SYNTHESIS OF PENTAZOCINE

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Synthetic studies of pentazocine and its intermediates are described and classified.

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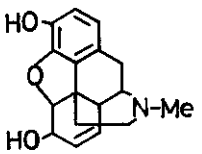
1 INTRODUCTION

An important problem in the pharmacological field for many years was to find new synthetic analgesics which are free of undesirable side effects, such as

Chart 1



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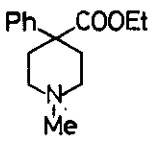

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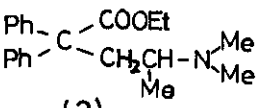

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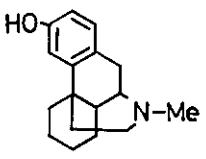

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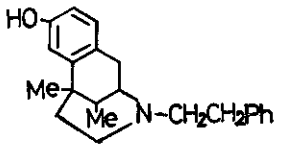

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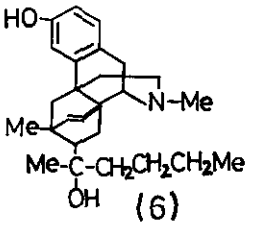
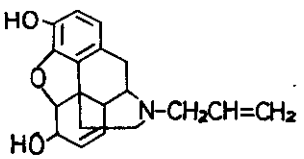


(6)

addiction. For this reason, research on the relationship between chemical structure and analgetic activity has been actively pursued by many researchers. For example, the syntheses of meperidine (2), methadone (3), dormoran (4) and phenazocine (5) as representative compounds have been reported, in which thebaine derivative (6) showed about 10,000 times as active as morphine (1) in analgetic potency. However, these strong analgesics had almost the same addiction-producing properties, and for that reason these compounds were referred to as narcotics.

Therefore, it often seemed impossible to achieve the desired separation of analgetic potency from addiction liability. Subsequently, the N-substituted compounds, nalorphine (7) and levallorphan (8), allyl analogues of compounds (1) and (4), respectively, were found to have a potent narcotic antagonistic effect, and nalorphine (7) is comparable to morphine in analgetic potency in man.

Chart 2



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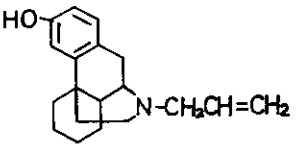

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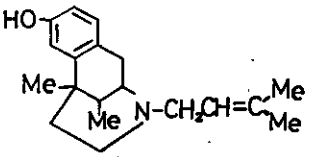


(9)

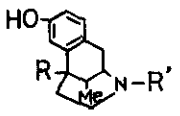
Based on these findings, there appeared to be a possibility of separating analgetic potency from addiction liability.

In 1966, 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine(pentazocine) (9) was recognized as a non-narcotic analgesic by the Committee on Drug Addiction and Narcotics, National Research Council and attracted the attention of the world. This compound, pentazocine (9), was synthesized by Archer and his co-workers in the Winthrop Laboratories in the United States and is now used clinically in many countries.

2. SYNTHESES OF PENTAZOCINE

Firstly, Archer and his associates synthesized N-substituted derivatives having allyl, 3-methyl-2-butenyl, cyclopropylmethyl, and other groups in the benzomorphane

Table 1



R	R′	Mp °C	Antagonist Activity mg/kg
Nalorphine (7)			0.13
Levallorphan (8)			0.052
N-Allylnormeperidine			Analgesic
Me	$CH_2CH=C(Me)_2$	145.4 – 148.6	3.9
〃	CH_2–cyclopropyl	200.5 – 203.8	0.019
〃	$CH_2CH=CH_2$	141.2 – 143.8	0.047
〃	CH_2CH_2–cyclopropyl	203 – 206	0.092
〃	CH_2–cyclohexyl	167.6 – 169.2	0.37
〃	CH_2–cyclopentyl	230.4 – 233.2 (HCl salt)	0.28
〃	CH_2CH_2Me		0.019
Et	$CH_2CH=CH_2$	166.4 – 168.2	0.049
〃	$CH_2CH=C(Me)_2$	161.6 – 164.2	10.9
〃	CH_2–cyclopropyl	180.8 – 183.2	0.024

nucleus, as shown in Table 1, based on the assumption that the pharmacological properties of nalorphine (7), levallorphan (8) and similar compounds would correlate with structure.[1]

As a result, the N-substituted compound (9) having a 3-methyl-2-butenyl group was found to be weak in antagonistic activity, and to have an analgetic activity in man. In the meanwhile, the pharmacological properties of this compound (9) were studied in many respects and, in 1966, (9) was recognized as a non-narcotic analgesic. Since pentazocine has appeared on the market as a non-narcotic analgesic, many other synthetic methods for this compound have been studied. These methods are described under the following classification:

