curve by that observed with the control solvent (10 μl of solvent H, N and D) and then multiplying by 100. While the control solvent H and N was non-effective against platelet aggregation, solvent D inhibited aggregation slightly.[23] The inhibition percentages thus obtained were not absolute, and therefore the relative potency of inhibition of a compound to a reference standard, adenosine, at the same concentration (RAD) was a direct measure of potency of inhibition. RAD was calculated by dividing the percent inhibition of a test compound with that of adenosine.

Acknowledgements The present authors express their sincere thanks to Miss I. Kawada for her technical assistances and to Dr. M. Ichino for his continuous interests throughout the work.

[Chem. Pharm. Bull. 25(7)1821—1826(1977)]

UDC 547.822.04 : 546.173.04

Studies on Pyrimidine Derivatives. II.[1] Reaction of Some Dimethyl- and Trimethyl-heteroaromatics with Ethyl Nitrite

HIROSHI YAMANAKA, HIROYUKI ABE, TAKAO SAKAMOTO, HIDETOSHI HIRANUMA, and ATSUKO KAMATA

Pharmaceutical Institute, Tohoku University[2]

(Received November 4, 1976)

Methyl groups at the 4-position of 2,4-dimethyl-, 2,4,6-trimethyl-pyridine, 2,4-dimethyl-, 2,4,6-trimethyl-pyrimidine, 2,4-dimethylquinoline, and 2,4-dimethylquinazoline were nitrosated selectively with ethyl nitrite in the presence of alkali amide in liquid ammonia to give the corresponding 4-aldoximes. On heating with phosphoryl chloride, the aldoximes were converted to 4-carbonitriles except 2-methylquinazoline-4-aldoxime which was sublimated with phosphorous pentoxide to afford 4-cyano-2-methylquinazoline.

Related to these synthetic experiments, the hydrogen-deuterium exchange reaction of the methyl groups was examined by means of the NMR technique. The observed results did not contradict the direction of nitrosation of the testing compounds.

Keywords——hydrogen-deuterium exchange of active methyl groups; nitrosation of active methyl groups; pyridine-4-aldoximes; 2-methylquinoline-4-aldoxime; pyrimidine-4-aldoximes; 2-methylquinazoline-4-aldoxime; 4-cyanopyridines; 4-cyano-2-methylquinoline; 4-cyanopyrimidines; 4-cyano-2-methylquinazoline

Many papers[3-7] related to the reactions of the active methyl groups attached to an electron-deficient heteroaromatic ring were published. For instance, Kato, *et al.*[8] described that the active methyl groups on a pyridine ring were nitrosated with pentyl nitrite under strongly basic conditions to give 2- or 4-pyridinealdoximes. They extended this reaction to some methylpyrimidine derivatives[9] to find that the activity of pyrimidine derivatives for this nitrosation exceeded than that of pyridine derivatives. However, in the case of compounds containing two or three active methyl groups in the same molecule, this reaction has not been well examined.

1) Part I: H. Yamanaka, S. Niitsuma, Y. Bannai, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2591 (1975).
2) Location: *Aobayama, Sendai*, 980, *Japan*.
3) J. Stanek, *Collection Czech. Chem. Commun.*, **15**, 1037 (1951).
4) Z. Arnold, *Collection Czech. Chem. Commun.*, **28**, 863 (1963).
5) T. Kato, Y. Goto, and M. Kondo, *Yakugaku Zasshi*, **84**, 290 (1964).
6) M.J. Weiss and C.R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).
7) J.C. Roberts, *J. Chem. Soc.*, **1952**, 3065.
8) T. Kato and Y. Goto, *Chem. Pharm. Bull.* (Tokyo), **11**, 461 (1963).
9) T. Kato, H. Yamanaka, and H. Hiranuma, *Yakugaku Zasshi*, **90**, 877 (1970).

