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# Pyrazolotropolones and Their Derivatives[1)]

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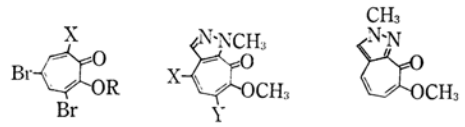
Two new methods have been developed to synthesize pyrazolotropone derivatives. 2-Methoxy-3, 5, 7-tribromotropone reacts with diazomethane to yield 4, 6-dibromo-7-methoxy-1-methyl-8(1*H*)-cyclohepta[c]pyrazolone, whereas the alkaline treatment of 4-acetyltropolone tosylhydrazone provides 3′-methylpyrazolo[3, 4-c]tropolone and 3′-methylpyrazolo[4, 3-d] tropolone. The structure of these products has been elucidated.

The reaction of diazomethane with troponoids, apart from the normal methylation of the tropolone hydroxyl, has been studied by Nozoe et al.,[2)] who found that the reagent attacked 2-halotropones and 4-methoxytropone to form pyrazolotropone derivatives, although the exact location of the pyrazole ring on the tropone nucleus was not established. We now wish to report on the structure of the products from a similar reaction of halomethoxytropones, as well as a new method to synthesize pyrazolotropolones.

3, 5, 7-Tribromotropolone[3)] (I), when treated in methanol with an excess of ethereal diazomethane at room temperature, first formed 2-methoxy-3, 5, 7-tribromotropone (II); this soon dissolved to an orange-red solution. The evaporation of the solvent, which served to liberate the hydrogen bromide, followed by alumina chromatography, yielded pale yellow, silky needles of III (m. p. 158°C) in a 30% yield. The same compound was also prepared in a 54% yield by the action of diazomethane on II.



I R=H, X=Br
II R=$CH_3$, X=Br
XII R=X=H

III X=Y=Br
IV X=Cl, Y=Br
or X=Br, Y=Cl
Va X=Y=H

Vb

1) Presented in part at the Tohoku Local Meeting of the Chemical Society of Japan, Yonezawa, June, 1963.
2) T. Nozoe, T. Mukai and T. Asao, to be published.
3) T. Nozoe, S. Seto, K. Kitahara, M. Kunori and Y. Nakayama, *Proc. Japan Acad.*, **26**, (7), 38 (1950).

Table I. NMR data*1

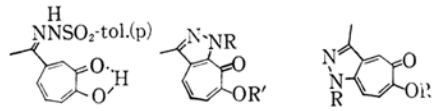
| Compd No. | C-$CH_3$ | O-$CH_3$ | N-$CH_3$ | $CH_3CO$ | Aromatic protons on 7-membered ring | Aromatic protons on 5-membered ring |
|---|---|---|---|---|---|---|
| III | | 3.97*2 | 4.47 | | 7.63 | 8.08 |
| IV | | 3.96 | 4.47 | | 7.40 | 8.11 |
| V | | 3.88 | 4.46 | | 6.4—6.9(m)*3 | 7.84 |
| | | | | | 7.0—7.3(q)*3 | |
| IX | 2.49 | | | 2.36 | 7.16(d, $J$=13) | |
| | | | | 3.61 | 7.40 | |
| | | | | | 8.88(d, $J$=13) | |
| XI | 2.51 | 3.94 | 4.47 | | 6.5—6.9(m)*3 | |
| | | | | | 7.0—7.3(q)*3 | |
| XIII | | 3.93 | 4.15 | | 7.80 | 8.46 |

*1 Spectra are refered to for deuteriochloroform solution. Chemical shift ($\delta$) is expressed in p. p. m. from internal tetramethylsilane, coupling constants ($J$) being in c. p. s.
*2 Singlet unless shape of signal is stated by d for doublet, q for quartet and m for multiplet.
*3 ABX type of pattern, representing two and one proton respectively.

The ultraviolet spectrum indicates the presence of a tropone nucleus in III, while its NMR spectrum (cf. Table I) shows the presence of O-$CH_3$ (3.97 p. p. m.),[4] N-$CH_3$ (4.47 p. p. m.), and two isolated nuclear protons at 7.63 p. p. m. and 8.08 p. p. m. These spectroscopic observations, together with the analytical data and the fact that hydrogen bromide was liberated during the reaction, indicate that III is a dibromomethoxy-*N*-methylpyrazolotropone.

