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Electrochemical Reduction of Some Pyrimidine Derivatives

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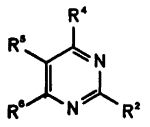
The reduction of some derivatives of pyrimidine has been investigated. 2-Phenylpyrimidines are reduced in a four-electron reaction with ring contraction to 2-phenylpyrroles; 4-phenylpyrimidine is in acid solution reduced in a one-electron reaction to bi(1,6-dihydro-4-phenylpyrimidyl-6) and 4-methyl and 5-methylpyrimidine are similarly reduced to dimeric 1,6-dihydro compounds in acid solution. 4-Trichloromethylpyrimidines have been reduced to dichloromethylpyrimidines in *N*,*N*-dimethylformamide; reduction of 2-cyanopyrimidines in this solvent leads to loss of the cyano group.

Pyrimidine and some of its derivatives have previously been investigated [1–5] by classical and ac polarography and cyclic voltammetry. In short, pyrimidine gives rise to two one-electron waves in the acid region; the waves merge at higher pH and this two-electron wave is in slightly alkaline solution followed by another two-electron wave which results in the formation of a tetrahydropyrimidine. In most cases the structure of the products have been deduced from their UV spectra.



1, $R^2 = C_6H_5$; $R^4 = R^6 = CH_3$; $R^5 = H$.
2, $R^2 = C_6H_5$; $R^4 = CH_3$; $R^5 = R^6 = H$.
3, $R^2 = R^5 = R^6 = H$; $R^4 = C_6H_5$.
4, $R^2 = R^5 = R^6 = H$; $R^4 = CH_3$.
5, $R^2 = R^4 = R^6 = H$; $R^5 = CH_3$.
6, $R^2 = C_6H_5$; $R^4 = CH_3$; $R^5 = H$; $R^6 = Cl$.
7, $R^2 = C_6H_5$; $R^4 = CCl_3$; $R^5 = R^6 = H$.
8, $R^2 = C_6H_5$; $R^4 = CCl_3$; $R^5 = H$; $R^6 = Cl$.
9, $R^2 = CN$; $R^4 = R^6 = CH_3$; $R^5 = H$.
10, $R^2 = C_6H_5$; $R^4 = OCH_3$; $R^5 = H$; $R^6 = CH_3$.

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In this investigation some pyrimidine derivatives (*1* – *10*) have been reduced in aqueous and aprotic media and the products isolated.

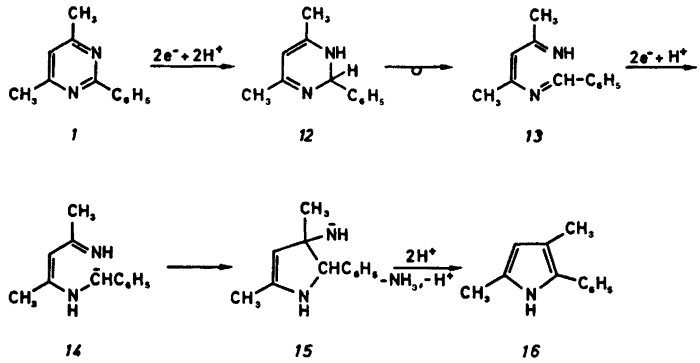
RESULTS AND DISCUSSION

In aqueous acid solution *1* shows a polarographic wave for which a pH-$E_{\frac{1}{2}}$ plot gives a straight line with a slope of −0.058 V per pH unit; at pH 3 $E_{\frac{1}{2}} = -1.13$ V *vs.* the saturated calomel electrode (SCE). Its height corresponds to a four-electron reduction as judged from a comparison with the polarographic wave-height of an equimolar solution of azobenzene; a coulometric investigation also gave $n = 4$ F M^{-1}. From pH 2.5 to 6 the first wave is followed by another wave with the height approximately corresponding to a one-electron wave; this wave was not investigated further. At pH > 7 the first wave decreases with increasing pH and disappears between pH 9 and 10.

The quaternary derivative (*11*) of *1*, 2-phenyl-1,4,6-trimethylpyrimidinium iodide, behaves similarly, but the halfwave potentials of the four-electron wave are independent of pH at pH < 2.

