benzoyl-1-methylimidazolyl-5)acetamidine (**8**)—A mixture of **2** (2.5 g) and dimethylacetamide dimethylacetal (7 ml) was heated at 70° for 14 hr, cooled and poured into hexane (300 ml). The solid was filtered off, washed with hexane and crystallised from methanol-isopropanol to yield **8** (1 g) m.p. 120-22°; M^+ 270 (Found: C, 66.8; H, 7.0; N, 20.6. $C_{15}H_{18}N_4O$ requires C, 66.7, H, 6.71, N, 20.7%).

2-[4-(*N, N-Dimethylformamidinyl-N'*)*benzoyl*]-5-(*N, N-dimethylformamidinyl-N'*)-1-*methylimidazole* (**11**)—A solution of 2-(*p*-nitrobenzoyl)-1-methyl-5-nitroimidazole (**10**) (3 g) in ethyl acetate (100 ml) was reduced with hydrogen over Raney Nickel (10 g) and anhydrous sodium sulphate (15 g) at 45°, until 6 mol of hydrogen were absorbed. The solution was filtered, the solvent removed *in vacuo*, the residue dried, treated with dimethylformamide dimethylacetal (25 ml) and left at room temperature for 24 hr. The oily reduction product went into solution and a yellow solid started separating slowly. The mixture was heated at 100° for 2.5 hr and cooled. The solid was filtered off washed with hexane and crystallised from methanol to yield **11** (1 g), m.p. 173-75°; M^+ 326 (Found: C, 62.2; H, 6.8; N, 25.8. $C_{17}H_{22}N_6O$ requires C, 62.6; H, 6.8; N, 25.8%).

2-*Methanesulphonyl*-1-*methyl*-5-*aminoimidazole* (**13**)**—A solution of nitroimidazole (**12**) (10.25 g) in ethyl acetate (75 ml) was shaken with 10% Pd/C (1.2 g) and hydrogen at 55 psi in a Parr apparatus for 15 hr until 3 mol of hydrogen were absorbed. The mixture was filtered and the filtrate concentrated to give crude **13** (4 g), which recrystallised from MeOH-ether (3 g), m.p. 123° (Found: C, 34.3; H, 5.3; N, 23.9. $C_5H_9N_3O_2S$ requires C, 34.3; H, 5.2; N, 24.0%); UV (EtOH): 274 nm (log ε 3.96).

General method of preparation of amides (**14**) *from the amine* (**13**)—A solution of 2-methanesulphonyl-1-methyl-5-nitroimidazole (**12**) (10 g) in ethyl acetate (150 ml) was hydrogenated in a Parr apparatus at 40 psi at room temperature over Raney nickel (25 g) and sodium sulphate (25 g) until 3 mol of hydrogen were absorbed (3 hr). The solution was filtered and the filtrate containing **13** was treated with an equivalent amount of the appropriate acid chloride and left at room temperature overnight. The solvent was removed *in vacuo* and the residue treated with ice and left for 4 hr. The solid formed was filtered off and crystallised to yield **14** (Table 1).

General method of preparation of thioureas (**15**) *from the amine* (**13**)—A solution of **13** prepared as above at room temperature was treated with the appropriate isothiocyanate and left for 24 hr. The solid obtained by concentrating the solvent was re-crystallised from a suitable solvent to give **15** (Table 1).

Bisimidazopyridine (**19**)—A solution of **12** (7 g) in ethyl acetate (150 ml) reduced as above was treated with *p*-nitrobenzaldehyde (5.3 g) in ethyl acetate (100 ml) and trifluoroacetic acid (1 drop) and left at room temperature for 1 week. The solid that separated was filtered off and crystallised from methanol ethyl acetate to yield **19** (0.5 g) m.p. > 300°; M^+ 402 (Found: C, 47.9; H, 4.0; N, 21.0; S, 7.9. $C_{16}H_{14}N_6O_5S$ requires C, 47.8; H, 4.3; N, 20.9, S, 8.0%).

Preparation of thioureas (**20b**) *and* (**20c**)—**20a** (5 g) in ethyl acetate (150 ml) was hydrogenated over Raney nickel (15 g) in the presence of anhydrous sodium sulphate (15 g) in a Parr apparatus at 40 psi until 3 mol of hydrogen were absorbed. The solution was filtered and the filtrate treated with an equivalent amount of the appropriate isothiocyanate. After 48 hr at room temperature, the solid formed was filtered off and crystsllised from a suitable solvent to yield **20b** and **20c** (Table 1).

