Applications of 1-Alkoxycarbonyl- and 1-Acyl-*v*-triazolo[4,5-*b*]pyridines as Acylating Reagents

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Selective *N*-protection of hydroxyamino esters has been readily achieved using 1-alkoxycarbonyl- or 1-acyl-*v*-triazolo[4,5-*b*]pyridines. The amide-type triazolides reacted with alcohols in the presence of DBU at room temperature to afford in high yields the corresponding esters. The different reactivity of 1- and 3-alkoxycarbonyl derivatives of the title bicyclic system toward primary amines has been further investigated.

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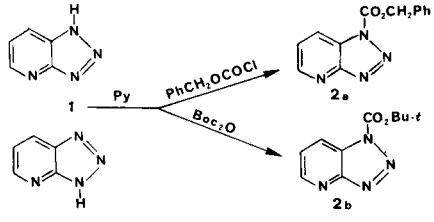
We have recently described the preparation of 1- and 3-alkoxycarbonyl-*v*-triazolo[4,5-*b*]pyridines which showed, in preliminary experiments, acylating properties [1]. In this paper we report further data on the different reactivity of the above isomeric derivatives and some applications of 1-substituted triazolides.

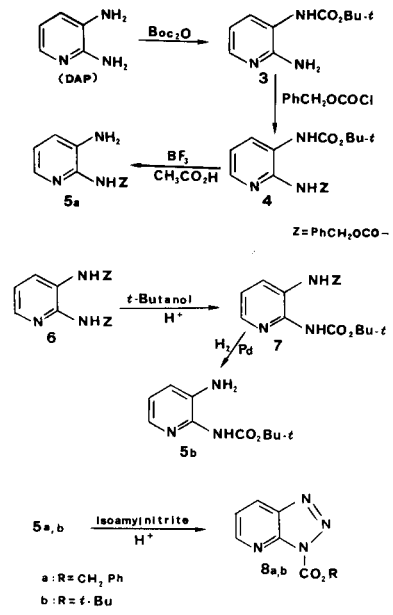
In order to permit the selective introduction of two classic protecting groups to the amine moiety of hydroxyamino esters we have synthesized 1- and 3-benzyloxycarbonyl-*v*-triazolo[4,5-*b*]pyridines **2a**, **8a** and the corresponding *t*-butoxycarbonyl derivatives **2b**, **8b**. Acylation of unsubstituted *v*-triazolo[4,5-*b*]pyridine (**1**) with benzyl chloroformate, in tetrahydrofuran (THF) containing pyridine (Py), afforded the 1-*Z* derivative **2a**. Analogous treatment with di-*t*-butyl dicarbonate (Boc_2O) gave the 1-Boc triazolide **2b**.

Scheme 1



The 1-position of the alkoxycarbonyl group was suggested by the similar outcome of the previously reported acylations of **1** [1]. Furthermore **2a** and **2b** showed melting points, ir and nmr spectra different from those of the corresponding triazolides **8a** and **8b**, unequivocally obtained by cyclization of the appropriate 2-(alkoxycarbonylamino)-3-aminopyridines **5a,b** with isoamyl nitrite in refluxing THF containing acetic acid. The intermediate 3-amino-2-(benzyloxycarbonylamino)pyridine (**5a**) and 3-amino-2-(*t*-butoxycarbonylamino)pyridine (**5b**) were prepared as shown in Scheme 2. Treatment of 2,3-diaminopyridine (DAP) with Boc_2O in boiling chloroform gave, as the main product, 2-amino-3-(*t*-butoxycarbonylamino)pyridine (**3**) [2]. This compound was further acylated with benzyl chloroformate to afford the dicarbamate **4**. Finally the Boc group was selectively removed by stirring at 0° a solution of **4** in acetic acid containing boron trifluoride to give the expected monocarbamate **5a**.

