Bull. Pharm. Sci., Assiut University
Vol, 9, Part 2 pp 105 - 118

SYNTHESIS OF SOME 2,7-DIAZABICYCLO {4.1.0} HEPT-3-ENE DERIVATIVES WITH ANALGESIC AND ANTICOCCIDIAL ACTIVITY

H.H. Farag, A.M. Abdel-Alim, H.Y. Hassan, H.A. Hemaiat-Allah, R.A. Abdel-Aal* and A.M. El-Badr**

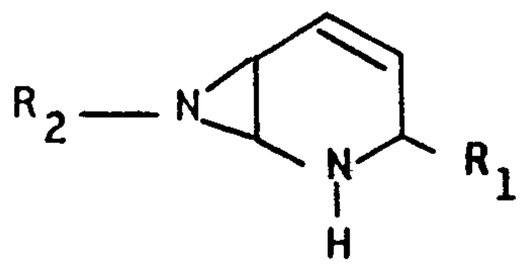
Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Departments of Pharmacology* and Parasitology**, Faculty of Medicine, Assiut University, Assiut, Egypt

ABSTRACT

The 1,3-dipolar cycloaddition reaction of arylsulphonyl azides to 1,3-disubstituted-1,4-dihydropyridines afforded 2,7-diazabicyclo {4.1.0} hept-3-ene derivatives (III). These compounds exhibited moresignificant analgesic and anticoccidial activities than aspirin and sulphaguanidine respectively.

INTRODUCTION

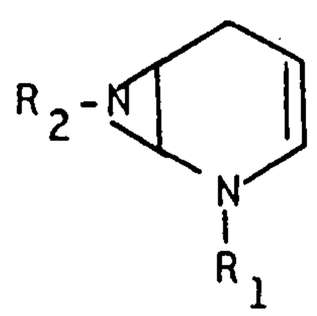
The regiospecific 1,3-dipolar cycloaddition reaction of organic azides to 1,2-dihydropyridines afforded 7-substituted 2,7-diazabicyclo {4.1.0}hept-4-enes[1] which elicited significant analgesic, antibacterial and antifungal activities[2].



(I)

R_1=n-Bu, Ph; R_2 =CN, MeOCO, $MeSO_2$, $PhSO_2$, p-H_2N-C_6H_4-SO_2, p-MeCONH-C_6H_4-SO_2.

Recently, 7-substituted 2,7-diazabicyclo {4.1.0} hept-3-enes (II) have been also investigated to possess a wide range of biological activities[3]. Thus, the most active analgesics IIa and IIc were more potent than aspirin and dextropropoxyphene, Compounds IIa-e exerted potent antiprotozoal activity against Trichomonas vaginalis at concentrations of less than 10 ug/ml of medium. Pharmacological screening also revealed moderate hypoglycemic (IIa), antiinflammatory (IIc), antidepressant (IId,e) and anthihistaminic (IIf) activities.

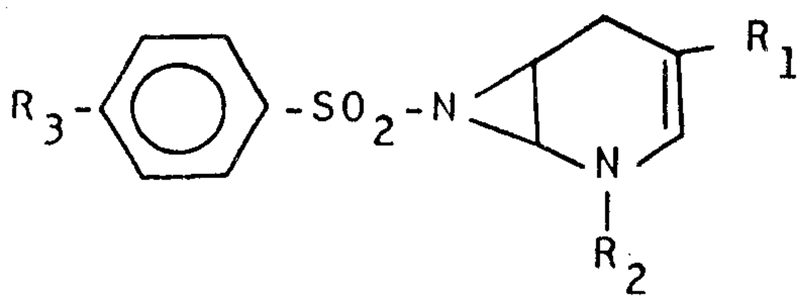


(II)

R_1,R_2=Me, CN(a); Me, $MeSO_2$(b); Me,$PhSO_2$(c); Me, p-H_2N-C_6H_4-SO_2(d); Me, p-MeCONH-C_6H_4-SO_2(e); H, $PhSO_2$(f).

Synthesis of Some 2,7-Diazabicyclo {4.1.0}Hept-3-ene Derivatives With Analgesic and Anticoccidial Activity.

Accordingly, the present work aims at the synthesis of similar 2,7-diazabicyclo {4.1.0} hept-3-enes (III) carrying different substituents at positions 2,4 and 7 which may augment the expected biological activities.



