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CARBON -13 NUCLEAR MAGNETIC RESONANCE SPECTRA OF 5-SUBSTITUTED 2-THIOURACIL DERIVATIVES.

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ABSTRACT

^{13}C NMR chemical shifts have been recorded for a number of 5-substituted 2-thiouracil derivatives. These derivatives were prepared from the corresponding esters in a two step reaction giving a pure grade products to be used as synthons for preparing 2-thioanalogues of (AZT).

3`-Azido-2`,3`-dideoxythymidine (AZT) was synthesized by Horwitz,[1] then reported by Mitsuya *et al.* [2] to inhibit significantly the replication of HIV. Since this drug causes severe side effects[3], many other nucleoside analogues were synthesized and their structural - antiviral activity relationships have been investigated.[4] Introduction of a methyl or ethyl group into position 5 of the pyrimidine base increases the activity[5]. As recorded in the literature [6-10] oxygen sulfur exchange for natural nucleoside was done through a complicated strategy to achieve 2- thiothymidine, whereas 4- thiothymidine was obtained by direct thionation. Synthesis of 5-substituted-2- thiouracil analogues of AZT aiming to get analogues less toxic and at least as active as AZT against human immunodeficiency virus is still needed.

These nucleosides can be prepared via coupling of 2- thiouracil derivatives with the appropriate azido sugar as reported.[11]

RESULTS AND DISCUSION

Synthesis of some 5-hydroxypyrimidines and 2-thiouracil derivatives were reported.[12-13] ^{13}C NMR spectra of some N-, O-, and S-methylated uracil and thiouracil derivatives were recorded and investigated by Still *et al.*[14]

Since the early pioneering work of Lauterbur[15], there have been recorded some investigations of the ^{13}C NMR spectra of some uracils.[16-18] But still there is an urgent need for preparing and recording different 5-substituted 2-thiouracils to be used as synthons for preparing 2-thio analogues of AZT. Therefore I decided to prepare and record the NMR spectra for 5 substituted 2-thiouracils to be used as synthons for 2-thio analogues of AZT with expected antiviral activity against human immunodeficiency virus (HIV) as a possible chemotherapeutic strategy.

In this investigation I used the preported [13]Chesterfield method by which 5-substituted-2-thiouracils were prepared in (50.1-21%) yield by formylation of the proper ester, then treating the crude product with thiourea.

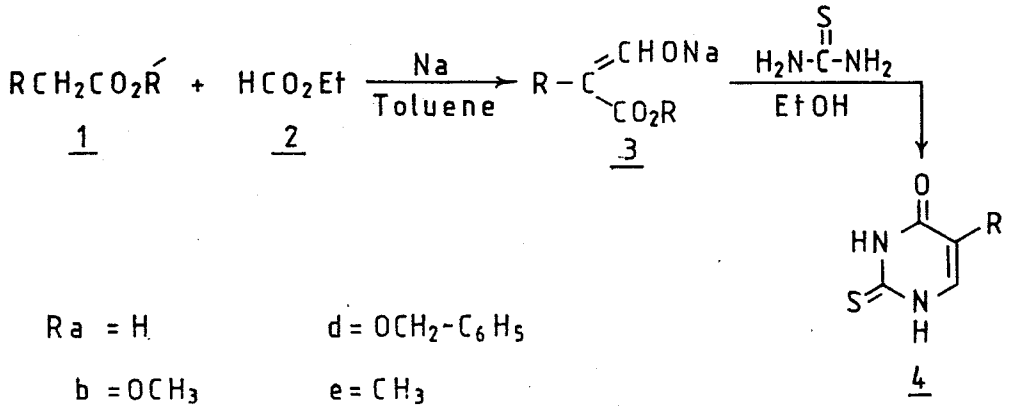
^{13}C NMR spectra were recorded and interpretted giving conclusive evidence for the productes structdure(4b-f)with the parent 2-thiouracil.[15]

^{13}C NMR sepectrum of 5-ethoxy-2-thiouracil (4c) revealed the $-CH_3$ and $-OCH_2$ at the expected fileds at. δ 14.24 and 64.90,respectively. The C=S (C-2) function appeared at 171.15 comparable to C = S of pyridine 2-thiones which has

been reported to appear at a similar field[19]. The carbonyl at C-4 appeared at 157.22. This is too high field for cyclic amide carbonyl and thus it is suggested that the molecule has considerable contribution of the charge separated resonance form indicated. However, the posibility that (4c) exists under the measurements conditions in the enol form can not be overlooked.