Scheme 2

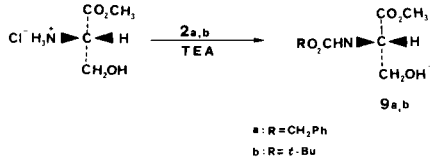


The Boc derivative **5b** was instead obtained starting from 2,3-bis(benzyloxycarbonylamino)pyridine (**6**) [1], which was converted to dicarbamate **7** by refluxing in *t*-butyl alcohol containing acetic acid [1]. Deprotection of the 3-amino group by hydrogenolysis on palladium led to **5b**. To confirm our preliminary data on the different reactivity of 1- and 3-alkoxycarbonyl-*v*-triazolo[4,5-*b*]pyridines toward aliphatic amines [1], the acylations of isopropylamine and benzylamine with 1- and 3-Boc triazolides **2b** and **8b** were carried out. All these experiments were per-

formed in deuteriochloroform solutions and the reaction outcomes monitored by ^1H nmr. Although a faster reaction rate was exhibited by 3-Boc derivative **8b**, isomerization of this compound to the 1-substituted triazolide **2b** was also observed. Beside, after the conversion of **8b** to **2b** was nearly complete, the acylation of the unreacted amine further proceeded and the yield of the corresponding carbamate became very close to that obtained starting from **2b**, which did not undergo any isomerization. Analogous experiments were performed on benzylamine with *Z*-derivatives **2a** and **8a**. Since both the acylations were complete within 15 minutes, the different reactivity of the two isomers could not be determined in this case.

Based upon these observations and considering that the preparation of 3-derivatives was more laborious, we decided to employ 1-substituted triazolides in the following applications. Selective *N*-protection of L-serine methyl ester was readily achieved by stirring at room temperature a mixture of the aminoester hydrochloride, triethylamine and **2a** or **2b**.

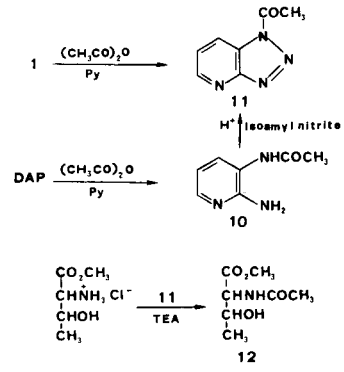
Scheme 3



Although the preparation of the *N*-Boc derivative **9b** required a long reaction time [3], the yields were in both cases good and no racemization occurred. Our results are similar to those recently reported by Kunieda *et al.* [5] on the use of 2-alkoxycarbonyl-2-oxazolones as amino-protecting reagents.

In order to examine whether the replacement of the alkoxycarbonyl group with a simple acyl one might affect the reactivity of 1-substituted triazolides, we have prepared 1-acetyl-1*H*-*v*-triazolo[4,5-*b*]pyridine (**11**). This compound was obtained both by treatment of **1** with acetic anhydride and by cyclization of 3-(acetylamino)-2-aminopyridine (**10**) with isoamyl nitrite. The monoamide **10** was prepared by treatment of a THF solution of DAP containing Py with acetic anhydride.

Scheme 4



The mp, ir and nmr spectra of **10** were different from those of the 2-acetylamino isomer [1]. Interestingly the amide-type triazolide **11** showed analogous properties to those exhibited by the corresponding urethane-type derivatives. In fact, in a preliminary acylation experiment performed on isopropylamine in deuteriochloroform solution, **11** quantitatively led to *N*-isopropylacetamide within half an hour. Furthermore the *N*-acetylation of D,L-threonine methyl ester proceeded readily under the conditions adopted earlier using the 1-alkoxycarbonyl derivatives **2a** and **2b**.

Murata [6] recently reported that some 1-acyl-1,2,4-triazoles reacted with methanol in the absence of a basic catalyst to afford the corresponding methyl esters. In accord with the selective acetylation of the amino group of threonine methyl ester, **11** failed to react at room temperature with cholesterol (in THF) or with estrone (in *N*,*N*-dimethylformamide). On the other hand good yields of cholesteryl or estrone acetate were observed when the above transacylations were performed in presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU).

