Studies Related to Antitumor Antibiotics. Part III.[1] Syntheses of 1,2,3,4,5,6-Hexahydro-2,3-benzazocin-5-ones as Possible Intermediates in the Biosynthesis of Mitomycins

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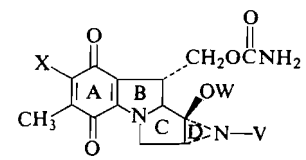
The synthesis of 8-methoxy-9-methyl-*N*-*p*-toluenesulfonyl-1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-one (**23**) and its conversion via transannular interaction to the 2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]indole ABC parent ring system of the antitumor antibiotic mitomycin C is described. The possible implication of this result in the biosynthesis of the mitosanes and the connection with the structurally and pharmacologically related pyrrolizidine alkaloids is discussed.

J. WILLIAM LOWN et TSUNEO ITOH. Can J. Chem. **53**, 960 (1975).

On décrit la synthèse de la méthoxy-8 méthyl-9 *N*-*p*-toluènesulfonylhexahydro-1,2,3,4,5,6 benzazocin-2,3 one-5 (**23**) et sa conversion, par l'intermédiaire d'une interaction transannulaire, en dihydro-2,3 1*H*-pyrrolo[1,2-*a*]indole qui comporte le système cyclique ABC du composé antitumoral et antibiotique mitomycin C. On discute de l'implication possible de ces résultats dans la biosynthèse des mitosanes et la relation avec les alkaloides pyrrolizidine qui leur sont reliés tant au point de vue de la structure que de la pharmacologie.

[Traduit par le journal]

The mitosane class of potent antitumor antibiotics (**1**), which contains several unique structural features including an aziridine group, has attracted considerable attention from synthetic chemists and pharmacologists (1, 2).



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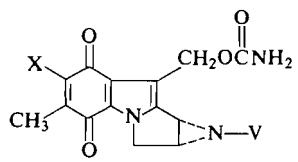

2

In part I of this series we explored some of the characteristics of the chiral aziridine moiety as they relate to the key alkylation role in the cytotoxic action of mitomycin C by irreversible cross linking of the complementary strands of DNA (3). Part II dealt with the spectroscopic evidence from c.m.r. and p.m.r. on the conjugative stabilization and conformation of the antibiotic (4). In the present paper we describe the synthesis of some 1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-ones which pertain to a possible biosynthetic pathway to mitomycin C.

In early work on the biosynthesis the structural similarity of the mitosanes to indole-related compounds suggested a biosynthetic relationship of the antibiotic to tryptophan. However, several compounds structurally or biosynthetically related to the indole nucleus of mitomycin C failed to induce any increase in antibiotic yield (5, 6*a*). Neither labelled tyrosine nor tryptophan contributes label to mitomycin. Recent work by Hornemann and co-workers (6) employing radioactive labelling with ^{14}C and ^{15}N has established the involvement of D-glucose in the construction of ring A and of D-glucosamine in the formation of rings C and D (6). L-Methionine is implicated in the methylation of sites 7 and 9a (6*a*, 7) whereas citrulline is an intermediate in the insertion of the carbamoyl side chain of mitomycin (6*c*).

The introduction of the 9a bridgehead oxygen function in **1** poses considerable problems both biosynthetically and in attempted total synthesis.

[1]For part II see ref. 4.

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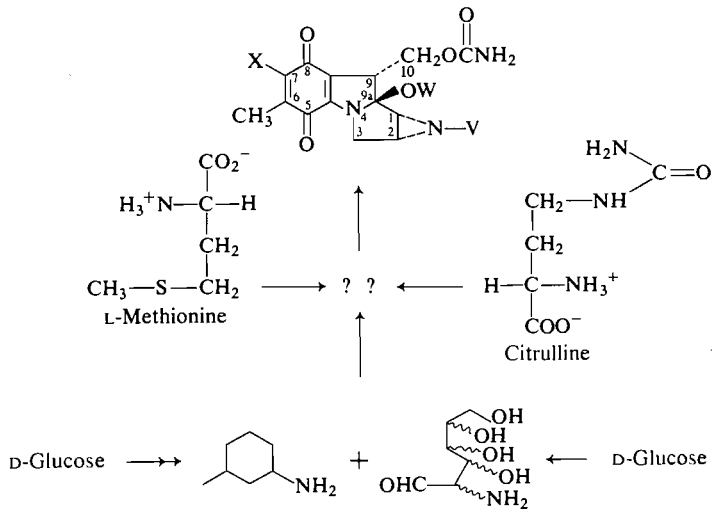
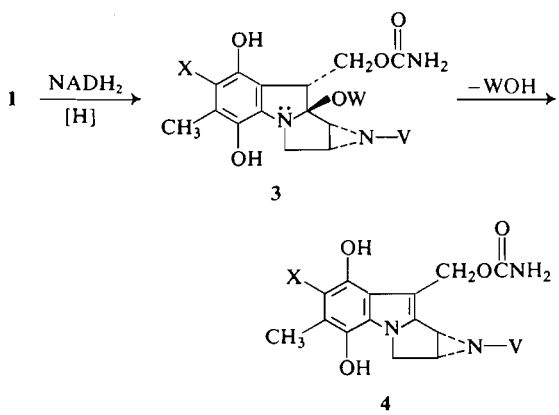


SCHEME 1

Previous synthetic explorations directed toward mitomycin have avoided the problem of introducing the 9a oxygen function and concentrated on the simpler aziridinomitosene structure, **2** (1*e*). The removal of the 9a group following enzymatic reduction of the mitosanes has been suggested as the primary mode of activation of mitomycin (2), *i.e.*