It is of value to report that in compound (4c) the double bond between C - 5 and C-6 is electron rich and thus both carbons in this double bond is expected to be shielded. C - 5 is shielded by N lone pair resonance (cf. Resonance form 4c (A). Also C - 6 is in turn shielded by oxygen lone pair resonance (cf. Form 4c (B). Thus, the values observed here look logical. However, assignment of these values to specefic carbons caused some confusion. I believe that C - 5 should be more shielded than C - 6 as although it is deshielded by being linked to more electronegative element of higher molecular weight, it is shielded by nitrogen lone pair resonance. Although oxygen lone pair would also shield C - 6, this shielding effect is expected to be of smaller magnitude as compared to nitrogen lone pair shielding effect of C - 5. Oxygen is more electronegative than nitrogen and thus has more tendency to retain its lone pair of electrons.

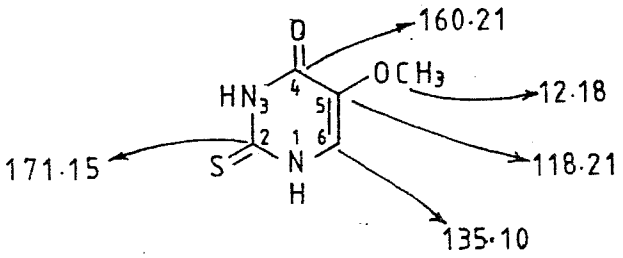
The mass spectrum of (4c) revealed molecular ion as a base peak. This underwent appreciable fragmentation via loss of ethyl yielding the dioxo compound that fragmented further into isocyanate.

