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VON BRAUN (BrCN) REACTION ON PROMETHAZINE AND MEBHYDROLINE

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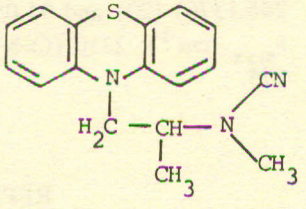
von Braun cyanogen bromide reaction on two antiallergic drugs, promethazine [10-(2-dimethyl amine) *Iso*prophyl] phenothiazine) and Mebhydroline (1-benzyl, 5 methyl, 3,4,5,6-tetrahydro γ-carboline) is described which has led to their cyano and some unusual derivatives.

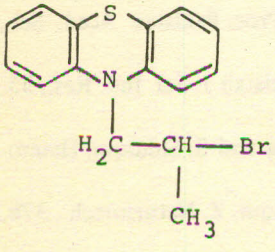
INTRODUCTION

The von Braun (BrCN) reaction and its extension to a number of alkaloidal bases and simpler aliphatic and aromatic amines, relating to studies in the correlation of structure and physiological activity has been described earlier [1-8]. In the present studies, the same reaction has been carried out on promethazine and mebhydroline resulting in the formation of following new derivatives possessing potential pharmacological significance. Characterization of these has been made through spectral studies.

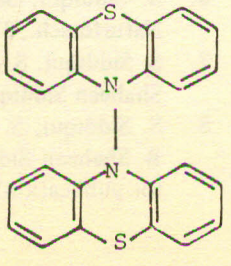
(1) *N*-Cyano *N*-demethyl promethazine



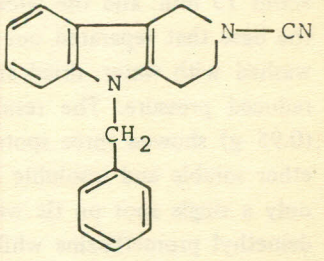
(2) 2-Bromo, *N-iso*propyl phenothiazine



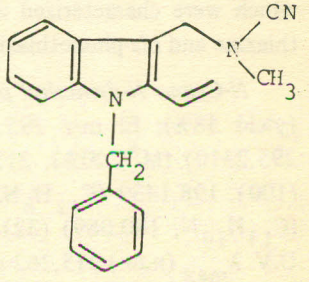
(3) *Bis*-phenothiazine



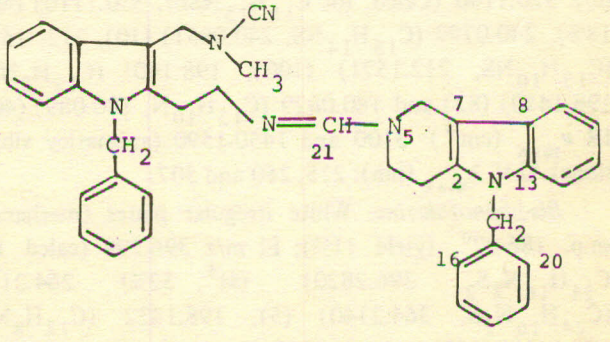
(4) *N*-Cyano *N*-demethyl mebhydroline



(5) *N*-Benzyl, *N*-Cyano *N*-methyl, 2-vinyl tryptamine



(6) 21-(*N*-Benzyl, *N*-Cyano , *N*-methyl, 2-ethylamino tryptamine) Δ^{21}-mebhydroline



The cyanamides described above, when subjected to partial hydrolysis and reduction under the reaction conditions employed in the previous studies, have so far failed to yield any uniform product.

EXPERIMENTAL

Meltings points were recorded in glass capillary tubes and are uncorrected. I.R. (chloroform) and U.V. (methanol) spectra were measured on JASCO IRA-I and Pye-Unicam SP-800 spectrometers respectively. Mass spectra were recorded on Finnigan MAT 112 and MAT 312 double focusing mass spectrometers connected to PDP 11/34 computer system. Purity of the samples was checked on t.l.c. (silica gel S.I..F. 254 precoated aluminium cards).

Reaction of Promethazine with BrCN. To a solution of promethazine (lg) in chloroform (20 ml) was added freshly prepared cyanogen bromide accompanied by good cooling and mechanical stirring. The stirring was continued for about 15 min. and the white crystalline hydrobromide of the base that separated out was filtered. The filtrate was washed with water, dried and freed of the solvent under reduced pressure. The resulting liquidish brown residue (0.95 g) showed three spots on tlc and was divided into ether soluble and insoluble fractions. The former showing only a single spot on tlc was characterized as *N*-cyano *N*-demethyl promethazine while the ether insoluble fraction was subjected to thick layer chromatography (silica gel, chloroform-methanol 9:1) affording two components which were characterized as 2-bromo, N-isopropyl phenothiazine and *bis*-phenothiazine.