Table I

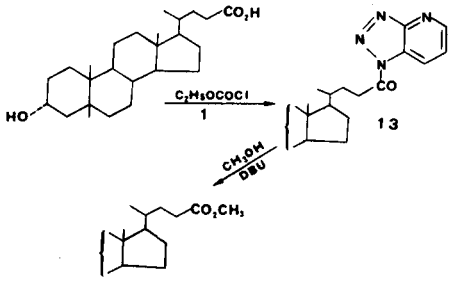
Spectral Data for Triazolides **2a**, **2b**, **8a**, **8b**, **11**, and **13**

Compound	^1H-NMR (δ) Pyridine Protons [a] α-H	β-H	γ-H	Other Signals	IR, cm $^{-1}$
2a	8.81		8.43	5.62 (2H, s, O-C*H*$_2$-Ph), 7.24-7.70 (6H, m, β-H and O-CH$_2$-*Ph*)	1777, 1581, 1420
2b	8.88	7.64	8.50	1.77 (9H, s, C(CH$_3$)$_3$)	1787, 1765, 1596, 1414
8a	8.93		8.50	5.67 (2H, s, O-C*H*$_2$-Ph), 7.30-7.77 (6H, m, β-H and O-CH$_2$-*Ph*)	1777, 1589, 1418
8b	8.92	7.54	8.54	1.78 (9H, s, C(CH$_3$)$_3$)	1767, 1588, 1404
11	8.91	7.67	8.70	3.02 (3H, s, CO-CH$_3$)	1750, 1596, 1414
13	8.90	7.68	8.72	0.68 (3H, s, 13-CH$_3$), 0.92 (3H, s, 10-CH$_3$), 3.33-3.81 (3H, m, 3β-H and CH$_2$-CO)	3368, 1756, 1598, 1414

[a] *Ortho* (α-H), *meta* (β-H) and *para* (γ-H) protons occur as double doublets ($J_{\alpha,\beta}$ = 5 Hz, $J_{\beta,\gamma}$ = 8.5 Hz, $J_{\alpha,\gamma}$ = 1.5 Hz), the β-H signal of **2a** and **8a** is superimposed on O-CH$_2$-Ph aromatics.

Finally, the 1-lithocholyltriazolide **13**, prepared by the mixed carboxylic-carbonic acid anhydride method from lithocholic acid and triazole **1**, was smoothly converted into methyl lithocholate by its treatment with methanol in presence of DBU.

Scheme 5



The easily prepared urethane- and amide-type 1-derivatives of *v*-triazolo[4,5-*b*]pyridine are solid reagents, which may be conveniently employed in *N*- or *O*-acylations performed under very mild conditions.

Table II

Alkoxycarbonylation of Primary Amines

Acylating agent	Amine	Time (hours)	Yield (%) [a]
2b	Benzylamine	0.5	38
		1.25	64
		6	80
8b	Benzylamine	0.5	57
		1.25 [b]	69
		6	82
2b	Isopropylamine	1	33
		2	42
		4	50
		24	64
8b	Isopropylamine	1	55
		2	62
		4 [b]	65
		24	69
2a	Benzylamine	0.25	100
8a	Benzylamine	0.25	100

[a] Yields calculated on the basis of intensities of $C(CH_3)_3$ or CH_2-N signals. [b] Nearly complete isomerization of 3- to 1-substituted triazolide.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus and are uncorrected. Optical rotations were taken at 20° with a Schmidt-Haensch Polartronic D polarimeter in a 1 dm cell. Infrared spectra (potassium bromide, unless otherwise specified) were recorded with a Perkin-Elmer 983 spectrophotometer. The ^1H nmr spectra were measured with a Varian EM-390 spectrometer using, unless otherwise specified, deuteriochloroform as the solvent (TMS as the internal standard). The coupling constants of resolved pyridine signals for all described compounds are those reported at footnote of Table I. Merck Silica gel 60 (230-400 mesh) was used for column chromatography; preparative layer chromatography (plc) was carried out with Merck F_{254} silica gel. The drying agent was sodium sulfate. Dry pyridine (Py) and tetrahydrofuran (THF) were used. Boron trifluoride ethyl etherate (50%, Merck & Co.) was employed without purification.

