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3-Azabicyclo[3.3.1]nonane Derivatives as Potential Analgesics

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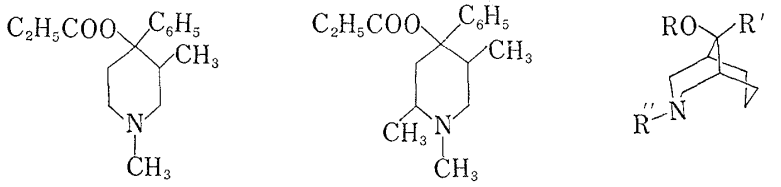
3-Azabicyclo[3.3.1]nonane derivatives were prepared and tested biologically. Some of these, 3-methyl-9β-alkoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (**6**—**8**) and their 3-(β-phenylethyl-) analogs (**18**—**20**) exhibited promising analgesic activities. Furthermore, 3-methyl-9-benzoyloxy-3-azabicyclo[3.3.1]nonane (**24** and **25**) displayed a marked local anaesthetic action.

The so-called "reversed ester" series of meperidine, derivatives of 4-phenylpiperidin-4-ol, has yielded compounds of greater analgesic effectiveness than the parent substance. Further, among the many other ramifications in the structure of the phenylpiperidinols, the introduction of a methyl group into the 3-position of the piperidine ring has been found to be most noteworthy. Thus, the resulting α- and β-prodines (**1**), trimeperidines (**2**), and so on were developed as promising analgesics and have been used clinically. However, in these materials, the methyl substituent on the piperidine ring gives rise to an asymmetric center which often results in the formation of a complex mixture of stereoisomers, making the synthetic route more troublesome.



1 **2** **3**

Chart 1

Consequently, with expectation of preparing some potent analgesics, we have examined the pharmacological properties of azabicyclic compounds (**3**) with a 3,5-methylene bridge in the piperidine ring, thus obviating the introduction of an unfavorable asymmetric center in the synthetic process.[2-4] In addition, the recently increased attention to the steric structure-activity relationship[5] on meperidine series has prompted us to study the analgesic activities of these azabicyclic compounds with a stereochemically-fixed skeleton.

A parent compound with three methylene bridge between the 3- and 5-positions of the piperidine ring, 3-methyl-9β[6]-hydroxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (**4**), was prepared from 3-methyl-3-azabicyclo[3.3.1]nonane-9-one[3] by successive treatment with phenylmagne-

1) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
2) I. Iwai and B. Shimizu, "Jap. Pat.," Sankyo Co., Ltd., 1964, 18038 (March 14, 1961): "Brit. Pat.," Sankyo Co., Ltd., 1964, 952137 (*Chem. Abstr.*, **61**, 5614 (1964)).
3) H. O. House and W. M. Bryant III, *J. Org. Chem.*, **30**, 3634 (1965).
4) S. Oida, M. Kurabayashi, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **14**, 1418 (1966).
5) P.S. Portoghese, A.A. Mikhail, and H.J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968) and its cited papers. Also see P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
6) The β-configuration indicates that the substituents are on the same side as the nitrogen atom, and the α-configuration indicates the other side, respectively.

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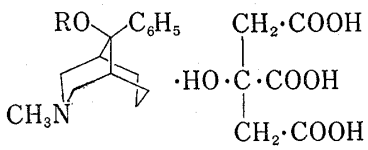
sium bromide and acid.[2,3] It was first found that the 9β-hydroxy compound (**4**) exhibited a slight analgesic properties as shown in the Table I.[7] On the other hand, a prodine analog of **4**, 3-methyl-9β-propionyloxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (**5**) showed high activity being superior to meperidine and displaying a lower toxicity. Thus, the 9β-propionyloxy compound (**5**) was regarded as a promising analgesic: however, **5** and its salts were found to be unstable towards heat, acid and alkali as described previously.[4] Accordingly, we turned to 9β-alkoxy derivatives of **4** which can be also prepared on treatment of **4** with acid and alcohol.[4,8] 9β-Methoxy (**6**) and 9β-ethoxy (**7**) derivatives thereby obtained surprisingly show-

Table I. Analgesic Effect of 3-Azabicyclo[3.3.1]nonane Derivatives[7]



