90. Hisao Tsukamoto, Eigo Takabatake, and Toshihiko Ariyoshi: Metabolism of Drugs. V.* Excretion Rate of a Metabolite of Ethylhexabital.

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It was previously reported that 5-(3′-oxo-1′-cyclohexen-1′-yl)-5-ethylbarbituric acid (3-keto-EHB***), which was pharmacologicaly inactive, was produced by the *in vivo*[1,2] and *in vitro*[3] metabolism of ethylhexabital (5-cyclohexenyl-5-ethylbarbituric acid, EHB). Unchanged EHB was isolated by Fretwurst, *et al.*[4] from human urine, but not from rabbit urine under our previous experimental conditions. The simultaneous determination of both EHB and 3-keto-EHB in the urine has been made possible by the use of paper chromatography in conjunction with ultraviolet spectrophotometry. This paper presents the excretion rates of 3-keto-EHB and EHB in the urine of intact or partially hepatectomized animals.

Materials and Methods

EHB was prepared by the removal of Ca from commercial Ethylhexabital Calcium**** and melted at 171~174°. 3-Keto-EHB was prepared by the oxidation[1] of EHB with CrO_3 and melted at 222°(decomp.). Both drugs were given as freshly prepared aqueous solutions containing 1.1 equivalent of NaOH. For the optical measurements, a Shimadzu photoelectric spectrophotometer with standard 10-mm. square quartz absorption cells was used.

Analytical Methods—In a glass-stoppered tube were placed 0.5 cc. of urine, 0.5 cc. of H_2SO_4 (0.02~0.1%; adjusting pH of medium to 5.0), and 12.5 cc. of ether. After shaking the mixture, 10 cc. of the ether phase was pipetted and evaporated to dryness. The residue was dissolved in MeOH and portions of this solution were applied to paper. Quantities of 25~50 γ of barbiturates in a volume of 0.05 to 0.1 cc. were suitable for chromatography. Ascending, one-dimensional chromatography on Toyo Roshi No. 50 filter paper with BuOH:5*N* NH_4OH (1:1, upper layer) was employed. The paper strip was cut into sections at interval of appropriate Rf values, each section was eluted with 5 cc. of borate-NaOH buffer (pH 11), and the absorptions were measured at 230, 239, and 250 mμ. In routine experiments, two sections of Rf 0.15~0.35 and 0.45~0.65 were cut out for 3-keto-EHB and EHB, respectively. For the blank, the urine collected just before the administration of drug was determined in the same manner as the sample. If the characteristic spectrum of EHB or 3-keto-EHB was recognized, the quantity of barbiturate was calculated from the optical density at 239 mμ. If unchanged EHB was undetectable in the urine by paper chromatography, the ether phase was directly extracted with borate-NaOH buffer (pH 11) and the absorption was measured. When a high dose of EHB was administered, the crystals of 3-keto-EHB were frequently deposited in the urine. In such cases, the urine was centrifuged and the supernatant was analyzed by the foregoing procedure. The precipitate was dissolved in ether and its aliquot was analyzed.

Experiments with Intact Animals—Rabbits: Male rabbits of 2~3 kg. in weight were used. Drugs were orally given by stomach tube. The urine was collected by catheter optionally; before the administration of drug, and 3, 6, 9, 24, and 48 hrs. later. The urine excreted in the cage was collected into a bottle and combined with the urine collected next time.

Rats: Drugs were subcutaneously injected to four male rats of about 200 g. in weight. The 24-hr. urine was collected and analyzed.

Experiments with Partially Hepatectomized Animals—Partial hepatectomy was performed under light ether anesthesia and approximately 50% of the total liver weight was removed.

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* Part Ⅳ. H. Tsukamoto, Y. Yamamoto: This Bulletin, **3**, 427 (1955).

** Katakasu, Fukuoka (塚元久雄, 高畠英伍, 有吉敏彦).

*** 3-Keto-EHB corresponds to EHB-M in the previous reports.

**** Adorm "Shionogi."

1) H. Tsukamoto, E. Takabatake, H. Yoshimura: This Bulletin, **2**, 201 (1954).
2) H. Tsukamoto, H. Yoshimura, S. Toki: *Ibid.*, **3**, 239 (1955).
3) E. Takabatake: *Ibid.*, **3**, 398 (1955).
4) F. Fretwurst, J. Halberkann, F. Reiche: Münch. med. Wochschr., **79**, 1429 (1932).

