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SYNTHESIS OF PYRAZOLONE DERIVATIVES—XXI[1]

ON THE REDUCTION OF 1-METHYL-2-PHENYL-1,2,3,10-TETRAHYDRO-4H-PYRAZOLO[3,4-c][1] BENZOTHIEPIN-3,4-DIONE WITH SODIUM BOROHYDRIDE

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Abstract—The selective reduction of α,β-unsaturated ketones and C=C double bonds of pyrazolo[3,4-c][1]benzothiepins with sodium borohydride was studied. The reduction of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-c][1]benzothiepin-3,4-dione (**1**) with sodium borohydride in refluxing methanol gave 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-c][1]benzothiepin-3-one (**2**). The mechanism of this unusual reaction in which the heterocyclic ketone was reduced to the corresponding methylene grouping with such a reagent was elucidated by the isolation of the following intermediates: 1-methyl-2-phenyl-1, 2, 3, 3a, 10, 10a-hexahydro-4H-pyrazolo[3,4-c][1]benzothiepin-3,4-dione (**6**) and 1-methyl-2-phenyl-1,2,3,3a,10,10a-hexahydro-4H-pyrazolo[3,4-c][1]benzothiepin-3-one (**4**).

The synthesis of 1 - methyl - 2 - phenyl - 1, 2, 3, 10 - tetrahydro - 4H - pyrazolo[3, 4-c][1]benzothiepin - 3, 4 - dione (**1**) was reported previously.[2] In continuation of this work, this paper deals with the reduction of **1** with sodium borohydride.

It is already well known that many heterocyclic ketones can be reduced to their corresponding secondary alcohols with sodium borohydride, but few have ever been reduced to methylenes by this method. It is also established that C=C double bonds are usually stable towards sodium borohydride.[3]

We now, however, have obtained 1-methyl-2-phenyl - 1,2,3,10 - tetrahydro - 4H - pyrazolo[3, 4-c][1]benzothiepin - 3 - one (**2**) by the use of sodium borohydride for the selective reduction of the α,β-unsaturated ketone of **1**.

The reduction of **1** with sodium borohydride in refluxing methanol gave a compound of m.p. 210–211° (**2**) whose IR spectrum did not show any absorption band attributable to a secondary alcohol. The absorption band at 1690 cm^{-1} due to a 7-membered ring ketone which was observed in the starting material (**1**), was not present in this compound (**2**). The UV spectrum of **2** was measured at 251 mμ (log ϵ: 4·06) which of shorter wavelength than that of **1**,[2] suggesting that the ketone was reduced. The molecular ion peak (*m/e*: 308) in the mass spectrum and the elemental analysis of **2** agreed with the formula of $C_{18}H_{16}ON_2S$. In the NMR spectrum three singlet peaks at 2·87, 3·70, and 4·00 ppm were attributed to N-methyl, methylene at 10-position, and methylene at 4-position, respectively.

In order to elucidate this structure, **2** was desulfurized by reduction in the presence of Raney nickel catalyst to give an open ring compound, 4-benzyl - 2,3 - dimethyl - 1 - phenyl - 3 - pyrazolin - 5 - one (**3**), which was identical with a sample synthesized by the reaction of 1-phenyl-3-methyl-4-benzyl-3-pyrazolin-5-one[4] with dimethylsulfate. The elemental analysis, IR spectrum, and NMR spectrum of this compound (**3**) was in full agreement with the assigned structure.

