
The author expresses his deep gratitude to Dr. Junzo Shinoda, President of this Company, and to Dr. Takeo Ishiguro, Director of this Laboratory, for their kind encouragement, and to Dr. Masao Shimizu, Acting Director, for kind and unfailing guidance. The author is also indebted to Messrs. B. Kurihara and K. Abe for elemental analyses.

Summary

Condensation product obtained by the Robinson-Schöpf method using glycine ester hydrochloride was reduced by lithium aluminium hydride and sodium borohydride. Some of the reduction products were synthesized from 3-tropanone (IV) and, on the basis of these experimental data, the structure of the above compound was established as (I).

(Received July 6, 1960)

UDC 547.834.3:543.422.4

48. **Fumihiko Uchimaru** : Studies on N-Substituted Nortropane Derivatives. III. The Infrared Spectra of N-Substituted 3α- and 3β-Nortropanols.

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In a preceding work of this series[1] N-substituted 3-nortropanones were reduced with complex metal hydride and corresponding 3α- and 3β-ols were obtained. The present report is concerned with the infrared spectra of these alcohols, especially on the difference between 3α- and 3β-ols in the region of C-O stretching vibration. This difference was utilized to presume the configuration of epimers obtained by reduction of some N-substituted 3-nortropanones.

1. Infrared Spectra of N-Substituted 3-Nortropanones

The infrared spectra of N-substituted 3-nortropanones, described in Part I,[2] are briefly summarized. The main absorptions of nine 3-nortropanones are shown in Table I.

Table I. Infrared Spectra of N-Substituted 3-Nortropanones (liquid film) (cm^{-1})

No.	Substituent at N N-R	Ketone $\nu_{C=O}$	Active methylene CO-CH$_2$-	Methine		C-N	Ester $\nu_{C=O}$	Others
				$\nu_{HC\equiv}$	$\delta_{HC\equiv}$			
1	N-H	1708	1398	2880	1335	1006		N-H 3260
2	N-CH_3	1709	1409	2875	1347	1006		
3	N-CH_2CH_2OH	1709	1407	2860	1348	1006		C-O 1049
4	N-CH_2COOCH_3	1713	1409	2880	1349	1008	1749	
5	N-$CH_2COOC_2H_5$	1714	1400	2880	1348	1007	1747	
6	N-$CH_2COOCH_2C_6H_5$	1714	1393	2880	1350	1007	1745	
7	$\text{N-CH}\begin{matrix}\diagup CH_3\\ \diagdown COOC_2H_5\end{matrix}$	1715	1412	2880	1347	1005	1742	
8	$\text{N-CH}\begin{matrix}\diagup CH_2CH_2SCH_3\\ \diagdown COOC_2H_5\end{matrix}$	1725	(1420)[b]	(2875)	1348	1005	1739	
9	N-CN[a]	1713	1403 1415	2890	1351	999		C≡N 2205

a) This sample was measured in KBr tablet.

b) Figures in parentheses indicate weak absorption or shoulder.

[*1] Hirakawabashi, Sumida-ku, Tokyo (内丸文彦).

1) Part II. F. Uchimaru : This Bulletin, **9**, 304 (1961).

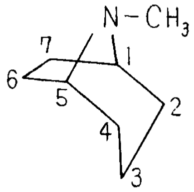
2) Part I. *Ibid.*, **9**, 300 (1961).

All of the compounds examined showed strong absorptions in the region of 1708~1725 cm^{-1}. The generally accepted range of C=O stretching frequency in cyclohexanones is 1706~1720 cm^{-1}, and that of cyclopentanones is 1745~1749 cm^{-1}.[3] Consequently the above absorptions are clearly the C=O stretching frequencies in a six-membered ring. For comparison, the C=O stretching frequencies which appeared in recent literature are summarized in Table II.

TABLE II. C=O Stretching Frequencies of Various Tropanones

Position of C=O	Tropanone	Accepted range[3] Cyclopentanone 1745~1749 (cm^{-1})	Accepted range[3] Cyclohexanone 1706~1720 (cm^{-1})
3	3-Tropanone[a,b]		1722 (Nujol) 1718 (CS_2)
	6-Hydroxy-3-tropanone[a]		1705 (Nujol) 1715 (CCl_4)
	6-Hydroxy-7-ethylthio-3-tropanone[c]		1708 (CH_2Cl_2)
2	L(+)-2-Tropanone[d]		1718 ($CHCl_3$, liq.)
	L(+)-Methiodide[d]		1736[g] (Nujol)
	Tropanone from Dioscorin (2-Tropanone)	A. R. Pinder[e]	1737 (liq.) 1740 (CCl_4)
		G. Büchi[f]	1723 (CS_2) 1730 (CCl_4)
6	6-Tropanone[e]	1750 (liq.) 1752 (CCl_4)	
	6-Tropanone methiodide[e]	1778[g] (Nujol)	

