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The reaction of ν-ketoacids or ν-aldehydo acids with *o*-amino amides results in the formation of 4-quinazolones. Using this reaction a number of polyheterosteroid analogs were synthesized. Thus, when 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzothiophene (**9**) was refluxed with levulinic acid (**10**) in a high boiling solvent, thiadiazasteroid analog (**11**) was obtained in 78% yield. It was found that this facile one-step reaction could be used to synthesize a variety of tetra and pentacyclic compounds. Nmr spectroscopy was used to assign stereochemistry to the 17-methyl "steroids" (**31**) and (**32**).

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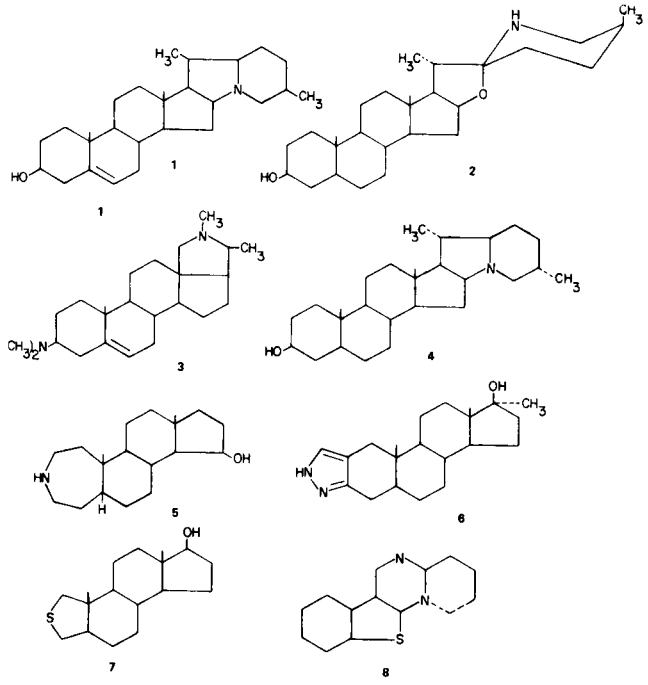
Steroids play an important role in the animal system both from the bio-chemical and pharmacological standpoint (2). In recent years particular attantion has been focused on heterosteroids (3). Several naturally occurring steroidal alkaloids such as solanidine (**1**), tomatidine (**2**), conessine (**3**), rubijervine (**4**), samanine (**5**) are known to possess significant physiological activity (4). A large number of synthetic heterocyclic steroids have been reported in which either an additional heterocyclic ring is fused with the steroid ring system (3a,b) or a hetero atom is incorporated in the steroid nucleus (5). In a few cases a total synthesis of this category of compounds has also been achieved (6). These heterocyclic steroids have displayed a wide spectrum of biological activity. Staozolol (7) (**6**), 17α-androstano[3,2-*c*]pyrazole, exhibit greatly increased anabolic/androgenic ratio whereas 2-thia-A-nor-5α-androstan-17β-ol (**7**) (8) is at par with testosterone in its androgenic activity. Heterosteroids with antihormonal



(9), hypochloesterolemic (10), vasodialatory (11), and antineoplastic (12) activity have also been synthesized. In this communication we report the synthesis of a series of thiadiazasteroid analogs of the general ring structure (8). In all these compounds a pyrimidine ring, which is known to confer useful biological activity to the molecule (13), has been incorporated.

The general approach in this synthesis is to react a bicyclic *o*-amino-amide with a carboxylic acid carrying a carbonyl function suitably located in the molecule (14). Rings A and B are provided by the aminoamide whereas rings C and D are formed during the course of its reaction with the acid. Thus when 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzothiophene (**9**) (15) was refluxed with levulinic acid (**10**) in solvents such as *o*-dichlorobenzene, xylene or toluene using a Dean Stark apparatus a solid separated out to which structure **11** has been assigned.

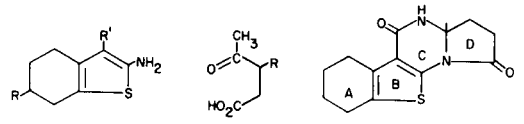
Alternatively, structure **12** could be assigned to the product obtained from **9** and **10**. In order to decide between these two structures, **11** and **12**, the product was treated with sodium hydride and methyl iodide at room temperature. The resulting compound **13** was identical with the one obtained by the reaction of **14** and levulinic acid as revealed by their physical and spectral data. This unequivocally rules out structure **12** for the product.