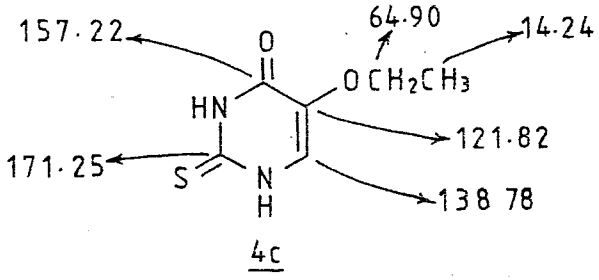


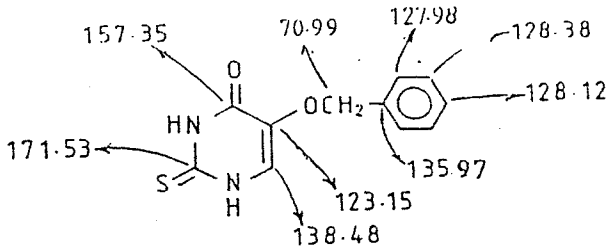
Ra = H d = OCH_2-C_6H_5

b = OCH_3 e = CH_3

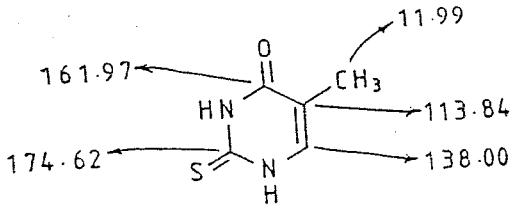
c = OC_2H_5 f = SCH_3



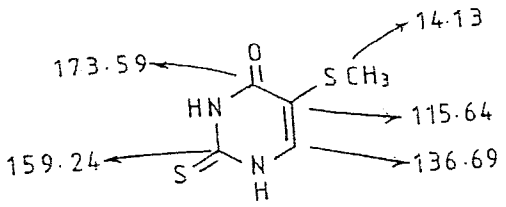



157·35
70·99
127·98
128·38
128·12
135·97
123·15
138·48
171·53
OCH2
HN
S
N
H
O

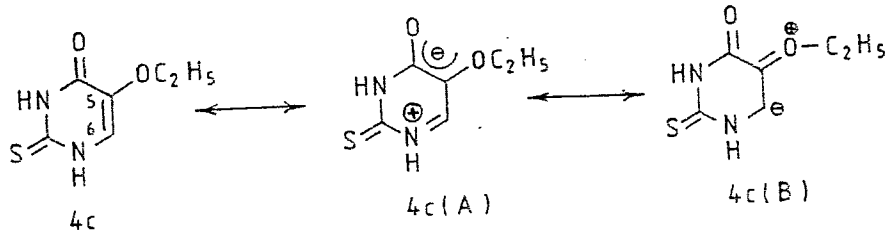
4d

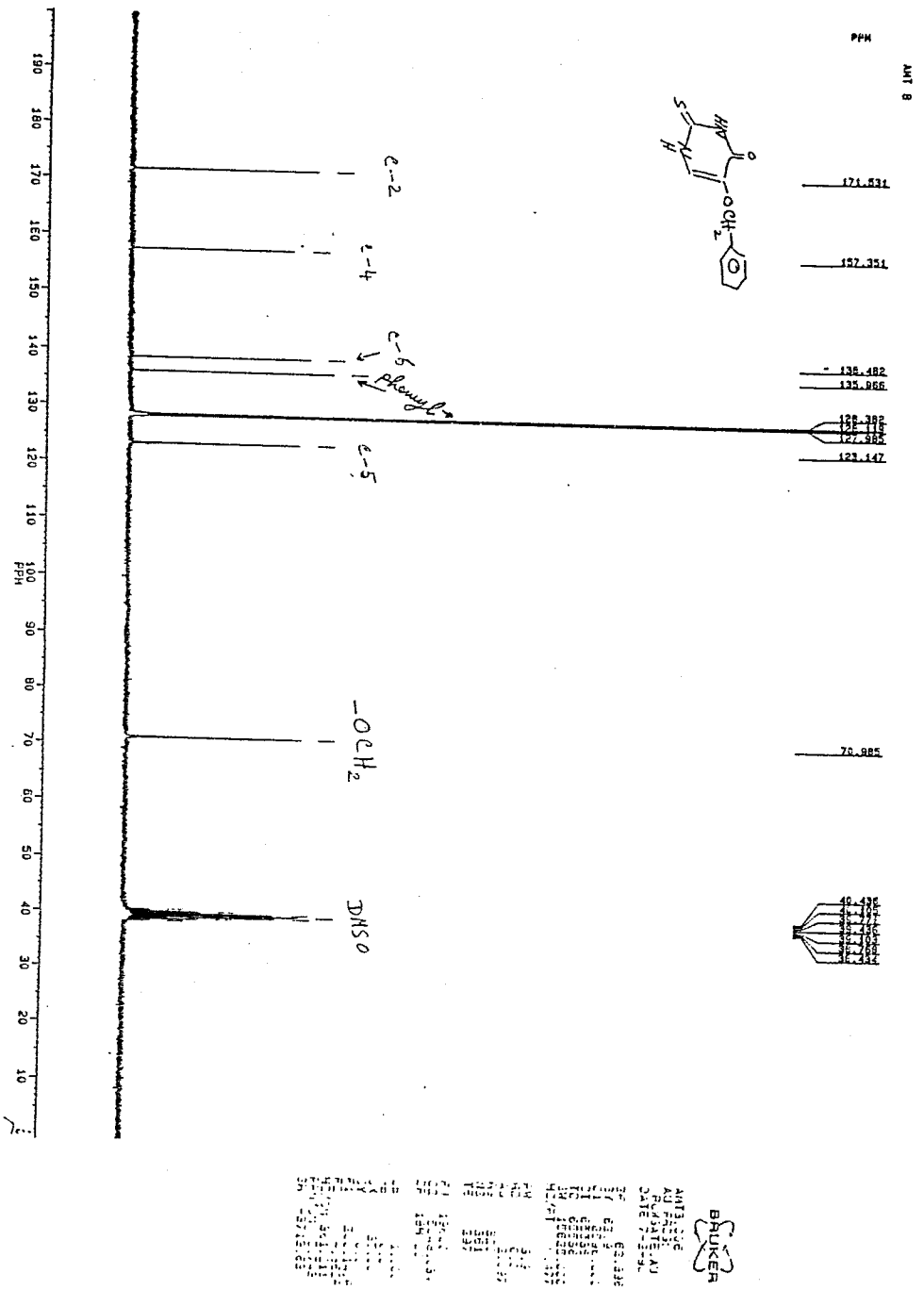

11·99
161·97