In this paper we wish to report that the methyl groups at the 4-position of such compounds as 2,4-dimethyl- (Ia), 2,4,6-trimethyl-pyridine (Ib), 2,4-dimethylquinoline (Ic), 2,4-dimethyl- (Id), 2,4,6-trimethyl-pyrimidine (Ie), and 2,4-dimethylquinazoline (If) are nitrosated predominantly with ethyl nitrite in the presence of alkali amide in liquid ammonia and that this reaction provides a method for the preparation of 4-cyano derivatives of alkylated monoazines and diazines.

Since the initial step of the nitrosation of an active methyl group under basic conditions is considered to abstract a proton from the methyl group, hydrogen-deuterium exchange of Ia—If was first examined. Thus, according to the method reported by Kawazoe, *et al.*,[10] a D_2O–CD_3OD solution of the testing compound (I) was heated at an appropriate temperature for an apporopiate period in a sealed NMR tube. The relative reactivity of the methyl groups was determined by measuring the time-dependent decrease of the areal intensity of

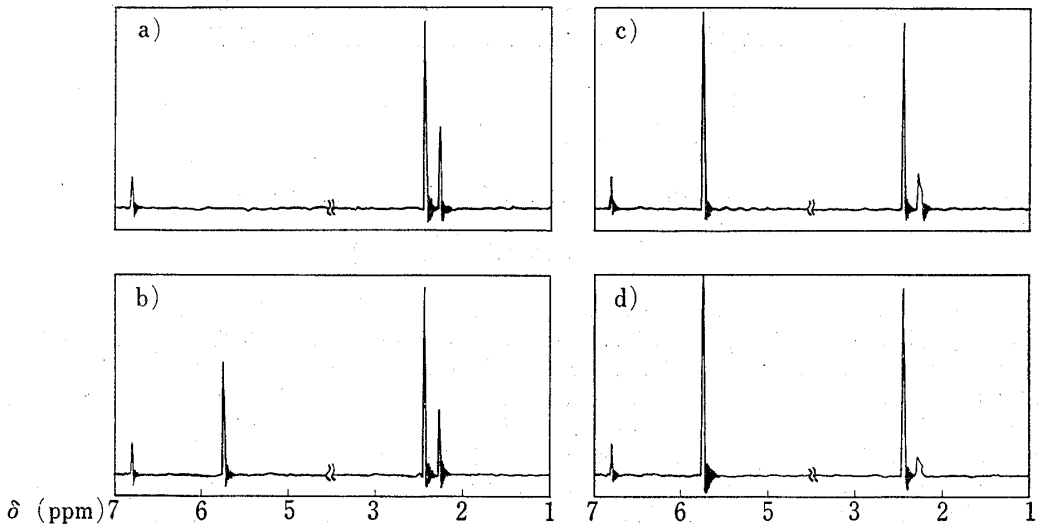

Fig. Time-dependent Deformation of NMR Spectra (Ib) owing to Hydrogen-Deuterium Exchange under Basic Conditions

NMR spectra were taken in 5% NaOD CD_3OD-D_2O solution with a Hitachi R-20 spectrometer at 60 MHz.
a) CD_3OD-D_2O room temp. b) 100°, 1 hr. c) 100°, 5hr. d) 100°, 10 hr.

Table I. Percentages of Areal Intensity Decrease of NMR Signals due to the Active Methyl Hydrogens[a)]

Compd. No.	Medium	Reaction Temp.(C°)	Reaction time		
			1 hr	5 hr	10 hr
Ia	5% NaOD	100	10	40	70
Ib	5% NaOD	100	10	40	90
Ic	5% NaOD	50	10	—	50[b)]
Id	1% NaOD	20	30	60	
Id	1% NaOD	50	100		
Ie	1% NaOD	20	10	20	
Ie	1% NaOD	50	50		
If	1% NaOD	20	100		

a) In all the cases, areal intensities due to the methyl groups at the 2-position were completely unchanged.
b) In this case, reaction time was two days.

10) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **15**, 1225 (1967).

NMR signals due to the methyl hydrogen concerned. In all the cases, the areal intensity of a signal due to a ring proton was used as an internal standard. The time-dependent deformation of nuclear magnetic resonance (NMR) spectra of Ib under these conditions was shown in Figure.

The results summarized in Table I showed the methyl groups at the 4-position of Ia—If possessing stronger acidity than that of the 2-position in the same molecule.

Thus, Ia was treated with 2 molar equivalents of ethyl nitrite in liquid ammonia in the presence of potassium amide to give 2-methylpyridine-4-aldoxime (IIa) as expected in considerable yield. The infrared (IR) spectrum of IIa shows an absorption band at 2700 cm^{-1} (OH) due to an aldoxime group, and the NMR spectrum indicates the existence of a methyl group at δ 2.92 (3H, s), an olefinic proton at δ 8.60 (1H, s), and three aromatic protons at δ 8.03 (2H, s), δ 8.34 (1H, s). These spectral data are consistent with IIa.

Nitrosation of other dimethyl- or trimethyl-heteroaromatics (Ib—If) under similar conditions as above, afforded the corresponding 4-aldoximes (IIb—IIf) which were observed to contain none of 2-aldoximes.[11] The melting points, yields and spectral data of IIa—f were summarized in Table II.

Table II. Melting Points, Yields, Spectral Data and Analytical Data of IIa—f

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1} (-OH)	NMR (CF_3COOH) δ (ppm) ($-CH_3$)	($-CH=N-$)	(Ring proton)	Formula	Analysis (%) Calcd. (Found.) C	H	N
IIa	154—156	37	2700	2.92(s, 3H)	8.60(s, 1H)	8.03(s, 2H) 8.34(s, 1H)	$C_7H_8N_2O$	61.75 (61.67)	5.92 (5.78)	20.58 (20.65)
IIb	198—200	40	2740	2.85(s, 6H)	8.30(s, 1H)	7.83(s, 2H)	$C_8H_{10}N_2O$	63.98 (63.94)	6.71 (6.72)	18.65 (18.81)
IIc	216—216.5	59	2700	3.10(s, 3H)	9.04(s, 1H)	7.70—8.80 (m, 5H)	$C_{11}H_{10}N_2O$	70.95 (70.67)	5.41 (5.32)	15.05 (15.08)
IId	170	79	2820	3.10(s, 3H)	8.37(s, 1H)	8.16 (d, 1H, J=7.2Hz) 8.92 (d, 1H, J=7.2Hz)	$C_6H_7N_3O$	52.84 (52.57)	5.15 (5.23)	30.64 (30.92)
IIe	200	87	2725	2.90(s, 3H) 3.26(s, 3H)	8.31(s, 1H)	7.92(s, 1H)	$C_7H_9N_3O$	55.61 (55.72)	6.00 (6.21)	27.80 (27.67)
IIf	210—212	71	2680	3.23(s, 3H)	9.16(s, 1H)	8.04—8.89 (m, 4H)	$C_{10}H_9N_3O$	64.16 (64.50)	4.85 (4.89)	22.45 (22.53)

On heating with excess phosphoryl chloride, these aldoximes (IIa—IIe) were transformed to the 4-cyano derivatives (IIIa—IIIe). Although the treatment of IIf with phosphoryl chloride resulted in a formation of a resinous product, sublimation of IIf with exess phosphorous pentoxide under reduced pressure gave rise to 4-cyano-2-methylquinazoline (IIIf).