3

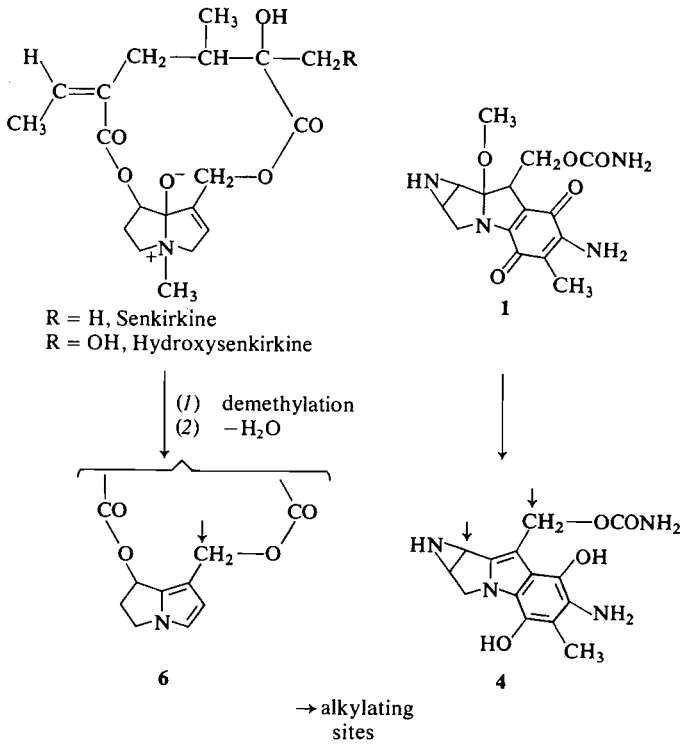
4

The reduced form of the aziridinomitosene (**4**) is then considered "activated", *i.e.*, capable of rapid bifunctional alkylation and hence covalent cross linking of DNA (2).

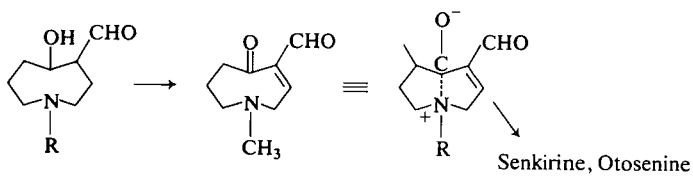
A possible clue to the origin of the 9a moiety and the biosynthetic formation of rings B and C in the mitosanes is provided by the pyrrolizidine alkaloids which they resemble in structure and function (Scheme 2) (2, 8–10). The comparison is even more striking between the pyrrole analogs of the alkaloids, *e.g.*, dehydrolasiocarpine and the activated form of mitomycin (8*b*). Compounds **6** and **4** are both bifunctional alkylating agents with similarly located linkage points. There is evidence that lasiocarpine brings about inhibition of DNA-dependent RNA-polymerase in rat liver suggesting covalent cross linking analogous to that of mitomycin C (11). Some pyrrolizidine alkaloids have mutagenic and tumor-inhibitory properties or cause chromosome breakage, and these conform to structure **6** (8*b*). The alkylating ability is for example associated with the possibility of alkyl–oxygen cleavage of the allylic ester grouping, analogous to the alkylating ability enhanced by indolic-conjugation found in **4**.

The relevant portion of the biosynthesis of the pyrrolizidine alkaloids (which proceeds from the amino acid ornithine) may be represented schematically (see Scheme 3) (12–16). An analogy for the transannular interaction envisaged in mitomycin biosynthesis is provided by the metabolic conversion of otosenine by rat liver microsomes to a pyrrole derivative considered to be dehydroretronecine (17).

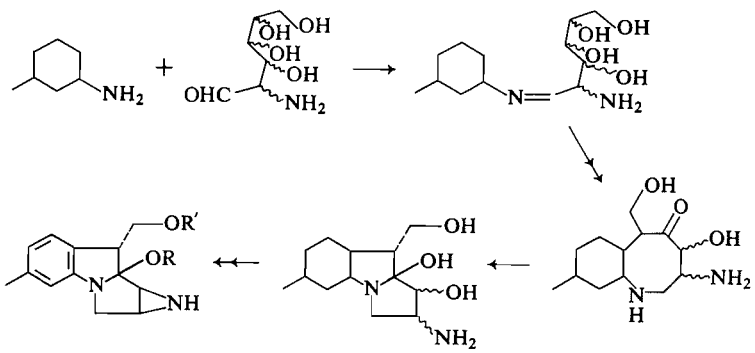
Comparison of Schemes 1 and 3 suggests the intermediate formation of a hexahydrobenzazocinone followed by an analogous transannular interaction as the origin of the 9a oxygen function (see Scheme 4). Transannular interactions in cyclic aminoketones of eight or more atoms