The permanganate oxidation of III gave, after thermal decarboxylation, 1-methylpyrazole-4-carboxylic acid, the structure of which was confirmed by the NMR spectrum of its methyl ester. This reaction establishes the presence of a pyrazole ring in III. The functional groups in the compound III are very inactive, and the only reaction registered was the acid-catalyzed exchange of one of the bromine atoms for a chlorine, thus yielding the corresponding bromochloro compound, IV (NMR Table I), although the position of the chlorine atom was not established. The catalytic reduction of III resulted in the absorption of two moles of hydrogen, and yielded V as yellow granules; the analysis and the ultraviolet spectrum of these granules suggest that the product is the corresponding methoxy-*N*-methylpyrazolotropone. Its NMR spectrum (cf. Table I) showed a singlet at 7.84 p. p. m. due to a proton on the pyrazole ring, and a complex multiplet, representing 3 protons, probably of the ABX type, between 6.4 and 7.3 p. p. m., besides signals due to a O-$CH_3$ (3.88 p.p.m.) and a N-$CH_3$ (4.46 p.p.m.). Compound V must, therefore, have one of the alternative structures, Va and Vb, deduced from the above evidence and from a consideration of the mode of action of diazomethane on $\alpha$, $\beta$-unsaturated ketones. However, the appearance of the *N*-methyl signal at such a low field in the NMR spectrum of V and no substantial deviation between those signals in IV and V can more easily be explained on the basis of the structure Va; the low field shift is apparently due to the paramagnetic anisotropy of the carbonyl group at the peri-position.[5]

During the investigation of the various reactions of 4-acetyltropolone, we have also found an effective, simple method for the synthesis of pyrazolotropolone. The *p*-tosylhydrazone VI of 4-acetyltropolone[6] was treated with potassium hydroxide in ethanol. The product was a mixture of VII (pale yellow needles; 40% yield) and VIII (orange prisms; 22% yield), both of which showed a positive ferric chloride coloration and exhibited ultraviolet spectra



VI VII R=R′=H VIII R=H
X R=H, R′=$COCH_3$ IX R=$COCH_3$
XI R=R′=$CH_3$

suggestive of the presence of a tropolone ring. That both VII and VIII contain a pyrazole ring fused with the tropolone nucleus was established by their permanganate oxidation, which yielded 5-methylpyrazole-3, 4-dicarboxylic acid. Although the acetylation of VIII gave the colorless *O, N*-diacetate (IX), the same reagent under similar conditions converted VII to only a pale yellow *O*-acetate (X), which gave a negative ferric chloride test. The methylation of VII, under the conditions described above for tribromotropolone, gave the corresponding *O, N*-dimethyl compound (XI), the NMR spectrum of which (Table I) could almost be imposed on that of V, except for the appearance of a

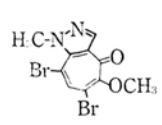
4) The assignment followed many precedences in bromotropolone methyl ethers; the methyl signal invariably appears in the region from 3.90 to 4.00 p. p. m. (J. Tsunetsugu and S. Itô, unpublished observation).

5) Similar situations can be found in the Varian NMR spectra catalog, Vol. I and II, Varian Associate, Palo Alto.

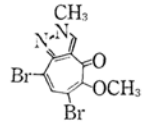
6) T. Nozoe, K. Takase and M. Ogata, *Chem. & Ind.*, **1957**, 1070.

singlet due to a C–$CH_3$ at 2.51 p.p.m. and the disappearance of the singlet at 7.84 p.p.m. due to the pyrazole proton. Once again, the appearance of the N–$CH_3$ signal at such a low field suggests the position of the methyl group. On the other hand, the NMR spectrum of IX showed an AB-type quartet and a singlet (Table I) in the aromatic region, thus disclosing the structures.