11) Previously we reported[9] that the reaction of Id with isoamyl nitrite in the presence of sodium amide in liquid ammonia afforded a mixture of 2-aldoxime and 4-aldoxime. We have reinvestigated this reaction and found that the conclusion previously described was uncorrect by following reasons. i) On treatment with dil. hydrochloric acid at room temperature, the mixture (mp 147—150°) turned to IId showing sharp melting point (mp 170°). J. Schneckenburger proved that the *syn* isomer of 1-oxidopyridine 4-aldoxime was more stable than the *anti* isomer which was easily converted to the *syn* isomer by treatment with dil. hydrochloric acid (*Archiv. Pharm.*, **302**, 494 (1969)). ii) The NMR spectrum of the mixture was simplified when it was taken in trifluoroacetic acid. iii) Reaction of the mixture with phosphoryl chloride gave 4-cyano-2-methylpyrimidine as a sole product. Therefore, the substance obtained previously may be a mixture of *syn-anti* isomers of 2-methylpyrimidine-4-aldoxime.

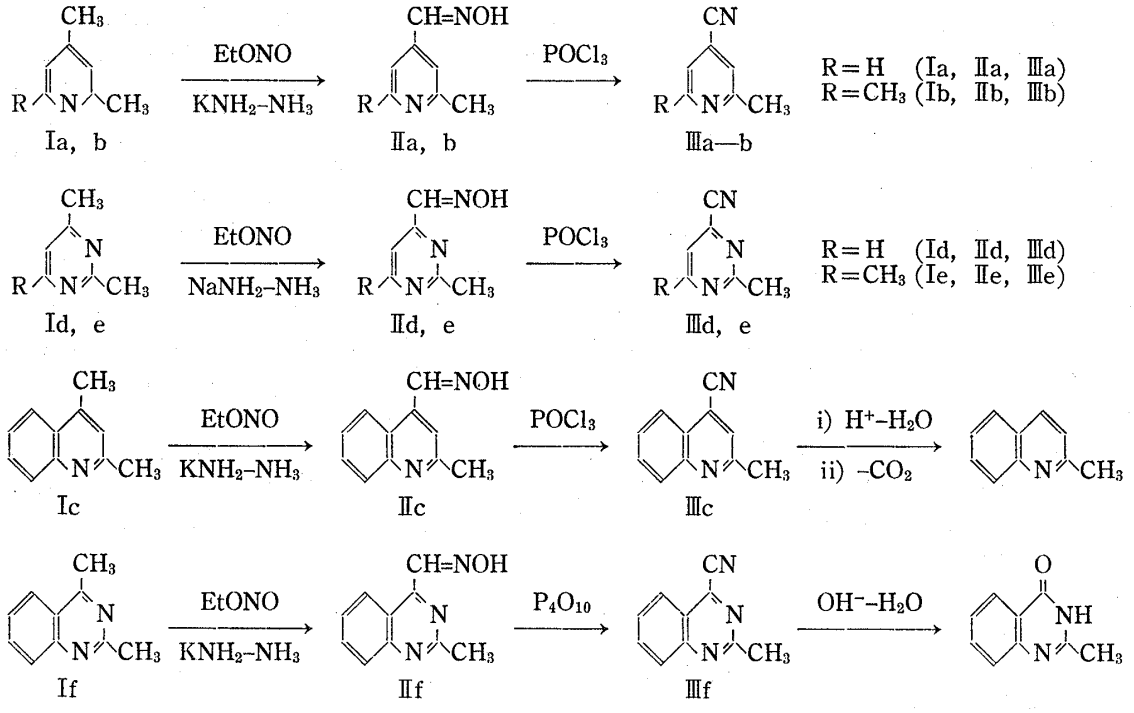

Chart 1

The structural assignment of IIIa—IIIf was achieved as follows: 4-Cyano-2-methylpyridine (IIIa),[12] 4-cyano-2,6-dimethylpyridine (IIIb),[13] 4-cyano-2-methylpyrimidine (IIId) and 4-cyano-2,6-dimethylpyrimidine (IIIe)[14] were identical with the authentic specimens prepared by the methods reported on the literatures. 4-Cyano-2-methylquinoline (IIIc) was hydrolyzed with sulfuric acid to give 2-methylquinoline-4-carboxylic acid (IV) which, on heating in boiling toluene, was decarboxylated to 2-methylquinoline (V). According to a similar method reported by Higashino,[15] 4-cyano-2-methylquinazoline (IIIf) was treated with aqueous potassium hydroxide at room temperature to afford 2-methyl-4-quinazolone (VI) which was identical with authentic specimen.[16]