Preparative reduction of *1* or *11* in acetate buffer at −1.55 V (SCE) gives 3,5-dimethyl-2-phenylpyrrole (*16*) in a four-electron reaction with the loss of ammonia or methylamine. The reaction is different from that reported for other pyrimidines[1–5] but similar to that occurring during the reduction [6] of *1* with zinc and acetic acid. The reaction sequence in Scheme 1 is proposed for the ring contraction.

The presence of a phenyl group in the 2-position changes the reduction of the pyrimidine



Scheme 1.

ring from a 1,6-reduction to a 1,2-reduction. This step is supported by the fact that if the reduction of *1* in DMF is stopped after the consumption of two electrons, hydrolysis of the product gives benzaldehyde (*17*) in good yield; *12* would be hydrolyzed to *17*. *12* would, however, not be reducible at the applied potential, but the ring-opened compound (*13*) would. The reduction of *13* would take place at the benzalimine electrophore and lead to a carbanion (*14*) as the protonation of the nitrogen would be faster than that of the benzylic carbon. It does not seem unlikely that *14* could be reduced further at the potential where the rather ill-defined second wave of *1* is observed, as *14* is an imine of an α,β-unsaturated ketone.

The carbanion, *14*, is well set for an attack on the imine, as the *cis*-configuration of the C(5)–C(6) double bond of *14* allows the carbanion to be formed close to the electrophilic centre of the imine. After ring-closure to *15* protonation of the amino group makes the elimination of ammonia to *16* possible.

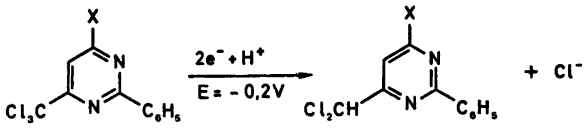
2 behaves similarly to *1*, polarographically and on preparative electrolysis; it forms *3*-methyl-2-phenylpyrrole (*18*) in a four-electron reduction. The NMR spectrum of the crude product indicated no 5-methyl-2-phenylpyrrole.

The reductive ring contraction of *10* goes more slowly; after the usual work-up without exclusion of oxygen the crude product contained 67 % of *10* and 33 % of 5(or 3)-methoxy-3(or 5)-methyl-2-phenylpyrrole (*19*). In the absence of reference spectra of close analogs a choice between the two possible isomers could not be made. The recovered *10* most likely stems from a reoxidized dihydro compound.

The phenyl group seems to be essential to direct the initial reduction toward the 1,2-bond rather than the 1,6-bond, as is found in pyrimidine. Other electron-attracting groups could presumably function in a similar way, provided that the activating group is neither reduced nor cleaved by reduction. A nitro group is reduced preferentially to the pyrimidine nucleus, and the activating group is lost in 2-cyano-4,6-dimethylpyrimidine and in 2-triethylammonio-4,6-dimethylpyrimidine.

Reduction of *1* in DMF containing tetrabutylammonium iodide (TBAI) gave *17*. *10* gave under similar conditions a product which from its ^{1}H NMR spectrum was assumed to be 6-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydropyrimidine; the compound decomposed slowly on purification on a column of silica and could be hydrolyzed to benzaldehyde. The absence of *19* indicates that *19* is not formed through the tetrahydro derivative, but instead according to Scheme 1.

3, *4* and *5* are reduced in accordance with the published reports.[1] In all cases a dimerized one-electron product was isolated from reduction in dilute hydrochloric acid; the dimerization took place at the 6-position rather than at the position (4) of the substituent. For *3* and *4* the ^{1}H NMR spectrum indicated a single product, whereas the spectrum of the reduction product of *5* (as dihydrochloride) showed the presence of two compounds. The mixture did not consist of the D,L and *meso*-isomers, but rather of two tautomeric dimers, suggested to be a 1,6-dihydro and a 3,6-dihydro form. Addition of sodium perchlorate precipitated a dimer as the perchlorate and both this product and that obtained



7 X=H
8 X=Cl

20 X=H
21 X=C

on evaporation of the mother liquor turned out to be a single isomer containing, presumably, the 1,6-dihydropyrimidine nucleus; a 3,6-(1,4)-dihydropyrimidine structure cannot, however, be excluded from the ^{1}H NMR spectrum.