(III)

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed at the unit of microanalysis, Faculty of Science, Cairo University. PMR spectra were determined on a Varian 60 MHZ Spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Intermediates: pyridinium salts (V)[4-8], dihydropyridines (VI)[4-12] and arylsulphonyl azides (VII)[13-16] were prepared, in good yields, according to reported procedures and their data are in good agreement with the published.

4-Ethoxycarbonyl -2-methyl-7-benzenesulphonyl-2,7-diazabicyclo {4.1.0} hept-3-ene (IIIa):

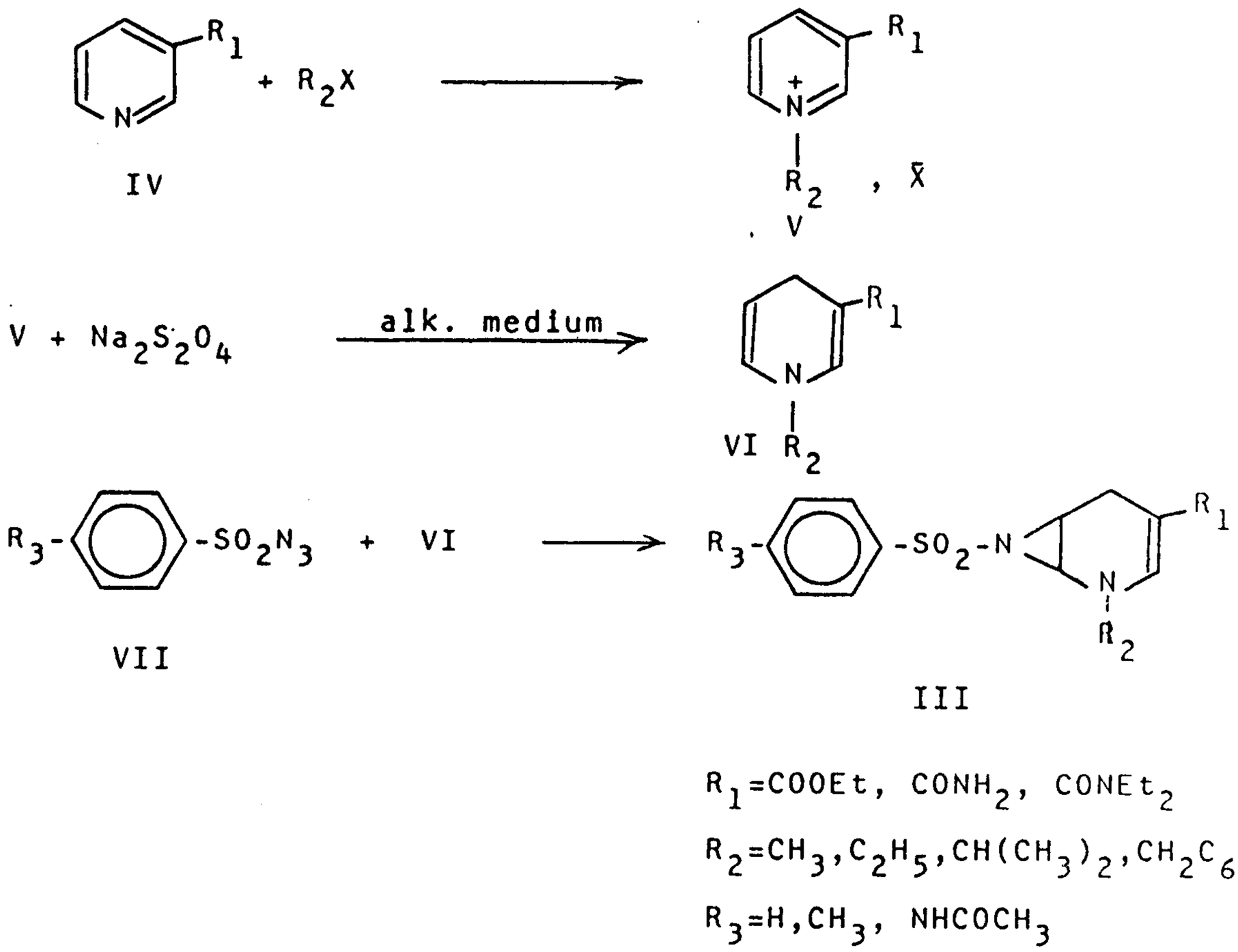
To a solution of 1.67 g (0.01 mole) of freshly prepared 3-ethoxycarbonyl-1-methyl-1,4-dihydropyridine (VI) in 75 ml of dichloromethane, a solution of 1.83 g (0.01 mole) of benzenesulphonyl azide(VII) in 75 ml of dichloromethane was dropped while stirring. Evolution of nitrogen was observed and the reaction mixture was further stirred for 2 hr. The solvent was distilled on a rotavapour, a white solid was obtained. The product was filtered, washed with dichloromethane, dried and crystallized from ethanol, yield 2.7 g (84%) m.p. 115-6°.