Table III. Physical Constants, Yields and Spectral Data of IIIa—f

Compd. No.	mp (°C)	bp (°C)	Yield (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (–CN)	NMR($CDCl_3$) δ (ppm) (–CH_3)	NMR($CDCl_3$) δ (ppm) (Ring proton)
IIIa	44— 46	110—130 (95mmHg)	73(36)	2240	2.64(s, 3H)	7.40(s, 2H) 8.70(d, 1H, J=6Hz)
IIIb	79— 80	92— 95 (25mmHg)	74(38)	2215	2.58(s, 6H)	7.14(s, 2H)
IIIc	105—106	—	94(61)	2220	2.80(s, 3H)	7.60—8.18(m, 5H)
IIId	29— 30.5	92— 93 (15mmHg)	67(46)	—	2.76(s, 3H)	7.46(d, 1H, J=4.8Hz) 8.75(d, 1H, J=4.8Hz)
IIIe	54— 56.5	113—115 (29mmHg)	56(55)	—	2.76(s, 3H) 2.60(s, 3H)	7.29(s, 1H)
IIIf	128—130	—	43 —	—	2.95(s, 3H)	7.58—8.26(m, 4H)

a) The figures given in a parenthesis show the yield obtained by one-step prepn. of III from I.

12) E. Ochiai and Y. Suzuki, *Pharm. Bull.*, **2**, 247 (1954).
13) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 925 (1959).
14) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 638 (1958).
15) T. Higashino, *Yakugaku Zasshi*, **80**, 1404 (1960).
16) S. von Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).

As shown in Table II, the yield of aldoximes seemed to be unsatisfactory, which was caused by the difficulties of purifying the aldoximes. In order to synthesize 4-cyano derivatives (IIIa—e) from the corresponding 2,4-dimethylheteroaromatics more conveniently, one-step preparation was investigated. Thus, phosphoryl chloride was added to the crude aldoxime obtained from acetone extracts of the reaction mixture and the solution was heated for an apropriate period. The yield of the cyano derivatives (IIIa—IIIe) synthesized through this method was summarized in parentheses in Table III.

The purity of IIIa—f was checked and confirmed by gas liquid chromatographic analysis.

Experimental[17]

Hydrogen-Deuterium Exchange Reaction of I——In a 10 ml solution of CD_3OD–D_2O (3: 1), metallic Na was added to prepare a NaOD solution. The testing compounds (*ca.* 20 mg) were dissolved in the NaOD solution containing a small amount of tetramethylsilane as internal standard, and warmed to 50° or 100° for an appropriate time in a NMR tube tightly covered by a tefron stopper. Then, the NMR spectra were measured with a Hitachi R-20 spectrometer, and the time-dependent decrease of signal intensities were recorded.

Reaction of Ia—f with EtONO in Liq. NH_3——General Procedure: In a 500 ml three necked flask, fitted with dry ice condenser and a mechanical stirrer, were placed 300 ml of liq. NH_3, metallic K or Na and a catalytic amount of anhyd. $FeCl_3$. After finishing the formation of KNH_2 or $NaNH_2$, I was added to the flask, and the solution was stirred for 1 hr at a boiling point of liq. NH_3. Then EtONO was added to the solution and the mixture was stirred for additional 1 hr. After neutralizing with NH_4Cl, the reaction mixture was condensed to dryness and the residue was extracted with acetone. Evaporation of the dried extracts afforded the crude products (II) which was purified by a column chromatography (Al_2O_3–$CHCl_3$) followed by recrystallization.

The results of elemental analysis of IIa—f were summerized in Table II.