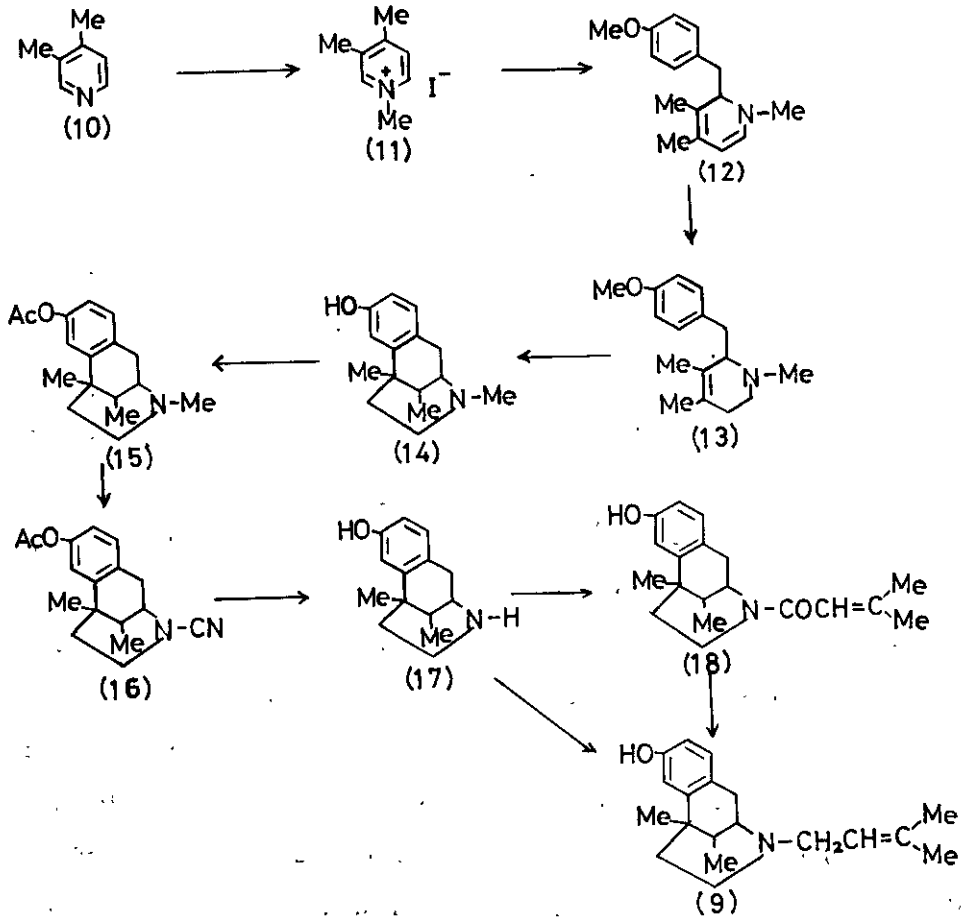
2-1 From 3,4-lutidine

(a) Archer and co-workers' method: Pentazocine (9) has been synthesized by condensation of 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (17), which had already been synthesized by May and co-workers[2] as shown in Chart 3, with 3-methyl-2-butenyl bromide or by acylation with senecioyl chloride followed yb lithium aluminum hydride reduction.[3]

Compound (17) was synthesized in the following manner. 1,3,4-Trimethylpyridinium iodide (11), which was obtained by quaternization of 3,4-lutidine (10) with methyl iodide, was treated with 4-methoxybenzyl chloride in the presence of magnesium via a Grignard reaction to give 1,2-dihydro-2-(4-methoxybenzyl)-1,3,4-trimethylpyridine (12). Catalytic hydrogenation of (12) on palladium-barium sulfate or preferably reduction with sodium borohydride afforded 1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-1,3,4-trimethylpyridine (13). Compound (13) was cyclized with either 48 % hydrobromic acid or 85 % phosphoric acid to give 1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (14). Then,

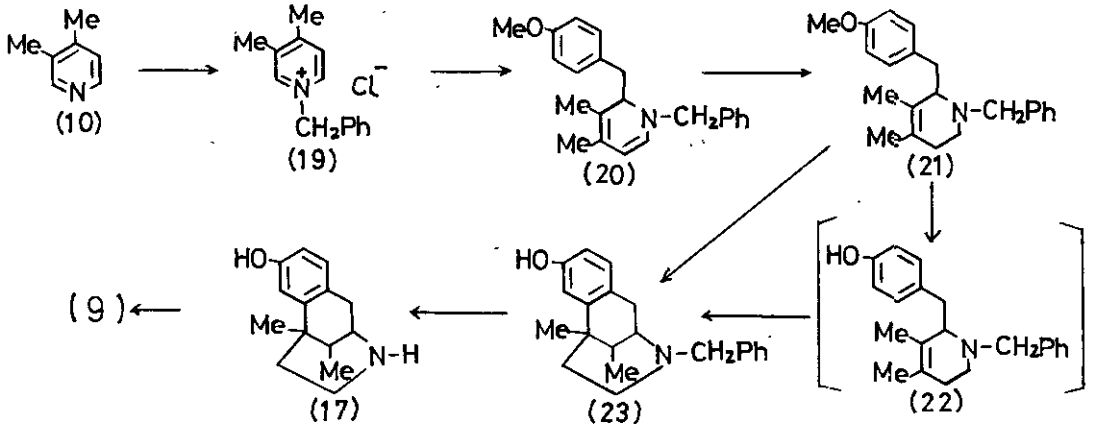
14 was converted into compound 15 ,which was subjected to the von Braun reaction to give compound 17 via compound 16 . Furthermore, the synthesis of 13 was also achieved by Stevens rearrangement .[4]