Substances No.	R	Activity ED_{50} (mg/kg, *s.c.*)	Toxicity LD_{50} (mg/kg, *s.c.*)
4	H	*ca.* 60	350
5	C_2H_5CO	8.9	316
6	CH_3	4.1	198
7	C_2H_5	5.3	263
8	C_3H_7	9.1	276
Meperidine hydrochloride		14	182
Morphine hydrochloride		5	560

ed a stronger activity which was more than three times that of meperidine. In direct contrast to the 9β-propionyloxy compound (**5**), these alkoxy derivatives (**6** and **7**) were found to be quite stable to heat, acid or alkali. Consequently, this high analgesic potency and accessible toxicity led to their selection for extensive pharmacological testing and clinical trials, the details of which will be announced in another paper.[9] The potency of these alkoxy derivatives

7) Evaluation of the analgesic effects of the azabicyclic compounds examined were carried out by using Haffner tail pinch method (F. Haffner, *Dtsch. Med. Wschr.*, **55**, 731 (1929); C. Bianchi and J. Fronceshjni, *Brit. J. Pharmacol.*, **9**, 280 (1954)). The materials were given as their hydrogen citrate salts, subcutaneously to male mice of the ddY strain. The analgesic potency was expressed as the ED_{50} calculated by the Litchfield–Wilcoxon's method (J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Therap.*, **96**, 99 (1949)) and compared with that of meperidine hydrochloride or morphine hydrochloride. Acute toxicities were also determined in 5—10 male mice of the ddY strain per dose. The materials were administered subcutaneously or intraperitoneally and mortalities were recorded 1 week later. The LD_{50} was also calculated by the Litchfield–Wilcoxon's method. These data were shown in Table I and II.

8) As discussed in our preceding paper,[4] this acid-catalysed etherification proceeds stereospecifically and the resulting ethers have a 9β-alkoxy-9α-phenyl configuration. This was indicated by their nuclear magnetic resonance spectra in consideration with the House's illustration[3] that the *N*-methyl proton signal in the spectra of 9β-hydroxy-9α-phenyl compounds (**4**) falls at 2.20—2.24 ppm and that of the 9β-phenyl-9α-hydroxy isomers shifts to a higher field about 0.2 ppm with an influence of the benzene ring current. The predominant formation of the 9β-alkoxy derivative would be explainable as follows: The displacement reaction in the 9 position is not a kinetically controlled process but includes an equilibrium between 9α- and 9β-isomers controlled by the stability of these components. The 9β-alkoxy isomer would be stabilized by an intramolecular hydrogen bond in an acidic medium as shown in the Chart and promotes the equilibrium to a 9β-isomer rich mixture.

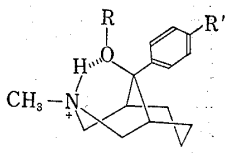


Chart 4

9) S. Kobayashi, K. Hasegawa, T. Oshima, and H. Takagi, *Toxicol. Appl. Pharmacol.*, in press.

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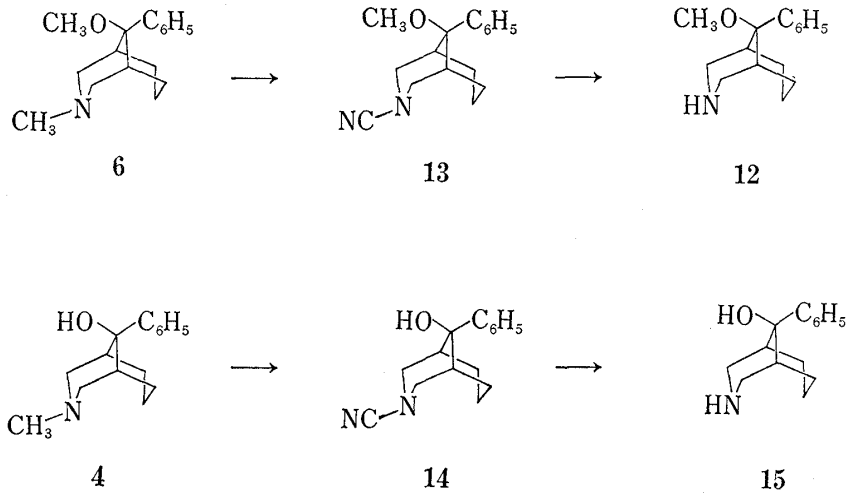
is effectively lowered by extension of the alkoxy carbon chain, as shown in the case of the 9β-propoxy analog (**8**).