In a similar manner **15**, **16**, **17** and **18** were prepared by treating **9** with γ-acetylbutyric acid, β-benzoylpropionic acid, γ-benzoylbutyric acid and β-(*p*-methoxy)benzoylpropionic acid respectively. Attempts to extend this synthesis to construct a bis-homo D ring by using δ-benzoylvaleric acid as the acid component were unsuccessful. *o*-Carboxyacetophenone (**19**) with **9** under similar conditions provided **21**. 18-Nor analog **22** was obtained by treating **9** with 3-hydroxyphthalide (**20**).

Efforts were then directed towards the introduction of a functional group at C-3 in **11**. 4-Benzoyloxycyclohexanone (**23**) was prepared by the method of Jones and Sondheimer (16). Using Gewald's conditions (15) **23** was converted to **24**. Reaction of **24** with levulinic acid afforded **25** in about 70% yield.

In order to introduce a functional group at C-17 in

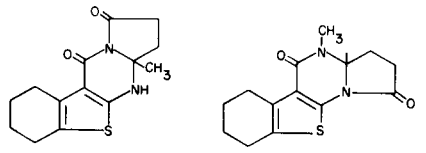
(**11**), β-acetyllevulinic acid (**26**) (17) was used as the acid component. The reaction of **26** with **9** however, gave **11**, instead of **27**. β-Acetyllevulinic acid is unstable at elevated temperatures and is transformed into angelica lactone (**28**) (17). That angelica lactone was the intermediate in the formation of **11** from **26** and **9** was proved in an independent experiment. The same tetracyclic compound **11** was obtained when **9** and **28** were allowed to react under identical conditions.



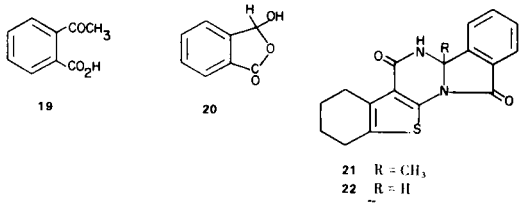
9 R = H, R' = $CONH_2$
14 R = H, R' = $CONHCH_3$
24 R = C_6H_5COO, R' = $CONH_2$
34 R = H, R' = $CSNH_2$

10 R = H
26 R = $COCH_3$
30 R = CH_3

11



12 **13**



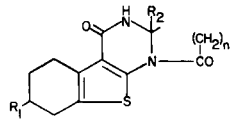
19 **20**

21 R = CH_3
22 R = H

Since the unsaturated lactone (**28**) could enter into this reaction as well as a carbonyl-bearing carboxylic acid, the reaction of isocoumarin (**29**) with **9** was attempted. There was no evidence for the occurrence of any reaction in this case even after a prolonged reaction time and the starting amide (**9**) was recovered unchanged.

The reaction of β-methyl levulinic acid (**30**) (18) with **9** was attempted for introducing a methyl group as a side chain at C-17. With an asymmetric center created at C-17, the possibility of two geometric isomers arises. The nmr spectrum of the crude product in deuteriochloroform was revealing. It showed two singlets at τ 8.4 and τ 8.57 and two doublets centered at τ 8.8 and τ 8.7 (J = 6 Hz). Column chromatography of the crude material provided two products, one of which had the singlet at τ 8.4 (C-13 C*H*$_3$) and the doublet centered at τ 8.8 (C-17 C*H*$_3$) whereas the second component showed the singlet at τ 8.57 (C-13 CH_3) and the doublet centered at τ 8.7 (C-17 CH_3).

In order to assign the stereochemistry to the two products advantage was taken of the lanthanide shift reagents which induce varying degrees of shift in the resonance signals of neighboring protons depending upon their orientation *vis-a-vis* the site of complexation of the reagent with the substrate (19). A deuterated chloroform solution of a mixture of unequal quantities of **31** and **32** was used to study the effect of the addition of varying quantities of $Eu(fod)_3$ on the relevant protons. It was observed that in one case the C-13 CH_3 and C-17 CH_3 show a downfield shift of 36 Hz and 23 Hz respectively when 40.4 mg. of $Eu(fod)_3$/41.6 mg. of the mixture was added. The second isomer showed a value of 26 Hz and 0 Hz for the corresponding protons. In both these compounds the two amide linkages provide the complexing site for the shift reagent. It, thus, appears that C-13 CH_3 and C-17 CH_3 in **31**, which suffer similar LIS should have *cis* configuration. On the other hand they should be in different geometric environment in **32** because C-13 CH_3