a) T. L. V. Ulbricht : Tetrahedron Letters, **1959**, 1, 5.
b) A. Nickon : J. Am. Chem. Soc., **77**, 4095 (1955).
c) R. Süess : Helv. Chim. Acta, **42**, 495 (1959).
d) M. R. Bell, S. Archer : J. Am. Chem. Soc., **80**, 6147 (1958).
e) J. B. Jones, A. R. Pinder : Chem. & Ind. (London), **1958**, 1000.
f) G. Büchi, *et al.* : J. Am. Chem. Soc., **80**, 6146 (1958).
g) C=O stretching vibration of methiodide shifts to a higher frequency.



As can be seen from Table II, the C=O stretching frequency of the ketone group in 3-position of tropane skeleton is distinctly different from that of the ketone at 6/7-position, and somewhat ambiguously from that of the ketone at 2-position. The above 3-nortropanone derivatives also show absorptions of a medium intensity in the region of 1393~1415 cm^{-1}, indicating the presence of an active methylene group adjacent to the carbonyl group.

As for the absorptions of methine group, the stretching and deformation frequencies of methine ≡C-H are generally weak and not for practical use but when a nitrogen or an oxygen atom is attatched directly to this group, these absorptions become somewhat intense.[4] Distinct ≡C-H absorptions listed in Table I correspond to this case.

2. Infrared Spectra of N-Substituted 3α- and 3β-Nortropanols

In the present work, the infrared spectra of N-substituted nortropanols derived from the above 3-nortropanones were measured and special consideration was made on the newly appeared absorption of a hydroxyl group.

The main absorptions of these tropanols are listed in Table III. None of these compounds showed the absorptions of a six-membered ring ketone described above and in their place, strong and broad bands appeared in the region of 3300~3400 cm^{-1}, showing the stretching vibration of a hydroxyl group. This absorption corresponds to the stretching frequency of a hydroxyl group with polymeric intermolecular hydrogen bond. In

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[3] L. J. Bellamy : "The Infra-red Spectra of Complex Molecules," (1958). Methuen & Co., London.
[4] N. B. Colthup : J. Opt. Soc. Am., **40**, 397 (1950).

Table III. Infrared Spectra of N-Substituted 3α- and 3β-Nortropanols (I)

No.	Substituent at N	Sample[a]		Hydroxyl		Methine		C-N	
			-OH	ν_{O-H}	ν_{C-O}	$\nu_{HC\equiv}$	$\delta_{HC\equiv}$		
1	$-CH_3$	L	a	(3350)	1046	2810	(1339)	1137	(1015)
2		L	e	3300	1065	2880	1350	1130	1014
3	-H	T	a	3280	1043	(2870)	1340	1130	1008
4		T	e	3380	1061	(2860)	1337	1125	1015
5	-CN	T	a	3410	1040	2865	1339	1138	1007
6		T	e	3420	1071	2855	1350	1129	1017
7	$-CONH_2$	T	e	(3190)	1057	2880	1351	1124	1008
8	$-CH_2CH_2OH$	T	a	3300	1045	2855	1345	1122	1014
9		L	e	3320	1060	(2870)	1348	1127	1013
10	$-CH_2COOC_2H_5$	L	a	3380	1046	(2875)	1342	1132	
11		L	e	3350	1065	2875	1347	1113	1015
12	$-CH_2COOH$	T	a	3360	1035	2920	1345	(1109)	1017

[a] L : liquid film, T : KBr tablet.

general, the main absorptions, such as the absorption of hydroxyl or carbonyl group, showed no significant difference between the two epimers. Nevertheless, a distinct regularity was found in the direction of shift of the C=O stretching frequencies between two epimers; compounds possessing an axial hydroxyl group showed their C-O stretching frequencies in the region of 1040~1047 cm^{-1}, while those possessing an equatorial hydroxyl group absorbed in a somewhat wide range of 1057~1071 cm^{-1}. This displacement of C-O stretching frequencies between axial and equatorial isomers is just the same as that shown by 3-hydroxy-5α-steroids[5] in which those possessing 3α-OH exhibit their C-O stretching frequencies at 1000 cm^{-1} and those possessing 3β-OH, at 1040 cm^{-1}. This difference of 40 cm^{-1} is greater than that in 3-tropanols. Although these data are not those measured in solution, like in the literature,[5] it seems possible to predict the configuration of hydroxyl group to some extent from their C-O stretching frequencies, as far as the tropane derivatives with a hydroxyl group at 3-position are concerned.