The rest 2,7-diazabicyclo compounds (IIIb-s) were similarly prepared and their data are listed in Table 1.

RESULTS AND DISCUSSION

I- Synthesis:

The suggested compounds III were synthesized by the 1,3-dipolar cycloaddition reaction of arylsulphonyl azides to 1,3-disubstituted-1,4-dihydropyridines at 25° according to the following scheme:



R_1=COOEt, $CONH_2$, $CONEt_2$

R_2=CH_3, C_2H_5, $CH(CH_3)_2$, $CH_2C_6H_5$

R_3=H, CH_3, $NHCOCH_3$

Synthesis of Some 2,7-Diazabicyclo {4.1.0} Hept-3-ene Derivatives With Analgesic and Anticoccidial Activity.

The prepared 2,7-diazabicyclo {4.1.0}hept-3-enes (IIIa-s,Table 1) are white crystalline powders, soluble in chloroform, dichloroethane, benzene, ether, slightly soluble in alcohol and insoluble in water. Their structures were confirmed by microanalysis, and pmr spectrometry. PMR spectra of compounds IIIa,f,k & s showed the characteristic signals which comply with the assigned structures.

IIIa: δ 8.0 (dd, 2H, ortho aromatic protons), 7.52 (m,3H, meta & para aromatic protons), 7.15(s, 1H, C_3H), 4.2 (q, 2H, OCH_2), 3.4-3.1 (m, 2H; C_1H, C_6H), 3.16 (s, 3H, N-CH_3), 2.55 (broad t, 2H, C_5H), 1.26 (t, 3H, CH_3).

IIIf: δ 8.15 (broad s, 1H, CONH), 7.95-7.5 (dd, 4H, C_6H_4), 7.2(s, 1H, C_3H), 4.22 (q, 2H, CH_2), 3.2 (m,2H,C_1H, C_6H), 3.16 (s, 3H, N-CH_3), 2.55 (broad t, 2H, C_5H), 2.16(s, 3H, CH_3CO), 1.3 (t, 3H, CH_3).

IIIK: δ 7.8-7.3 (dd, 4H, C_6H_4), 7.26 (s, 1H, C_3H), 5.85-5.65 (broad s, 2H, $CONH_2$), 4.92 (septet, 1H, $CH(CH_3)_2$), 3.43-3.17 (m, 2H; C_1H, C_6H), 2.63-2.35 (broad t, 2H, C_5H), 2.4 (s, 3H, $CH_3C_6H_4$), 1.2 (d, 6H, $(CH_3)_2CH$).

IIIs: δ 8.7 (broad s, 1H, CONH), 8.0-7.66 (dd, 4H, C_6H_4), 6.41 (broad s; 1H, C_3H), 3.8-3.1 (m, 8H; 3 CH_2, C_1H, C_6H), 2.5 (broad t, 2H, C_5H), 2.2 (s, 3H, CH_3CO), 1.2 (t, 9H, 3 CH_3).

II- Biological Screening:

A. Analgesic Activity:

(1) Materials and method:

Analgesic activity of nine 2,7-diazabicyclo {4.1.0} hept-3-enes III (Table 2) was evaluated by the phenylquinone writhing test[17] in comparison to aspirin as a reference drug. Ten adult albino mice weighing 18-22 g of either sex were used in each group. The test compounds as well as aspirin were suspended in a 1% solution of tween 80 in normal saline. Each group of animals was injected subcutaneously with the appropriate test compound (III) at a dose level of 60 mg/Kg animal body weight, and 30 min later each mouse received 0.03% p-benzoquinone solution in a volume of 0.1 ml/10 g of body weight intraperitoneally. The total number of writhes exhibited by each animal, during one hour, in the test group was recorded and compared to that of a vehicle-treated control group. The percent inhibition in number of writhes was calculated according to the following equation[3]:

$$\% \text{ Inhibition} = \frac{\text{(no. of writhes in treated group)}}{\text{(no. of writhes in control group)}} \times 100 - 100$$

Results are recorded in Table 2.