Rabbits: Two male rabbits were used to test the excretion rate of 3-keto-EHB in the intact condition for the first time. After one week, they were operated and tested next day.

Rats: Male rats weighing about 200 g. were divided into two groups of 7 animals each, one control and the other experimental. EHB was intraperitoneally injected 24 hrs. after the operation. At 6, 24, and 48 hrs. after a dose of EHB, the urine collected into a bottle was analyzed. The duration of anesthesia was taken as the period during which the animals would lie quietly on their back or sides.

Results and Discussion

A number of ultraviolet spectrophotometric procedures[5] have been developed for the determination of barbiturates in biological fluids and organs, but difficult to simultaneously determine both unchanged drug and its metabolites which contained the barbituric acid ring. The ultraviolet absorption spectra of EHB and 3-keto-EHB in buffers of various pH values are shown in Table I. Both exhibited a peak at 239 mμ in a range of pH 11~8. Buffer of pH 11 was chosen as a medium for optical measurement, because the extraction of barbiturates from ether solutions was more complete at this pH than at lower pH.

Table I. Ultraviolet Absorption Spectra of EHB and 3-Keto-EHB at Various pH

Solvent	EHB, 18 γ/cc.				3-Keto-EHB, 9 γ/cc.			
	Max.		Min.		Max.		Min.	
	Wave length mμ	Optical density	Wave length mμ	Optical density	Wave length mμ	Optical density	Wave length mμ	Optical density
0.45 *N* NaOH	255	0.588	235	0.286	255	0.600	239	0.525
0.1 *N* NaOH	252	0.530	232	0.380	254	0.598	239	0.538
pH 12	242	0.658	227	0.510	245	0.589	238	0.529
pH 11	239	0.770	none		239	0.726	none	
pH 10.5	239	0.780	〃		239	0.750	〃	
pH 10	239	0.777	〃		239	0.770	〃	
pH 9	239	0.740	〃		239	0.764	〃	
pH 8	239	0.643	〃		239	0.750	〃	
pH 5, 2	none		〃		none		〃	

The procedure of utilizing the difference between the absorption spectra of two barbiturates has been developed by Butler[6] for the simultaneous determination of barbiturate and its N-alkylated derivative. An attempt to apply this procedure for the determination of EHB and 3-keto-EHB was unsuccessful.

On the other hand, it was shown[7] that the paper chromatography was apparently suitable for separating barbiturates in the urine. The paper chromatograms of pure compounds (Table II) show that EHB and 3-keto-EHB were located in the sections of Rf 0.5~0.6 and 0.2~0.3, respectively, and that both were completely

Table II. Paper Chromatography of EHB and 3-Keto-EHB
(A mixture of EHB (50 γ) and 3-keto-EHB (50 γ) was chromatographed)

Wave length mμ	Rf							
	0.15~0.20	0.20~0.25	0.25~0.30	0.30~0.35	0.45~0.50	0.50~0.55	0.55~0.60	0.60~0.65
230	.050	.347	.189	.067	.067	.137	.132	.050
239	.067	.380	.195	.050	.055	.148	.147	.037
250	.051	.286	.148	.036	.037	.094	.094	.026

5) e. g. L. R. Goldbaum: Anal. Chem., **24**, 1604(1952); S. Goldschmidt, W. Lamprecht, E. Helmreich: Z. physiol. Chem., **292**, 125(1953).

6) T. C. Butler: J. Pharmacol. Exptl. Therap., **108**, 474(1953); Proc. Soc. Exptl. Biol. Med., **84**, 105(1953).

7) E. J. Algeri, J. T. Walker: Am. J. Clin. Path., **22**, 37(1952); E. J. Algeri, A. J. McBay: *Ibid.*, **23**, 654(1953); *ibid.*, **24**, 1139(1954); F. Dybing: Acta pharmacol. toxicol., **11**, 72(1955).

separated. Thus, the quantitative study on the metabolism of EHB has been made possible by the use of paper chromatography in conjunction with ultraviolet spectrophotometry. Table III shows the typical data of chromatogram of urine. Analytical recovery was about 85%.