Effects of structural changes on the analgesic activity of the 9β-methoxy derivative (**6**) were examined in the following way. Some phenyl variants, *p*-methylphenyl (**9**), *p*-methoxypheny (**10**), and *p*-chlorophenyl (**11**) analogs were synthesized analogously by treatment of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one with the corresponding arylmagnesium bromide, followed by etherification[8] with acid and methanol: however, these analogs did not show any notable activity as shown in the Table II. In order to prepare various N-substituted derivatives of the 9β-methoxy derivative (**6**), the N-desmethyl compound (**12**) was synthesized as follows. Treatment of **6** with cyanogen bromide in benzene gave a N-cyano compound (**13**), mp 130—132° in 70% yield. Treatment of **13** with lithium aluminum hydride in tetrahydrofuran furnishes the N-desmethyl compound (**12**) as a syrup but in a low yield; **12** formed an N-acetate, mp 114—116°. On the other hand, cyanogen bromide degradation of the 9β-hydroxy derivative (**4**) and treatment of the resulting N-cyano compound (**14**), mp 178—180° with lithium aluminum hydride afforded a 9β-hydroxy-N-desmethyl derivative (**15**), mp 153—155°, which was converted into **12**, mp 64°, in a good yield on treatment with methanol in the

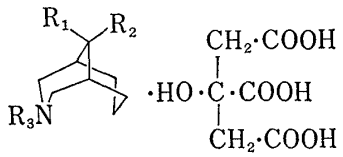


6 13 12

4 14 15

Chart 2

Table II. Analgesic Effect of 3-Azabicyclo[3.3.1]nonane Derivatives[7]



No.	Substances			Activity	Toxicity
	R_1	R_2	R_3	ED_{50} (mg/kg, *s.c.*)	LD_{50} (mg/kg, *s.c.*)
9	CH_3O	*p*-CH_3-C_6H_4	CH_3	50	>100
10	CH_3O	*p*-CH_3O-C_6H_4	CH_3	38	>200
11	CH_3O	*p*-Cl-C_6H_4	CH_3	>50	—
12	CH_3O	C_6H_5	H	>50	140
16	CH_3O	C_6H_5	$CH_3CH_2OCH_2CH_2$	14.5	*ca.* 200 (*i.p.*)
17	CH_3O	C_6H_5	CH_2=$CHCH_2$	17.2	*ca.* 300 (*i.p.*)
18	CH_3O	C_6H_5	$C_6H_5CH_2$	>50	>300
19	CH_3O	C_6H_5	$C_6H_5CH_2CH_2$	1.25	>400
20	C_2H_5O	C_6H_5	$C_6H_5CH_2CH_2$	4.1	200
21	C_6H_5	CH_3O	CH_3	*ca.* 5.0	50—100

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presence of acid. The N-desmethyl compound (**12**) thus obtained exhibited a strong toxicity, but no significant analgesic activity as shown in the Table II. It was found that the N-desmethyl (**12**) and N,O-demethylated compounds (**15**) are important metabolites of the 9β-methoxy derivative (**6**) which are detected when the latter is administered subcutaneously in rats or incubated with liver homogenates of rats.[10]

Some N-variants (**16**—**20**), which will be described below, were synthesized by treatment of the N-desmethyl compound (**12**) with alkyl halide or by the analogous N-alkylation of the N,O-de- methylated compound (**15**) followed by treatment with acidic alcohol. The N-(β-ethoxyethyl) compound (**16**) and the N-allyl compound (**17**) were only weakly active as shown in Table II, and the latter compound showed no morphine antagonistic action contrary to expectation. The N-benzyl compound (**18**) exhibited no marked activity while the N-phenethyl compound (**19**) showed high activity which was more than three times of that of the parent compound (**6**), and also with a lower toxicity. This is similar to the N-phenethyl variants of other analgesic phenylpiperidine derivatives including meperidine.[11] The ethoxy analog (**20**) of the N-phenethyl compound (**19**) exhibited weaker activity than that of **19**.

A C-9 isomer of the 9β-methoxy compound (**6**), 3-methyl-9α-methoxy-9β-phenyl-3-azabicyclo[3.3.1]nonane (**21**) was isolated from the recrystallization mother liquors of **6** in a low yield (*cf.* Experimental). The nuclear magnetic resonance (NMR) spectrum of **21** exhibited a singlet absorption at 1.98 ppm due to the N-methyl protons, suggesting that the methoxy group has α-configuration.[8] This isomer (**21**) showed a high analgesic activity almost equal to **6**. This suggests a low degree of stereochemical specificity for analgesic activity of these 9-methoxy compounds (**6** and **21**) and supports proposals[5] inferred by Portoghese, *et al.* from their study on meperidine analogs with a methylene bridge.