Since it appeared that the above mentioned reduction of **1** with sodium borohydride in refluxing methanol was critical, the reduction was carried out in tetrahydrofuran, cooling the reaction medium with ice. The IR spectrum of the resulting product (**4**) showed a strong absorption band at 3200 cm^{-1} due to a secondary alcohol which was initially assumed to be 1 - methyl - 2 - phenyl - 1,2,3,10-tetrahydro - 4 - hydroxy - 4H - pyrazolo[3,4 - c][1]-benzothiepin - 3 - one (**A**). However, the elemental analysis and the molecular ion peak of **4** (*m/e*: 326) in the mass spectrum agreed with the formula $C_{18}H_{18}O_2N_2S$ rather than with $C_{18}H_{16}O_2N_2S$ (**A**). In the NMR spectrum, the alcoholic proton of **4** (observed at 4·65 ppm) disappeared with D_2O-exchange. The geminally attached proton of the secondary alcoholic group was observed at 5·60 ppm and this splits to doublet coupling with a vicinal proton. Thus the structure of **4** was concluded to be 1 - methyl - 2 - phenyl - 1,2,3,3a,10,10a -

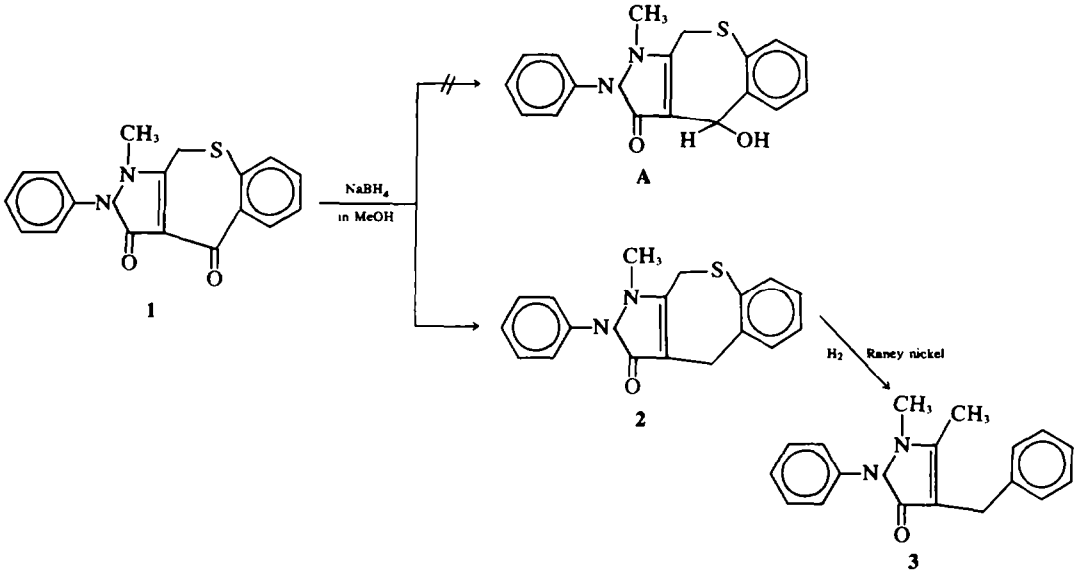


CHART 1

hexahydro - 4 - hydroxy - 4H - pyrazolo[3,4-c] [1]benzothiepin - 3 - one. Acetylation of **4** gave 1 - methyl - 2 - phenyl - 1,2,3,3a,10,10a - hexahydro - 4 - acetoxy - 4H - pyrazolo[3,4-c][1]benzothiepin - 3 - one (**5**).

cohol in the IR spectrum, and the aromatic ketone at 1695 cm^{-1} unreduced. Elemental analysis and molecular ion peak (*m/e*: 324) agreed well with the formula of $C_{18}H_{16}O_2N_2S$. This means that two H atoms have been added to the molecule of **6** which