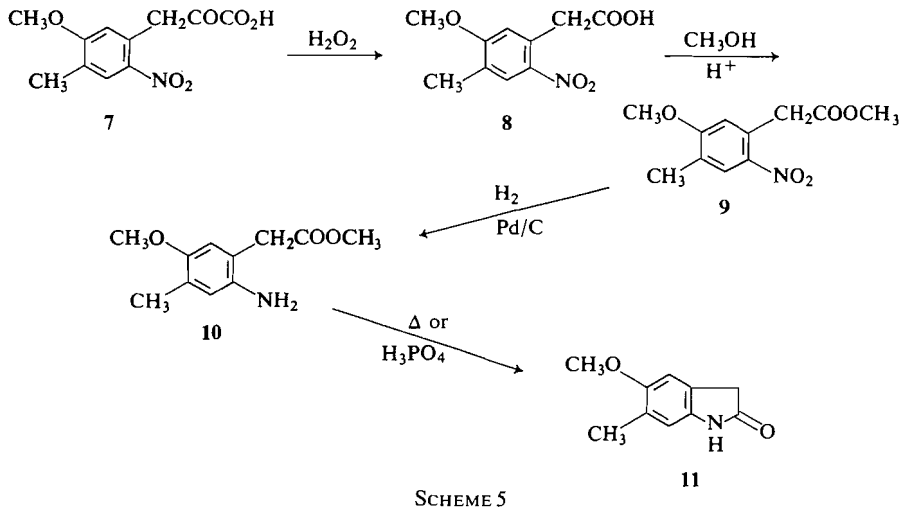
SCHEME 2



SCHEME 3



SCHEME 4



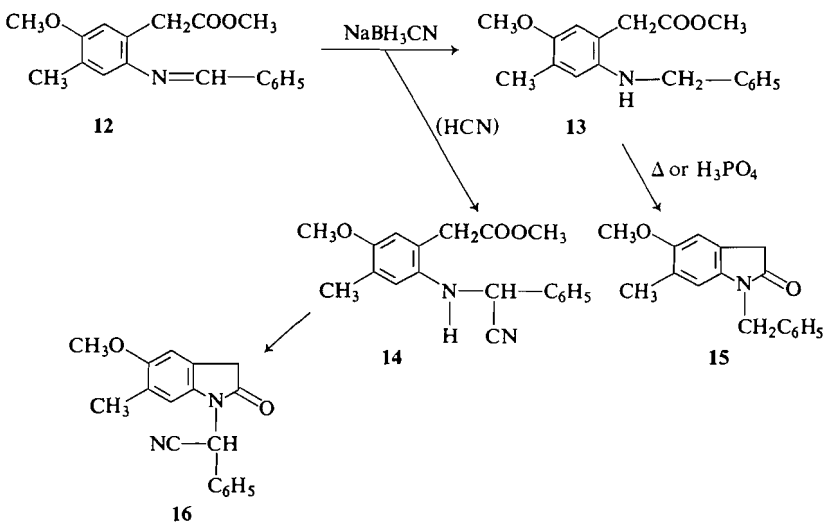
SCHEME 5

have been established by Leonard and coworkers (18*a–c*) and Johnson *et al.* (18*d*).

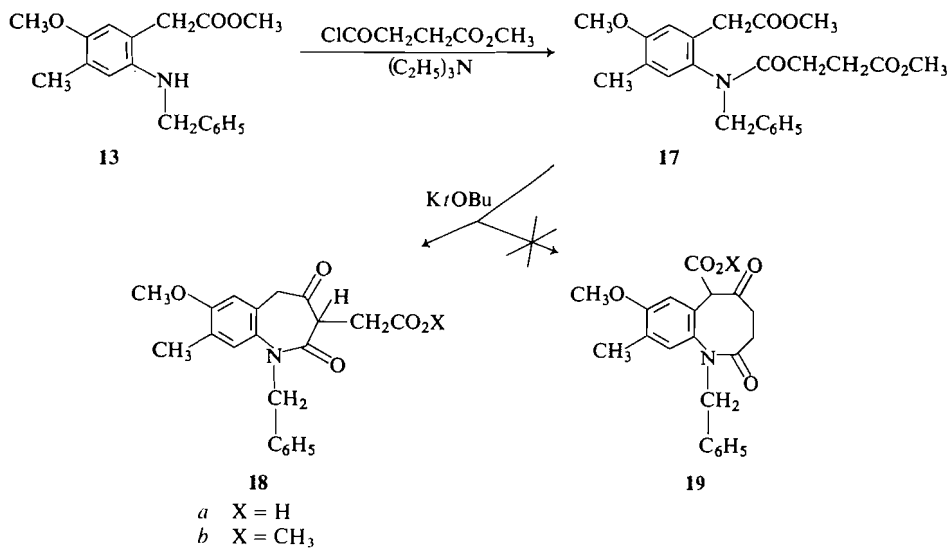
We considered that a comparable demonstration of the formation of rings A, B, and C from a suitably substituted hexahydrobenzazocinone would be valuable in pointing to its possible intermediacy in the biosynthesis. The interaction envisaged is different in type from that demonstrated by Leonard in that an aromatic amine is involved. However, successful ring closure of a benzazocinone might clarify the sequence of events in Scheme 4., *i.e.*, aromatization prior to transannular interaction or vice versa.

In our initial approach 5-methoxy-4-methyl-2-nitrophenylpyruvic acid (**7**) (19) was oxidatively decarbonylated to 5-methoxy-4-methyl-2-nitrophenylacetic acid (**8**) in 80% yield. Esterification of the latter followed by catalytic hydrogenation of the nitro group over palladium at atmospheric pressure afforded methyl 5-methoxy-4-methyl-2-amino-phenyl acetate (**10**) in 92.5% yield (Scheme 5).

The amino ester **10** was extremely labile and consequently, unless precautions were taken to cool the mixture during the catalytic hydrogenation, spontaneous ring closure to the indolinone **11** took place readily. This reaction



SCHEME 6



SCHEME 7

could also be accomplished quantitatively by brief warming of **10** with polyphosphoric acid. In view of its reactivity compound **10** was immediately converted into the anil **12**. Subsequent selective reduction of the imine function in the presence of the ester proved difficult; however the final method selected using sodium cyanoborohydride afforded the desired *N*-benzyl ester **13**. Careful chromatographic separation showed **13** to be accompanied by the two oxindoles **15** and **16**. The latter presumably arises from a Strecker-type addition (20) of the elements of hydrogen cyanide to **12** to form **14** which is unisolated but which would undergo rapid condensation to form **16**. Again these conclusions receive confirmation by the independent cyclization of **13** to **15** by warming with polyphosphoric acid (see Scheme 6).

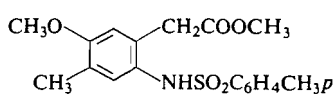
Compound **13** was acylated in 72.5% yield with 3-carbomethoxypropionyl chloride to give methyl 5-methoxy-5-methyl-2-[*N*-benzyl(3′-carbomethoxypropionamido)]phenyl acetate (**17**).

Base catalyzed cyclizations to form medium sized rings are well known to give variable yields (21). In this case treatment of **17** with potassium *tert*-butoxide gave the tetrahydrobenzazepin-2,4-dione-3-acetic acid derivative **18***a* in 63% yield by a Stobbe reaction, instead of the desired hexahydrobenzazocin-2,4-dione **19** (see Scheme 7).