	R_1	R_2	n
15	H	CH_3	3
16	H	C_6H_5	2
17	H	C_6H_5	3
18	H	$C_6H_4OCH_3$ (p)	2
25	C_6H_5COO	CH_3	2

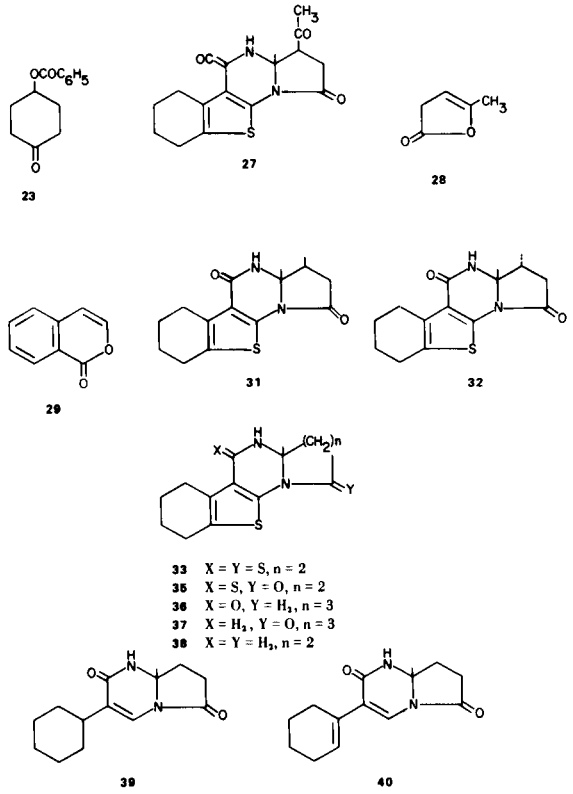
suffers a large shift whereas C-17 CH_3 is hardly affected. These results can be rationalized by assigning *trans* stereochemistry to **32**.

Thioamides such as, pyrimidine-4-thiones (13), thiosemicarbazones (20), thioureas (21) are also known to possess marked biological effects. It was, therefore, considered desireable to generate thiadiaza steroid analogs with a thioamide functionality. Several methods are available to introduce a thioamide group in these compounds (22). A facile method is to reflux **11** with phosphorus pentasulfide in pyridine (23). Under these reaction conditions the dithioamide (**33**) was formed. It is difficult, however, to selectively replace the C-11 or C-15 oxygen with sulfur using phosphorus pentasulfide.

By using a separate sequence of reactions it was possible to introduce a thiocarbonyl group at the 11-position selectively. The desired α-amino-thioamide (**34**) for this reaction was prepared by treating 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzothiophene (15) with phosphorus pentasulfide. Compound **34** could also be prepared from 2-amino-3-cyano-4,5,6,7-tetrahydrobenzothiophene by the method of Mautner (24) in poor yield after a prolonged reaction time. Reaction of **34** with levulinic acid afforded **35** in about 70% yield.

The reduction of **11** and **15** under different sets of conditions was also examined. When **11** was reduced with sodium dihydrobis-(2-methoxyethoxy) aluminate (25) both the amide functions were reduced and compound **38** was formed. Its structure was determined on the basis of analytical and spectroscopic data. The nmr spectrum of **38** showed a singlet integrating for two protons at τ 6.32. This singlet was absent in the starting amide (**11**) and has

been assigned to C-11 protons which are benzylic in nature and are further deshielded by the adjacent nitrogen atom. This assignment finds additional support in the fact that the benzylamine which has the methylene group in almost similar environment also appears as a singlet at τ 6.35. Reduction of **11** with Raney nickel gave **39** instead of the expected **40**.



When **15** was reduced with diborane, a compound was isolated in which only one of the carbonyl groups had been reduced. Two alternative structures **36** and **37** for this reduced compound are possible. A comparison of the nmr spectra of the reduced product with that of **38** showed the absence of the singlet in τ 6.23 region which we have previously assigned to the C-11 protons. Instead a broad multiplet which merged with signals from other deshielded protons in the region τ 6.8-7.3 was observed. Based on these considerations it appears that structure **36** best represents this reduction product.

It will be noticed that the foregoing synthesis of thiadiaza steroid analogs of the type **11** opens up the possibility of generating a large number of compounds which are analogs and homologs of **11**. Furthermore, by using conventional methods it is also possible to introduce a variety of functional groups in different positions of this basic structure.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer infracord and the ultraviolet spectra on a Beckman-DK-2A spectrometer in 95% ethanol solution at room temperature ($\simeq$ 25°). The mass spectra were obtained using a RMU-7 mass spectrometer. Nmr spectra were recorded on a Varian A 60A spectrometer in deuteriochloroform or DMSO-d_6 solution using tetramethyl-silane as an internal standard. Microanalyses were performed by Central Drug Research Institute, Lucknow, India.