113·84
174·62
138·00
CH3
HN
S
N
H
O

4e


14·13
173·59
115·64
159·24
136·69
S CH3
HN
S
N
H
O

4f


OC2H5
HN
S
N
H
O
4c
4c(A)
4c(B)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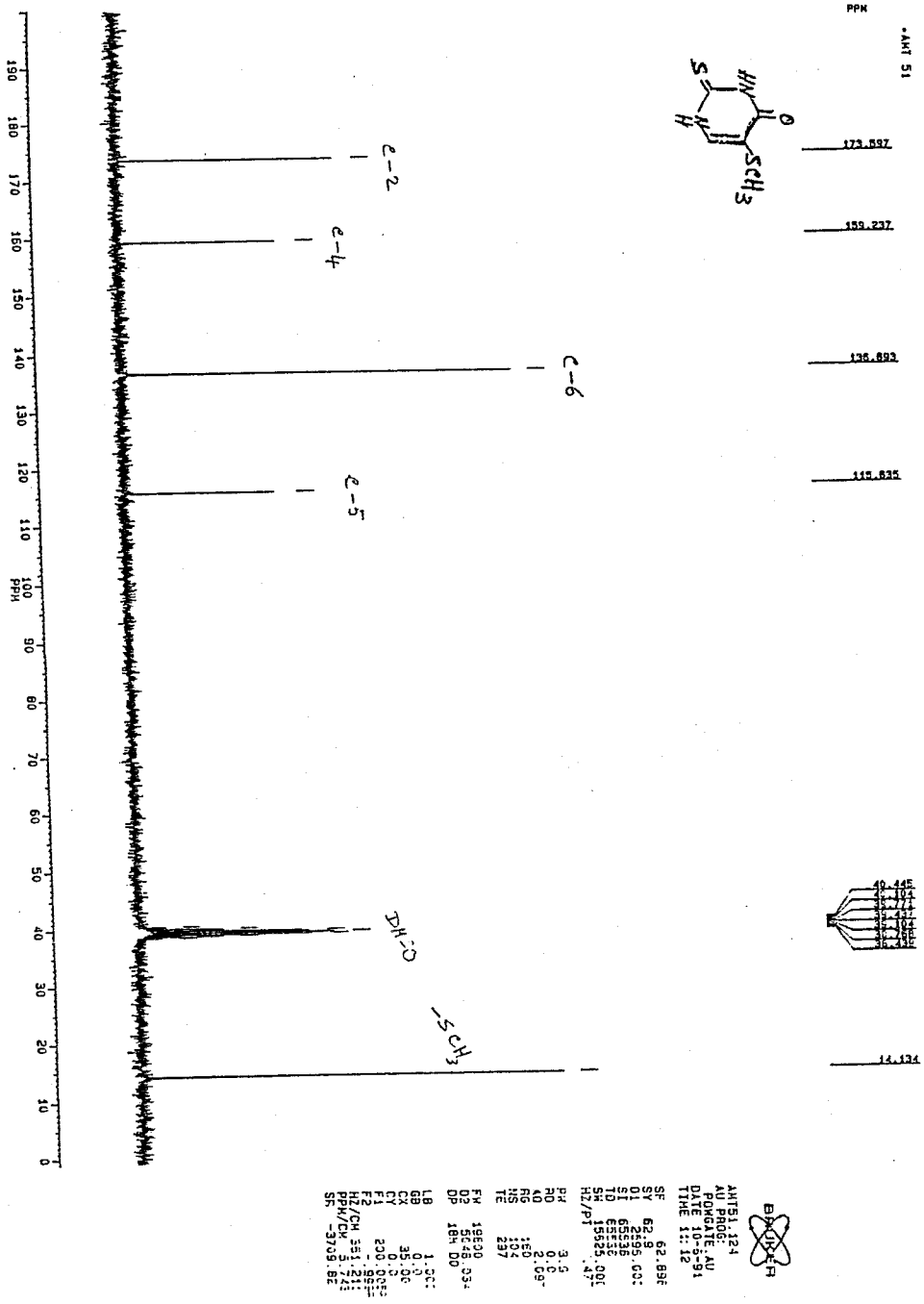
135.966
128.382
127.985
123.147
70.985
40.436
C-2
C-4
C-6
C-1'
C-5
-OCH2
DMSO
BRUKER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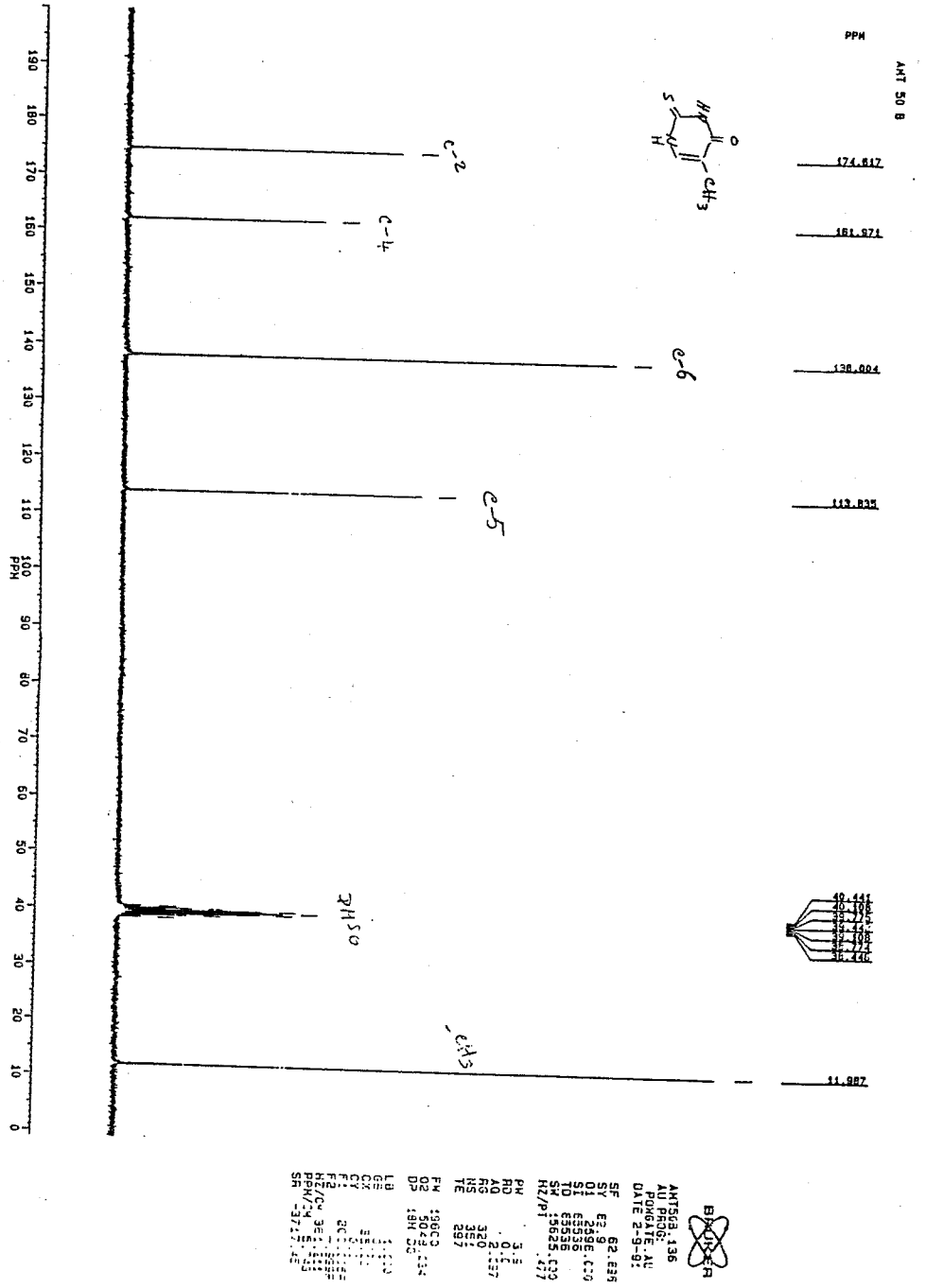
159.237
136.893
115.835
40.445
14.134
e-2
e-4
e-6
e-5
DMSO
-SCH3
AHTB1.124
AU PROG: AU
PDMGATE.AU
DATE 11-91
TIME 11:12
SF 62.89E
SY 62.9
D1 2595.CO:
SI 65536
TD 65536.00(
SW 15625.00(
HZ/PT .47
PW 3.0
PO 0.0
AQ 2.09
RG 160
NS 104
TE 237
FW 19630
D2 55248.03-
DP 18H.00
LB 1.00:
GB 0.0
SX 35.0:
SY 0.0
F1 200.00E
F2 -.95E
HZ/CM 551.21:
PPM/CM 3.74:
SR -3705.82
BRUKER
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