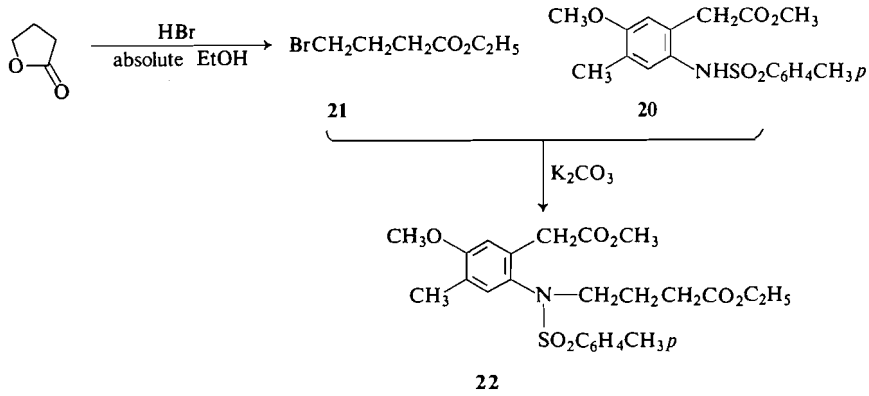
Evidence in support of structure **18***a* rests on the molecular composition and on the n.m.r. spectrum which shows an ABC pattern to be expected for $COCH{\cdot}CH_2CO_2H$ and not an A_2B_2 pattern which is seen in **17** and which would be expected for structure **19**. The i.r. spectrum shows absorption for seven-membered ketone at 1720 and normal acid at 1700 cm^{-1} and no evidence of chelation which would be expected for **19**. Compound **19** would also be expected to undergo ready decarboxylation.

Treatment of **18***a* with diazomethane in ether gave the ester **18***b*, the n.m.r. spectrum of which is similar to **18***a* and whose i.r. shows normal ketone and ester absorption at 1725 and 1715 cm^{-1}, respectively. In order to prevent the Stobbe reaction and favor Dieckmann condensation, an alternative approach was made via an intermediate which is incapable of forming a carbanion β to the nitrogen.

Formation of the *N*-*p*-toluenesulfonyl derivative from compound **10** proceeded smoothly in 72% yield. The product compound **20** has the distinct advantage over derivatives of the type **13** in that direct *N*-alkylation is possible via the *N*-sulfonyl anion of **20**. For example treatment of **20** with ethyl γ-bromobutyrate in the presence of potassium carbonate gave the *N*-alkylated product **22** (see Scheme 8). Treatment of **22**



20



SCHEME 8

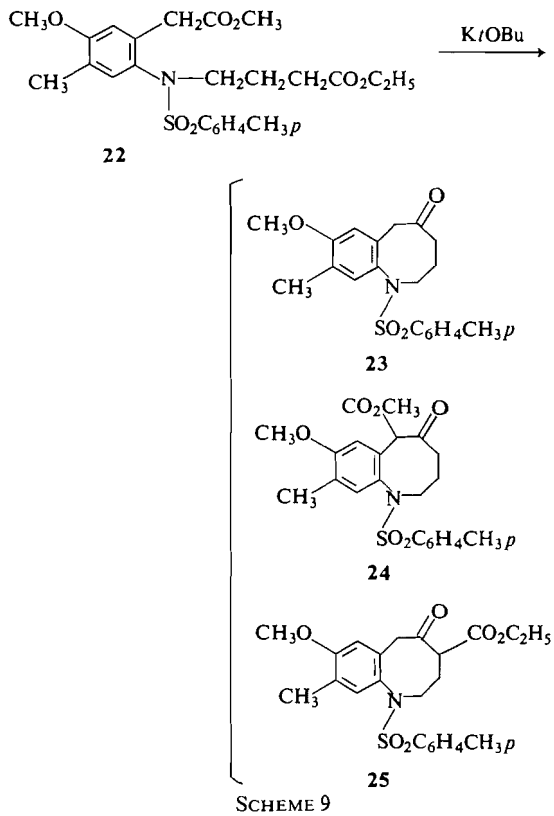
with potassium *tert*-butoxide in dry toluene afforded the desired 1,2,3,4,5,6-hexahydro-1,2-benzazocin-5-one **23** accompanied by small quantities of the analogs **24** and **25**. Compounds **24** and **25** were isolable as crystalline solids and characterized separately whereas **23** was obtained as an oil slightly contaminated with traces of **24** and **25** (Scheme 9). The spectral properties of all three compounds were consistent with their assigned structures (see Experimental).

Reductive cleavage of the N—S bond was accomplished with sodium in liquid ammonia; (this reagent has been used previously for the reductive cleavage of sulfur containing bonds (22)). The initial transannulated product **26** which was not isolated, eliminated water under these conditions to form the known compound **27** (19) in a reaction which is analogous to the conversion of **3** to **4** (Scheme 10). Compound **25** was accompanied by small amounts of **28** and **29** formed from the analogous ring closure of **24** and **25**, respectively. Compound **29** was isolated as a crystalline solid which could be characterized. The structure of **29** is given by its molecular composition and the n.m.r. spectrum which shows an ethyl ester and absence of vinylic absorptions and three groups of methylene absorptions (see Experimental).

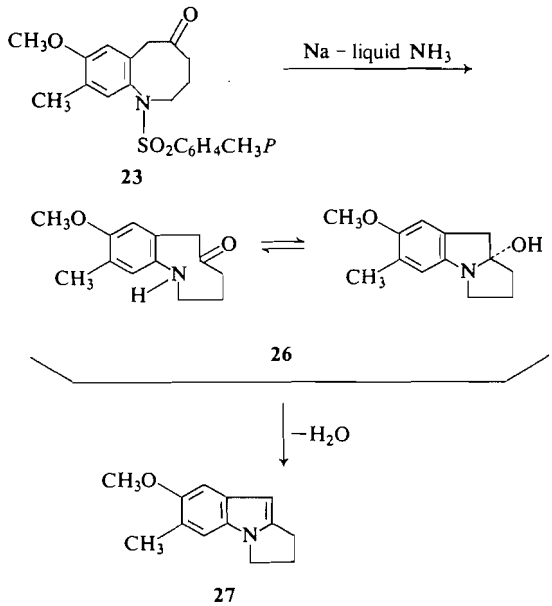
The above experiments with model systems provide a chemical basis for the suggested intermediacy of a hexahydrobenzazacinone and its transannular interaction to form rings A, B, and C of mitomycin C during its biosynthesis. This sequence of reactions also may provide an alternative approach to the presently unsolved problem of a total synthesis of mitomycin C.