Table III. Paper Chromatography of Urine Extract

Sample	Wave length	Rf 0.15~0.35 Time (hrs.) after administration 0	3	6	9	24	48	Rf 0.45~0.65 Time (hrs.) after administration 0	3	6	9	24
Degree of dilution		1/1000				1/200		1/60				
Control (no EHB)	mμ 230	027	027	031	065	047		074	075	075	074	
	239	023	020	026	056	039		053	056	054	052	
	250	016	016	017				044	050	048	042	
EHB, 200 mg./kg. per os	230	017	218	312	360	251	048	074	094*	127*	098*	
	239	014	252	361	430	285	039	054	090	095	089	
	250	012	186	268	315	206	028	043	088	093	089	046

* The absorption peak was exhibited at approximately 290 mμ.

Table IV shows the excretion rates of 3-keto-EHB in the urine of intact rabbits receiving EHB. Unchanged EHB was undetected in all cases.

The excretion of 3-keto-EHB was found early in the first 3 hrs. after the administration of EHB and completed within 24 hrs. at a dose of 100~200 mg./kg., or 48 hrs. at 400 mg./kg. per os. The detoxication capacity, the quantity of excreted 3-keto-EHB per hour, was nearly equal in the first 3 hrs. at each dose and was approximately 15 mg. At a dose of 100 mg./kg., this value was similar in the first and second 3 hrs. and markedly decreased in third 3 hrs. At a dose of 200 mg./kg., it was highest in second 3 hrs. (27.9 mg.) and decreased after 9 hrs. At a dose of 400 mg./kg., it had a peak in third 3 hrs. (28.9 mg.) and very markedly decreased after 24 hrs.

Concerning the total quantity of excreted 3-keto-EHB, the difference depending on dosage was not significant in the first 3 hrs. and then became marked and significant. The metabolic rates, the percentage of the total quantity of excreted 3-keto-EHB to the quantity obtainable by the complete transformation of EHB to 3-keto-EHB, gradually increased until 6 hrs. at a dose of 100 mg./kg., 9 hrs. at 200 mg./kg. and 24 hrs. at 400 mg./kg., and then their increasing rates became flat. However, the total metabolic rates were very nearly independent of doses and approximately 44%. This value is higher than the observation of Fretwurst, *et al.*[4] or our previous report[1] (less than 20%). There is a possibility of considerable loss in process of isolation and purification of 3-keto-EHB crystals in previous experiments.

It is concluded from these results that the detoxication activity for EHB plays equally in the first 3 hrs., independent of dosage, and that the maximum of detoxication capacity is approximately 28 mg. per hour. The higher the dose of EHB administered, the longer period of excretion of metabolite prolongs.

The ultraviolet absorption spectrum of eluate from a section of Rf 0.45~0.65 on chromatogram of urine extract exhibited a peak at about 290 mμ (Table III). This absorption peak was not recognized in control urine (no EHB was received). It is not yet identified whether this is another metabolite of EHB or not.

As shown in Table V, about 32% of 3-keto-EHB administered was rapidly excreted in the urine but the fate of the remainder was undetectable. The results obtained by rats were similar to rabbits as shown in Table VI.

It is known that the duration of anesthesia produced by barbiturates is pro-

TABLE IV. Excretion Rates of 3-Keto-EHB in the Urine of Intact Rabbits Receiving EHB