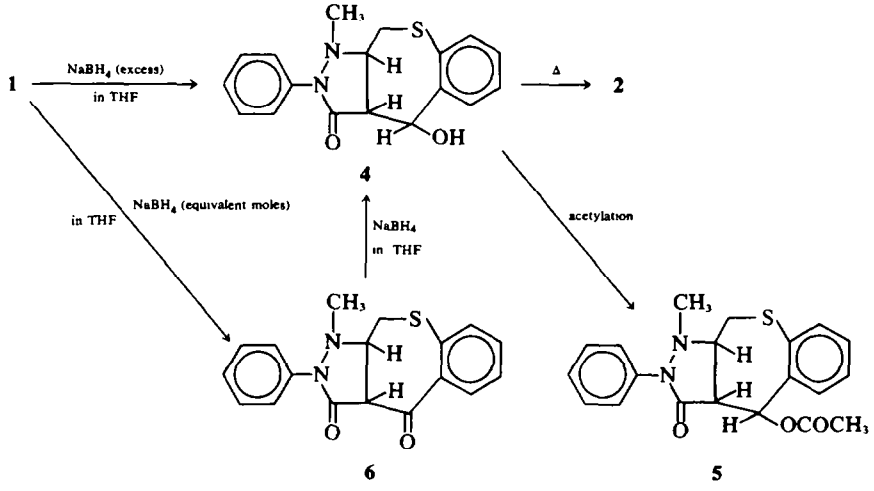
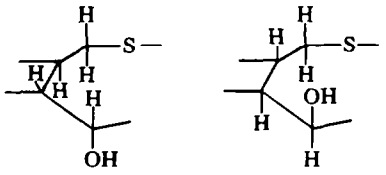


CHART 2

It might be thought that the formation of **4** would be due to excess borohydride reagent, and that one equivalent would reduce the seven-membered ring ketone to the alcohol (**A**). However, the reaction of **1** with one equivalent mole of sodium borohydride in tetrahydrofuran gave 1 - methyl - 2 - phenyl - 1,2,3,3a,10,10a - hexahydro - 4H - pyrazolo[3,4-c] [1]benzothiepin - 3,4 - dione (**6**). The compound **6** has no absorption attributable to a secondary alfact was confirmed by the NMR spectrum. The following experiment provided additional evidence for its structure: **6** was further reduced to **4** with sodium borohydride in tetrahydrofuran, and when **4** was allowed to react with sodium hydroxide in refluxing ethanol, **2** was obtained.

Compound **4** has three asymmetric C atoms and theoretically eight isomeric configurations. However, in the NMR spectrum of **4**, one proton at the

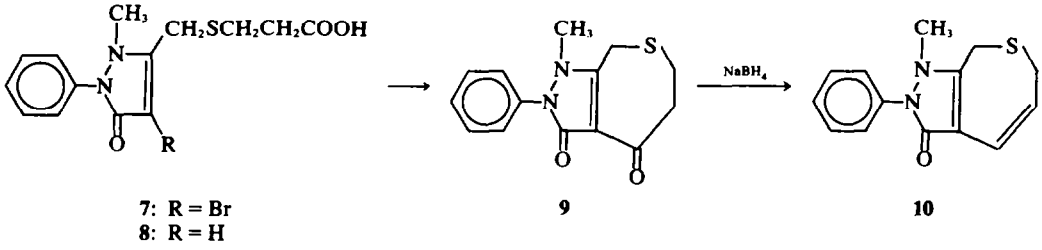
4-position splits to doublet thus coupling with the vicinal proton (3a). From this coupling constant ($J = 3$ c/s), the relationship of these two protons seems to be the *cis* form with each other. On the other hand, the 3a proton of **6** splits to doublet ($J = 9$ c/s) coupling with the 10a proton. This means that the 3a and the 10a protons are in a *trans* form with each other. Considering these facts, it seems that the possible configurations of **4** are 4-a and 4-b as shown in Fig 1.



4-a **4-b**

Fig 1.

In order to study the reduction of the related compounds of **1** with sodium borohydride, the bicyclic compound **9**, which lacks the benzene ring of the tricyclic system (**1**), and a ring opened compound (4-benzoyl antipyrine[2]) were synthesized as shown in Chart 3. The reduction of **9** gave **10**, and 4-benzoyl antipyrine afforded **11** in methanol or tetrahydrofuran. Thus no hydration of the pyrazoline C=C double bond occured in compounds **10** and **11**. The reaction mechanism of the synthesis of **2** from **1** seems to proceed as described in Chart 4. Initially the pyrazoline C=C double bond is hydrated to give **6** and then the excess reagent reduces the ketone to form the secondary alcohol (**4**), which gives a labile compound **2'** by releasing water with heating. Consideration of Hückels rule[5] suggests that the structure of **2** is more stable than that of **2'**.