Experimental

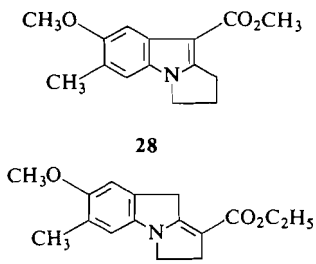
Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin-Elmer model 421 spectrophotometer and only the principal, sharply defined peaks are reported. The n.m.r. spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in $CDCl_3$, with tetramethylsilane as a standard. Line



SCHEME 9



SCHEME 10



positions are reported in p.p.m. from the reference. Mass spectra were determined on an Associated Electrical Industries MS-9 double focusing high resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kieselgel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin layer chromatography. Microanalyses were carried out by Mrs. D. Mahlow of this department.

5-Methoxy-4-methyl-2-nitrophenylacetic Acid (8)

5-Methoxy-4-methyl-2-nitrophenylpyruvic acid 7 (25.321 g, 0.100 mol) (19) was dissolved in a solution of 40.0 g (1.0 mol) of sodium hydroxide in 130 ml of water. Ice (50 g) was added, followed by the slow addition of a solution of 27 g of 30% hydrogen peroxide in 75 ml of water with continuous stirring. The solution was set aside at room temperature for 5 h then cautiously acidified with concentrated hydrochloric acid. The resulting solid was collected and purified by recrystallization from methanol affording 18.0 g (80% yield) of compound **8**, m.p. 154°.

Anal. Calcd. for $C_{10}H_{11}O_5N$ (mol. wt. 225.0637): C, 53.33: H, 4.92; N, 6.22. Found (mass spectrum, 225.0630): C, 53.08; H, 4.80; N, 6.15.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.27 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.07, (s, 2H, $—CH_2CO_2$), 6.71, 8.08 (s, 1H each, aryl). The i.r. ν_{max} ($CHCl_3$): 1710 (acid CO), 3500 cm^{-1} (acid OH).

Methyl 5-Methoxy-4-methyl-2-nitrophenylacetate (9)

A solution of 5.0 g (22 mmol) of 2-nitrophenylacetic acid **8** and 0.5 ml of concentrated sulfuric acid in 100 ml of methanol was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* and the resulting solid collected and purified by recrystallization from methanol to give 4.0 g (76.5% yield) of compound **9** as white needles, m.p. 123–124°.

Anal. Calcd. for $C_{11}H_{13}O_5N$ (mol. wt. 239.0799): C, 55.23; H, 5.48; N, 5.86. Found (mass spectrum 239.0798): C, 55.12; H, 5.64; N, 5.78.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.26 (s, 3H, CH_3), 3.75 (s, 3H, $—CO_2CH_3$), 3.96 (s, 3H, OCH_3), 4.05 (s, 2H, $—CH_2CO_2R$), 6.75, 8.07 (s, 1H, each, aryl).

Methyl 5-Methoxy-4-methyl-2-aminophenylacetate (10)

A mixture of 7.17 g (30 mmol) of methyl 5-methoxy-4-methyl-2-nitrophenylacetate (**9**) and 1.0 g of 5% palladium-on-charcoal in 160 ml of ethyl acetate was subjected to hydrogenation at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 6 h. Filtration and concentration of the solution gave a pale yellow oil which solidified on cooling. Crystallization from methanol gave 5.8 g (92.5% yield) of compound **10**, m.p. 158–160°. This material was extremely unstable and was immediately converted into the anil.

Anil of Methyl 5-Methoxy-4-methyl-2-aminophenylacetate (12)

To a solution of 4.180 g (20 mmol) of methyl 5-methoxy-4-methyl-2-aminophenylacetate **10** and 500 mg of *p*-toluenesulfonic acid in 30 ml of dry benzene was added a solution of 2.12 g (20 mmol) of benzaldehyde in 10 ml of dry benzene and the solution was stirred at ambient temperature overnight. The filtered solution was concentrated *in vacuo* to give 5.02 g (84.5% yield) of the Schiff base **12** as a yellow solid which was purified by recrystallization from methanol, m.p. 98°.

Anal. Calcd. for $C_{18}H_{19}O_3N$ (mol. wt. 297.1359): C, 72.70; H, 6.44; N, 4.71. Found (mass spectrum 297.1365): C, 72.54; H, 6.56; N, 4.68.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.22 (s, 3H, CH_3), 3.62 (s, 3H, $—CO_2CH_3$), 3.86 (s, 5H, CH_2CO_2R and OCH_3), 6.78, 6.96 (1H each, s, ring protons), 7.35–7.97 (aryl protons), 8.26 (s, 1H, $—N=CH—C_6H_5$). The i.r. spectrum ν_{max} ($CHCl_3$): 1730 cm^{-1} (C=O).

Methyl 2-Benzylamino-4-methyl-5-methoxyphenylacetate (13)

To a solution of 0.9 g of the Schiff base **12** in 5 ml of ethyl acetate was added a solution of 120 mg of sodium cyanoborohydride (23) in 3 ml of methanol, and the mixture stirred at room temperature for 6 h. The p*H*

of the solution was adjusted to 7.0 periodically by the addition of hydrochloric acid, the solution was filtered and concentrated *in vacuo*. The residual oil was treated with water and methylene chloride and the aqueous layer extracted several times with methylene chloride. Concentration of the dried extract gave 0.780 g of compound **13** as an oil.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.12 (s, 3H, CH_3), 3.54 (s, 2H, $CH_2CO_2CH_3$), 3.63 (s, 3H, CO_2CH_3), 3.73 (s, 3H, OCH_3), 4.86 (s, 2H, CH_2Ph), 6.54, 6.84, (s, 1H each, ring protons), 7.04–7.65 (m, 5H, aryl protons). The i.r. spectrum (film): 1695 (C=O), 3350 (NH) cm^{-1}.