Chart 3



(b) Kametani and co-workers' method: A simplified alternate synthesis of pentazocine (9) was reported in 1969.[5] Namely, the method from 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (23) is shown

Chart 4

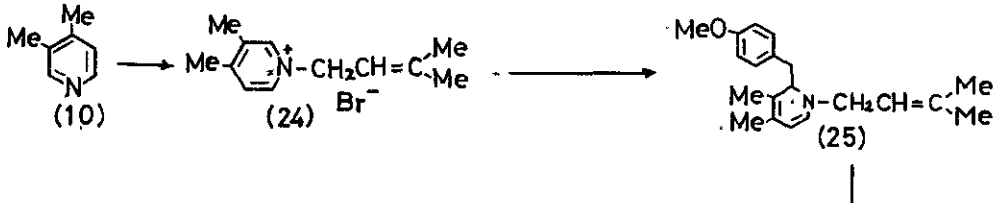


1-Benzyl-3,4-dimethylpyridinium chloride (19), which was obtained by quaternization of 3,4-lutidine with benzyl chloride, reacted with 4-methoxybenzyl chloride by a Grignard reaction to give 1-benzyl-1,2-dihydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (20). Reduction of 20 with sodium borohydride afforded 1-benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (21). When compound 21 was refluxed with 48 % hydrobromic acid for 30 - 40 h, the expected cyclization and demethylation occurred to give 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-

6,11-dimethyl-2,6-methano-3-benzazocine (23). In this case, the demethylated intermediate (22) separated as its hydrobromide, which on treatment with hydrobromic acid gave 23 . Then, catalytic hydrogenation of the hydrochloride of 23 in the presence of 10 % palladium-charcoal gave 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (17) in 90 % yield, which was identical with an authentic sample (prepared by demethylation of 14 via the von Braun reaction) on mixed mp and ir spectral comparison. The reaction of 17 with 3-methyl-2-butenyl bromide according to Archer's method[1] gave the expected pentazocine (9).

(c) Sumitomokagaku's method: Sumitomokagaku's group reported the simplest method in 1970. Namely, N-3-methyl-2-butenyl-3,4-dimethylpyridinium bromide (24), which was obtained by quaternization of 3,4-lutidine with 3-methyl-2-butenyl

Chart 5

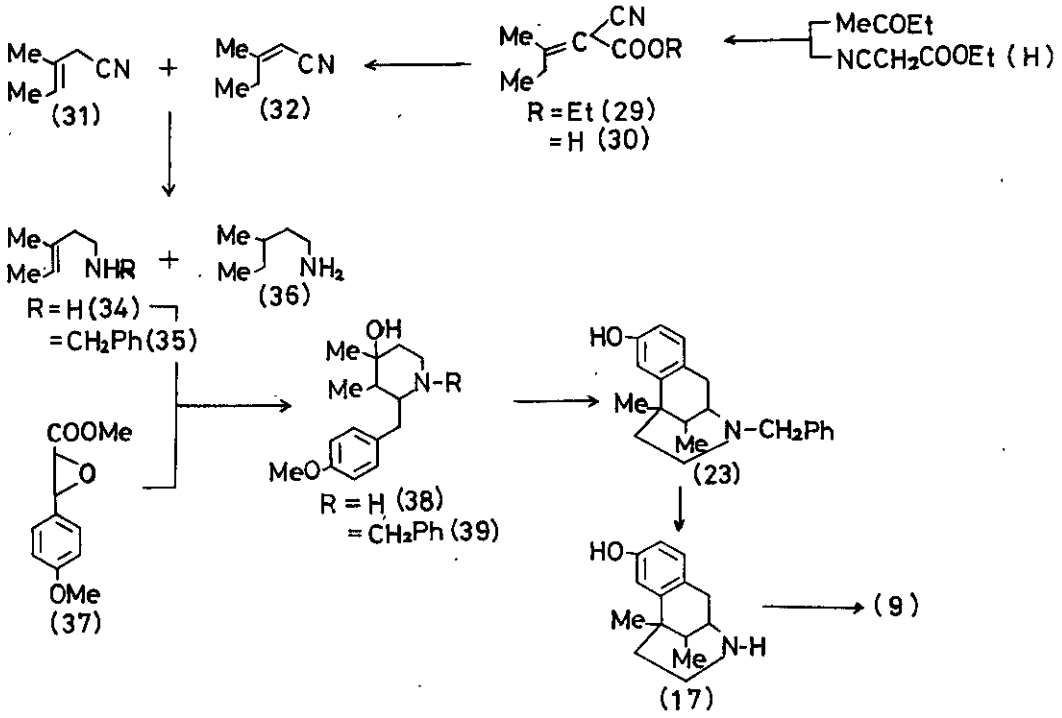


bromide, was subjected to a Grignard reaction, and then the resulting 1,2-dihydropyridine derivative (25) was reduced by sodium borohydride to give the corresponding 1,2,5,6-tetrahydropyridine (26). Finally, cyclization of 26 with polyphosphoric acid gave pentazocine (9) as shown in Chart 5.[6] Although this method is simple, undesirable products are obtained in the cyclization step. In fact, compounds 27 and 28 were obtained and pentazocine was not obtained in the author's experiments.[7]