7: R = Br
8: R = H

9 **10**

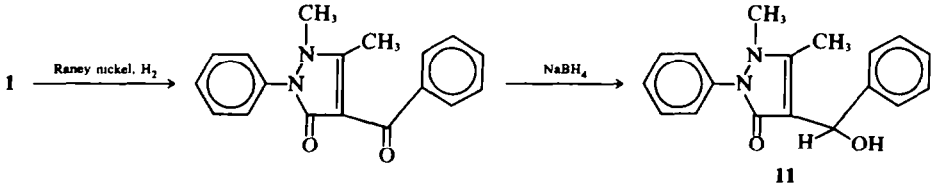


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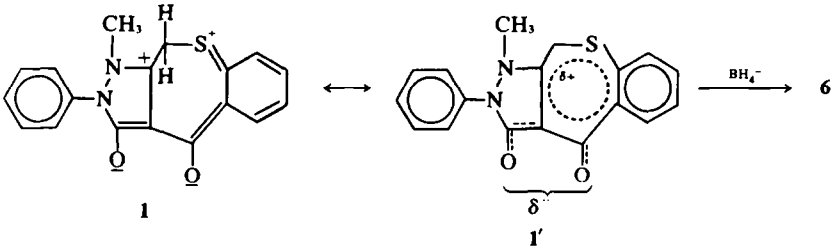
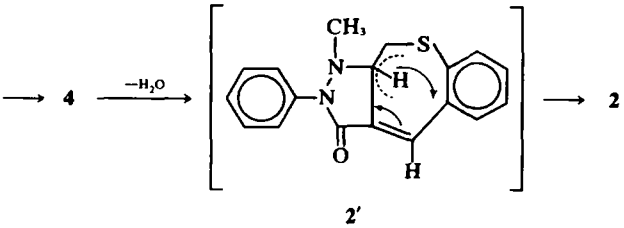
CHART 3



1 **1'**



2'

CHART 4

EXPERIMENTAL

All the m.ps were determined on a Yanagimoto Micro-Melting Point apparatus and were not corrected. The UV absorption spectra were recorded with a Hitachi Recording Spectrophotometer EPS-3T, and the IR absorption spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-S. The NMR spectra were measured with a Japan Electron Optics Laboratory Co. JNM-MH-60 spectrometer using TMS as internal standard. Mass spectra were evaluated on a Hitachi Mass Spectrometer, Model RMU-6E, equipped with a double focusing system.

1 - *Methyl* - 2 - *phenyl* - 1,2,3,10 - *tetrahydro* - 4*H* - *pyrazolo*[3,4-*c*][1]*benzothiepin* - 3 - *one* (**2**). (0·50 g) $NaBH_4$ were added to a stirred soln of **1** (1·6 g, 0·005 mole) in 50 ml MeOH. The mixture was refluxed for 3 h on a water-bath, and MeOH was distilled off. 10% H_2SO_4 was added to the residue and the insoluble substance was collected by filtration, and then recrystallized from EtOH to obtain 1·3 g (84%) of colorless needles, m.p. 206–208°; ν_{max} (KBr) 2850 (—CH_2—) and 1650 (N—CO—) cm^{-1}; λ_{max}^{EtOH} 251 mμ (log ϵ 4·06); *m/e* 308 (M^+); NMR ($CDCl_3$) ppm 2·87 (3H, s, CH_3), 3·70 (2H, s, —CH_2—), 4·00 (2H, s, —CH_2—S—), 7·10–7·75 (9H, m, aromatic protons). (Found: C, 70·17; H, 5·20; N, 8·90. $C_{18}H_{16}ON_2S$ requires: C, 70·10; H, 5·23; N, 9·08%).