2-Amino-3-carboxamido-4,5,6,7-tetrahydro[1]benzothiophene (**9**).

This compound was prepared by the method of Gewald and coworkers (15).

4-Benzoyloxycyclohexanone (**23**).

This compound was prepared by the procedure described by Jones and Sondheimer (16).

2-Amino-3-carboxamido-6-benzoyloxy-4,5,6,7-tetrahydro[1]-benzothiophene (**24**).

To a vigorously stirred suspension of **23** (6.54 g., 0.03 mole), 2-cyanoacetamide (2.52 g., 0.03 mole) and elemental sulfur (0.96 g., 0.03 g.-atom) in 85 ml. of 95% ethanol, was dropwise added 3 ml. of diethyl amine and the contents stirred overnight. Solid which separated out, was filtered and recrystallized from ethanol to give 3.9 g. (42.0%) of white crystalline product, m.p. 213°; ν max (nujol): 3340, 3210 (NH_2,$CONH_2$), 1715 (O-C-), 1630 ($CONH_2$); ms: m/e 316 (M^+), 194 (M^+ - $PhCO_2H$).

2-Amino-3-(*N*-methylcarboxamido)-4,5,6,7-tetrahydro[1]benzothiophene (**14**).

This was synthesized essentially according to the method described for **24** starting with cyclohexanone, *N*-methyl-2-cyanoacetamide and elemental sulfur in 29% yield, m.p. 192° (ethanol); ν max (nujol): 3400, 3350 (NH_2, CONH-), 1702 (CNH); ms: M^+ at m/e 210.

2-Amino-3-thiocarboxamido-4,5,6-tetrahydro[1]benzothiophene (**34**).

A solution of **9** (3.9 g., 0.02 mole) and phosphorus pentasulfide (4.4 g., 0.04 mole) in 80 ml. of pyridine was refluxed for 3 hours. Pyridine was then distilled off under reduced pressure and the residue triturated with chloroform. The solid, thus obtained, was recrystallized from DMF to give (**34**) in 65% yield, m.p. 255°.

β-Acetylevulinic Acid (**26**).

This compound was prepared according to Thiele, Tischbein and Lossow (17).

β-Methyllevulinic Acid (**30**).

This compound was synthesized by the method described by Bischoff (18b).

A general method for the synthesis of the tetracyclic compounds given in Table 1 is described below.

2-Amino-3-carboxamido-4,5,6,7-tetrahydro[1]benzothiophene (**9**) (5.88 g., 0.03 mole), 3.48 g. (0.03 mole) of levulinic acid and 100 ml. of xylene were taken in a 250 ml. flask fitted with a Dean Stark apparatus for water separation. *p*-Toluenesulfonic acid (0.5 g.) was added and the reaction mixture refluxed for 4 hours. Fifty ml. of xylene was distilled off and the remaining solution was allowed to cool when (**11**) separated out as a crystalline solid. It was filtered and recrystallized from dichloromethane-ethanol.

Table 1

Analytical and Spectral Data

Compound N.	M.p. °C	Yield %	Molecular Formula	λ max nm (log ε)	Analysis C	H	N	S
11	246	78	$C_{14}H_{16}N_2O_2S$	318 (4.118) Sh 257 (4.118) 225 (4.587)	60.69 (60.86)	5.94 (5.84)	10.03 (10.14)	11.45 (11.58)
13	189-190	63	$C_{15}H_{18}N_2O_2S$		M^+ at m/e 290			
15	307	77	$C_{15}H_{18}N_2O_2S$	317 (3.965) Sh 262 (3.932) 225 (4.452)	62.17 (62.06)	6.15 (6.25)	9.72 (9.65)	10.90 (11.05)
16	>320	61	$C_{19}H_{18}N_2O_2S$	317 (3.876) 260 (3.890) 225 (4.326)	67.64 (67.44)	4.96 (5.36)	8.15 (8.28)	
17	347	73	$C_{20}H_{20}N_2O_2S$		67.97 (68.17)	5.91 (5.72)	7.79 (7.95)	
18	320	58	$C_{20}H_{20}N_2O_3S$		64.90 (65.21)	4.78 (5.47)		
21	301	74	$C_{18}H_{16}N_2O_2S$	340 (3.819) 227 (4.316)	66.819 (66.66)	5.11 (4.97)	8.66 (8.64)	10.04 (9.86)
22	>320	81	$C_{17}H_{14}N_2O_2S$	342 (3.884) 231 (4.364)	65.84 (65.80)	4.50 (4.55)	9.23 (9.03)	10.21 (10.31)
25	215-216	68	$C_{21}H_{20}N_2O_4S$		63.50 (63.63)	5.22 (5.09)	7.02 (7.07)	
31 (*cis*)	259	42	$C_{15}H_{18}N_2O_2S$		61.83 (62.05)	6.84 (6.52)	9.52 (9.65)	
						cis-trans mixture		
32 (*trans*)	275	29	$C_{15}H_{18}N_2O_2S$			M^+ at m/e 290		
33	259-260	42	$C_{14}H_{16}N_2S_3$			M^+ at m/e 308		
35	249-250	68	$C_{14}H_{16}N_2OS_2$			M^+ at m/e 292		
36	219-221	27	$C_{15}H_{20}N_2OS$	332 (3.774) Sh 265 (3.751) 231 (4.425)	65.00 (65.19)	7.28 (7.30)	10.45 (10.14)	
38	98	86	$C_{14}H_{20}N_2S$		67.80 (67.72)	7.95 (8.12)	11.54 (11.28)	