Dose mg./kg.	Rabbit, Mark, Wt.(g.) Exptl. date	Time	Urine Vol.	3-Keto-EHB Concn.	3-Keto-EHB Amt. excreted		Time	Total excreted	Metabolic rate
		(hrs.)	(cc.)	(mg./cc.)	(mg.)	(mg./hr.)	(hrs.)	(mg.)	(%)
100	A 2980 Oct. 29	0~ 3	14.5	2.79	40.4	13.5	0~ 3	40.4	12.6
		3~ 6	18.0	2.69	48.4	16.1	0~ 6	88.8	27.7
		6~ 9	8.1	3.18	25.8	8.58	0~ 9	114.6	35.7
		9~24	89.0	0.27	23.6	1.57	0~24	138.2	43.1
	B 2840 Oct. 11	0~ 3	8.0	4.65	37.2	12.4	0~ 3	37.2	12.4
		3~ 6	16.5	2.97	49.0	16.3	0~ 6	86.2	28.8
		6~24	130.8	0.41	56.6	3.77	0~24	142.8	47.7
	C 2765 Oct. 19	0~ 3	9.0	6.30	56.7	18.9	0~ 3	56.7	18.9
		3~ 6	14.5	3.60	52.6	17.5	0~ 6	109.3	36.5
		6~ 9	11.6	0.93	10.8	3.58	0~ 9	120.1	40.0
		9~24	198.5	0.06	11.9	0.29	0~24	132.0	44.0
	Average	0~ 3				14.9	0~ 3	44.7	14.6
		3~ 6				16.7	0~ 6	94.8	31.0
		6~ 9				6.08	0~ 9	117.3	37.9
		9~24				1.18	0~24	137.6	44.9
200	A 3060 Oct. 19	0~ 3	15.5	3.26	50.4	16.8	0~ 3	50.4	7.9
		3~ 6	12.5	5.13	64.0	21.3	0~ 6	114.4	17.9
		6~ 9	10.2	5.74	58.5	19.5	0~ 9	172.9	27.0
		9~24	104.3	0.66	69.2	4.62	0~24	242.1	37.8
	B 2830 Oct. 29	0~ 3	5.8	6.53	37.9	12.6	0~ 3	37.9	6.3
		3~ 6	7.7	12.9	99.4	33.1	0~ 6	137.3	23.0
		6~ 9	6.0	12.4	74.6	24.9	0~ 9	211.9	35.4
		9~24	129.0	0.62	79.3	5.28	0~24	291.2	48.7
	C 2800 Oct. 11	0~ 3	8.0	7.25	58.0	19.3	0~ 3	58.0	9.7
		3~ 6	7.7	11.7	87.5	29.2	0~ 6	145.5	24.3
		6~24	123.6	1.12	138.4	9.23	0~24	283.9	47.4
	Average	0~ 3				16.3	0~ 3	48.8	8.0
		3~ 6				27.9	0~ 6	132.4	21.7
		6~ 9				22.2	0~ 9	192.4	31.2
		9~24				4.95	0~24	272.4	44.6
400	A 3020 Dec. 1	0~ 3	8.0	7.00	56.0	18.7	0~ 3	56.0	4.4
		3~ 6	7.8	12.2	95.3	31.8	0~ 6	151.3	11.8
		6~ 9	6.5	15.7	102.1	34.0	0~ 9	253.4	19.8
		9~24	83.0	3.78	310.0	20.6	0~24	563.4	44.0
		24~48	140.0	0.23	31.7	1.32	0~48	595.1	46.5
	B 2780 Dec. 1	0~ 3	5.6	9.10	50.9	17.0	0~ 3	50.9	4.3
		3~ 6	9.2	10.2	94.0	31.3	0~ 6	144.9	12.1
		6~ 9	5.0	12.9	64.5	21.5	0~ 9	209.4	17.5
		9~24	47.0	5.60	263.5	17.5	0~24	472.9	39.5
		24~48	157.5	0.15	23.4	0.98	0~48	496.3	41.5
	C 2550 Dec. 1	0~ 3	10.5	3.23	33.9	11.3	0~ 3	33.9	3.1
		3~ 6	15.5	3.05	47.3	15.8	0~ 6	81.2	7.3
		6~ 9	16.0	5.84	93.5	31.2	0~ 9	174.7	15.7
		9~24	58.5	4.85	283.5	18.9	0~24	458.2	41.2
		24~48	55.0	0.36	19.9	0.83	0~48	478.1	43.0
	Average	0~ 3				15.7	0~ 3	46.9	3.9
		3~ 6				26.3	0~ 6	125.8	10.4
		6~ 9				28.9	0~ 9	212.5	17.7
		9~24				19.0	0~24	498.2	41.6
		24~48				1.04	0~48	523.1	43.7

Table V. Excretion Rates of 3-Keto-EHB in the Urine of Rabbits receiving 3-Keto-EHB (Dose : 100 mg./kg., per os)

Rabbit No. Wt.(g.)	Time (hrs.*)	Urine Vol. (cc.)	Concn. (mg./cc.)	Amt. excreted (mg.)	Time (hrs.)	Total excreted (mg.)	Excretion rate (%)
1 (2200)	0~3	15.0	3.04	45.7	0~3	45.7	20.7
	3~6	12.0	1.69	20.3	0~6	66.0	29.9
	6~9	4.8	1.07	5.1	0~9	71.1	32.3
2 (2200)	0~3	14.5	2.96	43.0	0~3	43.0	19.6
	3~6	13.4	1.52	20.5	0~6	63.5	28.9
	6~9	8.6	0.88	7.6	0~9	71.1	32.5

* After 9 hrs. 3-keto-EHB was undetected.