4 - *Benzyl* - 2,3 - *dimethyl* - 1 - *phenyl* - 3 - *pyrazolin* - 5 - *one* (**3**). (a) A mixture of **2** (0·5 g) in 50 ml EtOH and Raney Ni prepared from (1 g) Al–Ni alloy was agitated in an autoclave for 7 h under a pressure of 80 kg/cm^2 H_2 at 60°. The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from petroleum benzine to obtain 0·2 g of colorless prisms, which were recrystallized again from water to give colorless needles of m.p. 65–67°; ν_{max} (KBr) 2850–3040 (—CH_2) and 1630 (N—CO—) cm^{-1}; λ_{max}^{EtOH} 242 mμ (log ϵ 4·03) and 271 mμ (log ϵ 4·06); NMR ($CDCl_3$) ppm 2·11 (3H, s, C—CH_3), 2·93 (3H, s, N—CH_3), 3·68 (2H, s, —CH_2—) and 7·25 (5H, s, aromatic protons). (Found: C, 77·38; H, 6·42; N, 10·05. $C_{18}H_{18}ON_2$ requires: C, 77·67; H, 6·52; N, 10·06%).

(b) A mixture of 4 - benzyl - 3 - methyl - 1 - phenyl - 3 - pyrazolin - 5 - one[4] (26·4 g) and Me_2SO_4 (12·6 g) was heated in an oil bath (160–170°) for 3 h. After cooling, 100 ml of 20% NaOH aq was added to the mixture, which was then heated again on a water-bath for 30 min. The mixture was extracted with benzene. The extracts were washed with water and dried over Na_2SO_4. Benzene was distilled off and the residue was recrystallized from water to obtain colorless needles of m.p. 64–66°, yield 25 g (90%).

1 - *Methyl* - 2 - *phenyl* - 1,2,3,3*a*,10,10*a* - *hexahydro* - 4*H* - *pyrazolo*[3,4-*c*][1]*benzothiepin* - 3 - *one* (**4**). To a cooled suspension of **1** (1·6 g; 0·005 mole) in 30 ml THF $NaBH_4$ (0·5 g; *ca* 0·01 mole) was added. The mixture was stirred for 1 h in an ice cooling bath. After the reaction, the solvent was evaporated and the residue was neutralized with 15% H_2SO_4 and extracted with ether. The extracts were washed with water and dried over Na_2SO_4. The evaporation of ether gave 1·1 g (67%) of prisms of m.p. 175–180°. Recrystallization from EtOH gave colorless prisms of m.p. 188–191°; ν_{max} (KBr) 3200 (OH) cm^{-1}; λ_{max}^{EtOH} 260 mμ (log ϵ 4·13); NMR ($CDCl_3$) ppm 2·75 (3H, s, N—CH_3), 2·25–4·25 (4H, m, methine and methylene protons), 5·60 (1H, d, J = 3 cps, H—C—OH), 4·65 (1H, broad, s, C—OH), and 7·00–7·75 (9H, m, aromatic protons). (Found: C, 66·40; H, 5·49; N, 8·52. $C_{18}H_{18}O_2N_2S$ requires: C, 66·23; H, 5·56; N, 8·58%). Mass Spectrum *m/e*: 326 (M^+).

Acethyl derivative of **4**. A mixture of dry pyridine (5 ml), Ac_2O (5 ml), and **4** (0·5 g) was allowed to stand overnight at room temp and then was poured into water. The resulting ppt was collected by filtration, dried, and recrystallized from petroleum benzine to give 0·42 g of crystalline powder of m.p. 83–85°; ν_{max} (KBr) 1750, 1680, 1650 (C=O) cm^{-1}; λ_{max}^{EtOH} 263 mμ (log ϵ 4·20). (Found: C, 65·42; H, 5·57; N, 7·39. $C_{20}H_{20}O_3N_2S$ requires: C, 65·20; H, 5·47; N, 7·60%).