N-Cyano N-demethyl promethazine, Light brown liquid (yield 58%); El m/z 295.2293 (calcd. for $C_{17}H_{17}N_3S$, 295.2310) (M^+, 20%), 212.1573 ($C_{13}H_{10}NS$, 212.1570) (100), 198.1439 ($C_{12}H_8NS$, 198.1410) (10) and 180.088 ($C_{13}H_{10}N$, 180.089) (32). IR ν_{max} cm^{-1}:2220 (C≡N). U.V. λ_{max} (n.m.) 215,262 and 305.

2-Bromo, N-isopropyl phenothiazine. Sharp colourless needles (moist methanol) m.p. 253-54°, (yield 18%), E.I. m/z 320.1140 (Calcd. for $C_{15}H_{15}NSBr$, 320.1110) (M^+, 18%), 240.0799 ($C_{15}H_{14}NS$, 240.0851) (10), 212. 1560 ($C_{13}H_{10}NS$, 212.1571) (100), 198.1401 ($C_{12}H_8NS$) 198.1410) (82) and 180.0829 ($C_{13}H_{10}N$, 180.089) (40). IR ν_{max} (cm^{-1}): 3100 and 1450-1590 (aromaticy vibrations). U.V. λ_{max} (nm): 215, 260 and 307.

Bis-phenothiazine. White irregular plates (methanol) m.p. 186-87°, (yield 11%); El m/z 396.299 (calcd. for $C_{24}H_{16}N_2S_2$, 396.2820) (M^+, 32%) 264.2137 ($C_{24}H_{16}N_2S$, 364.2140) (5), 198.1422 ($C_{12}H_8NS$, 198.1410) (100) and 166.0729 ($C_{12}H_8N$, 166.0739) (20). I.R. ν_{max} (cm^{-1}): 3150 and 1470-1600 (aromatic vibrations) U.V. λ_{max} (nm): 215, 265 and 308.

Reaction of mebhydroline with BrCN. Reaction of mebhydroline with BrCN was carried out following the procedure described for promethazine. The reaction product ultimately obtained was similarly divided into ether soluble and insoluble fractions. The former yielded N-cyano demthyl mebhydroline, while the ether insoluble fraction gave compound 5 and 6 through preparative thick layer chromatography (silica gel, chloroform-methanol 9.5:5).

N-Cyanodemethyl mebhydroline. Yellowish brown liquid (yield 43%); El m/z 287.1623 (calcd. for $C_{19}H_{17}N_3$, 287.1630) (M^+, 34%), 261.1531 ($C_{18}H_{17}N_2$, 261.1540) (12), 170.0962 ($C_{11}H_{10}N_2$, 170.0980) (10) and 91.0564 (C_7H_7 91.056) (100). I.R. ν_{max} (cm^{-1}): 2200 (C≡N). U.V. λ_{max} (nm) 220 and 280.

N-Benzyl, N -cyano, N methyl, 2-vinyl tryptamine. Yellowish liquid (yeild 19%); El m/z 301.1782 (calcd. for $C_{20}H_{19}N_3$, 301.1790) (M^+, 20%), 275.1689 ($C_{19}H_{19}N_2$, 275.1788) (5), 232.1279 ($C_{17}H_{14}N$, 232.1290) (24), 141.0576 ($C_{10}H_7N$, 141.0578) (18) and 91.0562 (C_7H_7, 91.0560) (100) I.R. ν_{max} (cm^{-1}): 2240 (C≡N). U.V.λ_{max} (nm): 220 and 270.

21 (N-Benzyl N-cyano, N-methyl, 2-ethyl aminotrptamine) Δ^{21} mebhydroline. Light yellow elongated rods (methanol), m.p. 160-61°, (yield 8.5%); El m/z 590.3573 (calcd. for $C_{39}H_{38}N_6$, 590.358) (M^+, 12%), 534.4350) ($C_{37}H_{34}N_4$, 534.4351) (20), 499.3101 ($C_{32}H_{31}N_6$, 499.302) (8), 302.1868 ($C_{20}H_{20}N_3$, 302. 1877) (12), 289.749 ($C_{19}H_{19}N_3$,289.179) (7), 246.1366 ($C_{18}H_{16}N$) 246.1376) (20) and 91.0539 (C_7H_7, 91.056) (100). I.R. ν_{max} (cm^{-1}): 2210 (C≡N). UV. λ_{max} (nm): 220,215 and 275.

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