PPM
AMT 50 8
174.617
161.971
138.004
113.835
40.441
11.987
C-2
C-4
C-6
C-5
DMSO
CH3
PPM

EXPERIMENTAL

^{13}C NMR and ^{1}H NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer . Mass spectra were recorded on a Varian MAT 311 A spectrometer. Microanalysis were carried out by Microanalytical Unit at Cairo University.

General procedure :

A mixture of the proper ester (0.1 mole) and ethyl formate (0.1 mole, 7.4 g) was added dropwise to a stirred suspension of sodium (0.1 mole, 2.3 g) in toluene (30 ml), the temperature being kept below 30°C for 24 hrs . The solvent was evaporated and to the crude viscous sodio -β - ester were added ethanol (20 ml) and thiourea (0.1 mole, 7.6 g) to give the corresponding 5-substituted -2-thiouracils (4b -f).

2-Thiouracil : [4a; $C_4H_4N_2OS$; (128 .15)] , ^{13}C NMR (DMSO) δ 105.2 (C - 5); 142.0 (C - 6); 160.9 (C -4) ; 175.9 (C - 2). [4]

5-Methoxy -2-thiouracil : [4b; $C_5H_6N_2O_2S$ (158.18). Methyl methoxyacetate (Ib, 0.1 mole, 10.4 g) was used to give 2-thio- 5-methoxyuracil (4a) as white crystals, recrystallized from water, M.P. 280 - 281 °C; yield 7.92 g (50 .1 %), ^{1}H NMR (DMSO) δ3.8 (s, 3H, CH_3); 7.05 (s, 1H, CH); 12.5 (br, 2H, 2NH). ^{13}C NMR (DMSO) δ 12 .18 (CH_3) ; 118.21 (C - 5); 135.10 (C - 6); 160.21 (C - 4); 171.15 (C-2).

$C_5H_6N_2O_2S$ Calcd C, 37.97; H, 3.82; N, 17.71; S, 20.27
Found C, 38.1; H 3.9; N, 17.4; S, 20.1%.

5-Ethoxy-2-thiouracil : [**4c**, $C_6H_8N_2O_2S$ (172.21). Ethyl ethoxyacetate (Ic, 0.1 mole, 13.2 g) was used to give 2-thio-5-ethoxyuracil (4c) as pale yellow crystals, recrystallized from water, M.P. 230 °C, yield 8.46 g (49 %), ^1H NMR (DMSO) δ 1.26 (3H, t, j = 7 Hz CH_3), 3.85 (2H, q, OCH_2), 7.03 (1H, s, 6-H); 12.35 (br. 2H. 2NH); ^{13}C NMR (DMSO) δ 14.24 (CH_3); 64.90 (OCH_3), 121.82 (C- 6), 138.78 (C - 5), 157.22 (C - 4); 171.25 (C -2); Ms: m/z (%) = 127 (M*, 100), 144 (64), 57 (89), 28 (42).

$C_6H_8N_2O_2S$ Calcd. C, 41.85; H, 4.68; N, 16.27; S, 18.62
Found C, 42.2; H, 4.6; N, 16.2; S, 18.6 %

5-Benzyloxy-2-thiouracil [**4d**, $C_{11}H_{10}N_2O_2S$ (234.28).