1 - *Methyl* - 2 - *phenyl* - 1,2,3,3*a*,10,10*a* - *hexahydro* - 4*H* - *pyrazolo*[3,4-*c*][1]*benzothiepin* - 3,4 - *dione* (**6**). To a suspension of **1** (1·6 g; 0·005 mole) in 30 ml THF $NaBH_4$ (0·23 g; *ca* 0·006 mole) was added. The mixture was stirred for 1 h at room temp. After the reaction, the solvent was distilled, the residue was then neutralized with 15% HSO_4 and extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The evaporation of $CHCl_3$ gave crystals which were recrystallized from EtOH to afford colorless needles of m.p. 144–145°; ν_{max} (KBr) 1695 (C=O), 1660 (N—CO—) cm^{-1}; λ_{max}^{EtOH} 244 mμ (log ϵ 4·27), 264 (4·13), 339 (3·77); *m/e* 324 (M^+); NMR ($CDCl_3$) ppm 2·58 (3H, s, N—CH_3), 3·15–4·22 (4H, m, methine and methylene), 7·22–7·85 (9H, m, aromatic protons). (Found: C, 66·44; H, 4·89; N, 8·36. $C_{18}H_{16}O_2N_2S$ requires: C, 66·65; H, 4·97; N, 8·64%).

(4 - *Bromo* - 2 - *methyl* - 5 - *oxo* - 1 - *phenyl* - 3 - *pyrazolin* - 3 - *yl*) *methylthiopropionic acid* (**7**). To 5% NaOH (80 ml) was added 0·05 mole β-mercaptopropionic acid (5·3 g) and 4 - bromo - 3 - bromomethyl - 2 - methyl - 1 - phenyl - 3 - pyrazolin - 5 - one[6] (17·3 g; 0·05 mole) in 50 ml EtOH. The mixture was refluxed on a water-bath for 1 h. EtOH was distilled off and the residue was dissolved in about 50 ml water. The soln was neutralized with 10% H_2SO_4 to obtain crystals, which were collected by filtration and recrystallized from EtOH to give colorless prisms of m.p. 145–146°; yield 17 g (92%); ν_{max} (KBr) 3300–2500 (OH), 1720, 1630 (C=O) cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ϵ 4·03); NMR (d-DMSO ppm 2·70–2·90 (4H, m, —S—CH_2—CH_2—), 3·18 (3H, s, N—CH_3), 3·90 (2H, s, —CH_2—), 7·25–7·35 (5H, m, aromatic protons. (Found: C, 45·42; H, 3·99; N, 7·66. $C_{14}H_{13}O_3N_2SBr$ requires: C, 45·29; H, 4·07; N, 7·55%).

(2 - *Methyl* - 5 - *oxo* - 1 - *phenyl* - 3 - *pyrazolin* - 3 - *yl*)*methylthiopropionic acid* (**8**). A mixture of **7** (18·5 g) conc HCl (16 g) and iron powder (10 g) was heated in a water-bath (50–60°) for 1 h. The black mixture was allowed to stand overnight at room temp. and then extracted with 500 ml of a mixture of $CHCl_3$ and EtOH (19 : 1). The extract was dried over Na_2SO_4. The solvent was evaporated to dryness and the residue was recrystallized from EtOH to give colorless prisms, 3·6 g (25%), m.p. 116–117°; ν_{max} (KBr) 3200–2500 (OH), 1710 (C=O) cm^{-1}; λ_{max}^{EtOH} 249 mμ (log ϵ 4·00), 278 (3·96); NMR (d-DMSO) ppm 2·75–2·90 (4H, m, —S—CH_2—CH_2—), 3·20 (3H, s, N—CH_3), 3·92 (2H, s, CH_2—S—), 5·59 (1H, s, olefinic proton), 7·48–7·58 (5H, m, aromatic protons). (Found: C, 57·59; H, 5·59; N, 9·54. $C_{14}H_{16}O_3N_2S$ requires: C, 57·52; H, 5·52; N, 9·58%).