Finally, we would like to mention other marked pharmacological properties of some azabicyclic compounds. 3-Methyl-9β-hydroxy-3-azabicyclo[3.3.1]nonane (**22**) and its 9α-hydroxy isomer (**23**) were prepared by reduction of 3-methyl-3-azabicyclo[3.3.1]nonane-9-one.[3] The 9β-hydroxy compound (**22**) showed hypotensive activity almost same as that of "Hexamethonium" in cats and slightly relaxation in isolated ileum of guinea pigs, while the 9α-hydroxy isomer (**23**) does not show any such activity except a weak antiinflammatory effect. The benzoate of **22** (**24**) displayed a marked local anaesthetic action almost equal to that of procaine hydrochloride, but weaker than cocaine hydrochloride, by corneal reflex test[12] of guinea pigs as shown in Table III and also exhibited slightly–spasmodic action in isolated ileum of the same animals. The benzoate of **23** (**25**) exhibited local anaesthetic activity weaker than its isomer (**24**). Furthermore, 3-methyl-8β-benzoyloxy-3-azabicyclo[3.2.1]octane (**26**), which was prepared by reduction of the corresponding C-8 ketone and benzoylation, showed a strong analogous action but its toxicity was quite high as shown in the Table III. These benzoates would be physiologically of interest as cocaine analogs.

22 23

Chart 3

Experimental[13]

Hydrogen Citrates——The preparation of free bases (**4**—**8**) was described in previous papers.[2-4] To a solution of an equivalent amount of citric acid in MeOH was added dropwise a solution of a base in ether

10) H. Murata and A. Yasumura, unpublished.
11) P.A. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960), and literatures cited therein.
12) E. Bulbring and I. Wajda, *J. Pharmacol. Exptl. Therap.*, **85**, 78 (1945).
13) Melting points are not corrected. NMR spectra were determined on a Varian A–60 spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br., broad.

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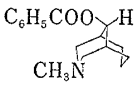
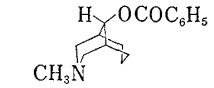
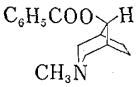
Table III. Local Anaesthetic Action of Azabicyclic Compounds

No.	Compounds[a]	Activity ED_{50} (%, w/v)	Toxicity LD_{50} (mg/kg, *i.p.*)
24		0.33	*ca.* 100
25		0.5—1	> 300
26		0.1—0.5	10—30
	procaine hydrochloride	0.36	—

a) Given as diluted HCl solutions.

and the resulting precipitates were collected. Recrystallization from MeOH gave analytical samples. Melting points and analyses of these hydrogen citrates are given in Table IV.

3-Methyl-9β-methoxy-9α-(*p*-tolyl)- (9), -9α-(*p*-methoxyphenyl)- (10), and -9α-(*p*-chlorophenyl)-3-azabicyclo[3.3.1]nonane (11)——As in the procedure described for **6**,[2-4] these compounds were prepared as follows: Treatment of a solution of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one[3] in tetrahydrofuran with an ethereal solution of *p*-tolylmagnesium bromide afforded a mixture of 3-methyl-9α-hydroxy-9β-(*p*-tolyl)-3-azabicyclo[3.3.1]nonane, mp 78°, needles, and its 9β-hydroxy-9α-(*p*-tolyl) isomer, mp 80°, needles. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found (for 9α-hydroxy compound): C, 78.07; H, 9.50; N, 5.71; (for 9β-hydroxy compound): C, 77.91; H, 9.44; N, 5.59.

Treatment of the mixture thereby obtained in boiling MeOH in the presence of H_2SO_4 gave **9**, mp 86—88°, as leaflets. *Anal.* Calcd. for $C_{17}H_{25}ON$: C, 78.71; H, 9.72; N, 5.40. Found: C, 78.66; H, 9.74; N, 5.26.