Unsubstituted *v*-Triazolo[4,5-*b*]pyridine (**1**).

A suspension of DAP (3 mmoles) in THF (15 ml), acetic acid (0.34 ml) and isoamyl nitrite (6 mmoles) was refluxed for 2 hours and evaporated under vacuum to give a solid residue which was chromatographed on a silica column (1:30) [dichloromethane-ethyl acetate (9:1) and (1:1) as eluant] to afford the title compound in quantitative yield, mp 207-208° dec (water), lit 205° dec [7]; ir: 1400, 802, 786 cm^{-1}; nmr (methanol-d_4): δ 7.55 (1H, dd, 6-H), 8.43 (1H, dd, 7-H), 8.77 (1H, dd, 5-H).

1-Alkoxycarbonyl-1*H*-*v*-triazolo[4,5-*b*]pyridines **2a,b**.

Acylation of unsubstituted *v*-triazolo[4,5-*b*]pyridine (**1**) with benzyl chloroformate or Boc_2O, performed as previously described [1], afforded **2a** or **2b** respectively, in quantitative yield.

Compound **2a** had mp 105-105.5° (ether).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.44; H, 4.09; N, 22.10.

Compound **2b** had mp 113-114° (ether).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.47; H, 5.45; N, 25.56.

Reaction of DAP with Boc_2O in Chloroform.

A mixture of DAP (4 mmoles) and Boc_2O (6 mmoles) in chloroform (8 ml) was refluxed for 3 hours. The solvent was evaporated under vacuum to give a residue which was chromatographed on a column of silica (1:50). Elution with dichloromethane-ethyl acetate (9:1) gave 1,3-di-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (0.349 g, 26%) [8]; further elution with dichloromethane-ethyl acetate (1:1) afforded 1-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (0.050 g, 5.3%) [8]. Finally, elution with dichloromethane-ethyl acetate (1:2) gave 2-amino-3-(*t*-butoxycarbonylamino)pyridine (**3**) (0.408 g, 49%) [8].

2-(Benzyloxycarbonylamino)-3-(*t*-butoxycarbonylamino)pyridine (**4**).

To a stirred suspension of **3** (1.72 g, 8.22 mmoles) in THF (50 ml) and Py (5.3 ml), cooled at 0°, benzyl chloroformate (32.2 mmoles) was added dropwise. After stirring at 0° for 15 minutes and at room temperature for 3 hours, ethyl acetate was added in in excess. The organic solution was washed with water, dried and evaporated under vacuum. The residue was chromatographed on a column of silica (1:50). Elution with dichloromethane-ethyl acetate (95:5 and 9:1) gave 1.57 g of nearly homogeneous 2-(benzyloxycarbonylamino)-3-(*t*-butoxycarbonylamino)pyridine (**4**), mp 127-128° (dichloromethane-ether); ir: 3346, 3184, 1722, 1543 cm^{-1}; nmr: δ 1.50 (9H, s, $C(CH_3)_3$), 5.24 (2H, s, O-CH_2-Ph), 7.05 (1H, dd, 5-H), 7.38 (5H, s, aromatic), 8.01 (1H, dd, 6-H), 8.28 (2H, dd, 4-H superimposed on a NH signal).

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.93; H, 6.16; N, 11.86.

3-Amino-2-(benzyloxycarbonylamino)pyridine (**5a**).