In borate buffer pH 9 *3*, *4*, and *5* are reduced to tetrahydropyrimidines, which are rather easily hydrolyzed with the loss of formaldehyde.[1]

Stepwise removal of clorine from chlorinated pyrimidines was found to be feasible in DMF containing a small concentration of a proton donor such as phenol or acetic acid. A cyclic voltammogram of *7* (5×10^{-3} M) at a glassy carbon cathode in DMF/TBAI containing 5×10^{-3} M phenol showed three irreversible waves at $E_p = -0.15, -0.95$, and -1.15 V (*vs.* Ag/AgI, 0.1 M I^-) followed by a reversible wave at $E_p = -1.71$ V. The three first waves correspond to the stepwise cleavage of the carbon-chlorine bonds whereas the reversible wave is due to the reduction of the resulting methylphenylpyrimidine to its anion radical.

Voltammetrically *8* behaves similarly to *7*, but it shows under similar conditions (concentration of phenol 10^{-2} M) at a mercury electrode four irreversible peaks at $E_p = -0.13, -0.80, -1.03$, and -1.33; the three first waves correspond to the stepwise removal of chlorine from the trichloromethyl group and the fourth one to the reduction of the chlorine in the nucleus. The four waves of *8* are followed by a reversible wave at $E_p = -1.68$ V.

Preparative reduction of *7* or *8* at the potential of the first wave gave the corresponding dichloromethyl compounds (*20*) and (*21*) in high yield (92 and 91.5%, resp.).

Under similar conditions *6* can be reduced to *2*.

The dichloromethyl groups of *20* and *21* are rather resistant to hydrolysis. Thus treatment of *21* with sodium ethoxide in ethanol yielded 4-dichloromethyl-6-ethoxy-2-phenylpyrimidine (*22*) and reflux of *20* with aqueous-alcoholic potassium hydroxide or hydrogen chloride left the starting material unchanged.

It could be expected that the hydrolysis of *20* and *21* would be slow due to the electron-withdrawing influence of the two nitrogen atoms, but the introduction of an ethoxy group in the pyrimidine nucleus in *22* should counteract that.

The stepwise removal of halogens from a trichloromethyl group by controlled potential reduction seems to be the method of choice for such reactions; it has previously been shown that even the fluorine atoms in trifluoromethylbenzene can be stepwise removed.[7]

EXPERIMENTAL

Chemicals. *N,N*-Dimethylformamide (DMF; Fluka, *puriss*) was dried over A4 molecular sieves and finally purified through a column of active aluminium. The tetraalkylammonium salts were obtained from Fluka, Switzerland.

4,6-Dimethyl-2-phenylpyrimidine (*1*) and 4-chloro-6-methyl-2-phenylpyrimidine (*6*) were prepared according to Ref. 8 and Ref. 9, resp. 4-Methyl-2-phenylpyrimidine (*2*) was obtained by controlled potential electrolysis of *6*, and 2-cyano-4,6-dimethylpyrimidine was prepared according to Ref. 10.

4-Chloro-2-phenyl-6-trichloromethylpyrimidine (*8*) was prepared by refluxing 6.75 g 6-methyl-2-phenyl-4(3*H*)pyrimidone with 16.8 g $POCl_3$ and 38 g PCl_5 for 5 h; after cooling the reaction mixture is poured on ice and the product extracted with chloroform, which was washed with water, dried and evaporated. The residue was recrystallized 3 times from ethanol to give 4 g of *8*, m.p. 122 °C. ^{1}H NMR spectrum of *8* ($CDCl_3$): δ 7.40 – 7.70 (m, 3 H); 7.80 (s, 1 H); 8.35 – 8.58 (m, 2 H).

2-Phenyl-4-trichloromethylpyrimidine (*7*) was obtained in an analogous way; the crude product was purified on a column of silica with a 1:1 mixture of hexane – dichloromethane as eluent, m.p. 85.8 °C. ^{1}H NMR spectrum ($CDCl_3$): δ 7.32 – 7.56 (m, 3 H); 7.69 (d, *J* 7 Hz, 1 H); 8.37 – 8.63 (m, 2 H); 8.91 (d, 7 Hz, 1 H).

Preparative electrolysis

Reduction of 2,4-dimethyl-2-phenylpyrimidine (1) 1 (2 g) was reduced, shielded from light, at −1.55 V (*vs.* SCE) in an aqueous acetate buffer pH 4.5 containing 40 % ethanol, $n = 4.17$ F mol^{-1}. After the reduction the pH of the catholyte was raised to 7 by addition of 25 % aqueous ammonia and the product extracted three times with diethyl ether. The extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent left a crude product which was recrystallized three times from light petroleum; yield 1.37 g of 3,5-dimethyl-2-phenylpyrrole (*16*) (74 %), m.p. 71 °C (71.5 – 72 °C).[11] ^{1}H NMR spectrum ($CDCl_3$): δ 2.19 (s, 6 H); 5.80 (d, 5 Hz, 1 H); 7.13 – 7.40 (m, 5 H); 7.50 – 7.85 (s, (br), 1 H). MS: M.w. 171.