Similarly, treatment of the same 9-one[3] with *p*-methoxyphenylmagnesium bromide afforded a mixture of the corresponding 9α-hydroxy compound, mp 119—121°, needles, and 9β-hydroxy compound, mp 94—96°, needles. *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found (for 9α-hydroxy compound): C, 73.43; H, 8.89; N, 5.55; (for 9β-hydroxy compound): C, 73.56; H, 8.99; N, 5.20.

Treatment of the mixture with methanolic H_2SO_4 gave **10**, mp 73—74°, as prisms. *Anal.* Calcd. for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.09; H, 9.00; N, 5.28.

Analogously, treatment of the 9-one with *p*-chlorophenylmagnesium bromide afforded a mixture of the corresponding 9α-hydroxy compound, mp 91—92°, needles, and its 9β-isomer, mp 86—87°, needles. *Anal.* Calcd. for $C_{15}H_{20}ONCl$: C, 67.78; H, 7.59; N, 5.27. Found: (for 9α-hydroxy compound): C, 67.78; H, 7.56; N, 5.17; (for 9β-hydroxy compound): C, 67.69; H, 7.53; N, 5.21.

Treatment of the mixture with methanolic H_2SO_4 gave **11**, mp 54—56°, as prisms. *Anal.* Calcd. for $C_{16}H_{22}ONCl$: C, 68.68; H, 7.93; N, 5.01. Found: C, 69.26; H, 8.03; N, 5.05.

3-Cyano-9β-methoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (13)——To a cooled solution of 5.0 g of 3-methyl-9β-methoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane[4] in 10 ml of $CHCl_3$ was added 10 ml of 35% solution of BrCN in $CHCl_3$ and the mixture was refluxed for 16 hr. Then, the mixture was poured into ice–water and the organic layer was collected. After successive washing with 2N HCl and H_2O, and drying, the $CHCl_3$ solution was evaporated *in vacuo*, leaving a crystalline mass which was recrystallized from MeOH to give 3.7 g of **13**, mp 130—132°, as prisms. IR ν_{max}^{Nujol}: 2180 cm^{-1}. NMR ($CDCl_3$) δppm: 1.2—2.5 (6H, m), 2.63 (2H, br.), 2.78 (3H, s), 3.33 (2H, br. d, J=11 cps), 4.03 (2H, dd, J=11 and 3 cps), 7.42 (5H, br. s). *Anal.* Calcd. for $C_{16}H_{20}ON_2$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.45; H, 7.98; N, 10.72.

3-Cyano-9β-hydroxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (14)——To a cooled solution of 30.0 g of 3-methyl-9β-hydroxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (**4**) in 50 ml of benzene was added dropwise a solution of 15.5 g of BrCN in 30 ml of benzene, and the resulting mixture was warmed at 60° for 7 hr. Then, the mixture was poured onto ice–water and the organic layer was collected. The H_2O layer was once extracted with $CHCl_3$ and the combined organic layer and extract was dried over anhyd. Na_2SO_4 and evaporated *in vacuo*, leaving a crystalline mass which was recrystallized from benzene to give 25.0 g (71.5%) of **14**, mp 178—180°, as prisms. IR ν_{max}^{Nujol} cm^{-1}: 3410, 2180. NMR ($CDCl_3$) δppm: 3.27 (2H, br. d), 4.07 (2H, dd), 7.43 (5H, s). *Anal.* Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.21; H, 7.39; N, 11.41.

9β-Hydroxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (15)——To a gently boiling, stirred solution of 3.14 g of $LiAlH_4$ in 30 ml of tetrahydrofuran was added dropwise a solution of 10.0 g of **14** in 50 ml of tetrahydrofuran and the mixture was refluxed for 5 hr. The cooled reaction mixture was diluted with *ca.* 150 ml of $CHCl_3$ and 80 ml of H_2O was carefully added with cooling and stirring. After filtration from the solid, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated *in vacuo*, leaving a viscous liquid which crystallized

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on digestion with ether. Recrystallization from ether gave 7.00 g (77.8%) of **15** as prisms of mp 153—155°. IR ν_{max}^{Nujol}: 3150 cm^{-1} (br.). NMR ($CDCl_3$) δppm: 1.1—2.2 (8H, m), 2.33 (2H, br.), 2.92 (2H, br. d, $J=12.5$ cps), 3.67 (2H, dd, $J=12.5$ and 3 cps), 7.2—7.7 (5H, m). *Anal.* Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.14; H, 8.82; N, 6.64.

Acetylation of **15** with Ac_2O–pyridine afforded the N-acetate, mp 153—155°, as prisms. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1617.