Following the procedure of Hiskey *et al.* [9], a solution of **4** (0.884 g, 2.57 mmoles) in acetic acid (2.6 ml) was treated with boron trifluoride etherate (1.03 ml) for 2 hours at 0°. The reaction mixture was then poured into saturated aqueous sodium bicarbonate and ethyl acetate was added in excess. The organic layers were washed with water, dried and evaporated under vacuum. The nearly pure residue (0.64 g) was crystallized from methanol-ether to give **5a** (0.5 g), mp 139-140°; ir: 3314, 1706, 1627 cm^{-1}; nmr (DMSO-d_6): δ 5.05 (2H, br s, NH_2), 5.15 (2H, s, O-CH_2-Ph), 7.09 (2H, m, 4-H and 5-H), 7.44 (5H, m, aromatic), 7.69 (1H, dd, 6-H).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 63.97; H, 5.39; N, 17.16.

Synthesis of 3-Amino-2-(*t*-butoxycarbonylamino)pyridine (**5b**).

Following our previously described procedure [1], 2,3-bis(benzyloxycarbonylamino)pyridine (**6**) [1] (2 mmoles) in *t*-butanol (60 ml) and acetic acid (1.2 ml) was refluxed for 2 hours and evaporated under vacuum. The

residue was chromatographed on a column of silica (1:50). Elution with dichloromethane-ether (95:5) afforded 0.503 g of an unresolved mixture of 3-(benzyloxycarbonylamino)-2-(*t*-butoxycarbonylamino)pyridine (**7**) and starting material. A solution of the above mixture in dichloromethane (20 ml) and acetic acid (2 ml) was subjected to catalytic hydrogenolysis, using palladium as catalyst (0.125 g), for 4 hours under standard conditions. Catalyst was removed by filtration through Celite. The solvent was evaporated and the residue was chromatographed on a column of silica (1:50). Elution with dichloromethane-ethyl acetate (8:2 and 7:3) afforded pure 3-amino-2-(*t*-butoxycarbonylamino)pyridine (**5b**) (0.23 g, 55% overall yield), mp 241-222° (methanol-ether) (with a Kofler hot-stage apparatus); ir: 3411, 1693, 1631 cm^{-1}; nmr: δ 1.50 (9H, s, $C(CH_3)_3$), 4.36 (2H, br s, NH_2), 7.02 (2H, m, 4-H and 5-H), 7.88 (1H, dd, 6-H), 8.41 (1H, br s, NH).

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.36; H, 7.34; N, 20.28.

3-Alkoxycarbonyl-3*H*-*v*-triazolo[4,5-*b*]pyridines **8a,b**.

A suspension of 2-(alkoxycarbonylamino)-3-aminopyridine **5a** or **5b** (1 mmole) in THF (5 ml), acetic acid (0.05 ml) and isoamyl nitrite (0.2 ml) was refluxed for 1 hour or 40 minutes respectively. Evaporation under vacuum gave pure **8a** or **8b** in quantitative yield.

Compound **8a** had mp 98-100° (dichloromethane-ether).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96, N, 22.04. Found: C, 61.22; H, 4.10; N, 21.85.

Compound **8b** had mp 86-87.5° (ether).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.71; H, 5.47; N, 25.34.

Isomerization of **8a** to **2a**.

The presence of small amounts of 3-substituted triazolide could be observed in some acylation experiment performed on triazole **1**. As an example of complete conversion of 3- to 1-substituted triazolide, the following procedure is described. To a mixture of **2a** and **8a** (0.54 g) in ethyl acetate (50 ml) and pyridine (0.05 ml), triazole **1** (0.05 g) was added. After stirring at room temperature for 24 hours, ether was added in excess. The organic layers, washed with 2*N* hydrochloric acid and water, were dried and evaporated under vacuum to give pure **2a** (0.54 g).

General Procedure for Alkoxycarbonylation of Benzylamine and Isopropylamine.