The reaction of diazomethane on tribromotropolone was extended to other bromotropolones, but it gave no definite product besides their methyl ether with the exception of 3, 5-dibromotropolone (XII). In the reaction, XII gave, together with 3, 5-dibromo-2-methoxytropone and 3, 5-dibromo-7-methoxytropone, colorless needles (XIII) with a m. p. of 235—236°C(decomp.), and with a molecular formula of $C_{10}H_8O_2N_2Br_2$. XIII exhibits an



XIIIa



XIIIb

ultraviolet spectra completely different from that of III, although it still retain a tropone nucleus. NMR spectrum (Table I) of XIII discloses the presence of O–$CH_3$, N–$CH_3$ and two isolated aromatic protons. The N–$CH_3$ signal appears at a much higher field than those in III, IV, V and XI, showing that they are free from the paramagnetic anisotropy of a carbonyl group, and that, therefore, they are remote from the carbonyl groups. On the other hand, the pyrazole proton at 8.46 p. p. m. is in an extremely low field compared with its counterparts in III, IV and V; this indicates that the pyrazole protons suffer from the anisotropy of the carbonyl group. With this information, the two alternative structures, XIIIa and XIIIb, were derived. However, study was discontinued because of the limited amount of material available.

## Experimental[7]

**4, 6-Dibromo-7-methoxy-1-methyl-8(1*H*)-cycloheptapyrazolone (III).**[8]— *a) From 3, 5, 7-Tribromotropolone (I).*—An excess of diazomethane (an ethereal solution) was added to the warm suspension of I (10 g.) in methanol (150 ml.). After all the solid had disappeared, leaving an orange red solution, the reaction mixture was left in the dark for two days at room temperature with further addition of diazomethane. The colorless needles (m. p. 155—156°C) which crystallized out were collected (2.77 g.) by filtration; the filtrate was evaporated to leave a dark tarry material (the liberation of hydrogen bromide was detected), which was then chromatographed on alumina, eluted with ether to give a further 0.70 g. of the material. Total yield; 2.97 g. (30.6%). Recrystallization from methanol-chloroform gave colorless silky needles (m. p. 158°C).

Found: C, 34.58; H, 2.47; N, 7.62. Calcd. for $C_{10}H_8O_2N_2Br_2$: C, 34.51; H, 2.32; N, 8.05%.

UV $\lambda_{max}^{MeOH}$ m$\mu$ (log $\varepsilon$): 245 (sh. 4.27), 264(4.34), 324(3.74), 335(sh. 3.70), 370(3.78).

IR: 1608, 1572, 1420, 1220, 986, 895, 861 $cm^{-1}$.

*b) From 2-Methoxy-3, 5, 7-tribromotropone (II).*—An ethereal diazomethane was added to a solution of 2.181 g. of II in 150 ml. of methanol; the solution thus obtained was left in the dark at room temperature for 2 days. After crystals had formed (943 mg., m. p. 148—151°C), the solution was treated exactly in the manner described above. The total yield of the crystals was 1.087 g. (53.5%). The compound was identified as III by a mixed melting point determination and by a comparison of the ultraviolet, infrared and NMR spectra.

**7-Methoxy-1-methyl-8(1*H*)-cycloheptapyrazolone (V).**—III (1.247 g.) was hydrogenated in a mixture of acetic acid (6 ml.) and ethyl acetate (60 ml.) in the presence of sodium acetate (990 mg.) and 5% palladium on charcoal (93 mg.). After a 2-molar uptake of hydrogen and the removal of the catalyst, the solvent was removed by distillation, leaving a brown residue; this residue was sublimed in vacuo to give yellow prisms (361 mg., 53%). Recrystallization from ethyl acetate yielded pale yellow prisms (m. p. 135—136°C).

Found: C, 63.06; H, 4.79; N, 14.48. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73%.

UV $\lambda_{max}^{MeOH}$ m$\mu$ (log $\varepsilon$): 230(4.56), 255(4.41), 306 (4.06), 321(4.10), 380(3.91).

IR: 1600, 1553, 1429, 1215, 1052, 896, 854, 794, 780 $cm^{-1}$.

**4(or 6)-Bromo-6(or 4)-chloro-7-methoxy-8-(1*H*)-cycloheptapyrazolone (IV).**—III (93 mg.) was heated under reflux for 3 hrs. with 6 N hydrochloric acid (9 ml.) in methanol (20 ml.), and then left overnight at room temperature. The colorless crystals which were thus formed were taken up (64 mg., 79%). Recrystallization from methanol yielded colorless plates (m. p. 143.5—144.5°C).