3. Sodium Borohydride Reduction of N-Substituted 3-Nortropanones

In the preceding paper,[1] the reduction products of ethyl 3-oxo-8-nortropaneacetate were reported. In entirely the same way, the two compounds reported in Part I of this series and presumed to be ethyl 3-oxo-α-methyl-8-nortropaneacetate (I) and ethyl 3-oxo-α-(2-methylthioethyl)-8-nortropaneacetate (IV) were reduced with sodium borohydride and the infrared spectra of resulting products were compared with those of of the compounds described above.

Sodium borohydride reduction of ethyl 3-oxo-α-methyl-8-nortropaneacetate was carried out in methanol and two bases were obtained after purification by alumina chromatography. The first eluted base crystallized from methanol to colorless prisms of m.p. 82~83°, $C_{12}H_{21}O_3N$. Its methiodide came as colorless needles of m.p. 158~160°, $C_{13}H_{24}O_3NI$. The base eluted later was an oil and, after further purification with alumina, was characterized as its methiodide of m.p. 184~185°, $C_{13}H_{24}O_3NI$. The two methiodides obtained here were proved to be distinctly different substances by mixed fusion and from infrared spectra. Consequently the reduction products of (I) with sodium borohydride were most likely to be stereoisomers, the former probably possessing an axial and the latter an equatorial hydroxyl group. For further confirmation, their infrared spectra in the region of C-O stretching vibration were examined. The former exhibited a band at 1047 cm^{-1} and the latter at 1064 cm^{-1} (Table IV). From these data, the structure of these two epimers was presumed to be (II) and (III).

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5) R. N. Johns, G. Roberts : J. Am. Chem. Soc., **80**, 6121 (1958).

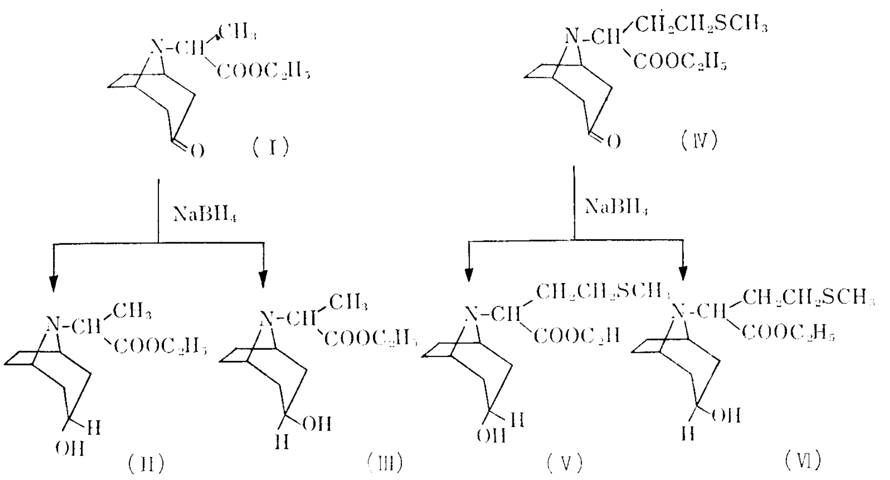

Chart 1.

Table IV. Infrared Spectra of N-Substituted 3α- and 3β-Nortropanols (II)

No.	Substituent at N	Sample[a)]		Hydroxyl		Methine		C-N	
			-OH	ν_{O-H}	ν_{C-O}	$\nu_{HC\equiv}$	$\delta_{HC\equiv}$		
13	$-CH{<}^{CH_3}_{COOC_2H_5}$	T	a	3300	1047	2885	1342	1137	1015
14		L	e	3340	1064	2875	1347	1145	1015
15	$-CH{<}^{CH_3}_{COOC_2H_5}\ CH_3I$	T	a	3350	1047	2880	1341	1143	1005
16		T	e	3325	1075	(2880)	1344	1137	1009
17	$-CH{<}^{CH_2CH_2SCH_3}_{COOC_2H_5}$	T	a	3230	1043	2875	1340		
18		L	e	3350	1063	(2870)	1347		1012

a) L : liquid film, T : KBr tablet

Sodium borohydride reduction of ethyl 3-oxo-α-(2-methylthioethyl)-8-nortropaneacetate (IV) gave the same result. Two isomers were obtained and it was concluded from their characters and infrared spectra that the one was an axial (V) and the other an equatorial compound (VI).