1 - *Methyl* - 2 - *phenyl* - 1,2,3,4,5,6,8 - *septahydro* - 4*H* - *pyrazolo*[3,4-*c*][2]*thiepin* - 3,4 - *dione* (**9**). P_2O_5 (16 g) was added to 85% phosphoric acid (10 ml) under good stirring in an oil bath (110–120°). Then **8** (2 g) was added in portions. Stirring and heating were continued for 3 h. The mixture was poured into water, saturated with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with water

and dried over Na_2SO_4. The evaporation of $CHCl_3$ gave 1·2 g (63·9%) of tan prisms. Recrystallization from EtOH gave colorless scales of m.p. 196–197°; ν_{max} (KBr) 1670 (C=O) cm^{-1}; λ_{max}^{EtOH} 297 mμ (log ε 4·14); NMR ($CDCl_3$) ppm 3·00 (4H, s, A_4 patern, S—CH_2—CH_2—), 3·35 (3H, s, N—CH_3), 3·90 (2H, s, CH_2—S—), 7·40–7·45 (5H, m, aromatic protons). (Found: C, 61·54; H, 4·95; N, 10·51. $C_{14}H_{14}O_2N_2S$ requires: C, 61·29; H, 5·14; N, 10·21%).

1 - *Methyl* - 2 - *phenyl* - 1,2,3,6 - *tetrahydropyrazolo*[3,4-*c*][2]*thiepin* - 3 - *one* (**10**). To a suspension of **9** (0·5 g) in 20 ml THF $NaBH_4$ (0·5 g) was added. The mixture was stirred in a cooling bath. The mixture became a transparent soln. The solvent was distilled off and 15% H_2SO_4 was added to the residue, which was extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The evaporation of $CHCl_3$ gave crystals, which were recrystallized from EtOH to obtain colorless needles of m.p. 155–156°, yield 0·37 g (78·6%). λ_{max}^{EtOH} 239 mμ (log ε 4·23), 310 (3·99); NMR ($CDCl_3$) ppm 3·17 (3H, s, N—CH_3), 3·57 (2H, d, J = 6 c/s, CH_2—CH=), 3·86 (2H, s, CH_2—S—), 6·15 (1H, a pair of triplet, J = 10·5 c/s, CH_2—CH=), 6·52 (1H, d, J = 10·5 c/s, —CH=), 7·38 (5H, s, aromatic protons). (Found: C, 64·82; H, 5·48; N, 10·69. $C_{14}H_{14}ON_2S$ requires: C, 65·10; H, 5·46; N, 10·85%).

4 - *Benzyloxy* - 2,3 - *dimethyl* - 1 - *phenyl* - 3 - *pyrazolin* - 5 - *one* (**11**). To a suspension of 4-benzoyl-2,3-dimethyl - 1 - phenyl - 3 - pyrazolin - 5 - one (0·1 g) in 20 ml THF $NaBH_4$ (0·5 g) was added. The mixture was stirred at room temp for 1 h. The solvent was distilled off and 15% H_2SO_4 was added to the residue, which was extracted with $CHCl_3$. The extracts were washed with water, dried over $NaSO_4$. The evaporation of $CHCl_3$ gave crystals, which were recrystallized from EtOH to obtain colorless needles of 144–145°, yield 73 mg (72·5%); ν_{max} 3240 (OH), 1640 (C=O) cm^{-1}; λ_{max}^{EtOH} 248 mμ (log ε 4·09), 278 (3·10); NMR ($CDCl_3$) ppm 2·07 (3H, s, C—CH_3), 3·02 (3H, s, N—CH_3), 5·73 (1H, s, methine), 7·33 (10H, s, aromatic protons). (Found: C, 73·16; H, 6·06; N, 9·29. $C_{18}H_{18}O_2N_2$ requires: C, 73·45; H, 6·16; N, 9·52%).

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