A solution of 1- or 3-alkoxycarbonyl-*v*-triazolo[4,5-*b*]pyridine **2a,b** or **8a,b** (0.2 mmole) and benzylamine (0.2 mmole) (0.23 mmole of isopropylamine and 0.2 mmole of **2b** or **8b**) in deuteriochloroform (1 ml), containing a few drops of TMS, stirred at room temperature in a sealed flask for 15 minutes, was filtered into a nmr tube and the reaction outcomes monitored (see Table II). The ^1H nmr data of benzylamine and isopropylamine carbamates are in accord with those previously reported [5,10].

N-Alkoxycarbonylation of L-Serine Methyl Ester with **2a** and **2b**.

To a suspension of L-serine methyl ester hydrochloride [11] (0.5 mmole) in THF (5 ml), **2a** (0.75 mmole) and triethylamine (0.07 ml) were added. After stirring at room temperature for 16 hours, ethyl acetate was added in excess. The organic layers, washed with 2*N* hydrochloric acid and water, were dried and evaporated under reduced pressure. Purification of the residue by plc [dichloromethane-methanol (95:5) as eluant] gave *N*-benzyloxycarbonyl-L-serine methyl ester (**9a**) (0.118 g, 92%), as an oil; $[\alpha]_D$, nmr, and ir data were in accord with those previously reported [12,13,14]. *N*-*t*-butoxycarbonyl derivative **9b** was prepared as above except that 1 mmole of **2b** was used, and stirring was continued for two days. Final plc afforded *N*-*t*-butoxycarbonyl-L-serine methyl ester (**9b**) (0.1 g, 90%), as an oil; $[\alpha]_D$ + 9° (c 1.0, chloroform); ir (tetrachloromethane): 1749, 1722, 1166 cm^{-1}; nmr: δ 1.45 (9H, s, $C(CH_3)_3$), 3.78 (3H, s, CO_2CH_3), 3.93 (2H, m, CH-CH_2), 4.37 (1H, m, CH-CH_2), 5.72 (1H, d, J = 7.5 Hz, NH). Optical rotation and spectral data were identical to those of an authentic sample [15].

Traces of triazole **1**, arising from decomposition on plc of the residual triazolides **2a** or **2b**, were removed by washing an ethereal solution of protected amino ester with 2*N* hydrochloric acid.

3-(Acetylamino)-2-aminopyridine (**10**).

To a stirred suspension of DAP (2 mmoles) in THF (8 ml) and Py (0.21 ml), cooled at 0°, acetic anhydride (2.2 mmoles) was added dropwise. After stirring at 0° for 15 minutes and at room temperature for 1¾ hours, the reaction mixture was evaporated under vacuum. The residue was chromatographed by plc [dichloromethane-methanol (95:5) as eluant] to give 3-(acetylamino)-2-aminopyridine (**10**) (0.2 g, 65%), mp 176-177° (ethyl acetate); ir: 3230, 1643, 1452 cm^{-1}; nmr (DMSO-d_6): δ 2.04 (3H, s, $COCH_3$), 6.59 (1H, dd, 5-H), 7.69 (1H, dd, 4-H), 7.83 (1H, dd, 6-H).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.54; H, 6.04; N, 27.69.

1-Acetyl-1*H*-*v*-triazolo[4,5-*b*]pyridine (**11**).

A suspension of **10** (1 mmole) in THF (5 ml), acetic acid (0.05 ml) and isoamyl nitrite (1.5 mmoles) was refluxed for 2 hours and evaporated under vacuum to give the triazolide **11** in quantitative yield, mp 111-112° (ether).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.76; H, 3.77; N, 34.54.

The title compound was also obtained in quantitative yield by acylation of **1** with acetic anhydride as earlier described for **2a,b**.

Acylation of Isopropylamine with **11**.

The reaction of isopropylamine (0.2 mmole) with amide-type triazolide **11** (0.2 mmole) in deuteriochloroform (1 ml), containing a few drops of TMS, was carried out as earlier described for the alkoxycarbonylations. The spectrum of the reaction mixture, determined after 30 minutes *ab initio*, provided evidence for both the *N*-isopropylacetamide formation (signals in accord with the literature data [16]), and the disappearance of the starting materials.