(2) Results and Discussion:

It has been reported[3], a compound causing a 30-50% reduction in the number of writhes is considered to be slightly active, whereas one causing a greater than 50% reduction is an active analgesic agent.

Accordingly, statistical analysis of results showed that both the test compounds (III) and aspirin exhibited a significant analgesic activity at a level of $P<0.01$. Moreover, all the test compounds are more active as analgesics than aspirin (Table 2). Thus, compounds carrying a carbamoyl substituent

at position 4 are about 1.4-1.54 as active as aspirin, while the ester containing compounds (IIIb,e) are slightly more active than aspirin.

B- Anticoccidial Activity:

(1) Materials and Method:

Seven diazabicylo compounds IIIe,f,k,m,o,q,and r (Table 1) were tested for anticoccidial activity on infected rabbits in comparison to sulphaguanidine as a reference drug according to a reported method[18].

Ten experimentally infected rabbits with hepatic and intestinal coccidiosis (Eiemeria stiedae and E. perforans), weighing 0.5-1.0 Kg (2-3 month old) of local breed were used in each group. The test compounds III as well as the reference drug were given orally by a stomach tube in the form of suspension in a 1% solution of carboxymethyl cellulose (CMC).

For diagnosis of cases of coccidiosis in rabbits, the faecal samples were collected daily according to Swan[19]. The degree of infection was determined by oocysts count per one high-power microscopic field[18].

90 Infected rabbits were divided into 9 groups. The number of oocysts per one high power microscopic field was determined for each animal before experiment. Each of the first seven groups of animals received orally a 60 mg/kg body weight of the appropriate test compound(III) for 10 consequent days. Sulphaguanidine (60 mg/kg) was also given orally to the 8th group, while the 9th group served as a control group and received the vehicle (1% CMC)orally. Each group of rabbits was kept separately, daily collection of faecal samples from each

rabbit for oocysts count was covered out and the number of oocysts per microscopic field was estimated.

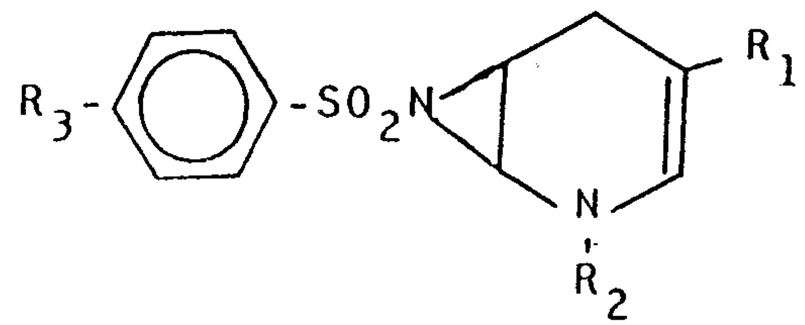
(2) Results and Discussion

Results revealed that the test compounds III are effective against rabbit coccidiosis. Generally, experimentally infected rabbits became free from infection after the 5th day from time of administration of the test compounds, while those rabbits treated with sulphaguanidine were free from infection after the 6th day.

It is of interest to mention that, complete inhibition of oocyst production was noticed after the 2nd day in those rabbits treated with compounds IIIf, m & q, while this inhibition was obtained after the 3rd day upon treatment with IIIe & o. Compounds r and k showed the same clearance of oocysts after the 4th and the 5th day respectively.

Superiority of anticoccidial activity of most of the test compounds III over sulphaguanidine might be explained on the basis that, sulphaguanidine inhibits only the growth of the asexual stages[20] of the parasite, while the test compounds, most prabably may inhibit the growth of both sexual and asexual stages of coccidia.

Table 1. 2,7-Diazabicyclo{4.1.0}hept-3-enes (IIIa-s).