9β-Methoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (12)——To a cooled solution of 1.019 g of **15** in 10 ml of absolute MeOH was added 1 ml of conc. H_2SO_4 and the mixture was refluxed for 7 hr. After concentrating to 1/3 volume, the mixture was poured into ice–water and extracted twice with $CHCl_3$ after making base by addition of conc. NH_4OH. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*, leaving 1.023 g of crude **12** as a syrup. Thin–layer chromatography (TLC) or vapor–phase chromatography of this syrup indicated that the syrup contained 10% of an isomeric substance. Distillation of this syrup yielded a syrup of bp 145° (0.3 mmHg) which crystallized on standing, giving **12** as prisms, mp 64°. IR ν_{max}^{liq} cm^{-1}: 3540, 3380, 2500 (br.). NMR ($CDCl_3$) δppm: 1.1—2.3 (6H, m), 2.78 (3H, s), 2.60 (2H, br.), 3.0—4.4 (4H, m), 6.91 (1H, br.), 7.42 (5H, br. s). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.05; H, 9.03; N, 6.07.

Acetylation of the syrup thus obtained with Ac_2O–pyridine gave an N-acetate of **12**, mp 115—121°, as plates (from benzene–hexane). IR ν_{max}^{Nujol}: 1640 cm^{-1}. NMR ($CDCl_3$) δ ppm: 1.1—2.2 (6H, m), 2.14 (3H, s), 2.70 (2H, br.), 2.81 (3H, s), 3.2—4.7 (4H, m), 7.44 (5H, br. s). *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.84; H, 8.51; N, 5.25.

The N-acetate of **12** was also obtained from the N-acetate of **15** by treatment with methanolic H_2SO_4.

Conversion of 13 into 12——To a solution of 4.1 g of $LiAlH_4$ in 50 ml of tetrahydrofuran was added a solution of 10 g of **13** in the same solvent and the mixture was refluxed for 3 hr. As described above for the preparation of **15**, treatment of the mixture followed by chromatographic purification gave a small amount of **12** as a syrup which was identified with the sample obtained earlier. Further, acetylation of the syrup afforded the N-acetate of **12**, mp 115—121°, which was also identified by comparison of physical properties.

3-(β-Phenylethyl)-9β-methoxy- (19) and -9β-ethoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (20)——A mixture of 3.0 g of **15**, 2.82 g of β-phenylethyl bromide, 9.0 g of K_2CO_3, and 50 ml of *sec*-BuOH was refluxed for 2 hr with stirring. The cooled mixture was filtered and the filtrate was evaporated *in vacuo* to dryness, leaving 4.4 g of 3-(β-phenylethyl)-9β-hydroxy-9α-phenyl-3-azabicyclo[3.3.1]nonane, mp 101—105°. IR ν_{max}^{Nujol}: 3470, 1049, 979, 771, 702. *Anal.* Calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 81.58; H, 8.38; N, 4.34.

To a solution of 4.9 g of the 9-hydroxy compound thus obtained in 50 ml of absolute MeOH was added dropwise 5 ml of conc. H_2SO_4 and the mixture was refluxed for 5 hr. Then, the mixture was concentrated *in vacuo* to half volume, diluted with 5 ml of H_2O, made basic with conc. NH_4OH and extracted twice with $CHCl_3$. Evaporation of the extract left 4.4 g of crude **19** as crystals, which were recrystallized from MeOH–ether to give prisms, mp 58—59.5°. IR ν_{max}^{Nujol} cm^{-1}: 1605, 1497, 1462, 1142, 1078. NMR ($CDCl_3$) δ ppm: 2.78 (3H, s), 7.28 (5H, s), 7.42 (5H, m). *Anal.* Calcd. for $C_{23}H_{29}ON$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.39; H, 8.70; N, 4.09.

In a similar way, treatment of the 9-hydroxy compound described above with ethanolic H_2SO_4 to afford the 9β-ethoxy compound (**20**) as syrup. The analytical sample was purified by column chromatography on silica gel. IR ν_{max}^{liq} cm^{-1}: 1600, 1495, 1454, 1070, 764, 700. *Anal.* Calcd. for $C_{24}H_{31}ON$: C, 82.47; H, 8.94; N, 4.01. Found: C, 82.33; H, 8.89; N, 3.84.