Table VI. Excretion Rate of 3-Keto-EHB in the Urine of Rats Receiving EHB or 3-Keto-EHB

Rat	Body wt. (g.)	Treatment (subcutan. inject.) (mg./100 g.)	Excreted 3-keto-EHB (mg./24 hrs.)	Metabolic rate (%)
1	200	EHB 7.5	8.52	53.0
2	270	〃	6.24	32.4
3	220	〃	8.54	48.5
4	230	〃	7.42	42.0
Average				44.0*
1	200	3-Keto-EHB 5.0	4.45	44.5
2	270	〃	4.56	33.8
3	220	〃	2.33	23.3
4	220	〃	3.10	28.2
Average				32.5

* Unchanged EHB was undetected.

longed by some treatments such as the administration of liver poisons[8] ($CHCl_3$ or CCl_4), partial hepatectomy,[9] or complete nephrectomy.[9] The slices or brei of liver or kidney are capable of metabolizing the barbiturates *in vitro*.[3,10,11] These facts suggest that the liver and kidney play important rôles in the detoxication of barbiturates. Masson and Beland[9] classified the barbiturates into four groups according to the site of their detoxication and said that EHB belonged to the group which is detoxicated approximately equally in the liver and kidney.

As shown in Tables VII and VIII, the period of excretion of 3-keto-EHB was prolonged and the total metabolic rate was decreased by a partial hepatectomy. The

Table VII. Effect of Partial Hepatectomy on the Excretion Rate of 3-Keto-EHB in the Urine of Rabbits (Dose : 200 mg. of EHB per rabbit)

Rabbit	Time	In intact condition		After partial hepatectomy	
		Total excreted	Metabolic rate	Total excreted	Metabolic rate
	(hrs.)	(mg.)	(%)	(mg.)	(%)
G	0~ 3	23.5	11.0	0.43	0.20
	0~ 6	68.9	32.2	9.35	4.37
	0~ 9	93.7	43.8	20.8	9.72
	0~24	108.0	50.4	31.4	14.7
	0~32			50.6	23.6
J	0~ 3	38.7	18.1	11.1	5.21
	0~ 6	92.3	43.2	27.9	13.1
	0~ 9	107.1	50.1	49.1	22.9
	0~24			82.8	38.7

8) T. Koppanyi, J. M. Dille, C. R. Linegar : J. Pharmacol. Exptl. Therap. **58**, 119(1936).
9) G. M. C. Masson, E. Beland : Anesthesiol., **6**, 483(1945).

Table VIII. Effect of Partial Hepatectomy on the Metabolic Rate of EHB in Rats
(Dose : 15 mg. of EHB per rat, intraperitoneal injection)

Rat No.	Body wt. (g.)	Removed liver (%)	Duration of anesthesia (min.)	Metabolic rate (%) 0~8 hrs.	8~24 hrs.	0~48 hrs.	Uechanged EHB (%) 0~8 hrs.	8~24 hrs.	0~48 hrs.
				Control Rats					
1	225	0	14	21.4	3.12	24.5			0
2	185	0	56	15.3	10.1	25.4			0
3	190	0	57	30.9	11.3	42.2			0
4	200	0	46	32.6	13.7	46.3			0
5	185	0	44	29.1	5.1	35.3*			0
6	210	0	47	37.0	0	37.0			0
7	210	0	8	36.2	7.3	43.5			0
Av.	200	0	39			36.3			0
				Partially Hepatectomized Rats					
11	185	55.3	83	22.7	0	22.7	1.89	0	1.89
12	190	36.1	60	34.8	6.70	41.5	5.15	0	5.15
13	210	44.8	99	22.1	0	22.1	3.56	0	3.56
14	185	32.9	81	0	18.2	18.2	0	0	0
15	165	25.0	77	0	11.0	11.0	0	0.8	3.40**
16	215	43.0	136	15.9	0	15.9	0	2.08	2.08
17	215	51.6	139	9.25	21.9	31.2	0	0	0
Av.	195	41.2	96			23.2			2.30

* During 24~48 hrs., 1.1% was excreted.
** During 24~48 hrs., 2.6% was excreted.

t-Test : Difference between intact group and partially hepatectomized group.
Duration of anesthesia : $t=4.49$
Metabolic rate : $t=2.59$
$t_{.01}=3.055$, $t_{.05}=2.179$ (d.f.=12)

duration of anesthesia of partially hepatectomized rats was significantly longer than that of the intact. Index of hepatic detoxication, the ratio of average duration of anesthesia of control animals to that of operated animals, was 39/96=0.41 and agreed with the value, 0.4, obtained by Masson and Beland.[9] The total quantity of 3-keto-EHB excreted in partially hepatectomized rats was significantly less than that in the intact, and unchanged EHB was also detected.