Resuction of 1 *in DMF 1* (2 g) was reduced in DMF/TBAI containing 5 % of water at −1.70 V (*vs.* Ag/AgI 0.1 M$^-$); after 2.9 F mol^{-1}, the catholyte was diluted with water, pH adjusted to 9, and extracted with diethyl ether. The ether was washed with water, dried and evaporated; the residue was purified on a column of silica with a 9:1 mixture of dichloromethane and hexane as eluent. 0.72 g of benzaldehyde was obtained.

Reduction of 4-methyl-2-phenylpyrimidine (2) *2* (2 g) was reduced at −1.50 V (*vs.* SCE) and worked up similarly to the reduction of *1*. The crude product was recrystallized from light petroleum to give 1.25 g (81 %) of 3-methyl-2-phenyl-pyrrole, *18*, m.p. 34.9 °C (34 °C).[12] ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3 H); 6.10 (tr, 2.7 Hz, 1 H); 6.68 (tr, 2.7 Hz, 1 H); 7.1 – 7.4 (m, 5 H); 7.7 – 8.3 (br.s, 1 H).

Reduction of 4-methoxy-6-methyl-2-phenylpyrimidine (10). 10 (1 g) was reduced in an aqueous-ethanolic acetate buffer and worked up as described for *1*, $n = 4.65$ F mol^{-1}; the catholyte was checked polarographically for the absence of unreduced *10*. The crude product contained, however, two thirds of *10* and one third of 3-(or 5-)methoxy-5-(or 3-)-methyl-2-phenylpyrrole (*19*); *19* was separated from *10* on a column of silica with a 6:4 mixture of light petroleum and ethyl acetate as eluent followed by a further purification on a column of silica with chloroform as eluent. ^{1}H NMR spectrum ($CDCl_3$) of *19*: δ 2.19 (s, 3 H); 3.77 (s, 3 H); 5.77 (d, 2.5 Hz, 1 H); 6.9 – 8.0 (m, 6 H). The compound is very sensitive to light and turns purple on exposure to diffuse daylight.

Reduction of 5-methylpyrimidine (5). 5 (2 g) was reduced in 0.1 M HCl at −0.85 V (*vs.* SCE), $n = 0.88$ F mol^{-1}. Evaporation of the catholyte left a residue, 2.50 g, which according to the ^{1}H NMR spectrum consisted of a 3:1 mixture of two dimers, A and B, as the dihydrochlorides. ^{1}H NMR spectrum of A, (D_2O): δ 1.82 (d, J 1.5 Hz, 3 H); 4.67 (s, 1 H); 6.47 (q, 1.5 Hz, 1 H); 8.11 (s, 1 H). ^{1}H NMR spectrum of B (D_2O): δ 1.90 (d, J 1.5 Hz, 3 H); 4.69 (s, 1 H); 6.38 (q, 1.5 Hz, 1 H); 8.18 (s, 1 H).

Addition of sodium perchlorate to an aqueous solution of the crude product precipitated a diperchlorate, ^{1}H NMR spectrum ($(CD_3)_2SO$): δ 1.72 (d, 1.5 Hz, 3 H); 4.57 (s, 1 H); 6.46 (q, 1.5 Hz, 1 H); 8.22 (s, 1 H); 11.6 (br.s., 1 H). Evaporation of the mother liquor left a mixture of sodium perchlorate and a diperchlorate with a ^{1}H NMR spectrum identical to that described above.

Reduction of 4-phenylpyrimidine (3). 3 (2 g) was reduced in 0.1 M HCl, $n = 0.80$ F mol^{-1}. Evaporation of the catholyte left a dimer as the dihydrochloride; it was dried by azeotropic distillation with n-butanol and recrystallized from aqueous ethanol, m.p. (decomp.) 272 – 274 °C. ^{1}H NMR spectrum (DMSO-d_6): δ 4.68 (d, 3.3 Hz, 2 H); 5.64 (d, 3.3 Hz, 2 H); 7.4 – 7.7 (m, 12 H); 8.32 (s, 2 H).