3-(β-Ethoxyethyl)- (16), 3-(2-Propenyl)- (17), and 3-Benzyl-9β-methoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane (18)——Similar to the preparation of **19**, treatment of **15** with β-ethoxyethyl bromide afforded the corresponding tertiary amine, bp 170—177° (0.15 mmHg, bath temp.). IR ν_{max}^{liq} cm^{-1}: 3400, 1460, 1100, 1039, 770, 701. *Anal.* Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.46; H, 9.46; N, 4.50.

Further treatment of the tertiary amine thus obtained with methanolic H_2SO_4 gave **16** as a syrup, bp 160—165° (0.2 mmHg, bath temp.). IR ν_{max}^{liq} cm^{-1}: 1458, 1112, 1080, 764, 702. *Anal.* Calcd. for $C_{19}H_{29}O_2N$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.04; H, 9.47; N, 4.91.

Treatment of **15** with allyl bromide gave a N-allyl derivative, mp 87—90°. IR ν_{max}^{Nujol} cm^{-1}: 3460, 1036, 996, 915, 760, 698. *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found: C, 78.61; H, 8.94; N, 5.30.

Treatment of the N-allyl derivative with methanolic H_2SO_4 also gave **17**, bp 175—180° (0.45 mmHg, bath temp.). IR ν_{max}^{liq} cm^{-1}: 1460, 1078, 994, 915, 772, 703. *Anal.* Calcd. for $C_{18}H_{25}ON$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.15; H, 9.24; N, 5.31.

Analogously, treatment of **15** with benzyl bromide gave a N-benzyl derivative, mp 89—90°, which was further treated with methanolic H_2SO_4, giving **18** as a syrup. IR ν_{max}^{liq} cm^{-1}: 1601, 1495, 1455, 1079, 764, 733, 702. The analytical sample was obtained as its hydrogen citrate.

3-Methyl-9α-methoxy-9β-phenyl-3-azabicyclo[3.3.1]nonane (21)——The mother liquor left by recrystallization of 3-methyl-9β-methoxy-9α-phenyl-3-azabicyclo[3.3.1]nonane[4] (**6**) was evaporated *in vacuo* and the

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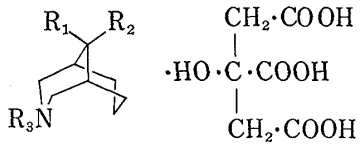
Table IV. Physical Constants of Azabicyclic Compound Hydrogen Citrates



No.	Compound R_1	Compound R_2	Compound R_3	mp (decomp.)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4	HO	C_6H_5	CH_3	160	$C_{21}H_{29}O_8N \cdot \frac{1}{2}H_2O$	58.32	6.99	3.24	58.74	7.01	3.27
5	C_2H_5-COO	C_6H_5	CH_3	160	$C_{24}H_{33}O_9N$	60.11	6.94	2.92	59.65	6.80	3.17
6	CH_3O	C_6H_5	CH_3	207	$C_{22}H_{31}O_8N$	60.40	7.14	3.20	60.21	7.19	3.12
7	C_2H_5O	C_6H_5	CH_3	151	$C_{23}H_{33}O_8N \cdot \frac{1}{2}H_2O$	59.99	7.44	3.04	60.29	7.40	3.10
8	C_3H_7O	C_6H_5	CH_3	148	$C_{24}H_{35}O_8N$	61.92	7.58	3.01	61.52	7.42	3.21
9	CH_3O	*p*-CH_3-C_6H_4	CH_3	205	$C_{23}H_{33}O_8N \cdot \frac{1}{2}H_2O$	59.98	7.44	3.04	60.32	7.28	3.05
10	CH_3O	*p*-CH_3O-C_6H_4	CH_3	174	$C_{23}H_{33}O_9N \cdot H_2O$	56.89	7.27	2.89	57.12	7.39	3.18
11	CH_3O	*p*-Cl-C_6H_4	CH_3	202	$C_{22}H_{30}O_8NCl$	55.99	6.40	2.96	60.41	6.80	2.66
12	CH_3O	C_6H_5	H	syrup	$C_{21}H_{29}O_8N$	58.38	7.10	3.40	58.11	7.20	3.14
16	CH_3O	C_6H_5	$CH_3CH_2OCH_2$-CH_2	amorphous	$C_{25}H_{37}O_9N$	60.59	7.53	2.83	60.73	7.60	3.22
17	CH_3O	C_6H_5	CH_2=$CHCH_2$	amorphous	$C_{24}H_{33}O_8N \cdot H_2O$	59.86	7.33	2.91	60.05	7.92	3.00
18	CH_3O	C_6H_5	$C_6H_5CH_2$	amorphous	$C_{28}H_{35}O_8N$	65.48	6.87	2.73	64.51	7.05	3.15
19	CH_3O	C_6H_5	$C_6H_5CH_2CH_2$	amorphous	$C_{29}H_{37}O_8N \cdot H_2O$	63.83	7.21	2.57	64.16	7.26	2.53
20	C_2H_5O	C_6H_5	$C_6H_5CH_2CH_2$	amorphous	$C_{30}H_{29}O_8N \cdot H_2O$	64.38	7.38	2.51	64.02	7.50	2.21
21	C_6H_5	CH_3O	CH_3	syrup	$C_{22}H_{31}O_8N \cdot H_2O$	58.01	7.30	3.08	58.14	7.05	2.99