2-Methylpyridine-4-aldoxime (IIa): According to the general procedure, IIa was obtained from Ia (3.21 g, 0.03 mol), metallic K (1.3 g, 0.033 g·atom) and EtONO (4.5 g, 0.06 mol), as colorless needles (from acetone), 1.51 g.

2,6-Dimethylpyridine-4-aldoxime (IIb): According to the general procedure, IIb was obtained from Ib (3.63 g, 0.03 mol), metallic K (1.3 g, 0.033 g·atom) and EtONO (4.5 g, 0.06 mol), as colorless needles (from acetone), 1.81 g.

2-Methylquinoline-4-aldoxime (IIc): According to the general procedure, IIc was obtained from Ic (4.71 g, 0.03 mol), metallic K (1.3 g, 0.033 g·atom) and EtONO (4.5 g, 0.06 mol), as colorless needles (from acetone), 3.0 g.

2-Methylpyrimidine-4-aldoxime (IId): According to the general procedure, IId was obtained from Id (1.08 g, 0.01 mol), $NaNH_2$ (1.2 g, 0.03 mol) and EtONO (1.5 g, 0.02 mol), as colorless needles, 0.91 g.

2,6-Dimethylpyrimidine-4-aldoxime (IIe): According to the general procedure, IIe was obtained from Ie (1.22 g, 0.01 mol), $NaNH_2$ (1.2 g, 0.03 mol) and EtONO (1.5 g, 0.02 mol) as colorless needles (from acetone), 1.32 g.

2-Methylquinazoline-4-aldoxime (IIf): According to the general procedure, IIf was obtained from If (2.37 g, 0.015 mol), metallic K (0.59 g, 0.015 g·atom) and EtONO (2.25 g, 0.03 mol), as colorless needles (from MeOH), 2.0 g.

Dehydration of IIa—e with $POCl_3$——General Procedure: A suspension of II in $CHCl_3$ and exess $POCl_3$ was refluxed for 1 hr. The resulting solution was concentrated under reduced pressure to give the orange red residue. The residue was poured into a mixture of 28% NH_4OH and ice, salted out with solid K_2CO_3 and extracted with benzene. After evaporating the solvent from the extract, the residue was purified by a column chromatography (Al_2O_3–benzene) followed by distillation or by recrystallization, to afford III.

The carbonitriles (IIIa, b, d, e) thus obtained were identical with authentic samples by the comparison of spectral data.

4-Cyano-2-methylpyridine (IIIa): By the general procedure, IIIa was obtained from IIa (1.1 g, 0.0081 mol), $POCl_3$ (31 g, 0.2 mol) and $CHCl_3$ (30 ml), as colorless needles (from petr. ether), 0.7 g.

4-Cyano-2,4-dimethylpyridine (IIIb): By the general procedure, IIIb was obtained from IIb (0.83 g, 0.0055 mol), $POCl_3$ (31 g, 0.2 mole) and $CHCl_3$ (30 ml), as colorless needles (from petr. ether), 0.54 g.

4-Cyano-2-methylquinoline (IIIc): By the general procedure, IIIc was obtained from IIc (3.2 g, 0.017 mol), $POCl_3$ (31 g, 0.2 mol) and $CHCl_3$ (30 ml), as colorless needles (from petr. ether), 2.7 g.

17) All melting points were uncorrected. NMR spectra were recorded on a Hitachi R-20 spectrometer (60 MHz) and chemical shifts are given in δ values (ppm) with TMS as internal standard. IR spectra were taken with a JASCO IRA-1 grating IR spectrometer.

4-Cyano-2-methylpyrimidine (IIId): By the general procedure, IId (1.0 g, 0.0073 mol) was treated with $POCl_3$ to give IIId, 0.58 g.

4-Cyano-2,6-dimethylpyrimidine (IIIe): By the general procedure, IIe (0.65 g, 0.0043 mol) was treated with $POCl_3$ (2 ml) to give IIIe, as colorless needles (from petr. ether), 0.32 g.