N-Acetyl-D,L-threonine Methyl Ester (**12**).

To a suspension of D,L-threonine methyl ester hydrochloride [17] (1 mmole) in THF (10 ml), **11** (1.2 mmoles) and triethylamine (0.14 ml) were added. After stirring at room temperature for 4 hours, the mixture was evaporated under vacuum. The residue was chromatographed on a column of silica (1:50). Elution with dichloromethane-ether (7:3) afforded triazole **1** (0.141 g); further elution with ether-ethyl acetate (8:2) afforded the title compound **12** (0.167 g, 96%) mp 101.5-102° (ethyl acetate-*n*-hexane), lit 105-106° (benzene) [18]; ir: 3372, 1754, 1644, 1526 cm^{-1}; nmr: δ 1.18 (3H, d, J = 6 Hz, CH-CH_3), 2.06 (3H, s, $COCH_3$), 3.76 (3H, s, CO_2CH_3), 4.35 (1H, br m, CH-CH_3), 4.58 (1H, dd, J = 9 and 3 Hz, CH-NH), 6.82 (1H, br d, J = 9 Hz, NH).

Acetylation of Estrone and Cholesterol with **11**.

To a solution of estrone (0.5 mmole) in dry *N,N*-dimethylformamide (1 ml), **11** (0.6 mmole) and DBU (0.1 ml) were added. The solution was stirred in a sealed flask at room temperature for 24 hours. Ethyl acetate was added in excess and the organic phase, washed with 2*N* hydrochloric acid and water, was dried and evaporated under vacuum. The residue was chromatographed on a column of silica (1:40); elution with dichloromethane afforded estrone acetate (0.14 g, 89%). Further elution with dichloromethane-ether (8:2) gave the starting steroid (11%).

Preparation of cholesteryl acetate was performed as above, using THF as the solvent. Chromatography of the residue on a column of silica (1:50) [*n*-hexane-dichloromethane (1:1) as eluant] gave cholesteryl acetate (0.17 g, 79%); final elution with dichloromethane afforded cholesterol (15%). Identification of steroidal acetates was made by ir and nmr comparison with commercial samples.

1-(3α-Hydroxy-24-oxo-5β-cholan-24-yl)-1*H*-*v*-triazolo[4,5-*b*]pyridine (**13**).

To a stirred solution of lithocholic acid (1 mmole) in THF (20 ml) and triethylamine (0.28 ml), cooled at 0°, ethyl chloroformate (1 mmole) was added dropwise. After stirring at 0° for 15 minutes, triazole **1** (1 mmole)

was added. The mixture was further stirred at 0° for 15 minutes and at room temperature for 45 minutes. Evaporation of the solvent under reduced pressure gave a residue which was partitioned between dichloromethane and 2*N* hydrochloric acid. The organic layers, washed with water and dried, were evaporated under reduced pressure to give nearly pure **13** (0.48 g), mp 198-199° (ethyl acetate); $[\alpha]_D$ + 19° (c 1.0, chloroform).

Anal. Calcd. for $C_{29}H_{42}N_4O_2$: C, 72.76; H, 8.84; N, 11.70. Found: C, 72.88; H, 8.75; N, 11.56.

Methyl Lithocholate from **13**.

To stirred solution of **13** (0.5 mmole) in THF (4 ml) and dry methanol (0.7 ml), DBU (0.08 ml) was added. After stirring at room temperature for 30 minutes, the solvent was evaporated under vacuum. The residue was partitioned between ethyl acetate and 2*N* hydrochloric acid. The organic solutions, washed with brine and dried, were evaporated under vacuum to give a nearly homogeneous residue (0.197 g). Chromatography on plc [dichloromethane-methanol (95:5) as eluant] afforded pure methyl lithocholate (0.157 g, 81%). The above ester had mp, ir and nmr spectra identical to an authentic sample [19].

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