(A) The proper ester i.e benzyl benzyloxyacetate (**Id**) $C_{16}H_{16}O_3$ (256.30) was prepared [14] as reported from ethyl chloroacetate and benzyl alcohol in presence of sodium metal (in equimolecular amounts) to give benzyl benzyloxy acetate, yield 30 %, b.p. 170 - 172 °C/0.6 mm.,

Calcd. C, 74.98; H, 6.29

Found C, 75.1; H, 6.2 % .

(B) Benzyl benzyloxyacetate **Id**, 0.1 mole (25.63 g), was used to prepare 5-benzyloxy-2-thiouracil (**4d**) as pale buff crystals recrystallized from ethanol, M.P. 229 - 230 °C, yield 5.1 g (21.8 %), ^1H NMR (DMSO): δ 4.95 (s, 2H, CH_2); 7.10 (s,1H, H - 6), 7.30 (M, 5H, arom . H), 12.30 (br, 2H, 2NH). ^{13}C NMR (DMSO) δ 70.99 (OCH_2), 123.15 (C - 5), 127.99, 128.12, 128.38, 135.97 (phenyl), 138.48 (C - 6), 157.35 (C - 4), 171.53 (C - 2); Ms: m / z (%) = , 234 (M^*, 18), 91 (100).

5-Methyl-2-thiouracil [**4e**, $C_5H_6N_2OS$ (142.61)]. Ethyl propionate (**1e**, 0.1 mole, 10.21 g) was used to obtain 5-methyl-2-thiouracil (2-thiothymine) (**4e**) as pale yellow crystals, recystallizd from water, M.P. 279 - 280 °C, yield 4.11 g (28.82 %); ^{1}H NMR (DMSO) δ 1.80 (s, 3H, CH_3) , 7.31 (s, 1H, H-6), 12.30 (br, 2H, 2NH). ^{13}C NMR (DMSO); δ 11.99 (CH_3), 113.84 (C - 5), 138.00 (C-6), 161.87 (C - 4), 174.62 (C - 2).

$C_5H_6N_2OS$ Calcd C, 42.11; H, 4.24; N, 19.64; S, 22.48
Found C, 42.1; H, 4.2; N, 19.6; S, 22.4 %.

Ms: m / z (%) = 142 (M*, 100), 84 (28), 55 (100), 54 (38), 28 (70).

5-Methylthio-2-thiouracil [**4f**, $C_5H_6N_2OS_2$ (174.68)]. Ethyl methylthioacetate (**1f**, 0.1 mole, 13.42g) gave 5-thiomethyl-2-thiouracil (**4f**) as buff crystals, recrystallized from methanol, M.P. 288 - 289 °C, yield 3.67 g. (21 %), ^{1}H NMR (DMSO) δ 2.30 (s, 3H, CH_3) 7.20 (s, 1H, H - 6); 12.54 (br, 2H, 2NH). ^{13}C NMR (DMSO) δ 14.13 (SCH_3), 115.64 (C - 5), 136.69 (C - 6); 159.24 (C - 4); 173.59 (C-2). Ms: m / z (%) = 174 (M^*, 100), 141 (12), 72 (20), 45 (25).

$C_5H_6N_2OS_2$ Calcd. C, 34.38; H, 3.46; N, 16.04; S, 36.75
Found C, 34.3; H 3.4; N, 16.0; S, 36.4 %

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دراسة أطياف الرنين النووى المغناطيسى للكربون ١٣ لبعض مركبات ٢ - ثيوبوراسيل

عبد المنعم الترجمان

قسم الكيمياء - كلية العلوم - جامعة المنوفيه

قد تم تسجيل أطياف الرنين النووى المغناطيسى لعدد من مشتقات ٢ - ثيوبوراسيل ودراستها وإثبات التركيب الجزيئى لها ومناقشة القيم المسجله لكل مجموعة جزيئية ومقارنتها بنتائج البحوث المنشوره فى هذا المجال.

هذه المركبات قد تم تحضيرها من الإسترات المقابله لها على خطوتين وتم بلورتها لتعطى عينات على درجه عالية من النقاوه لتستخدم فى تحضير متماثلات - تحتوى على ذرة كبريت فى الموضع ٢- للمركب المستخدم فى علاج مرضى الايدز AZT .