residue was chromatographed over silica gel. Fast running fractions eluted with benzene–hexane (1:1, v/v) was collected and evaporated, leaving **21** as a syrup. Successive fractions with the same solvent mixture was found by means of TLC to contain a mixture of **21** and **6** which was repeatedly chromatographed and afforded a further crop of **21** as a syrup. NMR ($CDCl_3$) δ ppm: 1.3—2.95 (12H, m), 1.98 (3H, s), 2.75 (3H, s), 7.15—7.6 (5H, m).

The hydrogen citrate of **21** gave a satisfactory analytical result, but was not obtainable as crystals.

3-Methyl-9β-benzoyloxy- (24) and-9α-Benzoyloxy-3-azabicyclo[3.3.1]nonane (25)——A solution of 1.48 g of 3-methyl-9β-hydroxy-3-azabicyclo[3.3.1]nonane[3] (**22**) and 1.47 g of benzoyl chloride in 25 ml of dry $CHCl_3$ was refluxed for 2 hr. The solvent was evaporated *in vacuo* and the residual syrup was triturated with ether, yielding a solid which was collected and washed with ether. The solid was dissolved in 15 ml of H_2O and made basic with conc. NH_4OH. The resulting syrup was extracted with ether and the extract was evaporated to leave a syrup which was triturated with MeOH, yielding 1.24 g of **24** as rods of mp 56.5—58.5°. IR ν_{max}^{Nujol}: 1722 cm^{-1}. NMR ($CDCl_3$) δ ppm: 2.18 (3H, s), 5.03 (1H, t, J=3 cps), 7.3—8.3 (5H, m). *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.02; H, 8.18; N, 5.38.

An etheral solution of **24** was treated with HCl gas to give its hydrochloride, mp 206—216° (decomp.).

The isomeric 9α-benzoyloxy derivative (**25**) was also prepared in the analogous way and melted at 105°. IR ν_{max}^{Nujol}: 1711 cm^{-1}. NMR ($CDCl_3$) δ ppm: 2.18 (3H, s), 2.40 (2H, br. d, J=12 cps), 2.97 (2H, br. d, J=12 cps), 5.03 (1H, t, J=3 cps), 7.3—8.3 (5H, m). *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.95; H, 8.04; N, 5.61.

3-Methyl-8β-benzoyloxy-3-azabicyclo[3.2.1]octane (26)——A solution of 1.41 g of 3-methyl-8β-hydroxy-3-azabicyclo[3.2.1]octane[3] and 1.41 g of benzoyl chloride in 15 ml of $CHCl_3$ was refluxed for 2 hr. The mixture was evaporated *in vacuo* and the crystalline residue was washed with ether, giving 2.66 g of crude hydrochloride of **26** which was recrystallized from acetone–EtOH to give crystals of mp 230° (decomp.).

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The crude hydrochloride was dissolved in H_2O and treated with excess conc. NH_4OH. The resulting syrup was extracted with ether and the extract was evaporated after drying, leaving 2.12 g of crude **26**, mp 61.5—63° which was recrystallized from MeOH to **26**, mp 62—63.5°, as prisms. IR ν_{max}^{Nujol}: 1725 cm^{-1}. NMR ($CDCl_3$) δ ppm: 2.30 (3H, s), 4.99 (1H, t, J=4.8 cps), 7.3—8.25 (5H, m). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.25; H, 7.81; N, 5.78.

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