2-2 From 1-amino-3-methyl-3-pentene

(a) Mannich reaction: A method for the synthesis of 23 , using 3,4-lutidine as a starting material, has been reported, and the synthesis of compound 14 has already been reported by Bayer's group.[8] Therefore, we have investigated the following method.[9] Heating ethyl 1-methylpropylidenecyanoacetate (29)[10] with pyridine hydrochloride gave 4-cyano-3-methyl-2-butene (31) together with the 1-butene isomer (32) in the ratio of 1 : 1 . The nitriles (31 and 32) were also obtained by the thermal decarboxylation of 30 , which was prepared by the condensation of ethyl methyl ketone with cyanoacetic acid, in the ratio of 6 : 4, respectively. Since separation of the above products was difficult, the mixture of 31 and 32 was used for the following reaction. Condensation of the hydrogenation products (34 and 36) of nitriles 31 and 32 with benzaldehyde, followed by reduction of the Schiff base with sodium borohydride, afforded 5-benzylamino-3-methyl-2-pentene (35) and 1-benzylamino-3-methylpentane. Treatment of the amines (34 and 36) with benzyl chloride gave the same products. A mixture of the benzylamine derivatives was heated in the presence of methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate (37) to give the diastereoisomeric piperidinols (39a and 39b), which were separated by alumina chromatography.

Chart 6



In this case the reaction of 34 and 36 with 37 also gave the diastereoisomers (38). Both of the piperidinols (39a and 39b) were heated with 48 % hydrobromic acid to afford 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (23). Finally, pentazocine (9) was obtained in the same manner as outlined in 2 - 1 (b).

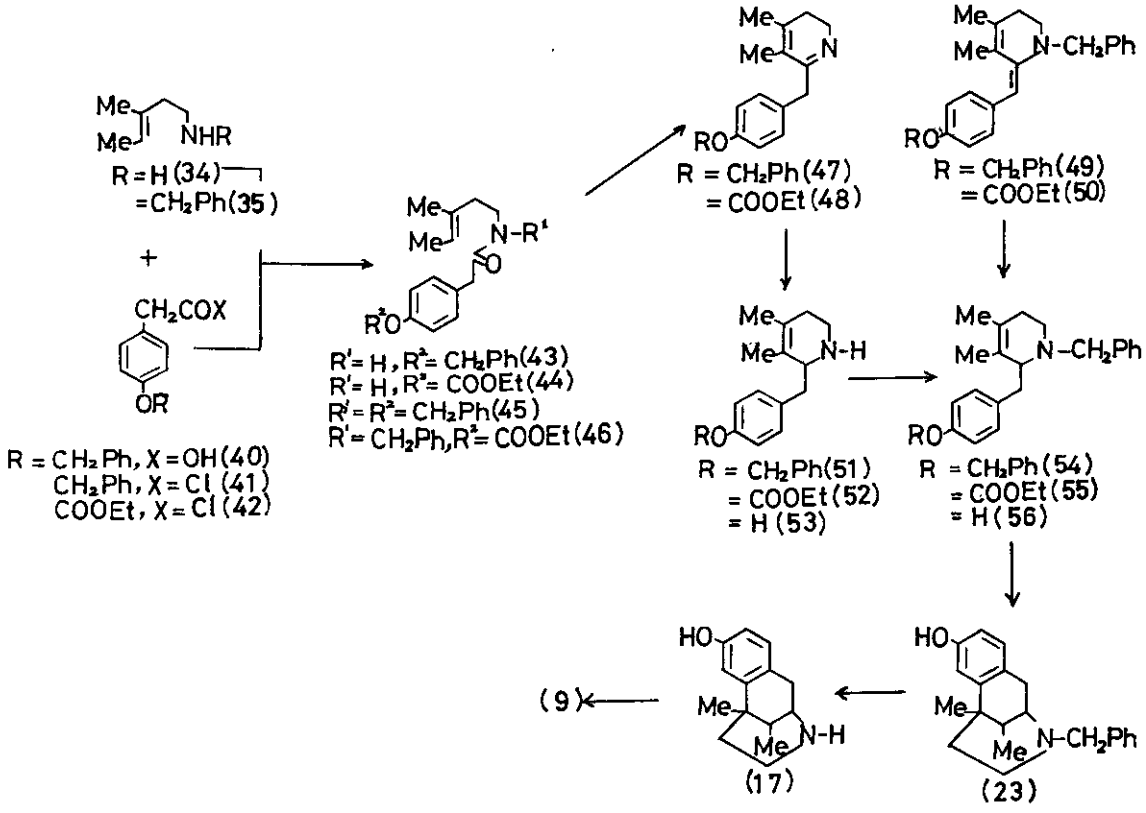
(b) Bischler-Napieralski reaction: Fusion of 3-methyl-3-pentenylamine (34) with 4-benzyloxyphenylacetic acid (40) gave the amide (43), which was also obtained from 4-benzyloxyphenacetyl chloride (41). The amide (44) was obtained from amine 34 and 4-ethoxycarbonyloxyphenylacetyl chloride (42). Cyclization of these products by a Bischler-Napieralski type reaction[11] with phosphoryl

chloride gave the dihydropyridines 47 and 48 ,respectively. Reduction of the cyclized products (47 and 48) with sodium borohyride gave the corresponding tetrahydropyridines (51 and 52), respectively.