III	R_1	R_2	R_3	Yield (%)	M.P. (°C)	Molecular* Formula	Microanalysis Calcd./Found C%	H%	S%
a	$COOC_2H_5$	CH_3	H	84	115-6	$C_{15}H_{18}N_2O_4S$	55.97 56.20	5.59 5.60	9.94 9.50
b	$COOC_2H_5$	C_2H_5	H	89	98-9	$C_{16}H_{20}N_2O_4S$	57.14 56.80	5.95 5.00	9.52 10.10
c	$COOC_2H_5$	CH_3	CH_3	92	115-6	$C_{16}H_{20}N_2O_4S$	57.14 57.00	5.95 5.70	9.52 9.10
d	$COOC_2H_5$	C_2H_5	CH_3	92	121-2	$C_{17}H_{22}N_2O_4S$	58.28 58.40	6.28 6.40	9.14 8.80
e	$COOC_2H_5$	CH_2-C_6H_5	CH_3	90	133-4	$C_{22}H_{24}N_2O_4S$	64.08 64.90	5.82 5.30	7.77 7.20
f	$COOC_2H_5$	CH_3	CH_3CONH	82	182-3	$C_{17}H_{21}N_3O_5S$	53.82 54.00	5.54 5.00	8.44 8.80
g	$COOC_2H_5$	C_2H_5	CH_3CONH	87	149-50	$C_{18}H_{23}N_3O_5S$	54.96 54.30	5.85 5.20	8.78 9.00
h	$CONH_2$	C_2H_5	H	53	204-5	$C_{14}H_{17}N_3O_3S$	54.72 53.90	5.54 4.90	10.42 10.90
i	$CONH_2$	CH_2-C_6H_5	H	97	193-4	$C_{19}H_{19}N_3O_3S$	61.79 61.80	5.15 5.50	8.67 9.00

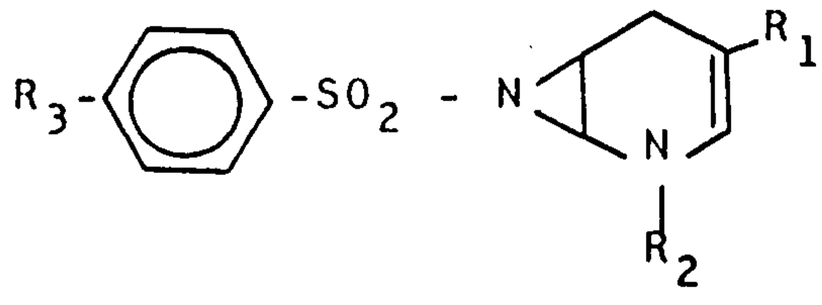
Table 1 . (Continued)

III	R_1	R_2	R_3	Yield (%)	M.P. (°C)	Molecular formula	Microanalysis: Calcd./Found C%	H%	S%
j	$CONH_2$	C_2H_5	CH_3	83	235-6	$C_{15}H_{19}N_3O_3S$	56.07 56.10	5.92 5.90	9.97 9.40
k	$CONH_2$	$(CH_3)_2CH$	CH_3	72	206-7	$C_{16}H_{21}N_3O_3S$	57.31 56.90	6.27 6.40	9.55 10.00
l	$CONH_2$	CH_2-C_6H_5	CH_3	87	192-4	$C_{20}H_{21}N_3O_3S$	62.66 62.70	5.48 5.70	8.35 8.30
m	$CONH_2$	CH_3	CH_3CONH	52	182-3	$C_{15}H_{18}N_4O_4S$	51.43 52.00	5.14 4.90	9.14 9.10
n	$CONH_2$	C_2H_5	CH_3CONH	65	236-8	$C_{16}H_{20}N_4O_4S$	52.74 51.90	5.49 5.20	8.79 9.00
o	$CONH_2$	CH_2-C_6H_5	CH_3CONH	92	198-9	$C_{21}H_{22}N_4O_4S$	59.15 58.80	5.16 5.20	7.51 8.00
q	$CON(C_2H_5)_2$	CH_3	CH_3	52	143-4	$C_{18}H_{25}N_3O_3S$	59.50 58.90	6.89 6.60	8.81 8.90
r	$CON(C_2H_5)_2$	CH_2-C_6H_5	CH_3	82	129-31	$C_{24}H_{29}N_3O_3S$	65.60 64.90	6.60 5.90	7.29 7.60
s	$CON(C_2H_5)_2$	C_2H_5	CH_3CONH	83	184-5	$C_{20}H_{28}N_4O_4S$	57.14 57.50	6.67 6.60	7.62 8.10

Compounds (IIIh-o) were crystallized from ethyl acetate while the rest compounds were crystallized from absolute ethanol.
Nitrogen analysis for: (IIIc,e,i,q,s) was done: Calcd./Found 8.35/8.50, 6.79/7.00, 11.41/10.70, 13.86/13.50, 13.33/13.50 respectively.