Reduction of the two compounds, (I) and (IV), did not give the amino acid-type product reported in Part II.

Experimental[*2]

Spectral Measurement——Infrared absorption spectra in the range of 4000~650 cm^{-1} were determined by the Hitachi EPI-2 double-beam spectrophotometer, equipped with NaCl prism. Samples were measured as a liquid film or in KBr disk. The accuracy of the frequency is assumed to be within ±2 cm^{-1}.

Reduction of Ethyl (±) 3-Oxo-α-methyl-8-nortropaneacetate (I) with Sodium Borohydride——To a solution of 1.39 g. of (I) in 20 cc. of MeOH 170 mg. of $NaBH_4$ was added during 5 min. After standing at room temperature for 3 hr. the mixture was added with 20 cc. of $CHCl_3$ and 10 cc. of H_2O, and extracted thoroughly with $CHCl_3$, which was dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil (1.2 g.) was chromatographed on 20 g. of alumina to give two fractions. The eluate of Et_2O gave 0.80 g. of a crystalline product (m.p. 74~78°) and the eluate of $CHCl_3$ yielded 0.29 g. of an oily substance (total yield, 82.5%). The first crystalline eluate after further purification on alumina (15 g.) gave 0.51 g. of crystals, m.p. 80~82°, which were recrystallized from Et_2O-petr. ether to colorless prisms of m.p. 82~83°. *Anal.* Calcd. for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31; N, 6.16. Found : C, 63.28; H, 8.82; N, 6.40.
Methiodide : Colorless needles (from Me_2CO-MeOH), m.p. 158~160°. *Anal.* Calcd. for $C_{13}H_{24}O_3NI$: C, 42.28; H, 6.55; N, 3.79. Found : C, 42.29; H, 6.59; N, 3.39.

The fraction eluted with $CHCl_3$ was further purified by alumina chromatography (5 g.) and 0.17 g. of oil was obtained by elution with Et_2O-$CHCl_3$ (1:1).

[*2] All melting points are uncorrected.

Methiodide : Colorless plates (from Me_2CO-MeOH), m.p. 184~185°. The mixed melting point with the above methiodide was 143~148°. *Anal.* Calcd. for $C_{13}H_{24}O_3NI$: C, 42.28; H, 6.55; N, 3.79. Found: C, 42.78; H, 6.11; N, 3.84.

Reduction of Ethyl (±) 3-Oxo-α-(2-methylthioethyl)-8-nortropaneacetate (IV) with Sodium Borohydride——A solution of 1.50 g. of (IV) in 20 cc. of MeOH was subjected to reduction by addition of 150 mg. of $NaBH_4$ during 5 min. After standing at room temperature for 3 hr., the solution was added with 20 cc. of $CHCl_3$ and 10 cc. of H_2O, and extracted thoroughly with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo* to leave 1.3 g. of bright yellow oil. Chromatographic purification of this oil with alumina (20 g.) gave 0.90 g. of a crystalline substance (m.p. 72~75°) eluted with Et_2O and 0.38 g. of oily substance eluted with $CHCl_3$ (total yield, 85%). The first crystalline material was further purified through a column of alumina (20 g.) and the eluate with Et_2O, after recrystallization from Et_2O-petr. ether, furnished colorless plates melting at 76~78°. *Anal.* Calcd. for $C_{14}H_{25}O_3NS$: C, 58.50; H, 8.77; N, 4.87. Found : C, 58.63; H, 8.49; N, 5.15.

The second fraction after further chromatography on alumina (10 g.) gave 0.27 g. of bright yellow oil by elution with Et_2O-$CHCl_3$ (1:1). Its methiodide did not crystallize. No other products were detected from elution of the column.

The author expresses his deep gratitude to Dr. Junzo Shinoda, President of this Company, and to Dr. Takeo Ishiguro, Director of this Laboratory, for kind encouragement, and to Dr. Masao Shimizu, Acting Director, for kind and unfailing guidance. The author is also indebted to Messrs. B. Kurihara and K. Abe for infrared spectral measurements and elemental analyses.

Summary

The infrared spectra of nine N-substituted 3-nortropanones were measured and their carbonyl frequency in 3-position was compared with that of other ketones located in a different position in tropane skeleton. Infrared spectra of several N-substituted 3-nortropanols were measured, especially in C-O stretching region. A regular difference between 3α- and 3β-ols was observed.

Some of the N-substituted 3-nortropanones were reduced with sodium borohydride and the structures of resulting bases were presumed from their infrared spectra.

(Received July 6, 1961)