Hydrolysis of the reduction product (52) without isolation gave 1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)pyridine (53). Treatment of the tetrahydropyridines (51 , 52 , and 53) with benzyl chloride gave the N-benzylated products (54 , 55 , and 56), respectively. Compound (56) was also obtained quantitatively by acidic or alkaline hydrolysis of 54 and 55 .

The reaction of 4-substituted phenacetyl chlorides 41 and 42 with N-benzyl-

Chart 7



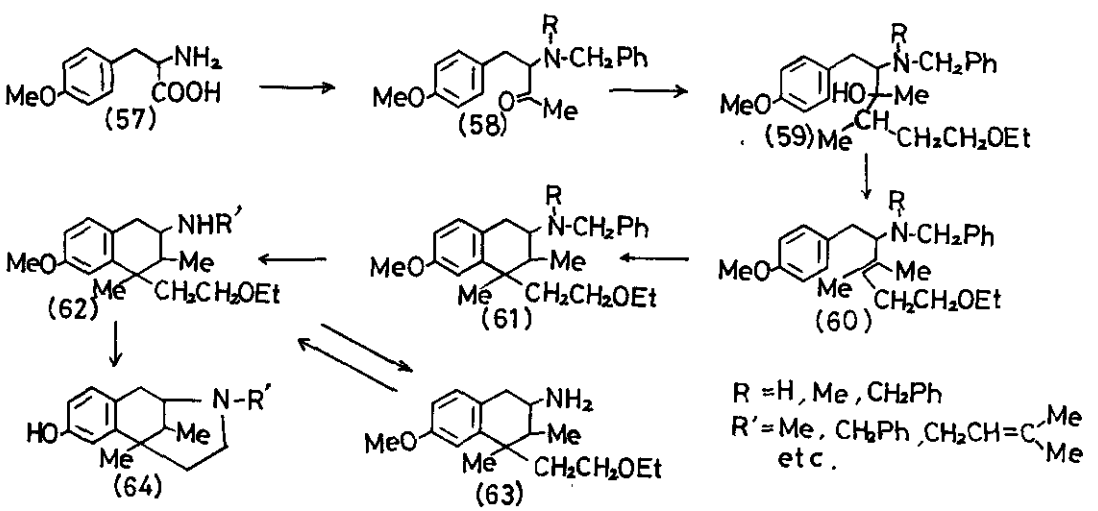
3-methyl-3-pentenylamine (35) gave the amides 45 and 46, respectively, which were cyclized with phosphoryl chloride by a Bischler-Napieralski type reaction without purification to give the expected 2-benzylidenetetrahydropyridines 49 and 50. Sodium borohydride reduction of 49 and 50 afforded the tetrahydropyridine derivatives 54, 55 and 56, which were identical with the products from the secondary amines 51, 52, and 53.

Cyclization of 1-benzyl-1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethylpyridine (56) with 48 % hydrobromic acid over 7 h gave, in 90 % yield, 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (23). Finally, pentazocine (9) was obtained in the same manner outlined previously.[12]

2-3 From an amino acid

A new synthetic method which used a tyrosine derivative (57) as a starting material was carried out in the following sequence (58 → 59 → 60 → 61 → 62 → 64),

Chart 8



as shown in Chart 8.[13]

However, there are other problems in the yield of this synthesis. Pentazocine (9) was synthesized by cyclization of (62), which was obtained by alkylation of (63) with 3-methyl-2-butenyl halide.

2-4 The introduction of 3-methyl-2-butenyl group into the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine nucleus

(a) Debenzylation of quaternary ammonium salt 65 by catalytic hydrogenation:

A method which does not involve compound 17 in the final step was investigated as follows.[5,12] Compound 23 was treated with 3-methyl-2-butenyl bromide to give 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (65). Finally, reductive debenzylation of 65 was investigated in the presence of palladium-charcoal. A number of examples of debenzylation by catalytic hydrogenation of N-benzyl derivatives of tertiary amines are known, but there are only a few examples of attempts to remove the N-benzyl