12a-Methyl-1,2,3,4,7,8,9,10-octahydro[1]benzothieno[2′,3′:4,5]-pyrimido[3,2-*a*]pyridine-11(12a*H*)one (**36**).

To a solution of **15** (2.9 g., 0.01 mole) in 100 ml. of anhydrous tetrahydrofuran cooled in an ice bath, was added 30 ml. of 1 molar solution of diborane in THF over a period of 15 minutes. It was stirred for 1 hour and then refluxed for another 2 hours. The reaction mixture was cooled and decomposed by a dropwise addition of 6*N* hydrochloric acid. THF was removed by distillation under vacuum and the residue extracted with dichloromethane. The dichloromethane extract was washed with water, dried (magnesium sulfate) and the solvent removed. Chromatography of the amide solid so obtained over alumina with chloroform as eluent provided (**36**) which was recrystallized from dichloromethane-hexane.

11a-Methyl-2,3,6,7,8,9,10,11-octahydro[1]benzothieno[2′,3′:4,5]-pyrimido[3,2-*a*]pyrrole (**38**).

To a solution of **11** (1.93 g., 0.007 mole) in 100 ml. of anhydrous benzene was carefully added 9 ml. of a 70% solution of sodium dihydrobis-(methoxyethoxyaluminate) in benzene. The contents were refluxed overnight, poured on ice and extracted with ether. The ether layer was washed with water, dried (magnesium sulfate) and solvent removed to give a crude solid which when recrystallized from ether-hexane provided pale yellow needles; ms: M^+ at m/e 248; ir (nujol) showed the absence of any absorption in the carbonyl region.

11a-Methyl-2,3,6,7,8,9-hexahydro[1]benzothieno[2',3':4,5]-pyrimido[3,2-*a*]pyrrole-3,10(1*H*)dithione (**33**).

A suspension of **11** (2.76 g., 0.01 mole) and phosphorus pentasulfide (5.21 g., 0.025 mole) in 120 ml. of pyridine was refluxed under a continuous flow of nitrogen gas for 4 hours. Pyridine was removed by distillation under vacuum. The residue was diluted with water and extracted with chloroform. Chloroform extract was washed with water, dilute hydrochloric acid, followed by water again, dried (magnesium sulfate) and solvent removed. The crude solid was crystallized from chloroform-hexane.

11,11a-Dimethyl-2,3,6,7,8,9-hexahydro[1]benzothieno[2',3':4,5]-pyrimido[3,2-*a*]pyrrole-3,10(1*H*)dione (**13**).

To a solution of **11** (2.76 g., 0.01 mole) in 100 ml. of anhydrous DMF was added sodium hydride (0.24 g., 0.01 mole) and the reaction mixture stirred at 40° for 20 hours. DMF was removed under vacuum. The residue was diluted with water and extracted with dichloromethane. The organic layer was washed with water, dried and the solvent removed. The residue was crystallized from benzene-hexane to provide the title compound.

1-Methyl-4-cyclohexyl-3,7-dioxo-2,6-diazabicyclo[4.3.0]nonene-4 (**39**).

A solution of **11** (2.76 g., 0.01 mole) in 150 ml. of ethanol containing approximately 25-30 g. of Raney nickel was refluxed for 16 hours. Raney nickel was filtered and the filtrate concentrated under vacuum. The residue was triturated with ether when a white solid was obtained. It was filtered and recrystallized from chloroform to give 1.34 g. (54%) of **39**, m.p. 158-159°; ms: M^+ at m/e 248; nmr (deuteriochloroform): 2.72 (broad S, 1H, CONH) 2.91 (S, 1H, olefinic H).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.61; H, 7.89; N, 10.90.

Acknowledgement.

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