4-Cyano-2-methylquinazoline (IIIf)——A mixture of IIf (0.5 g, 0.0027 mol) and P_4O_{10} (0.38 g, 0.0027 mol) was heated at 170° under reduced pressure to sublimated pale yellow crystals. The crystals were dissolved in C_6H_6 and passed through an alumina column for decoloration and recrystallized from petr. ether to give colorless needles, 0.197 g.

Acid Hydrolysis of 4-Cyano-2-methylquinoline (IIIc)——A solution of IIIc (2.0 g) in 75% H_2SO_4 (20 ml) was refluxed for 1 hr. The solution was neutralized with 3 N-NaOH to give colorless precipitates. The precipitates were collected by filtration and recrystallization from EtOH to yield colorless needles (IVc), mp 240—243° (dec.), 1.25 g (56%).

Decarboxylation of 2-Methylquinoline-4-carboxylic Acid (IVc)——A solution of IVc (1.2 g) in nitrobenzene (40 ml) was refluxed for 24 hr. After cooling, the solution was shaken with 3 N HCl and the HCl layer was made alkaline with 3 N NaOH followed by extraction with ether. The ether extract was concentrated to afford a pale yellow liquid, bp 120—125° (20 mmHg), 0.23 g (25%) which was identical with 2-methylquinoline by comparison of spectral data and by the mixed melting point test with its picrate (mp 192—194°).

Alkaline Hydrolysis of 4-Cyano-2-methylquinazoline (IIIf)——A suspension of IIIf (0.2 g) in 10% KOH (2.5 ml) was stirred at room temperature. After IIIf dissolved, AcOH (1.0 g) was added to the solution to give the precipitates which were collected by filtration. Recrystallization of the precipitates from EtOH gave 2-methyl-4-quinazolone (VI), mp 234—236°, 0.15 g (80%). VI was identical with the authentic sample by comparison of IR spectrum.

One-step Preparation of IIIa—e from Ia—e——The same method with the general procedure of nitrosation was used. The crude aldoximes (IIa—e) obtained from acetone extracts of the reaction mixture were treated with phosphoryl chloride. The treatment for dehydration of IIa—e with phosphoryl chloride was the same as the general procedure. The yields were summarized in parentheses in Table III.

Acknowledgement The authors are greatful to all the staffs of the Central Analysis Room of this Institute for elemental analysis and NMR spectra measurement.

[Chem. Pharm. Bull. 25(7)1826—1829(1977)]

UDC 615.322.011.5.07 : 581.192

A New Phytochemical Survey of Malaysia. IV. Chemical Screening

KAI CHEONG CHAN, KOK FEF MAK, and L.E. TEO

Department of Chemistry, University of Malaya[1]

(Received November 10, 1976)

Presented here are the results of further screening of Malaysian plants consisting of 148 species from 61 families, for the presence of alkaloids, saponins, steroids and triterpenes.

Keywords——phytochemical screening; alkaloids; saponins; steroids; triterpenes

In the three previous papers of this series[2-4] we have reported the results of a preliminary chemical investigation of 743 plant samples representing 540 species, distributed over 112 families and 333 genera. In this communication, we wish to present the results of chemical examination of further 273 samples, from 148 plant species belonging to 61 families. Of these 41 samples have given positive tests for alkaloids, 64 samples for saponins and 38 samples

1) Location: *Kuala Lumpur, Malaysia.*
2) Part II: J. Carrick, K.C. Chan, and H.T. Cheung, *Chem. Pharm. Bull.* (Tokyo), **16**, 2433 (1968).
3) K.C. Chan and L.E. Teo, *Chem. Pharm. Bull.* (Tokyo), **17**, 1284 (1969).
4) K.C. Chan and L.E. Teo, *Chem. Pharm. Bull.* (Tokyo), **20**, 1582 (1972).