Chart 9

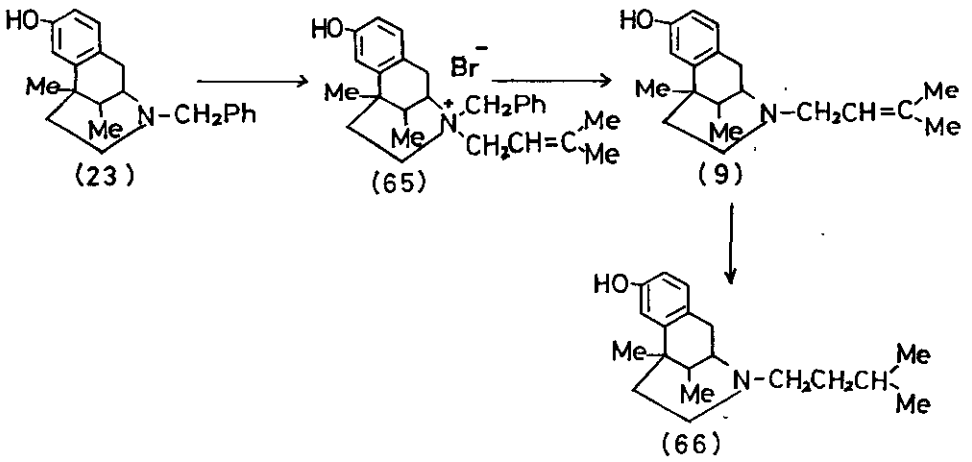
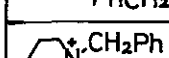
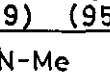
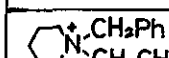
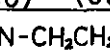
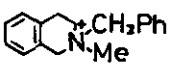
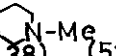


Table 2

Debenzylation of Quaternary Ammonium Salts

Quaternary ammonium salts (g)	Mp, °C (solvent of recrystn)	Thio-phenol (g)	aq. NaOH soln ml (%)	Temp. °C	Time hr	Tertiary amines, Yield (g) (%)
$(PhCH_2)_2\overset{+}{N}(Me)_2$ Cl^- (2.61)	93 – 95 (iso-PrOH)	5.5	10(20)	90	5	$PhCH_2N(Me)_2$ (1.4) (85.1)
$PhCH_2CH_2\overset{+}{N}(Me)_2CH_2Ph$ Cl^- (1.38)	169 – 172 (iso-PrOH/Et_2O)	2.75	10(20)	90	7	$PhCH_2CH_2N(Me)_2$ (0.52) (69.7)
$PhCH_2\overset{+}{N}(Et)_3$ Cl^- (1.9)	190 – 191 (decomp.) (iso-PrOH/Et_2O)	3.0	10(20)	90	10	$(Et)_3N$ (0.6) (22.1)
$PhCH_2\overset{+}{N}(Me)_2Ph$ Br^- (7.0)	110 – 111 (EtOH)	9.0	30(10)	60	3.5	$PhN(Me)_2$ (2.8) (96.6)
$Cyclohexyl\overset{+}{N}(Me)_2CH_2Ph$ Cl^- (4.0)	194 – 196 (Me_2CO)	5.2	20(10)	80	4	$Cyclohexyl\text{-}N(Me)_2$ (1.9) (95.0)
 Cl^- (3.73)	243 – 245 (decomp.) (iso-PrOH)	1.1	2(20)	90	5	 (1.0) (60.9)
 I^- (5.0)	192 – 193 (iso-PrOH)	5.0	11(10)	80	10	 (1.4) (76.1)
 Cl^- (1.37)	195 – 197 (iso-PrOH)	5.5	4(5)	70	7	 (0.38) (51.4)

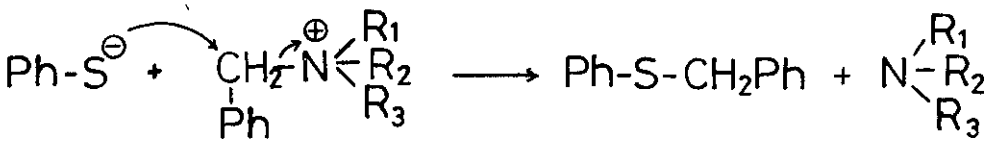
group of quaternary ammonium salts.[14] Therefore, after about one molar equivalent of hydrogen had been absorbed, we looked for evidence that 65 had been catalytically debenzylated to the pentazocine (9). In this case, the dihydropentazocine 66 and 23 were also formed as by-products. Catalytic hydrogenation of 65 in the presence of Raney-Ni also gave a mixture of 9, 23 and 66, but in the presence of Raney-Co (W-7), compound 9 was mainly obtained in about 80 - 90 % yield.

(b) Debenzylation of quaternary ammonium salt 65 by thiophenoxide anion: The selective N-debenzylation reaction of quaternary ammonium salts without hydrogenolysis has been investigated.[15] In general, the N-benzyl group of quaternary ammonium salts can be removed by reduction with sodium amalgam or pyrolysis. But, undesirable results have often been obtained with N-benzyl derivatives having other readily reducible functions such as halogeno, cyano, and nitro groups and double bonds.