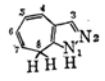
Found: C, 39.59; H, 2.82; N, 8.55. Calcd. for $C_{10}H_8O_2N_2BrCl$: C, 39.57; H, 2.66; N, 9.23%.

**1-Methylpyrazole-4-carboxylic Acid.**—An aqueous solution (100 ml.) of potassium permanganate (4.5 g.) was added, at 65—75°C, to III (679 mg.) dissolved in acetone (150 ml.). After the temperature had been kept constant for 6 hr., the reaction mixture was left overnight. The removal of the $MnO_2$ which had been precipitated and the evaporation of the solvent from a yellow filtrate left a colorless solid. The extraction of the residue by dry acetone and the concentration of the solvent gave colorless crystals (m. p. 175—177°C; 126 mg.; 38% yield). The sublimation of the crystal at 160°C yielded 65 mg. of colorless crystals (m. p. 169°C).

Found: C, 47.88; H, 4.72; N, 21.31, mol. wt. 124 (titration). Calcd. for $C_5H_6O_2N_2$: C, 47.62; H,

7) All melting points are uncorrected. The infrared spectra are referred to Nujol mull unless otherwise stated.

8) This nomenclature is based on the name, 1, 8-dihydrocycloheptapyrazole, of the hypothetic compound XV (numbering shown).



XV

4.82; N, 21.22%; mol. wt. 126.11.

UV $\lambda_{max}^{MeOH}$ mμ (log ε); 227(3.91).

IR: 1715, 1560, 1258, 1000, 931, 887 $cm^{-1}$.

*Methyl Ester.*—Prepared by the action of diazomethane and purified by alumina chromatography. Colorless leaflets; m. p. 62—62.5°C.

Found: C, 51.38; H, 5.82; N, 20.06. Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99%.

IR (KBr): 3145, 1706, 1553, 1458, 1431, 1232, 1008, 763 $cm^{-1}$.

NMR $\delta^{CDCl_3}$: 3.81(3H, S), 3.92(3H, S), 7.98(1H, S), 8.00 p. p. m. (1H, S).

**p-Toluenesulfonylhydrazone (VI) of 4-Acetyltropolone.**—A mixture of 4-acetyltropolone (5.00 g.), *p*-toluenesulfonylhydrazine (6.00 g.) and ethanol (30 ml.) was heated. The mixture changed into a solution at once, and soon the *p*-toluenesulfonylhydrazone (VI) was crystallized out as pale yellow prisms (m. p. 220°C (decomp.)) (10.52 g.).

Found: C, 57.57; H, 4.52; N, 8.22. Calcd. for $C_{16}H_{16}O_4SN_2$: C, 57.83; H, 4.85; N, 8.43%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε); 228 (4.36), 292(4.19), 384 (3.68).

**3'-Methylpyrazolo[3, 4-c]tropolone (VII) and 3'-Methylpyrazolo[4, 3-d]tropolone (VIII).**—To a solution of potassium hydroxide (3.0 g.) in ethanol (60 ml.), VI (5.10 g.) was added; the mixture was then refluxed for 7 hr. After the addition of water (40 ml.) and acidification with 6 N hydrochloric acid, the solution was allowed to stand overnight. The crystals thereby formed were colledted by filtration and recrystallized from dimethylformamide to give 3'-methylpyrazolo-[3, 4-c]tropolone (VII) as pale yellow needles (m. p. 211—212°C) (1.09 g.).

Found: C, 58.15; H, 4.38; N, 15.11. Calcd. for $C_9H_8O_2N_2 \cdot 1/2H_2O$: C, 58.73; H, 4.90; N, 15.13%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 226(4.28), 255(4.38), 305(3.80), 318(3.87), 379(sh. 3.88), 390(3.93).

*Acetate X*: m. p. 216—218°C, pale yellow needles (from ethanol).

Found: C, 60.51; H, 4.30; N, 12.83. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.54; H, 4.62; N, 12.84%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 233(4.30), 294(3.82), 307(3.79), 365(3.79), 380 (sh. 3.73).

The removal of ethanol from the mother liquor gave an oily material, which was solidified by allowing it to stand. This was warmed with methanol, and the sparingly-soluble part (m. p. 215—222°C) (1.00 g.) was recrystallized from dimethylformamide to give 3'-methylpyrazolo[4, 3-d]tropolone (VIII) as orange prisms (m. p. 225—226°C) (0.60 g.).