1-*Methanesulphonyl*-3-(5-*acetamido*-1-*methyl*-1*H*-*imidazol*-2-*yl*)-2-*imidazolidinone* (**21b**)—A solution of **21a** (9 g) in dimethylformamide (40 ml) and ethyl acetate (70 ml) was hydrogenated over Raney nickel (30 g) in the presence of anhydrous sodium sulphate (30 g) in a Parr apparatus at 45° until 3 mol of hydrogen were absorbed. The solution was filtered, the filtrate treated with acetic anhydride (12 ml) and left at room temperature for 48 hr. The solvent was removed under reduced pressure and the residue flushed with xylene

Table 1—Amides and Thioureas of 5-Aminoimidazoles

Compd	Solvent of crystallisation	Yield %	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
					C	H	N	C	H	N
14a	EtOH-Et_2O	35	155	$C_7H_{11}N_3O_3S$	38.71	5.11	19.35	38.42	5.43	19.32
14b	MeOH-EtOAc	45	146	$C_7H_{10}ClN_3O_3S$	33.41	4.00	16.70	33.66	4.27	16.51
14c	MeOH-EtOAc	35	254	$C_7H_9Cl_2N_3O_3S$	29.39	3.17	14.69	29.65	3.45	14.87
14d	MeOH	35	214	$C_{12}H_{12}N_4O_5S$	44.45	3.73	17.28	44.77	4.08	17.27
14e	MeOH	25	175	$C_{12}H_{12}ClN_3O_3S$	45.94	3.86	13.40	46.22	4.20	13.50
14f	EtOAc-Et_2O	25	185	$C_{13}H_{19}N_3O_6S$	48.78	5.19	11.38	48.49	5.41	11.58
14g	CH_2Cl_2	30	149	$C_{10}H_{11}N_3O_3S_2$	42.11	3.89	14.73	42.46	4.25	14.49
15a	CH_2Cl_2-Et_2O	45	191	$C_9H_{14}N_4O_4S_2$	35.30	4.61	18.30	35.24	4.98	18.25
15b	Me_2CO-EtOAc	60	158	$C_{13}H_{16}N_4O_4S_3$	40.21	4.15	14.43	40.54	4.48	14.41
20b	Me_2CO-EtOAc	25	194(d)	$C_9H_{14}N_4O_3S_2$	37.24	4.86	19.31	37.15	5.04	19.19
20c	Me_2CO	25	210	$C_{13}H_{14}N_4O_2S_2$	48.45	4.38	17.39	49.13	4.66	17.68

**Experiment performed by V P Arya & V Sadhale of our Research Centre.

and triturated with acetone (20 ml). The solid was filtered off and crystallised from methanol-acetone to yield **21b** (2 g), m.p. 226-28°; M^+ 301; PMR ($CD_3OD + CDCl_3$): δ 2.19 (3H, *s*, CH_3CO), 3.33 (2H, *m*, $CH_2-N-Het$), 3.43 (3H, *s*, CH_3SO_2), 4.03 (2H, *m*, CH_2N-SO_2), 4.58 (3H, *s*, $N-CH_3$), 6.83 (1H, *s*, C-4H) (Found: C, 40.0; H, 5.3; N, 23.6. $C_{10}H_{15}N_5O_4S$ requires C, 39.9; H, 5.0, N, 23.3%).

References

1 Schofield K, Grimmett M R & Keene B R T, *The azoles* (Cambridge University Press, Cambridge), 1976, 208.

2 Cavalleri B, Volpe G, Ripamouti A & Arioli V, *Arzneimittel – Forsch*, **27** (1977) 1131; Tomcufcik A S, *Medicinal chemistry: Part I*, edited by A Burger (Wiley-Interscience, New York), 1970, 573.

3 Lawson A, *J chem Soc*, (1956) 307.

4 Sudarsanam V, Nagarajan K, Arya V P, Kaulgud A P, Shenoy S J & Shah R K, *Indian J Chem*, **21B** (1982) 989.

5 Meola S, Riversa S, Stradi R & Giodia B, *J heterocycl Chem*, **17** (1980) 1041.

6 Nagarajan K, Arya V P, George T, Sudarsanam V, Shah R K, Nagana Goud A, Shenoy S J, Honkan V, Kulkarni Y S & Rao M K, *Indian J Chem*, **21B** (1982) 928.

7 Edwards D I, Rowley D A, Knox R J, Skolimovski I M & Knight R C, *Current chemotherapy and infectious diseases*, Vol. 1, Proceedings of the 11th ICC and 19th ICAAC, Boston, 1980, 561.

8 Nair M D, Sudarsanam V & Desai J A, *Indian J Chem*, **21B** (1982) 1027.

9 Fabio P F, Fields T L, Yang-i-Lin, Burden E J, Carvajal S, Murdock K C & Lang (Jr) S A, *J mednl Chem*, **21** (1978) 273.

10 Das B P & Boykin D W, *J mednl Chem*, **20** (1977) 531.