Reduction of 6-chloro-2-phenyl-4-trichloromethylpyrimidine (8). 8 (300 mg) was reduced in DMF/0.1 M tetrabutylammonium tetrafluoborate containing 0.5 % acetic acid at −0.2 V (*vs.* Ag/AgI, 0.1 M TBAI), $n = 1.86$ F mol^{-1}. The catholyte was diluted with water and the product extracted with diethyl ether, which was washed with water and dried over $MgSO_4$. Evaporation of the ether left a residue which was recrystallized from light petroleum yielding 0.244 g (92 %) of 4-chloro-6-dichloromethyl-2-phenylpyrimidine (*21*), m.p. 79.9 °C. ^{1}H NMR ($CDCl_3$): δ 6.56 (s, 1 H); 7.32 – 7.45 (m, 3 H); 7.51 (s, 1 H); 8.26 – 8.44 (m, 2 H). The δ-values for the dichloromethylproton and the 5-proton agree with those in 4-dichloromethylpyrimidine[13]

Reduction of 2-phenyl-4-trichloromethylpyrimidine (7). 7 (300 mg) was reduced under similar conditions as *8* at −0.25 V (*vs.* Ag/AgI), $n = 1.72$ F mol^{-1}. The crude extract was purified on a column of silica with a 1:1 mixture of hexane and dichloromethane as eluent giving 0.240 g (91.5 %) of 4-dichloromethyl-2-phenylpyrimidine (*20*), m.p. 45.4 °C. ^{1}H NMR ($CDCl_3$): δ 6.56 (s, 1 H); 7.32 – 7.57 (m, 4 H); 8.32 – 8.45 (m, 2 H); 8.86 (d, 5 Hz, 1 H).

Ethanolysis of 4-chloro-6-dichloromethyl-2-phenylpyrimidine (21). 21 (0.200 g) was refluxed 12 h with 0.2 M KOH in a 3:2 mixture of water and ethanol. After cooling the mixture was diluted with water, pH adjusted to 7 with acetic acid and the product extracted with diethyl ether. The ether was washed with an aqueous solution of $NaHCO_3$ and dried over $MgSO_4$; evaporation of the solvent left 240 mg of a crude oil which was crystallized from methanol giving 4-dichloromethyl-6-ethoxy-2-phenylpyrimidine, m.p. 78.7 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (tr, 7.5 Hz, 3 H); 4.53 (q, 7.5 Hz, 2 H); 4.68 (s, 1 H); 6.52 (s, 1 H); 7.25 – 7.45 (m, 3 H); 8.25 – 8.45 (m, 2 H).

Attempted hydrolysis of 4-dichloromethyl-2-phenylpyrimidine (20). 20 was refluxed 12 h with 0.2 M KOH in aquenous ethanol, with stochiometric amount of sodium ethoxide in ethanol, and with N HCl in aqueous ethanol. The starting material was recovered in all cases.

REFERENCES

1. Smith, D. L and Elving, P. J. *J. Am. Chem. Soc. 84* (1962) 2741.
2. Smith, D. L. and Elving, P. J. *Anal. Chem. 34* (1962) 930.
3. O'Reilly, J. E. and Elving, P. J. *J. Electroanal. Chem. 21* (1969) 169.
4. Elving, P. J., Pace, S. J. and O'Reilly, J. E. *J. Am. Chem. Soc. 95* (1973) 647.
5. Thevenot, D. *J. Electroanal. Chem. 46* (1973) 89.
6. Thompson, T. W. *J. Chem. Soc. Chem. Commun.* 532 (1968).
7. Lund, H. and Jensen, N. J. *Acta Chem. Scand. B 28* (1974) 263.
8. Pinner, A. *Ber. Dtsch. Chem. Ges. 26* (1893) 2122.
9. Evans, P. N. *J. Prakt. Chem. NF 48* (1893) 489.
10. Klötzer, W. *Monatsh. Chem. 87* (1956) 131, 526.
11. Guy, R. W. and Jones, R. A. *Aust. J. Chem. 19* (1966) 1871.
12. Severin, T., Adhikary, P., Dehmel, E. and Eberhard, I. *Chem. Ber. 104* (1971) 2856.
13. Brown, D. J. and Waring, P. *Aust. J. Chem. 27* (1974) 2251.

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