Found: C, 60.83; H, 4.34; N, 15.72. Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 228(4.27), 280(sh. 4.27), 287(4.31), 296(sh. 4.28), 398(3.61), 435(3.55).

*Acetate IX*: m. p. 169—170°C; colorless micro-needles (from acetic acid).

Found: C, 60.16; H, 4.26; N, 10.51. Calcd. for $C_{13}H_{12}O_2N_2$: C, 59.99; H, 4.65; N, 10.77%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 282(4.46), 315(sh. 4.02).

From the methanol-soluble part, *p*-tolyl *p*-toluenethiolsulfonate (0.60 g.), was obtained as colorless needles (m. p. 75—76°C (reported 76°C[9])) after recrystallization from methanol.

**1, 3-Dimethyl-7-methoxy-8-(1*H*)-cycloheptapyrazolone (XI).**—VII (603 mg.) was methylated with diazomethane under the conditions described for the compound III. After the reaction mixture had been left overnight, the solvent was distilled off, and the residue was chromatographed on alumina. Elution with benzene gave yellow crystals (587 mg., 84.5%). Recrystallization from benzene - petroleum ether (b. p. 60—80°C) gave yellow prisms (m. p. 81.5—82°C).

Found: C, 64.96; H, 5.55; N. 13.50. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.90; N, 13.70%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 230(4.37), 250(4.37), 302(3.98), 316(4.03), 370(3.94).

IR: 1623, 1603, 1553, 1425, 1214, 1028, 793, 768 $cm^{-1}$.

**The Permanganate Oxidation of Pyrazolotropolones VII and VIII.**—Into a solution of VII (0.53 g.) in a 0.4 N potassium hydroxide solution (25 ml.), finely-powdered potassium permanganate was stirred in small portions at room temperature; 2.65 g. of permanganate was thus smoothly consumed. After the mixture had been allowed to stand overnight, the excess permanganate was decomposed on the addition of methanol and the manganese dioxide was filtered off. The filtrate was slightly acidified with 6 N hydrochloric acid and concentrated under reduced pressure until crystals had begun to separate out. Acetone was then added, and the inorganic salts thereby separated were filtered off. After the mother liquor had been treated repeatedly in the same way, the acetone solution was evaporated to dryness; the subsequent addition of a small amount of water gave oxalic acid. From the water-soluble part, 5-methylpyrazole-3, 4-dicarboxylic acid (0.11 g.) was obtained as colorless microcrystals; this acid was identified with an authentic specimen[10] by a comparison of the infrared spectra.

Found: C, 38.60; H, 4.30; N, 14.77. Calcd. for $C_6H_6N_2 \cdot H_2O$: C, 38.30; H, 4.29; N, 14.89%.

The same oxidation of VIII (0.30 g.) with potassium permanganate also gave 5-methylpyrazole-3, 4-dicarboxylic acid (0.05 g.).

**The Reaction of Diazomethane with 3, 5-dibromotropolone (XII).**—The reaction was carried out with 100 mg. of XII in exactly the same way as was described in the above section. The product obtained by the evaporation of the solvent from the reaction mixture in vacuo was chromatographed on alumina. Elution with benzene gave colorless cytstals (30 mg.), which were recrystallized from chloroform to give colorless silky needles (XIII) (m. p. 235—236°C(decomp.)).

Found: C, 34.61; H, 2.30; N, 7.54. Calcd. for $C_{10}H_8O_2N_2Br_2$: C, 34.51; H, 2.32; N. 8.02%.

UV $\lambda_{max}^{MeOH}$ mμ (log ε): 240(sh. 4.70), 253(4.77), 260 (sh. 4.69), 347(4.24).

IR: 3125, 1616, 1587, 1221, 1012, 903, 865, 785, 765 $cm^{-1}$.

The authors wish to express their gratitude to Professor Tetsuo Nozoe, Tohoku University, for his interest, and to Professor W. A. Ayer, University of Alberta, Canada, for some of the NMR spectra included in this paper.

9) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 605 (1962).

10) K. V. Auwers and E. Cauer, *Ann.*, **470**, 304 (1929).