Mol. Wt. Calcd. for $C_{18}H_{21}NO_3$: 299. Found (mass spectrum): 299.

Further elution with benzene gave 180 mg of 5-methoxy-6-methyl-*N*-1′-cyanobenzyl-2-indolinone (**16**) as a white crystalline solid, m.p. 152–153° (methanol).

Anal. Calcd. for $C_{18}H_{16}O_2N_2$ (mol. wt. 292.1212): C, 73.95; H, 5.52; N, 9.58. Found (mass spectrum 292.1213): C, 73.91; H, 5.48; N, 9.39.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.16 (s, 3H, CH_3), 3.76 (s, 2H, —CH_2); 3.89 (s, 3H, OCH_3), 6.74, (s, 1H, 4 or 7 proton), 7.06 (s, 2H, 4 or 7 proton and —N—C*H*(CN)Ph), 7.66 (s, 5H, phenyl group). Further elution with benzene gave *N*-benzyl-5-methyl-2-oxindole (**15**). The spectral and physical data on this compound were identical with those described in its synthesis below.

*5-Methoxy-6-methyl-2-indolinone (**11**)*

A mixture of 1.5 g (7.1 mmol) of the amine **10** and some polyphosphoric acid (prepared from 7.5 ml of orthophosphoric acid and 7.5 g of phosphorous pentoxide) was heated at 130–140° with stirring for 15 min. After cooling, the mixture was treated with excess of cold water and the precipitated product was collected and purified by recrystallization from methanol affording 950 mg (74.5% yield) of compound **11**, m.p. 162–164°.

Anal. Calcd. for $C_{10}H_{11}O_2N$ (mol. wt. 177.0790): C, 67.78; H, 6.26; N, 7.91. Found (mass spectrum, 177.0794): C, 67.69; H, 6.11; N, 8.02.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.23 (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.87 (s, 1H), and 7.13 (s, 1H, aryl protons). The i.r. spectrum ν_{max} (film): 1655 (amide C=O), 3430 cm^{-1} (br, NH).

*N-Benzyl-5-methoxy-6-methyl-2-indolinone (**15**)*

A solution of 0.7 g (2.3 mmol) of methyl 2-benzylamino-4-methyl-5-methoxyphenyl acetate **13** in 15 ml of dry ether in a pressure bottle was warmed at 40–50° with stirring for 16 h. The solvent was removed *in vacuo* and crystallization of the residue from methanol gave 400 mg (65% yield) of *N*-benzyl-5-methoxy-5-methyl-2-indolinone (**15**), m.p. 103–104°.

Anal. Calcd. for $C_{17}H_{17}O_2N$ (mol. wt. 267.1259): C, 76.38; H, 6.41; N, 5.24. Found (mass spectrum 267.1256): C, 76.21; H, 6.51; N, 5.18.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.20 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 5.02 (s, 2H, NCH_2Ph), 6.78 (s, 1H), and 7.02 (s, 1H, oxindole ring protons), 7.47 (s, 5H, aryl). The i.r. spectrum ν_{max} ($CHCl_3$): 1675–1690 cm^{-1} (C=O).

*Methyl 2-[N-Benzyl-N-(3-carbomethoxypropionyl)]-amino-4-methyl-5-methoxyphenylacetate (**17**)*

To a solution of 5.3 g (17.4 mmol) of compound **13** and 1.92 g (18 mmol) of trimethylamine in 30 ml of dry benzene was added a solution of 2.61 g (17.4 mmol) of 3-carbomethoxypropionyl chloride in 10 ml of dry benzene. The mixture was stirred for 1 h then washed with water (3 × 20 ml) and the organic layer dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was purified by chromatography on silica gel. Elution with 4.0 g (72.5% yield) of compound **17** as a yellow oil.

Anal. Calcd. for $C_{23}H_{27}O_6N$ (mol. wt. 413.1838): C, 66.81; H, 6.58; N, 3.39. Found (mass spectrum 413.1842): C, 66.61; H, 6.62; N, 3.35.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.14 (s, 3H, CH_3), 2.10–2.83 (br m, 4H, —$CH_2CH_2CO_2R$), 3.50 s, 2H, —CH_2CO_2R), 3.80 (s, 6H, CO_2CH_3), 3.96 (s, 3H, CH_3O), ABq centered at 4.52 and 5.35, J = 14 Hz (2H, —CH_2Ph), 6.79 (s, 1H), and 6.98 (s, 1H, aryl ring protons). The i.r. spectrum ν_{max} ($CDCl_3$): 1645 (amide CO), 1725 cm^{-1} (ester CO).

*1-Benzyl-7-methoxy-8-methyl-2,3,4,5-tetrahydrobenzazepin-2,4-dione-3-acetic Acid (**18a**)*

A mixture of 0.78 g (20 mmol) of potassium and 4.5 g (62 mmol) of *tert*-butyl alcohol was allowed to react in 60 ml of freshly distilled toluene in a three-necked flask purged with nitrogen. The mixture was stirred and heated below the boiling point of the alcohol–toluene azeotrope until all of the potassium had reacted. The excess of alcohol was then removed by distillation. Dry toluene was introduced to bring the total volume in the flask to 150 ml and 3.10 g (7.5 mmol) of the diester **17** in 60 ml of dry toluene was added dropwise over a period of 12 h to the reaction mixture with vigorous stirring and refluxing. After cooling, the resulting mixture was neutralized with dilute hydrochloric acid and the organic layer dried ($MgSO_4$). Removal of the solvent *in vacuo* from the filtered solution afforded 1.79 g (63% yield) of 1-benzyl-7-methoxy-8-methyl-2,3,4,5-tetrahydrobenzazepin-2,4-dione-3-acetic acid (**18a**) as an oil.