Therefore, we have investigated the selective N-debenzylation reaction with thiophenol in the presence of aqueous alkaline solution. Shamma and his co-workers[16] have previously reported the demethylation of triethylamine methochloride with sodium thiophenoxide in 2-butanone, acetonitrile and dimethylformamide; but the application of this method to debenzylation has not yet been investigated. Heating of various N-benzylammonium salts with thiophenol in 5 - 20 % aqueous sodium hydroxide solution gave the corresponding debenzylated tertiary amines in good yield as shown in Table 2. Benzyl phenyl thioether was obtained as a by-product in all the reactions. This fact indicates that the reaction proceeds in one stage as follows.[17]

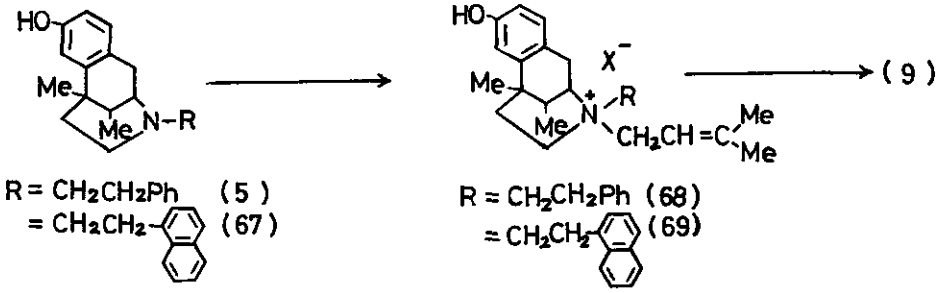
As an application of this method, the treatment of quaternary ammonium salt 65 with thiophenol in aqueous sodium hydroxide solution afforded a mixture of pentazocine (9) (51.0 %) and N-benzyl compound 23 (24.4 %) which were also formed in 58.7 % and 24.7 % yields, respectively, by heating 65 with an excess of sodium thiophenoxide in an organic solvent. This reaction provides a useful method for debenzylation.

Chart 10



(c) Hofmann degradation of quaternary ammonium salts 68 and 69 : It was reported[18] that the compound 68 and 69 , obtained by quaternization of phenazocine (5) and compound 67 with 3-methyl-2-butenyl halide, were subjected to Hofmann degradation in aqueous sodium hydroxide solution to give pentazocine (9) as shown in Chart 11. Meanwhile, phenazocine 5 and compound 67 were also synthesized by the Mannich reaction (see section 2-2 (a)).[19]

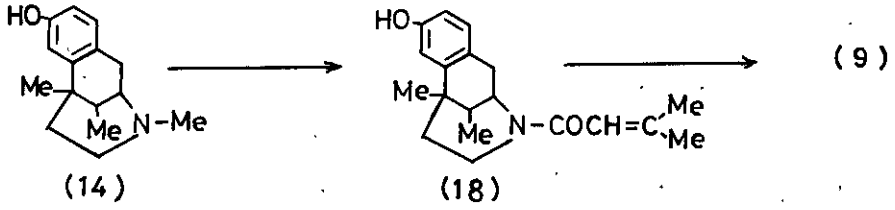
Chart 11



(c) Acylation of N-methyl derivative 14 and reduction: Instead of demethylation of compound 14 via the von Braun reaction, the direct acylation of 14 was adopted as shown in Chart 12.[20]

Compound 14 was treated with senecioyl chloride in benzene or toluene with cooling to give the acylated compound 18 in 88 % yield, which was reduced by diisobutyl aluminum hydride to give pentazocine (9) in 90 % yield. This method is superior to Archer's method in yield.

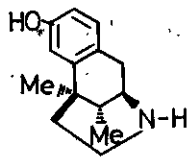
Chart 12



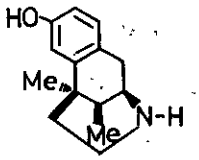
3 STEREOCHEMISTRY OF PENTAZOCINE AND ITS INTERMEDIATES

3-1 Optical resolution of pentazocine: Two racemates of (±)-cis- and (±)-trans-

Chart 13



(±)-Cis(17)



(±)-Trans(17)

isomers of compound 9 were synthesized.[21] The (±)-cis-isomer (17) was resolved with (+)-tartaric acid. The (−)-base (+)-tartrate was separated from aqueous solution and the (+)-base was recovered from the mother liquors of (−)-tartrates. quors of (−)-tartrates.

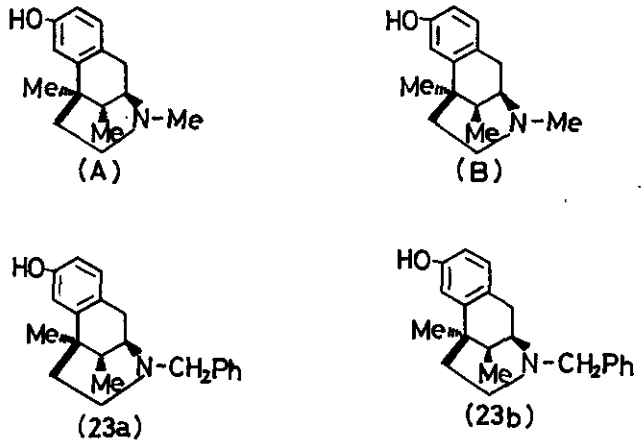
On the other hand, (±)-trans-isomer 17 was resolved in a similar manner to give the (−)-base (−)-quinate and (+)-base was recovered from the mother liquor. The latter compound was purified by crystallization of its hydrobromide. The N-3-methyl-2-butenyl derivatives were prepared from the corresponding nor-bases in the usual manner. These optically active isomers were evaluated as antagonists as shown in Table 3.