From these results it is clear that the liver plays an important rôle in the detoxication of EHB. It was not possible to estimate the relationship between the quantity of the liver removed and the duration of anesthesia or the excretion rate of 3-keto-EHB. In future we shall discuss the mechanism of detoxication of EHB in liver.

The authors are indebted to Shionogi & Co., Ltd. for their supply of EHB. This work was aided by a Grant in Aid of Scientific Research from the Ministry of Education, to which the authors' thanks are due.

Summary

The excretion rates of EHB and 3-keto-EHB in the urine of intact or partially hepatectomized animals receiving EHB or 3-keto-EHB were determined by use of paper chromatography in conjunction with ultraviolet spectrophotometry.

Unchanged EHB was undetectable in the urine of intact animals. Approximately 44% of EHB administered was converted to 3-keto-EHB and excreted independently of the dosage. The excretion of 3-keto-EHB began in a period of the first 3 hrs.

10) A. Dorfman, L. R. Goldbaum : J. Pharmacol. Exptl. Therap., **90**, 330 (1947)
11) T. C. Gould, F. E. Shideman : *Ibid.*, **104**, 427 (1952).

after an administration of EHB and completed within 24 hrs. (100 or 200 mg./kg.) or 48 hrs. (400 mg./kg.). About 32% of 3-keto-EHB administered was rapidly excreted but the fate of the remainder was undetectable.

Partial hepatectomy prolonged the period of excretion of 3-keto-EHB and decreased the quantity of that. Unchanged EHB was detected in partially hepatectomized rats.

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91. Takeo Ueda, Shigeshi Toyoshima, Kiyoshi Takahashi, and Masako Muraoka: Studies on Syntheses and Pharmacological Effects of N-Alkylephedrines and their Ammonium Salt Derivatives.[1]

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Ephedrine, as is well known, is one of the most interesting as a sympathomimetic in regard not only to toxicity (tachycardia, hypertension, anxiety, etc.), but also to its effectiveness. Many attempts have hitherto been made to improve ephedrine by decreasing toxicity and increasing the pharmacological effect, but according to the authors' view, it might be said that drugs which are reliably superior to ephedrine on the balance of effect and toxicity have not been found in any clinical trials.

For the purpose of finding improved substitutes for ephedrine, N-alkyl derivatives of ephedrine and their ammonium salts were taken up by the present authors.

It was reported by Misawa[2] that N-methylephedrine might possess an effect twice as strong as that of ephedrine regardless of its optical isomerism. However, it was shown by Shimamoto[3] that difference was found between the effects of three optical isomers of N-methylephedrine and that *l*-N-methylephedrine showed an effect only one-third as strong as that of *l*-ephedrine in the dog's bronchial preparation by the method of Konzett. Therefore, there remain many questions to be solved regarding pharmacological properties of N-alkylated ephedrine.

Misawa's work is of interest as indicating one direction of the improvements of ephedrine. Thus, in an attempt to remove the defects of ephedrine, N-alkyl derivatives of ephedrine were taken up by the present authors, since they have not been systematically studied with the exception of N-methylephedrine.

This paper describes the syntheses and pharmacological effects of N-alkylephedrines and their quaternary ammonium salts. Nitrogen atom in the side-chain in ephedrine was alkylated and the N-alkylephedrines thus obtained were converted into ammonium salt with methyl iodide (or ethyl iodide), because of the utility of ammonium salts of some kind of drugs.

Alkyl bromide to be employed as the alkylating agents were prepared in the usual manner. N-alkylation was effected by heating a mixture of ephedrine base and alkyl bromide at 140~170° for 3~5 hours under pressure, when the reaction proceeded with decreasing yield of the desired substance as the number of carbons in

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2) K. Misawa: Tokyo Med. J., **68**, No.3, 3 (1951); **71**, 439 (1954).
3) Shimamoto: Japan. J. Pharm. & Chem. **27**, 460 (1955).