Anal. Calcd. for $C_{21}H_{21}NO_5$ (mol. wt. 367): C, 69.27; H, 6.08; N, 3.67. Found (mass spectrum 367): C, 69.53; H, 6.21; N, 3.44.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.22 (s, 3H, CH_3), 2.92–4.20 (3H, ABC COC*H*—CH_2CO_2H), 3.80 (s, 3H, CO_2CH_3), 3.90 (s, 2H, CH_2CO), ABq centered at 4.78 and 5.40, J = 14.5 Hz (CH_2Ph), 6.53 (s, 1H, ring proton), 6.9–7.5 (m, 6H, phenyl and ring protons).

The i.r. ν_{max} (KBr disc): 1645 (), 1700 (CO_2H), 1720 (seven-membered ring C=O) cm^{-1}.

*Methyl 1-Benzyl-7-methoxy-8-methyl-2,3,4,5-tetrahydrobenzazepin-2,4-dione-3-acetate (**18b**)*

To a solution of 1.00 g (2.7 mmol) of the tetrahydrobenzazepindioneacetic acid in 45 ml of dry ether was added by distillation, an ethereal solution of diazomethane (prepared from 1.5 g of nitrosomethylurea and 20% sodium hydroxide solution). The mixture was stirred at ambient temperature for 18 h and taken to dryness to give an oil which was purified by chromatog-

raphy on neutral alumina giving 1.02 g (97% yield) of methyl 1-benzyl-7-methoxy-8-methyl-2,3,4,5-tetrahydrobenzazepin-2,4-dione-3-acetate (**18***b*).

Anal. Calcd. for $C_{22}H_{23}NO_5$ (mol. wt. 381.1576); C, 69.27; H, 6.08; N, 6.37. Found (mass spectrum, 381.1565): C, 69.53; H, 6.21; N, 3.42.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.20 (s, 3H, CH_3), 2.85–4.25 (ABC, 3H, $COCHCH_2CO_2H$), 3.64 (3,3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 3.89 (d, 2H, $—CH_2CO$), AB quartet centered at 4.72 and 5.44, J = 14.5 Hz, $—NHCH_2Ph$, 6.52 and 7.25 (s, 1H each, ring protons), 7.20 (s, 5H, phenyl group). The i.r. ν_{max} ($CHCl_3$): 1645 ($\diagdown$N—CO$\diagup$); 1715 (CO_2CH_3) and 1725 (seven-membered ketone) cm^{-1}.

*Methyl 5-Methoxy-4-methyl-2-toluenesulfonamidophenylacetate (**20**)*

To a solution of 4.18 g (20 mmol) of the *o*-aminophenylacetate **10** in 45 ml of dry pyridine was added 3.80 g (20 mmol) of *p*-toluenesulfonyl chloride. The solution was stirred for 3 h at room temperature then the pyridine was allowed to evaporate in the fume hood. The residue was shaken with chloroform and dilute hydrochloric acid and the organic layer was dried ($MgSO_4$). Concentration of the solution afforded 5.2 g (71.5% yield) of compound **20** as white crystals, m.p. 109–110°.

Anal. Calcd. for $C_{18}H_{21}O_5NS$ (mol. wt. 363.1140): C, 59.49; H, 5.83; N, 3.86. Found (mass spectrum 363.1136): C, 59.38; H, 5.85; N, 3.71.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.10, (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.20 (s, 2H, $—CH_2CO_2R$), 3.65 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 6.53 (s, 1H), 7.01 (s, 1H, phenyl ring protons), AB quartet centered at 7.20 and 7.58, J = 8.0 Hz (4H, toluenesulfonyl ring protons). The i.r. spectrum ν_{max} ($CHCl_3$): 1715 (ester C=O), 3350 cm^{-1} (sulfonamide NH).

*Methyl 5-Methoxy-4-methyl-2-[N-(3-carbomethoxypropyl)]-p-toluenesulfonamidophenyl Acetate (**22**)*

A mixture of 3.63 g (10 mmol) of methyl 5-methoxy-4-methyl-2-*p*-toluenesulfonamidophenylacetate **20**, 3.66 g (20 mmol) of ethyl γ-bromobutyrate, and 4.95 g (36 mmol) of anhydrous potassium carbonate in 60 ml of dry acetone was heated under reflux with stirring for 16 h. The reaction mixture was filtered and concentrated *in vacuo* and the oil was subjected to chromatography. Removal of the solvent afforded 4.5 g (94% yield) of **22** as an oil.

Anal. Calcd. for $C_{24}H_{31}O_7N^{32}S$ (mol. wt. 477.1822): C, 60.36; H, 6.54; N, 2.93. Found (mass spectrum 477.1833): C, 60.18; H, 6.63; N, 3.15.

The n.m.r. spectrum δ TMS ($CDCl_3$): 1.29 (t, 3H, $CH_3CH_2—$), 2.03 (s, 3H, $CH_3—$), 1.61–2.52 (m, 4H, $CH_3CH_2CH_2—$), 3.31–3.56 (m, 2H, CH_2CO_2R); 3.74 (s, 3H, CO_2CH_3), 3.87 (s, 3H, $CH_3O—$), 3.90–4.45 (m, 2H, $—CH_2CH_3$), 6.30 (s, 1H), 6.87 (s, 1H, phenyl ring protons), AB quartet centered at 7.28 and 7.55, J = 8.5 Hz (4H, aryl absorption). The i.r. spectrum ν_{max} ($CHCl_3$): 1725 cm^{-1} (C=O).