Table 3

Salt	Optical Isomer	Mp °C	$(\alpha)^{25}_{deg.D}$	Antagonist Act: mg/kg
Free base	dextro-cis	180.4-182.0	+ 135.5	14.0
〃	levo-cis	180.6-182.2	− 138.0	0.9
HCl salt	dextro-trans	254.5-255.0	+ 115.4	13.0
〃	levo-trans	254.0-256.0	− 116.3	0.55

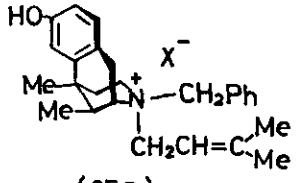
3-2 Configuration of intermediates 23 and 65 : Similarly, the presence of two diastereoisomers differing in configuration at the C_{11}-position of 23 was anticipated, but our sample was assumed to be only compound 23a having the 11α-methyl conformation because of the following reasons.[5a] The predominant conformer resulting from the above cyclization should be the one with the 11-methyl substituent oriented away from the nitrogen, namely, cis to the hydroxyaromatic ring (Chart 14).[5]

Chart 14

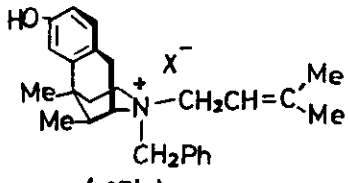


This assumption is based on an analogy with the morphinan synthesis[22] and also depends upon the "trans rule"[23] in the case of addition to olefinic bonds, namely, to the 3,4-double bond of (21). Fullerton and his co-workers[29] reported that the nmr spectra of the two diastereoisomers (A) and (B) showed the methyl signal at the C_{11}-position as a doublet in a field 25 Hz higher than that observed at the C_6-position in conformer A; whereas the signal at the C_{11}-position of B shifted to a lower field, and both signals at the C_6- and C_{11}-positions overlapped each other. The former data corresponds to the nmr spectral data of our sample. Thus, the 11-methyl substituent of 23 was assigned the configuration shown in structure(23a). In this case, the other conformer (23b) has not been isolated. Furthermore, the stereochemistry of the quaternary ammonium salt (65) obtained from the pentazocine intermediate 23 was also studied by us.[25] 3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (23), in

Chart 15



(65a)



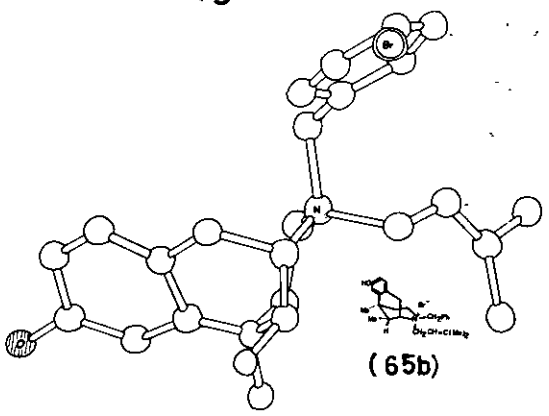
(65b)

which the methyl group at the C_{11}-position was in the cis-configuration to the aromatic ring as methioned above, was treated with an equimolar amount of 3-methyl-2-butenyl bromide to give a stereoisomeric mixture of quaternary ammonium salts in good yield. The mixture was separated into 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (65a), mp 164 - 166° (decomp.) and its epimer (65b), mp 210 - 212° (decomp.) in the ratio of 3 : 1 by fractional crystallization.

It is well known that in quaternization of cyclic amines, axial attack by the electrophile occurs in preference to equatorial attack when the substituent on the nitrogen atom is bulkier than the electrophile.[26,27]

Moreover, the stereochemistry of the piperidine moiety of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine was studied by kinetic and spectroscopic methods and also by X-ray analysis of cis-3-allyl and cis-3-cyclopropylmethyl derivatives; and the results indicated that the chair form was assumed and the substituent on the nitrogen had the equatorial orientation.[28,29] Therefore, the benzyl group on the nitrogen in the main product should have the equatorial orientation (65a) as shown in Chart 15. This fact was proven by the following reaction. Quaternization of pentazocine (9) by benzyl bromide gave a mixture (80 %) which was separated by crystallization into 65a and 65b (65a : 65b = 1 : 6). The latter compound (65b) was obtained as the main product, which proved the above conclusion to be correct. Furthermore, the structures of (65a) and 65b were supported by nmr spectral studies[25] and X-ray crystallographic studies[25] of the base of 65b. The mirror image of 65b is shown in the Figure.

Figure



(65b)

4 CONCLUSION

The various synthetic studies leading to pentazocine and its intermediates were summarized based on the information known as of July, 1973.

These studies were classified under the following methods; via the N-methyl derivative (14), via the N-benzyl derivative (23) and via phenazocine and a similar type compound (67). However, these methods have both merits and demerits, and so the appearance of more convenient synthetic methods would be desirable.

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