Synthesis of Some 2,7-Diazabicyclo {4.1.0}Hept-3-ene Derivatives With Analgesic and Anticoccidial Activity.

Table 2. Analgesic activity of 2,7-diazabicyclo {4.1.0} hept-3-enes (III) in comparison to aspirin.



III	R_1	R_2	R_3	% inhibition
b	$-COOC_2H_5$	C_2H_5	H	69.2
e	$-COOC_2H_5$	$CH_2-C_6H_5$	CH_3	70.2
i	$-CONH_2$	$CH_2-C_6H_5$	H	80.6
j	$-CONH_2$	C_2H_5	CH_3	85.6
k	$-CONH_2$	$(CH_3)_2-CH$	CH_3	85.1
n	$-CONH_2$	C_2H_5	CH_3CONH	86.0
q	$-CON(C_2H_5)_2$	CH_3	CH_3	84.4
r	$-CON(C_2H_5)_2$	$CH_2-C_6H_5$	CH_3	89.4
s	$-CON(C_2H_5)_2$	C_2H_5	CH_3CONH	89.9
Aspirin	---	---	---	58.2

REFERENCES

1) T.A. Ondrus, E.E. Knaus and C.S. Giam; Can. J. Chem. 57, 2342 (1979).

2) T.A. Ondrus and E.E. Knaus; Can. J. Pharm. Sci., 14, 55 (1979).

3) B.K. Warren and E.E. Knaus; J. Med. Chem., 24, 462 (1981).

4) A.G. Anderson and G. Berkelhammer; J. Amer. Chem. Soc., 80, 992 (1958).

5) C.M. Kimt and S. Chaykin; Biochemistry, 7, 2339 (1968).

6) A.C. Lovesey and W.C.J. Ross; J. Chem. Soc., 192 (1969).

7) D.J. Norris and R. Stewart; Can.J. Chem., 55, 1687 (1977).

8) K.E. Taylor and J.B. Jones; J. Amer. Chem. Soc., 98, 5689 (1976).

9) G. Blankenhorn and E.G. Moore; ibid. 102, 1092 (1980).

10) P. Karrer and F. Benz; Helv. Chim. Acta, 19, 1028 (1936).

11) P. Karrer and F.J. Stare; ibid, 20, 418 (1937).

12) P. Karrer and F. Blumer; ibid, 30, 1157 (1947).

13) H.E. Baumgarten; Org. Synth., Coll. Vol. 5, John Wiley & Sons, New York, (1973), p. 179.

14) T. Curtius and G. Kraemer; J. Prakt. Chem., 125, 303 (1930).

15) O.C. Dermer and M.T. Edmison; J. Amer. Chim. Soc., 77, 70 (1955).

16) O. Lindemann and W. Schultheis, Ann., 451, 241 (1927).

17) H.O. Collier, L.C. Dinneen, C.A. Johnson and C. Schneider; Br. J. Pharmacol. Chemother., 32, 295 (1968).

18) M.M. Abdel-Rahman, I.N. El-Akkad, M.H. Abdel-Rheem and A.M. Abdel-Rahman; J. Assiut Vet. Med., 5, 354 (1978).

19) R.A. Swan; Austral. Vet. J., 46, 25 (1970).

20) J.O. Joshua; Vet. Rec., 55, 149 (1943).

تخليق بعض مشتقات ٢ر٧- داى أزابايسيكلوهبتين ذات التأثير المسكن والمضاد للكوكسيديا

حسن حسن فرج ،عبد العليم محمد عبد العليم ،هدى يوسف حسن،حمدى على حماية الله رأفت عبد البديع عبد العال+ وعبد الرحمن محمود البدر++

قسم الكيمياء الصيدلية - كلية الصيدلة وقسمى الاقربازين+والطفيليات++

كلية الطب - جامعة اسيوط - اسيوط - مصر

تم تحضير مشتقات ٢ر٧ - داى أزابايسيكلوهبتين بالاضافة الحلقية ١ر٣ ثنائية القطب لازيلات سلفونيل الازيد على مشتقات ١ر٤ - داى هيدروبيريدين .

أثبتت الاختبارات البيولوجية أن بعض المركبات المستحدثة أكثر فاعلية فى تسكين الالم من عقار الاسبرين كما أن لها تاثير فعال ضد طفيل الكوكسيديا أكثر من تاثير عقار السلفا جوانيدين .

---

received in 2/9/1986 & accepted in 7/10/1986