*Dieckmann Condensation of Methyl 5-Methoxy-4-methyl-2-[N-(3-carbomethoxypropyl)]-p-toluenesulfonamidophenylacetate (**22**)*

A solution of 4.77 g (10 mmol) of diester **22** in 60 ml of dry toluene was added over a period of 3 h with vigorous stirring and continuous refluxing under nitrogen to a suspension of 5.75 g (0.05 mol) of potassium *tert*-butoxide in 150 ml of dry toluene. The solution was concentrated to about half the volume *in vacuo* and after cooling the filtered solution was washed with (*i*) dilute hydrochloric acid (3 × 25 ml) and (*ii*) water (2 × 15 ml) then dried ($MgSO_4$). Removal of the solvent and chromatography of the residual oil on silica gel with chloroform as eluant gave (*a*) an oil and (*b*) crystals.

Fraction *a* the oil was 8-methoxy-9-methyl-*N*-*p*-toluenesulfonyl-1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-one (**23**) 0.92 g (24.6% yield).

Anal. Calcd. for $C_{20}H_{23}NO_4S$ (mol. wt. 373.1348): N, 3.14. Found (mass spectrum 373.1337): N, 3.63.

The n.m.r. spectrum δ TMS ($CDCl_3$): 0.9–2.5 (m, 6H, CH_2), 2.02 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.30–4.2 (m, 2H, $ArCH_2CO$), 3.82 (s, 3H, OCH_3), 6.48, 6.66 (s, 1H, each phenyl ring proton), AB quartet centered at 7.30 and 7.67, J = 8.0 Hz (4H, $—C_6H_4CH_3$). The i.r. spectrum ν_{max} ($CHCl_3$): 1705 cm^{-1} (C=O).

Fraction *b* provided sufficient material (65 mg), m.p. 110–112° for an n.m.r. spectrum confirming the presence of both **24** and **25**.

The n.m.r. spectrum δ TMS ($CDCl_3$): 1.23 (t, 3H, $CH_3CH_2—$), 1.74–2.10 (br, *ca.* 6H, methylenes), 2.12, 2.14, (s, 3H each, ring CH_3), 3.66 (s, 3H, CO_2CH_3 of **24**), 3.79, 3.81 (s, 3H each, ring OCH_3), 4.02–4.38 (q, 2H, CH_2CH_3 for **25**), 6.70 and 6.76 (s, 1H each, phenyl ring protons), AB quartets centered at 7.18 and 7.56, J = 9.0 Hz (4H each, $SO_2C_6H_4CH_3$).

The i.r. spectrum ν_{max} (KBr disc): 1733 (eight-membered ring ketone), 1715 cm^{-1} (ester C=O). Fractional recrystallization of *b* from ether afforded pure methyl 8-methoxy-9-methyl-*N*-*p*-toluenesulfonyl-1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-one-2-carboxylate (**24**, 11 mg), m.p. 173°.

Anal. Calcd. for $C_{22}H_{25}O_6N^{32}S$ (mol. wt. 431.1403): C, 61.24; H, 5.84; N, 3.25. Found (mass spectrum, 431.1391): C, 61.45; H, 5.98; N, 2.89.

Recrystallization of the residue from the mother liquor gave ethyl 8-methoxy-9-methyl-*N*-*p*-toluenesulfonyl-1,2,3,4,5,6-hexahydro-1,2-benzazocin-4-carboxylate (**25**, 8 mg), m.p. 121°.

Mol. Wt. Calcd. for $C_{23}H_{27}O_6N^{32}S$: 445.1566. Found (mass spectrum): 445.1559.

*Reductive Cleavage of the N-Tosylhexahydrobenzazocinone **23** and Ring Closure to 2,3-Dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (**27**)*

To a stirred suspension of 873 mg (2.72 mmol) of the hexahydrobenzazocinone **23** in *ca.* 30 ml of liquid ammonia was added 230 mg (10 mgatom) of sodium and after 10 min a blue color developed. Ammonium chloride was added when the solution became colorless, then the ammonia was allowed to evaporate and methanol then water and chloroform were added. The organic layer was washed with water and dried ($MgSO_4$).

Evaporation of the solvent afforded an oil which was chromatographed on silica gel. Elution with chloroform gave 230 mg (45% yield) of 2,3-dihydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole (**27**), m.p. 112–113°, as needles crystallized from *n*-hexane. The m.p. was depressed (by admixture with traces of the corresponding pyrrolo[1,2-*a*]indoles **28** and **29**) compared with literature (19) value of 116–118°. The m.p. was undepressed upon admixture with an authentic sample of **27**.

Mol. Wt. Calcd. for $C_{13}H_{15}NO$: 201.1154. Found (mass spectrum): 201.1145.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.32 (s, 3H, 6-CH_3), 2.45–2.71 (m, 2H, —$CH_2CH_2CH_2$—), 2.97 (t, 2H, —$NCH_2CH_2CH_2$—), 3.86 (s, 3H, OCH_3), 3.96 (t, 2H, —N—CH_2—CH_2CH_2—), 6.04 (s, 1H, indole H), 6.96 (s, 1H), 6.98 (s, 1H, 5 and 9 ring protons).

Fractional crystallization of the mother liquor allowed the isolation of pure **29**, m.p. 118.9°.

Mol. Wt. Calcd. for $C_{16}H_{19}NO_3$: 273.1372. Found (mass spectrum): 273.1366.

The n.m.r. spectrum δ TMS ($CDCl_3$): 1.38 (t, 3H, CH_2CH_3), 2.21 (s, 3H, CH_3), 2.57 (quintet, 2H, —CH_2—), 3.19 (t, 2H, —CH_2—), 3.89 (s, 3H, OCH_3), 3.95 (q, 2H, —CH_2), 6.94, 7.55 (s, 1H each ring protons). The n.m.r. spectrum shows in addition an absorption due to **28**, a band 3.86 (s, 3H, —CO_2CH_3). The i.r. spectrum ν_{max} ($CHCl_3$): 1683 cm^{-1} (N—C=C—C=O). The mother liquor showed the presence of compound **28**.

Mol. Wt. Calcd. for $C_{15}H_{17}NO_3$: 259.1208. Found (mass spectrum): 259.1213.

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